I The Heat Capacity, Heats of Transition, Fusion and Vaporization, Vapor Pressure and Entropy of 1,1,1 Trifluoroethane

II Synthesis of Potential Antimalarials and Related Compounds

Thesis by

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I wish to express my appreciation to the members of the department for their assistance and guidance, and in particular to thank Dr. Buchman and Dr. Yost for the privilege of working with them.

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The Heat Capacity, Heats of Transition, Fusion and Vaporization, Vapor Pressure and Entropy of 1,1,1 Trifluoroethane

by Horace Russell, Jr., D. R. V. Golding, and Don M. Yost

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Part of the low temperature calorimetric research program of this laboratory has been the careful determination of the entropy of simple compounds in which hindered rotation about single bonds would be expected and for which straightforward and reliable statistical mechanical calculations can be made. Of the compounds available, ethane and similar molecules with two symmetrical groups on a common axis seem best suited for study both because of their convenient boiling points and because their configurations and normal frequencies can be readily determined. The existence of a barrier of about 3000 cal/mole hindering internal rotation in ethane was established by Kemp and Pitzer[1] and Kistiakowsky, Lacher and Stitt[1].

Rubin, Levedahl, and Yost[2] have found a barrier of about 2700 cal/mole for 1,1,1-trichloroethane, CH_3CCl_3. From the results reported in this paper the barrier in 1,1,1-trifluoroethane is about 3400 cal/mole. The fact that the values for these three molecules are the same within experimental error points to the interesting and significant possibility that the barrier is a function of the type of bonds formed by the carbon atom but is independent, to a first approximation at least, of the nature of the attached atoms.

Purification of CH_3CF_3 or Freon "F-143". The material used for the measurements was part of a redistilled sample furnished through the courtesy of Dr. A. F. Benning of the Jackson Laboratory

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[1] J. D. Kemp and K. S. Pitzer, THIS JOURNAL, 59, 276 (1937); G. B. Kistiakowsky, J. R. Lacher, and F. Stitt, J. Chem. Phys., 6, 407 (1938).
[2] T. R. Rubin, B. H. Levedahl, and D. M. Yost, to be published

of the du Pont Co. The material was carefully dried with P_2O_5, pumped to remove a small amount of dissolved air, and then fractionally distilled at a reflux ratio of about 40:1 through a 150 cm vacuum jacketed column packed with glass helices.

From the 316 g sample a 60 g first fraction was taken and a 94 g main fraction, leaving a 152 g last fraction as the most probable impurities are higher boiling. There was no detectable drift in the pressure of 695 ± 2 mm at 224.00° K during the distillation of most of the first fraction and all of the main fraction. The presence of a transition only five and a half degrees below the melting point made it impossible to determine the solid-insoluble liquid-soluble impurity by Raoult's law in a completely satisfactory way. However, several attempts indicated 0.02-0.05 mole % impurity and we believe that this is approximately correct. The final sample was weighed in a small steel bomb from which it was transferred into the calorimeter. The weight of the sample checked to 0.01% on its removal from the calorimeter.

The Heat Capacity and Density. All thermal measurements except that of the heat of vaporization were made in a new adiabatic calorimeter (gold plated, copper calorimeter II). The construction of this calorimeter is similar to one already described[3] except that greater pains were taken to prevent condensation in the filling tube. This tube is wound with No. 30 constantan wire down to the thermal anchor to the ring and the winding is covered with 0.00025

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[3] D. M. Yost, C. S. Garner, D. W. Osborne, T. R. Rubin, and H. Russell, THIS JOURNAL, 63, 3488 (1941).

in. Al foil. A radiation shiled protects the coil in the filling tube from the hydrogen tank. Thermocouple junctions at several points allow close control of the tube temperature. A further change was the installation of condenser plates within the calorimeter with which it is planned to make dielectric constant measurements in the future. A strain-free platinum resistance thermometer of laboratory designation[3] CT-7 was used for temperature measurements. The defined calorie of 4.1833 international joules is used throughout; the ice point is taken as 273.16° K.

The results of the heat capacity measurements are presented in Table 1. There were 1.1183 moles in the calorimeter. Values at even temperatures read from a smooth curve are given in Table II; the points between the transition at 156.35° and the melting point are purely arbitrary and are given because they were assumed to arrive at our heat of fusion. The error in the heat capacities may be as high as 2% at 15° K but decreases rapidly and above about 30° K (except for the transition region) is about ± 0.1%. The temperature interval used may be estimated from the spacing of the points in a single series as the final temperature of one point was the beginning temperature of the next. Corrections for vaporization were made using the observed vapor pressure and density. The maximum correction was 0.11%.

The density was determined by observing the volume of a weighed amount of CH_3CF_3 in a calibrated pyrex bulb immersed in a stirred alcohol bath. The four observed points are reproduced to better than 0.1% by the equation:

TABLE I

The Molal Heat Capacity of 1,1,1 Trifluoroethane
0°C = 273.16°K, molecular weight = 84.044

Series	T, °K	C_p cal/deg/mole
4	12.325	1.543
4	13.213	1.784
5	13.281	1.808
4	14.581	2.253
5	14.625	2.268
4	16.035	2.732
5	16.061	2.741
5	17.729	3.304
4	17.938	3.377
5	19.793	3.988
4	20.195	4.113
5	22.369	4.787
4	22.707	4.892
5	25.084	5.584
4	25.432	5.682
5	27.869	6.311
4	28.067	6.356
4	30.806	6.992
5	30.942	7.023
4	34.078	7.674
5	34.480	7.751
4	37.848	8.354
5	38.730	8.476
4	41.891	8.972
4	46.183	9.611
4	50.726	10.17
4	55.812	10.71
6	57.053	10.84
4	61.044	11.22
6	63.203	11.42
4	66.579	11.73
6	69.698	12.01
6	76.627	12.63
6	83.910	13.26
2	90.895	13.85
6	91.641	13.93
2	98.464	14.51
6	99.542	14.60
2	106.155	15.24
2	113.989	16.01
2	121.957	16.83
2	129.895	17.79
2	137.854	18.94
1	141.705	19.59
2	145.968	20.47
1	146.685	(20.57)[a]
3	151.381	21.87
1	152.137	(22.27)[a]
3	154.090	22.95
3	155.782	61.56
3	156.270	286.97
3	156.766	34.34
1	157.540	41.32
3	158.023	27.71
3	159.713	34.61
1	160.846	116.21
	161.82	M.P.
7	165.407	24.31
3	165.808	24.33
7	170.508	24.43
3	172.001	24.48
7	177.585	24.63
3	179.210	24.68
3	187.032	24.91
3	195.522	25.27
3	203.689	25.51
3	212.446	25.86
3	220.743	26.25

[a] Intermediate temperature not an equilibrium value

TABLE II

The Molal Heat Capacity of 1,1,1 Trifluoroethane
0°C = 273.16°K, molecular weight 84.044

T, °K	C_p cal/deg/mole
15	2.434
20	4.052
25	5.556
30	6.807
35	7.846
40	8.693
45	9.454
50	10.09
55	10.63
60	11.12
70	12.04
80	12.94
90	13.77
100	14.66
110	15.61
120	16.62
130	17.80
140	19.28
150	21.43
156.35	24.56[a]
156.35	Transition
156.35	(22.62)[b]
160	(23.26)[b]
161.82	(23.57)[b]
161.82	m.p.
165	24.31
170	24.43
180	24.70
190	25.01
200	25.37
210	25.76
220	26.21
225.855	b.p.

[a] Extrapolated value

[b] Arbitrary values for purposes of calculation

$d = 1.7374 - 0.00254\ T$ (197°K T 217°K)

The absolute accuracy is estimated to be ± 0.5%.

The Melting Point and the Heats of Transition and Fusion.

The results of the melting point determination are given in Table III.

TABLE III

The Melting Point of 1,1,1 Trifluoroethane
0°C = 273.16°K

Approx. % Melted	Time since energy supplied	$T_{obs.}$, °K
4	1 hr. 49 min.	161.614
27	1 hr. 26 min.	161.772
54	59 min.	161.797
81	58 min.	161.800

M.p. this sample = 161.80 ± 0.02°K

M.p. pure compound = 161.82 ± 0.04°K (-111.34°C)

The only previously reported melting point is -107°.[4]

The heat capacity curve of solid CH_3CF_3 begins to bend upward at about 130°K. The heat capacity rises steadily but gradually until about 155.8° K where it abruptly rises to very high values. At 158° K the heat capacity has decreased to a relatively low value but the melting point of 161.82° K is so close that reliable values cannot be obtained in this region. The observed values are shown in Table I.

[4] F. Swarts, Compt. Rend., 197, 1261 (1933)

It is evident that a transition occurs with a relatively small latent heat; the maximum of the heat capacity curve lies at 156.35 ± 0.1° K which may be taken as the transition point. There seems to be little hysteresis in the transition as no supercooling was observed and the heat capacity measurements were quite reproducible up to 155° K. As some premelting may have occurred any value for the heat of transition is somewhat arbitrary. That given was obtained by drawing a curve through the observed heat capacity up to 159.7° K ignoring the high values at 155.8 - 156.8° K. The heat added in excess of that included under the curve is taken as the heat of transition and is shown in Table IV.

TABLE IV

The Heat of Transition in 1,1,1 Trifluoroethane

Temp. Interval °K	Total heat added to compound cal/mole	$C_p dT$ cal/mole	Transition below starting temp. cal/mole	H Trans. cal/mole
155.352 - 157.205	115.88	45.49	0.21	70.60
155.486 - 157.379	117.43	46.79	0.28	70.92

The two values do not agree well and this is probably because the transition is not quite complete at the upper temperature. The higher value is then more nearly correct and is taken as the heat of transition; from the method of calculation it represents a lower limit. The exact value is of little importance for the entropy calculation as the overall energy input in this region is very precisely known.

The uncertainty in the heat of transition and the fact that the heat capacity of the high temperature form of the solid is not known prevents calculation of a unique value for the heat of fusion. The method of evaluation was as follows: a temperature interval starting below the transition and extending into the liquid range was selected; the heat of transition, 70.92 cal/mole, was subtracted from the total heat added; an arbitrary straight line (dotted in Fig. 1, values in Table II) was drawn from 156.35° to 161.82° K to represent the heat capacity of the high temperature form of the solid and the heat represented by the area under this curve and that absorbed by the calorimeter were subtracted from the total heat. Table V gives the value of the heat of fusion obtained in this way.

TABLE V

The Heat of Fusion of 1,1,1 Trifluoroethane

Tem. Interval °K	Total heat added to compound cal/mole	$\int C_{pd}T$ Including Transition cal/mole	ΔH Fusion at 161.82°K cal/mole
155.002 - 166.876	1832.2	352.2	1480.0
150.045 - 164.953	1896.4	416.4	1480.1
155.486 - 163.866	1747.5	267.5	1480.0
		Aver.	1480

The total elapsed time in the runs shown varied from 1 hr. 45 min. to 8 hrs. 23 min; the measurements were made over a period of two weeks. The melting points in Table IV when combined with the heat of fusion given show a 0.02 mole % impurity. Our observations seem to be best correslated by this value but it is pointed out that by assuming a different amount of impurity and a different heat capacity curve for the high temperature solid the value for the heat of fusion may be changed as much as one hundred calories. The effect on the entropy would be less than 0.02 cal/deg/mole, however.

The Vapor Pressure and Heat of Vaporization. A non-adiabatic calorimeter previously described[3] was used for these measurements. The vapor pressure was observed with a 13.5 mm mercury manometer read against a Gaertner steel meter bar suspended inside the manometer case. The results, corrected for capillary depression[5], temperature of the mercury and to g= 980.665, and given in Table VI. The error in the measurements is believed to be not greater than ± 0.1 mm.

The normal boiling point calculated from the equation is 225.855° K (−47.305° C). The only previously reported value found is −46.8° C[4].

The heat of vaporization measurements were made by collecting the vaporized gas in a thick-walled glass trap cooled in liquid air. A constant pressure was maintained by means of a 20 ℓ. buffer of dry nitrogen separated from the calorimeter system by a mercury

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[5] W. Carwood and H. S. Patterson, *Trans. Faraday Soc.*, *29*, 514 (1933).

TABLE VI

The Vapor Pressure of 1,1,1 Trifluoroethane

0°C = 273.16°K

T. °K	$p_{obs.}$ Int. mm. of Hg	$p_{calc.}$ (a) mm	$p_{calc} - p_{obs.}$ mm
173.614	26.17	26.17	0.00
185.857	70.62	70.58	+ .04
192.430	138.41	138.42	- .01
202.213	213.14	213.16	- .02
208.839	314.91	314.86	+ .05
214.215	423.26	423.27	- .01
218.845	538.79	538.83	- .04
222.542	648.04	648.00	+ .04
225.790	757.62	757.67	- .05

(a) $$\log_{10} P_{mm} = 48.37340 - \frac{2015.675}{T} - 16.81950 \log_{10} T$$

bubbler. The trap containing the condensed gas was sealed off and weighed at room temperature under pressure. In this way the same accuracy was achieved as on substances boiling at room temperature or above. The results are given in Table VII.

TABLE VII

The Heat of Vaporization of 1,1,1 Trifluoroethane

Moles Vaporized	Heat Added cal	Corrections cal	ΔH at 224.40°K and 0.9330 atm cal/mole
0.09356	434.12	- 5.42	4582
.09763	438.93	+ 8.50	4583
		Aver.	4583 ± 5

Calculated from the modified Berthelot equation with P_c = 42 atm[6] and T_c = 344.6° K.[4] Correction for gas imperfection = −180 cal. 4625

The Entropy from Calorimetric Data. The only uncertainty in the calculation of the entropy arises in the transition-fusion region. The method used was indicated in discussing the heats of transition and fusion; it seems a direct and reasonable one. Other methods could be used involving the assumption of a different heat capacity curve for the high temperature solid form and possibly more premelting but the difference in entropy between the two methods would almost surely be less than 0.03 cal/deg/mole. The extrapolation from 12° K to 0° K was made by using a Debye function plus an Einstein function, each for three degrees of freedom. The combined function fit the observed values to at least 25° K within a few tenths of a percent. The entropy calculation is summarized in Table VIII.

The Entropy from Molecular Data. Standard statistical mechanical formulae were used for the entropy calculations. The physical constants given by Birge[7] were used in conjunction with the defined calorie. The moments of inertia were calculated from the results of an unpublished electron diffraction investigation by Mr. William Shand at this Institute. The C-F bond distance is 1.37 ± 0.02 Å, the C-C-F

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[6] Estimated by the method of H. P, Meisener and E. M. Redding, *Ind. Eng. Chem.*, *34*, 521 (1942)

[7] R. T. Birge, *Rev. Mod. Phys.*, *13*, 235 (1941)

TABLE VIII

The Entropy of 1,1,1 Trifluoroethane

0°C = 273.16°K, molecular weight = 84.044

	S cal/deg/mole
0-12.182°K Debye function $O_d = 77.3$	0.548
Einstein function $O_e = 103.1$	.012
12.182 - 156.35°K, graphical	24.222
Transition (70.92/156.35)	.454
156.35 - 161.82°K, graphical	.794
Fusion (1480.0/161.82)	9.146
161.82 - 224.40°K, graphical	8.215
Vaporization (4583/224.40)	20.423
Entropy of real gas at 224.40°K and 709.08 mm (0.9330 atm)	63.814
Correction for gas imperfection[a]	.135
Entropy of ideal gas at 224.40°K and 0.9330 atm.	63.95 ± 0.10
Entropy of real liquid at b.p. of 225.855°K	43.56 ± 0.05
Entropy of ideal gas at 298.16°K and one atm.	66.87 ± 0.10

[a] $S_{ideal} - S_{real} = \frac{27RT_c^3\,P}{32\,T^3\,P_c}$, $T_c = 344.6$°K[4] , $P_c = 42$ atm[6]

angle $112°10^{1} \pm 2°$, and the F–C–F angle $107°32^{1} \pm 2°$. A tetrahedral methyl group with a C–H distance of 1.09 Å was assumed. The principle moments of inertia are $I_x = 159.4 \times 10^{-40}$ gcm^2, $I_y = I_z = 166.7 \times 10^{-40}$ gcm^2. The entropy due to the internal rotation was evaluated from the table of Pitzer and Gwinn[8]; the reduced moment of the methyl group is 5.125×10^{-40} gcm^2. The normal vibrations were assigned from the Raman lines given by Hatcher and Yost.[9] The original notebooks and plates were examined and two slight changes made. There was a typographical error in the lowest frequency published which should be 368 cm^{-1} instead of 358 cm^{-1}. The line 2792 cm^{-1} was assumed to be scattered from the 4047 Å Hg. line; it seems equally reasonable to assign it to the 4358 Å Hg. line with a value of 1025 cm^{-1} and this aids considerably in the analysis. The 1025 cm^{-1} frequency scattered from the 4047 Å Hg. line would overlap another line. By comparison with ethane and 1,1,1 trichloroethane a reliable assignment of the observed frequencies to normal modes can be made. The frequencies and their degeneracies are: 368(2), 541(2), 603(1), 829(1), 968 (1), 1025(2), 1279(2), 1450(1), 1450(2), 2975(1), 3040(2) cm^{-1}. A summary of the entropy calculation is given in Table IX. The best value for the barrier to internal rotation is seen to be 3450 cal/mole.

[8] K. S. Pitzer and W. D. Gwinn, J. Chem. Phys., 10, 428 (1942)

[9] J. B. Hatcher and D. M. Yost, J. Chem. Phys., 5, 992 (1937)

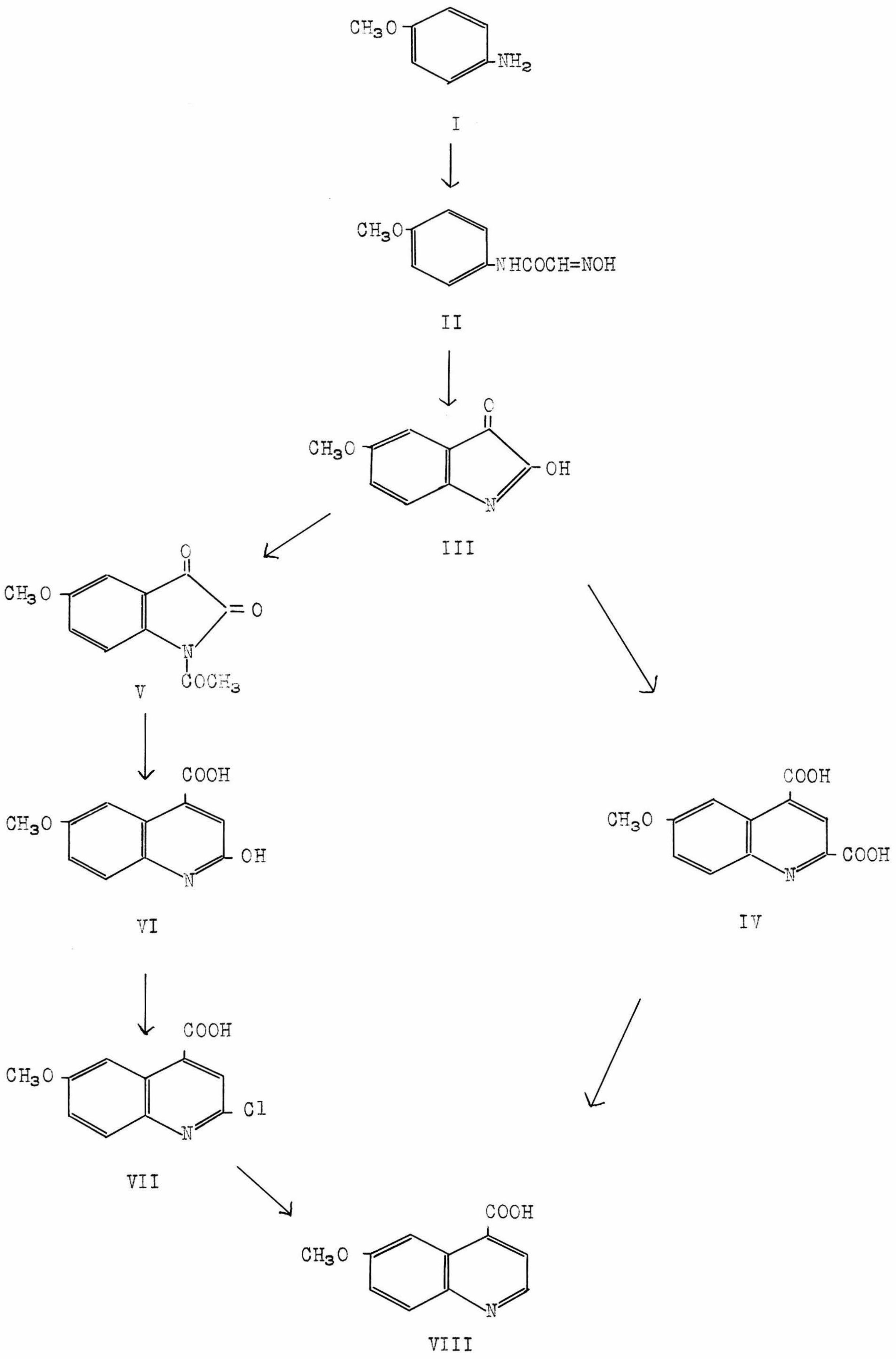
TABLE IX

The Entropy of 1,1,1 Trifluoroethane from Molecular Data

Ideal Gas at 224.40°K and 0.9330 atm

	Entropy cal/deg/mole
Translational	37.925
Rotational (excluding the internal rotation)	22.261
Vibrational	2.297
Entropy from molecular data excluding the entropy of internal rotation	62.48 ± 0.10
Calorimetric entropy	63.95 ± 0.10
Entropy contributed by internal rotation (experimental)	1.47 ± 0.14
Entropy of free rotation	3.28
Entropy of rotation with barrier of:	
3040 cal/mole	1.61
3450 "	1.47
3950 "	1.33

Synthesis of Quininic Acid from 5-Methoxyisatin


CH₃O
NH₂
I
CH₃O
NHCOCH=NOH
II
CH₃O
O
OH
N
III
CH₃O
O
O
N
COCH₃
V
CH₃O
COOH
OH
N
VI
CH₃O
COOH
COOH
N
IV
CH₃O
COOH
Cl
N
VII
CH₃O
COOH
N
VIII

Quininic acid (VIII) has been synthesized in several ways by Kaufmann[1], Rabe[2], Thielepape[3], Halberkann[4] and others. These syntheses involve a number of steps, and the yields are at best only moderate. Ainley and King[5] have considered the syntheses of the closely related cinchoninic acid (quinoline 4-carboxylic acid) and of quininic acid. The conclusion was that the most satisfactory synthesis of cinchoninic acid is that which proceeds through isatin as the intermediate. This synthesis was however, up to the present time, impractical for quininic acid because the corresponding 5-methoxy isatin (III) was not readily available. Hence an investigation of the synthesis of 5-methoxy isatin seemed desirable.

This research showed that by a suitable modification of the Sandmeyer procedure for making isatin and substituted isatins[6] III may be made from II. When II is heated with concentrated sulfuric acid and poured on to ice, following the usual procedure, little or no water-insoluble material is formed, and III cannot be isolated from the mixture. Sandmeyer suggested[6a] that in such cases sulfonation of II or of III or of both occurs. However, it was found that if certain reagents, in particular dimethyl sulfate in equimolar proportions with the sulfuric acid, were added to the sulfuric acid, the ring closure of II to III proceeds in ca. 35% yield.

[1] a) Ber. <u>45</u>, 1805 (1912); b) ibid. <u>51</u>, 116 (1918)

[2] Ber. <u>64</u>, 2488 (1931)

[3] a) Ber. <u>71</u>, 387 (1938); b) ibid. <u>72</u>, 1432 (1939)

[4] Ber. <u>54</u>, 3090 (1921)

[5] Proc. Roy. Soc. <u>B125</u>, 60 (1938)

[6] a) Helv. Chim. Acta <u>2</u>, 234 (1919); b) Organic Syntheses, Coll. Vol. I, p. 327, John Wiley and Sons, New York 1941

Other reagents which may be added with still less satisfactory results include water, methanol, and ethanol. The dimethyl sulfate seems to function mainly as a solvent and diluent since under the conditions of the reaction dimethyl sulfate and sulfuric acid do not react to form methyl sulfuric acid; indeed an appreciable portion of the dimethyl sulfate separates unchanged from the aqueous phase during hydrolysis of the reaction mixture and may be recovered.

The crude reaction product contains, in addition to ca. 35% of III, ca. 10% of the β-oxime of III as might be expected in view of similar observations of Wibaut and Geerling[7] in the case of isatin itself. Use of 100% sulfuric acid in place of the usual 96% minimized formation of the oxime, presumably by eliminating hydrolysis of II, but did not result in improved yields of III. The by-product β-oxime was identified by comparison with a sample prepared from III and hydroxylamine.[8] The two samples had the same pK $\sim$ 9.7 and mixed melting points showed no depression.

Neither o-methoxy isonitrosoacetanilid, the isomer of II which should give the corresponding 7-methoxy isatin on ring closure, nor p-ethoxy isonitrosoacetanilid, homolog of II, give any of the corresponding isatin when treated according to the usual Sandmeyer procedure. However, the ring closure of the latter compound to 5-ethoxy isatin may be accomplished by the above procedure for making III. On the other hand the o-methoxy isonitrosoacetanilid gives negative

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[7] Rec. trav. chim. 50, 47 (1931)

[8] cf. also Halberkann, Ber. 54, 3079 (1921)

results under the same conditions. It is assumed that this is due among other things to the fact that the ring closure can proceed at only half the rate that it may in other cases since only one position ortho to the nitrogen atom is open.

Two methods of preparing VIII from III were considered. Both methods are based on the fact that in aqueous base the isatin ring opens giving the salt of the corresponding o-aminophenylglyoxylic acid. Thus if V, the N-acetyl derivative of III, is treated with dilute base the isatin ring is opened and the acetyl group condenses with the keto group alpha to the carboxylate group to give the salt of 2-hydroxy 6-methoxy quinoline 4-carboxylic acid (VI)[5]. Some hydrolysis of V also occurs, and appreciable amounts of III are always recovered in this process. Treatment of VI with phosphorus oxychloride replaces the hydroxyl group with chlorine to give VII. Yields on this step were low, so the catalytic reduction of VII to VIII was not carried out. However, this step has been carried out by Thielepape[3b] and King and Work[10], as well as by H. Sargent[11]. The other method of synthesis considered consisted in the condensation of III with pyruvic acid[9] in the presence of strong alkali to give 6-methoxy quinoline 2,4 dicarboxylic acid (IV) which may be decarboxylated by heating to 200° in nitrobenzene. The decarboxylation of IV gives

[9] a) Pfitzinger, Jour. f. prakt. Chem. 56, 308 (1897); b) Halberkann, Ber. 54, 3090 (1921); c) Renshaw and Freedman, J. Amer. Chem. Soc. 61, 3320 (1939) (The volume of nitrobenzene given in this article is too small by a factor of ten.)

[10] J. Chem. Soc. 1942 403

[11] private communication

almost exclusively VIII rather than the 6-methoxy quinoline 2-carboxylic acid which might also be expected to form. VIII was identified as the methyl ester, ethyl ester and picrate of the ethyl ester. Decarboxylation of IV may also be carried out in quinoline, but the isolation of VIII is in this case not so convenient. No observable decarboxylation occurred when IV was refluxed with constant boiling hydrochloric acid. For the purposes of this research, the simplest method of purification of the crude VIII was to esterify it and distill the ester.

The second method of preparation, i.e. the condensation of III with pyruvic acid, is preferred. By this method the overall yield of ethyl quininate from p-anisidine is 10-17%. This yield is not an improvement over certain of the other available syntheses, notably those of Thielepape and of Rabe; however, since there are fewer steps, it may be considered to compare favorably with these.

Experimental:

All melting points reported are corrected.

p-methoxy isonitrosoacetanilid (II)

The method was that of Organic Syntheses[6b], starting in this case with 500 gm of p-anisidine (I), practical grade, which gave 671 gm (85%) of crude product, m.p. 170-174° dec. The previously reported[12] m.p. is 183°. The crude product was washed with ethanol

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[12] Brand and Völcker, Arch. Pharmaz. 272, 257 (1934)

and used directly. It may be purified by recrystallization from ethanol, or from acetone and water, m.p. 175-179° dec.

5-methoxy isatin (III)

A suitable flask (e.g. a one liter wide mouth erlenmeyer) was provided with an efficient stirrer and a thermometer which would be immersed in the reaction mixture. A mixture of 120 ml of concentrated sulfuric acid and 205 ml of dimethyl sulfate was placed in the flask and heated to 75°. With vigorous stirring 100 gm of powdered II was added during the course of two or three minutes. In the course of the addition the temperature rose to ca. 85° and the exothermic reaction continued for several minutes after the solid had been added. The temperature was maintained at 85° for 15 minutes after the addition of the solid was completed by cooling or heating as necessary, at no time allowing the reaction mixture to rise in temperature above 85°. The reaction mixture was then cooled rapidly to ca. 40° and poured slowly, with vigorous stirring on to an excess (ca. 1.5 kgm) of ice in such a manner that the temperature of no portion of the resulting aqueous solution was above room temperature. After several hours, the dark red precipitate was filtered off, suspended in water and ammonia added slowly until the aqueous phase was distinctly and persistently alkaline. The precipitate was then filtered and washed, suspended in 320 ml of boiling water and 160 ml of 6 N sodium hydroxide added. The resulting solution was cooled to 10-20° and slowly acidified with hydrochloric acid. The impurities, which precipitate first, were repeatedly filtered off, until the congo red endpoint was reached. A large excess of acid was then added, the solution filtered clear rapidly, and then warmed gently to 60° for 30 minutes. Crystals of III formed. The mixture was cooled and the III collected and washed, weight 38.5 gm (40%), m.p. 192-200°. The previously reported[13] m.p. is 200-202°.

Anal. $C_9H_7NO_3$	Calc.	C 61.1	H 3.95
	Found	C 61.3	H 4.26

The β-oxime of III was prepared in the usual manner with hydroxylamine hydrochloride in ethanol-pyridine, m.p. 242-243° dec. The previously reported[13] m.p. is 234-235°.

Anal. $C_9H_8N_2O_3$	Calc.	C 56.25	H 4.20	N 14.58
	Found	C 56.38	H 4.28	N 14.78

p-ethoxy isonitrosoacetanilid

This was prepared in exactly the same manner as the homologous methoxy compound. 78 gm of practical grade p-phenetidine gave 103 gm (87%) of crude product, m.p. 199-203°. The previously reported[6a] m.p. is 195°.

5-ethoxy isatin

The procedure was the same as that for III except that for 100 gm of p-ethoxy isonitrosoacetanilid it was necessary to use 147 ml of concentrated sulfuric acid and 252 ml of dimethyl sulfate. The yield was 28.3 gm (31%), m.p. 174-182°. Recrystallization from acetonitrile gave a product with m.p. 185-187°.

Anal. $C_{10}H_9NO_3$	Calc.	C 62.82	H 4.75	N 7.33
	Found	C 62.86	H 4.89	N 7.12[a]

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[13] Halberkann, Ber. 54, 3080 (1921)

[a] We are indebted to Mr. C. T. Redeman for a semi-micro Kjeldahl analysis of this compound.

6-methoxy quinoline 2,4 dicarboxylic acid (IV)

400 gm of 85% potassium hydroxide was dissolved in 700 ml of water, cooled to 30° and 38.5 gm of III was dissolved in the solution. The resulting solution was cooled to 20° and with vigorous stirring and cooling, 77 gm of 50% aqueous pyruvic acid was added in such a manner that the temperature remained between 20° and 25°. The mixture was allowed to stand for two days at room temperature during which time the reaction mixture set to a semi-solid mass. Sufficient water was added to dissolve the solid, the solution was cooled, and 12 N hydrochloric acid was added until the first permanent precipitate appeared. 200 ml of glacial acetic acid was then added slowly followed by more hydrochloric acid to bring the pH to the congo red endpoint. The mixture was cooled, the precipitate collected and dried, m.p. 235-243° dec. The previously reported[13] m.p. is 239-240°. This product may be used without further purification for decarboxylation. The dimethyl ester of IV was prepared from the crude product using diazomethane, m.p. 162-163°.

Anal. $C_{14}H_{13}NO_5$	Calc.	C 61.09	H 4.76
	Found	C 60.99	H 4.68

Quininic acid, ethyl ester

A volume of nitrobenzene sufficient to provide 35-40 ml per gram of quininic acid formed was heated to 180° and the crude IV was added with vigorous stirring. The suspension was heated gradually to 200° over a period of 15-20 minutes or until the evolution of gas had ceased. The solution was cooled and the precipitate collected, washed free of nitrobenzene with ether. The crude VIII thus obtained was refluxed for 5 hours with absolute ethanol (8 ml per gm of crude acid) and concentrated sulfuric acid (0.66 ml per gm of crude acid). At the end of this period, one-half to two-thirds of the ethanol was distilled out, the solution cooled and ice and excess 15 N ammonia were added. The precipitate was collected, dried, and distilled in vacuo, b.p. 140°/0.1 mm, m.p. 68-69°, weight 22.5 gm (45%) from 38.5 gm of 5-methoxy isatin. The picrate of the ester melted at 153-154° after recrystallization.

The methyl ester of VIII was prepared from the crude acid by means of diazomethane, m.p. 85.5-86.5°.

<u>6-methoxy 2-chloro quinoline 4 carboxylic acid</u> (VII)

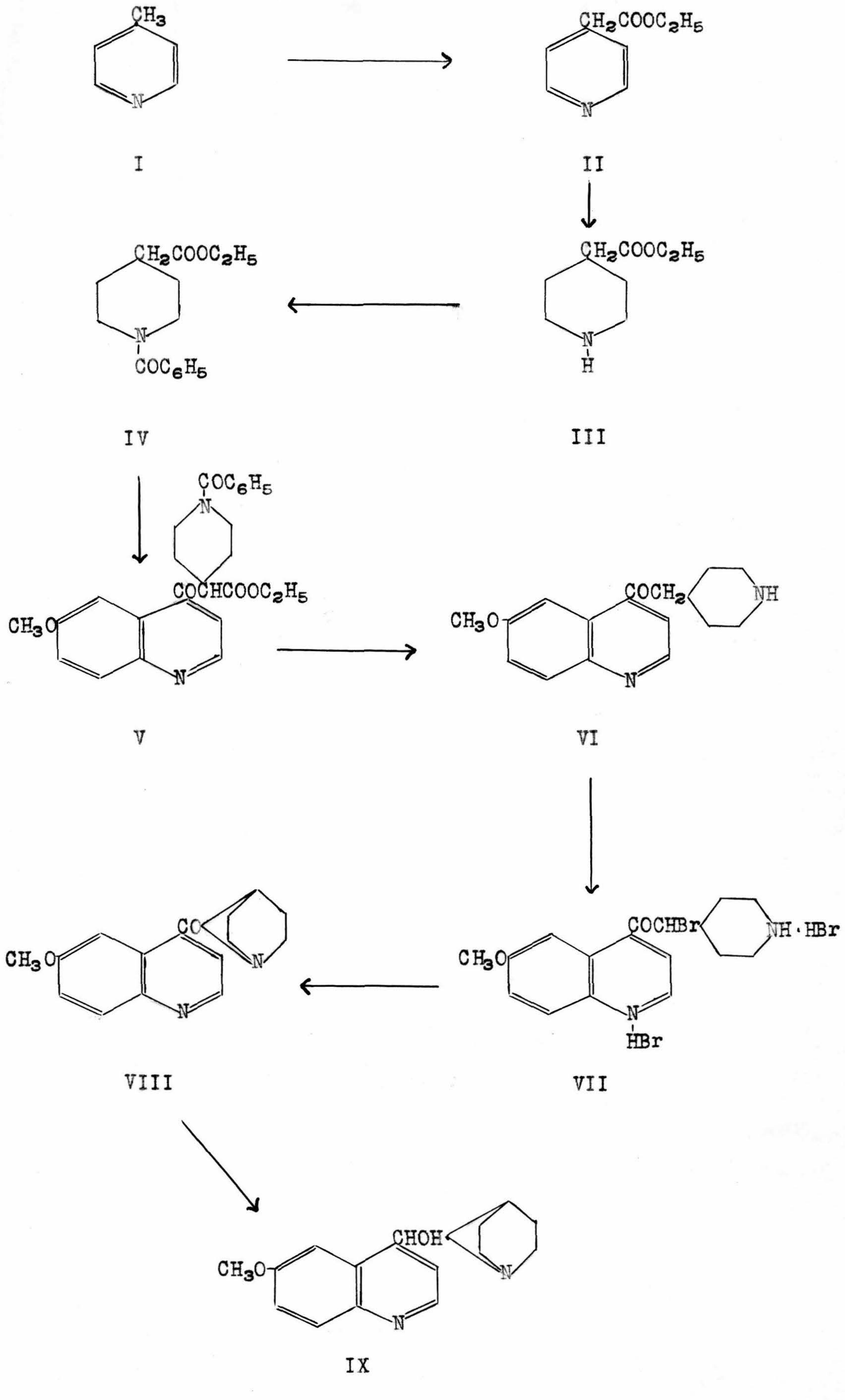
N-acetyl 5-methoxy isatin (V) was prepared by refluxing III in acetic anhydride[13], m.p. 145-147°, b.p. 171°/1 mm. The previously reported m.p. is 144-145°. V was then converted to 6-methoxy 2-hydroxy quinoline 4 carboxylic acid by the method of Ainley and King[5] and of Halberkann[13], m.p. 330° dec. The previously reported[3] m.p. is 330-332°. Then, following Ainley and King's procedure, 2.19 gm of crude VI were refluxed for 30 minutes with 5 ml of phosphorus oxychloride, the mixture cooled and poured into water. The precipitate was collected, reprecipitated from carbonate solution and dried, weight 1.08 gm (43%), m.p. 214-222°. After recrystallization from ethanol the m.p. was 219-221°. The previously reported[3] m.p. is 226-227°.

The methyl ester was prepared from the crude acid by means of diazomethane, m.p. 123.7-124.0°.

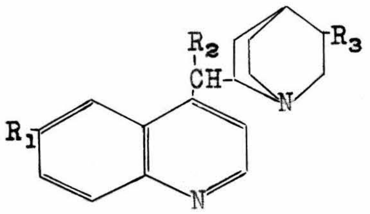
Anal.	$C_{12}H_{10}ClNO_3$	Calc.	C 57.26	H 4.00
		Found	C 57.52	H 4.06

Carbinol Amines Related to Quinine

(6'-methoxyquinolyl 4'-)-(1 azabicyclo (2,2,1) heptyl 7-) carbinol



CH3
N
I
CH2COOC2H5
N
II
CH2COOC2H5
N
H
III
CH2COOC2H5
N
COC6H5
IV
COC6H5
N
COCHCOOC2H5
CH3O
N
V
COCH2
NH
CH3O
N
VI
COCHBr
NH·HBr
CH3O
N
HBr
VII
CO
N
CH3O
N
VIII
CHOH
N
CH3O
N
IX



Rubane $(R_1 = R_2 = R_3 = H)$

Quinine $\left\{\begin{array}{l} R_1 = -OCH_3 \\ R_2 = -OH \\ R_3 = -CH = CH_2 \end{array}\right\}$

Quinine is not a completely satisfactory antimalarial, but it is nevertheless the best such agent known for certain purposes. Since the synthesis of quinine itself does not seem practical at present, not only because of synthetic difficulties but also because of the large number of possible stereoisomers (16), and since carbinol amines structurally similar to quinine are known to have antimalarial activity[1], the syntheses described in this and the following section were carried out. The carbinol IX, which might loosely be called a homolog of quinine was synthesized by the series of reactions shown. The preparation of ethyl-α-pyridyl acetate is discussed in a later section. Compounds III to VIII were prepared by methods similar to those employed in the synthesis of the analogous 6'-methoxyrubanone-9 by Rabe[2] and by Prelog[3].

The structure of the ketone VIII may be considered to have been verified by the mode of synthesis since the reactions are standard ones; however, as further verification, the ultraviolet absorption spectra of the ketone in water at two different pH's were compared with similar spectra of the 6'-methoxyrubanone-9[4,5] (Figs. 1a, 1b). The similarity between the curves is quite satisfactory.

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[1] cf e.g. King and Work, J. Chem. Soc. 1940, 1307

[2] a)P. Rabe and W. Schuler Ber. 76, 318 (1943); b)P. Rabe and G. Hagen Ber. 74, 636 (1941). This article gives a review of work done in this field.

[3] V. Prelog, R. Seimerth, S. Heimbach-Juhasz, P. Stern, Ber. 74, 647 (1941)

[4] prepared by D. R. Howton

[5] Spectra taken by Mrs. M. Howton

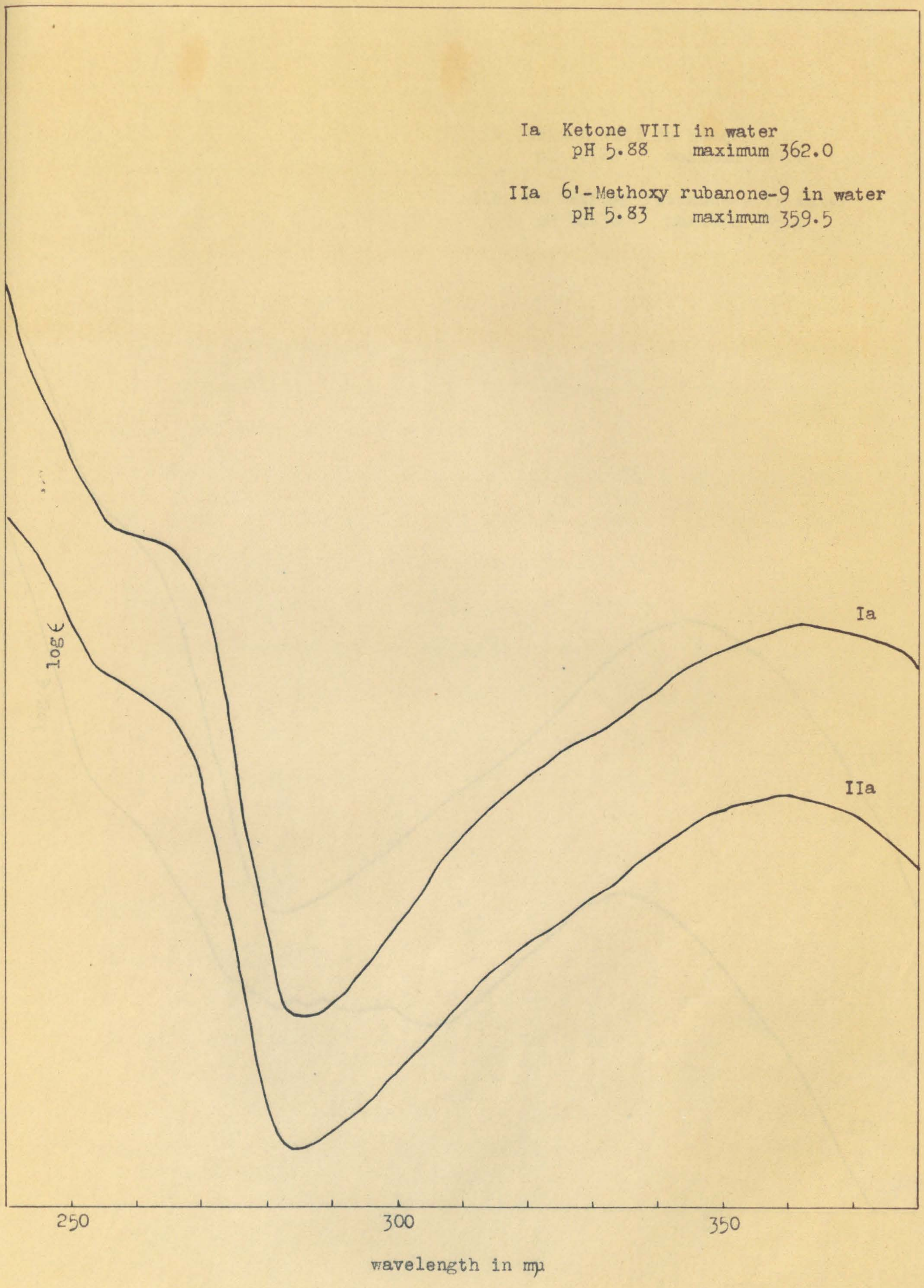
Ia Ketone VIII in water
pH 5.88 maximum 362.0
IIa 6'-Methoxy rubanone-9 in water
pH 5.83 maximum 359.5
log ε
Ia
IIa
250
300
350
wavelength in mμ

Fig. 1 a

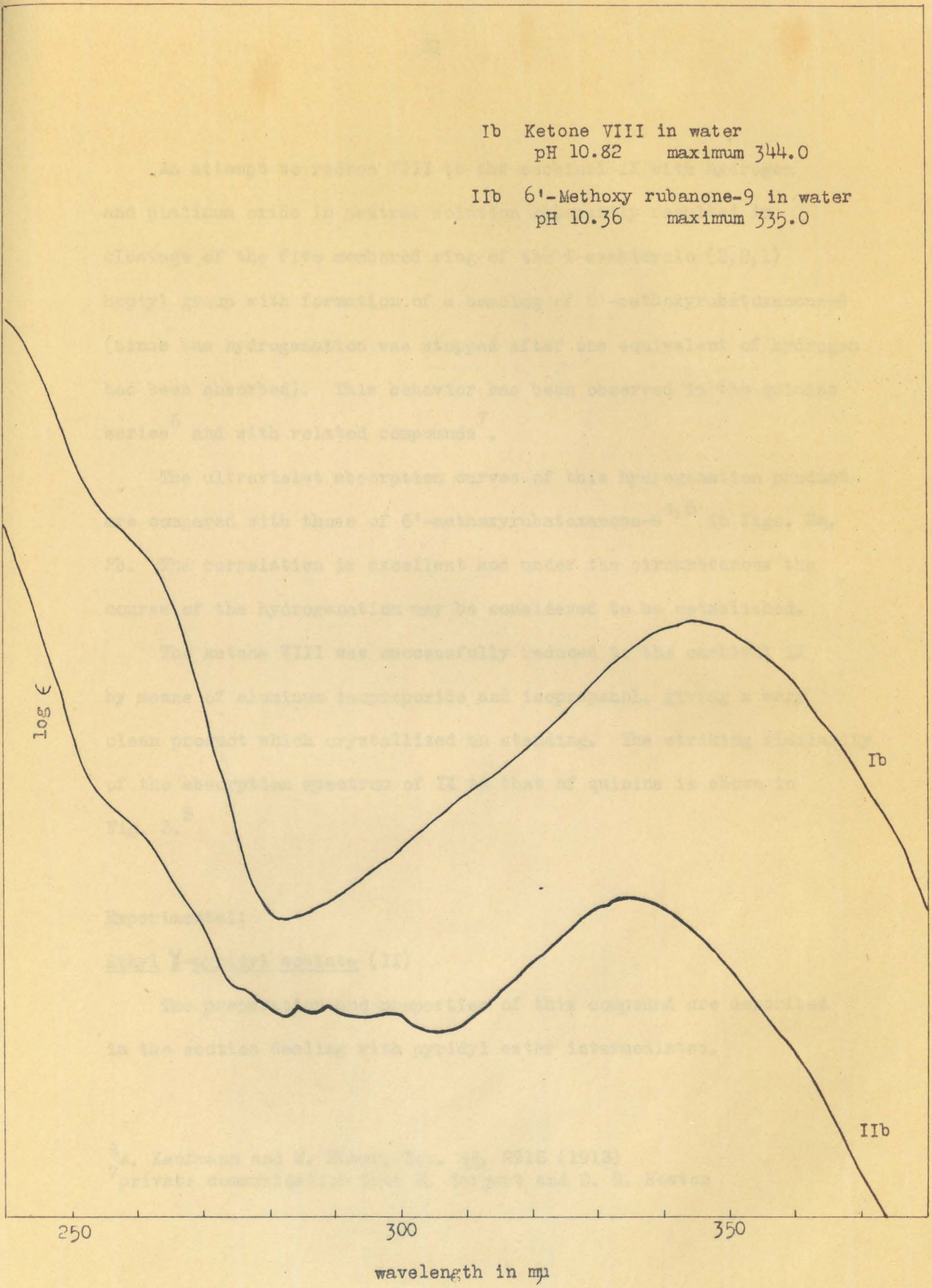
Ib Ketone VIII in water
pH 10.82 maximum 344.0
IIb 6'-Methoxy rubanone-9 in water
pH 10.36 maximum 335.0
Ib
IIb
log ε
250
300
350
wavelength in mμ

Fig. 1 b

An attempt to reduce VIII to the carbinol IX with hydrogen and platinum oxide in neutral solution apparently resulted in cleavage of the five membered ring of the 1-azabicyclo (2,2,1) heptyl group with formation of a homolog of 6'-methoxyrubatoxanone-9 (since the hydrogenation was stopped after one equivalent of hydrogen had been absorbed). This behavior has been observed in the quinine series[6] and with related compounds[7].

The ultraviolet absorption curves of this hydrogenation product are compared with those of 6'-methoxyrubatoxanone-9[4,5] in Figs. 2a, 2b. The correlation is excellent and under the circumstances the course of the hydrogenation may be considered to be established.

The ketone VIII was successfully reduced to the carbinol IX by means of aluminum isopropoxide and isopropanol, giving a very clean product which crystallized on standing. The striking similarity of the absorption spectrum of IX to that of quinine is shown in Fig. 3.[5]

Experimental:

Ethyl γ-pyridyl acetate (II)

The preparation and properties of this compound are described in the section dealing with pyridyl ester intermediates.

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[6] A. Kaufmann and M. Huber, Ber. 46, 2913 (1913)
[7] private communication from H. Sargent and D. R. Howton

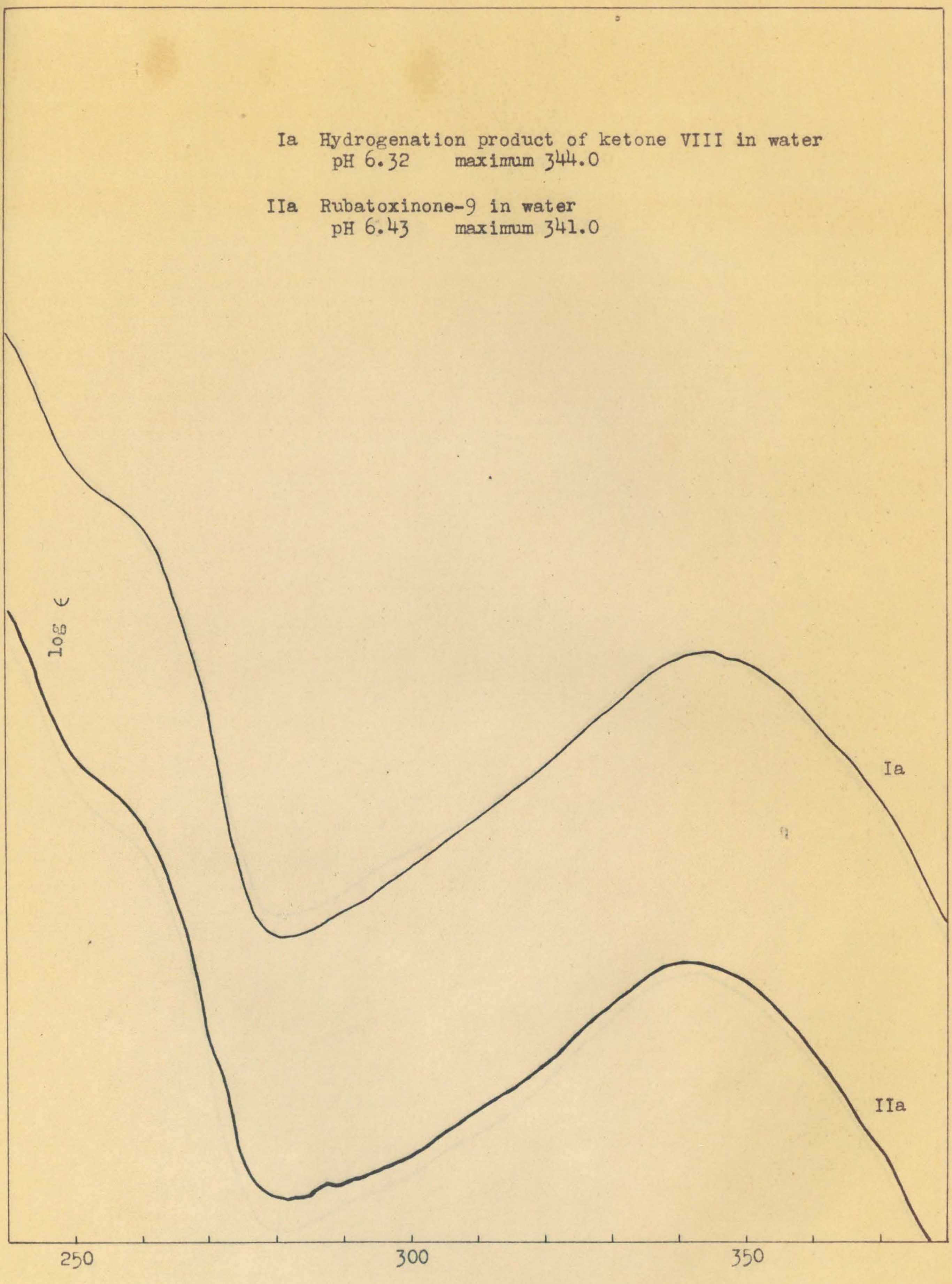

Ia Hydrogenation product of ketone VIII in water
pH 6.32 maximum 344.0
IIa Rubatoxinone-9 in water
pH 6.43 maximum 341.0
log ε
Ia
IIa
250
300
350
wavelength in mμ

Fig. 2 a

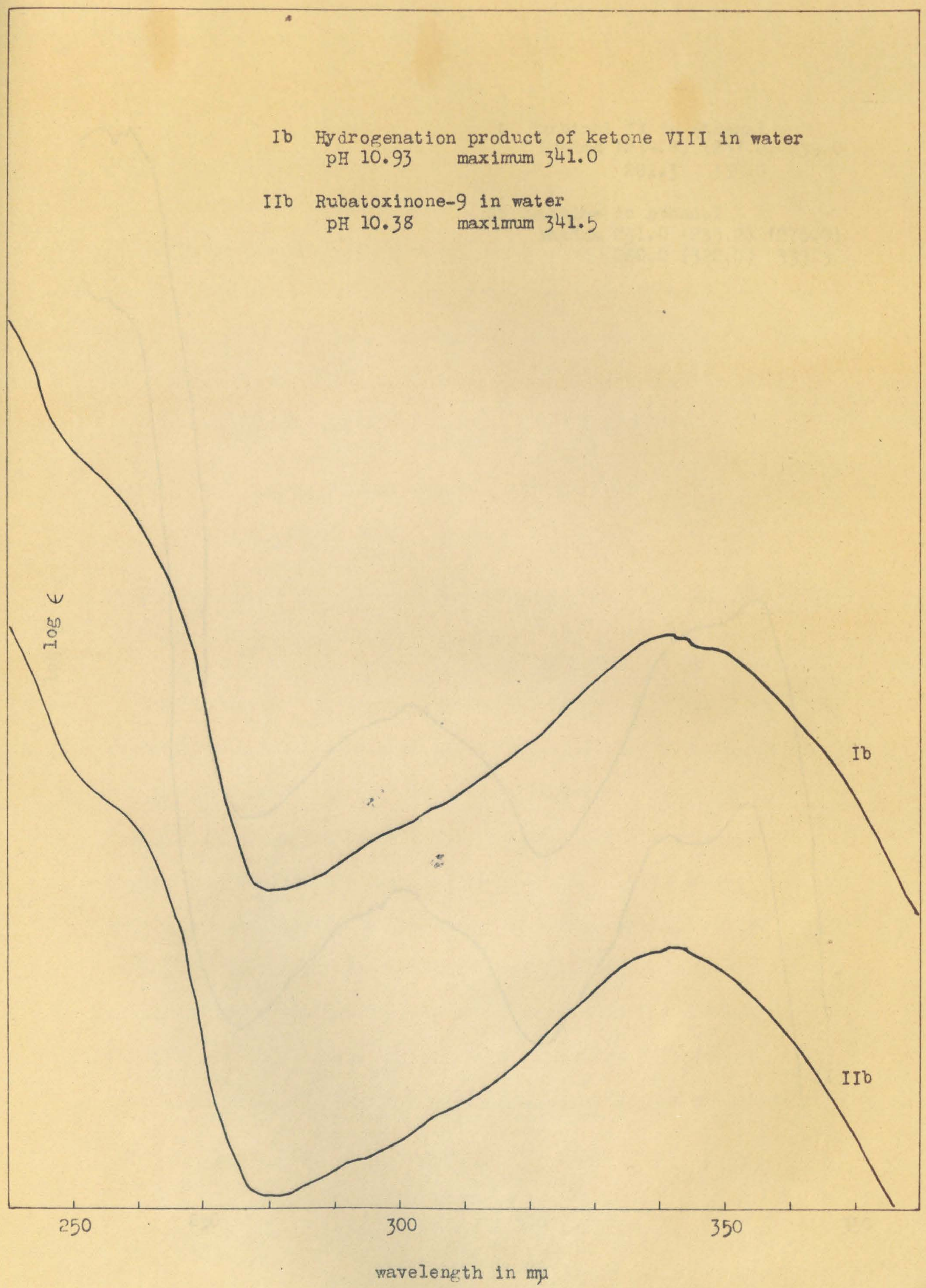

Ib Hydrogenation product of ketone VIII in water
pH 10.93 maximum 341.0
IIb Rubatoxinone-9 in water
pH 10.38 maximum 341.5
log ε
Ib
IIb
250
300
350
wavelength in mμ

Fig. 2 b

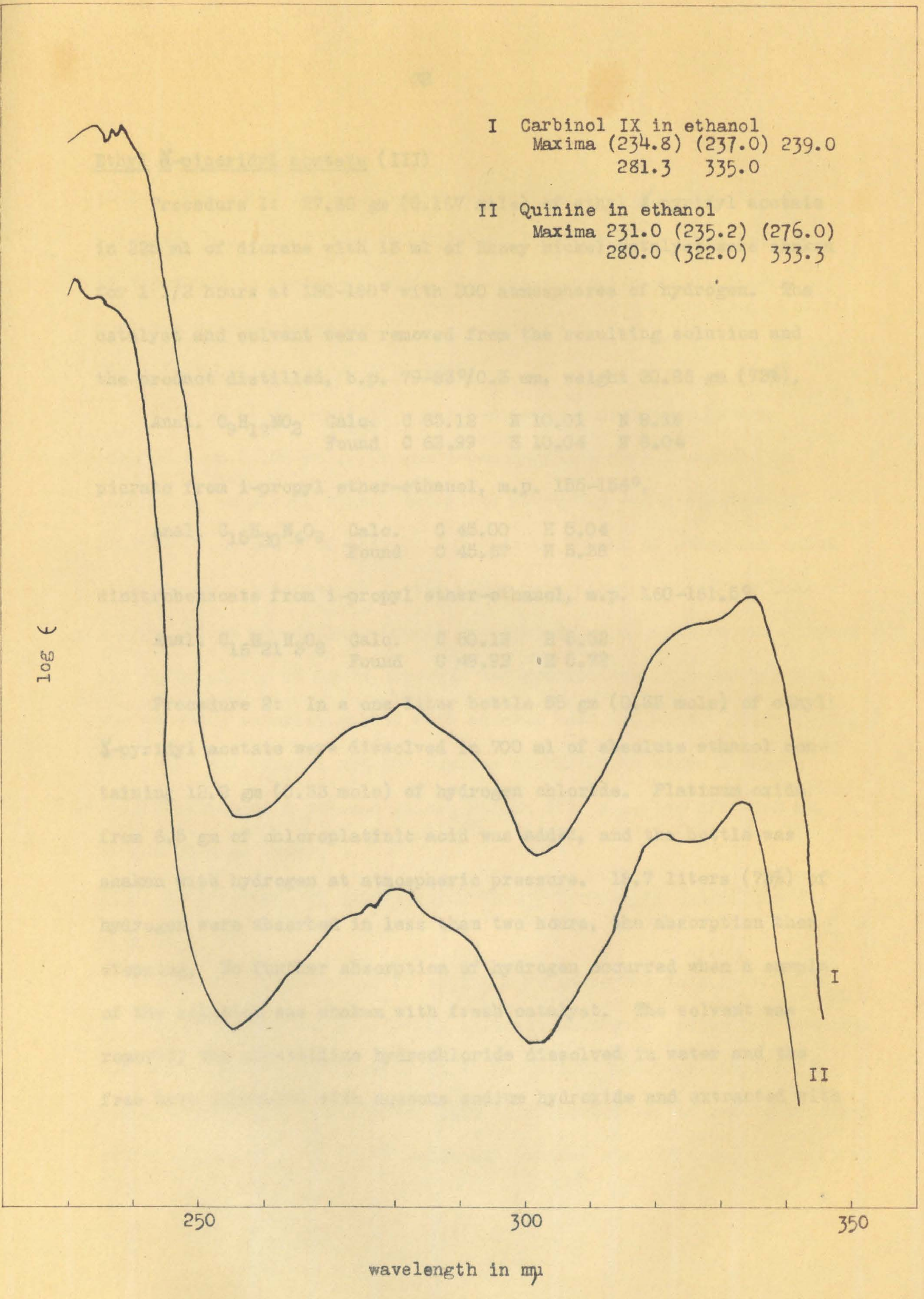

I Carbinol IX in ethanol
Maxima (234.8) (237.0) 239.0
281.3 335.0
II Quinine in ethanol
Maxima 231.0 (235.2) (276.0)
280.0 (322.0) 333.3
log ε
I
II
250
300
350
wavelength in mμ

Fig. 3

Ethyl γ-piperidyl acetate (III)

Procedure 1: 27.63 gm (0.167 mole) of ethyl γ-pyridyl acetate in 225 ml of dioxane with 13 ml of Raney nickel catalyst were shaken for 1 1/2 hours at 180-190° with 200 atmospheres of hydrogen. The catalyst and solvent were removed from the resulting solution and the product distilled, b.p. 79-83°/0.3 mm, weight 20.86 gm (73%),

Anal. $C_9H_{17}NO_2$ Calc. C 63.12 H 10.01 N 8.18
Found C 62.99 H 10.04 N 8.04

picrate from i-propyl ether-ethanol, m.p. 155-156°,

Anal. $C_{15}H_{20}N_4O_9$ Calc. C 45.00 H 5.04
Found C 45.67 H 5.38

dinitrobenzoate from i-propyl ether-ethanol, m.p. 160-161.5°.

Anal. $C_{16}H_{21}N_3O_8$ Calc. C 50.12 H 5.52
Found C 49.92 H 5.72

Procedure 2: In a one liter bottle 55 gm (0.33 mole) of ethyl γ-pyridyl acetate were dissolved in 700 ml of absolute ethanol containing 12.2 gm (0.33 mole) of hydrogen chloride. Platinum oxide from 6.5 gm of chloroplatinic acid was added, and the bottle was shaken with hydrogen at atmospheric pressure. 18.7 liters (75%) of hydrogen were absorbed in less than two hours, the absorption then stopping. No further absorption of hydrogen occurred when a sample of the solution was shaken with fresh catalyst. The solvent was removed; the crystalline hydrochloride dissolved in water and the free base liberated with aqueous sodium hydroxide and extracted with ether. The ether solution was dried and distilled giving a main fraction, b.p. 90-95°/0.5 mm weight 35.3 gm (62.5%). This method of reduction is preferred since subsequent experiments indicated that the product is purer.

Ethyl γ-(N-benzoyl piperidyl) acetate (IV)

61.7 gm (0.36 mole) of ethyl γ-piperidyl acetate together with 85.5 gm (1.08 mole) of anhydrous pyridine were dissolved in 1600 ml of anhydrous ether, heated to refluxing and a solution of 56.2 gm (0.40 mole) of benzoyl chloride in 300 ml of ether was added with vigorous stirring at a rate which maintained a steady reflux. A crystalline precipitate formed immediately. The mixture was stirred and refluxed for 22 hours, cooled, the precipitate filtered off and the ethereal solution washed with aqueous base and acid. After drying, the ether was removed and the residue distilled in vacuo giving a main fraction of a viscous golden yellow oil, b.p. 184-189°/0.2 mm, weight 93.4 gm (94%).

Ethyl α-(γ-(N-benzoyl piperidyl))β-keto-β-(6-methoxy quinolyl 4-) propionate (V)

1.46 gm (0.0633 mole) of sodium were converted to sodium amide in liquid ammonia using a ferric chloride catalyst. After the ammonia had evaporated, a solution of 15.88 gm (0.0575 mole) of ethyl γ-(N-benzoyl piperidyl) acetate and 14.6 gm (0.0633 mole) of carefully dried ethyl quininate in 30 ml of anhydrous benzene was added and the mixture heated with vigorous stirring at 100° for 17 hours. Ice was added to the resulting paste, then water, and the phases were separated. The aqueous phase was washed with benzene and the benzene phases extracted with aqueous base. The combined aqueous solutions were filtered, chloroform added, and the mixture saturated with carbon dioxide. The resulting chloroform extract was dried and the solvent removed at reduced pressure leaving 14 gm of a thick red gum which was used directly for the subsequent step.

(6-methoxy quinolyl-4-)-(γ-piperidyl bromomethyl) ketone dihydrobromide(VII)

14 gm (0.03 mole) of crude V was refluxed in 140 ml of 6 N hydrochloric acid for 6 hours. 80% of the theoretical amount of carbon dioxide was collected in an attached eudiometer, the main portion of it being evolved in the first two hours of refluxing. After cooling, the benzoic acid was extracted from the solution with ether, chloroform added, and the mixture cooled in ice. The solution was neutralized with cold 50% aqueous sodium hydroxide giving a deep red chloroform extract which was immediately extracted with a weighed amount of 48% hydrobromic acid (35 ml, 52.1 gm) and the weight of product, 7.5-8.0 gm, obtained from the gain in weight.

The solution of the amino ketone dihydrobromide was warmed to 50° and one equivalent (4.15 gm, 0.026 mole) of bromine was carried in to the stirred solution in a stream of nitrogen during the course of 45 minutes. After cooling, some gummy material which separated was removed, and the hydrobromic acid removed in vacuo, leaving an oil which crystallized. The crystals were washed with absolute ethanol and i-propyl ether giving 5.0 gm of recrystallized product, m.p. dec. 208-209° (not a true melting point).

Anal.	$C_{17}H_{21}Br_3N_2O_2$	Calc.	C 38.88	H 4.03	N 5.34
		Found	C 38.72	H 4.39	N 5.28

(6'-methoxy quinolyl 4'-)-(1-azabicyclo (2,2,1) heptyl 7-) ketone (VIII)

In a 125 ml bottle 2.8 gm (0.0053 mole) of VII was dissolved in 40 ml of water, 40 ml of ether added, then 20 ml of saturated aqueous sodium carbonate solution, the air space remaining in the bottle swept out with nitrogen and the mixture shaken for three hours. The light yellow ether phase was then separated, the aqueous phase extracted with ether, and the combined ether extracts dried over sodium sulfate. The ether was removed in a stream of nitrogen leaving a golden orange oil which was reduced directly, monohydrochloride, yellow rectangular prisms from ethanol, m.p. 216-128.5° dec.,

Anal.	$C_{17}H_{19}ClN_2O_2$	Calc.	C 64.04	H 6.01	N 8.79
		Found	C 63.73	H 6.04	N 8.36

monopicrate, plates from acetonitrile, m.p. 216-217.3° dec.

Anal.	$C_{23}H_{21}N_5O_9$	Calc.	C 54.01	H 4.14
		Found	C 54.23	H 4.28

Spectra:

A solution of the hydrochloride in water at a concentration of 2.50 mgm/100 ml, pH 5.88 was made up, its spectrum taken, the solution made basic, pH 10.82, and its spectrum taken again. This was compared with spectra of 6'-methoxyrubanone-9 in water at a concentration of 1.40 mgm/100 ml at corresponding pH's.

		max. in mμ	log ε
Ketone VIII	pH 5.88	362.0	3.644
	pH 10.82	344.0	3.649
6'-methoxyrubanone-9	pH 5.83	359.5	3.627
	pH 10.36	335.0	3.643

(6'-methoxyquinolyl-4')-(1-azabicyclo (2,2,1) heptyl-7) carbinol (IX)

The crude ketone VIII from 2.8 gm (0.0053 mole) of VII was dissolved in 200 ml of anhydrous isopropanol, 11 gm (0.054 mole) of aluminum isopropoxide was added and the solution distilled slowly through a short fractionating column for 46 hours with occasional addition of isopropanol. No test for acetone in the distillate (with 2,4-dinitrophenylhydrazine) was observed after 24 hours. Most of the alcohol was distilled out, ice was added, then chloroform and sufficient 6 N sodium hydroxide to bring the pH 9.4 (thymolphthalein). The combined chloroform extracts were dried over sodium sulfate and the solvent removed in vacuo leaving a light orange oil which crystallized on standing. After recrystallization from absolute ethanol in large rhombic prisms the m.p. was 166.3-167.0°.

Anal.	$C_{17}H_{20}N_2O_2$	Calc.	C 71.80	H 7.09
		Found	C 71.86	H 7.35

The other racemate is presumably in the non-crystalline oil remaining in the mother liquors, but has not as yet been isolated.

Spectrum:

The spectrum of an ethanolic solution of concentration 1.94 mgm/100 ml was taken. It is compared with that of an ethanolic solution of quinine of concentration 1.9 mgm/100 ml.

	max in mμ	log ε
Carbinol IX	(234.8)	4.410
	(237.0)	4.408
	239.0	4.412
	281.3	3.530
	335.0	3.691
Quinine	231.0	4.489
	(235.2)	4.454
	(276.0)	3.526
	280.0	3.550
	(322.0)	3.633
	333.3	3.684

(6'-methoxy quinolyl 4'-)-(γ-piperidylmethyl) ketone

The ketone VIII from 2.0 gm (0.0048 mole) of VII in 25 ml of methanol together with the catalyst from 1 gm of Adams sodium nitrate-platinum oxide mixture was shaken with hydrogen at one atmosphere. The reaction was stopped when one equivalent of hydrogen had been absorbed although hydrogen was still being absorbed. The solvent and catalyst were removed, and the oil which remained converted to the hydrochloride. The material crystallized from ethanol in feathery clusters, m.p. 211.5-212.8°.

Spectra:

Spectra in water at a concentration of 1.48 mgm/100 ml were taken at two pH's as for the ketone VIII and were compared with spectra of 6'-methoxyrubatoxanone-9 in water at a concentration of 1.7 mgm/100 ml.

	pH	max. in mμ	log ε
Ketone X	6.32	344.0	3.624
	10.93	341.0	3.625
6'-methoxyrubatoxanone	6.43	341.0	3.578
	10.38	341.5	3.567

Carbinol Amines Related to Quinine

6-methoxyquinolyl-4-di-n-hexylaminomethyl carbinol

$$\mathrm{ArCOCH_2Br} + 2\ \mathrm{HNR_2}$$

$$\downarrow$$

$$\mathrm{ArCOCH_2NR_2} + \mathrm{R_2\overset{+}{N}H_2\ Br^-}$$

$$\downarrow$$

$$\mathrm{ArCHOHCH_2NR_2}$$

I Ar = 6-methoxyquinolyl 4-

R = n-hexyl

II Ar = phenyl

R = n-butyl

For the preparation of α-aryl β-dialkylamino ethanols the mode of synthesis, namely condensation of a secondary amine with an α-halogen (aryl) ketone with subsequent reduction of the ketone to the carbinol, is a general one. It was observed however in the course of this work as well as in previous work by W. H. McNeely, that the ketone intermediates were quite unstable. This is in agreement with similar observations of King and Work[1] and of Jacobs[2]. Yields were low, even though the condensation was carried out under mild conditions. In accordance with observations of Jacobs, when the amino-ketones were synthesized in an atmosphere of nitrogen, side reactions as evidenced by low yields and the formation of colored products were diminished.

Tests carried out on a model compound, phenyl di-n-butylaminomethyl ketone, indicated that the compound is readily attacked by gaseous oxygen at the methylene carbon atom adjacent to the carbonyl group. In this case benzoic acid and di-n-butylamine were easily isolated from the oxidation products, though these are undoubtedly not the primary products of the oxidation. Under similar conditions, the hydrochloride of the amino-ketone is not appreciably oxidized. These observations may be compared with those of James and Weissberger[3] on the oxidation of α-aminodesoxybenzoin in aqueous solution. They found that the rate of oxidation

[1] a)J. Chem. Soc. <u>1940</u>, 1307; b) ibid. <u>1942</u>, 401
[2] R. L. Jacobs, private communication
[3] J. Amer. Chem. Soc. <u>59</u>, 2040 (1937)

was proportional to the hydroxyl ion concentration and to the amine concentration but was independent of the oxygen pressure. The amino-ketone also oxidized 1.7 times as rapidly as the corresponding hydroxy ketone which has been shown by Weissberger to oxidize by an enolic mechanism. They concluded that the oxidation, in aqueous solution, of the amino-ketone proceeds by an enolic mechanism and that the enolization is the rate-determining step. In aqueous solution hydrogen peroxide was isolated as one of the primary oxidation products. It seems reasonable to assume a similar mechanism for the oxidation observed in this research, even though the reactions were carried out either in anhydrous ether or with the free base. The probable primary product in the case of phenyl di-n-butylaminomethyl ketone would then be benzoyl di-n-butylaminomethyl hydrogen peroxide.

Although the experiments were only of a semi-quantitative nature, it is possible to calculate from the data an approximate rate constant assuming that the reaction is first order with respect to the ketone and perhaps with respect to the oxygen (in case the enolization is not the rate determining step), a reasonable assumption since one mole of oxygen is absorbed per mole of ketone. This rate constant gives a half-life of less than one hour on the basis of either assumption. Since in the preparation of the ketone it is necessary to stir the ethereal solution for two hours or more it is evident that considerable loss will occur unless air is excluded.

6-methoxy quinolyl 4-di-n-hexylaminomethyl carbinol was prepared for test essentially by the method of King and Work[1a] except that the ketone was made under nitrogen and reduced to the carbinol by aluminum isopropoxide instead of by catalytic hydrogenation. The mode of reduction used does not necessarily represent an improvement over the catalytic method.

Experimental

Phenyl di-n-butylaminomethyl ketone

49 gm (0.38 mole) of di-n-butylamine were dissolved in 70 ml of anhydrous ether, the system swept out with nitrogen, and a solution of 25.2 gm (0.126 mole) of phenacyl bromide in 80 ml of ether was added dropwise with stirring. A crystalline precipitate of the amine hydrobromide formed, and the mixture was stirred for 2 1/2 hours, filtered, the precipitate washed with ether and the solvent stripped from the combined filtrate and washings. Distillation of the residual oil in vacuo with nitrogen gave a main fraction of a golden yellow oil, b.p. 122-123°/1.1 mm, weight 21.5 gm (0.087 mole, 65%),

Anal. $C_{16}H_{25}ON$				
	Calc.	C 77.74	H 10.20	N 5.67
	Found	C 77.72	H 9.92	N 6.08

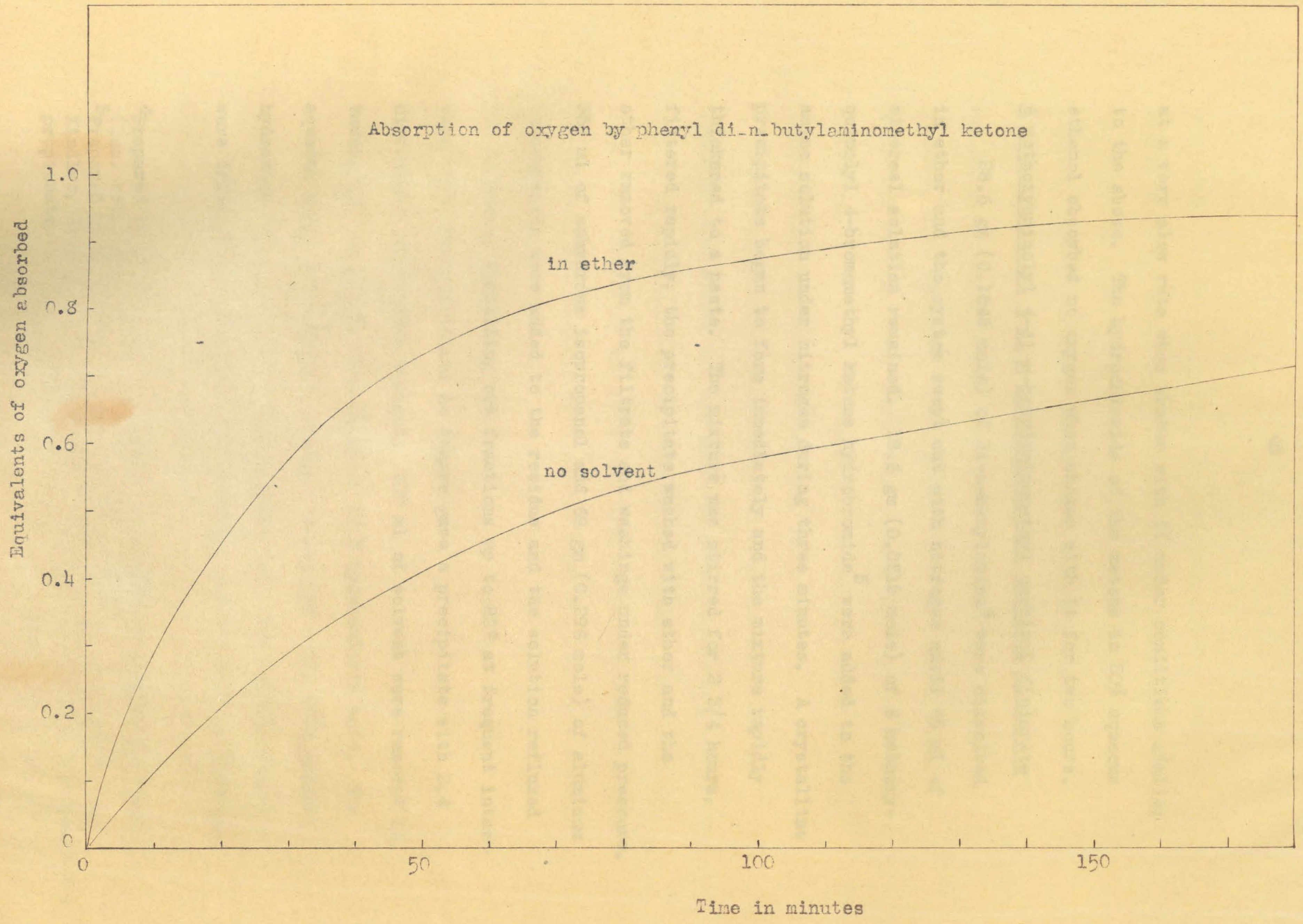
3,5 dinitrobenzoate, m.p. 154-155°;picrate an oil. (In a previous preparation McNeely obtained a picrate which on recrystallization melted 87.5-89°.)

Autoxidation of phenyl di-n-butylaminomethyl ketone

0.172 gm (0.000697 mole) of ketone with no solvent absorbed oxygen gas at a moderate rate until approximately one equivalent was absorbed in 12 hours (Fig. 1), the absorption continuing beyond this at a slow rate, approximately 1.3 moles being absorbed in 26 hours. From the red oil which remained benzoic acid (m.p. 121.8-122.0°) and di-n-butylamine (3,5 dinitrobenzoate m.p. 147-149°) were isolated by first extracting with cold aqueous 3 N potassium hydroxide, adding ether and separating the phases. Acidification of the aqueous solution gave the acid; addition of ethereal 3,5 dinitrobenzoic acid to the dried ether phase precipitated the amine salt. The identities were confirmed by mixed melting points with known samples.

Treatment of an ethereal solution of the ketone with oxygen under the same conditions resulted in the absorption of approximately 0.9 of an equivalent of oxygen in two hours (Fig. 1). Assuming $-d(B)/dt = k(B)(O_2)$ then from these data $k \sim 0.07$ min^{-1} atm^{-1} and if the extrapolation from an oxygen pressure of 1.0 atmosphere to 0.2 atm is valid this gives a half-life of 50 min. for a pressure of 0.2 atm. of oxygen, or if $-d(B)/dt = k(B)$ then $k \sim 0.07$ and the half life for any oxygen pressure exceeding some critical one is 10 min.

Treatment of the ethyl ether used as a solvent with oxygen under the same conditions resulted in no observable absorption of oxygen. Phenacyl bromide in ether absorbed a small amount of oxygen


Absorption of oxygen by phenyl di-n-butylaminomethyl ketone
Equivalents of oxygen absorbed
1.0
0.8
0.6
0.4
0.2
0
in ether
no solvent
0
50
100
150
Time in minutes

at a very slow rate when shaken with it under conditions similar to the above. The hydrochloride of the ketone in 50% aqueous ethanol absorbed no oxygen when shaken with it for two hours.

6 methoxyquinolyl 4-di-n-hexylaminomethyl carbinol dipicrate

28.6 gm (0.1545 mole) of di-n-hexylamine[4] were dissolved in ether and the system swept out with nitrogen until 65 ml of ethereal solution remained. 18.6 gm (0.0515 mole) of 6 methoxyquinolyl 4-bromomethyl ketone hydrobromide[5] were added to the amine solution under nitrogen during three minutes. A crystalline precipitate began to form immediately and the mixture rapidly thickened to a paste. The mixture was stirred for 2 3/4 hours, filtered rapidly, the precipitate washed with ether and the ether removed from the filtrate and washings under reduced pressure. 350 ml of anhydrous isopropanol and 69 gm (0.296 mole) of aluminum isopropoxide were added to the residue and the solution refluxed for 52 hours, distilling out fractions up to 82° at frequent intervals until the distillate no longer gave a precipitate with 2,4 dinitrophenylhydrazine reagent. 200 ml of solvent were removed in vacuo, ice was added, then 75 ml of 12 N hydrochloric acid. The aqueous phase was then made strongly basic (pH ~ 10) with sodium hydroxide solution and the phases separated. The organic phases were dried, the solvent removed in vacuo, and the residue extracted

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[4] Prepared by A. O. Reims according to the method of King and Work (loc. cit.) from benzylamine and hexyl bromide.

[5] Prepared by W. H. McNeely by the method of Rabe, Pasternack, and Kindler, Ber. 50, 144 (1917) from ethyl β-keto β-(6 methoxyquinolyl 4-) propionate.

with ether, filtering off an amorphous precipitate. Ethereal picric acid was added slowly and the solution decanted from the tarry material which precipitated first. Excess picric acid was added, the dipicrate of the carbinol filtered off, and washed with cold acetonitrile, giving 10.73 gm, m.p. 160-165°. An additional 2.05 gm were recovered from washings and mother liquors, m.p. 158-165°. Total yield 12.78 gm (0.0152 mole, 29.4%) of material m.p. 165°. The melting point given in the literature[1a] is 173°. A sample of the material above was recrystallized from acetonitrile, m.p. 169°.

The dihydrochloride was prepared from the dipicrate by treating with excess 6 N hydrochloric acid, extracting the picric acid with ethyl acetate, then making the aqueous phase strongly basic and extracting the free base with ether. Gradual addition of ethereal hydrochloric acid precipitated the dihydrochloride, m.p. 155° dec.

Anal. $C_{24}H_{40}Cl_2N_2O_2$	Calc.	C 62.73	H 8.78	N 6.10
	Found	C 61.26	H 8.53	N 6.90

Pyridyl Ester Intermediates

Ethyl α- and γ-pyridyl acetic esters were required as starting materials for syntheses of carbinol amines such as the (6'-methoxy quinolyl 4'-)-(1-azabicyclo (2,2,1) heptyl 7-) carbinol described in a preceding section and for (6'-methoxy quinolyl 4'-)-(α-piperidylmethyl) carbinol, a homolog of the (6'-methoxy quinolyl 4'-)-(α-piperidyl) carbinol prepared by Ainley and King[1] and shown by them to have antimalarial activity. α-pyridyl acetic acid has been prepared[2] from α-picoline by condensation with benzaldehyde to form α-stilbazole which was converted to the corresponding acetylene compound through the dibromide. The resulting phenyl α-pyridyl acetylene was hydrated to α-phenacyl pyridine. Beckman rearrangement of the oxime of this ketone gave the anilide of α-pyridyl acetic acid. The method is a cumbersome one at best, and since relatively large quantities were required, a single-step synthesis of ethyl α-pyridyl acetate was devised, based on the fact that the hydrogens of the α- and γ-methyl groups of alkyl pyridines and related compounds are "active" hydrogens. It is possible to prepare metal derivatives[3] of α- and γ- picolines and related compounds and hence to use them in ester and Wurtz type syntheses. The preparation of ethyl α- and γ-pyridyl acetates consists in the condensation in liquid ammonia at

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[1] Proc. Roy. Soc. B125, 60 (1938)

[2] a) Oparina, Chem. Zentr. 106 I, 2536 (1935); b) Clemo, Morgan and Raper, J. Chem. Soc. 1935, 1743; c) cf. also Scheuing and Winterhalder, Ann. 473, 126 (1929) for a similar synthesis of a different compound.

[3] cf. e.g. Tchitchibabin, Bull. soc. chim. (5) 5, 429 (1938)

its normal boiling point, of the appropriate picoline with ethyl carbonate by means of potassium amide. Sodium amide, presum~~e~~ably because of its low solubility in liquid ammonia, did not give satisfactory results. Yields are only of the order of 25-35% (based on the amount of picoline taken as starting material), but the reaction is very clean and no higher boiling material or tar is formed. The principal secondary product is ethyl imidodicarboxylate formed from the carbonate and the amide.

The method should be of fairly wide applicability. Using liquid ammonia as the reaction medium seems to have decided advantages. Thus for example Tchitchibabin[4] warmed α-picoline with ethyl benzoate and sodium amide with such poor results that he apparently did not pursue the investigation of ester type condensations of picoline further. On the other hand when in this research ethyl benzoate was added to a solution of picolyl potassium in liquid ammonia, a yield of 60% of the expected α-phenacyl pyridine was obtained. Little previous work has been done on ester condensations of α- or γ- alkylated pyridines or related compounds. The review of Bergstrom and Fernelius[5] covers most of the work which has been done. Bergstrom[5] has carried out some ester condensations between potassium salts of 2- and 4- methyl quinolines, benzoquinolines and quinoxalines and certain esters, in ether as a solvent. He observed that only those potassium salts soluble in ether would react. The

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[4] Rec. trav. chim. 57, 582 (1938)
[5] Chem. Rev. 20, 413 (1937)

greater solvent power of liquid ammonia for compounds of this type makes this limitation less serious. M. J. Beets[6] treated picolyl lithium with acetic anhydride and with ethyl acetate and obtained the expected dehydroisopellitierine but no details or yields are given in the abstract available. The other methods available forthe preparation of carbalkoxylated pyridines consist in the condensation of halides with metal derivatives or with "active" hydrogens. In this research the condensation of α-picoline and ethyl chlorocarbonate in the presence of sodium amide was carried out and ethyl pyridyl acetate obtained in ca. 20% yield but a large amount of higher boiling bases and tar was also formed. Elderfield and coworkers[7] report that they have prepared ethyl α-pyridyl acetate from picolyl lithium and ethyl chlorocarbonate. α- and γ- pyridyl malonic esters have been prepared from the α- and γ-bromopyridines by condensation with sodio-malonic ester[8] or with barbituric acids[9] followed by hydrolysis of the barbituric acid ring.

The proposed preparation of (6'-methoxy quinolyl 4'-)-(α-piperidylmethyl) carbinol was not carried through since all attempts to condense the ethyl (α-N-benzoyl piperidyl)) acetate with ethyl quininate failed. The condensation was tried with sodium amide and with sodium triphenylmethyl. This result is not unexpected since Clemo, Morgan and Raper[10] were unable to condense the corresponding methyl ester of the benzoyl compound with itself.

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[7] private communication from R. C. Elderfield

[8] L. A. Walter and S. M. McElvain, J. Amer. Chem. Soc. 57, 1891 (1935)

[9] Ger. Pat. 638821, Chem. Zentr. 108 I, 2262 (1937); cf. also Fr. Pat. 77374 Chem. Zentr. 106 I, 3816 (1935) and Ger. Pat. 596729 Chem. Zentr. 105 II, 1024 (1934)

[10] J. Chem. Soc. 1936, 1025

Experimental:

Ethyl α-pyridyl acetate

58.6 gm (1.5 gm atom) of potassium metal were dissolved and rapidly converted to potassium amide in ca. 1200 ml of liquid ammonia containing a small amount of anhydrous ferric chloride as catalyst. 56 gm (0.6 mole) of redistilled α-picoline were added dropwise with stirring to the solution giving a red solution of the picolyl potassium. 150 gm (1.2 moles) of redistilled ethyl carbonate were then added to the ammonia solution of the salt with vigorous stirring. A vigorous reaction occurred as the drops of carbonate struck the solution, and the color of the mixture changed to a faint yellow during the addition. The mixture was allowed to stir for 15 minutes after the addition of the carbonate was complete, at the end of which time it was a thick colorless paste and most of the ammonia had evaporated. 500 ml of anhydrous ether were added, and the resulting suspension was stirred for 4 hours, warming to room temperature with a bath after 2 hours if necessary. An aqueous solution of 81 gm (1.5 moles) of ammonium chloride was added to the ethereal suspension, little or no heat evolution occurring. The ammonia was then neutralized with acetic acid, the phases separated, the aqueous phase extracted with ether and the combined ether phase dried over potassium carbonate. Ethereal hydrochloric acid was then added to the dry ether solution until the bases were completely precipitated. After decantation of the ether, the hydrochlorides were dissolved in water and the free bases liberated by the addition of excess potassium carbonate. The bases were extracted with ether and after drying and removal of the ether the bases were distilled. After a forerun of unchanged picoline the product distilled, b.p. 90-95°/1 mm, weight 28 gm (28%), picrate from ethanol in prisms, m.p. 137.5-138.7°. The previously reported[2b] m.p. is 136-137°. The amide was prepared in aqueous ammonia and recrystallized from i-propyl ether-ethanol in needles, m.p. 181.5-182.3°.

Ethyl γ-pyridyl acetate

This was prepared by exactly the same procedure as the α-isomer, starting in this case with γ-picoline. The product weighed 33-40 gm (33-40%) and had a b.p. 90-100°/1 mm.

Anal.	$C_9H_{11}NO_2$	Calc.	C 65.44	H 6.71	N 8.48
		Found	C 63.71	H 7.04	N 8.55

The picrate crystallized from ethanol in blades with m.p. 120.5-121.5°.

Anal.	$C_{15}H_{14}N_4O_9$	Calc.	C 45.69	H 3.58
		Found	C 46.30	H 3.67

The dinitrobenzoate crystallized from i-propyl ether-ethanol had a m.p. 111-112.3°.

Anal.	$C_{16}H_{13}N_3O_8$	Calc.	C 50.93	H 4.01
		Found	C 50.82	H 4.16

The monohydrate crystallized in long efflorescent prisms from i-propyl ether.

Anal.	$C_9H_{13}NO_3$	Calc.	C 59.01	H 7.15
		Found	C 59.06	H 6.94.

α-phenacyl pyridine

This was prepared in the same manner as the ethyl α-pyridyl acetate using ethyl benzoate in place of ethyl carbonate. In this case the crude reaction mixture, in ether, was extracted with aqueous hydrochloric acid and the solution of base hydrochlorides then neutralized and extracted with ether, the ether removed, and the bases distilled, giving unchanged picoline. The product distilled at 130-131°/0.3 mm and had a melting point of 54°, weight 84 gm (60%). The previously reported[11] m.p. is 56°.

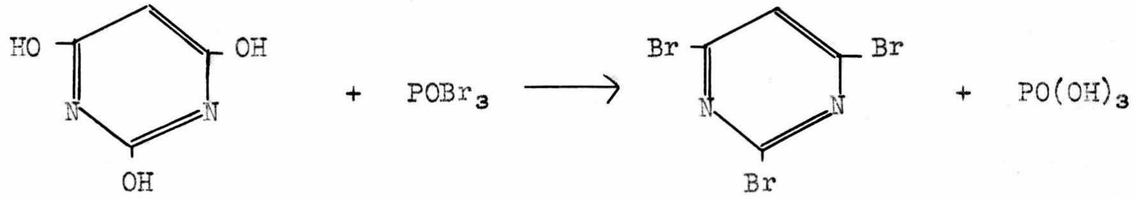
Ethyl α-piperidyl acetate

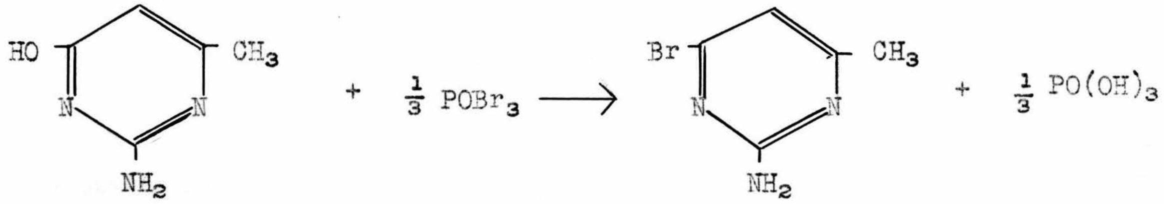
The method was essentially the same as procedure 1 for the corresponding γ- isomer except that the reduction occurred with Raney nickel under 150 atmospheres of hydrogen at 120° or less depending on at what temperature the shaking was begun. The product distilled at 82-83°/1 mm, and weighed 28 gm (68%). The picrate melted at 132-133° after crystallization from i-propyl ether-ethanol. The previously reported[2b] m.p. is 125°.

Anal. $C_{16}H_{21}N_3O_8$				
	Calc.	C 50.13	H 5.52	N 10.96
	Found	C 50.17	H 5.54	N 10.99

The dinitrobenzoate crystallized from i-propyl ether-ethanol melted 126.5-127°. The N-benzoyl derivative was prepared in the same manner as that of the γ- isomer, b.p. 172.5-174°/1 mm.

Bromopyrimidines


HO
OH
N
N
OH
+ POBr₃
Br
Br
N
N
Br
+ PO(OH)₃


HO
CH₃
N
N
NH₂
+ 1/3 POBr₃
Br
CH₃
N
N
NH₂
+ 1/3 PO(OH)₃

While some substituted pyrimidines with a bromine in the 5- position have been prepared[1], only one, namely 2,4,5,6-tetrabromopyrimidine has been prepared[2] with one or more bromine atoms in the 2, 4 (or 6) positions. This latter was prepared by the action of a mixture of phosphorus pentabromide and phosphorus oxychloride on the corresponding oxygen compound, a procedure which gives a mixture of halogenated products. On the other hand several pyrimidines with chlorine in the 2, 4 (or 6) positions have been prepared[3] by the action of phosphorus oxychloride on the corresponding hydroxy compound.

This research has shown that it is possible to prepare, in moderate to poor yields, bromopyrimidines with bromine in the 2, 4 (or 6) positions by the analogous reaction of the hydroxypyrimidines with phosphorus oxybromide. 2,4,6-tribromopyrimidine and 2-amino,4-methyl,6-bromopyrimidine were prepared by this method from barbituric acid and 2-amino,4-methyl,6-hydroxypyrimidine respectively.

Experimental:

The following procedures were used, but they do not necessarily represent the optimum conditions.

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[1] a) Huber and Holscher, Ber. <u>71B</u>, 87 (1938); b) Wheeler and Johnson, Amer. Chem. J. <u>29</u>, 504

[2] Emery, Ber. <u>34</u>, 4180 (1901)

[3] a) Gabriel, Ber. <u>33</u>, 3667 (1900); ibid. <u>34</u>, 3363 (1901); b) v. Merkatz, Ber. <u>52</u>, 870 (1919); c) Wheeler and Johnson, J. Amer. Chem. Soc. <u>52</u>, 1152 (1930) and others

2,4,6-tribromo pyrimidine

10 gm of barbituric acid and 143 gm of phosphorus oxybromide[4] were heated at 150-160° for five and one half hours, the mixture cooled and added slowly to an ice-ether mixture which had been cooled to -10°. The precipitate which came down was collected, extracted with ether and the combined ethereal extracts dried. The ether was removed and the crude product which remained was distilled. Weight 15 gm (60%) b.p. 124°/5 mm, m.p. 113-115°.

Anal.	$C_4HBr_3N_2$	Calc.	C 15.18	H 0.32	N 8.84
		Found	C 15.34	H 0.41	N 8.61

2-amino,4-methyl,6-bromo pyrimidine

30 gm of crude 2-amino 4-methyl 6-hydroxy pyrimidine (m.p. 300-302° dec), prepared by the method of Jaeger[5] from guanidine carbonate and acetoacetic ester were treated with 135 gm of molten phosphorus oxybromide, whereupon a reaction ensued immediately. The mixture was heated to 135°0140° for forty five minutes, cooled and added slowly to 600 gm of ice with good stirring. To the resulting aqueous solution 15 N ammonia was added slowly with cooling. The solution was decanted from a red gummy precipitate which came down while the solution was still strongly acid, and the crude product precipitated by adding an excess of the ammonia. It was partially purified by dissolving in hydrochloric acid and reprecipitating with ammonia. The crude solid weighed 22 gm from which ca. 10-15 gm of pure product may be isolated by recrystallization from *i*-propyl

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[4] b.p. 89-90°/20 mm; prepared by the method of Berger, Bull. soc. chim. 3 (5), 721 (1908)

[5] Ann. 262, 365 (1891)

ether (m.p. 146–148.5°) or from acetone and water (m.p. 153°) the latter being the procedure of Mr. M. M. Rapport.

Anal.	$C_5H_6BrN_3$	Calc.	C 31.94	H 3.22	N 22.35
		Found	C 31.84	H 2.98	N 22.23

Summary

Part I

Certain thermodynamic properties of 1,1,1 trifluoroethane have been measured and from these the entropy has been determined. By comparison of the experimentally determined entropy with that from molecular data, the barrier restricting rotation about the C-C bond of the molecule was determined to be 3450 calories. This value is the same within experimental error as the barrier in ethane and in 1,1,1 trichloroethane, though the slightly higher value may have some significance.

Part II

Syntheses of certain compounds with possible antimalarial activity and of some intermediates for these and similar compounds have been carried out. The synthesis of quininic acid has been improved. New methods have been developed for the preparation of pyridyl esters and certain bromopyrimidines. The synthesis of quinine analogs has been studied.

Propositions

1. It is proposed the structure $(\mathrm{RR'}\underset{\cdot\cdot}{\mathrm{C}}:\underset{:\ddot{\underset{\cdot\cdot}{\mathrm{O}}}:}{\mathrm{N}}::\mathrm{O})^{-}$ proposed by Kuhn and Shriner for the optically active salts of secondary nitroparaffins is improbable since carbon would be expected to be at least as labile as nitrogen.

> Hass and Riley, Chem. Rev. 32, 400 (1943
> Taylor and Baker, Sidgwick' Organic Chemistry of Nitrogen, p. 239 Oxford 1937

2. It is proposed that a qualitative explanation of the anomalous viscosity of liquid sulfur may be based on the assumption that the phenomenon is essentially a cooperative one.

> Bacon and Fanelli, J. Amer. Chem. Soc. 65, 639 (1943)
> Powell and Eyring, J. Amer. Chem. Soc. 65, 648 (1943)
> Lewis and Randall, J. Amer. Chem. Soc. 33, 476 (1911)

3. Yields of quininic acid from quinine are increased when the chromic acid oxidation is carried out in the presence of Manganese dioxide.[α] In the light of other work[β] it is proposed that this is due to the elimination of Cr^{V} compounds. It is also proposed that this principle (the elimination of active intermediates) should be capable of extension to some other oxidizing agents.

> [α]John, Ber. 63, 2657 (1930)
> [β]Wagner, Z. anorg. u. allg. Ch. 168, 279 (1928)
> Westheimer and Novick, J. Chem. Phys. 11, 506 (1943)

4. The Rankine magnetic balance is proposed as an instrument which should be useful in kinetic and structural studies since it is free from certain of the limitations of the Gouy type.

> Burris and Hause, J. Chem. Phys. 11, 442 (1943)
> Iskenderian, Phys. Rev. 51, 1092 (1937); 52, 1244 (1937)

5. It is proposed that the reactions of oxygen and of nitrogen oxides on carbonyl and related compounds proceed by similar mechanisms.

E. Gilman and T. B. Johnson, J. Amer. Chem. Soc.
50, 3341 (1928)
Dulon, Chem. Abstracts 28, 7255 (1934)
Bouveault and Locquin, Bull. soc. chim. (3) 31, 1169 (1904)
Giacolone, Gazz. chim. ital. 61, 828 (1931)
Gorislavets Chem. Abstracts 37, 6550 (1943)

6. It is proposed that the melting of a crystalline solid does not take place at a single temperature but is a continuous process. The melting point is then not always a reliable criterion of (im)purity.

Seitz, Modern Theory of Solids, McGraw Hill
Ubbelohde, Trans. Far. Soc. 34, 282 (1938)
Frenkel, J. Chem. Phys. 7, 200, 538 (1939)
Lennard-Jones and Devonshire, Proc. Roy. Soc. A170,
464 (1939)
Lichtenecker, Z. Elektrochem. 48, 601 (1942); Chem. Abstracts.

7. Yields are improved when heterocycles are aminated in the presence of nitrate ion[α]; nitration of benzene and nitrobenzene procedes more smoothly in the presence of metal ions[β]; iodination of aromatic hydrocarbons occurs in good yield in the presence of peroxydisulfate and certain metal ions[ββ]. It is proposed that these and other examples may be explained on a common basis by assuming an oxidative step or steps in some substitution processes.

[α] Leffler, Organic Reactions (ed. Adams) p. 96, New York 1943
[β] Georgienskii, Chem. Abstracts 37, 6650 (1943)
[ββ] Marko and Belyaev, Chem. Abstracts 37, 6250 (1943)

8. Adams platinum oxide catalyst does not reduce pyridine compounds well if at all, but the salts are usually reduced easily. It is proposed that this may be explained on the basis of the coordination properties observed for nickel, palladium, and platinum (zerovalent compounds).

Burbage and Fernelius, J. Amer. Chem. Soc. 65, 1484 (1943)

9. It is proposed that the ester condensation may be extended considerably in scope using hydrocarbon and heterocycle metal derivatives. Liquid ammonia may be used to advantage as a solvent in some cases.

> Morton, Little and Strong, J. Amer. Chem. Soc. 65, 1339 (1943) and previous papers of this series
> Bergstrom and Fernelius, Chem. Rev. 20, 413 (1937)

10. Ethyl α-pyridyl acetate is reduced with exceptional ease to the piperidyl compound by means of Raney nickel and hydrogen. It is proposed that this may be explained by the following type of tautomerism and resonance: