I. THE SYNTHESIS OF CONFORMATIONALLY STABLE CARBOHYDRATES

II. STUDIES ON SYNTHETIC SESQUITERPENES RELATED TO EREMOPHILONE

Thesis by

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To Carl Niemann

ACKNOWLEDGMENTS

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ABSTRACT

I. The synthesis of conformationally stable carbohydrates by use of the dialdehyde cyclization method of Baer and Fischer has been investigated. The synthesis of two new 3-C-alkyl-3-aminoaldohexose derivatives was achieved and the full structure elucidation of one of these compounds, methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranoside hydrochloride, has been accomplished.

II. A study of the stereoselective synthesis of compounds related to eremophilone by use of the Michael reaction has been performed and the synthesis of compounds stereochemically related to eremophilone has been accomplished.

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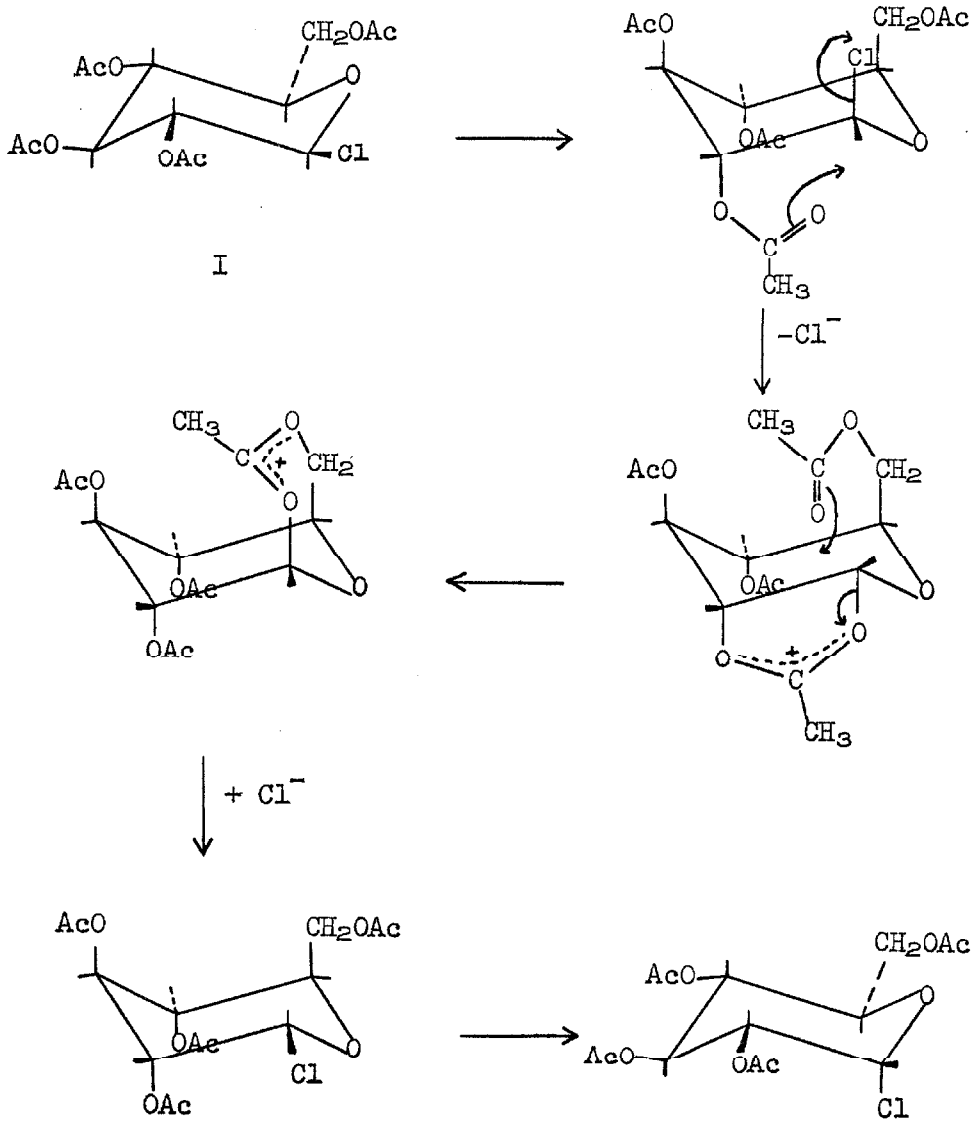
I.

THE SYNTHESIS OF CONFORMATIONALLY STABLE CARBOHYDRATES

INTRODUCTION

Many reactions of pyranoside forms of carbohydrate derivatives are difficult to interpret because of their conformational indeterminacy. It has often been found necessary to invoke unstable conformations to explain observed results (1-4). For example, the rapid anomerization of tetra-O-acetyl-β-D-glucopyranosyl chloride (I) to the α isomer is thought



to proceed (1) via a conformational change from the C1 form to the 1C form followed by neighboring group participation of the C-2 acetoxy group leading to the expulsion of chloride ion. Displacement on C-1 by the C-6 acetoxyl group followed by capture of a chloride ion would then lead to the α-chloro isomer. In order to help clarify this and other problems (1-4), the synthesis of conformationally stable carbohydrates was initiated.

It was expected that a tert-butyl group would be the most suitable for "anchoring" a carbohydrate pyranose ring in one conformation. A synthetic sequence based on the work of Baer and Fischer (5-8) was adopted. The sequence as planned is shown in Figure 1.

Condensations of dialdehyde III with the appropriate nitroalkanes followed by hydrogenation (except in the case of nitroethane) were carried out with the following results:

(a) Nitromethane: the results of Baer and Fischer (6) and Baer (7) were obtained.

(b) Nitroethane: a 44% yield of a mixture of crystalline isomers of nitrosugar IV (R = $-CH_3$) was isolated (cf. 9-11).

(c) 1-Nitropropane: a 2.5% yield of a crystalline compound identified as a methyl 3-ethyl-3-amino-3-deoxy-β-L-hexopyranoside hydrochloride V, R = $-CH_2CH_3$, inverted configuration at C-5) was obtained; determination of the configuration of the compound was not accomplished.

(d) 2-Methyl-1-nitropropane: a 0.93% yield of a crystalline compound identified as methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranoside hydrochloride (VII) was isolated.

(e) 2,2-Dimethyl-1-nitropropane: no product could be isolated.

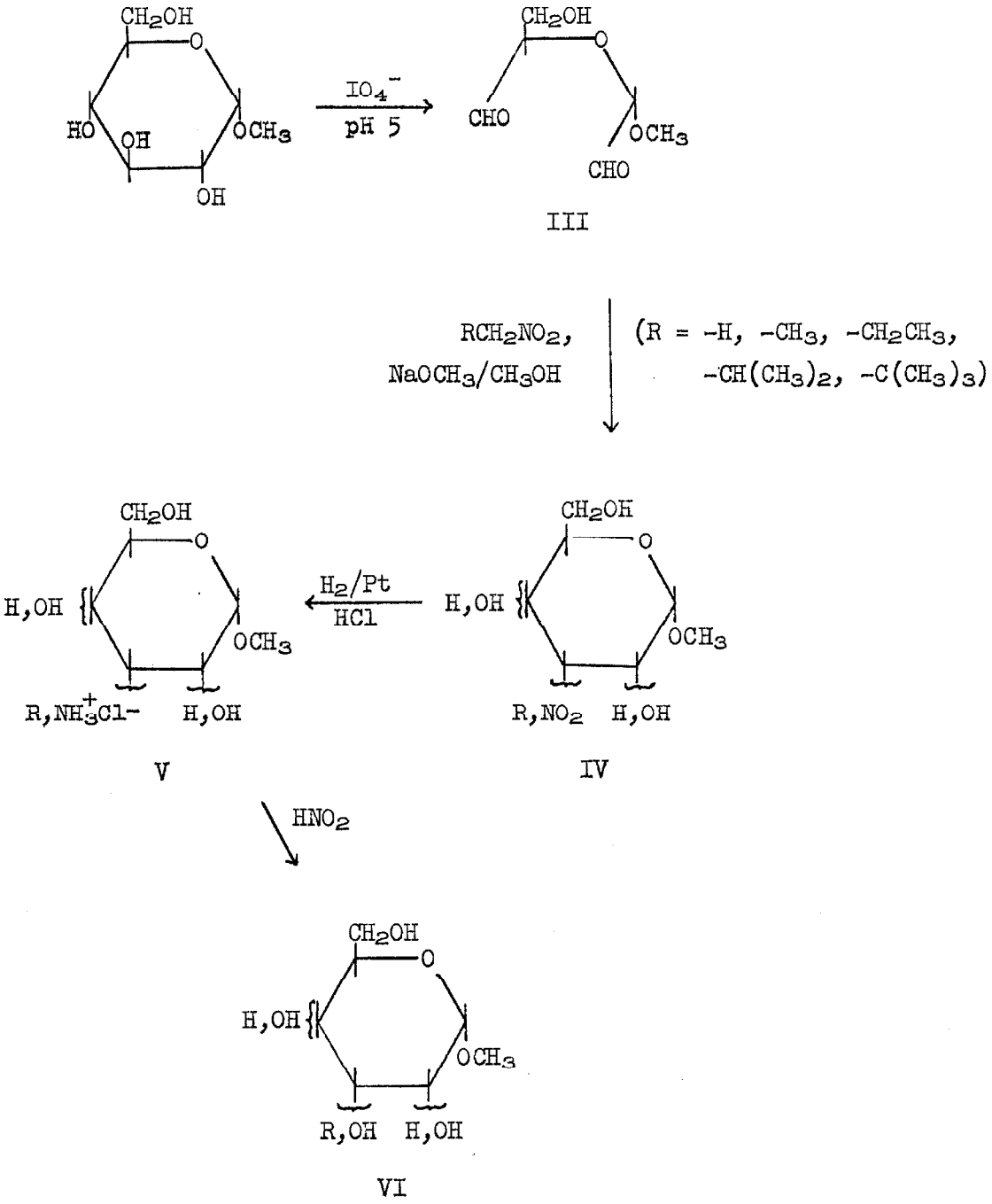
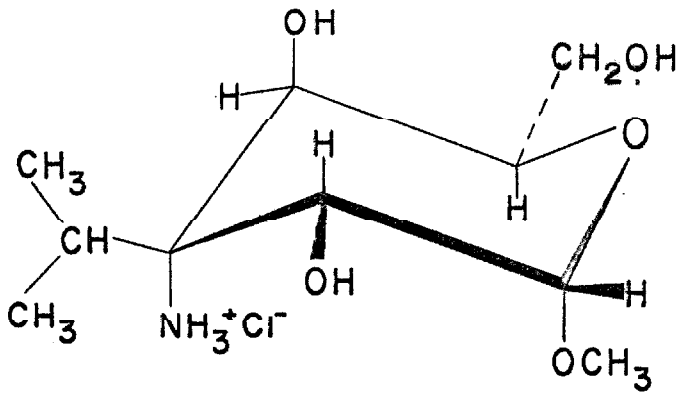


Figure 1. Planned sequence for the synthesis of formationally stable carbohydrates.



VII

Conversion of the aminosugars obtained to hydroxy derivatives was not attempted.*

The structure of aminosugar VII was determined by an analysis of the nuclear magnetic resonance (NMR) spectrum of the peracetyl derivative of VII. NMR spectra were obtained at 60 and 100 Mc., with spin-decoupling at 100 Mc. Assignments of chemical shifts and coupling constants were confirmed and refined by calculation of the spectra by means of a computer program in routine use at the California Institute of Technology (12).

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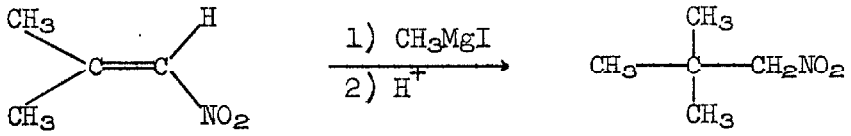
*The research project was terminated shortly after the death of Prof. Niemann, research adviser for the project.

RESULTS AND DISCUSSION

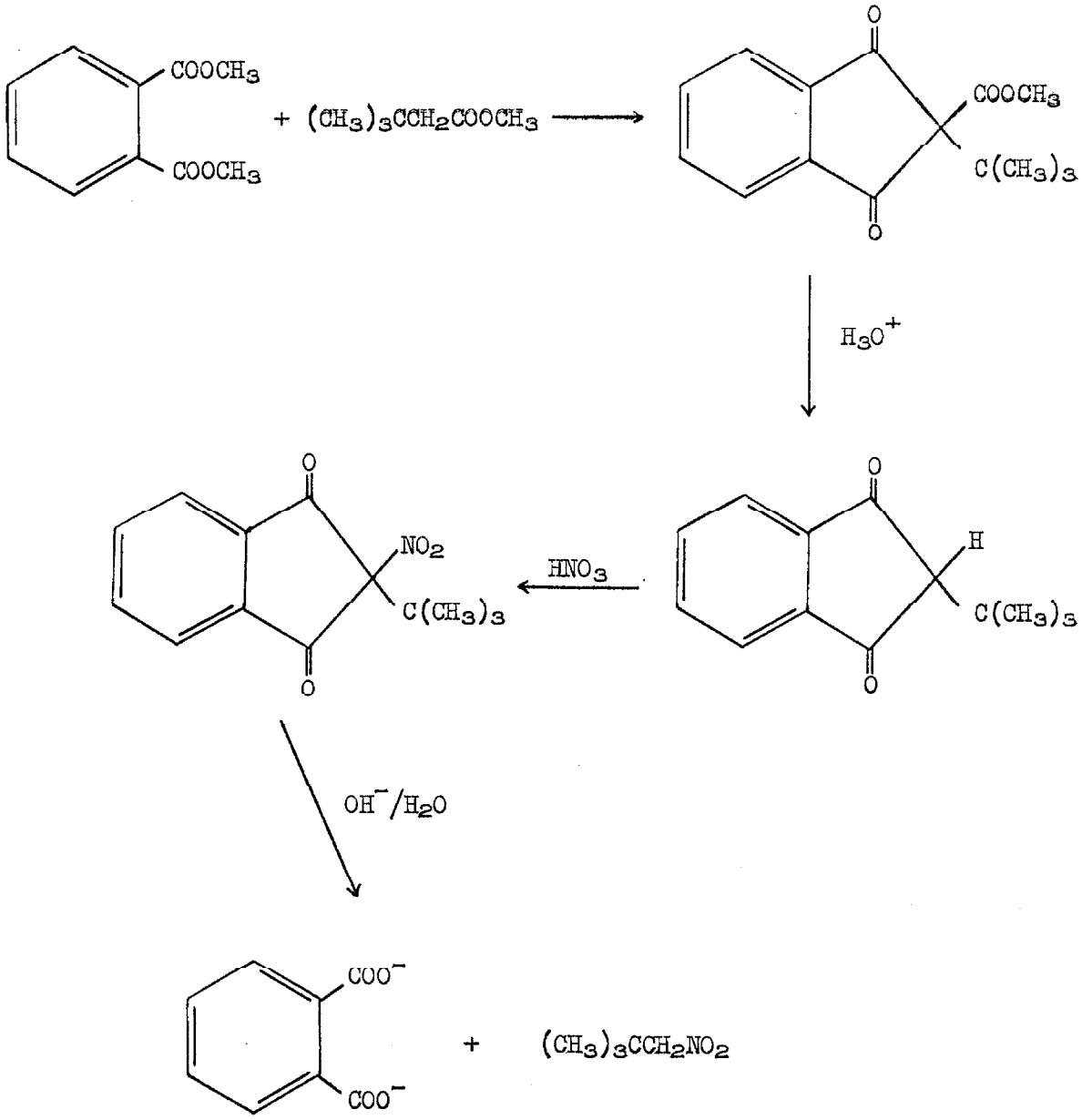
Synthesis of 2,2-Dimethyl-1-nitropropane

The choice of the method of Baer and Fischer (5-7) for the synthesis of conformationally stable carbohydrates necessitated the facile synthesis of 2,2-dimethyl-1-nitropropane (IX, "nitroneopentane"). The compound cannot be prepared (13) by the usual method (14) of displacement on the alkyl halide by nitrite ion. The only feasible route (15) to the compound, albeit in low yield, is via the 1,4 addition of methylmagnesium iodide to 2-methyl-1-nitropropene (VII).



VIII IX

It had been suggested by Kornblum (14) (who failed to note the above synthesis) that "it is quite possible that nitroneopentane, $(CH_3)_3CCH_2NO_2$, can be prepared via an indanedione" (cf. Figure 2). To test this suggestion, the more readily available methyl isovalerate ($(CH_3)_2CHCH_2COOCH_3$) was condensed with dimethyl phthalate using sodium hydride as the catalyst. Subsequent hydrolysis and decarboxylation yielded 8% of 2-isopropyl-1,3-indanedione along with recovered dimethyl phthalate. It appeared that the methyl isovalerate was undergoing self-condensation even though its concentration in the reaction mixture was kept at a minimum by its slow addition to the mixture of dimethyl phthalate and base. In view of the work of Koelsch and Byers (16), it is not surprising that the yield of alkylindanedione was so low. These workers

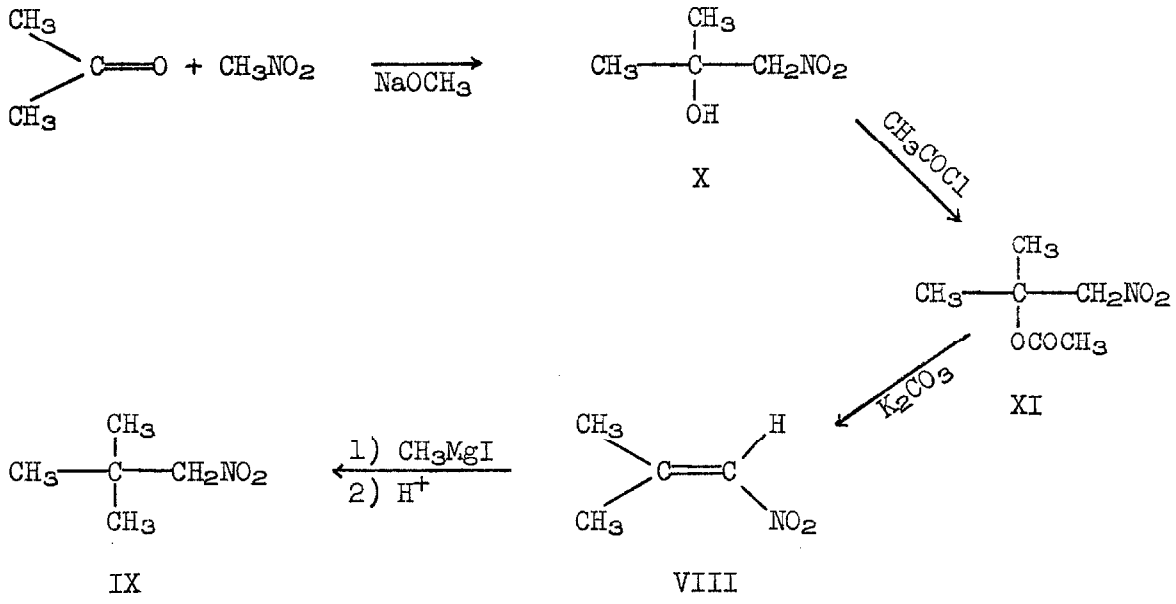


IX

Figure 2. Sequence for the synthesis of 2,2-dimethyl-1-nitropropane (IX) suggested by Kornblum (14).

found that condensations of diethyl phthalate with ethyl valerate and ethyl caproate yielded only 17 and 18%, respectively, of 2-n-alkyl-1,3-indanediones. It would be expected that branching at the carbon atom β to the carboxylate function would provide additional steric hindrance to reaction thereby lowering the yield of alkylindanedione. It was therefore concluded that condensation of dimethyl phthalate with methyl β,β-dimethylbutyrate would be less successful than the above case and this approach was therefore abandoned.

The following reaction sequence was used for the synthesis of 2,2-dimethyl-1-nitropropane (IX):



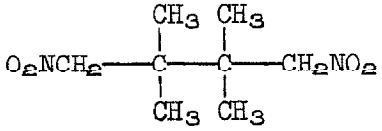
Acetone was condensed with nitromethane by the method of Lambert and Lowe (17) yielding 2-methyl-1-nitro-2-propanol (X) in conversions of 15-20%. Recovered acetone and nitromethane were recycled with additional starting material to raise the total yield of product to 46% over ten runs. 2-Methyl-1-nitro-2-propyl acetate (XI) was prepared

from the alcohol by reaction with acetyl chloride without solvent. The reaction proceeded at a satisfactory and controllable rate initially at 0° with evolution of gaseous hydrogen chloride. The temperature was gradually raised to 70-80° to hasten completion of the reaction while most of the remaining hydrogen chloride in the reaction mixture was boiled out under vacuum (water aspirator). The residual hydrogen chloride in the product was removed by washing with aqueous sodium bicarbonate solution. The acetate (XI) was thus prepared in 90% yield (distilled).

Elimination of the elements of acetic acid from 2-methyl-1-nitro-2-propyl acetate (XI) was accomplished essentially by the method of Levy and Scaife (18). It was found that lower reaction temperature (75° instead of 110-120° (18)) and longer reaction time (1½ hrs. instead of 40 min. (18)) gave the highest yield (78%) of 2-methyl-1-nitropropene (VIII). By carrying out the reaction in a distillation apparatus under vacuum (13 mm.), the nitro-olefin could be removed from the reaction mixture as formed. This procedure minimized polymerization of the product. It is known that some α-nitro-olefins (e.g., nitroethylene, 2-nitropropene) are unstable on standing and polymerize rapidly on heating or treatment with base (19).

The synthesis of 2,2-dimethyl-1-nitropropane (IX) was carried out according to Buckley and Ellery (15) in consistent yields of 30-32% (five runs) although a 42% yield has been claimed (15) for the reaction. The low yield may result partly from polymerization of the nitro-olefin before the addition of methylmagnesium iodide can take place. The low yield is partially accounted for by a side reaction which yields a small

amount (< 10%) of a crystalline compound, m.p. 143-144°, also noted by Buckley and Ellery (15). They assign to the compound an empirical formula of $C_4H_8NO_2$ on the basis of elemental analysis. A structure can easily be assigned to the compound on the basis of its IR and NMR spectra (cf. Table I). A parent peak in the mass spectrum was not observed; such behavior of aliphatic nitro compounds has been noted (20). The only structure consistent with these data is 2,2,3,3-tetramethyl-1,4-dinitrobutane (XII).



XII

The mechanism whereby 2,2,3,3-tetramethyl-1,4-dinitrobutane (XI) is produced may be similar to the induced dissociation hypothesis advanced by Kharasch and Reinmuth (21) to explain the "coupling" of alkyl halides in Grignard reactions. Homolytic scission of the methyl-magnesium bond of methylmagnesium iodide induced by 2-methyl-1-nitropropene (VIII) would lead to a methyl radical and a resonance-stabilized radical XIII as shown in Figure 3. Coupling of a pair of radicals XIII would lead to the salt XIV, which on hydrolysis would yield 2,2,3,3-tetramethyl-1,4-dinitrobutane (XII).

TABLE I

Spectral Properties of Selected Nitroalkanes

Compound	IR[a] NO_2 Absorptions	NMR[b] Chemical Shifts			Ratio of Integrals, Methyl Protons: Methylene Protons
		Methyl Protons	Methylene Protons	Methine Proton	
Compound, "$C_4H_8NO_2$," m.p. 143-144°	6.46, 7.32μ	δ 1.13(s)[c]	δ 4.30(s)		3:1
2,2-Dimethyl-1-nitropropane (IX)	6.50, 7.31μ	δ 1.12(s)	δ 4.17(s)		9:2
2-Methyl-1-nitropropane	6.48, 7.30μ	δ 1.05(d)	δ 4.20(d)	δ 1.63(m)	3:1

[a] Determined in $CHCl_3$ solution.

[b] Determined in CCl_4 solution; all observed resonances are tabulated.

[c] s = singlet, d = doublet, m = multiplet.

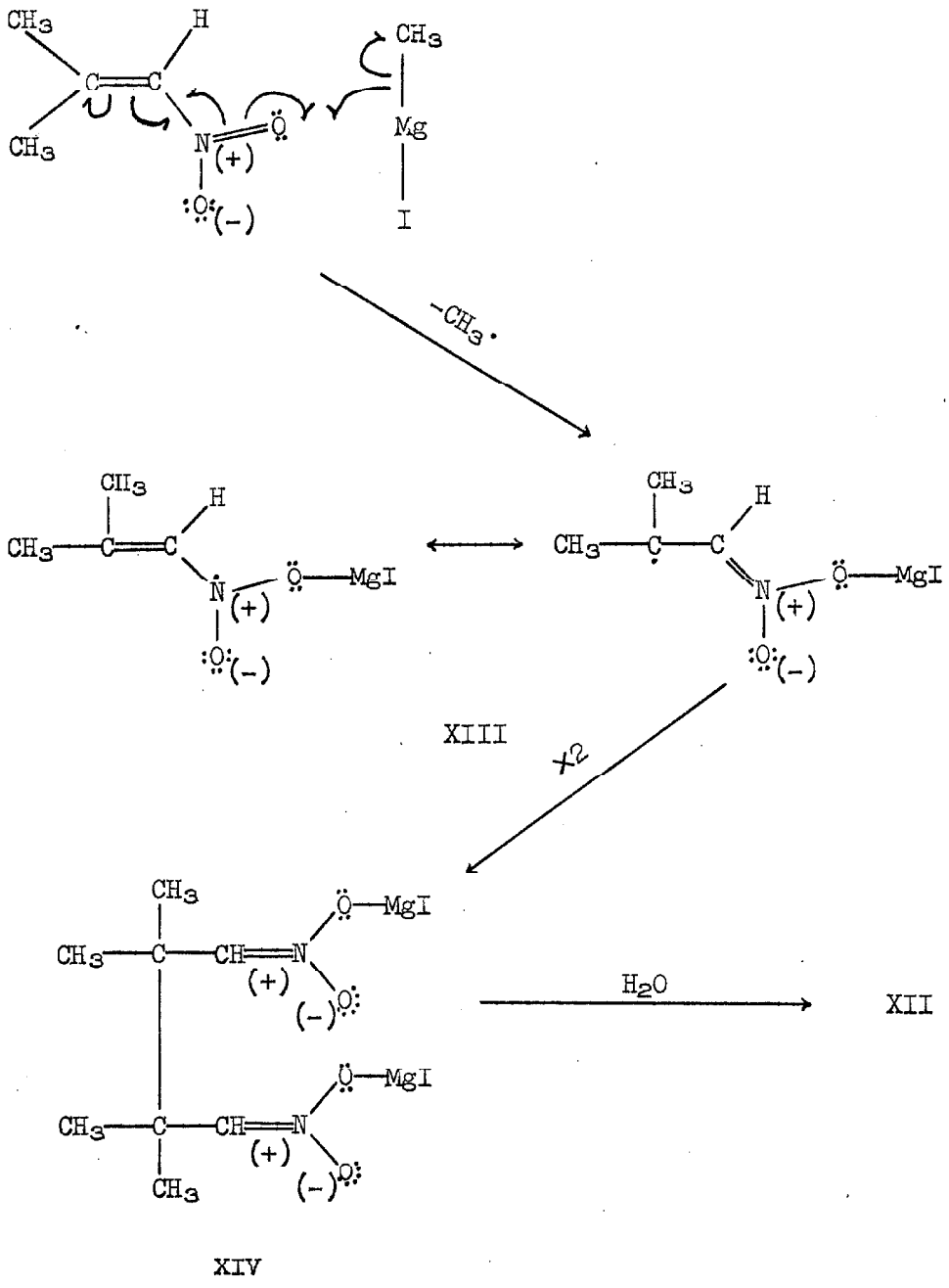
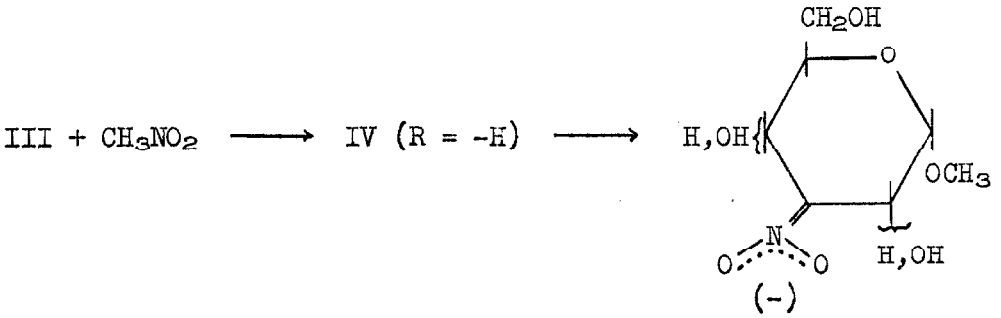


Figure 3. Possible mechanism for the synthesis of 2,2,3,3-tetramethyl-1,4-dinitrobutane (XII).

Condensations of Dialdehyde III with Nitroalkanes and Isolation of Products

The condensations of sugar dialdehydes (e.g., III) with nitromethane are well documented (8, and references cited therein). Condensations with nitroethane have been examined to a limited extent (9-11, 22), but no study of condensations with other nitroalkanes has been reported.

Condensations of dialdehyde III were carried out with nitromethane, nitroethane, 1-nitropropane, 2-methyl-1-nitropropane and 2,2-dimethyl-1-nitropropane (IX) in methanol using sodium methoxide as catalyst. Pertinent data on the reaction conditions employed with each nitroalkane are shown in Table II. The disappearance of aldehyde was followed by use of Benedict's reagent on small aliquots of the reaction mixtures. In all cases, aldehyde concentration diminished to an equilibrium level during the reaction time; with nitromethane the aldehyde disappeared completely. This behavior is consistent with the reactions involved. Condensation of nitromethane with dialdehyde III will ultimately lead to the aci-nitro form of the cyclized product IVa; the cyclization is



IVa

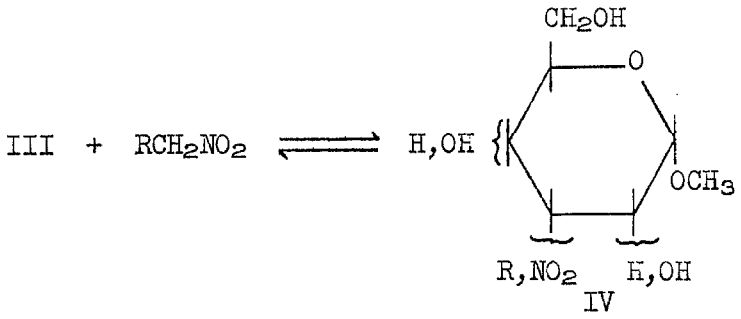
TABLE II

Reactions of Nitroalkanes with Dialdehyde III

Nitroalkane	Reaction Time	Reaction Temp.	Observations*
Nitromethane	40 min.		Absence of aldehyde noted after 30 min.
Nitroethane	4 hrs.		Aldehyde persisted after 4 hrs.
1-Nitropropane	24 hrs.	Room temp. (20-25°)	Test with Benedict's reagent positive at end of reaction time; darkening of reaction mixture noted near end of reaction time.
2-Methyl-1-nitro-propane	12 hrs.	Room temp.	"
2,2-Dimethyl-1-nitro-propane (IX)	12 hrs.	Room temp.	"

*Disappearance of aldehyde from the reaction mixture was followed by use of Benedict's reagent on small aliquots of the reaction mixtures.

therefore essentially an irreversible process since, under the reaction conditions (sodium methoxide in methanol), the product IV is immediately converted to anion IVa. However, when substituted nitromethanes are used, this anion cannot be formed and the cyclization becomes freely reversible:

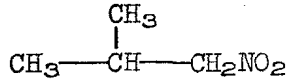
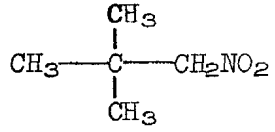


A summary of the yields of crystalline products obtained from the condensations or from the hydrogenation products of the cyclization reactions is shown in Table III. It will be noted that the yields of isolated product decrease strikingly as the degree of substitution of the nitroalkane increases.

In only one of the reactions of dialdehyde III with the various nitroalkanes was there obtained a crystalline product. The condensation with nitroethane (room temperature, 4 hrs.) yielded 44% of an apparent mixture of isomers of nitrosugar IV, R = $-CH_3$ (m.p. 175-196° decomp.). Baer and Rao (9,10) obtained a 20% yield of product from the reaction (room temperature, 3 hrs.) which appeared to them to be homogeneous (m.p. 206-208°, constant on recrystallization from ethanol). However, on hydrogenation they obtained methyl 3-methyl-3-amino-3-deoxy-α-D-gluco-(or allo)-pyranoside hydrochloride (XV) and methyl 3-methyl-3-amino-3-deoxy-β-L-gluco-(or allo)-pyranoside hydrochloride (XVI), the

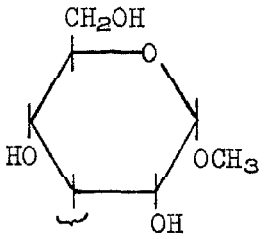
TABLE III

Isolated Yields of Products Obtained from Condensation of Dialdehyde III with Nitroalkanes

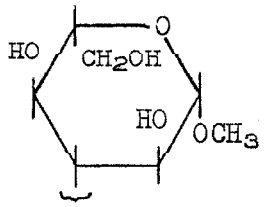
Nitroalkane	Product(s) Obtained	Yields
Nitromethane CH_3NO_2	Methyl 3-amino-3-deoxy-α-D-manno-pyranoside hydrochloride (XVII); Methyl 3-acetamido-3-deoxy-2,4,6-tri-O-acetyl-α-D-glucopyranoside (XVIII) (6,7)	30% 8% 38%[a]
Nitroethane $CH_3-CH_2NO_2$	Methyl 3-methyl-3-nitro-3-deoxy-α-D-gluco-(or allo)-pyranoside and methyl 3-methyl-3-nitro-3-deoxy-β-L-gluco-(or allo)-pyranoside (9,11)	44%[b]
1-Nitropropane $CH_3-CH_2-CH_2NO_2$	Methyl 3-ethyl-3-amino-3-deoxy-β-L-hexopyranoside hydrochloride (XIX)	2.5%
2-Methyl-1-nitropropane 	Methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranoside hydrochloride (VII)	0.93%
2,2-Dimethyl-1-nitropropane (IX) 	None	——

[a] Baer (7) reports obtaining 30% of XVII and 30% of XVIII, total yield, 60%.

[b] Baer and Rao (9,10) report obtaining 20%.

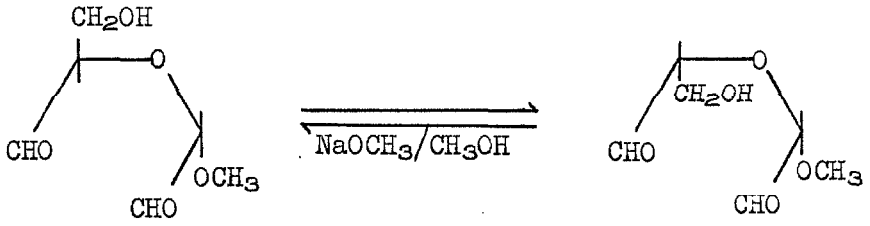


XV



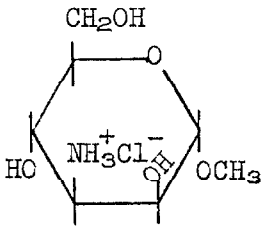
XVI

latter resulting from dialdehyde III having undergone epimerization to dialdehyde IIIa.

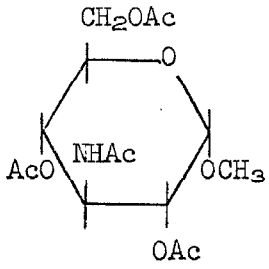


III IIIa

The crude products from the other condensations were hydrogenated to yield crystalline aminosugar hydrochlorides. From nitromethane there was obtained a 30% yield of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (XVII); Baer (7) also reports a 30% yield of XVII. Acetylation of the mother liquors from the crystallization of XVII yielded 8% of methyl 3-acetamido-3-deoxy-2,4,6-tri-O-acetyl-α-D-glucopyranoside (XVIII); Baer (7) reports 30%. The hydrogenated cyclization product



XVII



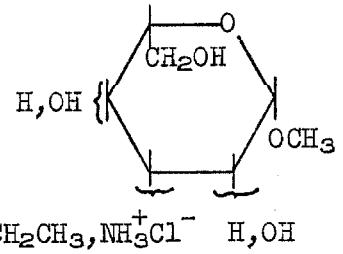
XVIII

from 1-nitropropane was allowed to stand at room temperature, and after more than a month a small amount of an aminosugar hydrochloride crystallized spontaneously. This crystalline product served as a source of seeds for later preparations.

A method for the isolation of aminosugars was devised to purify the hydrogenation products from the condensation of dialdehyde III with substituted nitromethanes. While an acidic ion exchange resin (e.g., Amberlite IR-120) could have been used to remove amino-compounds from the crude hydrogenation products, use of such resins introduced the possibility of hydrolysis of the acetal portions of the aminosugar molecules. Advantage was taken of the facts that (a) ammonium ions are held more strongly by strongly acidic ion exchange resins (e.g., Amberlite IR-120, a sulfonated styrene-divinylbenzene copolymer) than are sodium ions (23,24) and (b) on increasing the size of alkyl or aryl substituents on an ammonium ion increases its affinity for strongly acidic resins (25). It was concluded, therefore, that aminosugars (as their ammonium salts) could be separated from non-ionic compounds by a displacement technique (cf. 26).

A sodium form column of Amberlite IR-120 was prepared by the passage of a 1.0 M. solution of sodium chloride through a column of the acid form of the resin until the effluent was no longer acidic; the column was then washed free of sodium chloride with water. A solution of the crude aminosugar hydrochloride mixture in water was slowly passed through the column followed by washing with water until the effluent failed to yield a precipitatate on addition of silver nitrate. The aminosugars were eluted from the column by the slow passage of a 0.25 M. solution of sodium carbonate through the column, which converted the ammonium-form sugars into free aminosugars and rapidly washed them from the column. The eluant was collected in fractions and all fractions possessing optical activity were combined, freed of inorganic salts and neutralized with hydrochloric acid.

The ion exchange purified 3-ethylaminosugar IV, R = $-CH_2CH_3$, from the condensation with 1-nitropropane on seeding and crystallization from absolute ethanol yielded 2.5% of a methyl 3-ethyl-3-amino-3-deoxy-β-L-hexopyranoside hydrochloride (XIX), m.p. 228° (decomp.). The infrared



XIX

spectrum (KBr) is shown in Figure 4. That this compound possessed the β-L configuration was ascertained as described later (p. 21).

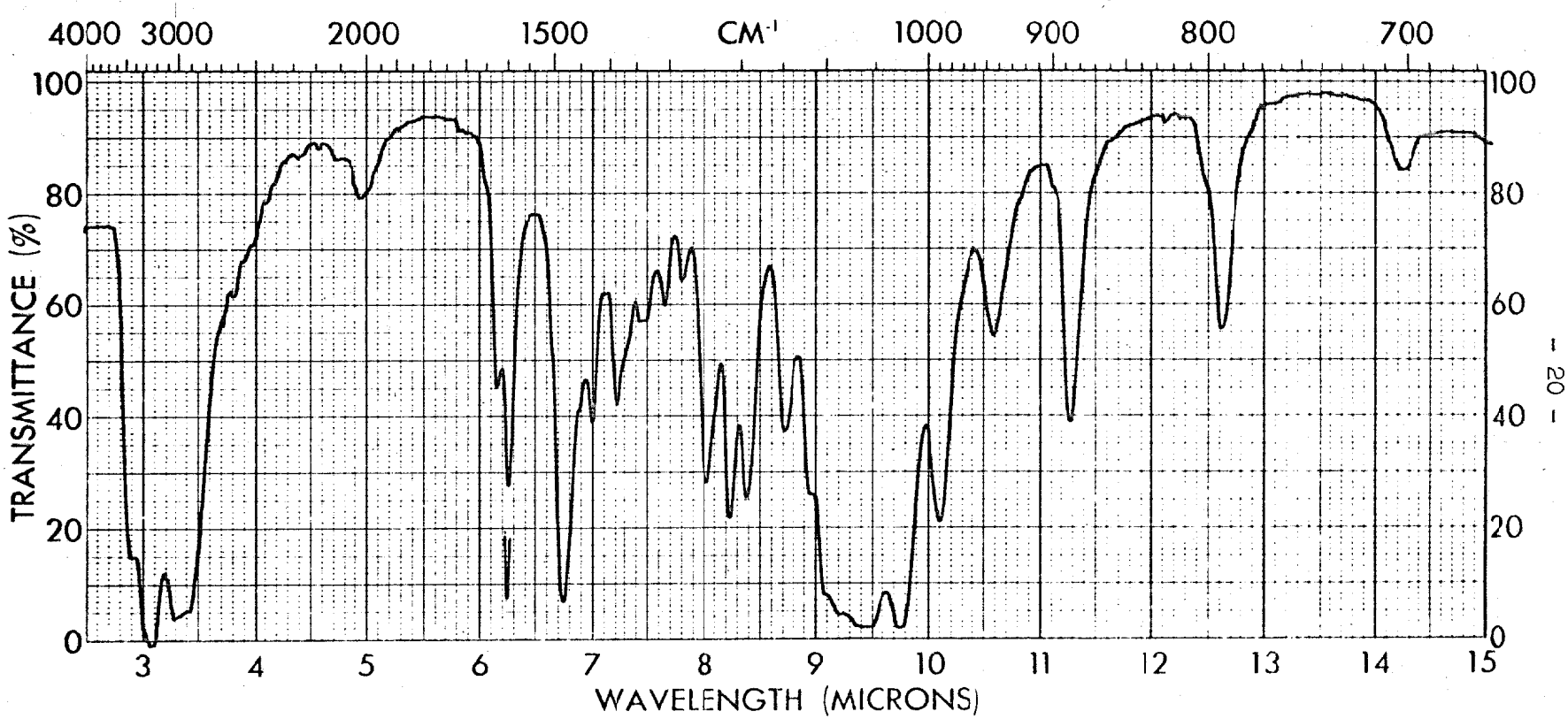


Figure 4. Infrared spectrum (KBr) of methyl 3-ethyl-3-amino-3-deoxy-β-L-hexopyranoside hydrochloride (XIX).

The ion exchange-purified product of 3-isopropylaminosugar IV, R = $-CH(CH_3)_2$, failed to crystallize under a variety of conditions. Paper chromatography as described in the Experimental section (p. 45) indicated the presence of two amino compounds. Preparative paper chromatography (in several runs) yielded a few mg. of a crystalline substance which on addition to the bulk of the ion exchange-purified product furnished a 0.93% yield of methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranoside hydrochloride (VII), m.p. 218° (decomp.). The infrared spectrum (KBr) of VII is shown in Figure 5.

Ion exchange purification of 3-tert-butylaminosugar IV, R = $-C(CH_3)_3$, yielded only a small amount of dark "purified" product which failed to crystallize. Paper chromatography also failed to lead to any crystalline product.

Characterization of the Unknown 3-Alkylaminosugars

The unknown 3-alkylaminosugars described above (XIX and VII) posed a formidable characterization problem. In addition to the unknown stereochemistry at carbons 2, 3 and 4, the possibility of epimerization at carbon 5 as observed by Baer and Rao (9-11) needed to be considered also.

A simple experiment was devised to determine the stereochemistry of carbon 5. It was reasoned that periodate oxidation of each of the two 3-alkylaminosugars would lead to either of the two dialdehydes III or IIIa, dialdehyde III resulting from a methyl glycoside possessing an α-D configuration and dialdehyde IIIa resulting from a methyl glycoside possessing a β-L configuration:

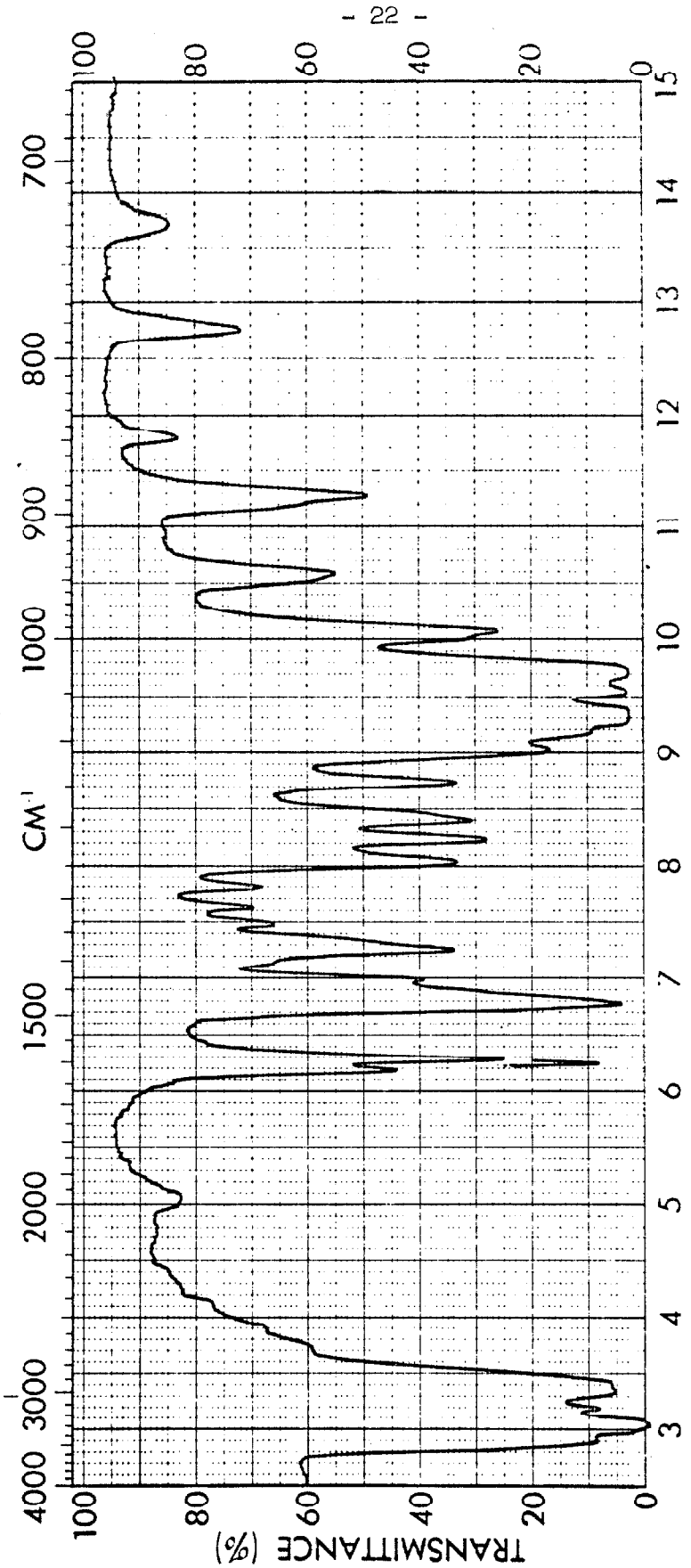
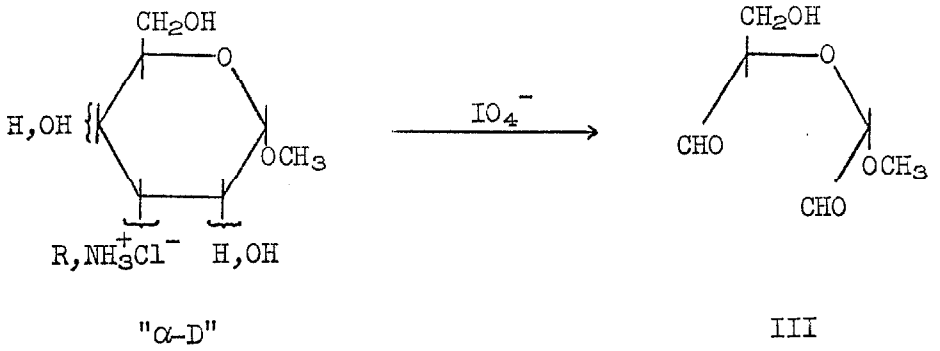
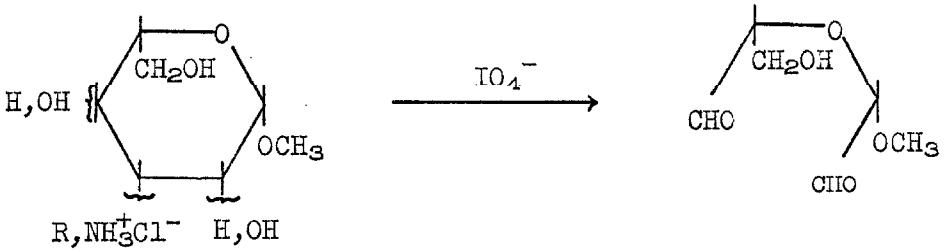


Figure 5. Infrared spectrum (KBr) of methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulcpyranoside hydrochloride (VII).



"α-D" III



"β-L" IIIa

It was further reasoned that identification of the product dialdehyde would be greatly facilitated merely by the comparison of the final optical rotations of the oxidation reaction mixtures with the final rotation of oxidation mixtures of methyl glycosides of known configuration (leading therefore to dialdehydes of known configuration) observed under identical reaction conditions (i.e., concentrations, pH, etc.; see Experimental section, p. 47). Since no methyl β-L-aldohexopyranoside was readily available, a β-D compound, methyl β-D-glucopyranoside, was used; in this case, the product dialdehyde would have an optical rotation equal in magnitude but opposite in sign to that obtained from a β-L compound. Pertinent data for compounds thus oxidized are shown in Table IV. It will be noted that within experimental error the oxidation of methyl α-D-gluco-

TABLE IV

Oxidation of Methyl Glycosides by Periodate[a]

Compound Oxidized	Concentration in Reaction Mixture	Time Required to Reach Constant α	Final α Observed[b]
Methyl α-D-gluco-pyranoside (II)	0.031 mmole/ml.	50 min.	+0.220°
Methyl β-D-gluco-pyranoside	0.032 mmole/ml.	70 min.	-0.270°
Methyl 3-amino-3-deoxy-α-D-mannopyrancside hydrochloride (XVII)	0.030 mmole/ml.	30 min.	+0.218°
Methyl 3-ethyl-3-amino-3-deoxy-β-L-hexopyranoside hydrochloride (XIX)	0.032 mmole/ml.	60 min.	+0.271°
Methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranosidc hydrochloride (VII)	0.031 mmole/ml.	60 min.	+0.220°

[a]See Experimental section for experimental details.

[b]All readings are ± 0.002°.

pyranoside (II) and methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (XIX) lead to the same value of final $\alpha_{observed}$, indicating that the presence of ammonium chloride in the reaction mixture exerts no significant effect on the final rotation.

From the data in Table IV it is seen that the 3-ethylaminosugar possesses the β-L configuration while the 3-isopropylaminosugar possesses the α-D configuration.

The most straightforward method for the determination of the stereochemistry of carbons 2, 3 and 4 of the compounds was considered to be the analysis of the nuclear magnetic resonance (NMR) spectra of the compounds or suitable derivatives. NMR spectra (60 Mc.) of the aminosugar hydrochlorides in D_2O, dimethylformamide and dimethylsulfoxide failed to resolve the individual resonances of the ring protons. It was then decided to investigate the NMR spectra of the peracetyl derivatives of the alkylaminosugars.

Acetylation of the methyl 3-methyl-3-amino-3-deoxy-β-L-hexopyranoside hydrochloride (XIX) by heating with acetic anhydride, acetic acid and sodium acetate failed to yield products with spectral properties (IR and NMR) consistent from run to run. This puzzling situation could not be resolved.

Acetylation of methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranoside hydrochloride (VII) yielded a peracetyl derivative XX which could not be obtained crystalline. The infrared spectrum of XX is shown in Figure 6. The 60 Mc. NMR spectrum of XX was obtained in CCl_4 (cf. Figures 7 and 10) and in $CHCl_3$, but the resonances could not be unambiguously assigned to the various ring protons. Consequently, the NMR spec-

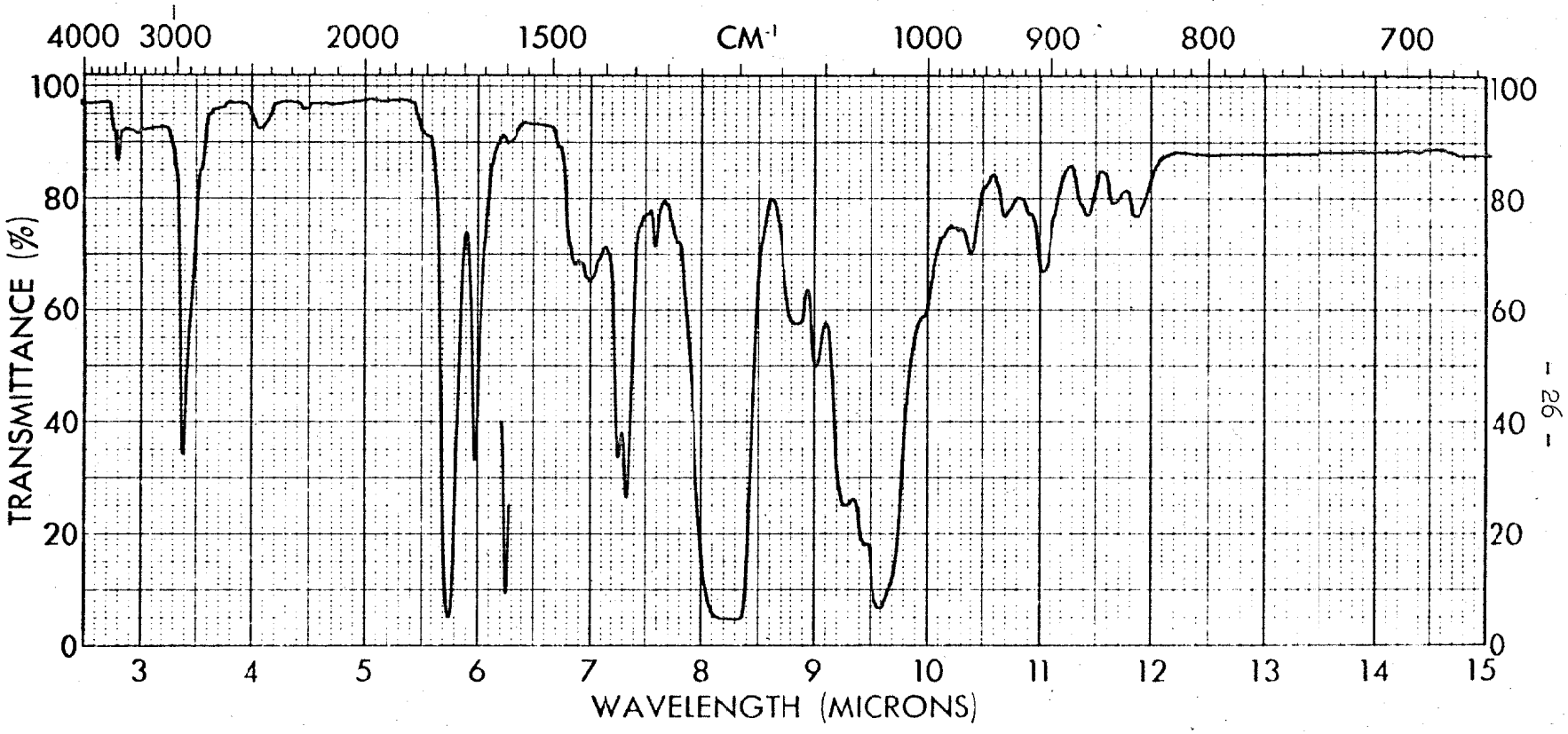


Figure 6. Infrared spectrum ($CHCl_3$) of methyl 3-isopropyl-3-acetamido-3-deoxy-2,4,6-tri-O-acetyl-α-D-gulopyranoside (XX).

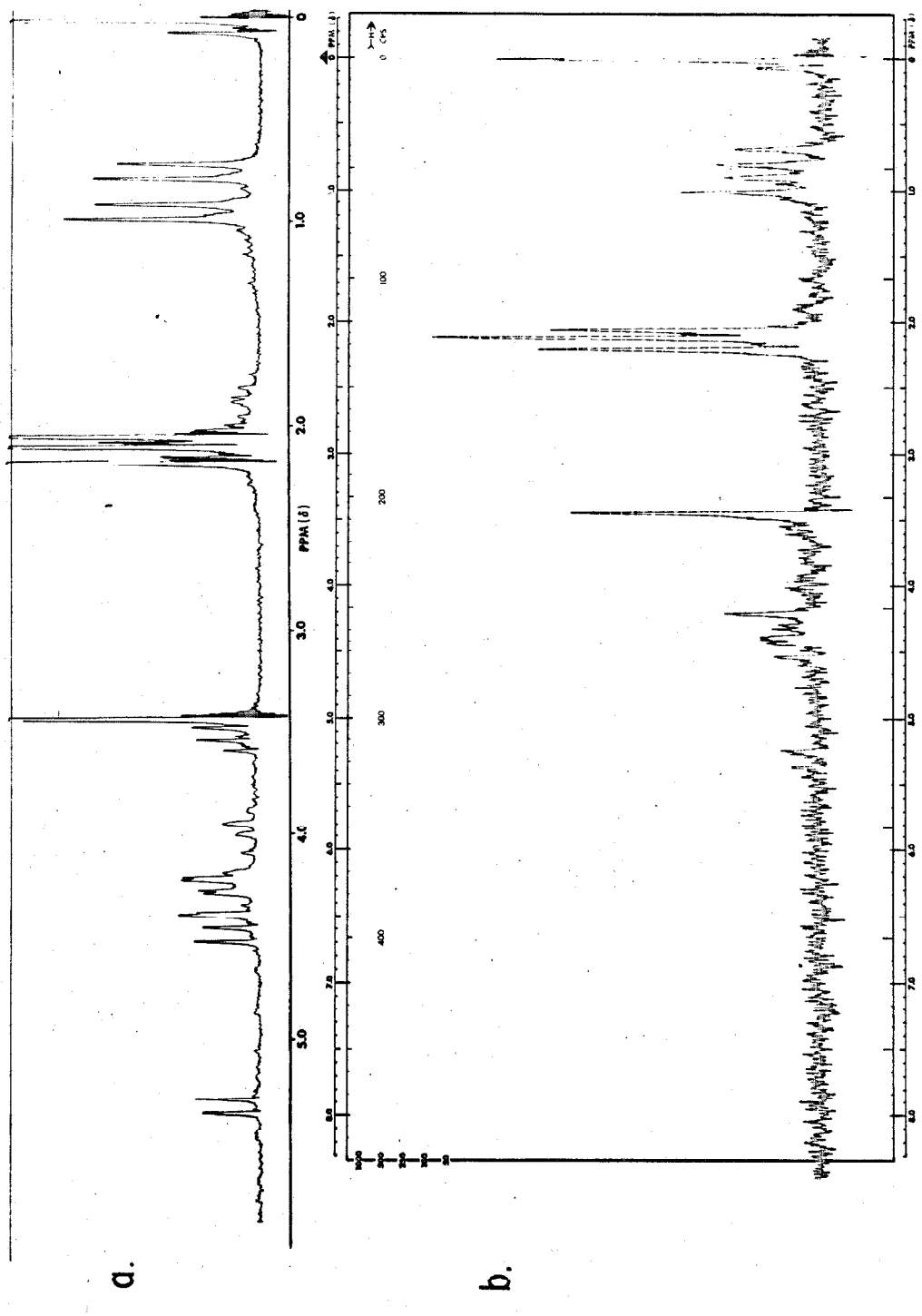


Figure 7. Nuclear magnetic resonance spectra (CCl_4) of methyl 3-isopropyl-3-acetamido-3-deoxy-2,4,6-tri-O-acetyl-C-D-gulopyranoside (XX) at (a) 100 Mc. and (b) 60 Mc.

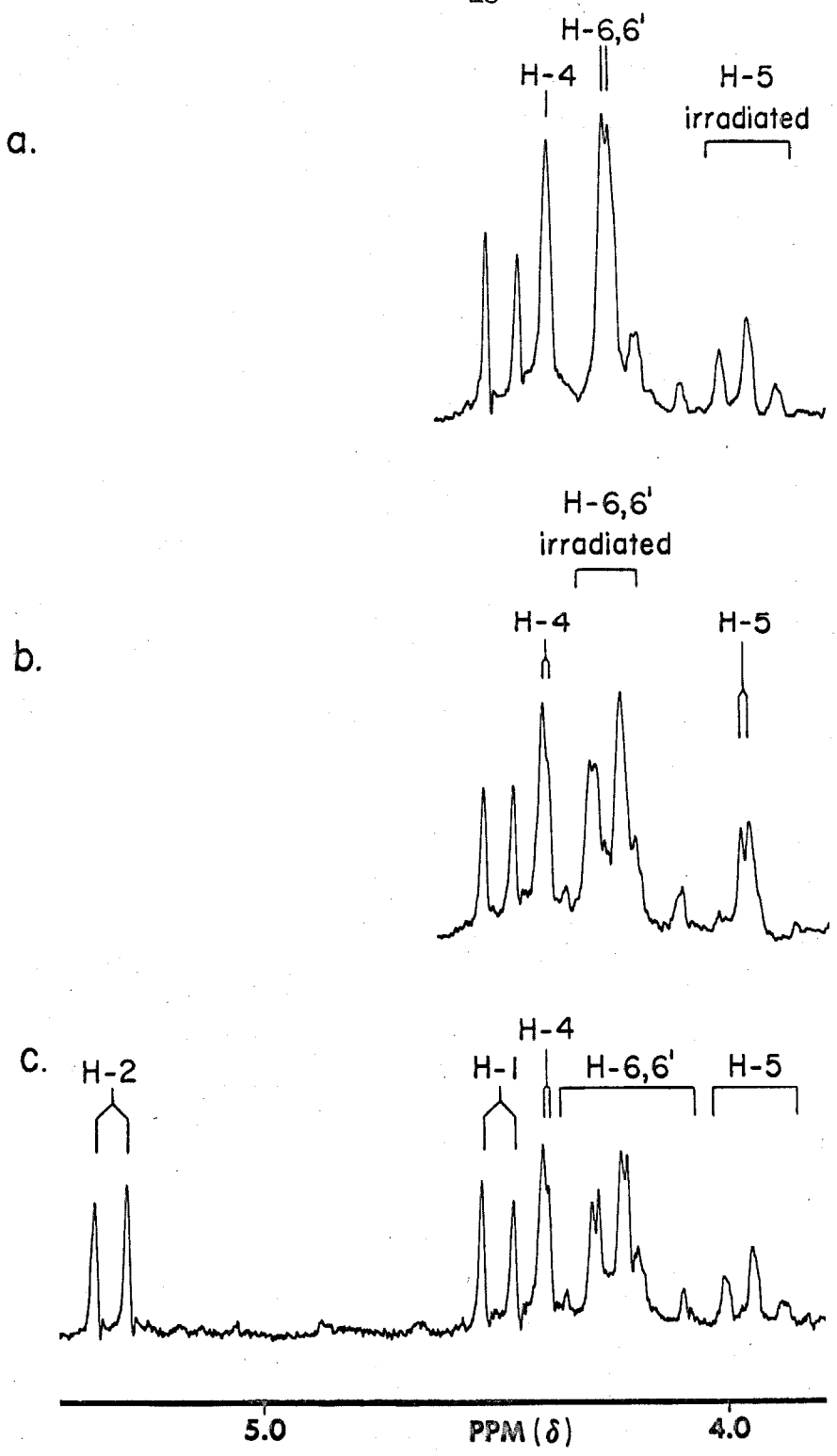


Figure 8. Spin-decoupled partial nuclear magnetic resonance spectra of XX. (a) H-5 irradiated. (b) H-6,6' irradiated. (c) Normal spectrum.

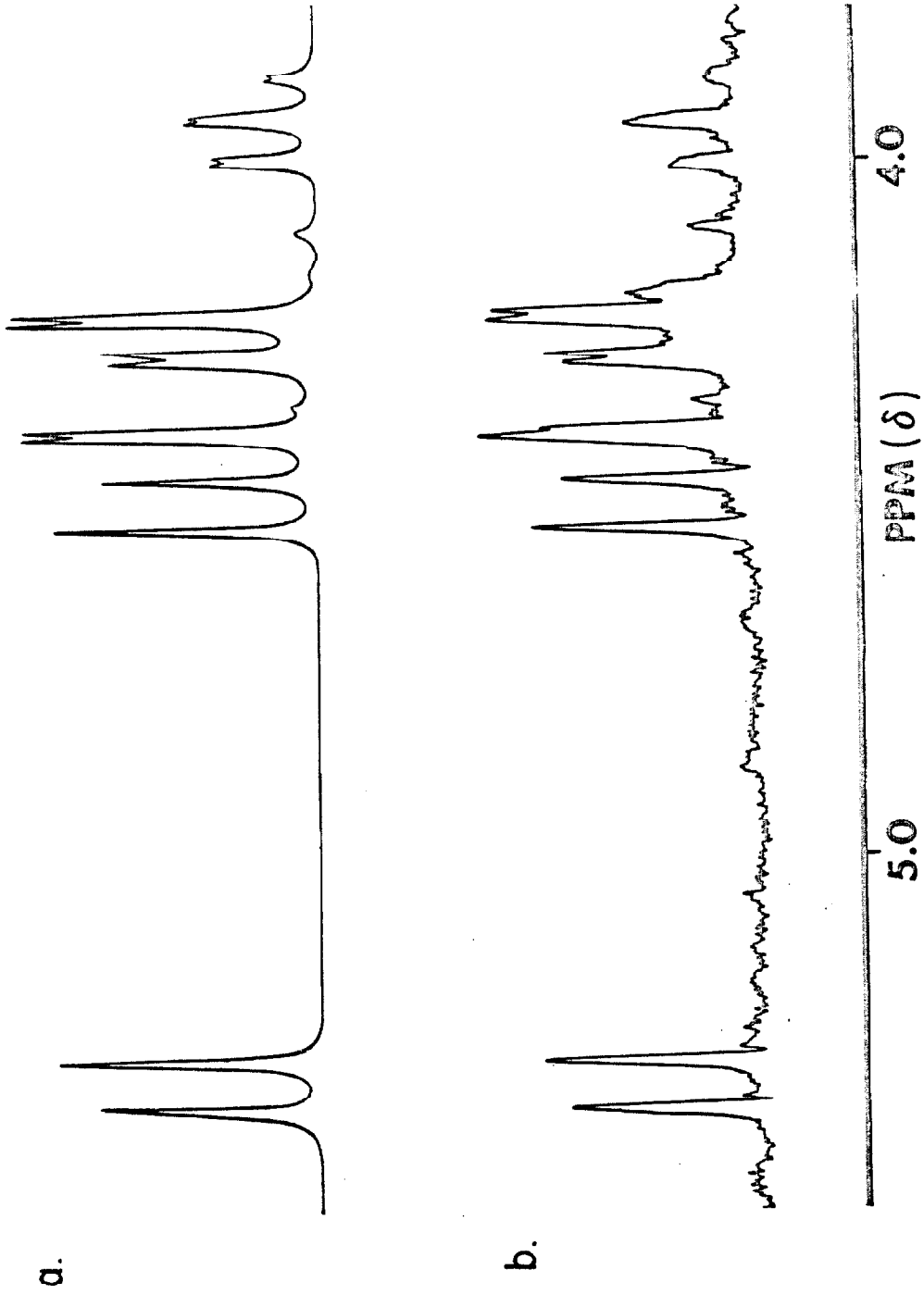


Figure 9. (a) Calculated and (b) observed nuclear magnetic resonance spectra (ring protons) of XX at 100 Mc.

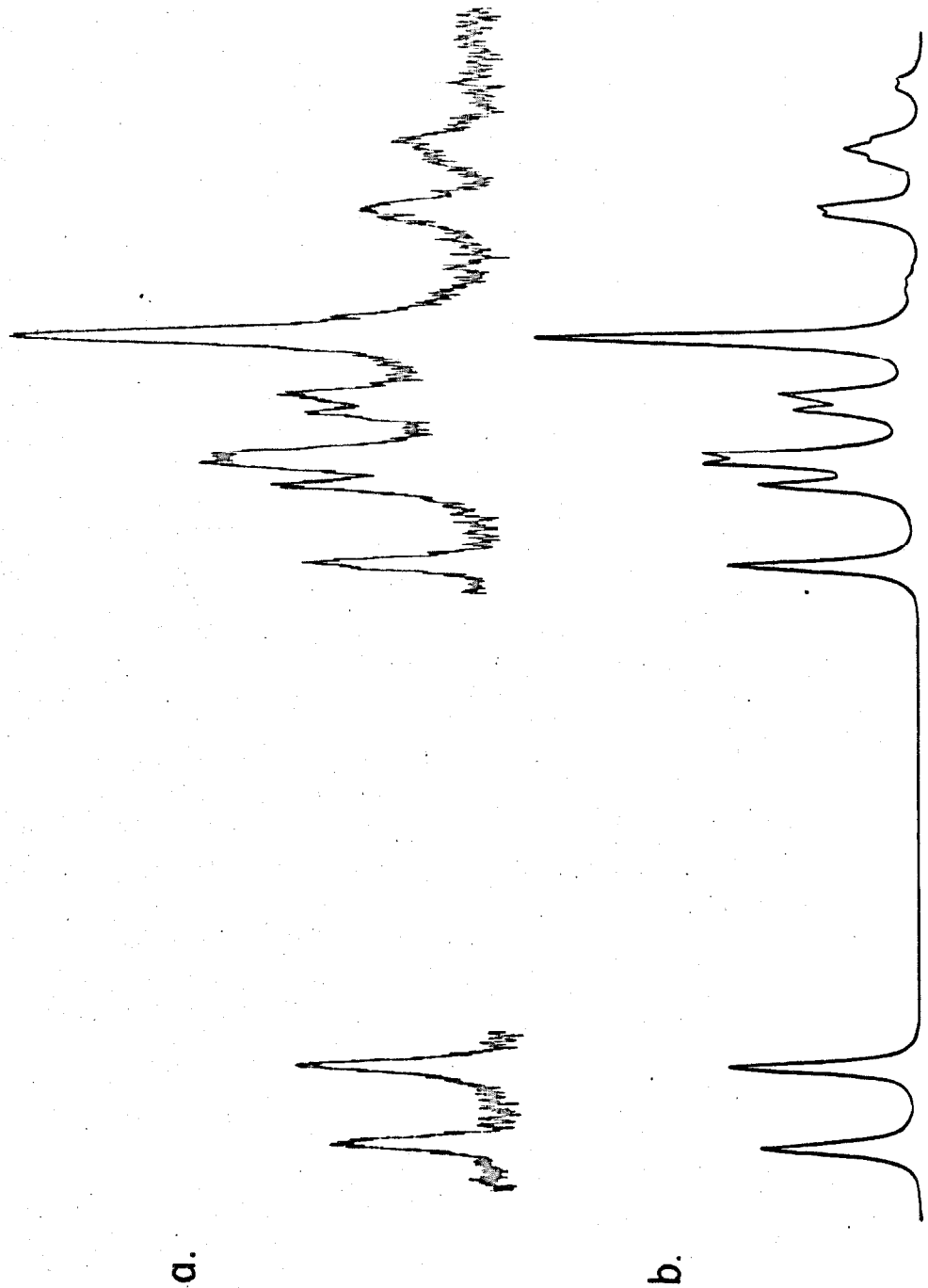
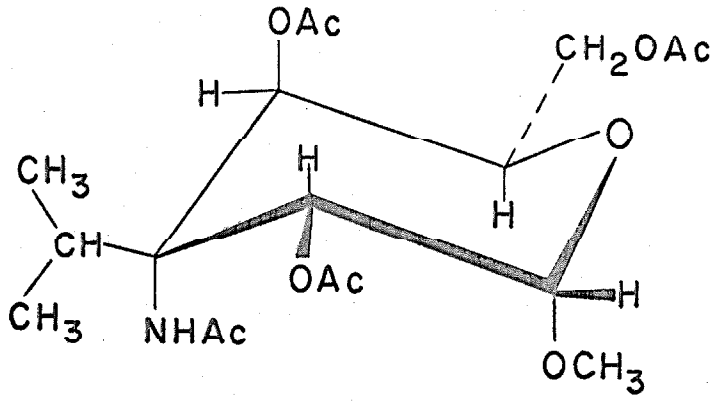


Figure 10. (a) Observed and (b) calculated nuclear magnetic resonance spectra (ring protons) of XX at 60 Mc.



XX

trum (CCl_4) was obtained at 100 Mc. with spin decoupling (cf. Figures 7-9). The doublet at δ 5.33 (J = 7.0 c.p.s.) was assigned to H-2 on the basis of similar work by Baer and Rao (10) on peracetyl derivatives of XV and XVI and the doublet at δ 4.68 (J = 7.0 c.p.s.) was assigned to H-1; irradiation of either doublet caused the other doublet to collapse to a singlet. The doublet* assigned to H-4 (δ 4.38) and the multiplet assigned to H-6 (δ ~ 4.25) were shown to collapse to a singlet and an apparent doublet, respectively, on irradiation of H-5. Irradiation of H-6 caused the H-5 multiplet to collapse to a doublet.

Assignment of other resonances in the spectrum was straightforward and followed examples of previous workers (9,10,27-32). The chemical shift of one of the acetoxyl resonances (δ 2.17 in $CHCl_3$, δ 2.20 in CCl_4) suggested that it was axially oriented (cf. 27-32). The chemical shift of the acetamido-methyl proton resonance (δ 2.05 in $CHCl_3$ and CCl_4) was

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*The asymmetry of the H-4 doublet (Figures 7-9) is an experimental artifact dependent on the direction of field sweep.

upfield from the range observed (28,29,31) for equatorially oriented acetamido groups (δ 1.90-1.97) and was very near values observed (29) for axial acetamido groups (δ 2.06, 2.08); axial orientation was therefore indicated. The methoxy-proton resonance (δ 3.37 in $CHCl_3$, δ 3.43 in CCl_4) was within the range of observed values for axial methoxy groups (δ 3.36-3.45) (9,10,28,31). The appearance of the isopropyl group as a pair of doublets at δ 0.75 and δ 0.95 (cf. Figure 7) indicated a high degree of asymmetry about the isopropyl group.

To confirm the assignments of the chemical shifts and coupling constants of the ring protons and to determine these parameters precisely for the purpose of deducing the structure of peracetyl derivative XX, a computer program (12) was used to calculate the spectrum. By varying the values of the input parameters (chemical shifts and coupling constants), a best fit of the observed 100 Mc. spectrum of the ring protons (in CCl_4) was obtained as shown in Figure 9. The chemical shifts and coupling constants found to give the best fit are shown in Table V. The values of the chemical shifts used in the operation of the program were expressed in cycles per second at 100 Mc. and increased with increasing field strength. While the values stated for the actual chemical shifts in Table V may have varied from the real values of the chemical shifts (experimental error), it is important to note that the differences among the values of the chemical shifts are very close (< 0.1 c.p.s.) to the differences among the real values. It must also be noted that changes of as little as 0.1 c.p.s. in any of the values of the chemical shifts or coupling constants (especially those involving H-6 and H-6') cause changes in calculated transition frequencies of the same order of magni-

TABLE V

Best-fit Parameters for the Calculation of the
100 Mc. NMR Spectrum of the Ring Protons of
Methyl 3-Isopropyl-3-acetamido-3-deoxy-α-D-gulopyranoside (XX)

	Chemical Shifts	
Proton	Value Used in Calculation	Actual Value
H-2	15.0 c.p.s.	533.0 c.p.s. (δ 5.33)
H-1	98.8 "	449.2 " (δ 4.49)
H-4	109.0 "	439.0 " (δ 4.39)
H-6	120.2 "	427.8 " (δ 4.28)
H-6'	125.3 "	422.7 " (δ 4.23)
H-5	152.7 "	395.3 " (δ 3.95)

Coupling Constants

$J_{1,2}$ = 7.0 c.p.s.

$J_{4,5}$ = 1.0 c.p.s.

$J_{5,6}$ = 4.9 c.p.s.

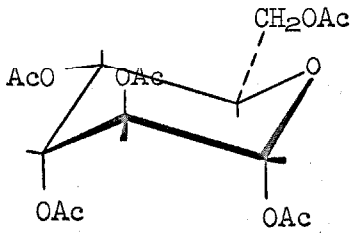
$J_{5,6'}$ = 6.7 c.p.s.

$J_{6,6'}$ = - 11.6 c.p.s.

tude (~ 0.1 c.p.s.) and noticeably alter the appearance of the plotted spectrum.

As a test of the accuracy of assignment of the values of chemical shifts and coupling constants, the 60 Mc. NMR spectrum was calculated. The values used for the chemical shifts were those shown in Table V (under "Values Used in Calculation") multiplied by the factor 0.6; the values of the coupling constants were unchanged. The result of this calculation was plotted and is shown in Figure 10. The very close fit of the calculated and experimental 60 Mc. spectra confirm the chemical shift and coupling constant assignments.

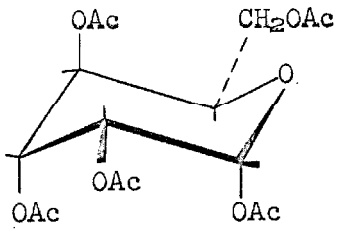
With the data indicated above it was possible to assign structure XX to the peracetylated 3-isopropylaminosugar and structure VII to the 3-isopropylaminosugar hydrochloride. The assignment of a chair conformation to XX is reasonable in view of other work (32); for example, Coxon (32) found that penta-O-acetyl-α-D-altropyranose (XXI) existed in



XXI

solution in essentially one conformation, that shown in XXI, even though the compound possessed three axial acetoxyl groups and only two equatorial substituents. In the present case, then, the $-CH_2OAc$ group would be expected to be equatorially oriented. The periodiate oxidation indicated that the aminosugar possessed the α-D configuration, which fixes the methoxy group in an axial orientation; this assignment is corroborated by the chemical shift of the methoxy protons (see above, p. 32) The chemical shift of the acetamido-methyl protons (δ 2.05) indicates that this group is also axially oriented. It is noteworthy here that Baer and Rao (9,10) observed the acetamido-methyl proton resonances of their acetylated 3-methylaminosugars (peracetylated derivatives of XV and XVI) at δ 1.93, in the range for equatorial acetamido groups (28,29,31). The presence of one acetoxyl resonance (δ 2.17 in $CHCl_3$) in the range observed (27-32) for axial acetoxyl groups (δ 2.14-2.19) and the small value of the H-4, H-5 coupling constant (1.0 c.p.s.), which precludes a trans-diaxial orientation of H-4 and H-5, indicate that H-4 is equatorial and the acetoxy group on carbon 4 of XX is axial. The remaining acetoxy group, that on carbon 2 (δ 2.08 in $CHCl_3$) is then assigned an equatorial orientation, completing the structural assignment of XX and VII.

The coupling constant observed between H-1 and H-2 (6.6 c.p.s. in $CHCl_3$, 7.0 c.p.s. in CCl_4), while larger than those usually noted for axial-equatorial vicinal hydrogens in acetylated carbohydrates (27,28,31, 32), is only slightly larger than that noted (27) for the H-1, H-2 coupling constant in penta-O-acetyl-α-D-gulopyranose (XXII) (6.2 c.p.s. in $CHCl_3$). Since the peracetyl 3-isopropylaminosugar XX also possesses the gulo-configuration, the value for this particular coupling constant does



XXII

not hamper the assignment of structures XX and VII.

Conclusion

The synthesis of conformationally stable carbohydrates, wherein a tert-butyl group serves as an "anchor" for a particular conformation, by use of the dialdehyde cyclization method of Baer and Fischer (5-7) was found to be an unfeasible approach to such compounds. However, the synthesis of two new 3-C-alkyl-3-aminoaldohexose derivatives was achieved and the full structure elucidation of one of these compounds, methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranoside hydrochloride (VII), was accomplished.

EXPERIMENTAL

Melting points were determined in capillary tubes in a Büchi melting point apparatus and are corrected. Boiling points are uncorrected. Infrared (IR) spectra was determined on Perkin-Elmer Infracord models 137 and 237 spectrophotometers. Nuclear magnetic resonance (NMR) spectra were determined on Varian Associates A-60 and A-60A spectrometers and are reported in delta units (δ, parts per million) downfield from tetramethylsilane. Optical rotations were measured on a Bendix Ericsson U.K. Ltd. ETL-NPL Automatic Polarimeter Type 143A using a cell with a path length of 4.0 cm. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

2-Isopropyl-1,3-indanedione. A modification of Fieser's method (33) was used. To a mixture of 10.0 g. of dimethyl phthalate (0.052 mole; Eastman Organic Chemicals) and 4.1 g. of sodium hydride (0.17 mole; Metal Hydrides Incorporated, as a dispersion in mineral oil) heated at 140-150° was added 5.0 g. of methyl isovalerate (0.043 mole) in 15 ml. of xylene over $1\frac{1}{2}$ hrs. Heating of the mixture was continued for 1 hr. and the mixture was then cooled. A solution of 11 ml. of acetic acid in 30 ml. of methanol was added dropwise with stirring to destroy the excess sodium hydride. The mixture was then evaporated under reduced pressure to a residue to which was added 50 ml. of water and 15 ml. of conc. hydrochloric acid. The mixture was refluxed for 2 hrs. After being cooled, the mixture was diluted with 10 ml. of benzene and shaken. The organic phase was dried over calcium chloride, evaporated under reduced pressure and distilled to yield 5.2 g. of distillate, b.p. 135-

145°/7 mm. Gas chromatography on Apiezon J at 210° indicated that the major component of the distillate was dimethyl phthalate and that 2-isopropyl-1,3-indanedione (detected in the effluent gas as an orange spot on filter paper moistened with aqueous sodium hydroxide solution held to the gas outlet) to be present in a yield of 8%.

2-Methyl-1-nitro-2-propanol (X). A solution of 1.40 g. of nitromethane (2.3 moles; Matheson, Coleman and Bell) in 600 ml. of acetone (8.2 moles) was treated with a solution of 6.6 g. of sodium methoxide (0.11 mole) in 50 ml. of methanol by the method of Lambert and Lowe (17). Workup and fractional distillation through a 12 inch vigreux column yielded 52.4 g. (19%) of 2-methyl-1-nitro-2-propanol (X), b.p. 76-79°/10 mm. (lit. (17), 76-77°/10 mm.). $\lambda_{max}^{CHCl_3}$ 2.70μ (OH), 6.54, 7.19μ (NO_2).

2-Methyl-1-nitro-2-propyl acetate (XI). To 162 g. of 2-methyl-1-nitro-2-propanol (X, 1.36 moles) stirred at 0° was added 118 g. of acetyl chloride (1.50 moles) dropwise over 15 min. The temperature of the reaction mixture rose gradually and hydrogen chloride soon began boiling off. Finally, the reaction mixture was warmed to 70-80° under reduced pressure (water aspirator) to remove most of the hydrogen chloride produced. The reaction product was then carefully poured into 400 ml. of saturated aqueous sodium bicarbonate, shaken and separated. The product was dried over calcium chloride and distilled to yield 197 g. (90%) of 2-methyl-1-nitro-2-propyl acetate (XI), b.p. 56-58°/1 mm. (lit. (17), 86-88°/13 mm.).

2-Methyl-1-nitropropene (VIII). A modification of the method of Levy and Scaife (18) was used. A mixture of 152 g. of 2-methyl-1-nitro-2-propyl acetate (XI, 0.94 mole) and 3.0 g. of potassium carbonate (0.02 mole) was heated for 2 hrs. at 75° and then slowly distilled under vacuum (1½ hrs. at 13 mm.). The distillate was dissolved in 300 ml. of ether and was washed successively with three 200 ml. portions of water and 50 ml. of saturated aqueous sodium bicarbonate. The solution was dried over calcium chloride and evaporated under reduced pressure to remove most of the solvent. The residue was distilled to yield 75.8 g. (78%) of 2-methyl-1-nitropropene (VIII), b.p. 57-60°/13 mm. (lit. (34), 56°/11 mm.). $\lambda_{max}^{CHCl_3}$ 6.10μ (C=C), 6.46, 7.33μ (NO_2), 12.20μ (C=CH).

2,2-Dimethyl-1-nitropropane (IX). The procedure of Buckley and Ellery (15) was followed. Yields of 30-32% of 2,2-dimethyl-1-nitropropane (IX), b.p. 59-62°/32 mm. (lit. (15), 77-78°/65 mm.), were obtained. $\lambda_{max}^{CHCl_3}$ 6.50, 7.31μ (NO_2); NMR δ 4.17, 1.12 (sharp singlets).

The residues from distillations of 2,2-dimethyl-1-nitropropane preparations partially crystallized on cooling. The crystals were filtered and recrystallized from methanol to yield a colorless substance of m.p. 143-144°. This compound was apparently the same as that noted by Buckley and Ellery (15), m.p. 144°, to which they ascribe the empirical formula $C_4H_8NO_2$ on the basis of elemental analysis. The compound showed IR (chloroform) absorptions at 6.46μ and 7.32μ (NO_2). The NMR spectrum showed sharp singlets at δ 1.13 and δ 4.30 with areas in the ratio 3:1. On the basis of these data, it is concluded that this compound is 2,2,3,3-tetramethyl-1,4-dinitrobutane (XII).

2-Methyl-1-nitropropane. The general method of Kornblum, Taub, and Ungnade (13) was followed. To a stirred mixture of 150 g. of silver nitrite (0.98 mole; Mallinckrodt Chemical Works) in 200 ml. of ether cooled in an ice bath was added in the dark 195 g. of 2-methyl-1-iodopropane (1.06 moles; Matheson, Coleman and Bell) over 45 min. The mixture was allowed to warm to room temperature and was then stirred at room temperature in the dark for 9 days. The silver salts were removed by filtration and washed with a small amount of ether, and the filtrate and washings were combined. The ether solution was fractionally distilled to yield 31.1 g. (31%) of 2-methyl-1-nitropropane, b.p. 68-70°/62 mm. (lit. (13), 71°/65 mm.). $\lambda_{max}^{CHCl_3}$ 6.48, 7.30μ (NO_2); NMR δ 1.05 (doublet, J = 6.7 c.p.s.; methyl protons), 4.20 (doublet, J = 7.0 c.p.s.; methylene protons), 1.63 (multiplet, methine proton).

Methyl-α-D-glucopyranoside (II) was prepared according to a published procedure (35).

D'-methoxy-D-hydroxymethyl-diglycolic aldehyde (III) was prepared in essentially quantitative yield as a colorless syrup from methyl α-D-glucopyranoside (II), m.p. 168-169°, lit. (35), 167-169°) according to a published procedure (6).

Condensations of D'-methoxy-D-hydroxymethyl-diglycolic aldehyde (III) with nitroalkanes. The method of Baer (7) was used. Equivalent amounts of dialdehyde III, nitroalkane and sodium methoxide in methanol were allowed to react for the lengths of times specified in Table II (p. 14) at the specified temperatures.

Methyl-3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (XVII). A syrupy mixture of methyl 3-nitro-3-deoxy-α-D-hexopyranosides prepared as described above from 25 mmoles of dialdehyde III was dissolved in 100 ml. of water; 0.1 g. of platinum oxide (Engelhard Industries Inc.) was added and the mixture was hydrogenated at room temperature and 40 p.s.i. H_2 for 4 hrs. The reaction mixture was filtered and the filtrate was neutralized to pH 5 with 1N hydrochloric acid. The solution was then evaporated under reduced pressure to a syrup which dissolved in 25 ml. of absolute ethanol and again evaporated under reduced pressure to a partly crystalline residue. Trituration with a small amount of absolute ethanol and filtration yielded 1.8 g. of crude product which was recrystallized from 95% ethanol to yield 1.75 g. (30%, based on dialdehyde III used) of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (XVII), m.p. 200-205° (decomp.) (lit. (6), 205°, decomp.), $[\alpha]_D$ +60° (water, c - 1.18) (lit. (6), +60.0°).

Methyl 3-acetamido-3-deoxy-2,4,6-tri-O-acetyl-α-D-glucopyranoside (XVIII). All non-crystalline material from the above described synthesis of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (XVII) was heated with a mixture of 5 g. of anhydrous sodium acetate and 50 ml. of acetic anhydride under gentle reflux for 10 min. The solution was then cooled and evaporated under reduced pressure to a dark, viscous residue. The remaining acetic anhydride was destroyed by the addition of 25 ml. of methanol. The solution was then evaporated under reduced pressure to a viscous residue, which was taken up in 35 ml. of chloroform and 35 ml. of water. The phases were separated

and the aqueous phase was extracted with two 25 ml. portions of chloroform, which were added to the previous organic phase. The chloroform solution was then washed with 15 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to a syrupy residue. The residue was dissolved in a small amount of 95% ethanol, cooled in an ice bath and scratched to yield, in two crops, 0.8 g. of crude product. Recrystallization yielded, in two crops, 0.72 g. (8%, based on dialdehyde III used) of methyl 3-acetamido-3-deoxy-2,4,6-tri-O-acetyl-α-D-glucopyranoside (XVIII), m.p. 176-177° (lit. (7), 177-178°), $[\alpha]_D$ + 109° (chloroform, c = 0.786) (lit. (7), + 107.5°).

Methyl 3-methyl-3-nitro-3-deoxy-α-D-hexopyranosides (IV, R = $-CH_3$). Workup of a condensation of 100 mmoles of dialdehyde III with nitroethane as described above gave a partly crystalline product which yielded in several crops from absolute ethanol 10.3 g. (44%) of methyl 3-methyl-3-nitro-3-deoxy-α-D-hexopyranosides. Recrystallization of a small amount of material from absolute ethanol gave a product with m.p. 175-196° (decomp.).

Methyl 3-ethyl-3-amino-3-deoxy-β-L-hexopyranoside hydrochloride (XIX). The syrupy product from a condensation of 0.20 mole of dialdehyde III with 1-nitropropane (Eastman Organic Chemicals; distilled before use) was dissolved in 100 ml. of water; the solution was filtered to remove a small amount of suspended insoluble oily matter. To the filtrate was added 2.0 g. of platinum oxide (Engelhard Industries Inc.) and the mixture was hydrogenated at room temperature and 40 p.s.i. H_2. The slow

uptake of hydrogen ceased after 72 hrs. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to a syrupy residue. The syrup was dissolved in 100 ml. of water and neutralized to pH 5 and 1N hydrochloric acid, and the solution was concentrated to 100 ml. The solution was then slowly passed through a column containing 80 ml. of Amberlite IR-120 (Na^+) (prepared by passing 1.0 M. sodium chloride through the H^+ form of the resin until the effluent was neutral to litmus followed by washing with water until the effluent failed to precipitate silver chloride on addition of silver nitrate solution) and the column was washed with water until the effluent failed to yield a precipitate on addition of silver nitrate solution. Amino-compounds were then eluted from the column by the slow passage of 0.25 M. sodium carbonate through the column and were collected in fractions. All fractions possessing optical activity were combined and evaporated to a partly crystalline residue. The mixture was triturated with absolute ethanol and filtered. The filtrate was evaporated and triturated with absolute ethanol in like manner until all inorganic salts were removed. The syrupy product was then dissolved in 25 ml. of water and neutralized to pH 5 with 1N hydrochloric acid. The solution was evaporated under reduced pressure to a syrupy residue which was dissolved in absolute ethanol and evaporated under reduced pressure several times. The syrup was then dissolved in 10 ml. of absolute ethanol, seeded with crystals of product obtained from spontaneous crystallization of a solution of the crude product from a previous preparation and placed in a freezer at -15° to yield in several crops 1.31 g. (2.5%, based on dialdehyde III used) of methyl 3-ethyl-3-amino-3-deoxy-β-L-hexopyranoside

hydrochloride (XIX). Recrystallization from methanol-nitromethane gave an analytical sample having m.p. 228° (decomp.), $[\alpha]_D$ + 47° (water, c = 1.27). The IR spectrum (KBr) is shown in Figure 4 (p. 20).

Anal. Calcd. for $C_9H_{20}NO_5Cl$: C, 41.94; H, 7.82; N, 5.44. Found: C, 42.09; H, 7.96; N, 5.32.

Periodate oxidation of the compound as described later indicated that it possessed the β-L configuration and that epimerization had taken place at C-5.

Methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranoside hydrochloride (VII). The syrupy product from the condensation of 75 mmoles of dialdehyde III with 2-methyl-1-nitropropane was dissolved in 50 ml. of water; a small amount of a dark insoluble oil separated, which was removed by filtration. To the filtrate was added 1.0 g. of platinum oxide (Engelhard Industries, Inc.) and the mixture was hydrogenated at room temperature and 40 p.s.c. H_2 for 72 hrs. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to a syrupy residue. The syrup was dissolved in 50 ml. of water and neutralized to pH 5 with 1N hydrochloric acid. The solution was then slowly passed through a column containing 50 ml. of Amberlite IR-120 (Na^+) (prepared as described above) and the column was washed with water until the effluent failed to yield a precipitate on addition of silver nitrate solution. Amino-compounds were eluted from the column by the slow passage of 0.25 M. sodium carbonate through the column and were collected in fractions. All fractions possessing optical activity were

combined and evaporated to a partly crystalline residue. The mixture was triturated with absolute ethanol and filtered. The filtrate was evaporated and triturated with absolute ethanol in like manner until all inorganic salts were removed. The syrupy product was then dissolved in 25 ml. of water and neutralized to pH 5 with 1N hydrochloric acid. The solution was evaporated under reduced pressure to a syrupy residue which was dissolved in absolute ethanol and evaporated under reduced pressure several times. All attempts to crystallize the residue, with and without solvents, failed. Paper chromatography of the product on Whatman #1 filter paper with elution by 4:1:1 n-butanol:ethanol:water and development by ninhydrin showed spots with R_f values of 0.8 and 0.5 (cf. methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (XVII), R_f = 0.4, and D-glucosamine hydrochloride, R_f = 0.2). Preparative paper chromatography of about 40 mg. of crude product was carried out in several runs on Whatman #1 filter paper with elution by the same solvent system. Strips were cut from the preparative chromatograms and treated with ninhydrin reagent to indicate the exact positions of the eluted bands. The bands with R_f values of 0.5 were cut from the several chromatograms and extracted with a small amount of boiling methanol. The methanol solution was evaporated under reduced pressure to a small partly crystalline residue. Trituration of the residue with a few drops of absolute ethanol followed by centrifugation and removal of the supernate yielded a few mg. of crystalline residue. These crystals were transferred to the bulk of the crude product, which was dissolved in 10 ml. of absolute ethanol and kept in a freezer at -15°. Crystallization proceeded very slowly, requiring a few weeks to yield, in three crops, 190 mg. (0.93%, based on

dialdehyde III used) of methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranoside hydrochloride (VII), m.p. 210-215° (decomp.). Recrystallization from methanol-nitromethane yielded an analytical sample having m.p. 218° (decomp.), $[\alpha]_D$ + 70° (water, c = 0.97). The IR spectrum (KBr) is shown in Figure 5 (p. 22).

Anal. Calcd. for $C_{10}H_{22}NO_5Cl$: C, 44.20; H, 8.16; N, 5.16. Found: C, 43.91; H, 8.09; N, 4.91.

Periodate oxidation of the compound as described later indicated that it possessed the α-D configuration.

Methyl 3-isopropyl-3-acetamido-3-deoxy-2,4,6-tri-O-acetyl-α-D-gulopyranoside (XX). A mixture of 70 mg. of methyl 3-isopropyl-3-amino-3-deoxy-α-D-gulopyranoside hydrochloride (VII), 70 mg. of anhydrous sodium acetate and 2 ml. of acetic anhydride was heated at gentle reflux for 5 min. and cooled. To the mixture was then added 10 ml. of methanol to destroy the excess acetic anhydride, and the mixture was evaporated under reduced pressure. The residue was dissolved in 10 ml. of chloroform and 10 ml. of water and the phases were separated. The aqueous phase was extracted with 10 ml. of chloroform, which was added to the previous organic phase. The chloroform solution was washed with 5 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. All attempts to crystallize the crude product from a variety of solvent systems under various conditions failed. The IR spectrum (chloroform) of the crude product is shown in Figure 6 (p. 26). The NMR spectrum is discussed in the Results and Discussion section.

Hydrogenation of product from condensation of dialdehyde III and 2,2-dimethyl-1-nitropropane (IX). The syrupy product from the condensation of 25 mmoles of dialdehyde III with 2,2-dimethyl-1-nitropropane (IX) was dissolved in 30 ml. of water; a small amount of dark insoluble oil separated, which was removed by filtration. To the filtrate was added 2.0 g. of platinum oxide (Engelhard Industries, Inc.) and the mixture was hydrogenated at room temperature and 40 p.s.i. H_2 for 84 hrs.; consumption of a small amount of hydrogen took place during the first 24 hrs. with none being used during the rest of the reaction time. Isolation of amino-compounds by means of the ion exchange technique described above and conversion to hydrochloride derivatives yielded 0.56 g. of a dark product from which no crystalline material could be obtained.

Oxidation of methyl glycosides by periodate--general method. A reaction mixture composed of 0.3 mmole of methyl glycoside, 5.0 ml. of 0.20 M. sodium acetate, 2.0 ml. of 0.40 M. sodium metaperiodate and 3.0 ml. of water (or components in the same proportions) was prepared; the solution then initially contained 0.03 mmole of methyl glycoside per ml. of reaction mixture. A portion of the solution was transferred to a cell with a path length of 4.0 cm. and the optical rotation of the solution was followed as it changed with time at room temperature (~ 25°) by means of an automatic polarimeter.* Data for methyl glycosides oxidized are shown in Table IV (p. 24).

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*Bendix Ericsson U.K. Ltd. ETL-N Automatic Polarimeter Type 143A.

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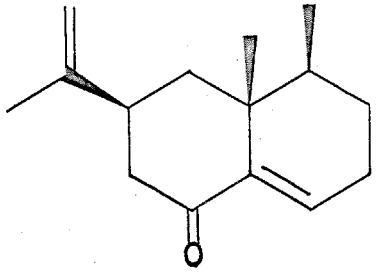
II.

STUDIES ON SYNTHETIC SESQUITERPENES RELATED TO EREMOPHILONE

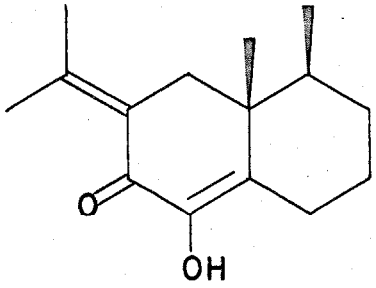
INTRODUCTION

Eremophilone

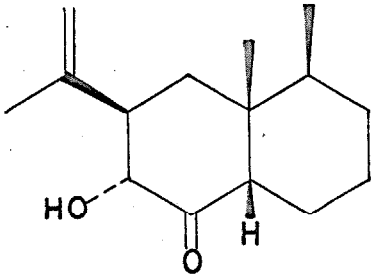
Eremophilone (I) is a non-isoprenoid sesquiterpene ketone which is a principal constituent of the wood oil of Eremophila mitchelli, a large bush found in the drier parts of southeastern Australia. The isolation and initial description of eremophilone, along with hydroxyeremophilone (II), and hydroxydihydroeremophilone (III), isolated



I



II

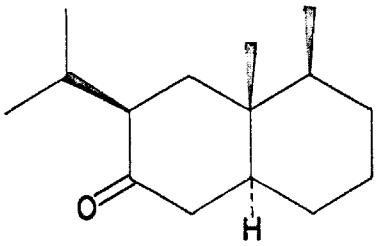


III

from the same wood oil, was first published by Simonsen and his coworkers in 1932 (1). The gross structure of eremophilone was established in 1939 (2), but it was not until 1959 (3) that its relative configuration was determined. The relative configuration of hydroxydihydroeremophilone (III) was established by means of an X-ray crystallographic analysis (4) in 1956. Later, work was published (1960) which related eremophilone (I) and hydroxydihydroeremophilone (III) through a common degradation product (5). This degradation product was

also synthesized from a compound of known absolute configuration (5) and thus established the absolute configuration of eremophilone (I).

The synthetic sequence (5) that established the absolute configuration of eremophilone (I) involved the intermediate trans-5β,10β-dimethyl-3β-isopropyl-2-decalone (IV), which possesses the eremophilone

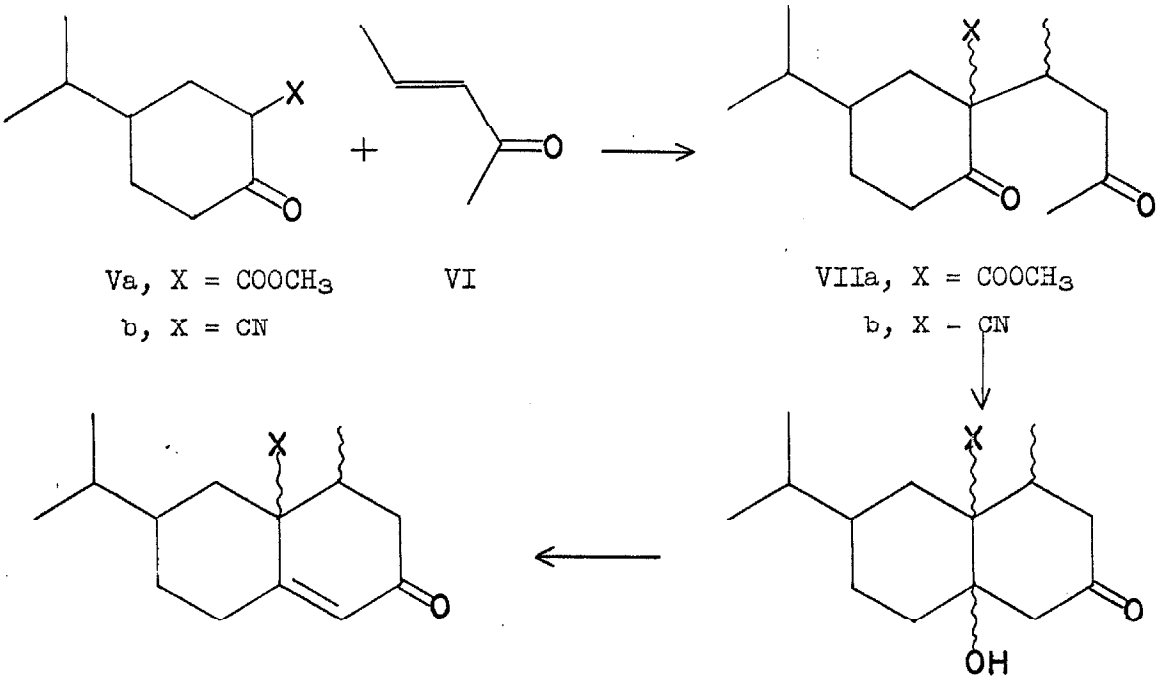


IV

stereochemistry about the asymmetric carbon atoms bearing the alkyl substituents. Each of these centers of asymmetry was introduced individually in the course of the reaction sequence. It was of interest, therefore, to investigate the possibility of introducing stereoselectively two or pernaps even all three centers of asymmetry in eremophilone (I) at one time.

Proposed Synthesis

A synthetic sequence employing a Michael condensation in which the three asymmetric centers in eremophilone (I) were simultaneously generated appeared to be the most promising approach. Also, it appeared to offer an opportunity of investigating a hitherto unexplored aspect of the stereochemistry of the Michael reaction. The proposed reaction sequence involved the following crucial sequence:



Va, X = $COOCH_3$
b, X = CN

VI

VIIa, X = $COOCH_3$
b, X = CN

VIIIa, X = $COOCH_3$
b, X = CN

IXa, X = $COOCH_3$
b, X = CN

It should be noted that the relative configuration of the three asymmetric centers is established in the initial condensation and is unaffected by the subsequent cyclization and dehydration to the octalone derivative IX.

The Michael Donor

In considering the stereochemical course of such a Michael condensation, the configuration of the anion of the Michael donor V must be examined. The anion itself will certainly exist as an enolate ion and will predominantly take the half-chair form shown in Figure 1. Another half-chair form having an axially oriented isopropyl group may also be present to a slight extent; boat forms will be negligible. Examination of models of the anion as shown in Figure 1 provides no compelling steric

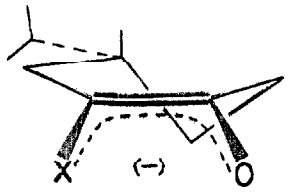
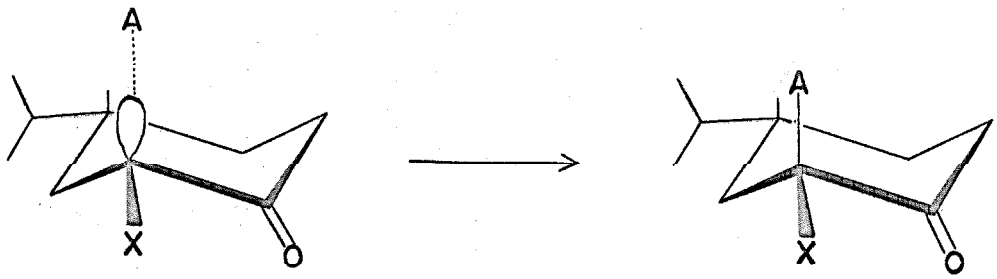


Figure 1. Preferred conformation of anion of Michael donor V.

argument for preference of attack on a Michael acceptor on either side of the conjugated system. However, electronic factors will greatly influence the course of the reaction.

It has been noted (6-11) in many cases (protonations, alkylations) that attack on the side of the π system leading to an axially oriented substituent (proton, alkyl group) was greatly favored. The behavior of such systems can be rationalized by considering the orientation of the orbital containing the lone pair of electrons in the transition state. A much greater degree of stabilization of the transition state could be achieved if the orbital were axially oriented and able to overlap with the π system of the carbonyl group. Therefore, it would be expected that Michael donor V would preferentially lead to a transition state and product as shown in Figure 2. The resulting product would then have the isopropyl and activating groups cis to each other.



X = $COOCH_3$, CN

A = Michael acceptor

Figure 2. Preferred transition state and product.

Orientation of the Michael Acceptor during the Reaction

The determination of the configuration at the carbon atom β to the carbonyl group (C 4) in octalone derivative IX with respect to the activating group depends on the mode of approach of the anion and the Michael acceptor trans-3-penten-2-one (VI). The reactants may approach each other in several ways ultimately resulting in an octalone IX having the methyl group and the activating group X either cis or trans to each other. An example of this situation is shown in Figure 3. The anion of Michael donor V reacting with trans-3-penten-2-one (VI) can give four possible isomers of octalone IX as shown in Figure 4.

An interesting possibility in the Michael condensation arises from the fact that partial charges reside on the carbonyl groups of the donor and acceptor molecules (12). It might be expected that in the absence of a polar medium (i.e., no solvent or non-polar solvent) inter-

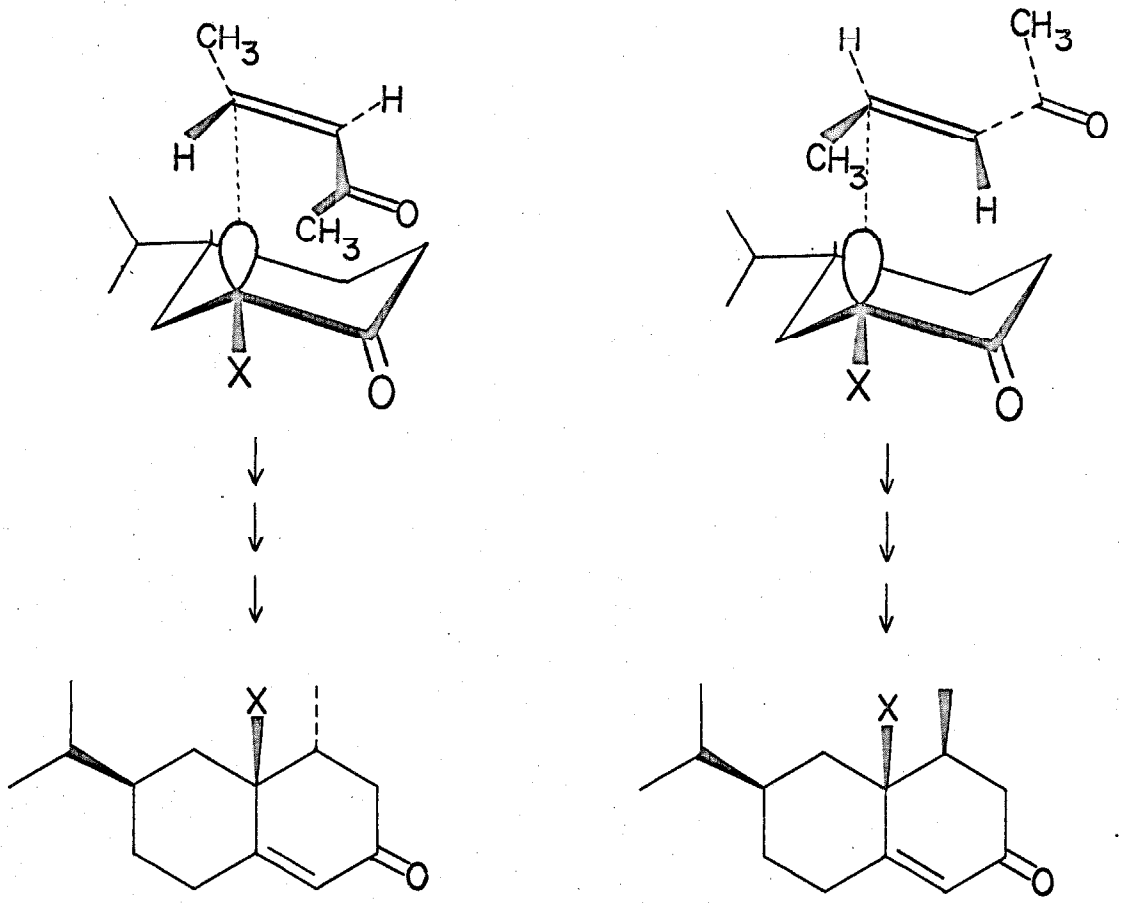


Figure 3. Modes of approach of Michael donor and acceptor.

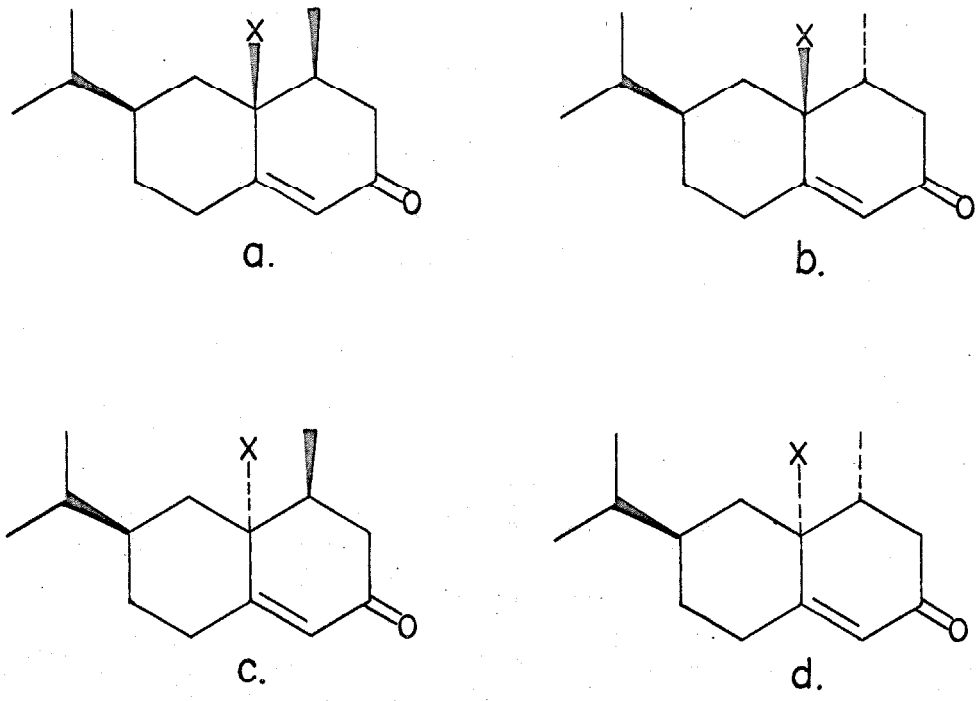


Figure 4. Possible isomers of octalone derivative IX.

action of the partial charges could be observed (cf. Figure 5). Such an interaction, coupled with the steric and electronic requirements of the donor and acceptor in the transition state, could serve to orient the donor and acceptor with respect to each other so that stereoselectivity of the product would result. Thus, a partial charge interaction could lead to condensation reactions as shown in Figure 5. Of these two possibilities, that shown in Figure 5a would clearly be the more preferred, since the steric interactions between the donor and acceptor would be much less than for the case shown in Figure 5b. The latter situation would involve prohibitive steric interaction between the β methyl group of trans-3-penten-2-one (VI) and the hydrogens on carbons 3 and 4 of the Michael donor; also, the α hydrogen of trans-3-penten-2-one would strongly interact sterically with the axial hydrogen on carbon 6. Consequently, it would be expected that the situation depicted in Figure 5a would be applicable to this example and would result in an octalone derivative IX in which all three substituents were cis to each other. The question of whether trans-3-penten-2-one (VI) assumes a cisoid or transoid conformation in the reaction is immaterial to the above argument.

In view of the foregoing considerations, it would be concluded that if it were possible to perform the Michael condensation of donor V and trans-3-penten-2-one (VI) under non-polar conditions the major product after cyclization and dehydration would be expected to be the isomer of octalone IX having the three substituents (isopropyl, methyl and activating groups) all cis, which is the eremophilone (I) stereochemistry. It would also be expected that as solvent polarity increased the effect of partial charge interaction would decrease, resulting in alteration of

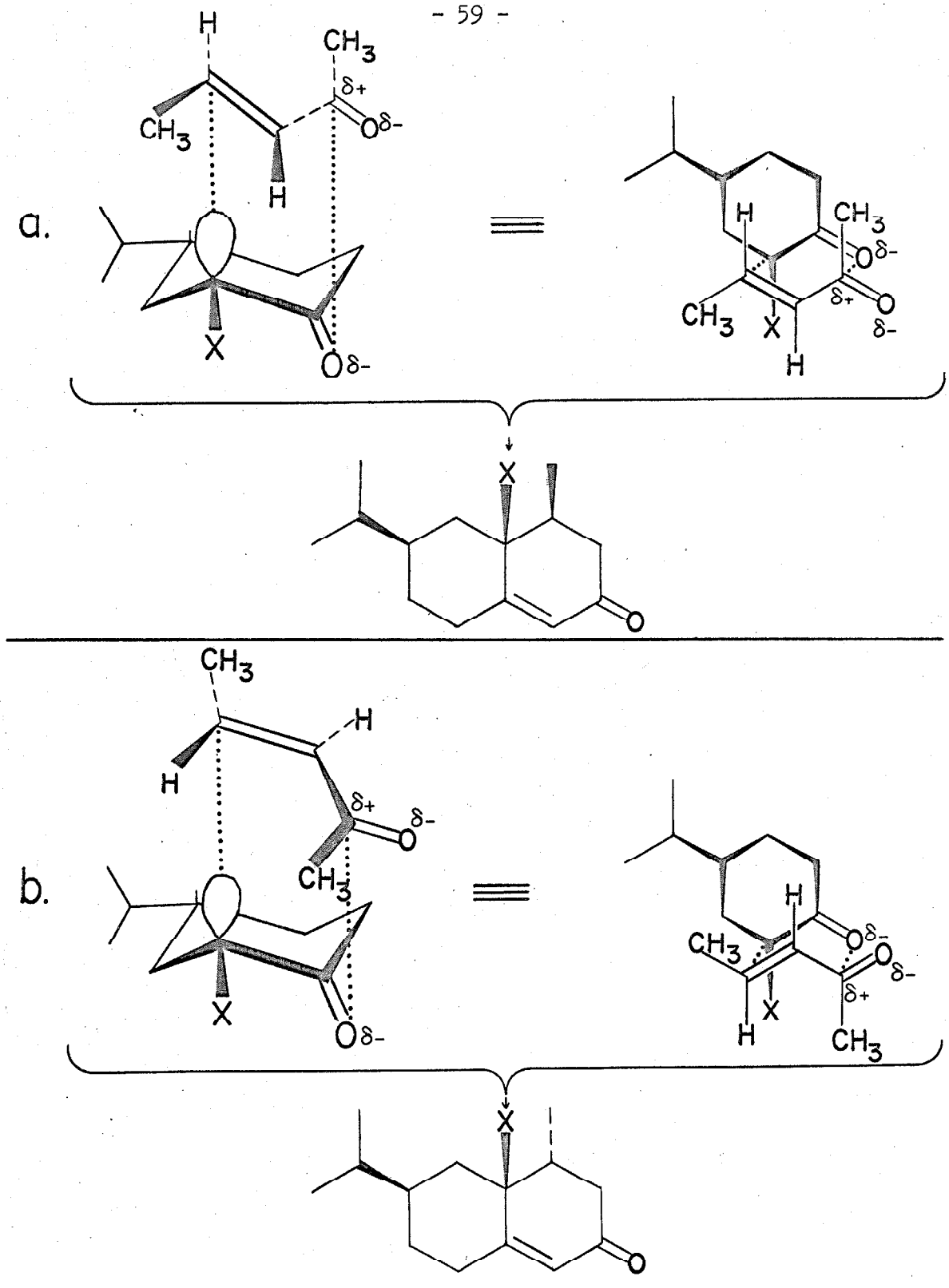


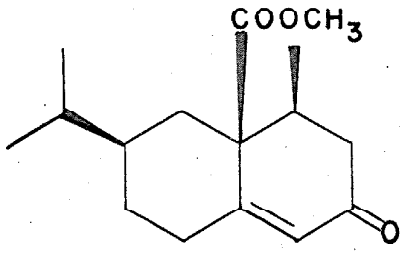
Figure 5. Modes of partial charge interaction.

the product distribution, i.e., the relative ratios of isomers of octalone IX (Figure 4).

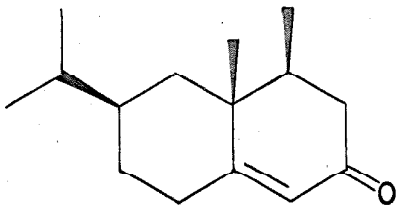
Present Investigation

An investigation designed to search out a partial charge interaction effect as proposed above has been carried out, though unsuccessfully. Unfortunately, the Michael condensation was found not to proceed to any significant extent without solvent or in any solvent less polar than methanol. In fact, in methanol, with sodium methoxide as catalyst, 2-oxo-5-isopropylcyclohexanecarbonitrile (Vb) failed to yield any product recognizable as an octalone derivative IXb and 2-carbomethoxy-4-isopropylcyclohexanone (Va) yielded less than 50% of a mixture of isomers of octalone derivative IXa. No other set of conditions was found which yielded any of the desired octalone IX.

There was isolated from the one successful Michael condensation a 5% yield of 4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{1,9}$-2-octalone (X). This compound was shown to have the stereochemistry stated by comparison of the infrared spectra of 4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI) obtained from the compound by a multi-step transformation



X



XI

with authentic 4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI) obtained by synthesis from eremophilone (I).

RESULTS AND DISCUSSION

Michael Donors and Acceptor

The compounds used in the study of the stereochemistry of the Michael reaction to be described herein were prepared for the most part by adaptations of literature procedures (cf. Figure 6).

p-Isopropylphenol (XII) was hydrogenated (13) at 200° and 2000 p.s.i. H_2 over Raney nickel to yield nearly quantitatively 4-isopropylcyclohexanol (XIII); XIII was in turn oxidized (13) with aqueous sodium dichromate-sulfuric acid to 4-isopropylcyclohexanone (XIV) in 91% yield.

2-Carbomethoxy-4-isopropylcyclohexanone (Va) was prepared in 59% yield by carbomethoxylation of XIV by an unpublished procedure (14). 2-Oxo-5-isopropylcyclohexanecarbonitrile (Vb) was synthesized from XIV in an overall yield of 44% by the reaction sequence (15,16) shown in Figure 6. 2-Oxocyclohexanecarbonitrile was also prepared by the same reaction sequence. 2-Methyl-4-isopropylcyclohexanone (XVIII) was prepared by the sequence indicated in Figure 6 (15,17) from 4-isopropylcyclohexanone (XIV) in an overall yield of 25%.

Trans-3-penten-2-ol (XIX) was prepared from trans-crotonaldehyde and methylmagnesium iodide in 70% yield. The alcohol (XIX) was oxidized to trans-3-penten-2-one (VI) in 41% yield with aqueous chromic acid-acetone (18).

Results of Michael Reactions

Michael reactions of various Michael donors with trans-3-penten-2-one (VI) were performed under varying conditions as indicated in Table I. All reactions attempted without solvent or in benzene or less polar

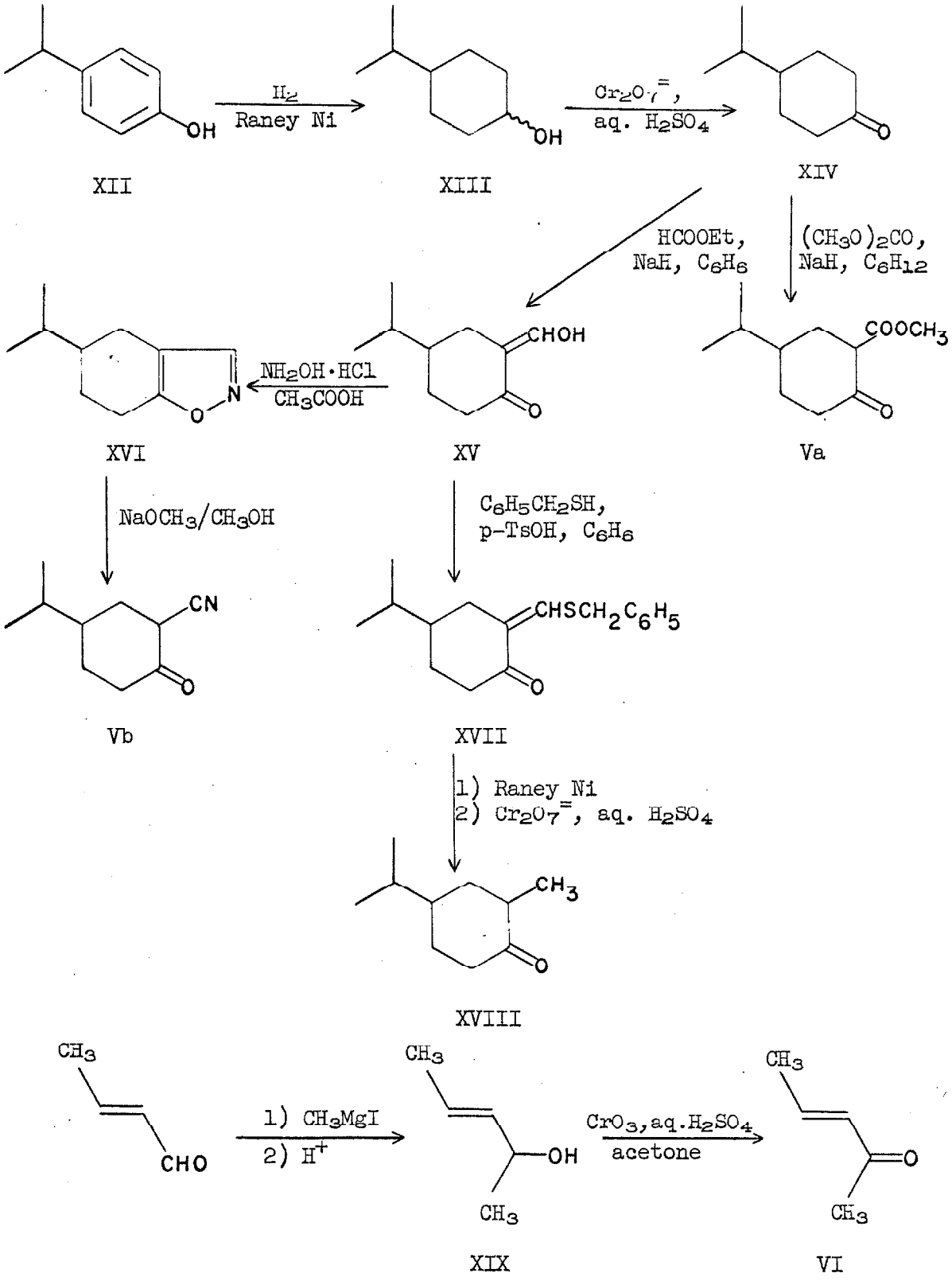


Figure 6. Reaction sequences leading to Michael donors and acceptor.

TABLE I

Michael Reactions Attempted with Various Michael Donors and trans-3-penten-2-one as the Michael Acceptor

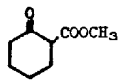
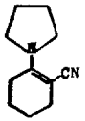
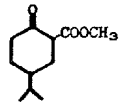
Michael donor used	Equivalents of trans-3-penten-2-one used based on Michael donor	Base/Solvent used (number of equivalents of base used based on Michael donor)	Temp. of reaction, time of reaction	Observations
2-carbomethoxycyclohexanone, 	1.0	$NaOCH_3/CH_3OH$ (1.3)	room temp., 24 hrs.	Reaction followed by buildup of UV λ_{max} at 240 mμ; ~ 20 hrs. required to reach maximum optical density. Workup yielded 27% of a crystalline compound, 4-methyl-10-carbomethoxy-$\Delta^{1,9}$-2-octalone, m.p. 62°; for details see Experimental section (p. 93).
"	1.0	$NaOCH_3$/none (0.1)	room temp., 15 hrs.	None of the above product isolable. The anion salt of the keto-ester appeared to have precipitated from the reaction mixture.
"	2.3	piperidine/none (0.2)	120°, 4 hrs.	Sealed tube. No reaction; partial decarboxylation apparent by evolution of a gas dissolved in the reaction mixture which was liberated on opening of the tube and by loss of carbomethoxy-proton absorption in the NMR.
2-oxocyclohexane-carbonitrile 	1.0	$NaOCH_3/CH_3OH$ (1.0)	room temp., 18 hrs.	No reaction; ketonitrile recovered.
"	1.0	KO-t-Bu/t-BuOH (0.1)	room temp., 14 hrs.	No reaction; ketonitrile recovered.
2-(N-pyrrolidinyl)-cyclohexen-1-carbonitrile (XX) 	2.0	none/benzene	80-85° (reflux), 24 hrs.	Dark oil obtained as product; IR and NMR spectra indicated extensive decomposition.
2-carbomethoxy-4-isopropyl-cyclohexanone (Va) 	1.5	$NaOCH_3/CH_3OH$ (1.0)	room temp., 20 hrs.	Most of ketoester recovered. NMR indicated the possible presence of a small amount of the Michael alduct.
"	1.5	$NaOCH_3/CH_3OH$ (1.0)	70-75°, 6 hrs.	5% of crystalline 4β-methyl-6β-isopropyl-10β carbomethoxy-$\Delta^{1,9}$-2-octalone, m.p. 74°, obtained; for details of experimental procedure, see Experimental section (p. 94).
"	1.5	piperidine/benzene (1.0)	70°, 6 hrs.	No reaction ; ketoester recovered.

TABLE I--continued

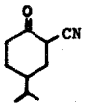
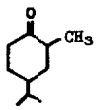
Michael donor used	Equivalents of trans-3-penten-2-one used based on Michael donor	Base/Solvent used (number of equivalents of base used based on Michael donor)	Temp. of reaction, time of reaction	Observations
2-carbomethoxy-4-isopropyl-cyclohexanone (Va)	2.0	piperidine/cyclohexane (2.0)	80-85° (reflux), 2 hrs.	No reaction; ketoester recovered.
"	1.8	piperidine/none (0.2)	150°, 2 hrs.	Sealed tube. No reaction; ketoester recovered.
"	1.6	piperidine/none (1.0)	160°, 3 hrs.	Sealed tube. Extensive decarboxylation apparent by NMR; IR, UV and NMR spectra indicate possible presence of α,β-unsaturated ketone.
"	2.5	piperidine/none (0.6)	200°, 8 hrs.	Sealed tube. Essentially complete decarboxylation; IR, UV and NMR spectra indicate possible presence of α,β-unsaturated ketone.
"	1.5	KO-t-Bu/t-BuOH (1.0)	70-75° (reflux), 1½ hrs.	Dark reaction product obtained; on chromatography, no fraction could be obtained as desired product.
2-oxo-5-isopropyl-cyclohexanecarbonitrile (Vb) 	1.0	$NaOCH_3/CH_3OH$ (1.0)	room temp., 25 hrs.	No reaction; ketonitrile recovered.
"	2.0	$NaOCH_3/CH_3OH$ (0.5)	70-75°, 1 hrs.	Ketonitrile consumed in the reaction; IR and NMR spectra of the product consistent with those expected of the Michael adduct.
"	2.0	$NaOCH_3/CH_3OH$ (1.1)	70-75°, 6 hrs.	General decomposition evident; no building of UV λ_{max} ~ 240 mμ, but general increase in optical density at 200-350 mμ.
"	2.4	Triton B*/CH_3OH (1.0)	70-75°, 4 hrs.	General decomposition evident; no buildup of UV λ_{max} ~ 240 mμ, but general increase in optical density at 200-350 mμ.
"	1.0	KO-t-Bu/t-BuOH (1.0)	room temp., 14 hrs.	No reaction; ketonitrile recovered.
"	2.0	KO-t-Bu/t-BuOH (2.2)	70-75°, 1½ hrs.	Reaction mixture rapidly darkened; no buildup of UV λ_{max} ~ 240 mμ. Decomposition evident.

TABLE I—continued

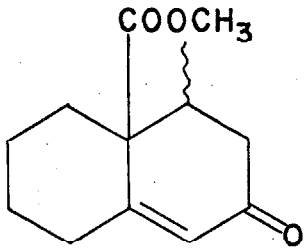
Michael donor used	Equivalents of trans-3-penten-2-one used based on Michael donor	Base/Solvent used (number of equivalents of base used based on Michael donor)	Temp. of reaction, time of reaction	Observations
2-methyl-4-isopropyl-cyclohexanone (XVII) 	2.9	$NaOCH_3/CH_3OH$ (1.8)	70–75°, 2 hrs.	IR, UV and NMR spectra indicate, at most, very little desired product, 4,10-dimethyl-6-isopropyl-$\Delta^{1,9}$-2-octalone, present in reaction product.
"	1.5	KOH/EtOH (0.5)	90°, 20 min.	IR, UV and NMR spectra indicate very little, if any, desired product, 4,10-dimethyl-6-isopropyl-$\Delta^{1,9}$-2-octalone, present in reaction product.
"	1.4	KO-t-Bu/t-BuOH (1.1)	room temp., 45 min.	Reaction mixture rapidly darkened; IR, UV and NMR spectra failed to indicate the presence of any desired product.
"	2.5	$NaCCH_3/Et_2O$ (2.5)	35–40° (reflux), 1 hr. and room temp., 18 hrs.	Reaction mixture darkened; spectra indicate extensive decomposition.
"	2.5	Et_3N/none (0.8)	200°, 1 1/4 hrs.	Sealed tube. No reaction; starting ketones recovered.
"	2.5	Et_3N/none (0.8)	250°, 2 hrs.	Sealed tube. No reaction; starting ketones recovered.
"	2.5	Et_3N/none (0.8)	280°, 12 hrs.	Sealed tube. IR, UV and NMR spectra of the reaction mixture failed to indicate the presence of any desired product; decomposition apparent.

*Benzyl trimethylammonium hydroxide.

solvents gave no products recognizable (by IR, UV, NMR, etc.) as either a Michael adduct VII or cyclized products VIII or IX. However, in two of the sealed tube reactions (160°, 5 hrs.; 200°, 8 hrs.) using 2-carbomethoxy-4-isopropylcyclohexanone (Va) with piperidine as catalyst, the product contained an α,β-unsaturated ketone although the NMR spectra indicated only the slight presence of carbomethoxy protons in the first case and their absence in the second case.

Reactions of the various Michael donors performed in tert-butyl alcohol with potassium tert-butoxide as catalyst at room temperature and at 70-75° (cf. Table I) resulted in either recovery of starting Michael donor or decomposition of the reactants to dark-colored products.

Reactions performed in methanol with sodium methoxide as catalyst were the only experiments to yield positive results. A reaction of the model compound 2-carbomethoxycyclohexanone with trans-3-penten-2-one (VI) was carried out at room temperature (cf. 19), the production of α,β-unsaturated ketone (4-methyl-10-carbomethoxy-$\Delta^{1,9}$-2-octalone (XXI))



XXI

being monitored by UV on small aliquots of the reaction mixture. A maximum concentration of α,β-unsaturated ketone was achieved in about 20 hrs. Subsequent workup of the reaction mixture yielded a crude product whose

UV absorption indicated about a 45% yield of octalone XXI (mixture of isomers) and which furnished a 27% yield of a crystalline isomer of XXI, m.p. 62°. Similar reactions at room temperature with 2-carbomethoxy-4-isopropylcyclohexanone (Va) and 2-oxo-5-isopropylcyclohexanecarbonitrile (Vb) showed with the former compound (Va) only a slight diminution in the quantity of ketoester in the reaction mixture and with the latter compound (Vb) no observable reaction. It is interesting to note that the introduction of an isopropyl group at C-4 of 2-carbomethoxycyclohexanone markedly reduces the reactivity of Va toward the Michael acceptor.

Raising of the reaction temperature to 70-75° with 2-carbomethoxy-4-isopropylcyclohexanone (Va) allowed the reaction to proceed. The concentration of α,β-unsaturated ketone (monitored by UV) initially increased rapidly and reached a maximum at 6 hrs., remaining unchanged thereafter. Soon after heating of the reaction mixture commenced, a granular precipitate appeared, which was identified as sodium carbonate. The amount of this precipitate, if derived from the ketoester Va (which seems likely), corresponds to decarboxylation to the extent of 20-30% of the ketoester initially present. Workup of the reaction mixture yielded a crude product whose UV absorption indicated about a 50% yield of α,β-unsaturated ketone product (IXa). After chromatography this product furnished a 5% yield of 4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{1,9}$-2-octalone (X), m.p. 74°. The structure elucidation of this compound will be described later (p. 70).

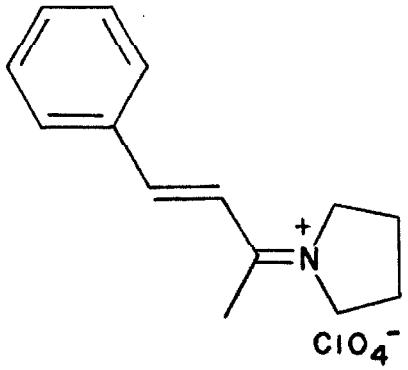
The reaction of 2-oxo-5-isopropylcyclohexanecarbonitrile (Vb) with trans-3-penten-2-one (VI) using sodium methoxide in methanol when

carried out at 70-75° appeared initially to yield the Michael adduct VIIb, but longer heating did not furnish the desired octalone IX as did the reaction with 2-carbomethoxy-4-isopropylcyclohexanone (Va). Instead of the building of a UV absorption maximum at ~ 240 mμ, a general increase in the optical density over the range 200-350 mμ was observed. This phenomenon might be attributable to a retrograde Michael reaction (i.e., reversal) (cf. 20) followed by decomposition and/or polymerization of the reactants.

Several reactions were attempted with 2-methyl-4-isopropylcyclohexanone (XVIII) with the intention of synthesizing octalone XI (and its isomers) in one step. However, no octalone derivatives were obtained. These results are not surprising in view of the fact that in even the most favorable cases simple ketones give low yields of Michael adducts (cf. 20).

In addition to the experiments described above, two other experiments using model compounds were attempted. An experiment was performed (cf. Table I) using as the Michael donor the pyrrolidine enamine of 2-oxocyclohexanecarbonitrile (2-(N-pyrrolidinyl)-cyclohexen-1-carbonitrile (XX)), which was expected to react with trans-3-penten-2-one (VI) in the manner of other enamines (21) to yield Michael adducts. However, the product obtained was a dark oil whose IR and NMR spectra showed little detail but rather indicated extensive decomposition of the reactants.

The other model experiment used as the Michael acceptor the iminium perchlorate of an α,β-unsaturated ketone, which was expected to be a good acceptor because of the formal positive charge on nitrogen in the iminium ion. N-Cinnamylidenepyrrolidinium perchlorate (XXII) (22)



XXII

was refluxed in methanol with 2-carbomethoxy-4-isopropylcyclohexanone (Va) and triethylamine (catalyst). However, workup yielded recovered ketoester Va and polymeric material.

Relation of the Stereochemistry of Octalone X to Eremophilone

The crystalline isomer of 4-methyl-6-isopropyl-10-carbomethoxy-$\Delta^{1,9}$-2-octalone (IXa) isolated as described above was shown to possess the all-cis configuration (X) by relating its structure to eremophilone (I) as shown in Figure 7. Ketoester X was converted to an ethylene ketal in the usual manner. The ketal-ester XXIII was then reduced with lithium aluminum hydride to the ketal-alcohol XXIV.

Oxidation of XXIV by the method of Sarett and co-workers (23) furnished ketal-aldehyde XXV in 15% yield. In addition to XXV, another compound was isolated in about 20% yield. This compound was thought to have structure XXVI on the basis of the following data. The infrared

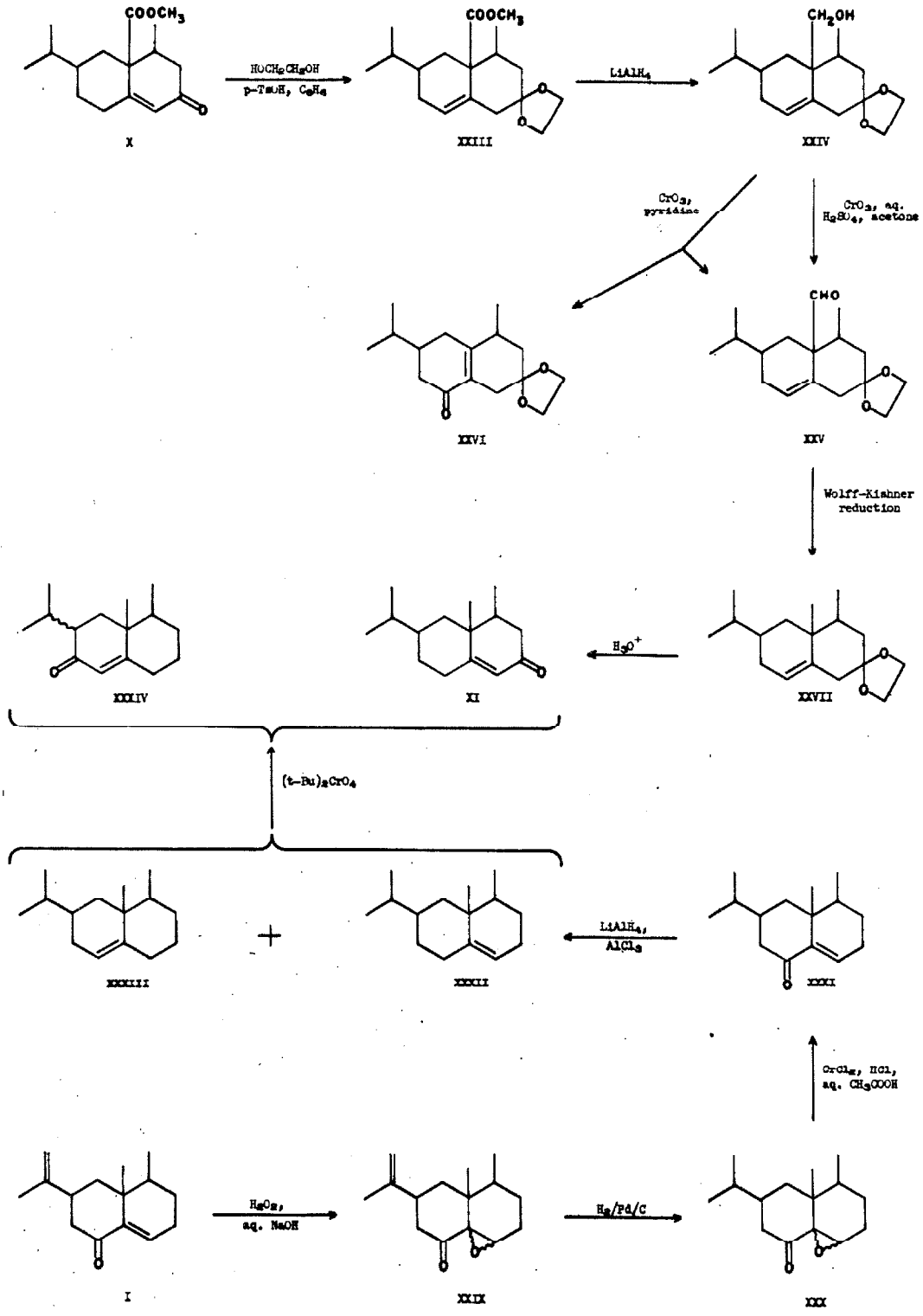


Figure 7. Reaction sequence relating the stereochemistry of ketoester X to eremophilone (I).

spectrum indicated only the presence of a transoid α,β-unsaturated ketone in the carbonyl region (strong maximum at 6.03μ with a weaker peak at 6.15μ). That the conjugated C=C bond was tetrasubstituted was indicated by the ultraviolet spectrum (λ_{max}^{EtOH} 245 mμ) and the absence of vinyl proton absorption in the NMR. The mass spectrum showed a base peak at m/e 264 (the expected parent peak for XXVI) with prominent peaks at m/e 192 and 86; a molecular weight of 264 was indicated by elemental analysis ($C_{16}H_{24}O_3$). The two prominent peaks in the mass spectrum (m/e 192, 86) can be rationalized in terms of XXVI in the manner of Djerassi and co-workers (24) as shown in Figure 8.

A mechanism whereby XXVI can be produced from ketal-alcohol XXIV is suggested in Figure 9. Epoxidation of the double bond by chromium trioxide (cf. 25,26) followed by rearrangement of the epoxide with loss of the angular substituent would lead to an alcohol (or possibly a chromate ester), which, under the reaction conditions, would be oxidized to ketone XXVI.

Use of the method of Jones and co-workers (18) in the oxidation of ketal-alcohol XXIV (CrO_3, aqueous H_2SO_4, acetone) furnished ketal-aldehyde XXV in much improved yield (84%). A Wolff-Kishner reduction (27) of XXV yielded ketal XXVII, which was hydrolyzed in aqueous sulfuric acid-methanol to yield α,β-unsaturated ketone XI, (±)-4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone. The IR and NMR spectra were found to be different from those of dihydronootkatone (XXVIII) (28). The IR spectrum (in CS_2) of (±)-XI is shown in Figure 11 (p. 82).

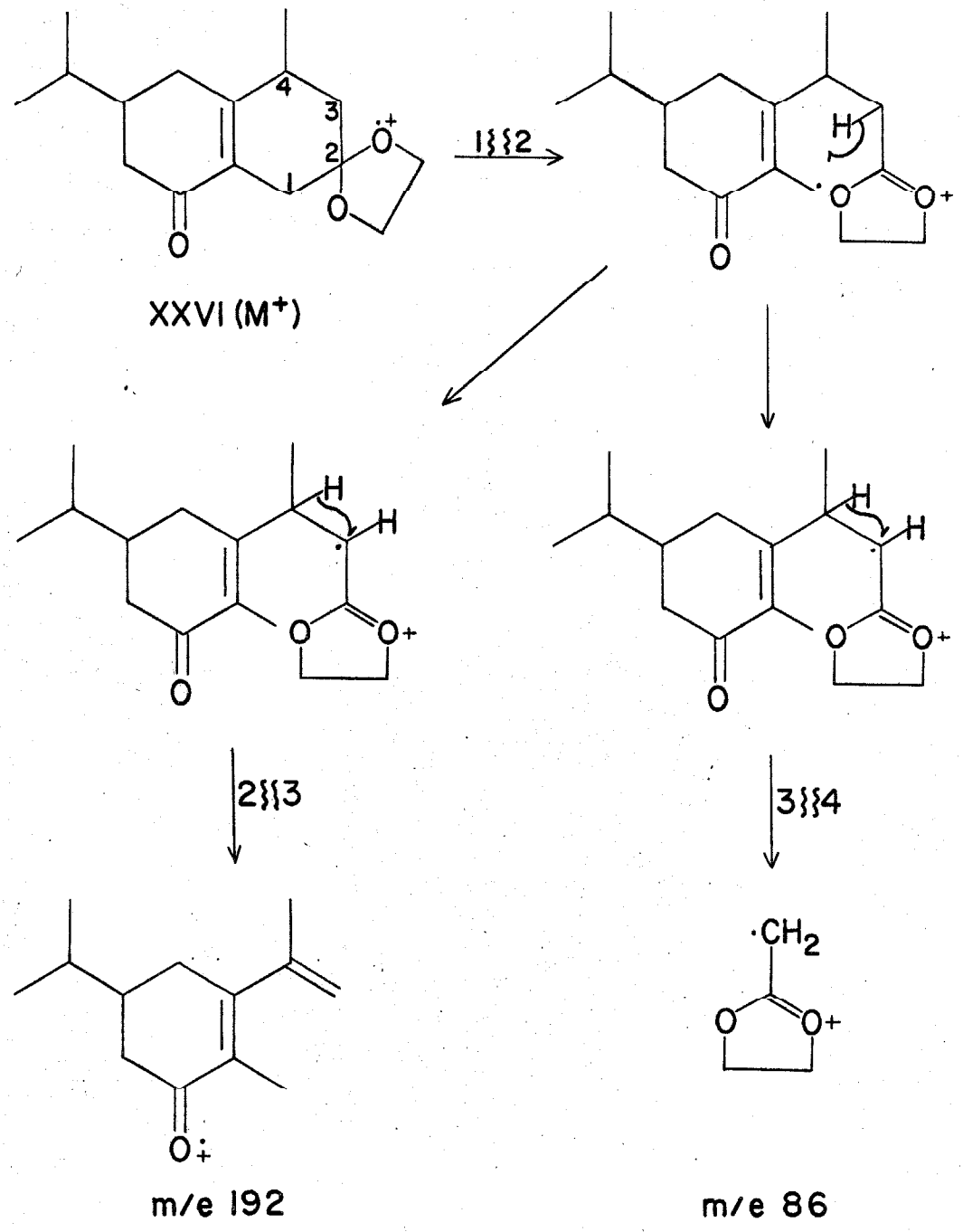


Figure 8. Fragmentation sequence leading to the m/e 192 and 86 ions in the mass spectrum of XXVI.

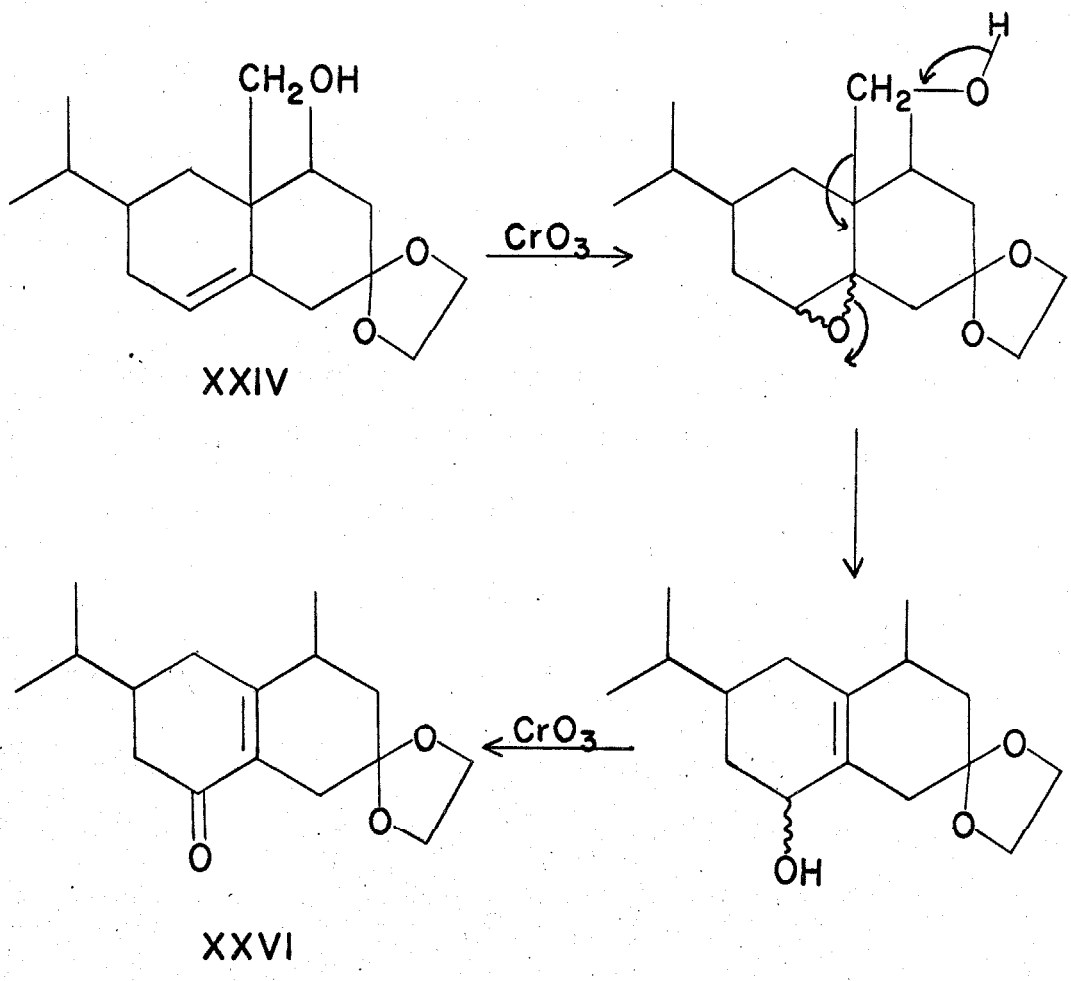
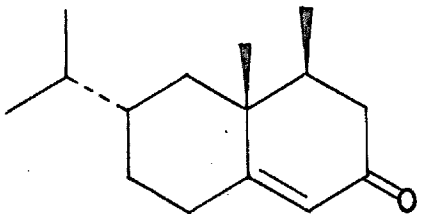


Figure 9. Suggested mechanism for the production of XXVI.



XXVIII

The mixture of isomers of 4-methyl-6-isopropyl-10-carbomethoxy-$\Delta^{1,9}$-2-octalone (IXa) was converted to the mixture of isomers of 4,10-dimethyl-6-isopropyl-$\Delta^{1,9}$-2-octalone by the reaction sequence indicated above for pure isomer X (cf. Figure 7). The appearance of the NMR spectrum of the mixture was much more similar to the NMR spectrum of dihydronootkatone (XXVIII) than to that of the pure isomer XI. Gas chromatography of the mixture of ketones using various adsorbents (Carbowax, diethyleneglycol succinate (DEGS), silicone oil, silicone gum rubber) gave only a single peak. Mixtures of isomers XI and XXVIII also gave a single peak with every adsorbent.

In order to obtain another isomer of 4,10-dimethyl-6-isopropyl-$\Delta^{1,9}$-2-octalone for the purpose of determining the composition of the mixture of isomers of the octalone derivative, eremophilone (I) was converted to octalone XI by the reaction sequence shown in Figure 7. Before this route was settled upon, a number of other possible reaction sequences were investigated; a summary of these is shown in Figure 10.

Attempted selective hydrogenation of eremophilone (I) to dihydroeremophilone (XXXI) was unsuccessful. Hydrogenation over palladium on carbon in methanol resulted in saturation of both carbon-carbon double

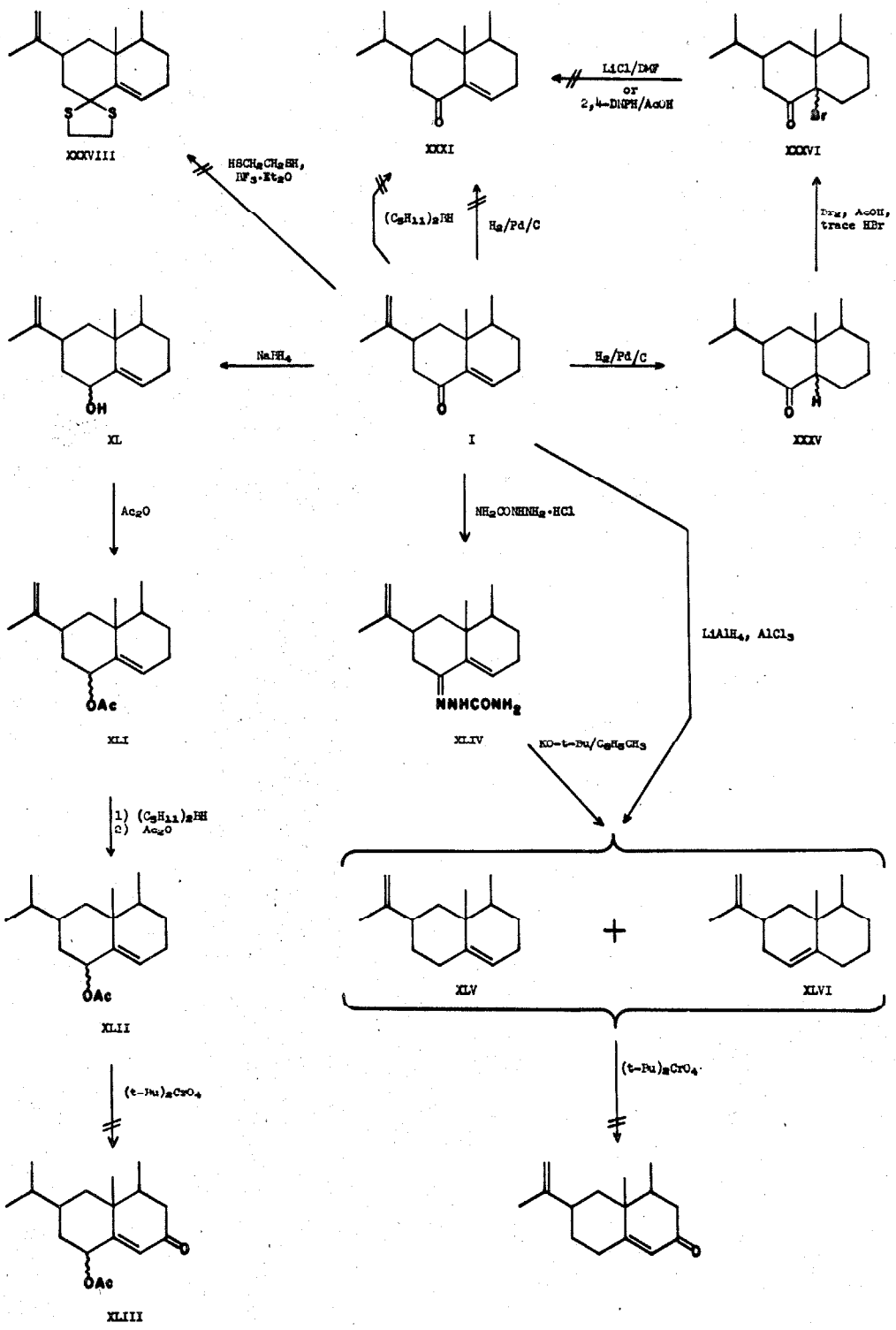
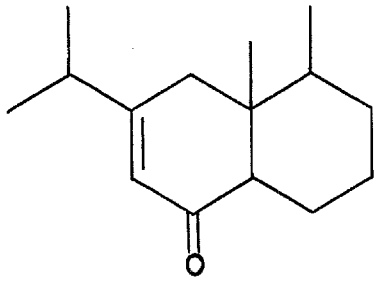


Figure 10. Other reaction sequences investigated.

bonds at approximately the same rate, the conjugated bond being hydrogenated at a slightly faster rate.

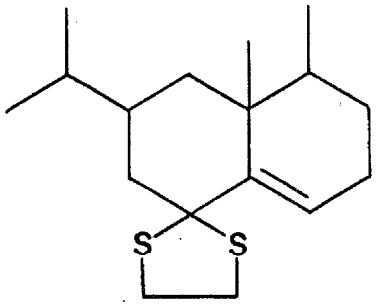
Tetrahydroeremophilone (XXXV), prepared by hydrogenation of eremophilone (I), was easily converted (29) to the α-bromoketone XXXVI. Dehydrobromination of XXXVI with either lithium chloride in dimethylformamide (30) or 2,4-dinitrophenylhydrazine in acetic acid (31) failed to yield dihydroeremophilone (XXXI). The former reagent gave an α,β-unsaturated ketone whose IR, UV and NMR spectra indicated that it was a transoid α,β-unsaturated ketone, possibly XXXVII. The latter reagent



XXXVII

did not furnish the 2,4-dinitrophenylhydrazone of an α,β-unsaturated ketone but did yield a small amount of tetrahydroeremophilone-2,4-DNP, m.p. 177°, UV λ_{max}^{EtOH} 364 mμ, and a larger amount of a 2,4-DNP of a saturated ketone, m.p. 199-203°, UV λ_{max}^{EtOH} 365 mμ. It was determined that the latter compound did not contain bromine, but its structure remained undetermined.

An attempt to selectively hydroborate the terminal methylene group in eremophilone (I) with disiamylborane (32) also led to extensive reduction of the carbonyl group. Attempts to prepare eremophilone ethylenethioketal (XXXVIII) by Fieser's methods (33) (ethanedithiol, boron trifluoride etherate, with and without acetic acid as solvent) also failed, as did later attempts to prepare dihydroeremophilone ethylenethioketal (XXXIX).



XXXIX

Eremophilone (I) was reduced with sodium borohydride in methanol to yield an apparent mixture of epimeric eremophilols (XL). Acetylation furnished eremophilol acetate (XLI), also an apparent mixture of epimers. Reduction of eremophilol acetate (XL) with one equivalent of disiamylborane (32) resulted in partial reduction of the ester in addition to reduction of the terminal methylene group. Treatment of the product

with two additional equivalents of disiamylborane followed by acetylation of the product furnished dihydroeremophilol acetate (XLII). Tert-butyl chromate oxidation (34) of XLII and chromatography of the reaction product failed to yield any of the unsaturated ketoester XLIII.

Eremophilone semicarbazone (XLIV) was prepared (1) and reduced to the olefins XLV and XLVI by a modified Wolff-Kishner procedure (35) using potassium tert-butoxide in toluene. The method employed (35) was designed to minimize rearrangement of the olefinic bond in Wolff-Kishner reductions of α,β-unsaturated ketones (35). Gas chromatography showed the product to contain two compounds in the ratio of 4.5:1, presumably a mixture of XLV and XLVI. Oxidation of the mixture with tert-butyl chromate (34) followed by chromatography yielded a small amount of material showing α,β-unsaturated ketone absorption in the IR (6.00μ) but which also showed strong absorption at 5.79μ (saturated ketone or ester?). Since the yield of the reaction was very low and isolation of the product difficult, it was considered infeasible to continue with this reaction sequence.

Eremophilone (I) was reduced with lithium aluminum hydride and aluminum chloride (36) to a mixture of olefins XLV and XLVI, which was then oxidized with tert-butyl chromate (34). Workup of the oxidation mixture yielded no significant amount of α,β-unsaturated ketone.

Oxidation of eremophilone (I) with alkaline hydrogen peroxide (1) furnished eremophilone oxide (XXIX) in 74% yield (cf. Figure 7). The configuration of the epoxide was not determined. Examination of the NMR spectrum of the small amount of mother liquor from the crystallization of eremophilone oxide (XXIX) indicated that only one isomer of the

epoxide was formed in the reaction. Dihydroeremophilone oxide (XXX) was prepared in 95% yield by hydrogenation of XXIX over palladium on carbon. It was found that hydrogenation for periods of time longer than that required for uptake of one equivalent of hydrogen resulted in lower yields. These lower yields apparently resulted from catalytic reduction of the epoxide to an alcohol.

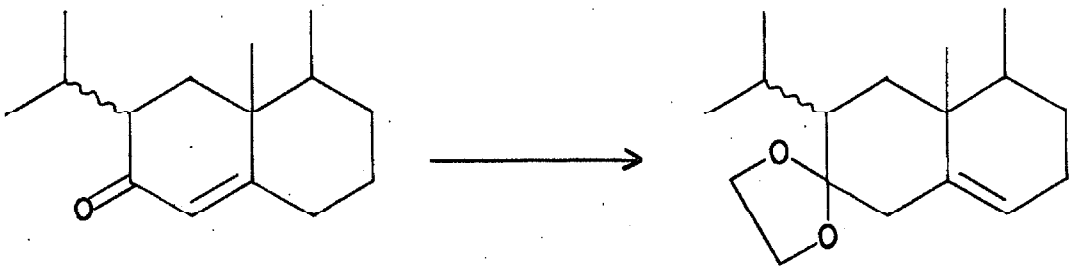
Reduction of dihydroeremophilone oxide (XXX) with chromous chloride in aqueous hydrochloric and acetic acid (37) at room temperature furnished dihydroeremophilone (XXXI) in 85% yield. It was found that allowing the reaction to proceed for a longer time than that used by previous workers (37) resulted in high yields and eliminated the need for an additional reaction (refluxing with hydrochloric acid in acetone (37)) to dehydrate the keto-alcohol intermediate.

Dihydroeremophilone (XXXI) was reduced with lithium aluminum hydride and aluminum chloride (36) to dihydroeremophilene (XXXII) and isomeric olefin XXXIII. Gas chromatography of the product, however, showed three peaks in the ratios 7.0:3.6:1.0. The identification of XXXII and XXXIII with individual g.c. peaks was not attempted, nor was the identification of the third peak attempted.

The mixture of olefins XXXII and XXXIII was oxidized with tert-butyl chromate in carbon tetrachloride (34). Several chromatographic separations of the dark reaction product furnished an 8% yield of (-)-4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI) and a 7% yield of 5β,10β-dimethyl-3-isopropyl-$\Delta^{1,9}$-2-octalone (XXXIV). Octalone XI was identical in all its spectral and chromatographic properties with octalone XI synthesized from 4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{1,9}$-

2-octalone (X) and therefore established the stereochemistry of X. The infrared spectra (in CS_2) of (-)-XI obtained from eremophilone (I) and (±)-XI obtained from X are shown in Figure 11.

Octalone XXXIV was found to be very similar to octalone XI in its spectral properties. Mass spectrometry and elemental analysis corroborated structure XXXIV. Ketone XXXIV was converted to an ethylene ketal (XLVII) and the mass spectrum of XLVII was obtained. The spectrum showed



XXXIV XLVII

a base and parent peak at m/e 264 with prominent peaks at m/e 221, 178, 141, and 91. The observation of an ion with mass 141 (not observed in the mass spectra of other compounds in this study) can easily be rationalized in terms of structure XLVII in view of other work (24) as shown in Figure 12. This provides additional corroboration of structure XLVII and therefore structure XXXIV. The configuration of carbon 3 of XXXIV is uncertain because of possible epimerization of this asymmetric center during the workup and subsequent chromatography of the oxidation reaction product.

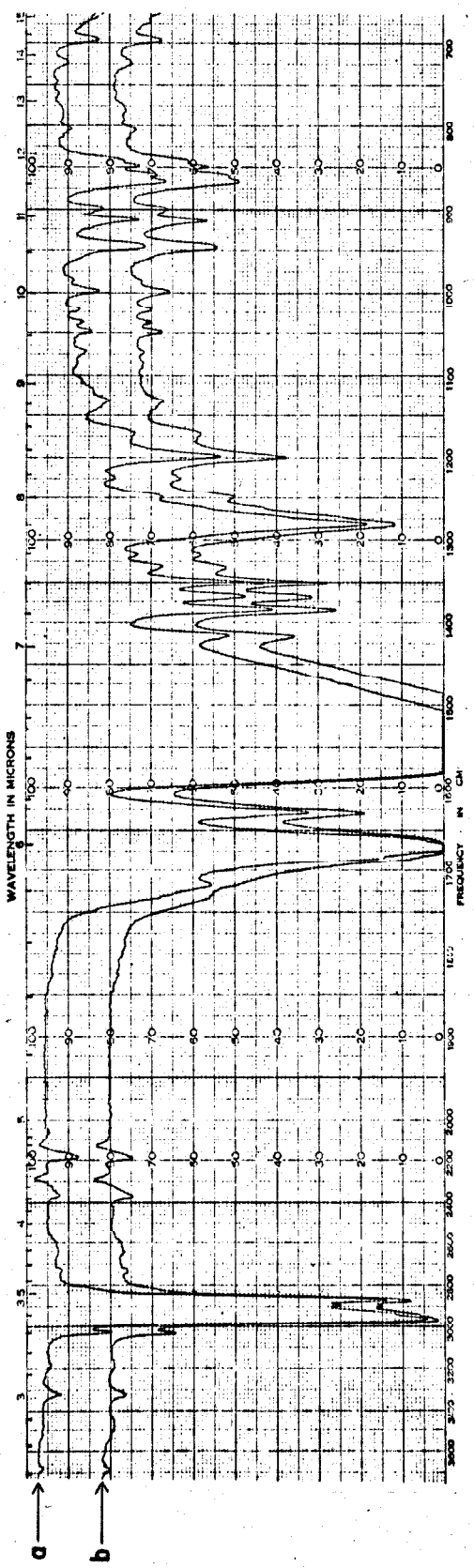


Figure 11. Infrared spectra (CS_2) of

(a) (±)-4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI)

(b) (-)-4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI)

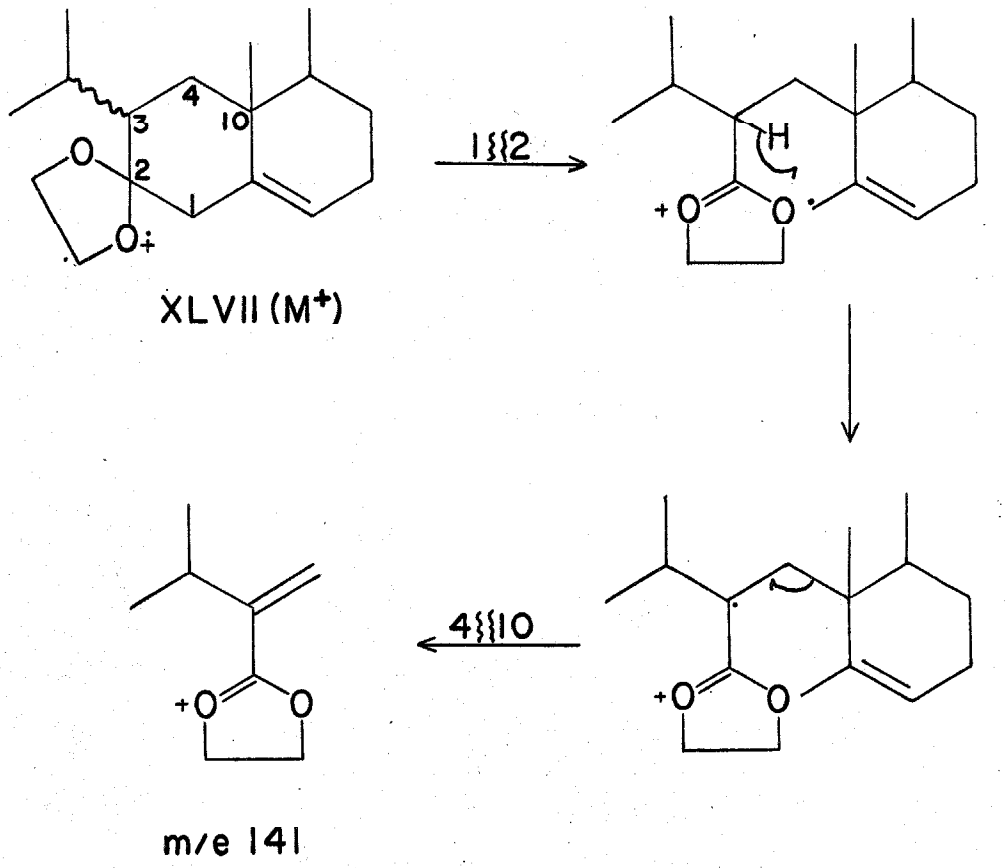


Figure 12. Fragmentation sequence leading to the m/e 141 ion in the mass spectrum of XLVII.

Conclusion

The Michael reactions investigated in this work have led to the synthesis of compounds possessing the eremophilone stereochemistry. Although the isolated yield of octalone X was low, the objective of synthesizing a compound related to eremophilone in which the stereochemistry of all of the asymmetric centers was established at one time has been accomplished. Octalone X and the compounds synthesized from it should be of potential synthetic utility in the synthesis of compounds in the eremophilone series. Since the yield of octalone X was so low (thus limiting the amount available) and subsequent reactions did not always proceed in high yield, the conversion of octalone X to dihydroeremophilone (XXXI) was not accomplished.

As for the possible role of partial charge interaction as an orienting factor in the Michael reaction as presented in the Introduction, no conclusion about such an effect could be reached. It would have been most interesting to know the relative amounts of isomers of octalone IXa; inferences as to the orientation of the Michael donor and acceptor during the reaction could then be made from such data. Since only one set of reaction conditions yielded octalones IXa, drawing conclusions about the orientation of donor and acceptor on the basis of differing yields obtained under different reaction conditions was also not possible.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage with microscopic magnification and are corrected. Boiling points are uncorrected; boiling points of compounds synthesized only in small quantity (< 1 g.) were determined indirectly and are approximate. Infrared (IR) spectra were determined on a Perkin-Elmer Infracord model 137 spectrophotometer unless otherwise stated. Ultraviolet (UV) spectra were determined on a Cary Model 11 recording spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined on Varian Associates A-60 and A-60A spectrometers and are reported in delta units (δ, parts per million) downfield from tetramethylsilane. Mass spectra were determined on a Consolidated Electrodynamics Corporation Model 103-C spectrometer. Optical rotations were measured on a Bendix Ericsson U.K. Ltd. ETL-NPL Automatic Polarimeter Type 143A using a cell with a path length of 4.0 cm. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

2-Oxocyclohexanecarbonitrile. 2-Hydroxymethylenecyclohexanone (38) was prepared by a modified method of Johnson and Posvic (15). To a mixture of 24.5 g. of cyclohexanone (0.25 mole; Matheson, Coleman and Bell, distilled before use) and 39.0 g. of sodium methoxide (0.75 mole; Matheson, Coleman and Bell) in 500 ml. of benzene stirred in an ice bath under nitrogen was added dropwise 74.1 g. of ethyl formate (1.00 mole; Matheson, Coleman and Bell) in 100 ml. of benzene over 30 min. The mixture was allowed to stir and warm to room temperature over a period of 12 hrs. The mixture was then cooled in an ice bath and 100 ml. of water

was added. The resulting phases were separated and the organic phase was extracted twice with 50 ml. portions of 5% aqueous sodium hydroxide. The combined aqueous extract was neutralized with 200 ml. of 10% hydrochloric acid and the resulting phases were separated. The aqueous phase was extracted with 100 ml. of ether and the ethereal extract was combined with the previously obtained organic phase. The solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield 31 g. (98%) of crude 2-hydroxymethylenecyclohexanone (38) as an orange-colored oil, which was used immediately in the next step.

4,5,6,7-Tetrahydro-1,2-benzisoxazole (38) was prepared by the method of Johnson and Shelberg (16). The 31 g. of crude 2-hydroxymethylenecyclohexanone obtained above treated as prescribed (16) yielded on distillation 9.6 g. (32%) of 4,5,6,7-tetrahydro-1,2-benzisoxazole as a nearly colorless liquid, b.p. 80-90°/5 mm.(lit. (38), 90-95°/14 mm), which was used immediately in the next step.

A solution of the above 9.6 g. of 4,5,6,7-tetrahydro-1,2-benzisoxazole in 50 ml. of ether was treated with a solution of 5 g. of sodium methoxide in 50 ml. of methanol at 0° by the method of Johnson and Shelberg (16). Workup and distillation yielded 6.5 g. (68%) of 2-oxocyclohexanecarbonitrile, b.p. 95-100°/1 mm. (lit., 129-131°/7 mm. (39); 120-122°/5 mm. (40)). λ_{max}^{film} 4.45μ (C≡N), 4.54μ (conj. C≡N), 5.80μ (C=O).

4-Isopropylcyclohexane (XIII) was prepared by the method of Frank, Berry and Shotwell (13). A solution of 150 g. p-isopropylphenol (XII), 1.10 moles; Dow Chemical Company) in 100 ml. of ethanol was hydrogenated over 10 g. of W-2 Raney Nickel (41) at 200° and 2000 p.s.i. H_2. Uptake of three equivalents of hydrogen required 6-12 hrs. Filtration

to remove the catalyst followed by fractional distillation yielded 147 g. 4-isopropylcyclohexanol (97%), b.p. 90-91°/8 mm. (lit. (13), 123-124°/40 mm.), n_D^{28} 1.4596 (lit. (13), n_D^{20} 1.4660).

4-Isopropylcyclohexanone (XIV) was prepared by the method of Frank, Berry and Shotwell (13). To a stirred mixture of 46.0 g. of 4-isopropylcyclohexanol (XIII, 0.32 mole) and 33.0 g. of sodium dichromate dihydrate (0.11 mole) in 300 ml. of water at room temperature was added 35 ml. of conc. sulfuric acid (0.66 mole) over a period of 1 hr. The mixture warmed itself to 60-70° during the course of the reaction. After stirring for an additional 1½ hrs., the mixture was cooled and the phases were separated. The aqueous phase was washed with 100 ml. and 50 ml. portions of ether. The organic phases were combined, washed with 40 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and distilled to yield 41.3 g. (91%) of 4-isopropylcyclohexanone (XIV), b.p. 95-96°/15 mm. (lit (13), 90-91°/13 mm.), n_D^{24} 1.4557 (lit (13), n_D^{20} 1.4560). λ_{max}^{film} 5.84μ.

2-Carbomethoxy-4-isopropylcyclohexanone (Va) was prepared according to an unpublished procedure (14). A stirred mixture of 29 g. of sodium hydride (1.2 moles; Metal Hydrides Inc., as dispersion in mineral oil; washed free of oil by repeated decantation with cyclohexane) and 109 g. of dimethylcarbonate (1.2 moles; Eastman Organic Chemicals) in 1.5 l. of cyclohexane was brought to reflux under nitrogen. A solution of 41.0 g. of 4-isopropylcyclohexanone (XIV, 0.29 mole) in 50 ml. of cyclohexane was added dropwise to the refluxing mixture over a period of 6 hrs. The reaction mixture was stirred under reflux for 85 hrs. and

then distilled until 700 ml. of distillate had been collected. The residual reaction mixture was cooled in an ice bath and 75 g. of acetic acid (1.25 moles) was added dropwise with vigorous stirring over 30 min. Then 200 ml. of water was added and the resulting phases were separated. The aqueous phase was extracted with three 100 ml. portions of ether and the ether extracts were combined with the previous organic phase. The combined organic phase was washed with 100 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was fractionally distilled to yield 34.1 g. (59%) of 2-carbomethoxy-4-isopropylcyclohexanone (Va), b.p. 69-70°/0.25 mm., n_D^{25} 1.4803. λ_{max}^{film} 5.72μ (ester C=O), 5.82μ (ketone C=O), 6.03μ (conj. ester C=O); NMR δ 3.72 (carbomethoxy protons).

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.47; H, 9.18.

2-Oxo-5-isopropylcyclohexanecarbonitrile (Vb). 2-Hydroxymethylene (XV) was prepared by a modified method of Johnson and Posvic (15). To a mixture of 35.6 g. of 4-isopropylcyclohexanone (XIV, 0.25 mole) and 39.0 g. of sodium methoxide (0.75 mole; Matheson, Coleman and Bell) in 600 ml. of benzene stirred in an ice bath under nitrogen was added dropwise 74.1 g. of ethyl formate (1.00 mole; Matheson, Coleman and Bell) in 100 ml. of benzene over 30 min. The mixture was allowed to stir and warm to room temperature over a period of 16 hrs. The mixture was then cooled in an ice bath and 100 ml. of water was added. The resulting phases were separated and the organic phase was extracted with 100 ml. of 5% aqueous sodium hydroxide. The combined aqueous solution was neu-

tralized with 200 ml. of 10% hydrochloric acid and the resulting phases were separated. The aqueous phase was extracted with 100 ml. of ether and the extract was combined with the previous organic phase. The solution was dried over anhydrous sodium sulfate and evaporated to 40 g. (96% yield) of crude 2-hydroxymethylene-4-isopropylcyclohexanone (XV) as an orange-colored oil, which was used immediately in the next step.

5-Isopropyl-4,5,6,7-tetrahydro-1,2-benzisoxazole (XVI) was prepared by the method of Johnson and Shelberg (16). The 40 g. of 2-hydroxymethylene-4-isopropylcyclohexanone (XV) obtained above treated as prescribed (16) yielded 32 g. (81%) of crude 5-isopropyl-4,5,6,7-tetrahydro-1,2-benzisoxazole (XVI) as a dark oil, which was used immediately in the next step.

A solution of the above 32 g. of crude 5-isopropyl-4,5,6,7-tetrahydro-1,2-benzisoxazole (XVI) in 100 ml. of ether was treated with a solution of 8 g. of sodium methoxide in 100 ml. of methanol at 0° by the method of Johnson and Shelberg (16). Workup and fractional distillation yielded 18 g. (56%) of 2-oxo-5-isopropylcyclohexanecarbonitrile (Vb), b.p. 121-122°/1 mm., n_D^{26} 1.4795. λ_{max}^{film} 4.45μ (C≡N), 4.54μ (conj. C≡N), 5.80μ (C=O).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.84; H, 8.90; N, 8.39.

2-Methyl-4-isopropylcyclohexanone (XVIII). 2-Benzylthiomethylene-4-isopropylcyclohexanone (XVII) was prepared by the procedure of Ireland and Marshall (17). A solution of 40 g. of 2-hydroxymethylene-4-isopropylcyclohexanone (XV; 0.24 mole; crude product, prepared as de-

scribed above), 31 g. of benzyl mercaptan (0.25 mole; Matheson, Coleman and Bell), and 0.1 g. of p-toluenesulfonic acid monohydrate (0.0005 mole; Matheson, Coleman and Bell) in 250 ml. of benzene was refluxed for 8 hrs., water being removed from the reaction as formed by means of a Dean-Stark trap. The reaction mixture became black soon after refluxing commenced. After cooling to room temperature, the reaction mixture was washed with 50 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to a black residue. Distillation of the residue yielded 44 g. (67%) of 2-benzylthiomethylene-4-isopropylcyclohexanone (XVII), b.p. 130-140°/1 mm. λ_{max}^{film} 6.01, 6.48μ; λ_{max}^{EtOH} 312 mμ (ε 18,300).

A mixture of 44 g. of the above described 2-benzylthiomethylene-4-isopropylcyclohexanone (XVII, 0.16 mole) and 200 g. of W-2 Raney Nickel (41) in 600 ml. of ethanol was stirred and heated at 70° for 1 hr. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated by evaporation under reduced pressure and fractionally distilled to yield 16.5 g. of a product whose IR spectrum (λ_{max}^{film} 2.99μ) indicated reduction of the carbonyl group.

To a stirred mixture of the above 16.5 g. of product and 10.9 g. sodium dichromate dihydrate (0.036 mole) in 100 ml. water (cf. 13) was added 12 ml. of conc. sulfuric acid (0.22 mole) over 30 min. After stirring for an additional 1½ hrs., the two-phase reaction mixture was separated and the aqueous phase was extracted twice with 50 ml. portions of ether. The organic phases were combined, washed with 25 ml. saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was distilled to yield

14.7 g. (40%) of 2-methyl-4-isopropylcyclohexanone (XVIII), b.p. 88-90°/9 mm., n_D^{25} 1.4545. λ_{max}^{film} 5.84μ.

Anal. Calcd. for $C_{10}H_{18}$: C, 77.87; H, 11.76. Found, C, 77.96; H, 11.88.

A 2,4-dinitrophenylhydrazone was prepared which had, after recrystallization from ligroin (b.p. 60-70°), m.p. 104-106°.

Anal. Calcd. for $C_{16}H_{23}N_4O_4$: C, 57.30; H, 6.91; N, 16.71. Found: C, 57.44; H, 6.84; N, 16.62.

Trans-3-penten-2-ol (XIX). A solution of 416 g. of methylmagnesium bromide (2.5 moles) in 2.0 ℓ. of ether was prepared from 355 g. of methyl iodide (2.5 moles; Matheson, Coleman and Bell) and 61 g. of magnesium (2.5 g.-atoms) in the usual manner. The solution was cooled in an ice bath and 175 g. of trans-crotonaldehyde (2.5 moles; Matheson, Coleman and Bell, distilled before use) was added dropwise with stirring over 1 hr. The mixture was stirred for an additional 15 min. and then 250 ml. of water was carefully added with cooling. The ether phase was decanted and the aqueous phase and precipitated salts were washed with 250 ml. of ether. The ethereal solutions were combined, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was distilled to yield 135 g. (70%) of trans-3-penten-2-ol (XIX), b.p. 41-43°/23 mm. (lit. (42), 120°/740 mm.).

Trans-3-penten-2-one (VI). To a solution of 119 g. of trans-3-penten-2-ol (XIX, 1.38 moles) in 200 ml. of acetone cooled in a brine bath was added with stirring under nitrogen over a period of 3 hrs. a

solution of chromic acid prepared from 92.5 g. of chromium trioxide (0.925 mole), 78 ml. of conc. sulfuric acid (1.47 moles) and 280 ml. of water (18). The mixture was then stirred for an additional ½ hr., after which the phases were separated. The aqueous phase was saturated with sodium chloride and extracted with 100 ml. and 50 ml. portions of ether. The ethereal solutions were combined, washed successively with 50 ml. of saturated aqueous sodium bicarbonate and three 50 ml. portions of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and fractionally distilled through a 10 inch vigreux column to yield 47 g. (41%) of trans-3-penten-2-one (VI), b.p. 119-124° (lit. (43), 122-123°/740 mm.). λ_{max}^{film} 5.99μ (conj. C=O), 6.14μ (conj. C=C); λ_{max}^{EtOH} 220 mμ (ε 14,300). The NMR spectrum showed a typical trans-crotyl vinyl proton splitting pattern at δ 6.0-7.5.

General method used for Michael reactions and subsequent cyclizations. Summarized in Table I (p. 64) are the results of various experiments involving the condensations of various β-ketoesters and β-ketonitriles with trans-3-penten-2-one (VI) with varying catalysts and conditions. All experiments (except those carried out in sealed tubes) were carried out in essentially the same manner: in flame- or oven-dried flasks with magnetic stirring under nitrogen, using reflux condensers where appropriate. Workup consisted of neutralizing the base with acetic acid followed by extraction and isolation of the ether-soluble, non-acidic, essentially non-volatile components (i.e., trans-3-penten-2-one (VI) not included) of the reaction mixture and characterization of these components by the usual methods of IR, UV, NMR, TLC and GC. Reactions performed in sealed tubes were carried out by sealing the re-

actants in thick-walled Pyrex tubing while cooled in a dry ice-acetone bath under nitrogen at less than 1 atm. pressure; products were isolated and characterized as for the other reactions.

Reaction of 2-carbomethoxy-4-isopropylcyclohexanone (Va) with N-cinnamylidenepyrrolidinium perchlorate (XXII). A solution of 1.0 g. of 2-carbomethoxy-4-isopropylcyclohexanone (Va, 5 mmoles), 1.5 g. of N-cinnamylidenepyrrolidinium perchlorate (XXII, 5 mmoles) (22) and 1.0 g. of triethylamine (10 mmoles) in 25 ml. of methanol was refluxed under nitrogen for 3 hrs. The solution was cooled and diluted with 50 ml. of water and 50 ml. of ether to give, besides the two liquid phases, a dark gummy residue which was nearly insoluble in ether and in benzene. Isolation of organic material from the ether phase yielded recovered 2-carbomethoxy-4-isopropylcyclohexanone (Va).

4-Methyl-10-carbomethoxy-$\Delta^{1,9}$-2-octalone (XXI). A solution of sodium methoxide in methanol was prepared from 460 mg. of sodium metal (20 mg.-atoms) in 20 ml. of methanol. To the solution were then added, under nitrogen, 2.1 g. of 2-carbomethoxycyclohexanone (15 mmoles; prepared by Dr. Morris Brown by a published procedure (44)) and 1.3 g. of trans-3-penten-2-one (VI, 15 mmoles). The solution was stirred at room temperature for 24 hrs. while the production of α,β-unsaturated ketone was monitored by UV on small aliquots of the reaction mixture; about 20 hrs. was required for the concentration of α,β-unsaturated ketone to reach a maximum (λ_{max} 240 mμ). Acetic acid was then added to neutralize the base in the reaction mixture. The solution was diluted with 25 ml. of water and extracted twice with 25 ml. portions of ether, which were

combined. The ethereal solution was washed with 5 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was dissolved in 3 ml. of ether, cooled in a dry ice-acetone bath with scratching and filtered to yield 1.1 g. of crude product. Recrystallization from ether-ligroin (b.p. 60-70°) yielded, in two crops, 0.90 g. (27%) of 4-methyl-10-carbomethoxy-$\Delta^{1,9}$-2-octalone (XXI), m.p. 62°. $\lambda_{max}^{CHCl_3}$ 5.79μ (ester C=O), 6.01μ (conj. C=O), 6.14μ (conj. C=C); λ_{max}^{EtOH} 239 mμ (ε 13,500); NMR δ 5.97 (singlet; vinyl proton), 3.83 (carbomethoxy protons).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.26; H, 8.16.

A synthesis of 4-methyl-10-carbethoxy-$\Delta^{1,9}$-2-octalone (m.p. 76°) has been reported (19).

4β-Methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{1,9}$-2-octalone (X). A solution of sodium methoxide in methanol was prepared from 700 mg. of sodium metal (30 mmoles) in 30 ml. of methanol. To this solution were then added, under nitrogen, 6.0 g. of 2-carbomethoxy-4-isopropylcyclohexanone (Va, 30 mmoles) and 3.8 g. of trans-3-penten-2-one (VI, 45 mmoles). The solution was heated at 70-75° under nitrogen for 6 hrs., the production of α,β-unsaturated ketone being monitored by UV on small aliquots of the reaction mixture; a precipitate identified as sodium carbonate formed in the reaction mixture soon after heating commenced. The concentration of α,β-unsaturated ketone, as measured by UV, reached a maximum after 4-5 hrs. The reaction mixture was then cooled to room temperature, neutralized with acetic acid and evaporated under reduced

pressure to a viscous residue, which was dissolved in 25 ml. of water and 25 ml. of ether. The phases were separated and the aqueous phase was extracted with 25 ml. of ether, which was combined with the previous organic phase. The ether solution was washed with 25 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure to 7.7 g. of a viscous orange-colored oil. The crude product had a UV λ_{max}^{EtOH} 241 mμ, ϵ = 6900, based on the molecular weight of the desired compound (264.4), corresponding to a yield of desired product of ~ 50% based on a value of ϵ of 13,000 to 14,000. The product was dissolved in 20 ml. of ether and cooled in a dry ice-acetone bath with stirring and scratching, and the mixture was filtered with suction at dry ice-acetone temperature to yield 0.4 g. of crude crystalline product. The mother liquor was chromatographed on 70 g. of silicic acid (Mallinckrodt Chemical Works, 100 mesh, prepared for use by fractional concentration of lower mesh particles by differential sedimentation in water and oven-drying overnight at 110°), being eluted with benzene containing increasing concentrations of ether, and the fractions possessing the IR characteristics of the desired product (ester band at 5.8μ and α,β-unsaturated ketone band at 6.0μ) were combined to give 5.8 g. of partially purified product. The combined fractions were dissolved in 8 ml. of ether and 8 ml. of ligroin (b.p. 30-60°) and cooled in a dry ice-acetone bath with seeding to yield an additional 0.2 g. of crude crystalline product. The crude products were combined and recrystallized from ligroin (b.p. 60-70°) to yield, in two crops, 0.38 g. (5%) of 4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{1,9}$-2-octalone (X), m.p. 72-73°. Recrystallization raised the melting

point to 74°. $\lambda_{max}^{CHCl_3}$ 5.79μ (ester C=O), 6.01μ (conj. C=O), 6.14μ (conj. C=C); λ_{max}^{EtOH} 240 mμ (ε 13,600); NMR δ 5.97 (singlet; vinyl proton), 3.78 (carbomethoxy protons). An analytical sample was obtained by vacuum sublimation.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.35; H, 8.89.

Gas chromatography of the mixture of isomers of 4-methyl-6-isopropyl-10-carbomethoxy-$\Delta^{1,9}$-2-octalone (IXa) on various adsorbents (carbowax, diethyleneglycol succinate (DEGS), silicone oil, silicone gum rubber, UCON polar) gave only partial separation of isomers with the best separation being given by diethyleneglycol succinate (5%) at 210°. This adsorbent furnished a g.c. trace which showed the isomers of IXa as three overlapping peaks. One of these peaks (that representing X, the crystalline isomer described above) was, however, almost completely separated from the other two peaks. Since four structural isomers of octalone IXa are possible (cf. Figure 4, p. 57), the three apparent peaks in the g.c. of IXa may represent the four isomers of IXa; a peak corresponding to the fourth isomer may be buried under the other three peaks.

The g.c. peak corresponding to crystalline isomer X represented about 30% of the total area of the peaks. The total area of the peaks, in turn, represented about a 50% yield of product octalones IXa. After X was crystallized from the reaction product (in 5% yield) the area of the g.c. peak fell to about two-thirds of its original area relative to the other peaks, thus indicating that the actual yield of X may have

been as high as 15%. This conclusion, of course, must be based on the assumption that the fourth, missing peak (isomer of IXa) was not to be found coincident with that of X.

2-Ethylenedioxy-4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{8,9}$-octalin (XXIII). A mixture of 607 mg. of 4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{1,9}$-2-octalone (X, 2.30 mmoles; m.p. 74°), 40 mg. of p-toluenesulfonic acid monohydrate (0.23 mmole; Matheson, Coleman and Bell) and 2.5 g. of ethylene glycol (40 mmoles) in 35 ml. of benzene was refluxed for 14 hrs., water being removed from the reaction mixture as formed by means of a Dean-Stark trap. The reaction mixture was cooled, washed with 10 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure to 789 mg. (~ 100% yield) of crude 2-ethylenedioxy-4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{8,9}$-octalin (XXIII). λ_{max}^{film} 5.79μ (ester C=O); NMR δ 5.3-5.5 (broad; vinyl proton), 3.80 (ethylenedioxy protons), 3.57 (carbomethoxy protons). Distillation of a small part of the crude product afforded an analytical sample, b.p. 130°/0.1 mm.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.88; H, 9.17.

2-Ethylenedioxy-4β-methyl-6β-isopropyl-10β-hydroxymethyl-$\Delta^{8,9}$-octalin (XXIV). To a solution of 770 mg. of 2-ethylenedioxy-4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{8,9}$-octalin (XXIII, 2.3 mmoles; crude product, prepared as described above) in 50 ml. of ether was added 360 mg. of lithium aluminum hydride (9.5 mmoles; Metal Hydrides, Inc.). The mixture was stirred at room temperature for 3 hrs. and was then

cooled in an ice bath and decomposed by the careful dropwise addition of saturated aqueous sodium sulfate. The ether solution was decanted from the precipitated salts and the precipitate was washed with a small amount of ether. The combined ether solution was evaporated under reduced pressure to 662 mg. (95% yield) of crude 2-ethylenedioxy-4β-methyl-6β-isopropyl-10β-hydroxymethyl-$\Delta^{8,9}$-octalin (XXIV). λ_{max}^{film} 2.93μ (OH), 6.0-6.2μ (C=C); NMR δ 5.5-5.7 (broad; vinyl proton), 3.83 (ethylenedioxy protons).

2-Ethylenedioxy-4β-methyl-6β-isopropyl-$\Delta^{8,9}$-octalin-10β-carboxaldehyde (XXV). To a solution of 303 mg. of 2-ethylenedioxy-4β-methyl-6β-isopropyl-10β-hydroxymethyl-$\Delta^{8,9}$-octalin (XXIV, 1.1 mmoles; crude product, prepared as described above) in 2.5 ml. of dry pyridine (distilled from barium oxide) was added 210 mg. of chromium trioxide (2.1 mmoles; dried under vacuum over phosphorous pentoxide) in 7 ml. of dry pyridine (23). The mixture was stirred at room temperature for 4 hrs. Then 15 ml. of ether and 1 g. of Celite was added and the mixture was filtered. The filtrate was evaporated under reduced pressure to a brown oil whose IR spectrum (film) showed absorption at 5.82μ and 6.02μ. The crude product was chromatographed on 15 g. of alumina (Woelm neutral activity grade II), being eluted with benzene containing increasing concentrations of ether. Fractions containing material showing IR absorptions (film) at 3.71-3.75μ (aldehyde C-H) and at 5.82μ (aldehyde C=O) were combined to yield 46 mg. (15%) of crude 2-ethylenedioxy-4β-methyl-6β-isopropyl-$\Delta^{8,9}$-octalin-10β-carboxaldehyde (XXV).

Later chromatography fractions yielded, after distillation, 60 mg. of a compound (XXVI) showing strong IR (film) absorption at 6.03μ with a weaker peak at 6.15μ (transoid α,β-unsaturated ketone). The UV spectrum had λ_{max}^{EtOH} 245 mμ (ε = 10,800 for mol. wt. = 264). The NMR spectrum showed a singlet for the ethylenedioxy protons at 232 c.p.s. and showed no vinyl proton or aldehyde proton absorption. The mass spectrum showed a base peak at m/e 264 (parent peak?) with prominent peaks at 192 and 86.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.71; H, 9.17.

An improved method for the synthesis of 2-ethylenedioxy-4-methyl-6-isopropyl-$\Delta^{8,9}$-octalin-10-carboxaldehyde (XXV) was found to be the following. A solution of 628 mg. of 2-ethylenedioxy-4β-methyl-6β-isopropyl-10β-hydroxymethyl-$\Delta^{8,9}$-octalin (XXIV 2.2 mmoles; crude product, prepared as described above) in 15 ml. of acetone (distilled from potassium permanganate) was cooled in an ice bath while 0.75 ml. of a solution of chromic acid prepared by dissolving 10.0 g. of chromium trioxide and 9.0 ml. of conc. sulfuric acid in 30 ml. of water (18) was added dropwise with stirring over 1 min. The reaction mixture was then stirred at 0° for 10 min., after which the mixture was diluted with 25 ml. of ether, washed successively with 10 ml. of water and 10 ml. of saturated aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation under reduced pressure yielded a crude product whose IR spectrum (film) indicated the presence of some unoxidized starting alcohol. The crude product was then re-oxidized by the above procedure with 0.25 ml. of chromic acid solution being used. Workup as above

yielded 518 mg. (84%) of crude 2-ethylenedioxy-4β-methyl-6β-isopropyl-$\Delta^{8,9}$-octalin-10β-carboxaldehyde (XXV). λ_{max}^{film} 3.73μ (aldehyde C-H), 5.82μ (aldehyde C=O); NMR δ 9.32 (aldehyde proton), 5.5-5.7 (vinyl proton), 3.80 (ethylenedioxy protons). The need for re-oxidation may have been caused by coprecipitation of unused oxidizing agent with Cr(III) salts, making the reagent unavailable for oxidation.

2-Ethylenedioxy-4β,10β-dimethyl-6β-isopropyl-$\Delta^{8,9}$-octalin (XXVII). A solution of 518 mg. of 2-ethylenedioxy-4β-methyl-6β-isopropyl-$\Delta^{8,9}$-octalin-10β-carboxaldehyde (XXVI, 1.9 mmoles; crude product, prepared as described above) and 4.0 g. of hydrazine hydrate (80 mmoles; Matheson, Coleman and Bell, 99-100%) in 30 ml. of diethylene glycol (Matheson, Coleman and Bell, reagent grade) was heated at 120-130° for 1½ hrs. under nitrogen, after which 0.2 g. of sodium hydroxide (5 mmoles) was added (27). Immediately there began an evolution of gas which slackened after about 5 min. The temperature of the reaction mixture was raised to 200° for 1½ hrs. After being cooled to room temperature, the solution was diluted with 125 ml. of water and extracted with 75 ml., 50 ml., and 50 ml. portions of ether. The ether extracts were combined, washed successively with 25 ml. of water and 50 ml. of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on 4.0 g. of alumina (Woelm neutral activity grade II), being eluted with benzene, to yield 421 mg. of crude product which was distilled to yield 246 mg. (50%) of 2-ethylenedioxy-4β,10β-dimethyl-6β-isopropyl-$\Delta^{8,9}$-octalin (XXVII), b.p. 100°/1 mm. NMR δ 5.2-5.3 (broad; singyl proton), 3.80 (ethylenedioxy protons) mass spectrum m/e 264 (M^+), 220, 205, 177, 150,

135, 121, 113 (base peak), 91.

(±) 4β,10β-Dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI). A solution of 246 mg. of 2-ethylenedioxy-4β,10β-dimethyl-6β-isopropyl-$\Delta^{8,9}$-octalin (XXVII, 0.93 mmole) and 2 ml. of 5% aqueous sulfuric acid in 10 ml. of methanol was heated under reflux for 1 hr. The solution was then cooled, diluted with 20 ml. of water and extracted with 20 ml. and 15 ml. portions of ether. The extracts were combined, washed with 10 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was distilled to yield 181 mg. (88%) of (±)-4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI), b.p. 100°/1 mm. The IR spectrum (film) showed strong absorption at 6.00μ (conjugated C=O) with a weaker band at 6.14μ (conjugated C=C); the IR spectrum in carbon disulfide* showed a strong absorption maximum at 5.97μ (1675 $cm.^{-1}$) with a weaker band at 6.14μ (1630 $cm.^{-1}$) (cf. dihydronootkatone, strong maximum at 5.97μ (1675 $cm.^{-1}$) with a weaker band at 6.17μ (1620 $cm.^{-1}$). The UV spectrum had λ_{max}^{EtOH} 241 mμ (ε 15,200). The NMR spectrum showed a singlet vinyl proton absorption at 339 c.p.s. and a complex methyl region (cf. dihydronootkatone (XXVIII), vinyl proton absorption at 335 c.p.s. and a different array of peaks in the methyl region). Mass spectrum m/e 220 (M^+), 178 (base peak), 177, 151, 149, 135, 121, 107, 91.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.82; H, 10.71.

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*Recorded on a Beckman Instruments, Inc., model IR-7.

2-Ethylenedioxy-4-methyl-6-isopropyl-10-carbomethoxy-$\Delta^{8,9}$-octalin (XXIII) - mixture of isomers. The mother liquors from the crystallization of 4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{1,9}$-2-octalone (IXa) were concentrated and distilled to yield a fraction of b.p. 100-120°/0.1 mm. whose IR, UV, and NMR spectra indicated the dominant presence of isomers of 4-methyl-6-isopropyl-10-carbomethoxy-$\Delta^{1,9}$-2-octalone (IXa). A solution of 6.9 g. of this fraction and 0.5 g. of p-toluenesulfonic acid monohydrate in 150 ml. of benzene was refluxed with 15 g. of ethylene glycol for 16 hrs. by the method described above for the all-β isomer of the compound. Workup as described yielded 8.3 g. of crude product. λ_{max}^{film} 5.79μ (ester C=O); NMR δ 5.3-5.7 (broad; vinyl proton), 3.82 (broad; ethylenedioxy protons), 3.58-3.63 (broad; carbomethoxy protons). All attempts to obtain crystalline material from this product under a variety of conditions failed.

2-Ethylenedioxy-4-methyl-6-isopropyl-10-hydroxymethyl-$\Delta^{8,9}$-octalin (XXIV) - mixture of isomers. The 8.3 g. of crude product obtained from the above described preparation of the mixture of isomers of 2-ethylenedioxy-4-methyl-6-isopropyl-10-carbomethoxy-$\Delta^{8,9}$-octalin (XXIII) was dissolved in 100 ml. of ether and treated with 0.78 g. of lithium aluminum hydride by the method described above for the all-β isomer. Workup yielded 6.0 g. of crude product which was chromatographed on 75 g. of silicic acid (Mallinckrodt Chemical Works, 100 mesh, prepared for use as described above). The fractions containing alcohols were eluted with 50/50 ether/benzene (v./v.) and combined to yield 4.1 g. of partially purified product. All attempts to obtain crystalline material under a variety of conditions failed.

2-Ethylenedioxy-4-methyl-6-isopropyl-$\Delta^{8,9}$-octalin-10-carboxaldehyde (XXV) - mixture of isomers. The 4.1 g. of product from the above described preparation of the mixture of isomers of 2-ethylenedioxy-4-methyl-6-isopropyl-10-hydroxymethyl-$\Delta^{8,9}$-octalin (XXIV) was dissolved in 15 ml. of acetone (distilled from potassium permanganate), cooled in an ice bath and treated with 6 ml. of chromic acid solution (18) as described above for the all-β isomer of the compound. Workup yielded 3.0 g. of crude product. λ_{max}^{film} 3.7μ (aldehyde C-H), 5.81μ (aldehyde C=O).

2-Ethylenedioxy-4,10-dimethyl-6-isopropyl-$\Delta^{8,9}$-octalin (XXVII) - mixture of isomers. The 3.0 g. of product from the above preparation of the mixture of isomers of 2-ethylenedioxy-4-methyl-6-isopropyl-$\Delta^{8,9}$-octalin-10-carboxaldehyde (XXV) was dissolved in 50 ml. of diethylene glycol (Matheson, Coleman and Bell, reagent grade) and treated with 15 g. of hydrazine hydrate (Matheson, Coleman and Bell, 99-100%) and 0.5 g. of sodium hydroxide as described above for the all-β isomer. Workup yielded 2.3 g. of crude product. λ_{max}^{film} 5.7-6.4μ (weak); NMR δ 5.0-5.3 (broad; vinyl proton), 3.82 (ethylenedioxy protons).

4,10-Dimethyl-6-isopropyl-$\Delta^{1,9}$-2-octalone (XI) - mixture of isomers. The 2.3 g. of product from the above described preparation of the mixture of isomers of 2-ethylenedioxy-4,10-dimethyl-6-isopropyl-$\Delta^{8,9}$-octalin (XXVII) was treated with 10 ml. of 5% aqueous sulfuric acid and 50 ml. of methanol by the method described above for the all-β isomer of the compound. Workup furnished 1.8 g. of crude product which was fractionally distilled to yield 0.97 g. of product, b.p. 90-100°/1 mm.

λ_{max}^{film} 6.00μ (conj. C=O), 6.18μ (conj. C=C), λ_{max}^{EtOH} 240 mμ; NMR δ 5.58-5.66 (broad; vinyl proton; the appearance of the NMR spectrum was much more similar to that of dihydronootkatone (XXVIII) than to that of 4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI) described above.

Isolation of eremophilone (I). An alumina column was prepared from 1.0 kg. of alumina (Woelm neutral activity grade I) by the slurry method in ligroin (b.p. 30-60°; J. T. Baker Chemical Company reagent grade) to give a column 41 cm. × 6 cm. diam. A solution of 66.6 g. of wood oil of Eremophila mitchelli (Museum of Applied Arts and Sciences, Sydney, N.S.W., Australia) in 200 ml. of ligroin was introduced onto the top of the column and eluted with ligroin with increasing percentages of ethyl ether (Mallinckrodt Chemical Works, anhydrous reagent grade) and subsequently with ether containing increasing percentages of methanol. Pertinent data are shown in Table II.

The IR spectra of the various fractions indicated the initial appearance of carbonyl compounds in fraction 2 and the initial appearance of hydroxylic compounds in fraction 11. Fraction 3 was dissolved in 50 ml. of ether, cooled in a dry ice-acetone bath, seeded with eremophilone and filtered with suction at dry ice-acetone temperature to yield 9.0 g. of crude eremophilone. Recrystallization from methanol yielded, in three crops, 6.45 g. of eremophilone (I), m.p. 38-39° (lit. (1), 41-42°), $[\alpha]_D$ -173° (methanol, c = 0.406) (lit. (1), -207°). $\lambda_{max}^{CHCl_3}$ 5.95μ (conj. C=O), 6.17μ (conj. C=C), 11.17μ (trisubstituted C=C); λ_{max}^{EtOH} 242 mμ (ε 7400) (lit. (45), 241 mμ (ε 7600)); NMR δ 5.63 (triplet, J = 3.6 c.p.s.), 4.72 (doublet, J = 1.0 c.p.s.; terminal methylene pro-

TABLE II

Chromatography of Wood Oil of Eremophila Mitchelli

Fraction	Volume	Eluant	Weight
1	500 ml.	100% ligroin (30-60°)	0.03 g.
2	500	"	0.83
3	500	"	17.45
4	500	"	1.24
5	500	"	0.72
6	500	5% Et_2O/ligroin	0.51
7	500	10 "	1.16
8	500	10 "	1.51
9	500	20 "	1.00
10	500	20 "	0.84
11	500	40 "	0.78
12	500	40 "	0.73
13	500	70 "	0.62
14	500	100% Et_2O	0.83
15	500	"	0.93
16	500	"	0.73
17	1000	5% CH_3OH/Et_2O	8.76
18	500	5 "	14.38
19	500	5 "	1.52
		total	54.57 g.

tons), 1.73 (doublet, J = 1.0 c.p.s.; vinylmethyl), mass spectrum m/e 218 (M^+), 176, 133, 119, 108 (base peak), 91. Yield of eremophilone, 9.7% by weight.

Fractions 4 to 13 were combined (9.11 g.), dissolved in 20 ml. of ether, cooled in a cry ice-acetone bath and seeded with eremophilone to yield only a very small amount of crystalline eremophilone, which was not isolated.

In another experiment, 59.0 g. of wood oil of Eremophila mitchelli was chromatographed on 0.95 kg. of alumina (Woelm neutral activity grade I) with isopentane (Phillips Petroleum Company, pure grade, 99 mole % minimum) being used in place of ligroin. A yield of 5.3 g. of eremophilone (I) (9.0% by weight) was obtained, with the eremophilone being more evenly distributed among fractions eluted with isopentane and ether.

A semicarbazone (XLIV) was prepared and was found to crystallize only with great difficulty, the purest product being obtained by crystallization from benzene-hexane, m.p. 195-200° (lit. (1), 202-203°).

Attempted selective catalytic hydrogenation of eremophilone (I). A mixture of 218 mg. of eremophilone (I, 1.00 mmole; m.p. 38-39°) in 20 ml. of methanol and 50 mg. of 5% palladium on carbon was hydrogenated quantitatively at 1 atm. pressure. Uptake of one equivalent of hydrogen was very rapid, requiring less than one minute. Quick cessation of the reaction by removal of excess hydrogen followed by filtration and evaporation of the filtrate yielded 216 mg. of residue. The IR and NMR spectra of the residue indicated the reduction of both of the C=C double bonds in nearly equal proportion, with the conjugated double bond being reduced at a slightly faster rate.

Tetrahydroeremophilone (XXXV). A mixture of 500 mg. of eremophilone (I, 2.30 mmoles; m.p. 38-39°) in 25 ml. of methanol and 50 mg. of 5% palladium on carbon was hydrogenated at 1 atm. pressure until uptake of two equivalents of hydrogen was observed. Filtration to remove the catalyst followed by evaporation under reduced pressure and distillation yielded 498 mg. (98%) of tetrahydroeremophilone (XXXV), b.p. 100°/1 mm. (lit. (1), 165°/17 mm.), n_D^{25} 1.4883 (lit. (1), n_D^{25} 1.4909). λ_{max}^{film} 5.86μ; mass spectrum m/e 222 (M^+), 207, 179, 153 (base peak), 140, 109. Gas chromatography on 20% carbowax 20M at 210° showed two peaks of approximately equal area, presumably cis and trans isomers of tetrahydroeremophilone (XXXV).

A 2,4-dinitrophenylhydrazone was prepared which had, after recrystallization from ethanol, m.p. 177-178° (lit. (1), 178-179°).

Bromotetrahydroeremophilone (XXXVI). To a solution of 111 mg. of tetrahydroeremophilone (XXXV, 0.50 mmole) in 20 ml. of acetic acid was added 0.02 ml. of 40% aqueous hydrobromic acid (Merck and Co., Inc.) and a solution of 85 mg. of bromine (0.52 mmole) in 1 ml. of acetic acid at room temperature (29). The orange solution gradually faded and became colorless in about 4 min.; after a reaction of 5 min., the solution was diluted with 50 ml. of water and most of the acetic acid was neutralized by the addition with cooling of 40% aqueous sodium hydroxide. The solution was then extracted twice with 50 ml. portions of ether, and the combined ether extract was washed with 50 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was distilled to yield 120 mg. (80%) of bromotetrahydroeremophilone (XXXVI), b.p. 100°/0.4 mm.

λ_{max}^{film} 5.86μ; the fingerprint region of the IR (8-15μ) was very different from that of tetrahydroeremophilone (XXXV). The NMR spectrum showed no absorption downfield from δ 3.0, the region in which α-protons of α-bromoketones would be expected to absorb.

Attempts to dehydrobrominate bromotetrahydroeremophilone (XXXVI). (A) Dehydrobromination by lithium chloride in dimethylformamide. A solution of 120 mg. of bromotetrahydroeremophilone (XXXVI, 0.40 mmole) and 0.60 g. of lithium chloride (14 mmoles; dried under vacuum over phosphorous pentoxide) in 20 ml. of dimethylformamide (Matheson, Coleman and Bell, reagent grade) was heated at 100° under nitrogen for 2 hrs. (30). After cooling to room temperature, the solution was diluted with 50 ml. of water and extracted twice with 25 ml. portions of ether. The ether extracts were combined, washed successively with 25 ml. of water and 25 ml. of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The IR spectrum (film) of the residue showed a strong absorption at 6.00μ (conj. C=O) with a weak absorption at 6.15μ (conj. C=C), indicative of an α,β-unsaturated ketone with a transoid structure. The UV spectrum showed λ_{max}^{EtOH} 239 mμ. The NMR spectrum showed a vinyl proton singlet at 349 c.p.s.

(B) Dehydrobromination with 2,4-dinitrophenylhydrazine in acetic acid. A solution of 160 mg. of bromotetrahydroeremophilone (XXXVI, 0.53 mmole) and 110 mg. of 2,4-dinitrophenylhydrazine (0.55 mole) in 5 ml. of acetic acid was heated to boiling under nitrogen for 15 min. (31). On cooling, a small amount of solid separated (~ 10 mg.) which was recrystallized from ethanol-ethyl acetate to give a crystalline

compound, m.p. 177°, which was undepressed by admixture of tetrahydroeremophilone 2,4-dinitrophenylhydrazone, m.p. 177-178°; the UV spectrum showed λ_{max}^{EtOH} 364 mμ. In addition, a compound was isolated (~ 50 mg.) which had, after recrystallization from ethanol, m.p. 199-203°, and whose UV spectrum showed λ_{max}^{EtOH} 365 mμ; qualitative analysis showed the absence of bromine in the compound. Further investigation of the reaction product failed to yield any indication of the presence of the 2,4-dinitrophenylhydrazone of an α,β-unsaturated ketone (λ_{max} ~ 385 mμ).

Hydroboration of eremophilone (I). To a solution of 200 mg. of eremophilone (I, 0.92 mmole) in 1 ml. of ether maintained at 0° was added under nitrogen one equivalent of disiamylborane (32) in 1 ml. of tetrahydrofuran. The solution was allowed to stand at 0° for 30 min. and then at room temperature for 1 hr., after which 1 ml. of acetic acid was added, and the solution was again allowed to stand for 30 min. The solution was then diluted with 5 ml. of water and extracted with 10 ml. of ether. The ethereal solution was washed with 10 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure to 195 mg. of residue. The IR spectrum (film) indicated extensive reduction of the carbonyl group while the NMR spectrum indicated the presence of product retaining the terminal methylene group.

Attempts to synthesize eremophilone ethylenethioketal (XXXVIII). (A) Without solvent. The procedure of Fieser (33) was followed. To a solution of 100 mg. of eremophilone (I, 0.46 mmole) in 0.15 g. of ethanedithiol (1.6 mmoles; Aldrich Chemical Company) was added 0.1 ml. of

boron trifluoride etherate in ethyl ether (Matheson, Coleman and Bell, practical, 47%) at 0°. The reaction mixture immediately darkened and warmed itself to room temperature. After standing at room temperature for 15 min., the reaction mixture was diluted with 20 ml. of ether, washed successively with 25 ml. of 5% aqueous sodium hydroxide and 25 ml. of water, dried over anhydrous sodium sulfate and evaporated under reduced pressure to yield a dark residue whose IR and NMR spectra showed very little detail but rather indicated extensive degradation of the starting material.

(B) With acetic acid as solvent. The procedure of Fieser (33) was followed. To a solution of 100 mg. of eremophilone (I, 0.46 mmole) and 0.15 g. of ethanedithiol (1.6 mmoles) in 0.5 ml. of acetic acid was added 0.1 ml. of boron trifluoride etherate in ethyl ether at room temperature. The solution gradually darkened with standing over a period of 15 min. Workup of the solution as described above for the reaction without solvent also gave a dark product whose IR and NMR spectra indicated decomposition.

Eremophilol (XL). To a solution of 218 mg. of eremophilone (I, 1.00 mmole) in 5 ml. of methanol was added 100 mg. of sodium borohydride (2.5 mmoles; Metal Hydrides Inc., 98+%) at room temperature. The solution immediately became warm. After 10 min., the solution was diluted with 10 ml. of water and extracted with three 10 ml. portions of ether. The extracts were combined, washed with 10 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure to 220 mg. (100% yield) of crude

eremophilol (XL) (46). λ_{max}^{film} 3.00μ; NMR δ 5.5-5.8 (broad; vinyl proton), 4.67 (terminal methylene protons).

Eremophilol acetate (XLI). A solution of 220 mg. of eremophilol (XL, 1.00 mmole) and 1 ml. of acetic anhydride in 2 ml. of acetic acid was warmed on a steam bath for 30 min. After cooling to 50°, the solution was diluted with 1 ml. of methanol and allowed to stand for 15 min. The solution was then diluted with 25 ml. of water and extracted with three 10 ml. portions of ether. The combined ether extract was washed successively with 25 ml. of water and 25 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was distilled to yield 223 mg. (84%) of eremophilol acetate (XLI), b.p. 110°/0.3 mm. λ_{max}^{film} 5.76, 8.07μ; NMR δ 5.08-5.25, 5.67-5.83 (broad; vinyl proton in α and β isomers of XLI ?), 4.67 (terminal methylene protons).

Dihydroeremophilol acetate (XLII). To a solution of 106 mg. of eremophilol acetate (XLI, 0.41 mmole) in 1 ml. of dry tetrahydrofuran (distilled from lithium aluminum hydride) cooled in an ice bath was added one equivalent of disiamylborane (32) in tetrahydrofuran. The solution was allowed to stand at room temperature for 1 hr., after which 1 ml. of acetic acid was added and the solution was again allowed to stand at room temperature for 1 hr. The solution was then diluted with 10 ml. of water, neutralized to pH 7 with saturated aqueous sodium bicarbonate and extracted with 20 ml. of ether. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The NMR spectrum of the residue indicated partial reduction of

the terminal methylene group and also showed decreased acetyl proton absorption indicating partial reduction of the ester. The residue was then treated with two equivalents of disiamylborane by the same procedure to yield a product whose IR spectrum (film) showed hydroxyl absorption at 2.92μ and also showed loss of the sharp absorption at 6.07μ (terminal methylene group) present in eremophilol acetate. The crude product was dissolved in 1 ml. of acetic acid and 1 ml. of acetic anhydride and then warmed in a water bath to 60° and allowed to stand overnight while cooling to room temperature. To the reaction mixture was then added 1 ml. of methanol to destroy the excess acetic anhydride, and the solution was diluted with 10 ml. of water and neutralized to pH 7 with saturated aqueous sodium bicarbonate. The solution was extracted with 20 ml. of ether and the ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was distilled to yield 62 mg. (58%) of dihydroeremophilol acetate (XLII), b.p. 100°/0.3 mm. λ_{max}^{film} 5.76, 8.08μ; NMR δ 5.08-5.25, 5.67-5.83 (broad, vinyl proton in α ans β isomers of XLII ?).

Tert-butyl chromate oxidation of dihydroeremophilol acetate (XLII). The method of Heusler and Wettstein (34) was used. To a stirred solution of 62 mg. of dihydroeremophilol acetate (XLII, 0.23 mmole) in 3 ml. of carbon tetrachloride was added 1.5 ml. of a solution of tert-butyl chromate (34) prepared from 7.2 ml. of 0.2 M. tert-butyl chromate in carbon tetrachloride, 2.2 ml. of acetic acid and 0.9 ml. of acetic anhydride. The solution was heated at 80° for 9 hrs. The solution was then cooled in an ice bath and 2 ml. of saturated aqueous oxalic acid was added to destroy the excess oxidizing agent and stirring

was continued for an additional 30 min. The phases were then separated and the aqueous phase was washed with 5 ml. of carbon tetrachloride, which was combined with the previous organic phase. The organic phase was washed with 5 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure to a dark oil. The IR spectrum (film) showed strong absorption at 5.77μ with a weak absorption at 5.99μ. The NMR spectrum lacked outstanding features, especially noteworthy being the absence of a strong acetyl proton peak as present in the NMR spectrum of dihydroeremophilol acetate (XLII). Chromatography on silicic acid (Mallinckrodt Chemical Works, 100 mesh, prepared for use as described above) failed to yield any fractions showing more than weak α,β-unsaturated ketone absorption in the IR (6.0μ).

Wolff-Kishner reduction of eremophilone semicarbazone (XLIV) - synthesis of eremophilene and isomeric olefin. The method of Grundon, Henbest and Scott (35) was used. A mixture of 100 mg. of eremophilone semicarbazone (XLIV, 0.36 mmole) and 250 mg. of potassium tert-butoxide (2.2 mmoles; MSA Research Corporation, sublimed) in 5 ml. of toluene was refluxed under nitrogen for 6 hrs. After cooling, the mixture was poured into 25 ml. of 5% aqueous sulfuric acid, shaken, and the resulting phases were separated. The organic phase was washed with 10 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure to a dark oil. The residue was passed through a column of 1 g. of alumina (Woelm neutral activity grade II), being eluted with hexane. The eluant was evaporated

under reduced pressure and distilled to yield 50 mg. (68%) of olefinic product, eremophilene (XLV) (47) and isomeric olefin (XLVI), b.p. 90°/1 mm. λ_{max}^{film} 6.10μ (1639 $cm.^{-1}$), 11.32μ (883 $cm.^{-1}$) ($C{=}CH_2$) (lit. (47), 885, 1642, 1780 $cm.^{-1}$); NMR 4.65 (broad; terminal methylene protons), 5.2-5.6 (broad; vinyl proton). Gas chromatography on 20% silicone oil at 165° showed peaks with retention times of 17.5 and 18.2 min. with areas in the ratio of 4.5:1.

Tert-butyl chromate oxidation of eremophilene (XLV) and isomeric olefin XLVI from eremophilone semicarbazone (XLIV). The method of Heusler and Wettstein (34) was used. To a stirred solution of 63 mg. of eremophilene (XLV) and isomeric olefin XLVI (0.31 mmole; prepared by Wolff-Kishner reduction of eremophilone semicarbazone (XLIV) as described above) in 3 ml. of carbon tetrachloride was added 1.0 ml. of a solution of tert-butyl chromate (34) prepared from 7.2 ml. of 0.2 M. tert-butyl chromate in carbon tetrachloride, 2.2 ml. of acetic acid and 0.9 ml. of acetic anhydride. The solution was heated at 80-85° for 12 hrs. The solution was then cooled to room temperature and 2.5 ml. of saturated aqueous oxalic acid was added to destroy the excess oxidizing agent and stirring was continued for an additional hour. The phases were then separated and the aqueous phase was extracted with 3 ml. of carbon tetrachloride, which was combined with the previous organic phase. The organic phase was washed with 5 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure to a dark oil. Distillation yielded 65 mg. of nearly colorless liquid, b.p. ~ 90-120°/0.5 mm, which showed absorption in the IR (film) at 5.76-5.86μ (broad), 5.97μ and 11.29μ. Thin-layer

chromatography on Silica gel G (Brinkmann Instruments, Inc.) showed several spots. Chromatography on 1 g. of silicic acid (Mallinckrodt Chemical Works, 100 mesh, prepared for use as described above) with elution by cyclohexane containing increasing percentages of benzene yielded several fractions (most of the reaction product) showing IR (film) absorptions at 5.77-5.79μ with little or no absorption at 6.0μ (conjugated C=O) and at 6.0μ and 11.3μ (terminal methylene group). Only one fraction (eluted with benzene), ~ 5 mg., showed strong absorption at 6.00μ (conjugated C=O) but also showed strong absorption at 5.79μ. Further work with this material was deemed unfeasible.

Reduction of eremophilone (I) with lithium aluminum hydride-aluminum chloride - synthesis of eremophilene (XLV) and isomeric olefins. The general method of Broome, et al. (36) was used. To a stirred mixture of 350 mg. of lithium aluminum hydride (9.2 mmoles) in 5 ml. of ether cooled in an ice bath was added 100 mg. of eremophilone (I, 0.47 mmole) in 1 ml. of ether. The reaction mixture was stirred at room temperature for 30 min. and then cooled to 0° while a solution of 1.9 g. of anhydrous aluminum chloride (14 mmoles) in 8 ml. of ether was added over 2 min. The mixture was then refluxed for 1 hr. After cooling in an ice bath, the reaction mixture was decomposed by the careful dropwise addition of saturated aqueous sodium sulfate until a heavy precipitate of salts and a clear supernate was obtained. The ether solution was then decanted and the precipitated salts were washed with 5 ml. of ether, which was added to the decanted solution. The ether solution was washed with 5 ml. of saturated aqueous sodium bicarbonate, dried

over anhydrous sodium sulfate and evaporated under reduced pressure. Distillation yielded 61 mg. (65%) of eremophilene (XLV) (47) and isomeric olefins, b.p. 90°/1 mm. λ_{max}^{film} 5.85μ (1709 cm.$^{-1}$), 6.10μ (1639 cm.$^{-1}$), 11.30μ (885 cm.$^{-1}$) (lit. (47), 885, 1642, 1780 cm.$^{-1}$); NMR δ 5.25-5.67 (broad; vinyl proton), 4.68 (doublet, J = 1.0 c.p.s.; terminal methylene protons). Gas chromatography on 20% silicone oil at 165° showed peaks with retention times of 17.5, 18.1 and 21.2 min. with relative areas of 6.0, 2.3 and 1.0 respectively. The predominant product from this reaction and the predominant product from the reduction of eremophilone semicarbazone (described above) exhibited identical gas chromatographic behavior.

Tert-butyl chromate oxidation of eremophilene (XLV) and isomeric olefin XLVI from lithium aluminum hydride-aluminum chloride reduction of eremophilone (I). The method of Heusler and Wettstein (34) was used. A solution of 61 mg. of olefinic product (XLV and XLVI, 0.30 mmole) from the lithium aluminum hydride-aluminum chloride reduction of eremophilone (I) (described above) in 3 ml. of carbon tetrachloride was treated with 1.0 ml. of tert-butyl chromate reagent as described above for the oxidation of the olefinic product of the reduction of eremophilone semicarbazone (XLIV). The crude product, 57 mg., showed absorption in the IR (film) at 5.78μ (strong) and at 6.00μ (weak). Chromatography on silicic acid (Mallinckrodt Chemical Works, 100 mesh, prepared for use as described above) failed to yield any fractions showing significant α,β-unsaturated ketone absorption in the IR (6.0μ).

Eremophilone oxide (XXIX) was prepared by the procedure of Bradfield, Penfold and Simonsen (1). A solution of 2.60 g. of eremophilone (I) (11.9 mmoles) in 50 ml. methanol was treated by the prescribed method (1) to yield 2.07 g. (74%) of eremophilone oxide (XXIX), m.p. 60-61° (lit. (1), 63-64°), $[\alpha]_D$ -176° (methanol, c = 0.336) (lit. (1), -208°). $\lambda_{max}^{CHCl_3}$ 5.82μ (C=O), 6.10, 11.18μ ($C=CH_2$); NMR δ 4.75 (doublet, J = 1.0 c.p.s.), 2.83-2.97 (epoxy-ring proton).

The mother liquor was extracted twice with 50 ml. portions of ether. The ether extracts were combined, washed with 10 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated to a nearly colorless oil which on crystallization from aqueous methanol yielded an additional 0.09 g. of eremophilone oxide (XXIX), m.p. 60-61°. Total yield, 2.16 g. (78%). Examination of the IR and NMR spectra of the small amount of mother liquor remaining failed to provide any evidence for the presence of an isomeric eremophilone oxide.

Dihydroeremophilone oxide (XXX). An abbreviated procedure for the preparation of this compound has been described (1). A solution of 2.16 g. of eremophilone oxide (XXIX, 9.2 mmoles) in 50 ml. of methanol was hydrogenated at 1 atm. over 50 mg. of 5% palladium on carbon. Uptake of one equivalent of hydrogen required 60 min. The catalyst was then immediately removed by filtration and the filtrate was evaporated under reduced pressure. The residue was crystallized from aqueous ethanol to yield in two crops 2.08 g. (95%) of dihydroeremophilone oxide (XXX), m.p. 50-51° (lit. (1), 53-54°), $[\alpha]_D$ -177° (methanol, c = 0.394) (lit. (1), -205°). $\lambda_{max}^{CHCl_3}$ 5.82μ; NMR δ 2.80-2.90 (broad;

epoxy-ring proton). Hydrogenation for periods of time longer than that required for uptake of one equivalent of hydrogen resulted in reduced yields.

Dihydroeremophilone (XXXI). A modification of a method of Mills, et al. (37) was used. A solution of 2.08 g. of dihydroeremophilone oxide (XXX, 8.8 mmoles) in 40 ml. of acetic acid was stirred at room temperature under nitrogen while 60 ml. of a 0.5 M. solution of acidic (HCl) chromous chloride (48) was added. The solution was stirred at room temperature for $2\frac{1}{2}$ hrs. and then poured into 250 ml. of water. The solution was extracted with three 50 ml. portions of methylene chloride and the extracts were combined. The organic solution was washed successively with 50 ml. of water and 50 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was distilled to yield 1.65 g. (85%) of dihydroeremophilone (XXXI), b.p. 100°/1 mm., n_D^{25} 1.5015, $[\alpha]_D$ -175° (methanol, c = 0.411). λ_{max}^{film} 5.92μ (conj. C=O), 6.16μ (conj. C=C); λ_{max}^{EtOH} 242 mμ (ε 6500); NMR δ 6.43 (triplet, J = 3.9 c.p.s.; vinyl proton); mass spectrum m/e 220 (M^+), 205, 178 (base peak), 153, 149, 135, 121, 109, 107.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.69; H, 11.08.

Attempt to synthesize dihydroeremophilone ethylenethioketal (XXXIX). The method of Fieser (33) was used. To a solution of 45 mg. of dihydroeremophilone (XXXI, 0.20 mmole) and 0.20 g. ethanedithiol (2.1 mmoles, Aldrich Chemical Company) in 0.3 ml. of acetic acid was

added 0.2 ml. of a solution of boron trifluoride etherate in ethyl ether (Matheson, Coleman and Bell, practical, 47%) at room temperature. After standing for 15 min., the solution was worked-up as described above for the attempted synthesis of eremophilone ethylenethioketal (XXXVIII). The IR and NMR spectra of the product showed little detail. Thin-layer chromatography showed several spots. Chromatography on silicic acid failed to yield any material identifiable as dihydroeremophilone ethylenethioketal (XXXIX).

Reduction of dihydroeremophilone (XXXI) with lithium aluminum hydride-aluminum chloride - synthesis of dihydroeremophilene (XXXII) and isomeric olefins. The general method of Broome, et al. (36) was used; 796 mg. of dihydroeremophilone (XXXI, 3.62 mmoles) was reduced with 1.10 g. of lithium aluminum hydride (29 mmoles) and 11.6 g. of anhydrous aluminum chloride (87 mmoles) as described above for eremophilone (I). Workup and distillation yielded 693 mg. (93%) of olefinic product, b.p. 90-95°/1 mm., n_D^{25} 1.4969, $[\alpha]_D$ + 22° (chloroform, c = 0.257). λ_{max}^{film} 5.87, 11.78, 12.17, 12.42μ; NMR δ 5.2-5.6, 5.8-6.1 (broad). Gas chromatography on 20% Carbowax 20M at 150° (1/8" × 6' column, He flow rate 45 cc./min. at 25 p.s.i. He inlet pressure) showed three peaks with retention times of 4.0, 5.8 and 6.9 min. With relative areas of 7.0, 3.6 and 1.0 respectively. The mass spectrum showed a base peak at m/e 163 with prominent peaks at 206 (parent peak, 45% of base peak), 191, 161, 121, 107, 105, 95, 93 and 91.

(-)-4β,10β-Dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI). The method of Heusler and Wettstein (34) was used. To a stirred solution of 669 mg. of dihydroeremophilene (XXXII) and isomeric olefin XXXIII (3.25 mmoles; prepared by the lithium aluminum hydride-aluminum chloride reduction of dihydroeremophilone (XXXI) as described above) in 15 ml. carbon tetrachloride was added 10.3 ml. of a solution of tert-butyl chromate (34) prepared from 7.2 ml. of 0.2 M. tert-butyl chromate in carbon tetrachloride, 2.2 ml. of acetic acid and 0.9 ml. of acetic anhydride. The solution was heated at 55-60° for 12 hrs. The solution was then cooled in an ice bath and 20 ml. of saturated aqueous oxalic acid was added to destroy the excess oxidizing agent and stirring was continued for an additional hour. The phases were then separated and the aqueous phase was extracted with 10 ml. of methylene chloride, which was combined with the previous organic phase. The organic phase was washed with 25 ml. of saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated under reduced pressure to 559 mg. of a brown oil which showed broad carbonyl absorption in the IR (film) with peaks at 5.88μ and 6.00μ.

Chromatography of the oil on 20 g. of silicic acid (Mallinckrodt Chemical Works, 100 mesh, prepared for use by fractional concentration of lower mesh particles by differential sedimentation in water and oven-drying overnight at 110°; column dimensions, 27 cm. × 1.5 cm. diam.) with elution by benzene containing increasing percentages of ethyl ether yielded fractions showing two different α,β-unsaturated ketones: Ketone "A" (eluted with benzene) showed IR absorption (film) at 6.00μ (strong; conjugated C=O) and 6.18μ (weak; conjugated C=C) and

ketone "B" (eluted with 10% ether in benzene) showed absorption at 6.00μ (strong; conj. C=O) and 6.15μ (weak; conj. C=C). Ketone "B" also contained carbonyl-compound impurities absorbing in the IR at 5.7-5.9μ.

Rechromatography of fractions containing ketone "B" on 3 g. of alumina (Woelm neutral activity grade I) with elution by benzene containing increasing percentages of ether yielded 70 mg. of material showing α,β-unsaturated ketone absorption in the IR. Gas chromatography (20% Carbowax 20M, 210°) indicated the presence of a small amount of ketone "A" remaining in the purified ketone "B." Preparative thin-layer chromatography on Silica gel PF (Brinkmann Instruments Inc.) with elution by 10% ether in benzene followed by elution of the adsorbent by ether, concentration of the ethereal solution and distillation yielded 55 mg. of (-)-4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI) (8% based on the total olefinic starting material), b.p. 100°/1 mm., n_D^{25} 1.5089, $[\alpha]_D$ -165° (methanol, c = 0.394). The compound was identical in all its spectral and chromatographic properties with the (±)-4β,10β-dimethyl-6β-isopropyl-$\Delta^{1,9}$-2-octalone (XI) obtained by synthesis from 4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{1,9}$-2-octalone (X), m.p. 74°, prepared as described above.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.90; H, 11.07.

Chromatography fractions containing ketone "A" were combined and rechromatographed on alumina (Woelm neutral activity grade I) with elution by benzene. Distillation of recovered ketone yielded 48 mg. (7% based on the total olefinic starting material) of ketone "A,"

5,10-dimethyl-3-isopropyl-$\Delta^{1,9}$-2-octalone (XXXIV), b.p. 100°/1 mm., n_D^{25} 1.5030, $[\alpha]_D$ -1.4° (methanol, c = 0.360). λ_{max}^{film} 5.99μ (conj. C=O), 6.18μ (conj. C=C); λ_{max}^{EtOH} 241 mμ (ε 14,900); NMR δ 5.60 (singlet; vinyl proton); mass spectrum m/e 220 (M^+), 205, 178 (base peak), 163, 135, 122, 121, 107, 91.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.86; H, 10.99.

2-Ethylenedioxy-5,10-dimethyl-3-isopropyl-$\Delta^{1,9}$-2-octalone (XLVII). A solution of 35 mg. of 5,10-dimethyl-3-isopropyl-$\Delta^{1,9}$-2-octalone (XXXIV) and 0.5 g. of ethylene glycol was heated in 30 ml. of benzene with 10 mg. of p-toluenesulfonic acid as described above for the preparation of 2-ethylenedioxy-4β-methyl-6β-isopropyl-10β-carbomethoxy-$\Delta^{8,9}$-octalin (XXIII). Workup and distillation yielded 30 mg. of product, b.p. 110°/0.2 mm. NMR δ 5.1-5.3 (broad; vinyl proton), 3.83 (ethylenedioxy protons); mass spectrum m/e 264 (M^+, base peak), 221, 178, 141, 91.

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P R O P O S I T I O N S

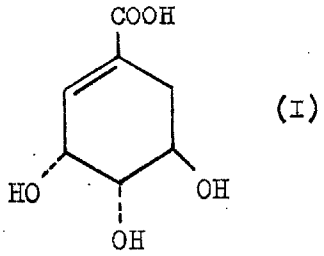
PROPOSITION I

The implication of p-hydroxyphenylpyruvic acid in the biosynthesis of lignin in sugar cane plants is disputed. A refutation of the experimental evidence is given and an experiment to settle the problem is proposed.

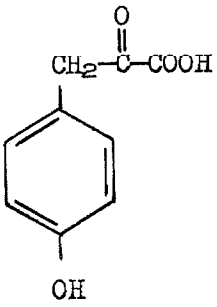
* * * * * * *

In a number of papers and review articles (1-8) and a monograph (9), Nord and Schubert and co-workers have postulated this scheme for the biosynthesis of lignin:

Carbon dioxide
↓
Carbohydrate (glucose)
↓
Shikimic acid (I)
↓
Phenylpyruvic acid and
p-Hydroxyphenylpyruvic acid (II)
↓
Primary lignin building stones
↓
Secondary lignin building stones
↓
Lignin



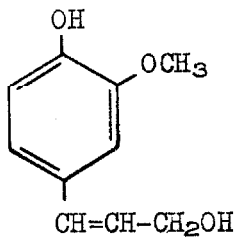
(I)



(II)

The intermediacy of glucose metabolites (demonstrated in Norway spruce) (1) and shikimic acid (demonstrated in sugar cane) (2) have been established with a high degree of probability. The evidence for the intermediacy of phenylpyruvic acid is admittedly uncertain (10); the evidence

regarding p-hydroxyphenylpyruvic acid (II) will be discussed in subsequent paragraphs. The primary building stones are thought to be of the coniferyl alcohol (III) type while the secondary building stones are



(III)

thought to be dimers, trimers, tetramers, or higher polymers of the primary building stones, which then become linked to form lignin (cf. 11).

The experiment upon which the assertion of the intermediacy of p-hydroxyphenylpyruvic acid has been made has been recounted in more than one journal (3-6) and is as follows: p-Hydroxyphenylpyruvic acid-$C^{14}OOH$ was fed to the youngest leaves (cut) of a mature, growing sugar cane plant (Saccharum officinarum). The plant was allowed to grow for 15 days, after which it was cut; the lignin was then isolated as Klason lignin.* 71% of the introduced radioactivity was found in the lignin. Vanillin obtained by degradation of the lignin (oxidation with nitrobenzene in aqueous base, 160°, under pressure) was found to be devoid of activity. This was interpreted as indicating "that the carboxyl carbon

*The preparation of Klason lignin (12) consists in extracting pulverized wood (or sawdust, 60 to 80 or 80 to 100 mesh) with a minimum-boiling alcohol-benzene mixture, then with hot water, followed by treatment with 72% sulfuric acid at 20° and dilution to 3% acid and boiling under reflux; the residue from this treatment is Klason lignin.

of the p-hydroxyphenylpyruvic acid was not randomized with the C_6-C_1 moiety of the lignin building units, thereby implying that the aromatic ring of the acid may be converted into the aromatic rings of lignin, also without randomization (5). Alkaline fusion (KOH, 285°) of the Klason lignin yielded oxalic acid which contained a part of the radioactivity of the isolated lignin (amount unspecified). With this datum, Acerbo, Schubert, and Nord concluded,

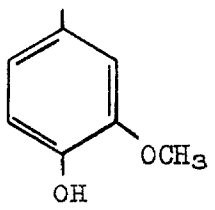
> Therefore, the sidechain of the introduced p-hydroxyphenylpyruvic acid, which contained the radioactivity, may not be involved in the aromatization process but, rather, it too might be retained as a unit, presumably affording a "connecting link" between the several aromatic rings of the lignin polymer. Accordingly it may be concluded that p-hydroxyphenylpyruvic acid is a precursor of lignin building stones and may therefore function as an intermediate on the pathway between shikimic acid, derived from carbohydrates, and the lignin building stones, in the biogenesis of lignin itself. (5)

An alternate fate for p-hydroxyphenylpyruvic acid in this experiment is discounted by the authors (3) in the statement, "In agreement with the findings of Mason and Cronyn (13), the assumption of the formation of a dehydrogenation polymerisate (DHP) is pointless." The experiment referred to (13) consisted in the demonstration that purified polyphenoloxidase isolated from mushrooms did not consume oxygen when incubated with a solution of coniferyl alcohol but that some other (undetermined) enzyme or enzyme system was responsible for the oxygen uptake observed with crude enzyme preparations.

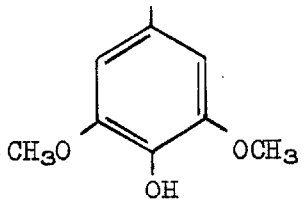
It is proposed that Nord and Schubert and co-workers have not demonstrated the probability that p-hydroxyphenylpyruvic acid is a precursor of lignin in the sugar cane plant. If the acid were converted to any water-insoluble, alcohol-benzene-insoluble, acid-stable compound or polymer (e.g., a dehydrogenation polymer), it would remain with the

lignin during its isolation and would give rise to the observed results. The citing of the work of Mason and Cronyn (13) with polyphenoloxidase does not alter the fact that other enzymes (e.g., peroxidases) are present in plant tissue which have been found to catalyze the oxidation and polymerization of coniferyl alcohol and coniferin (oxidation taking place at the double bond) (14). Thus, it is possible that if p-hydroxyphenylpyruvic acid were converted by the plant to p-hydroxycinnamic acid or p-hydroxycinnamyl alcohol, the p-hydroxyphenylpyruvic acid could be substantially converted to a dehydrogenation polymer, and thus be different from true lignin.

In view of the above cited work of Nord and Schubert and coworkers (1-9), it is interesting to note that Billek (15) and Kratzl and Billek (16) found that p-hydroxyphenylpyruvic acid-3-C^{14} was not converted to lignin in spruce (15) and pine (16). Also, the experiments of Brown, Wright and Neish (17) with p-hydroxyphenylpyruvic acid-3-C^{14} fed to wheat, buckwheat and sage demonstrated the conversion of the acid to guaiacyl and syringyl lignin in wheat but not in buckwheat or sage;



(guaiacyl-)



(syringyl-)

these results they attribute to the unique ability of grasses to convert p-hydroxyphenylpyruvic acid to the corresponding lactic acid, thence to p-hydroxycinnamic acid. It has since been asserted by the Nord school

(9,18) that "since the sugar cane plants employed in our experiments are considered to be 'grasses,' they are thus able to utilize p-hydroxyphenylpyruvic acid for lignin biosynthesis." (17) However, in spite of this argument by analogy, Nord and Schubert and co-workers have not demonstrated the conversion of the disubstituted benzene derivative, p-hydroxyphenylpyruvic acid, to the trisubstituted benzene moieties of lignin (i.e., guaiacyl derivatives).

Therefore, it is proposed that the experiment done by Acerbo, Schubert, and Nord (6) be repeated using p-hydroxyphenylpyruvic acid with C^{14} in the aromatic ring or C-3 of the sidechain rather than in the carboxylate function and that the isolated lignin be oxidized to vanillin to determine the extent of conversion of the acid to the true lignin building units.

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PROPOSITION II

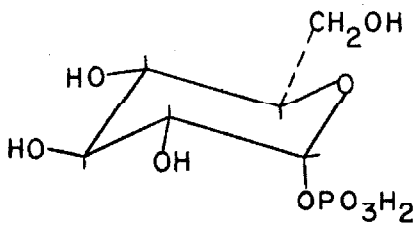
An experiment is proposed to help elucidate the mode of binding of α-D-glucose derivatives by sucrose phosphorylase.

* * * * * * * *

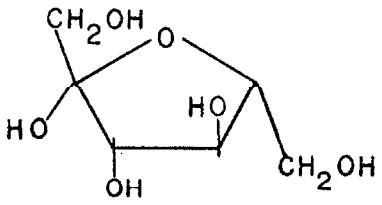
Sucrose phosphorylase, an induced enzyme obtained from Pseudomonas saccharophila, Pseudomonas putrefaciens and Leuconostoc mesenteroides (1,2), reversibly catalyzes the reaction

α-D-glucose-1-phosphate (I) + fructose (II) $\rightleftharpoons$

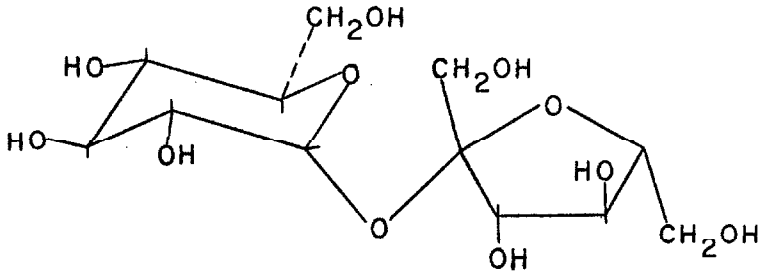
sucrose (III) + inorganic phosphate.



I



II



III

It has been demonstrated that the enzyme can exchange inorganic phosphate (labelled with P^{32}) with the phosphate moiety of α-D-glucose-1-phosphate (1) and that the point of cleavage is the glycosidic carbon-oxygen bond rather than the oxygen-phosphorous bond (O^{18}-tagged phos-

phase) (3). Evidence for a glucose-enzyme complex has been obtained (4) by the demonstration that denatured enzyme isolated from the rapid quenching (boiling methanol) of the enzymatic reaction with uniformly C^{14}-labelled sucrose yielded radioactive protein while an identical experiment using sucrose labelled with C^{14} only in the fructose portion of the molecule failed to yield radioactive protein.

While a number of acceptors other than fructose and phosphate have been found for the glucosyl moiety (e.g., L-sorbose (5), D-xylulose (6), L-arabinose (7), L-arabinulose (7), D-rhamnulose (8)), nothing has been found to be able to substitute for the glucosyl moiety. α-D-Galactose-1-phosphate, α-D-mannose-1-phosphate, α-D-xylose-1-phosphate, and α-L-glucose-1-phosphate have all been found incapable of serving as substrates;* the last would not be entirely unexpected. α-D-Xylose-1-phosphate differs from α-D-glucose-1-phosphate (both pyranoses) only in the absence of C-6, a hydroxymethyl group; it would appear therefore that the C-6 group is essential to the functioning of α-D-glucose-1-phosphate as substrate for the enzyme. In the cases of α-D-galactose-1-phosphate and α-D-mannose-1-phosphate, inversion of configuration of a single carbon atom (C-4 in galactose, C-2 in mannose) results in inability to serve as substrate. The inability of these two compounds to serve as substrates may arise from either of these possibilities: (a) the presence of the hydroxyl group in a configuration different from that of glucose may sterically hinder binding to the active site or (b)

---

*According to Doudoroff (2), the compounds were not substrates when the rates of phosphate production were less than five percent of that observed with α-D-glucose-1-phosphate.

the absence of the hydroxyl group in the proper configuration (i.e., glucose configuration) might make bonding much less effective.

A simple experiment is proposed by which the above possibilities can be distinguished, thus furnishing information about the binding of substrates to the active site of the enzyme. Advantage can be taken of the fact that glucose strongly and reversibly inhibits the enzymic reaction (2), presumably by combination with the active site. An equilibrium dialysis experiment using glucose, isomeric aldohexoses (e.g., galactose, mannose) and the deoxyglucoses (2-, 3-, 4- and 6-deoxyglucose) could be used to determine the association constants for the equilibria

$$\text{aldohexose} + \text{enzyme} \rightleftharpoons \text{aldohexose-enzyme complex}$$

and thus provide data from which inferences about the binding of glucose to the active site of the enzyme. For example, if the association constants for glucose and 4-deoxyglucose were nearly the same but much larger than that for galactose (which has a 4-hydroxyl group in a configuration opposite to that of glucose), the logical conclusion would be that the 4-hydroxyl group of glucose is unnecessary for binding but that inversion of configuration at C-4 results in steric hindrance to binding. In this manner, some specific characteristics of the substrate requirements of sucrose phosphorylase would be obtained.

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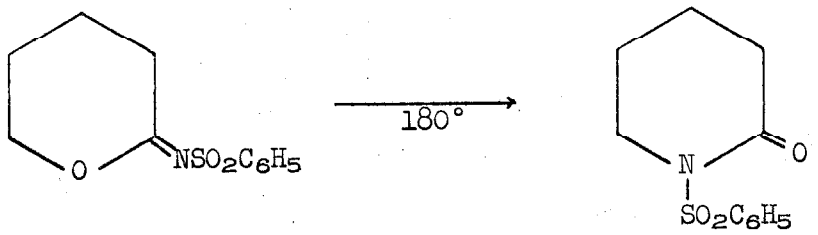
PROPOSITION III

An experiment to elucidate the mechanism of the thermal rearrangement of 2-sulfoniminopyrans to sulfonyl 2-piperidones is proposed.

* * * * * * * *

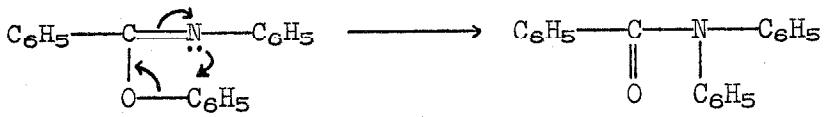
Franz, et al. (1) have observed the thermal rearrangement of N-phenylsulfonyltetrahydropyranon-2-imine (I) to N-phenylsulfonyl-2-piperidone (II). The authors state (1) that "although the conversion of



I II

1 to 2 is formally a rearrangement of the Chapman type, the mechanism is unknown. A polymerization-depolymerization sequence may be operative."

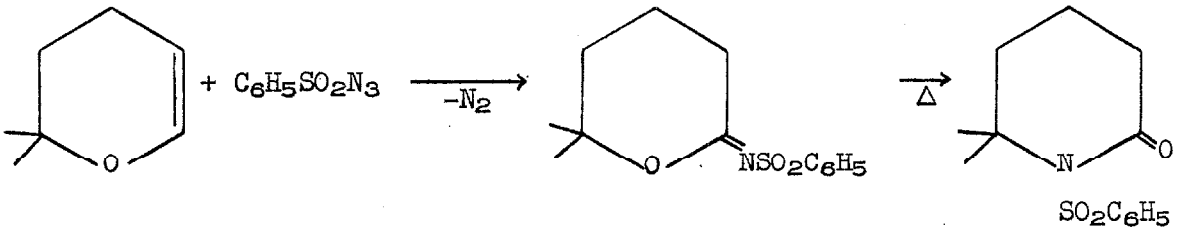
A mechanism for the rearrangement, investigated by Chapman (2) but first reported by Mumm, et al. (3), was proposed by Wiberg and Rowland (4):



While the pyran ring of I would severely restrict the approach of the sulfonimino group to the methylene group α to the ether linkage,

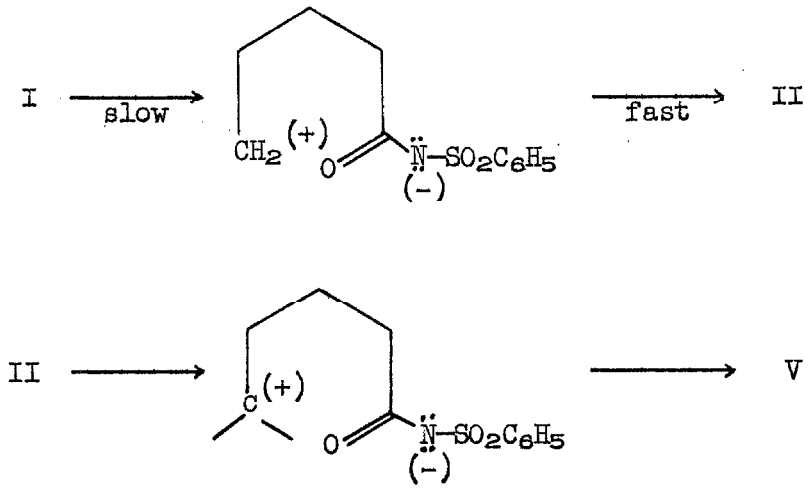
the elevated temperature (180°) might impart sufficient energy to the molecule to make a displacement of the type cited above possible.

It is proposed that the thermal rearrangement of pyranonimine IV, easily accessible (1) from 6,6-dimethyl-(4H)-dihydropyran (III) (5), be attempted.



III IV V

It is expected that if the mechanism cited above is applicable to the rearrangement of I to II, then the rearrangement of IV to a piperidone would be much more difficult owing to steric hindrance by the methyl groups. However, if pyranonimine IV should rearrange more easily than I, a mechanism involving initial scission of the CH_2-O bond could be invoked:



In this case, the intermediate dipolar ion obtained from IV would be expected to be of lower energy relative to IV than that obtained from I relative to I, resulting in a lower activation energy for the initial bond cleavage in IV and therefore a faster rate of rearrangement.

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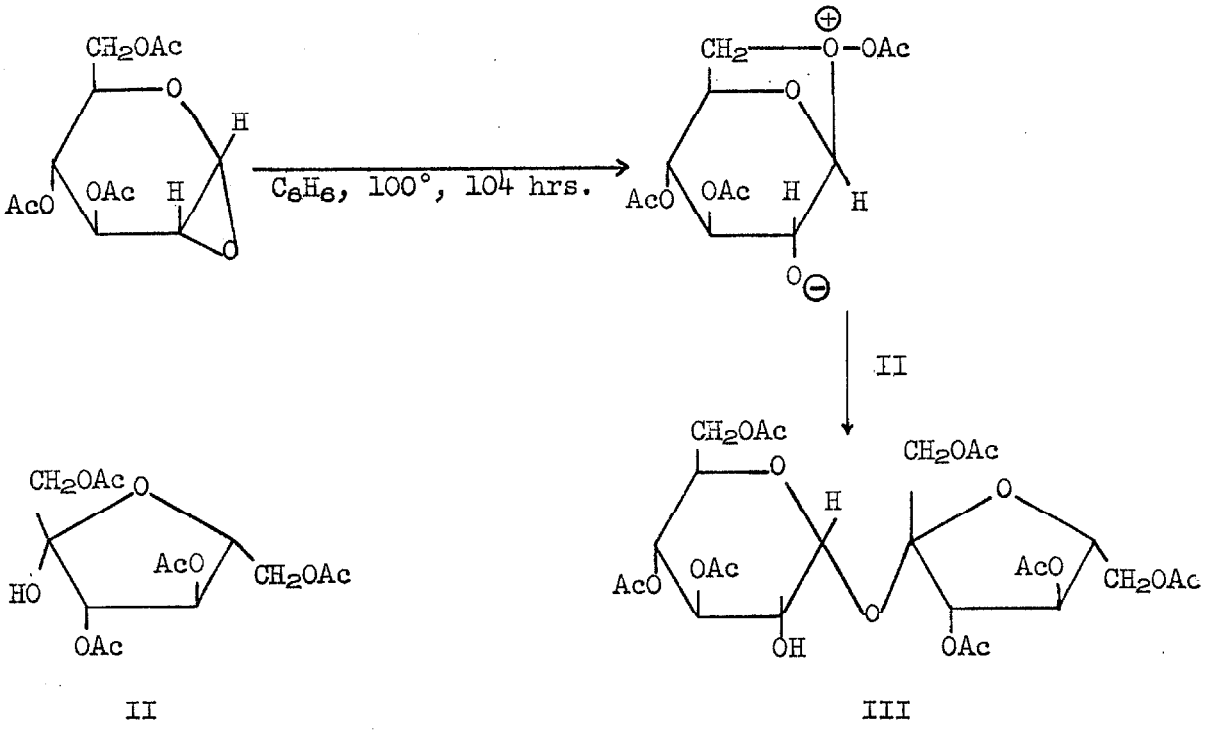
PROPOSITION IV

A method for the synthesis of disaccharides possessing an α-glycosidic linkage is proposed and its application to the synthesis of sucrose is discussed.

* * * * * * * *

While the synthesis of disaccharides possessing a β-glycosidic linkage by the Koenigs-Knorr reaction is well known (1,2), there is no good general method available for the synthesis of disaccharides possessing an α-glycosidic linkage. This lack of a good synthetic procedure is accentuated by the fact that the chemical synthesis of sucrose (isolated as sucrose octa-acetate) by Lemieux and Huber (3) was accomplished in only 5.5% yield by an unfavorable reaction sequence:*

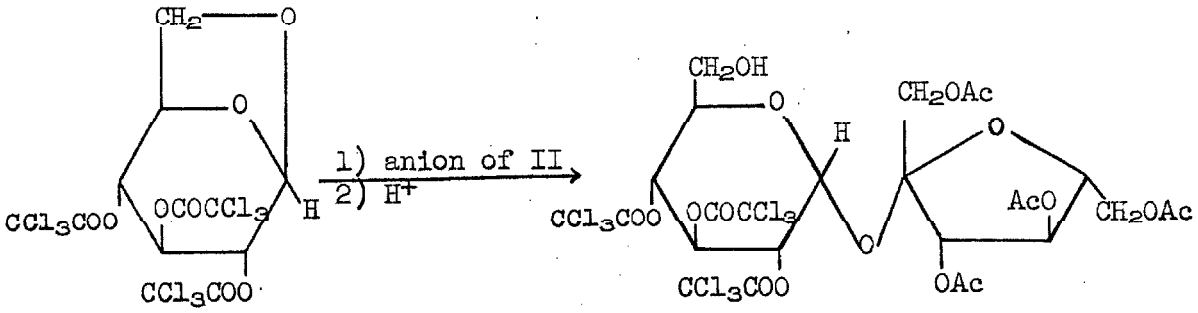


II III

*The structures of the intermediates shown are those of Lemieux and Huber (3).

The mechanism postulated for the reaction (3) first necessitates a conformational change in I to a high energy form in which the $-CH_2OAc$ group is axial and is able to displace the epoxide on C-1. A second displacement by the tetra-O-acetyl-fructose II then yields sucrose hepta-acetate III.

An alternative to this type of reaction sequence, and possibly a general method for the synthesis of α-glycosides of the disaccharide type, is proposed. Displacement of the 1,6-anhydro linkage in a 1,6-anhydro-β-glycoside (e.g., 1,6-anhydro-2,3,4-tri-O-trichloroacetyl-β-D-glucopyranose* (IV)) by the anion of a sugar with one free hydroxyl group (e.g., II) would lead to disaccharides possessing an α-glycosidic linkage (e.g., sucrose derivative V).



IV V

The ease with which the reaction would proceed is open to question. While the reactivity of alkoxides toward 1,6-anhydrosugars is unknown, the reaction would be expected to be facilitated for this reason: 1,6-Anhydrosugars are highly strained compounds and considerable conformational energy would be released by scission of the anhydro linkage,

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*Trichloroacetyl masking groups would eliminate the possibility of neighboring group participation by acetyl groups.

thereby providing a driving force for the reaction. It would be expected that to get the reaction to proceed satisfactorily, moderately vigorous conditions would be necessary, perhaps as vigorous as those used by Lemieux and Huber (3).

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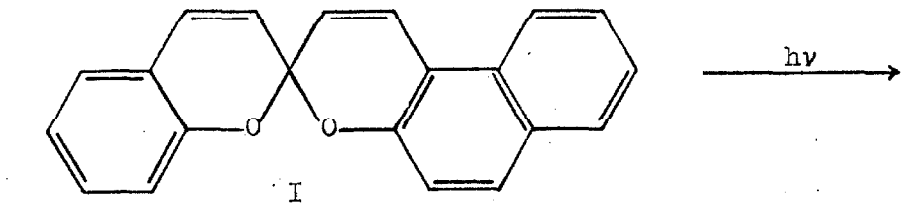
PROPOSITION V

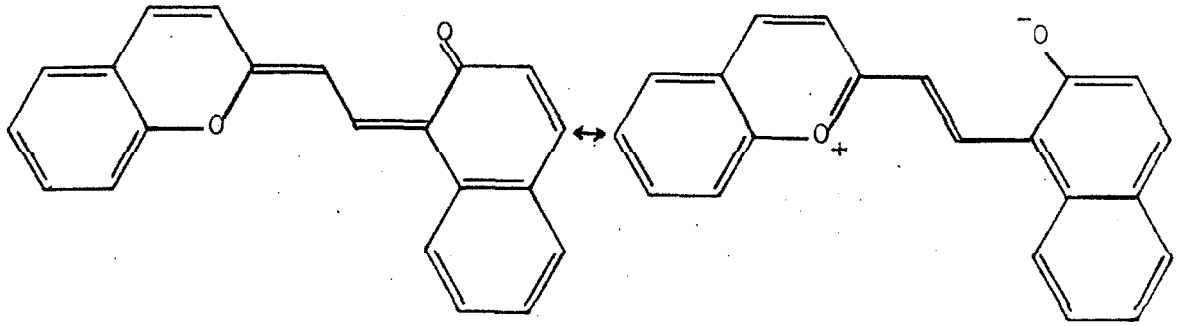
An experiment to demonstrate the ring opening of spiropyrans as an explanation of their thermochromic and photochromic properties is proposed.

* * * * * *

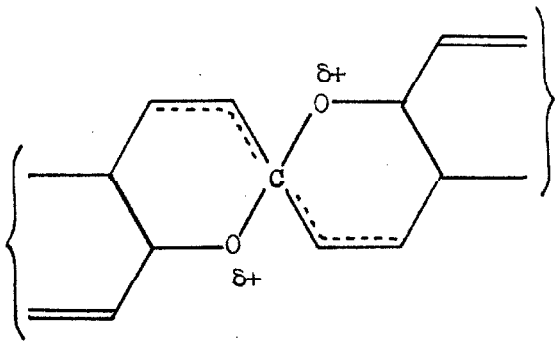
Hirschberg and Fischer (1), have studied the thermochromic and photochromic properties of a number of spiropyrans (e.g., benzo-β-naphthospiropyran, I) and have postulated the colored thermochromic and photochromic products to be "open form" quinonoid-type compounds.



I



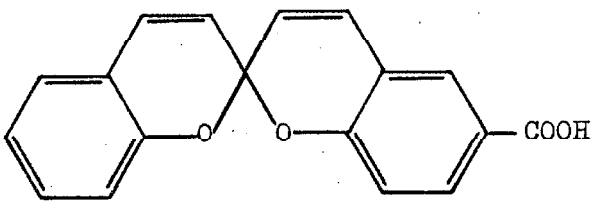
Recently, Becker and Roy (2) have discussed the electronic transitions involved in leading to ring opening. However, it has since been proposed (3) that the thermochromic properties of spiropyrans can be explained by invoking an sp^2-hybridized spiro carbon atom with four bonds to carbon lying in a plane as shown:



This seems highly untenable.

It is proposed that confirmation of the open form be gained by taking advantage of the fact that these spiropyrans are potentially optically active (i.e., possess no mirror plane); on heating (solution) or irradiation, these compounds would pass through planar intermediates on ring scission, thereby destroying optical activity. Racemization would necessitate the breaking of a bond to the asymmetric carbon atom and would therefore corroborate the postulated thermochromic and photochromic products. I propose that an optically active spiropyran be prepared and that it be irradiated as per Hirschberg and Fischer (1) to determine whether there is loss of optical activity on irradiation.

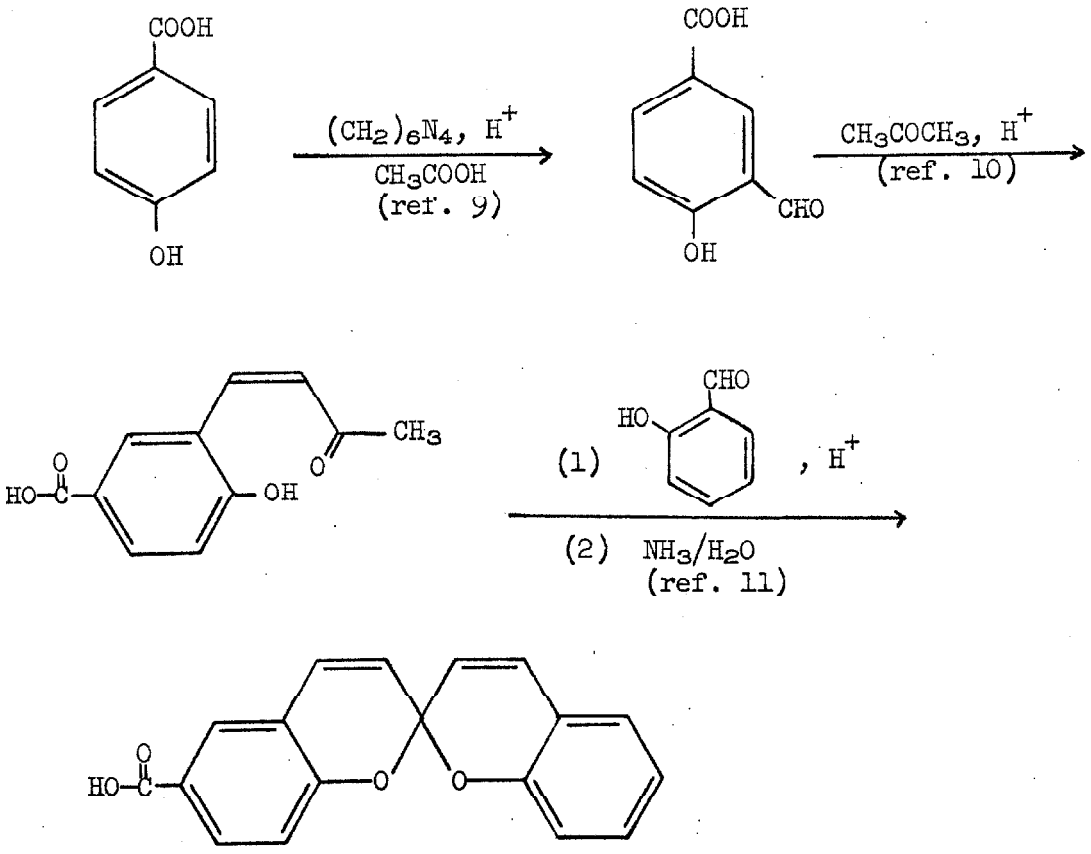
For the purpose of preparing the optical isomers of a spiropyran, I propose that dibenzospiropyran be prepared with a carboxylic acid group substituted on the molecule (II), thereby enabling salt



II

formation with an optically active base and subsequent fractional crystallization in a manner similar to that of Theilacker (4) with bianthrone-3-carboxylic acid quinine salt. Unlike Theilacker's case, in which the salts of the optically active acids could be prepared whereas the free acids could not be obtained optically active because of rapid racemization, this acid (II) should be obtainable in a state of at least partial optical purity. While the activation energy for the transformation of bianthrone to its green form is about 3.5 to 8.0 kcal./mole (5) ($\Delta H = 3.4$ (± 0.3) kcal./mole (6)), that for the photochromic transformation of dibenzospiropyran (which has been observed not to be thermochromic (7)) is much higher, and though not accurately determinable, is higher than that for di-β-naphthospiropyran (11.0 kcal./mole) (8). However, should the optically active acids not be isolable, mutarotation of the salts (cf. 4) would also demonstrate the scission of a bond to the optically active carbon.

The dibenzospiropyran-carboxylic acid (II) can be prepared according to this scheme:



II

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