

- I. The Constitution of Naphthenic Acids
- II. Heterocyclic Nitrogen and Sulfur Studies
- III. The Structure of Pirylene

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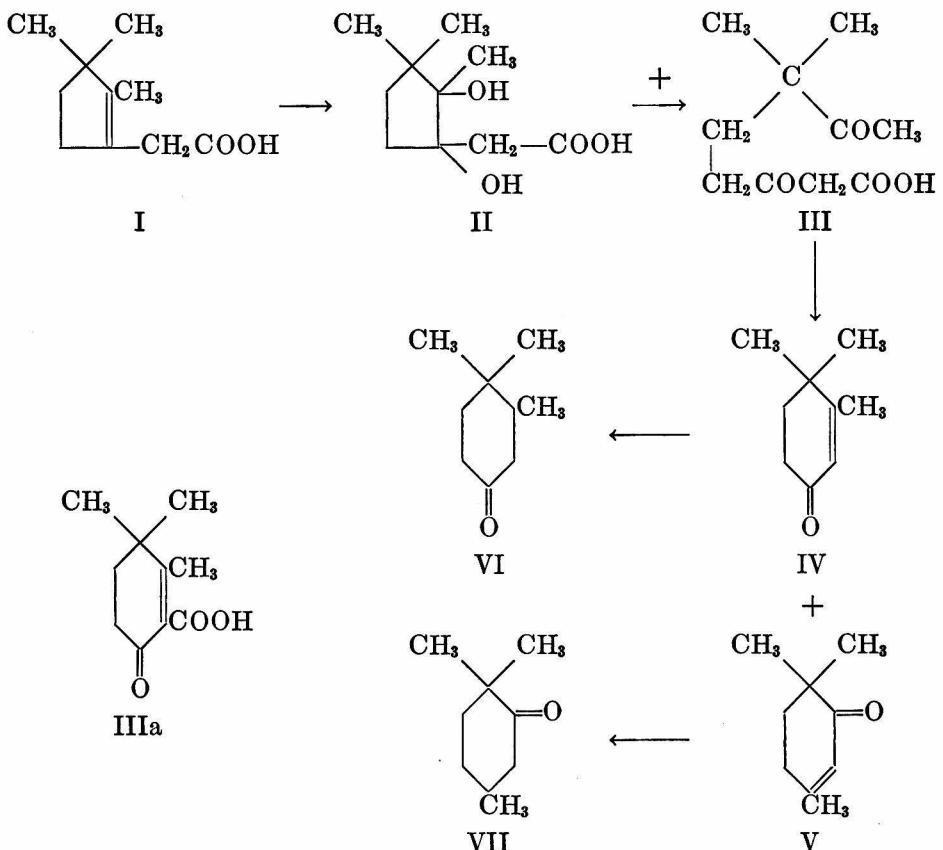
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TIEMANN'S "ISOCAMPHORPHORONE"¹

EDWIN R. BUCHMAN AND HERBERT SARGENT

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In 1897 Tiemann reported (3) that the permanganate oxidation of β -campholenic acid (I) yielded dihydroxydihydro- β -campholenic acid (II), small amounts of a ketonic acid ("campholonic acid") and a syrupy aliphatic acid which was not isolated in pure form. Under the conditions employed, this latter constituted the principal reaction product. Heating this material, either alone or in the presence of water, led to the elimination of carbon dioxide and water from the molecule with consequent formation of a ketone ("isocamphorophorone"). To this ketone, Tiemann assigned the structure (IV) based on a careful study of its oxidation products.



¹ The " β -camphorophorone" of Kerp and Müller (1) has also been referred to (2) as "isocamphorophorone."

At the time of these experiments, the structure of (I) was not known; it was impossible therefore correctly to interpret² the mechanism of formation of a compound having the structure (IV). Shortly after the publication of this work, however, the constitution of β -campholenic acid (I) became known (5) and Bouveault (5 b) postulated³ formula (III) for Tiemann's syrupy acid, the precursor of (IV). Subsequently "isocamphorphorone" has been reported (7) only by von Braun and collaborators who prepared it according to the original directions.

The ketone (IV) was needed in this Laboratory as starting material for another investigation (8). Accordingly, the literature preparation (3) was repeated and it was found that the material resulting was not homogeneous but a mixture of isomers. This finding is not surprising, since two trimethylcyclohexenones, (IV) and (V) might be expected to result from the intermediate (III).⁴ We were able to show that our isomers correspond in structure to (IV) and (V), and thus the essential validity of the Bouveault formulation may be regarded as established.

The mixture obtained by following carefully Tiemann's directions was fractionated *in vacuo* through a precision column to give the pure unsaturated ketones. The higher-boiling material was found to correspond to formula (IV); upon oxidation, it gave the dimethylketocaproic acid to be expected from this structure. The lower-boiling isomer was shown to be identical with 3,6,6-trimethylcyclohexen-2-one (V) previously synthesized by von Auwers (9). The reduction of (IV) led to the saturated ketone (VI) while (V) gave the known (10) inactive pulenone (VII).

The evidence, which is summarized in Table I, indicates that Tiemann obtained an "isocamphorphorone" preparation which consisted for the most part of (IV). However, some (V) was also present in the material which he investigated, since the oxime which he reported must have been derived from the latter. The von Braun preparation was also without doubt a mixture.

Since one of the objects of this work was to obtain the ketone (IV) for further synthetic operations, the utilization of (II) in this connection was studied. It was found that (II) was oxidized smoothly⁵ by lead tetraacetate, and under conditions described in the Experimental Part, a ketonic product was obtained in which only the isomer (IV) could be detected. The action of hydrogen

² Tiemann's assumed intermediate (3) should be stricken from the literature (4) and replaced by (III).

³ Bouveault's mechanism is not mentioned in "Beilstein" in connection with "isocamphorphorone" (6). Perhaps traceable to this oversight is von Braun's failure (7) to recognize (see below) that his "isocamphorphorone" was a mixture.

⁴ Actually Bouveault (5b) assumed a second intermediate (IIIa), formed from (III) by loss of water. If dehydration of (III) were to precede decarboxylation, two isomeric unsaturated keto acids would result, only one of which would decarboxylate readily. Such a stepwise transformation would provide a plausible explanation for exclusive isolation of (IV) from (III). However there is no evidence that this mechanism obtains under the Tiemann conditions.

⁵ The ready reaction indicates (12) that the OH groups in (II) are *cis* to each other, a structure in accord with the mode of formation of (II) and its inability to lactonize.

TABLE I

	"ISOCAMPHORHORONE" TIEMANN (3)	IV ^a	V ^b	REDUCED "ISOCAMPHORHORONE" VON BRAUN (7)	VI	VII ^c
Boiling point	b.p. ₁₃ 97-99° b.p. ₇₆₀ 217°	b.p. ₁₃ 98°	b.p. ₁₃ 86°	b.p. ₁₁ 70-75° b.p. 184-188°	b.p. ₁₃ 80-81°	b.p. ₁₃ 66-67°
Density	d_4^{20} 0.9424	d_4^{25} 0.944	d_4^{25} 0.927		d_4^{25} 0.911	d_4^{25} 0.890
Refractive index	n_D 1.48458	n_D^{20} 1.4908 n_D^{25} 1.4889	n_D^{20} 1.4798 n_D^{25} 1.4780		n_D^{20} 1.4552 n_D^{25} 1.4535	n_D^{20} 1.4442 n_D^{25} 1.4425
Semicarbazone	m.p. 211°	m.p. 206.5-207.0° forms rapidly	m.p. 201.0-201.1° forms slowly	m.p. 177°	m.p. 208.0-209.0°	m.p. 176.0-176.3°
Derivative with hydroxylamine	hydroxylamino- oxime m.p. 153°	oxime m.p. 53.8-54.5°	hydroxylamino- oxime m.p. 156.5-157.0°	m.p. 100°	m.p. 72.5-73.5°	m.p. 94.5-94.8°
Derivative with <i>p</i> - nitrobenzaldehyde				m.p. 226°	di- <i>p</i> -nitrobenzal derivative m.p. 223.0-223.2°	mono- <i>p</i> -nitroben- zal derivative m.p. 117.5-118.0°
Reaction with bi- sulfite		none	none		reacts readily	none

^a The data in this column do not fit the C₉H₁₄O ketone described by Pringsheim and Schreiber (11) for which structure (IV) has been considered.

^b von Auwers and Hessenland (9) found: b.p.₇₅₃ 208°, b.p.₁₅ 86-88°, $d_4^{16.5}$ 0.9317, $n_D^{16.5}$ 1.47958, semicarbazone, m.p. 200-201° (forms slowly).

^c von Auwers and Hessenland (10) found: b.p.₃₉ 90-92°, semicarbazone, m.p. 176-177°. Cornubert and Humeau (10) found: b.p. 182-184°, d_4^{24} .8871, n_D^{24} 0.1.4432, oxime, m.p. 93.5°, no reaction with bisulfite.

peroxide on (I) was also investigated. The major product resulting was shown to be a lactone derived from the stereoisomer (trans position of the OH groups) of (II) which has been obtained (13) by direct oxidation of dihydro- β -campholenolactone.

EXPERIMENTAL PART

β -Campholenic acid (I) (3). Three hundred grams of hydriodic acid ($d = 1.7$) was heated to boiling in a flask fitted with a reflux condenser, and 300 g. of d -camphor oxime (crude, containing some camphor) was added in 50-g. portions with manual shaking. After each addition, the mixture was refluxed for a few minutes to ensure complete reaction, and after the final addition, refluxing was continued for five minutes. Several such reaction mixtures were combined, diluted with water, extracted with ether, and the ether extract washed with sodium carbonate solution. The crude β -campholenonitrile obtained after removal of the ether was converted without further purification to (I). Crude nitrile (1476 g. from 1770 g. of camphor) was saponified by refluxing for 12 hours with a solution of 640 g. of sodium hydroxide in 1500 cc. of water and 2500 cc. of ethanol. Alcohol was removed by distillation, water was added, the solution acidified, and the liberated acid removed by repeated extraction with low-boiling ligroin (b.p. 30-60°). The ligroin solution was dried with sodium sulfate, saturated with dry ammonia, and the precipitated ammonium salt filtered off. Additional amounts were recovered from the mother liquors by washing with water, acidifying, taking up in ligroin, drying, and again saturating with ammonia. Ligroin was used here rather than ether (3) because of the hygroscopic nature of the crude ammonium salt. A total of 908 g. of ammonium salt of (I) was obtained (42% based on camphor, other runs gave on the same basis as high as 53%; distilled β -campholenonitrile yielded 82% of ammonium salt). The first crop of ammonium salt proved to be sufficiently pure for most purposes; recrystallization, attended by considerable loss, could be effected from isopropyl alcohol. The free acid was obtained from its salt by Tiemann's procedure, m.p. 50.2-50.7° from petroleum ether or methanol.

Permanganate oxidation of (I): (a) Tiemann's conditions (3). Eighty grams of pure (I) was dissolved in a solution of 20 g. of sodium hydroxide in 300 cc. of water, and a saturated solution of 81 g. of potassium permanganate in water was added over a period of about 15 minutes keeping the temperature at about 0° by addition of ice to the reaction mixture. Manganese dioxide was removed and the solution concentrated on the steam-bath to a small volume (evaporation *in vacuo* was not feasible due to excessive frothing). The organic acids were liberated and taken up in ether in the usual manner (3); after removal of solvent, the residue was recrystallized from benzene. The yield of dihydroxydihydro- β -campholenic acid (II) was 20 g. (20%); after repeated recrystallization from ethyl acetate and from isopropyl ether-alcohol, it melted at 141.0-142.0° [143.6-144.6° corr.; Tiemann (3) reported 146°]; the composition was checked by analysis.

The mother liquors from the dihydroxy acid were concentrated to a syrup and divided into two portions, each of about 25 g. One portion was distilled in a vacuum and the distillate, collected to 135° at 13 mm., carefully fractionated through a precision column. At 13 mm. there was obtained 4.1 g. of (V), b.p. 87-88°, 1.3 g. of an intermediate fraction, and 0.7 g. of (IV), b.p. 98-99°; no dihydro- β -campholenolactone (see below) could be detected in the residue. The other portion was placed in a flask with 300 cc. of 30% sulfuric acid and steam distilled. The organic matter in the distillate was separated by ether extraction and redistilled as above; 2.5 g. of (V), 0.9 g. of an intermediate fraction, and 1.7 g. of (IV) were obtained.

The higher-boiling material from this last experiment consisted for the most part of a fraction b.p. 127° at 13 mm. which was identified as dihydro- β -campholenolactone, owing its formation undoubtedly to the action of acid on (I). The lactone (analysis) gave a hydrazone (14), m.p. and mixed m.p. with an authentic sample 155.5-156.0° (from alcohol). Dihydro- β -campholenolactone was made [compare (13)] for comparison, by the action of 67% sulfuric acid on (I), b.p. (13 mm.) 126-127°, m.p. 37-38° (thermometer in melt) (15).

Tiemann's directions for obtaining "campholonic acid" were followed in detail but no material resulted which gave a semicarbazone under the usual conditions. To determine whether (II) could have been the precursor (16) of Tiemann's "campholonic acid", this substance was heated in sulfuric acid solution. Such treatment destroyed the dihydroxy acid, as shown by the fact that the product no longer reacted with lead tetraacetate; however no ketone derivative was obtained with semicarbazide.

(b) *Modified conditions.* It was found that oxidation of the ammonium salt of (I) gave results which could not be distinguished from those obtained with the free acid; all large-scale permanganate oxidations, therefore, were conducted with the more readily available salt. Amounts of permanganate larger than those used by Tiemann were employed, since the foregoing results indicate an incomplete oxidation, and since it seemed that an excess of oxidant would probably not react further upon (II) and (III) [confirmed experimentally for (II)]. Whereas the simplest procedure (3) leading directly to (IV) and (V) is to steam distill the strongly acidified filtrate from the permanganate oxidation, these conditions result in the destruction of any (II) present. The evaporation of the slightly alkaline solution resulting from the oxidation apparently involves a small loss of material; however this operation permits the convenient isolation of (II) and utilization of it for conversion into unsaturated ketone.

For preparation of the ketone mixture in quantity, the following procedure was adopted. One hundred eighty-five grams (1 mole) of ammonium salt was dissolved in 500 cc. of water and 60 g. of sodium hydroxide pellets dissolved in 100 cc. of water was added. The solution was poured on 2 liters of crushed ice, and 210 g. of potassium permanganate dissolved in about 4 liters of water was allowed to run in gradually over a period of about 10 minutes while the iced mixture was being constantly shaken by hand in a 12-liter flask. After coagulation of the manganese dioxide by heating and addition of "filter aid", the material was filtered with suction, the filter cake thoroughly stirred with hot water, filtered, and the two filtrates combined. The filtrates from several 1-mole portions were combined at this point and evaporated in a current of air at about 40-50°. From the acidified residue, crystalline (II) was obtained by continuous extraction with ether [it is not necessary to isolate (II); the total extract, after removal of solvent, may be treated as given for the mother liquors from (II)] in slightly better than 20% yield. The mixture of (II) and (III) present in the mother liquors was first treated with lead tetraacetate to convert (II) to (III) and the resulting reaction mixture then acidified with sulfuric acid and steam distilled. In this way a 9-14% yield of mixed ketones [approximately equal amounts of (IV) and (V)] was obtained directly, plus an additional 10% of (IV) from oxidation of the crystalline (II) (see below).

3,4,4-Trimethylcyclohexen-2-one (IV) was isolated by careful refluxation of the unsaturated ketone mixture, b.p. (13 mm.) 98°, d_4^{25} 0.944, n^{20}_{D} 1.4908, n^{25}_{D} 1.4889 (these constants are altered somewhat on standing, due perhaps to auto-oxidation).

Anal. Calc'd for $C_9H_{14}O$: C, 78.21; H, 10.21.
Found: C, 77.79; H, 10.20.

(IV) did not react when treated with aqueous bisulfite solution in the usual manner. The semicarbazone melted at 206.5-207.0° (from alcohol).

Anal. Calc'd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52.
Found: C, 61.73; H, 8.65; N, 21.66.

The oxime came out as an oil which crystallized after standing for two months. Recrystallized from petroleum ether at low temperature, it melted at 53.8-54.5°.

Anal. Calc'd for $C_9H_{16}NO$: C, 70.55; H, 9.87; N, 9.14.
Found: C, 70.87; H, 10.01; N, 9.43.

That no hydroxylaminooxime is formed must be ascribed to the steric effect of the *gem*-dimethyl grouping.

Three grams of (IV) was suspended in 40 cc. of water and a saturated solution of 9 g. of potassium permanganate in water was added slowly with shaking, in an ice-bath. The oxidation mixture was then heated to coagulate the manganese dioxide, filtered, and the filtrate evaporated at near room temperature to a small volume. The residue, after acidification with sulfuric acid, was extracted with ether, the ether extract dried and evaporated. From the oily acids was obtained a semicarbazone which gave analysis for $C_9H_{17}N_3O_2$, m.p. 182.5-183.0° decomp. (from alcohol-water). The keto acid was regenerated from the semicarbazone with oxalic acid and treated with hydroxylamine; the oxime was isolated by continuous extraction with ether and recrystallized from isopropyl ether, m.p. 95.3-95.8°. There has been reported (17) for 4,4-dimethylhexan-5 acid: semicarbazone, m.p. 185°; oxime, m.p. 97-98°.

A smaller amount of oxidant gave a different result [compare (3)]. One and one-half grams of (IV) was oxidized with 1.0 g. of potassium permanganate in a manner similar to the above. After evaporation of the resulting solution, acidification of the residue precipitated an oil which solidified on cooling, m.p. 39.0-39.5°, from petroleum ether. Although the small amounts available prevented a thorough examination, this material must be regarded as 3,4,4-trimethylcyclohexandione-1,2 (18). The semicarbazone, m.p. 189-190° (from alcohol) turned yellow on standing [compare the monosemicarbazone of *p*-menthane (19)].

Anal. Calc'd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89.
Found: C, 57.27; H, 8.46; N, 20.64.

3,6,6-Trimethylcyclohexen-2-one (V) was obtained as above, b.p. (13 mm.) 86°, d_4^{25} 0.927, n^{20D} 1.4798, n^{25D} 1.4780 (analysis). (V) did not react with bisulfite. The semicarbazone (analysis) m.p. 201.0-201.1° (from alcohol), formed very slowly (rate approximately 1/50 of that of formation of the isomer). With hydroxylamine, the 3-hydroxylamino-3,6,6-trimethylcyclohexanone oxime was readily obtained, m.p. 156.5-157.0° from alcohol.

Anal. Calc'd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04.
Found: C, 58.24; H, 9.59; N, 15.39.

3,4,4-Trimethylcyclohexanone (VI) was obtained in good yield by catalytic reduction of (IV) in methanol using a palladium-charcoal catalyst and a pressure above atmospheric of 30 lbs. per sq. in. The saturated ketone boiled at 80-81° at 13 mm., d_4^{25} 0.911, n^{20D} 1.4552, n^{25D} 1.4535.

Anal. Calc'd for $C_9H_{16}O$: C, 77.09; H, 11.50.
Found: C, 76.80; H, 11.13.

(VI) reacted readily with aqueous alcoholic sodium bisulfite solution giving a crystalline bisulfite addition compound from which (VI) was regenerated on treatment with alkali. The semicarbazone melted at 208.0-209.0° (from alcohol-water).

Anal. Calc'd for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71; N, 21.30.
Found: C, 60.64; H, 9.58; N, 21.21.

The oxime, after recrystallization from alcohol, melted at 72.5-73.5°.

Anal. Calc'd for $C_9H_{17}NO$: C, 69.63; H, 11.04.
Found: C, 69.96; H, 11.07.

A yellow di-*p*-nitrobenzal derivative was formed when (VI) was heated with *p*-nitrobenzaldehyde in the presence of aqueous alcoholic potassium carbonate; only one isomer could be detected, m.p. 223.0-223.2° (from benzene).

Anal. Calc'd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89.
Found: C, 68.42; H, 5.37; N, 7.15.

2,2,5-Trimethylcyclohexanone (VII) was obtained by reduction of (V) in the same manner as its isomer was obtained from (IV), b.p. 66–67° at 13 mm., d_4^{25} 0.8905, n^{20D} 1.4442, n^{25D} 1.4425, no reaction with bisulfite. The composition of (VII) and of its derivatives was checked by analysis; semicarbazone m.p. 176.0–176.3° (from alcohol), oxime, plates, m.p. 94.5–94.8° (from alcohol). The mono-*p*-nitrobenzal derivative was obtained by heating (VII) and *p*-nitrobenzaldehyde in alcohol with a few drops of aqueous sodium hydroxide, almost colorless crystals, m.p. 117.5–118.0° (from alcohol).

Anal. Calc'd for $C_{12}H_{18}NO_3$: C, 70.30; H, 7.01; N, 5.12.
Found: C, 70.67; H, 7.36; N, 5.22.

Lead tetraacetate oxidation of (II). To 63.5 g. of (II) dissolved in 150 cc. of glacial acetic acid, 160 g. of lead tetraacetate was added in portions, with stirring. A spontaneous rise in temperature took place; cooling of the reaction flask was effected by running tap water. After standing for 10 minutes, the reaction mixture was poured into 3.5 liters of water containing 105 g. of sulfuric acid and steam distilled. The distillate was neutralized, extracted thoroughly with ether, and the ether extract fractionated. Thirty and five-tenths grams of crude ketone was obtained, approximately 75% of which boiled at 97.5–98.0° at 13 mm. on redistillation through a precision column. The ketone (V) could not be detected; thus the yield of (IV) was 52%. In another experiment, 73 g. of lead tetraacetate was used to oxidize 63.5 g. of (II); a smaller yield of mixed ketones was obtained.

(II) was esterified by heating with ethanol and dry hydrogen chloride. The product, b.p. (2 mm.) 107–112° (analysis for $C_{12}H_{22}O_4$), in benzene solution reacted vigorously with lead tetraacetate.

Hydrogen peroxide oxidation of (I). Both the free acid (I) and its ammonium salt reacted readily with hydrogen peroxide to give, in each case the same major product. Eight and four-tenths grams of (I) was placed in a flask with 14 cc. of glacial acetic acid and 20 cc. of 30% hydrogen peroxide and heated to boiling for 2 hours. The reaction mixture was evaporated and water added to the residue; the oily, water-insoluble material resulting soon crystallized, yield 5.0 g. After recrystallization from isopropyl ether-alcohol, it melted at 143.0–143.5° and was identified as hydroxydihydro- β -campholenolactone (13) (analysis, lactone nature). No oxidation was observed on treatment of the lactone with lead tetraacetate or with chromic acid.

On heating the lactone with ethanol and dry hydrogen chloride, an oil was obtained, b.p. (2 mm.) 104–106°, (found: C, 67.0; H, 9.1) which did not react with lead tetraacetate. Saponification of the oil with alkali followed by acidification did not regenerate the parent lactone, indicating that deep-seated changes in the molecule had taken place.

SUMMARY

The synthesis of 3,4,4-trimethylcyclohexen-2-one, 3,6,6-trimethylcyclohexen-2-one, 3,4,4-trimethylcyclohexanone, and 2,2,5-trimethylcyclohexanone starting from β -campholenic acid has been described.

Tiemann's "isocamphorhorone" is a mixture of the two above-named isomeric unsaturated cyclic ketones.

PASADENA, CALIF.

REFERENCES

- (1) KERP AND MÜLLER, *Ann.*, **299**, 233 (1898).
- (2) HARRIES, *Ann.*, **330**, 190 (1904).
- (3) TIEMANN, *Ber.*, **30**, 242 (1897); see also *Ber.*, **28**, 2166 (1895).
- (4) BEILSTEIN, "Handbuch der organischen Chemie," 4th Ed., **1921**, Vol. III, page 466.
- (5) (a) BLANC, *Bull. soc. chim.*, (3) **19**, 357 (1898); (b) BOUVEAULT, *Bull. soc. chim.*, (3) **19**, 565 (1898); (c) see BREDT, *Ann.*, **314**, 392 (1901).

- (6) BEILSTEIN, "Handbuch der organischen Chemie," 4th Ed., **1925**, Vol. VII, page 65.
- (7) VON BRAUN, KELLER AND WEISSBACH, *Ann.*, **490**, 188 (1931) [*Chem. Abstr.*, **26**, 427 (1932); *Chem. Zentr.*, **102**, II, 3460 (1931)]; formulas for (IV) and (VI) are incorrectly given.
- (8) BUCHMAN AND SARGENT, *J. Org. Chem.*, **7**, 148 (1942).
- (9) AUWERS AND HESSENLAND, *Ber.*, **41**, 1812 (1908).
- (10) Reference 9, page 1814; CORNUBERT AND HUMEAU, *Bull. soc. chim.*, (4) **49**, 1474 (1931).
- (11) PRINGSHEIM AND SCHREIBER, *Chem. Zentr.*, **98**, II, 1225 (1927).
- (12) CRIEGEE, KRAFT, AND RANK, *Ann.*, **507**, 159 (1933); BARTLETT AND BAVLEY, *J. Am. Chem. Soc.*, **60**, 2416 (1938); CRIEGEE, BÜCHNER, AND WALTHER, *Ber.*, **73**, 571 (1940).
- (13) TIEMANN, *Ber.*, **30**, 404 (1897).
- (14) BLANC, *Compt. rend.*, **146**, 79 (1908).
- (15) Compare ASAHIWA AND TUKAMOTO, *Ber.*, **70**, 584 (1937).
- (16) Compare KOMPPA AND BECKMANN, *Ber.*, **69**, 2783 (1936); DELÉPINE, *Bull. soc. chim.*, (5) **4**, 1145 (1937).
- (17) Reference 4, pages 708, 709.
- (18) Compare WALLACH, *Ann.*, **437**, 186 (1924).
- (19) CUSMANO, *Chem. Zentr.*, **85**, I, 977 (1914).

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NAPHTHENIC ACID STUDIES. I. THE SYNTHESIS OF
3,3,4-TRIMETHYLCYCLOPENTANONE¹

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As a degradation product of certain naphthenic acids, von Braun (1) obtained a ketone $C_8H_{14}O$ to which he assigned the structure (V). In spite of the importance of a verification by synthesis, all attempts (2) to prepare the trimethylcyclopentanone (V) have been unsuccessful.²

A number of possible methods for obtaining (V) were considered. These will be outlined here briefly as information on the synthesis of ketones of this type is rather widely scattered in the literature.

A. Conversion of β,β,β' -me₃-adipic acid (me₃ = trimethyl) to (V). While the transformation of me₃-succinic acid to the adipic acid fails (2), the conventional route *via* reduction by appropriate methods (4) of the anhydride of α,β,β me₃-glutaric acid (5) is still open. The desired acid may also be expected [compare formation (6) of β,β -me₂-adipic acid] to result from the oxidation of 3,4,4-me₃-cyclohexanone (I) [preparation from camphor (7); possible preparation from xylenol (8)] or of 3,3,4-me₃-cyclohexanone [possible preparation from me₃-dihydroresorcin (9)]. The preparation of adipic acids by oxidation of Diels-Alder adducts is undoubtedly general (10); conditions for obtaining the required adduct from me₃-ethylene and butadiene are however not yet established (11).

B. Ring contraction (12) of (I) or of 3,3,4-me₃-cyclohexanone. Two cyclopentanones are possible from each ketone; analogies (13) predict that in both cases (V) would be the chief product.

C. Shift (14) of the carbonyl group in 2,2,3-me₃-cyclopentanone (15) or in 2,3,3-me₃-cyclopentanone (15) to the neighboring position. The possibility of a Wagner rearrangement (compare 6 b) during the dehydration step impairs the value of this method.

D. Oxidative transformations starting from 1,1,2-me₃-cyclopentene-2 (16) [compare the formation (17) of cyclopentenone from cyclopentene]. Although the use of selenium dioxide is not indicated (18) here, auto-oxidation might be successful (19).

E. Modification of 3,3,4,4-me₄-cyclopentanone syntheses (20) to fit the present case.

F. See following communication.

It was decided to attempt the utilization of the trimethylcyclohexanone (I) as starting material for both methods (A) and (B). The steps which finally led to (V) are indicated on the chart. Although the direct oxidation of (I) to (IV) could not be accomplished, the adipic acid (IV) was easily obtained³ (21) from the diketone (III) [or enol form of (III)], which was made *via* the dibromo ketone (II)⁴ as intermediate [model experiments decided against direct oxidation

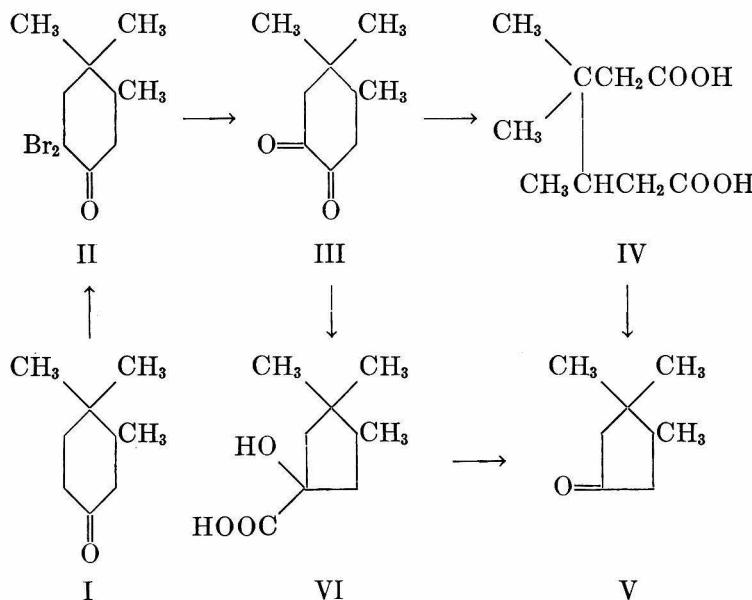
¹ The results contained in this paper were presented before the Pacific Division of the American Association for the Advancement of Science at the Pasadena meeting, June 18, 1941.

² The naphthene ketone has been referred to by von Braun (3) as "der Synthese leider nicht zugänglich".

³ An alternative path leading to (IV) involves the oxidation (23) of the oxymethylene ketone from (I).

⁴ We prefer to give this dibromide the structure (II) rather than that of a 3,4,4-trimethyl-2,6-dibromocyclohexanone, since we feel that Wallach's arguments (12 a) in favor of the latter formulation are inconclusive.

(22) of (I) to (III)]. (IV) was smoothly converted to the desired ketone (V). Whereas theoretically the steps leading from (I) to (III) could give rise to two isomeric diketones, the results (see Experimental Part) indicated that little, if any, of a second isomer was formed. That it is (III) which is obtained and not its isomer follows conclusively, aside from the fact that the isomer of (III),



3,4,4-trimethylcyclohexandione-1,2 is reported (7) to have other properties, from the demonstration of two unsubstituted α positions in our ketone (V). The synthesis of (V) by method (B) [(III) \rightarrow (VI) \rightarrow (V)] was also achieved; the properties of (V), made by both paths, agree.

TABLE I

	BOILING POINT	SEMICARBAZONE	OXIME	DI- <i>p</i> -NITROBENZAL DERIVATIVE
Ketone from naphthenic acids.....	172-174°	m.p. 162-163°	b.p. ₁₄ 116-120°	m.p. 188-190°
3,3,4-Trimethylcyclopentanone.....	172-173°	m.p. 213.5-214.0°	m.p. 99.8-100.0°	α -form, m.p. 204.7-205.1° β -form, m.p. 202.0-202.5°

In Table I, these properties of the synthetic ketone (V) are compared with those given by von Braun (1, 3) for his naphthene ketone. The non-identity of the two substances is beyond question, as there is no doubt that the von Braun semicarbazone was accurately characterized. An unusual feature en-

countered in characterizing (V) was the isolation from it of two di-*p*-nitrobenzal derivatives (24); although four cis-trans isomers are possible, it is customary to encounter but one derivative in reactions of this type.⁵

It is obvious that since the structure assigned by von Braun to his naphthenic acid degradation product is in error, his structures for the parent naphthenic acids also are in need of revision. The correct formulation of the von Braun petroleum acids will be discussed in a future communication from this Laboratory.

EXPERIMENTAL PART

Preliminary experiments. 3,4,4-Trimethylcyclohexanone (I) was prepared from a mixture of 3,4,4-trimethylcyclohexen-2-one and 3,6,6-trimethylcyclohexen-2-one (7) by catalytic reduction and isolation over the bisulfite addition compound; its constants were the same as those found (7) for material prepared by reduction of pure unsaturated ketone. The oxidation of (I) was carried out with potassium permanganate and with nitric acid under conditions which lead to the formation of adipic acid from cyclohexanone. With permanganate, an oily mixture of organic acids was obtained from which no (IV) could be isolated even by the use of seed crystals. With nitric acid there was evidence that nitration took place.

2,2,5-Trimethylcyclohexanone (7) was oxidized (22) by heating with selenium dioxide in ethanol; no appreciable amount of diketone was obtained.

Cyclohexanone (20 g.) was brominated (12) with four atoms of bromine, and the product treated with alkali at room temperature. After acidification, the diketone was taken up in ether (12 b), the ether removed, and the residue mixed with 20 cc. of 30% hydrogen peroxide. The oxidation takes place only in the presence of alkali, which must be added cautiously, as the reaction is exothermic and accompanied by gas evolution. Sodium hydroxide solution was therefore added slowly to the diketone-hydrogen peroxide mixture until it remained strongly basic. After acidification of the reaction product, 2.5 g. of adipic acid was isolated by recrystallization (8% yield from cyclohexanone).

Twenty grams of cyclohexanone was brominated as before, and the product treated with alkali in two steps (12 a). The crude hydroxy acid formed was oxidized with potassium permanganate in dilute sulfuric acid solution (25), a procedure found to give better results than the lead dioxide method (12 a). Two and one-tenth grams of cyclopentanone was isolated, a 12% yield from cyclohexanone.

3,4,4-Trimethyl-6,6-dibromocyclohexanone (II). Two grams of (I) was dissolved in 8 cc. of glacial acetic acid, the solution cooled to 0°, and 4.6 g. of bromine was added slowly with continued cooling. The resulting pale orange solution was poured into ice-water and the organic phase separated by centrifuging; additional small amounts of crude dibromide were obtained by extraction of the aqueous layer with ether. Occasionally the dibromide started to crystallize during the washing with ice-water, otherwise it could be obtained crystalline by strong cooling of a dry petroleum ether-alcohol solution. Recrystallized from petroleum ether, it melted at 81.2-81.7°.

Anal. Calc'd for C₉H₁₄Br₂O: C, 36.27; H, 4.73; Br, 53.63.
Found: C, 36.27; H, 4.80; Br, 53.56.

4,4,5-Trimethylcyclohexandione-1,2 (III). The crude dibromide obtained from 2 g. of (I) was shaken vigorously for 1.5 hours with a solution of 2 g. of potassium hydroxide in 20 cc. of water. (Because of the insolubility of the dibromide, aqueous alcoholic sodium

⁵ The di-*p*-nitrobenzal derivative from (I) for which the same number of forms are theoretically possible, was isolated (7) only in a single modification.

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hydroxide was used in larger runs; this was added in portions and the reaction brought to completion by warming to about 35°.) The resulting yellow solution was filtered from small amounts of tarry matter using "filter aid", and acidified with 6 N hydrochloric acid. The oil which precipitated crystallized (in other experiments the oil was first steam distilled and the diketone isolated from the steam distillate) on strong cooling, was filtered, washed with water, and recrystallized from petroleum ether, *m.p.* 93.5–94.1°.

Anal. Calc'd for $C_9H_{14}O_2$: C, 70.10; H, 9.15.
Found: C, 69.79; H, 9.02.

β,β,β' -Trimethyladipic acid (IV). Pure (III) was almost quantitatively converted by alkaline peroxide oxidation to (IV); it was found convenient however to prepare (IV) from crude steam distilled (III). Crude (III) (3.3 g.) obtained from 10 g. of (I) was mixed with 30 cc. of 30% hydrogen peroxide in a 125-cc. flask, and 30% sodium hydroxide solution added cautiously until there was no further evidence of reaction. The reaction mixture was acidified and the precipitate, which crystallized very slowly, removed by filtration and washed with petroleum ether. The crude (IV) was recrystallized from a mixture of isopropyl ether and a little alcohol, seeding and allowing time for complete crystallization. Two crystal forms, triangular plates and rhombs, were noted, both melting at 127.3–127.6° (mixed *m.p.* same). The yield of pure (IV) [1.75 g. = 13% from (I)] corresponded closely to the weight of crude acid isolated from the acidified reaction mixture, indicating that crude (III) contained no appreciable amount of isomer.

Anal. Calc'd for $C_9H_{16}O_4$: C, 57.43; H, 8.57.
Found: C, 57.27; H, 8.72.

Preparation of 3,3,4-trimethylcyclopentanone (V) from (IV). One and one-half grams of pure (IV) and 0.13 g. of manganese carbonate were placed in a small distilling flask and heated in a metal-bath at 280–320° for one-half hour. One gram of (V) was obtained, which boiled almost entirely at 168–169° (172–173° corr.) at 742 mm., d_{4}^{25} 0.892, n_{D}^{25} 1.4386.

Anal. Calc'd for $C_8H_{14}O$: C, 76.14; H, 11.18.
Found: C, 75.95; H, 11.00.

The semicarbazone melted at 213.5–214.0° (from alcohol).

Anal. Calc'd for $C_9H_{17}N_3O$: C, 58.98; H, 9.35; N, 22.93.
Found: C, 59.38; H, 9.44; N, 22.76.

The oxime melted at 99.8–100.0° (from alcohol).

Anal. Calc'd for $C_8H_{15}NO$: N, 9.92. Found: N, 10.14.

The condensation between (V) and *p*-nitrobenzaldehyde was effected by heating the components in alcohol, either with a drop of aqueous sodium hydroxide or with a few drops of sodium carbonate solution; in both cases a mixture of isomers resulted. The separation of the α -form in the pure state was accomplished by several recrystallizations from benzene; orange-yellow needles, *m.p.* 204.7–205.1°. The isolated clusters of massive rhombs which constitute the β -form were mechanically separated from the tufts of needle crystals. They were slightly paler in color than the α -form, melted at 202.0–202.5° (from benzene), and when mixed with the latter depressed the *m.p.* considerably.

Anal. Calc'd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14.
Found: (α -form) C, 67.83; H, 5.13; N, 7.19.
Found: (β -form) C, 68.03; H, 5.44; N, 7.27.

A suitable adsorbent for a chromatographic separation of the two forms was not found.

1-Hydroxy-3,3,4-trimethylcyclopentanecarboxylic acid (VI). Twenty grams of (I) in 60 cc. of glacial acetic acid was cooled until crystals of solvent started to separate and, with

continued external cooling, brominated over a 25-minute period with 45.8 g. of bromine in 40 cc. of acetic acid. The product was washed with ice-water and the crude dibromide mixed with 50 cc. of water and 30 cc. of alcohol, cooled, and shaken with a solution of 40 g. of sodium hydroxide in 150 cc. of water (the latter being added slowly and with cooling). As soon as the dibromide had gone into solution, the reaction mixture was filtered, the tar dissolved in alcohol and treated anew with 10 g. of sodium hydroxide in 50 cc. of water, and this reaction product, after adding water to throw out insoluble material and filtering using "filter aid", was combined with the main filtrate. The combined filtrates were evaporated together with an additional 10 g. of sodium hydroxide on the steam-bath for 18 hours, excess 40% sulfuric acid was added to the residue, and the pale yellow oil which separated taken up in ether and the aqueous phase repeatedly extracted with the same solvent. The combined ether solutions on evaporation gave an oil which crystallized in part. The oil was filtered from the crystals (1.5 g.) and the mother liquors distilled *in vacuo*. The distillate (mostly boiling at *ca.* 125° at 2 mm.) also crystallized in part to give 1.9 g. of crystals [total yield of crystalline (VI) 13.5% from (I)]. The distilled crystals (1.9 g.) were recrystallized from petroleum ether-alcohol, yielding 1.0 g. of pure α -isomer m.p. 114.0–114.5° (in another experiment this higher-melting form was obtained by recrystallization of undistilled crystalline acid).

The undistilled crystalline acid above (1.5 g.) proved to be a mixture consisting of the acid just described together with a more slender needle-shaped variety. A small amount of the latter (β -isomer) was obtained in a pure form by repeated recrystallization from petroleum ether-alcohol, m.p. 109–110° (mixed m.p. with its isomer 88–96°).

Anal. Calc'd for $C_9H_{16}O_3$: C, 62.76; H, 9.37.
 Found: (α -form) C, 62.90; H, 9.50.
 Found: (β -form) C, 62.89; H, 9.57.

Preparation of (V) from (VI). A solution of 0.43 g. of potassium permanganate in 40 cc. of water and 2 cc. of concentrated sulfuric acid was added in portions to 0.70 g. of (VI) (pure α -form) heated to 40°. The reaction proceeded smoothly and the product was isolated by steam distillation in the usual manner, yield 0.45 g. (V) obtained in this way had the same properties as the ketone from (IV); the derivatives were identical (mixed m.p.'s). In another experiment, crude (VI), a mixture of oil and crystals, was oxidized with permanganate; not only was the ketone obtained very similar in properties to pure (V), but also in its behavior towards the usual ketone reagents it proved to be indistinguishable from the latter (indication for substantial purity of crude (III)].

SUMMARY

The synthesis of 3,3,4-trimethylcyclopentanone has been accomplished. This ketone is not identical with the $C_8H_{14}O$ ketone obtained by von Braun from naphthenic acids and consequently the formulation of certain naphthenic acids as related to this ketone is in error.

PASADENA, CALIF.

REFERENCES

- (1) VON BRAUN, *Ann.*, **490**, 100 (1931).
- (2) VON BRAUN, KELLER, AND WEISSBACH, *Ann.*, **490**, 179 (1931).
- (3) VON BRAUN, MANNES, AND REUTER, *Ber.*, **66**, 1500 (1933).
- (4) Compare BLANC, *Bull. soc. chim.*, (3) **33**, 879, 897 (1905); (4) **3**, 286 (1908).
- (5) KON AND THORPE, *J. Chem. Soc.*, **121**, 1795 (1922); see PANDYA AND THORPE, *J. Chem. Soc.*, **123**, 2855, 2858 (1923).

(6) (a) CROSSLEY and RENOUF, *J. Chem. Soc.*, **91**, 63 (1907); **87**, 1487 (1905); (b) CHAVANNE, MILLER, and CORNET, *Chem. Abstr.*, **26**, 2712 (1932) [*Bull. soc. chim. Belg.*, **40**, 673 (1931)]; (c) DEY and LINSTEAD, *J. Chem. Soc.*, **1935**, 1064; (d) RYDON, *J. Chem. Soc.*, **1936**, 594.

(7) BUCHMAN and SARGENT, *J. Org. Chem.*, **7**, 140 (1942).

(8) See AUWERS and KEIL, *Ber.*, **35**, 4216 (1902); compare MILLER and ADAMS, *J. Am. Chem. Soc.*, **58**, 788 (1936).

(9) See CROSSLEY and RENOUF, *J. Chem. Soc.*, **99**, 1101 (1911); compare reference 6a.

(10) Compare FARMER and WARREN, *J. Chem. Soc.*, **1929**, 899; DIELS and ALDER, *Ber.*, **62**, 2087 (1929).

(11) See ALDER and WINDEMUTH, *Ber.*, **71**, 1939 (1938).

(12) Compare WALLACH, (a) *Ann.*, **414**, 296 (1918); (b) *Ann.*, **437**, 148 (1924).

(13) Compare reference 12a, page 317; reference 12b, page 160.

(14) Compare KOMPPA, KلامI, and KUVAJA, *Naturwissenschaften*, **27**, 197 (1939); *Ann.*, **547**, 185 (1941).

(15) BEILSTEIN, "Handbuch der organischen Chemie," 4th Ed., **1925**, vol. VII, page 26.

(16) BEILSTEIN, "Handbuch der organischen Chemie," 4th Ed., **1922**, vol. V, page 74, 75; **1930**, supplementary vol. V, page 37.

(17) DANE and EDER, *Ann.*, **539**, 207 (1939); DANE, SCHMITT, and RAUTENSTRAUCH, *Ann.*, **532**, 29 (1937).

(18) GUILLEMONAT, *Ann. chim.*, (11) **11**, 143 (1939).

(19) Compare DUPONT, ZACHAREWICZ, and DULOU, *Compt. rend.*, **198**, 1699 (1934).

(20) FRANCIS and WILLSON, *J. Chem. Soc.*, **103**, 2238 (1913); INGOLD and SHOPPEE, *J. Chem. Soc.*, **1928**, 365 [compare GUHA and SESHADRIENGAR, *Ber.*, **69**, 1208 (1936)]; see also FARMER and KRACOVSKI, *J. Chem. Soc.*, **1927**, 683.

(21) Compare GODCHOT and CAUQUIL, *Compt. rend.*, **202**, 326 (1936).

(22) Compare RILEY, MORLEY, and FRIEND, *J. Chem. Soc.*, **1932**, 1875; reference 21.

(23) Compare Ruzicka, SCHINZ, and SEIDEL, *Helv. Chim. Acta*, **23**, 935 (1940).

(24) Compare CORNUBERT, *Compt. rend.*, **190**, 440 (1930); CORNUBERT and DE DEMO, *Compt. rend.*, **194**, 1587 (1932).

(25) Compare reference 12a, page 343.

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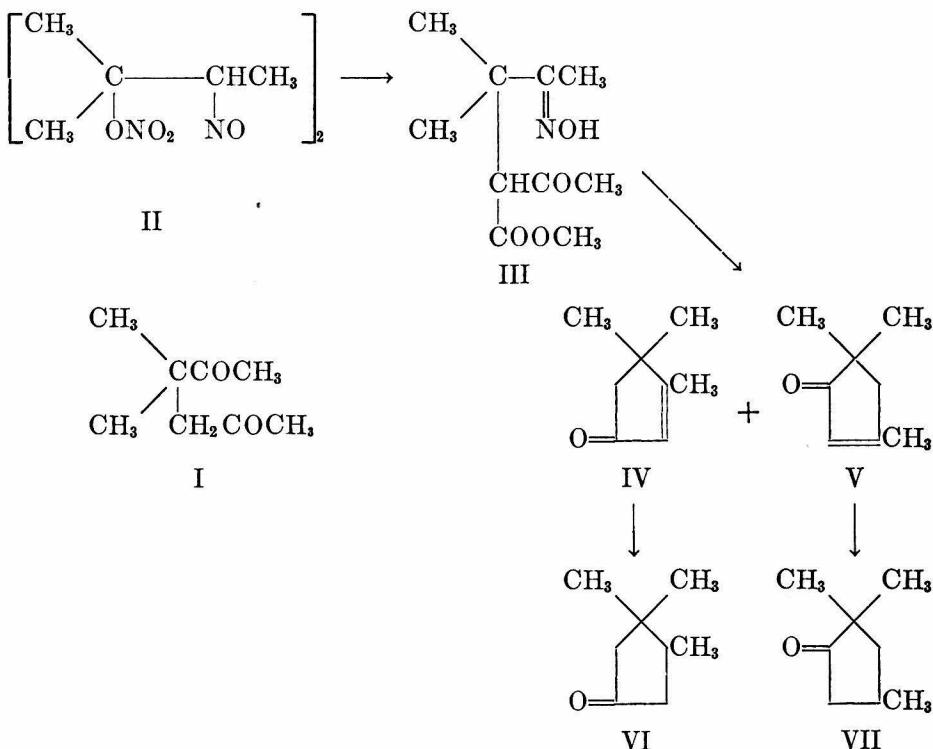
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THE SYNTHESIS OF 3,3,4-TRIMETHYLCYCLOPENTANONE. II

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The preceding paper (1) reports the synthesis of the above-named ketone by two closely related paths; several possible alternative methods of synthesis are also listed. To these may be added the following: 3,3-dimethylhexandione-2,5 (I) on cyclization (2) should yield a mixture of (IV) and (V) from which the desired ketone (VI) could be obtained. (I) might conceivably be made by methylation of acetylacetone or by the action of chloroacetone on sodium methyl isopropyl ketone.



The literature (3, 4) discloses that the equivalent of these reactions has already been carried out by Wallach. His synthesis started from "bis-trimethylethylene nitrosate" (II) which was condensed with sodium methyl acetoacetate to give the compound (III). Treatment of this latter with 50% potassium hydroxide yielded an unsaturated ketone fraction which, on the basis of analogy (5), would be expected to be a mixture of (IV) and (V). Actually Wallach (3) characterized but one trimethylecyclopentenone, which he regarded as (V);

reduction (4) of his crude ketone product gave a mixture of saturated isomers. While pointing out that these isomers¹ might correspond to (VI) and (VII), Wallach left open the question of assigning definite structures.

The repetition of these experiments led to the isolation from (III) of two isomeric unsaturated ketones, which were separated by careful fractionation; reduction afforded the corresponding saturated ketones. The structure of the higher-boiling saturated isomer is established by virtue of its identity with ketone (VI) obtained (1) from 3,4,4-trimethylcyclohexanone. The structures of the parent unsaturated ketone (IV) and of the related pair (V) and (VII) follow indirectly and find further substantiation in the properties of these substances (see Table I). A comparison of the Table with that in the paper next preceding

TABLE I

	IV ^a	V	VI ^b	VII ^c
Boiling point	b.p. ₂₀ 87.5-88.0°	b.p. ₂₀ 76.5-77.0°	b.p. ₇₄₂ 173-175°	b.p. ₇₄₂ 157-158°
Semicarba- zone	m.p. 199.5-200.0° forms rapidly	m.p. 205.0-205.5° forms slowly	m.p. 213.5-214.0°	m.p. 171.0-171.3°
Derivative with hydroxyl amine	oil presumably an oxime	oxime	m.p. 99.8-100.0°	m.p. 79.7-80.0°
Derivatives with <i>p</i> -ni- trobenzal- dehyde			di- <i>p</i> -nitrobenzal derivatives m.p. 204.7-205.1° m.p. 202.0-202.5°	mono- <i>p</i> -nitro- benzal deriva- tive m.p. 99.3-99.5°
Reaction with bisulfite	none	none	reacts slowly	none

^a Wallach (3) reported as a derivative of this compound the semicarbazone, m.p. 199-200°.

^b Wallach (4) reported for this compound: b.p. 167-171°, semicarbazone, m.p. 214°, oxime, m.p. 110°.

^c Wallach (4) reported for this compound: b.p. 162-168°, semicarbazone, m.p. 178°, oxime, m.p. 78°.

(5) brings out not uninteresting resemblances between the 5-ring ketones (IV), (V), (VI), and (VII) and their correspondingly numbered 6-ring analogs.

The author wishes to thank Dr. E. R. Buchman for suggesting this problem and for helpful advice in connection with the work.

EXPERIMENTAL PART

*Preparation of unsaturated ketone mixture.*² "Bis-trimethylethylene nitrosate" (II) was prepared as indicated in the literature (7) by passing oxides of nitrogen into a solution of 60 cc. of trimethylethylene in 150 cc. of glacial acetic acid which was kept cooled to the

¹ Chemisches Zentralblatt (6) refers to these as 2,2,4-trimethylcyclopentanone "Nr. 1" and "Nr. 2". It is thus understandable how any but the most thorough literature survey would have failed to disclose their bearing upon the naphthene ketone problem (1).

² No appreciable amount of 3-methylcyclopenten-2-one was obtained from the action of aqueous alkali on acetylacetone; much tar was formed.

point where solid acetic acid separated. The nitrogen dioxide was generated by the action of nitric acid on copper turnings (superior to the action of concentrated nitric acid on arsenic trioxide); the passage of gas was stopped as soon as the solution turned green, and the crystals which had separated were filtered off and washed with acetic acid and with water. The resulting white crystalline material³ was air dried (44% yield); further small amounts of crude (II) were precipitated from the mother liquors by addition of water.

The nitrosate prepared in this manner proved suitable for conversion into (III); Wallach (3) had claimed that a specially purified (II) was necessary. Nine and six-tenths grams of sodium was dissolved in 160 cc. of methanol, 52 g. of methyl acetoacetate added, and the solution cooled. Sixty-four grams of (II) was then added and the mixture heated cautiously to initiate the reaction which proceeded exothermally; cooling of the reaction flask with running tap water was necessary to prevent loss of solvent through the condenser. The reaction was complete in five minutes, at the end of which the solvent was removed *in vacuo* and the residue refluxed for four hours from a copper retort with 450 g. of potassium hydroxide and 450 cc. of water, and then steam distilled. In a parallel experiment, after the reaction was complete, the solution was filtered from the sodium nitrate which had separated, the filtrate evaporated and (III) isolated from the residue by recrystallization from alcohol-acetone; m.p. 148.5-149.0° (analysis), turns reddish on exposure to light.

The steam distillates from three of the above sized runs were combined, saturated with ammonium sulfate, extracted several times with isopropyl ether, the ether extracts dried over sodium sulfate and fractionated.⁴ The main fraction, b.p. 75-90° at 20 mm., consisted for the most part of (IV) and (V) and amounted to 73 g., 49% yield from (II).

3,4,4-Trimethylcyclopenten-2-one (IV) was obtained in an 11% yield from (II) on fractionation of the unsaturated ketone mixture through a precision column, b.p. 87.5-88.0° at 20 mm., d_4^{20} 0.925, n_{D}^{20} 1.4720. Analysis and behavior on reduction disclosed the presence of a small amount of nitrogen-containing impurity; the constants given are therefore only approximately correct for pure (IV).

Anal. Calc'd for $C_8H_{12}O$: C, 77.37; H, 9.74.
Found: C, 76.64; H, 9.97.

(IV) did not react with aqueous sodium bisulfite solution. The oxime was obtained as an oil; the semicarbazone formed readily, m.p. 199.5-200.0° from ethanol.

Anal. Calc'd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19.
Found: C, 59.84; H, 8.31; N, 23.60.

3,5,5-Trimethylcyclopenten-2-one (V) was obtained as above in 12% yield from (II), b.p. 76.5-77.0° at 20 mm., d_4^{20} 0.906, n_{D}^{20} 1.4608.

Anal. Calc'd for $C_8H_{12}O$: C, 77.37; H, 9.74.
Found: C, 76.35; H, 9.87.

(V) also did not form a bisulfite addition compound. The product obtained with hydroxylamine was found difficult to purify by recrystallization; it was sublimed at 2 mm. and the crystalline sublimate recrystallized from isopropyl ether, needles, m.p. 108.0-108.2°.

Anal. Calc'd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06.
Found: C, 69.23; H, 9.41; N, 10.28.

³ Attention may be directed to the fact that (II) cannot be stored. An explosion occurred when a sample, which had stood in a stoppered bottle for 2½ weeks without noticeable alteration, suddenly decomposed completely.

⁴ From the forerun was isolated about one-half gram of acetone oxime (analysis, mixed m.p.) b.p. *ca.* 61° at 20 mm., m.p. 61.0-61.2° from petroleum ether. With an equivalent amount of picric acid this substance gave a picrate, quite soluble in the usual solvents, m.p. 82.0-82.2° from isopropyl ether-alcohol (analysis). The addition compound lost its acetone oxime on drying *in vacuo* at room temperature.

The analysis discloses that the derivative is an oxime; higher molecular weight amorphous material also sublimed, so that the formation of hydroxylaminooxime cannot be excluded. By comparison with its isomer, the semicarbazone formed at an extremely slow rate; for its preparation the components were allowed to stand in aqueous solution at room temperature for two weeks, m.p. 205.0-205.5° from ethanol-water.

Anal. Calc'd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19.
Found: C, 59.96; H, 8.31; N, 23.53.

3,3,4-Trimethylcyclopentanone (VI) was prepared by catalytic reduction (5) of (IV), b.p. 169-171° (173-175° corr.) at 742 mm., d_4^{25} 0.892, n_{D}^{25} 1.4380 (analysis). The crude reduction product contained a small amount of volatile base, possibly ammonia, arising from the nitrogen-containing impurity in (IV). (VI) reacted slowly with saturated aqueous bisulfite solution [means of separation from (VII)]. The derivatives, including the di-*p*-nitrobenzal derivatives, were identical with those described (1) previously (mixed m.p.'s). The m.p. of the oxime (100.8-101.0° corr.) was unchanged after repeated recrystallization (Wallach reported 110°).

2,2,4-Trimethylcyclopentanone (VII) was formed by catalytic reduction of (V), b.p. 153-154° at 742 mm., d_4^{25} 0.871, n_{D}^{25} 1.4279.

Anal. Calc'd for $C_8H_{14}O$: C, 76.14; H, 11.18.
Found: C, 75.15; H, 11.26.

(VII) did not form a bisulfite addition compound. It reacted with semicarbazide somewhat less readily than its isomer; semicarbazone m.p. 171.0-171.3° from alcohol.

Anal. Calc'd for $C_9H_{17}N_3O$: N, 22.93. Found: N, 22.90.
The oxime was crystallized from alcohol and sublimed at 3 mm. for analysis, m.p. 79.7-80.0°; *in vacuo* it is noticeably volatile even at room temperature.

Anal. Calc'd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92.
Found: C, 68.02; H, 10.59; N, 10.11.

A pale yellow mono-*p*-nitrobenzal derivative was obtained in the usual manner, m.p. 99.3-99.5° from methanol.

Anal. Calc'd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40.
Found: C, 69.95; H, 6.93; N, 5.94.

SUMMARY

A convenient method for the synthesis of 3,3,4-trimethylcyclopentanone has been described.

3,4,4-Trimethylcyclopenten-2-one, 3,5,5-trimethylcyclopenten-2-one and 2,2,4-trimethylcyclopentanone have been characterized.

PASADENA, CALIF.

REFERENCES

- (1) BUCHMAN AND SARGENT, *J. Org. Chem.*, **7**, 148 (1942).
- (2) Compare ROBINSON, *J. Chem. Soc.*, **1938**, 1390; see also GOLDBERG AND MÜLLER, *Helv. Chim. Acta*, **21**, 1699 (1938).
- (3) WALLACH, *Ann.*, **408**, 202 (1915).
- (4) WALLACH, *Ann.*, **437**, 193 (1924).
- (5) BUCHMAN AND SARGENT, *J. Org. Chem.*, **7**, 140 (1942).
- (6) *Chem. Zentr.*, Formula index 1922-1924, page 223.
- (7) WALLACH, *Ann.*, **241**, 288, (1887).

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MERCAPTOTHIAZOLES: OXIDATION AND ALKYLATION STUDIES

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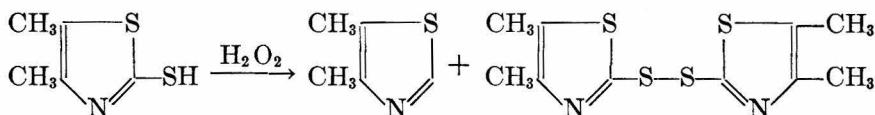
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Since the discovery (1) of the presence of the thiazole nucleus in vitamin B₁, there has been a revival of interest in chemistry pertaining to the thiazole ring (2). We have investigated the feasibility of preparation of thiazoles unsubstituted in the 2 position from the readily obtainable 2-mercaptop compounds, since the problem has a bearing on possible vitamin syntheses.¹ The oxidative replacement by hydrogen of the mercapto group in compounds containing the grouping $-\text{N}=\text{C}(-\text{SH})-\text{N}=$ in which the mercapto group is joined to a heterocyclic ring is easily accomplished (3), and it was to be expected that analogous methods would be successful with mercaptothiazoles which correspond to the type $-\text{N}=\text{C}(-\text{SH})-\text{S}-$.

In fact, the oxidation of 2-mercaptop-4-methylthiazole by hydrogen peroxide in both neutral and alkaline solution has already been reported by Ochiai and Nagasawa (2b); 4-methylthiazole is formed in the former case, 4-methylthiazole-2-sulfonic acid in the latter. The oxidation of 2-mercaptopthiazoles by peroxide has also been the subject of several patents (4). The reaction is carried out in strongly acid medium, and high yields of the corresponding unsubstituted thiazoles are claimed. Apparently other oxidizing agents have not previously been employed in this connection.

The present paper deals with a study of the oxidation of 2-mercaptop-4,5-dimethylthiazole, using as oxidizing agents hydrogen peroxide and nitric acid (3), both of which reagents have been used to remove SH groups from analogous ring structures. Hydrogen peroxide was employed in neutral solution and in conjunction with varying amounts of acid, with the results which are summarized in the accompanying table. It is evident that, while some of the desired thiazole is produced by neutral peroxide, it is advisable to work at moderately high acid concentrations. When the reaction is carried out in neutral or slightly acid solutions 4,5-dimethylthiazole-2 disulfide forms the bulk of the reaction product,

¹ The possibility of effecting this reaction by use of either hydrogen peroxide or nitric acid was first pointed out by one of us (E. R. B.) in French Patent 803495 (1936) issued to the Research Corporation.



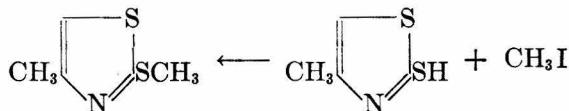
while at high acid concentrations this oxidation product is not detected. Dilute nitric acid was found also to be an efficient agent for removal of the mercapto group. The yield of unsubstituted thiazole is about the same as when strongly acid peroxide is used; no by-products were isolated.

The 2-mercaptopthiazoles are easily prepared from ammonium dithiocarbamate plus the proper α -halogeno ketone. The analogous reaction with dithiocarbamic esters should lead to thiazole-2 thioethers. This was confirmed by experiment: methyl dithiocarbamate gave with chloroacetone

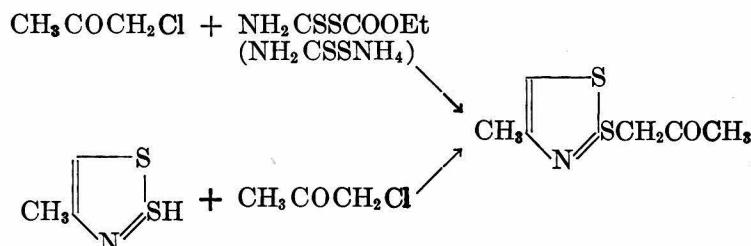
TABLE I
HYDROGEN PEROXIDE OXIDATION OF 2-MERCAPTO-4,5-DIMETHYLTHIAZOLE.
INFLUENCE OF ACID CONCENTRATION

Mercaptothiazole	PARTS BY WEIGHT OF:			YIELD OF 4,5-DIMETHYLTHIAZOLE
	Hydrochloric acid Sp. gr. 1.19	Water	Hydrogen Peroxide 30%	
58	—	275-300	136	10-11%
58	20	220	136	34%
58	40	200	136	52-60%
58	240	—	136	60%

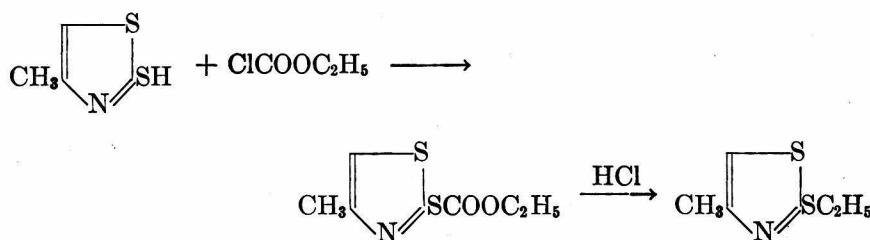
2-methylthio-4-methylthiazole, which was conveniently obtained also by methylation (5) of 2-mercaptop-4-methylthiazole with methyl iodide.



Chloroacetone reacted with S-carbethoxy dithiocarbamate but the product was not the expected S-carbethoxythiazole; instead it was shown to be 2-acetonylthio-4-methylthiazole (the amphoteric nature of which is noteworthy), best obtained by the action of chloroacetone upon 2-mercaptop-4-methylthiazole (no bicyclic thiazolium salt is formed), and which was further detected among the products of the reaction between chloroacetone and ammonium dithiocarbamate.



The action of ethyl chlorocarbonate upon 2-mercaptop-4-methylthiazole was found also to proceed in a somewhat anomalous fashion. At room temperature 2-carbethoxythio-4-methylthiazole was formed in good yields but, if the reaction mixture was heated at 100°, carbon dioxide was eliminated with consequent formation of 2-ethylthio-4-methylthiazole. A



parallel to this reaction is the production of S-ethylisothiourea chloride from ethyl chlorocarbonate and thiourea (6).

Mention should also be made of a curious decomposition which thiazole-2 disulfides appear to undergo, especially when in a not highly purified state. 4,5-Dimethylthiazole-2 disulfide, on standing at room temperature for several months in a loosely stoppered flask, was found to have decomposed. In addition to a small amount of unchanged disulfide, 2-mercaptop-4,5-dimethylthiazole, 4,5-dimethylthiazole-2-monosulfide² and sulfuric acid were shown to be present. The mechanism of this internal oxidation-reduction (15) is not clear; tentatively it may be looked upon as hydrolytic cleavage (5) under mild conditions yielding an unstable intermediate (8), which then acts as an oxidizing agent upon other constituents present. The amounts of decomposition products which were isolated are roughly in agreement with the equation:



² The same thiazole monosulfide was also obtained in small amounts in one of the peroxide oxidation experiments; compare the formation of thiazoline-2 monosulfide by treatment of 2-mercaptopthiazoline with nitrous acid (7).

EXPERIMENTAL PART

Preparation of Mercaptothiazoles

The ammonium dithiocarbamate was made by the interaction of alcoholic ammonia and carbon disulfide (9) and was used without purification. The chloroacetone was Eastman's practical grade containing some asym-dichloroacetone which, however, did not interfere in the reactions studied. 3-Chlorobutanone-2 was prepared by the action of sulfonyl chloride on methyl ethyl ketone (10) and separated from the simultaneously formed isomer by fractional distillation. 3-Bromobutanone-2 was prepared by bromination of methyl ethyl ketone in the presence of water at room temperature (11); 1-bromobutanone-2 was present in the higher-boiling fraction obtained on distillation of the reaction product.

Chloroacetone and the isomeric bromobutanones were found to react rapidly with ammonium dithiocarbamate. In preparing mercaptothiazoles from such reactive halides, it was found necessary to avoid an excess of α -halogeno ketone during the reaction, since otherwise extensive amounts of by-product were formed. The procedure adopted was to add the theoretical amount of halogen ketone slowly through a dropping-funnel to a suspension of the dithiocarbamate in absolute alcohol, meanwhile agitating the mixture constantly in an ice-bath. The reactants were allowed to stand at room temperature for 12 hours, heated for 1 hour on a water-bath, and the product worked up in a suitable manner.

2-Mercapto-4-methylthiazole (5, 12). The reaction mixture from 60 g. of chloroacetone and 71.5 g. of ammonium dithiocarbamate in 140 cc. of absolute alcohol was filtered and the solid washed with absolute alcohol. Evaporation of the filtrate gave an oil, which on seeding and shaking with water was transformed into a crystalline cake. This was pressed on tile, yielding 51.5 g. (85%) of substantially pure material, m.p. 88.0-88.5° from isopropyl ether-alcohol. Small amounts could be distilled; b.p. at 3 mm. *ca.* 188°.

2-Mercapto-4,5-dimethylthiazole. (a) *Preparation from 3-chlorobutanone-2*. To 10 g. of ammonium dithiocarbamate suspended in 20 cc. of absolute alcohol was added 11.7 g. of chloro ketone. The mixture was heated for one-half hour on a water-bath, after which the solvent was evaporated and the residue treated with water. Filtration yielded 6.4 g., m.p. 163°.

(b) *Preparation from 3-bromobutanone-2*. The condensation of 29.4 g. of bromo ketone with 21.4 g. of ammonium dithiocarbamate in 45 cc. of absolute alcohol was effected, and the solvent removed by evaporation. To the residue water was added, the solution filtered, and the material thus obtained pressed on tile; yield 21.5 g. (75%), m.p. 163° from alcohol. For analysis a portion was recrystallized from ethyl acetate, m.p. 163.5-163.8°.

Anal. Calc'd for $C_6H_7NS_2$: C, 41.35; H, 4.86; N, 9.64.

Found: C, 41.55; H, 4.73; N, 9.71.

2-Mercapto-4-ethylthiazole. Thirty-three grams of brominated methyl ethyl ketone, b.p. at 23 mm. 58-68°, and 24 g. of ammonium dithiocarbamate in 50 cc. of absolute alcohol were allowed to react in the usual manner. After removal of the solvent and treatment with water, the solid mass remaining was well washed with ether. The 12 g. of ether-insoluble material thus obtained was identified as 2-mercaptop-4,5-dimethylthiazole. The ether solution, on evaporation, yielded 18 g. of impure crystalline material which was pressed on tile and recrystallized from ethyl

alcohol, giving 2-mercapto-4-ethylthiazole, m.p. 87.0-87.1°, stable, white, silvery needles (crude material easily oxidized by air).

Anal. Calc'd for $C_6H_7NS_2$: C, 41.35; H, 4.86; N, 9.64.
Found: C, 41.21; H, 4.78; N, 9.96.

Oxidation of Mercaptothiazoles

Oxidation of 2-mercapto-4-methylthiazole. To a continuously agitated suspension of 10 g. of the mercaptothiazole in 45 cc. of water, 26 g. of commercial 30% hydrogen peroxide was added slowly from a dropping-funnel, keeping the temperature at 65-70°. The reaction proceeded with evolution of heat. After the addition, the mixture was heated at 80° for 15 minutes and was then cooled to 0°. The light brown oil which had formed solidified to a crystalline cake. This was separated from the aqueous portion (see below) and pressed on tile, yielding 6 g. of substantially pure disulfide, nearly white crystals from alcohol, m.p. 61.0-61.5°.

Anal. Calc'd for $C_8H_8N_2S_4$: C, 36.90; H, 3.10; N, 10.76.
Found: C, 36.79; H, 2.99; N, 10.64.

The purified disulfide decomposed on standing over a period of months; the decomposition products were not investigated. An attempt was made to prepare this same disulfide by condensing together chloroacetone with thiram disulfide (13) in the presence of alcohol; no disulfide was obtained.

The aqueous portion (see above) was washed with ether, then made strongly alkaline with sodium hydroxide, and the liberated base taken up in ether. After drying over sodium sulfate and distilling, 0.5 g. of 4-methylthiazole boiling at 70-71° at 59 mm. was obtained and identified by its characteristic picrate, m.p. 181° (2b).

4,5-Dimethylthiazole. Ten grams of 3-chlorobutanone-2 dissolved in 10 cc. of absolute alcohol was treated at 0° with 8.5 g. of crude thioformamide and the mixture kept at 0-4° for 4 days and then for 3 days at room temperature. 6 N Hydrochloric acid was added, the solution washed with ether, and excess solid potassium hydroxide carefully added. The liberated base was taken up in ether and fractionated, yield 2.3 g., b.p. (59 mm.) 81-83°.

Anal. Calc'd for C_6H_7NS : C, 53.06; H, 6.23; N, 12.38.
Found: C, 53.22; H, 6.26; N, 12.63.

The picrate, obtained with ethereal picric acid, precipitated immediately, m.p. 186-187° from ethanol; the methiodide formed slowly on mixing the components, m.p. 223-223.5° (decomp.) from ethanol.

Oxidation of 2-mercapto-4,5-dimethylthiazole with hydrogen peroxide. (a) *Oxidation in neutral solution.* Thirty-four grams of commercial hydrogen peroxide was neutralized by titrating with 18.4 cc. of standard sodium hydroxide solution, using phenolphthalein as indicator. The neutral solution was added slowly (15 minutes) through a dropping-funnel to the continuously agitated suspension of 14.5 g. of mercaptothiazole in 50 cc. of water, keeping the temperature between 65-70°; a yellow oil precipitated out. When the addition was completed, the mixture was heated to 80° for 15 minutes and then allowed to cool. On standing, the oil crystallized to a solid cake, which was separated from the aqueous portion and pressed on tile. The yield was 11 g. (76%), m.p. 51.6-52.0° after recrystallization from ethyl alcohol.

Anal. Calc'd for $C_{10}H_{12}N_2S_4$: C, 41.63; H, 4.19; N, 9.71.
Found: C, 41.49; H, 4.40; N, 10.04.

The disulfide is weakly basic in nature, dissolving readily in 6 N hydrochloric acid

and precipitating unchanged on dilution of the resulting solution; it does not form a stable picrate.

The aqueous solution from the above reaction was extracted with ether and evaporated on the water-bath to a small volume. The thiazole base was liberated with excess potassium hydroxide, taken up in ether and distilled. One and one-tenth grams of pure 4,5-dimethylthiazole was obtained, b.p. (59 mm.) 82°. The picrate and methiodide were prepared and did not depress the melting point when mixed with authentic samples.

In a similar experiment, 2.9 g. of mercaptothiazole suspended in 12 cc. of water was oxidized by addition of 6.8 g. of neutralized 30% hydrogen peroxide; 0.25 g. of 4,5-dimethylthiazole was obtained.

(b) *Oxidation in moderately acid solution.* To a suspension of 2.9 g. of mercaptothiazole in 11 cc. of water and 1 g. of C.P. hydrochloric acid (sp. gr. 1.19), 6.8 g. of commercial 30% hydrogen peroxide was added slowly at 70-75° as in (a). The reaction mixture was worked up as above, giving 1.25 g. (44%) of the disulfide and 0.75 g. (34%) of 4,5-dimethylthiazole.

The same amount (2.9 g.) of mercaptothiazole, suspended in 10 cc. of water and 2 g. of C.P. hydrochloric acid, was oxidized by 6.8 g. of 30% hydrogen peroxide giving 1.15 g. (52%) of 4,5-dimethylthiazole. In this experiment [and also in (c) below] an evolution of heat was noted on the addition of hydrogen peroxide, and it was necessary to cool externally to keep the temperature at about 70°; no disulfide was obtained.

(c) *Oxidation in strongly acid solution.* As in the above experiments, 13.6 g. of 30% hydrogen peroxide was added to 5.8 g. of mercaptothiazole in 24 g. of C.P. hydrochloric acid. No disulfide was isolated; 2.7 g. (60%) of 4,5-dimethylthiazole was obtained. In another experiment carried out with these relative proportions of reactants, a slightly lower yield of 4,5-dimethylthiazole was obtained, and from the residue remaining after distillation of the volatile base, a small amount of low-melting crystalline material was isolated. After recrystallization from alcohol it melted at 41.0-41.2° [b.p. (2 mm.) ca. 190-200°], and gave analytical figures agreeing with those calculated for the thiazole monosulfide.

Anal. Calc'd for $C_{10}H_{12}N_2S_2$: C, 46.84; H, 4.72; N, 10.93.

Found: C, 47.28; H, 4.85; N, 11.21.

With ethereal picric acid it formed a monopicrate, bars or tufts from ethanol, m.p. 111.0-111.2°.

Anal. Calc'd for $C_{16}H_{15}N_5O_7S_2$: N, 14.43. Found: N, 14.20.

Oxidation of 2-mercaptop-4,5-dimethylthiazole with nitric acid. It was found that dilute nitric acid (1 volume of nitric acid, sp. gr. 1.42, plus 3 volumes of water) reacted vigorously with the mercaptothiazole when heated to about 80°. Because of the rapid gas evolution accompanying the reaction, no attempt was made to carry out the oxidation on larger than 1 g. portions of the mercaptothiazole, each such portion being heated with 25 cc. of dilute acid until the reaction had ceased, and then afterwards to boiling for a few minutes. Ten such reaction mixtures were combined, evaporated to a small volume, and the free base isolated and characterized as before. Distillation gave 5.0 g. (65%) of pure product.

Thiazole Thioethers

Treatment of mercaptothiazoles with excess of an appropriate reagent containing a reactive halogen, was found the most convenient method (5) for preparing this class of substances. In the cases studied the reaction took place readily to give almost

quantitative yields of the crystalline hydro-halogen salts, easily purified by washing with ether, from which the free bases could be obtained simply and easily. This was accomplished by dissolving in water, adding excess of alkali carbonate, and extracting with ether. From the ether solution after drying over sodium sulfate, the base was usually isolated by distillation *in vacuo* (in the case of a solid thioether by evaporation of solvent and recrystallization). The simple alkylthiothiazoles are stable liquids possessing a characteristic odor, and are not very readily soluble in ether; the picrates, formed when ethereal solutions of the components are mixed, crystallize out on standing.

2-Methylthio-4-methylthiazole. (a) *From 2-mercapto-4-methylthiazole.* When the mercaptothiazole was mixed with methyl iodide at room temperature, either alone or in the presence of ether, a spontaneous reaction took place with evolution of heat. The free base, b.p. (3 mm.) 65-68° was obtained in good yield.

Anal. Calc'd for $C_6H_7NS_2$: C, 41.35; H, 4.86; N, 9.64.

Found: C, 41.12; H, 4.88; N, 9.62.

The picrate was recrystallized from ethyl acetate, m.p. 123.5-123.7°.

(b) *From methyl dithiocarbamate.* A mixture of 6 g. of methyl dithiocarbamate (14), 5.2 g. of chloroacetone, and 6 cc. of absolute alcohol was refluxed for 12 hours on a water-bath. The product was taken up in water, washed with ether, and the base isolated in the usual manner, yield 3 g., b.p. (3 mm.) 65-68°, picrate, m.p. and mixed m.p., 123.5-124.0°.

2-Methylthio-4,5-dimethylthiazole. (a) *From 2-mercapto-4,5-dimethylthiazole.* Three grams of mercaptothiazole was mixed with methyl iodide and the resulting paste allowed to stand for 48 hours. The yield of base was 3 g. (91%) b.p. (2 mm.) 87°.

Anal. Calc'd for $C_6H_9NS_2$: C, 45.25; H, 5.70; N, 8.80.

Found: C, 45.23; H, 5.85; N, 9.14.

The picrate was recrystallized from ethanol, m.p. 134.5-135.5°.

(b) *From methyl dithiocarbamate.* Ten grams of chlorobutanone, 10 g. of methyl dithiocarbamate, and 10 cc. of absolute alcohol were allowed to stand at room temperature for 4 days. After working up, 0.5 g. of 2-methylthio-4,5-dimethylthiazole (low yield evidently due to incomplete reaction) was obtained, having the same properties as the base obtained by method (a).

2-Ethylthio-4-methylthiazole. A methanol solution of 2 g. of 2-mercapto-4-methylthiazole was treated with ethyl bromide. After standing at room temperature for several hours, a second liquid phase made its appearance, and after 24 hours a crystalline cake of 2-ethylthio-4-methylthiazole hydrobromide had formed. The yield of base was 2.4 g., b.p. 83-85° at 4 mm.

Anal. Calc'd for $C_6H_9NS_2$: C, 45.25; H, 5.70; N, 8.80.

Found: C, 44.82; H, 5.62; N, 8.56.

The picrate melted at 114.0-114.5° (from ethanol).

2-Carbethoxythio-4-methylthiazole. 2-Mercapto-4-methylthiazole (2.5 g.) and ethyl chlorocarbonate (2.25 g.) were placed in a stoppered flask equipped with a calcium chloride tube and the mixture allowed to stand at room temperature for 5 days. The reaction took place for the most part during the first hour, the mercaptothiazole going into solution and the carbethoxythiomethylthiazole hydrochloride crystallizing out. After washing with ether, water was added, which led to the formation of two phases [evidently the hydrochloride is largely dissociated in solution (5)]. Sodium carbonate was added and the base isolated in the usual manner, yield 2.65 g., b.p. 123-125° at 4 mm.

Anal. Calc'd for $C_7H_9NO_2S_2$: C, 41.36; H, 4.46; N, 6.89.

Found: C, 41.39; H, 4.54; N, 7.01.

The thiazole thioether does not form a stable picrate.

When the above reaction was carried out on a water-bath instead of at room temperature, there was a noticeable evolution of carbon dioxide, which was complete after 3 hours. No carbethoxythiomethylthiazole could be detected among the reaction products. Instead there were formed considerable amounts of 2-ethylthio-4-methylthiazole, which was isolated and identified (picrate, m.p. and mixed m.p. 114.0-114.5°); 2-mercaptop-4-methylthiazole was also isolated and identified by mixed m.p. with an authentic sample. Another experiment, in which 2-mercaptop-4-methylthiazole had been allowed to remain in contact with chlorocarbonic ester for four months at room temperature, gave approximately equal amounts of carbethoxythiomethylthiazole and ethylthiomethylthiazole. 2-Carbethoxythiomethylthiazole free base, when treated with gaseous hydrochloric acid and heated at 100° for 45 minutes (after which time carbon dioxide evolution had stopped), was found to have been converted to 2-ethylthio-4-methylthiazole.

S-Carbethoxy dithiocarbamate. Thirty-three grams of ethyl chlorocarbonate was added slowly with shaking to a suspension of 33 g. of ammonium dithiocarbamate in 60 cc. of absolute alcohol kept at 0°. Reaction took place with formation of a white solid. The mixture was allowed to stand for one-half hour at room temperature, after which the solvent was evaporated and the residue washed well with water and pressed on tile. The product, yield 37 g. (75%) was substantially pure, m.p. 98.9-99.4° from ethyl acetate, easily soluble in ether.

Anal. Calc'd for $C_4H_7NO_2S_2$: C, 29.08; H, 4.27; N, 8.48.

Found: C, 29.22; H, 4.40; N, 8.73.

In another experiment the reaction was carried out with less strong cooling (acetone as reaction medium). A spontaneous evolution of heat was noted and, in addition to the ether-soluble fraction, there was obtained a small amount of material insoluble in both ether and water. It consisted of a yellow powder which melted above 200°. This material was extracted with hot alcohol, giving a solution which on cooling yielded needles having no definite melting point. Recrystallization from alcohol gave an apparently homogeneous product.

Anal. Calc'd for $C_6H_7N_3O_2S_2$: C, 28.90; H, 2.83; N, 16.85.

Found: C, 29.24; H, 3.32; N, 16.82, 16.95.

On the basis of the analysis and method of formation the substance may be formulated as S-carbethoxy trithiocyanurate. The alcoholic mother liquors on evaporation yielded crystalline material of non-homogeneous appearance; possibly di- and tri-S-carbethoxy trithiocyanurates were present.

2-Acetylthio-4-methylthiazole. (a) *From 2-mercaptop-4-methylthiazole.* A mixture of mercaptopthiazole, chloroacetone, and ether or methanol was allowed to stand for 12 hours and the resulting hydrochloride recrystallized from alcohol, m.p. 158.5-159.0°.

Anal. Calc'd for $C_7H_{10}ClNO_2S_2$: C, 37.57; H, 4.51; N, 6.26.

Found: C, 37.52; H, 4.77; N, 6.03.

The addition of base to the aqueous solution of the hydrochloride caused an oil to precipitate which dissolved again in excess 6 N sodium hydroxide, could be precipitated from basic solution by addition of hydrochloric acid; and redissolved in excess of either acid or base. The organic base had the m.p. 45.5-46.0° from alcohol, b.p. ca. 112-115° at 3 mm., easily soluble in ether.

Anal. Calc'd for $C_7H_9NO_2S_2$: C, 44.89; H, 4.84; N, 7.48.

Found: C, 44.88; H, 4.70; N, 7.52.

(b) *From chloroacetone.* Eleven grams each of ammonium dithiocarbamate and chloroacetone were heated with anhydrous ether for 1 hour on the water-bath. Fil-

tration of the reaction products and evaporation of the filtrate yielded 3.5 g. of material which was identified as 2-acetonylthio-4-methylthiazole hydrochloride. Evidently the ether solution contained an intermediate (5) which during evaporation reacted with chloroacetone to give the ether-insoluble product isolated.

The same hydrochloride was obtained from the reaction between 3.3 g. of S-carbethoxy dithiocarbamate and 1.85 g. of chloroacetone in 4 cc. of absolute alcohol, either on refluxing for 4 hours on a water-bath, or after standing at room temperature for one month.

Spontaneous Decomposition of Thiazole Disulfide

Decomposition of 4,5-dimethylthiazole-2 disulfide. Pure disulfide, m.p. 51.5°, was substantially unaltered after standing loosely stoppered for three months. Crude disulfide, m.p. 48°, after standing the same length of time, was found to be converted largely into decomposition products (strong qualitative test for sulfate ion). Seven and two-tenths grams of such material was treated with 60 cc. of concentrated hydrochloric acid, giving a clear yellow solution. Two hundred cubic centimeters of water was added, which caused an immediate crystalline precipitate. By cooling and filtering, it was possible to separate 3.6 g. of 2-mercaptop-4,5-dimethylthiazole (mixed m.p.); no disulfide separated at this point. Making the filtrate alkaline, extracting the precipitated oil with ether, and removing the solvent yielded about 2.5 cc. of oil. Treatment of this with ethereal picric acid and separation of the picrate formed gave 1.0 g. of 4,5-dimethylthiazole-2 monosulfide picrate (mixed m.p. and analysis) corresponding to 0.5 g. of monosulfide. The residual oil which did not form a picrate was taken up in 6 N hydrochloric acid, washed with ethyl acetate, and the base liberated with alkali. The oil obtained in this manner crystallized on cooling, giving 1.2 g. of unchanged disulfide (mixed m.p.).

SUMMARY

1. The oxidative replacement by hydrogen of the 2-mercaptop group in thiazoles may conveniently be effected either by hydrogen peroxide in acid solution or by dilute nitric acid.
2. Thiazole-2 thioethers are best prepared by direct etherification of the corresponding mercaptothiazole. In some cases they may be obtained by interaction of the appropriate ester of dithiocarbamic acid with an α -halogeno ketone. A thiazole-2 carbethoxythioether, in the presence of dry hydrogen chloride, was rendered unstable, yielding S-ethylmercaptopthiazole and carbon dioxide.
3. A thiazole-2 disulfide was shown to decompose spontaneously in contact with the atmosphere, giving thiazole-2 monosulfide, 2-mercaptopthiazole and sulfuric acid.

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REFERENCES

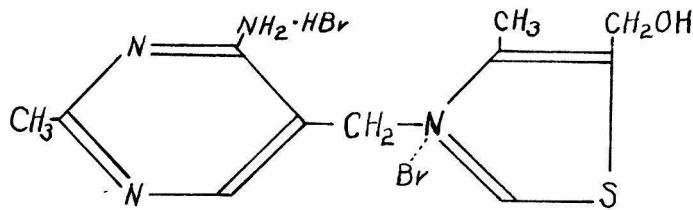
- (1) CLARKE AND GURIN, *J. Am. Chem. Soc.*, **57**, 1876 (1935).
- (2) (a) KONDO AND NAGASAWA, *J. Pharm. Soc. Japan*, **57**, 249, 308 (1937); (b) OCHIAI AND NAGASAWA, *J. Pharm. Soc. Japan*, **59**, 43 (1939) [*Chem. Abstr.*, **32**, 1699, 3398 (1938); **33**, 3791 (1939)]; (c) *Ber.*, **72**, 1470 (1939).

- (3) HOUBEN-WEYL, "Die Methoden der organischen Chemie," 2nd Ed., Georg Thieme (Leipzig), 1922, Vol. 2, page 164.
- (4) F. HOFFMANN LA-ROCHE AND Co., English Patent 492637 (1938); French Patent 833717 (1938); SPIEGELBERG, U. S. Patent 2179984 (to Hoffmann La-Roche, Inc.) (1939).
- (5) Compare LEVI, *Gazz. chim. ital.*, **61**, 719 (1931) [*Chem. Abstr.*, **26**, 1602 (1932); *Chem. Zentr.*, **103**, I, 1097 (1932)].
- (6) DIXON, *J. Chem. Soc.*, **83**, 566 (1903).
- (7) GABRIEL AND STELZNER, *Ber.*, **28**, 2932 (1895).
- (8) Compare FROMM, *Ann.*, **348**, 159 (1906).
- (9) BEILSTEIN, "Handbuch der organischen Chemie," 4th Ed., Julius Springer (Berlin), 1921, Vol. 3, page 216.
- (10) (a) HENRY, *Chem. Zentr.*, **71**, I, 1123 (1900); (b) VAN REYMENTANT, *Chem. Zentr.*, **72**, I, 95 (1901).
- (11) Compare: ref. (10b); FAWORSKI AND ISSATSCHENKO, *J. prakt. Chem.*, [2] **88**, 657 (1913); *Chem. Zentr.*, **84**, I, 1007 (1913).
- (12) MIOLATI, *Gazz. chim. ital.*, **23**, I, 575 (1893) [*Jahresber. Fortschr. Chem.*, 1725 (1893)].
- (13) FREUND AND BACHRACH, *Ann.* **285**, 201 (1895).
- (14) DELÉPINE, *Compt. rend.*, **135**, 975 (1902); *Bull. soc. chim.* [3] **29**, 52 (1903); von BRAUN, *Ber.*, **35**, 3380 (1902).
- (15) Compare FOWKES AND McCLELLAND, *J. Chem. Soc.*, **1941**, 187.

Synthesis of the Vitamin B₁ Analog from 4-Methyl-5-(hydroxymethyl)-thiazole

By Edwin R. Buchman and Herbert Sargent

4-Methyl-5-(hydroxymethyl)-thiazole (I) was required for the synthesis of the analog of vitamin B₁.



Its possible preparation by methods A - E was investigated.

A. Th-CHO (II)^{1,2} $\xrightarrow{\text{Al(O isopr)}_3}$ Th-CH₂OH (I)

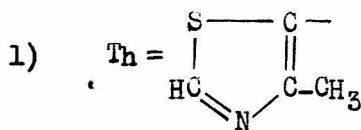
B. CH₃COCH₂CH₂OH (III) $\xrightarrow{\text{Br}_2-\text{H}_2\text{O}}$ HCSNH₂ (I) + isomer (IV)

Ba. CH₃COCH₂CH₂OCOCH₃ (V) $\xrightarrow{\text{SO}_2\text{Cl}_2}$ HCSNH₂ $\xrightarrow{\text{Th-CH}_2\text{OCOCH}_3}$ (VI) + isomer (VII)

C. CH₃COCH₂Cl (VIII) $\xrightarrow{\text{HCHO}}$ CH₃COCHClCH₂OH (IX) $\xrightarrow{\text{HCSNH}_2}$ (I)

D. ³ Th-CH₂COOC₂H₅ (X)^{4,5} $\xrightarrow{\text{NH}_3}$ Th-CH₂CONH₂ (XI)^{4,6} $\xrightarrow{\text{Br}_2-\text{KOH}}$ Th-CH₂NH₂ (XII) $\xrightarrow{\text{HNO}_2}$ (I)

E. CH₃COCH=CH₂ (XIII) $\xrightarrow{\text{Br}_2}$ CH₃COCHBrCH₂Br (XIV) $\xrightarrow{\text{HCSNH}_2}$ Th-CH₂Br (XV)



- 2) Buchman and Richardson, J. Am. Chem. Soc., 61, 891 (1939).
- 3) The Simonini reaction (Monats. 13, 320 (1892) Jahresber. Chem., 1892, 1436) offers a shorter route to Th-CH₂OH from Th-CH₂COOH; this reaction was not investigated.
- 4) Cerecedo and Tolpin, J. Am. Chem. Soc., 59, 1660 (1937).
- 5) a) Andersag and Westphal, U.S. Patent 2139570 (to Winthrop Chemical Co., Inc.);
 b) I. G. Farbenindustrie, A.-G., English Patent 456751 Chem. Zentr., 108 I, 2868 (1937);
 c) German Patent 702436 (Andersag and Westphal inventors).
- 6) Price and Pickel, a) J. Am. Chem. Soc., 63, 1067 (1941);
 b) U.S. Patent 2209092 (to National Oil Products Co.).

The patent literature^{5b} claims the preparation of (I) from (XV) made according to E. We have not been able to realize the preparation of (XV) by this path. The preparation of (I) by method B has been reported by Pesina⁷; in our own work we have obtained (I) as well as its isomer,

- 7) Pesina, J. Gen. Chem., (U.S.S.R.) 9, 804 (1939) (C.A. 34, 426 (1940)).

4-(β-hydroxyethyl)-thiazole (IV), by this procedure.

Of the four successful syntheses (A,B,Ba,C) presented here, the first (A), is of interest inasmuch as the structure of (I) follows from its synthesis in this manner. Method C is by far the most convenient; it involves but few steps and the presence of isomer could not be detected in the product.

The preparation of the vitamin B₁ analog from (I) by the Williams-Cline⁸ method has been reported in the patent literature⁹; physiological data

- 8) Williams and Cline, J. Am. Chem. Soc., 58, 1504 (1936); Cline, Williams and Finkelstein, J. Am. Chem. Soc., 59, 1052 (1937).

9) I.G. Farbenindustrie, A.-G., English Patent 471416 (1937) Chem. Abstr., 32, 1051 (1938) Chem. Zentr., 109 I, 939 (1938); I.G. Farbenindustrie, A.-G., German Patent 685032 (1939) Chem. Abstr., 34, 3763 (1940); I. G. Farbenindustrie, A.-G., German Patent Osterreich, 159315 (1940).

have also been published¹⁰. Through the courtesy of the Merck Institute

10) Schultz, Zeit. Physiol. Chem., 265, 113 (1940).

for Therapeutic Research, our analog, prepared in the accepted manner, was tested for antineuritic activity by the rat curative method. No vitamin B₁ potency in doses up to 500 μ was detected. Schultz¹⁰ had reported antineuritic potency with pigeons; the discrepancy may be traced to the difference in test object. Professor James Bonner of this Institute has tested the ability of our analog to support growth of the microorganism, Phycomyces Blakesleeanus; his findings were entirely negative. Dr. E. Heegaard in these Laboratories, has examined the analog pyrophosphoric ester and reports¹¹ that the compound is unable to function as cocarboxylase.

11) E. Heegaard, Thesis.

These results were not entirely unexpected. A series of vitamin analogs¹² previously prepared in this Laboratory from 4-methylthiazoles

12) Buchman and Richardson, to be published in J. Am. Chem. Soc.

(including 4-methyl-5-(α -hydroxyethyl)-thiazole, 4-methyl-5-(β -hydroxypropyl)-thiazole and 4-methyl-5-(γ -hydroxypropyl)-thiazole) was found to possess no vitamin activity when tested on rats. Further the negative results

with *Phycomyces Blakesleeanus* might have been predicted from the findings¹³

13) Bonner and Erickson, *Am. J. Botany*, 25, 685 (1938); see also Bonner and Buchman, *Proc. Nat. Acad. Sci.*, 25, 164 (1939).

made with this microorganism employing the series of analogs¹² already mentioned. One may conclude¹⁴ that even small changes in the vitamin B₁

14) Compare Stein, Sampson, Cline and Stevens, *J. Am. Chem. Soc.*, 63, 2059, (1941).

molecule may be expected to result in complete inactivity.

Experimental

4-Methyl-5-(hydroxymethyl)-thiazole (I) (Method A).— A specially purified thiazole aldehyde (II), m.p. 75.6-76.1° from isopropyl alcohol, (picrate, m.p. 105.0-105.6° from ether) was used in these experiments. Four grams of (II) was mixed with 75 cc. of isopropyl alcohol (distilled over a small amount of sodium) and 8 g. of aluminum isopropylate and the mixture distilled under a short column at such a rate that acetone was removed as formed. After two hours the distillate gave no further test for acetone with dinitrophenylhydrazine. Most of the isopropyl alcohol was then distilled off, 5 cc. of water and approximately 20 g. of potassium hydroxide were added to the residue and it was extracted repeatedly with ether until a portion of the extract gave no precipitate with ethereal picric acid. Solvent was removed in vacuo from the combined extracts and

the residue distilled in vacuo, yield 3.2 g. (80%) of rather viscous oil, which on redistillation boiled almost entirely at 113-114° at 2 mm. After standing for about two months the substance crystallized, m.p. 65.8-66.2° from benzene.

Anal. Calcd. for C_5H_7NOS : C, 46.49; H, 5.46; N, 10.84.

Found: C, 46.73; H, 5.43; N, 10.93.

Super-cooled liquid (I) had d_4^{26} 1.240, picrate, m.p. 133.5-133.7° from alcohol (analysis for $C_{11}H_{10}N_4O_8S$), picrolonate, from components in methanol, m.p. 205.5-205.7° from alcohol (lit.⁷ m.p. 196-197°).

Attempts to effect the catalytic reduction of (II) were unsuccessful; small amounts of (II) completely inhibited¹⁵ the reduction of benzaldehyde

15) Compare ref. 2, footnote 15.

(Adams' platinum catalyst). The reduction of (II) with aluminum amalgam and moist ether however led to a small yield of (I) which was isolated as the picrate (mixed m.p.).

(I) was converted to (VI) by treatment with excess acetic anhydride and a drop of concentrated sulfuric acid. The reaction mixture was washed with ether and the base liberated from the aqueous solution of the residue with potassium carbonate, taken up in ether and converted to the picrate, m.p. 132.5-133.1°, rhombs from ethanol, which considerably depressed the m.p. when mixed with (I) picrate.

Anal. Calcd. for $C_{13}H_{12}N_4O_9S$: C, 39.00; H, 3.02; N, 14.00.

Found: C, 39.27; H, 3.11; N, 14.09.

A mixture of 0.4 g. of (I) and 0.4 cc. of aqueous hydrobromic acid

(saturated at 0°) was heated for ten hours in a sealed tube at 100°. The contents were evaporated in *vacuo* to a small volume, taken up in water and the base liberated with potassium carbonate, taken up in ether and dried over sodium sulfate. Even in solution, (XV) reacted appreciably with itself; on evaporation (XV) was left as an oil, a powerful lachrymator (compare benzyl bromide), which in five to ten minutes was converted to a water soluble resin. With ethereal picric acid there was obtained the picrate which was recrystallized from ethyl acetate (recrystallization from water yielded (I) picrate, mixed m.p.), m.p. 137.5-138.0°.

Anal. Calcd. for $C_{11}H_9BrN_4O_7S$: C, 31.36; H, 2.15; N, 13.30.
Found: C, 31.74; H, 2.63; N, 13.74.

(I) was dissolved in three volumes of concentrated sulfuric acid and the mixture heated for two hours at 115°. After cooling and diluting with 4 cc. of water, the product was treated with excess potassium carbonate and extracted with ether. From the concentrated extracts, ethereal picric acid threw down an oily picrate which soon crystallized and, after recrystallization from water, melted at 180.0-180.2°. The analysis gave figures for the dipicrate of di- (4-methylthiazolyl-5)-methyl ether.

Anal. Calcd. for $C_{22}H_{18}O_1S_2$: C, 37.82; H, 2.60; N, 16.04.
Found: C, 38.12; H, 2.73; N, 16.37.

(I) (Method B).— Butanol-1-one-3 (III) was prepared according to the literature¹⁶; from 500 g. of acetone, 35 g. of product¹⁷ was obtained,

16) Bayer and Co., German Patent 223207; Friedlaender, *Fortschritte der Teerfarbenfabrikation*, 10, 1007; *Chem. Zentr.*, 81, II, 347 (1910); see also White and Howard, *J. Chem. Soc.*, 1943, 25.

17) Unsuccessful attempts were made to improve upon this procedure; the method of Quattlebaum, U.S. Patent 2064564 (to Union Carbide and Carbon Corporation) gave poor results.

b.p. 65-70° at 8 mm. To 17.6 g. (0.2 mole) of (III) dissolved in 90 cc. of water, was added with stirring 32 g. (0.2 mole) of C.P. bromine, while the temperature was maintained at about 20° by external cooling with tap water. The bromine was added from a dropping funnel at such a rate¹⁸

18) When bromination was carried out more rapidly, the product, on treatment with thioformamide, gave no appreciable amount of thiazole (acetopropyl alcohol brominated under these conditions (Buchman, J. Am. Chem. Soc., 58, 1803 (1936)) gave a relatively good yield of thiazole).

that the solution remained practically colorless during the initial part of the reaction; as the reaction proceeded the solution assumed an orange color; the same slow rate of addition was maintained throughout. After the addition (ten and three-quarters hours) the reaction mixture was decanted from about 1 cc. of heavy oil which had formed, was saturated with ammonium sulfate and extracted several times with ether. Evaporation of solvent at room temperature in vacuo yielded 30.0 g. (39%) of almost colorless oil (compare ref. 7).

Brominated (III) (15.0 g.) was mixed with 8.3 g. of crude thioformamide and 10 cc. of absolute alcohol, the reactants were kept at 0° during the mixing. After the mixture stood for one week in the ice-box and then for two days at room temperature, it was worked up, yield of crude thiazole, b.p. 90-110° at 2 mm., 3.7 g.¹⁹ (28% from (III)). This material

19) Compare ref. 7; a parallel experiment in which the reactants were mixed at room temperature gave 2.75 g.

(6.45 g.) was added to a hot solution of the theoretical amount (11.5 g) of picric acid in ethyl acetate. On cooling, needle crystals separated which were identified as (I) picrate²⁰ (mixed m.p.). The mother liquors on

20) In another experiment in which an evidently less pure sample of (III) was used, the picrate after several recrystallizations from alcohol and from ethyl acetate melted at 160.5-161.5°. Anal. Calcd. for $C_{13}H_{14}N_4O_8S$: C, 40.41; H, 3.65; N, 14.50. Found: C, 40.83; H, 3.73; N, 14.35. This material did not depress the m.p. (Buchman and Richardson, to be published in J. Am. Chem. Soc.) of a like picrate obtained from a brominated crude acetone-acetaldehyde condensation product; evidently it is formed from brominated diacetone alcohol.

further cooling and standing deposited a mixture of needles and diamond-shaped tablets; separation was accomplished by seeding a supersaturated solution in ethyl acetate with either form, allowing it to crystallize, removing the crystals and obtaining the other form from the mother liquors. The diamond-shaped crystals, (IV) picrate, melted at 132.5-133.0° (from alcohol or ethyl acetate) and considerably depressed the m.p. when mixed with either (I) picrate or (VI) picrate.

Anal. Calcd. for $C_{11}H_{10}N_4O_8S$: C, 36.87; H, 2.81; N, 15.64.
Found: C, 36.83; H, 2.88; N, 15.62.

These crystals exhibited dimorphism; when suddenly introduced into a bath at 122° they liquefied and after resolidification melted at 132.5°; interesting is also the fact that small amounts of this picrate could be distilled without appreciable decomposition. From the above reaction, 3.0 g. of (IV) picrate was obtained together with 5.8 g. of its isomer. One may conclude that the bromination of (III) gave the 2- and 4-bromo derivatives in a ratio of approximately 2 : 1.

(I) (Method Ba).- Ten grams of (III) was conveniently acetylated by mixing with 20 g. of acetic anhydride and adding a drop of concentrated sulfuric acid. The reaction proceeded with evolution of heat; the mixture was allowed to stand for one-half hour and fractionated in vacuo, yield 9.0 g. of (V), b.p. (8 mm.) $76-78^{\circ}$ ²¹ (analysis). This method of acetyl-

21) The values in the literature are not in good agreement: b.p. (15 mm.) 96° ¹⁶, b.p. (30 mm.) $125-130^{\circ}$ ²²; b.p. (30 mm.) $98-102^{\circ}$, Chem. Zentr., 104 I, 1961 (1936).

ation (compare ref. 16) was found superior to methods involving acetylation in the presence of pyridine either with acetic anhydride²² or with

22) Compare Morgan and Holmes, J. Chem. Soc., 1932, 2667.

acetyl chloride. At room temperature (V) goes into solution slowly on shaking with water, probably due to hydrolysis.

(V) (8.4 g.) dissolved in 8 cc. of C.P. benzene was chlorinated at room temperature by adding dropwise with stirring and under anhydrous conditions 8.7 g. of sulfonyl chloride. After removal of solvent in vacuo, there remained 10.8 g. of oil²³ which condensed in alcohol solution with

23) This material decomposed extensively when fractionated at 8 mm.

8 g. of crude thioformamide. The mixture was allowed to stand at room temperature for one week and then worked up; yield of crude thiazole, b.p. (3 mm.) $90-99^{\circ}$, 1.8 g. (16%). This was treated with the theoretical amount of picric acid in ethyl acetate and the resulting picrates were recrystallized from alcohol; (VI) picrate was isolated (mixed m.p.).

Crude (VI)-(VII) mixture (2.5 g.) was saponified by heating for 10 minutes with 10 cc. of 20% aqueous potassium hydroxide, yield of (I)-(IV) 0.6 g.²⁴. From this, (I) and (IV) were isolated as picrates (mixed

24) There is evidence that the low yield was due to partial destruction of the thiazole ring by the strong caustic; saponification with acid should be satisfactory.

m.p.'s) by the procedure described above.

Chloroacetone (VIII).-- In connection with the investigation described below, it was found that a commercial preparation of (VIII), although agreeing in b.p. and density with the literature description, nevertheless, reasoning from analytical results obtained, contained considerable amounts of asyndichloroacetone which is known to have nearly the same b.p. (VIII), reasonably free from higher chlorinated products was made by chlorinating 2320 g. (40 moles) of C.P. acetone with a relatively small amount (320 g. 2.37 moles) of sulfonyl chloride (practical grade). The latter was added slowly with stirring from a dropping funnel over a period of five and one-half hours, with precautions to exclude moisture and with the reaction flask immersed in an ice bath. After removal of excess acetone in *vacuo*, the residue was washed with aqueous potassium carbonate solution, dried²⁵ over sodium sulfate and fractionated. The yield was

25) (VIII) apparently forms a constant boiling mixture with water and acetone.

158 g., b.p. 118-120°, 72% based on sulfonyl chloride; a portion, b.p. 119.1-119.3° had d_4^{25} 1.115²⁶.

26) Similar values were observed on other preparations made by this method; the lowest density (d_4^{27} 1.101) recorded in this research was of a sample recovered after reaction with less than the theory of formaldehyde. The figures reported for (VIII) (d_4^{16} 1.162, Linnemann, Ann., 134, 171 (1865); d_4^{13} 1.158, Cloez, Ann. chim. phys., 6 9, 158 (1886)) indicate a considerable admixture of dichloroacetone; it is doubtful whether any of the physical constants recorded for (VIII) are valid for the pure substance.

2-Chlorobutanol-1-one-3 (IX)²⁷.- To a mixture of 62.5 g. of (VIII)

27) The preparation of (IX) from (XIII) and hypochlorous acid appears to offer no advantages over the method described here. Although the reaction between (VIII) and formaldehyde has not previously been studied, the work of Pictet and Misner, Ber., 45, 1802 (1912) indicates the direction which the reaction would be expected to take; compare also H.O.L. Fischer, Baer, Pollock and Niedecker, Helv. Chim. Acta, 20, 1214 (1937).

(see above) and 1.7 g. of C.P. potassium carbonate, 29.0 g. of 37% aqueous formaldehyde (reagent grade) was added dropwise with stirring in an ice bath over a period of four hours; the reaction was slightly exothermic. Stirring was continued for twenty-four hours at room temperature; the reaction mixture was then extracted with ether and the extracts dried over sodium sulfate and fractionated in vacuo. After removal of (VIII), 18.0 g. of distillate was obtained, b.p. 50-90° at 5 mm. This material is sufficiently pure for conversion to (I); on refractionation at 5 mm. there was considerable loss due to the instability of the compound; even on standing it was converted slowly to an insoluble substance. Analysis was carried out on a sample b.p. (5 mm.) 70°.

Anal. Calcd. for $C_4H_7ClO_2$: C, 39.20; H, 5.76. Found: C, 39.14; H, 5.45.

The residue from the above distillation crystallized on standing;

the crystals were freed from oil (yield 3.5 g.) and recrystallized from toluene, white needles, m.p. 63.2-63.7°, readily soluble in water and the usual organic solvents except petroleum ether and carbon tetrachloride; on exposure to light the crystals turn reddish. The analysis indicates the probable formula $\text{CH}_3\text{COCCl}(\text{CH}_2\text{OH})_2$.

Anal. Calcd. for $\text{C}_5\text{H}_9\text{ClO}_3$: C, 39.36; H, 5.95. Found: C, 39.16; H, 5.81.

(I) (Method C).- (IX) (4.0 g., b.p. 70-76° at 5 mm.) was mixed at 0° with 2.8 g. of crude thioformamide and 3.0 cc. of ethanol. After standing for two weeks, the mixture was worked up, yield of base 0.95 g. From this, 2.0 g. of (I) picrate was obtained; no indication could be found of the presence of the isomeric picrate.

Preparation of Thiamin Analog⁹.- One part of (I) mixed with one part of 2-methyl-6-amino-5-bromomethylpyrimidine dihydrobromide (obtained from Merck & Co., Inc. and giving analytical figures close to those expected), and two parts of n-butyl alcohol were heated 20 minutes at 117° while stirring occasionally to ensure intimate mixing⁸. The mixture was then diluted with ether, centrifuged and the residue washed with several small portions of absolute alcohol. The crude analog was then dissolved in hot ethanol-water, decolorized with charcoal and allowed to crystallize. For physiological tests the analog was given one more recrystallization from ethanol-water. Yield approximately 20%, needles m.p. 231°d.

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{Br}_2\text{N}_4\text{OS}\cdot\frac{1}{2}\text{H}_2\text{O}$: C, 31.37; H, 4.07; N, 13.30. Found: C, 31.51; H, 4.05; N, 13.37.

4-Methyl-5-(carbethoxymethyl)-thiazole (X)²⁸. - Ethyl levulinate

28) The experimental work reported in this connection represents an extension of accounts in the literature^{4,5}. In connection with earlier work (Buchman, Williams and Keresztesy, J. Am. Chem. Soc., 57, 1849 (1935)), these authors (unpublished work) made a search for 4-methylthiazole-5-acetic acid among the products of oxidation of the vitamin thiazole with nitric acid; none of this acid was found (compare oxidation of 4-methyl-5-(hydroxypropyl)-thiazole). For comparison, 4-methylthiazole-5-acetic acid⁴ were synthesized (at Teachers College, Columbia University); the methyl ester was made by condensation of brominated methyl levulinate (Kondo, Ohno and Irie, J. Pharm. Soc. Japan, 57, 78 (1937); compare Pauly, Gilmour and Will, Ann., 403, 150 (footnote) (1914)) with crude thioformamide and also by the action of diazomethane on the corresponding acid⁴, b.p. (3 mm.) 88-92°, b.p. (13 mm.) 128-130° (these values are not in agreement with the b.p. (18 mm.) 111° reported⁴ by Cerecedo and Tolpin), picrate, m.p. 139.5-140.0°⁴ (analysis), difficultly soluble in ether (means of separation from 4-methyl-5-(carbomethoxy)-thiazole picrate). The reduction of (X) with sodium and alcohol (compare ref. 4, 5b, c) has been carried out by one of us (E.R.B.) and the reaction products subjected to biological assay; the presence of vitamin thiazole could not be detected (compare Erlenmeyer and Simon, Helv. Chim. Acta, 25, 528 (1942)).

(213 g., b.p. 78-80° at 8 mm.) dissolved in 145 cc. of benzene (some experiments were run without solvent) was conveniently chlorinated by adding with stirring at 0° and under anhydrous conditions 200 g. of sulfuryl chlorice over a period of four and one-half hours; careful fractionation of the product gave 203 g. (76%) of chloro ester²⁹ b.p. 84-86° at 8 mm.

29) Compare Conrad and Guthzeit, Ber., 17, 2286 (1884).

Chloroester (72 g.) was condensed with 52 g. of crude thioformamide and 20 g. of alcohol, the reaction mixture allowed to stand for two weeks and worked up, yield 34.1 g. (45%) of crude (X), b.p. 112-114° at 5 mm. Thiazole (11.3 g.) made in this fashion was treated with 14 g. of picric acid in ethyl acetate and the crystalline picrate (20 g.) recrystallized

from alcohol. The picrate of (X) (6.3 g.) was obtained, m.p. 126.5-126.6° (ref. 4 gives m.p. 130°); the mixture of picrates in the mother liquors was separated by recrystallizing several times alternatively from ethanol and from ethyl acetate. Additional (X) picrate was recovered together with a second picrate (1.9 g.), m.p. 128.0-128.5° (mixed m.p. with (X) picrate 113-116°, isomeric³⁰ with (X) picrate.

30) Chlorination of levulinic ester proceeds therefore in two directions. The structures assigned to (X) and to (XI) follow from the conversion of (XI) into $\text{Th}^1\text{-CH}_2\text{CN}$ and $\text{Th}\text{-CH}_2\text{CH}_2\text{NH}_2$ (carried out in this Laboratory by Drs. E. M. Richardson and M. J. Schlatter; compare ref. 6). $\text{ThCH}_2\text{CH}_2\text{NH}_2$ has been independently synthesized by methods indicative of structure (Harington and Moggridge, J. Chem. Soc., 443 (1939); compare ref. 5).

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_9\text{S}$: C, 40.58; H, 3.41; N, 13.52.

Found: C, 40.89; H, 3.38; N, 13.29.

(X) was regenerated from the picrate, b.p. 114-115° at 3 mm. (considerably higher than found for crude base), d_4^{25} 1.160, hydrochloride, m.p. 154.2-155.2° from alcohol-ether; on long standing (X) deteriorates, possibly due to self-alkylation.

Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{NO}_2\text{S}$: C, 51.87; H, 5.99; N, 7.56. Found: C, 51.4; H, 6.13; N, 7.80.

4-Methylthiazole-5-acetamide (XI) was prepared by treatment of (X) (regenerated from picrate) with 20% methyl alcoholic ammonia. More conveniently it was made^{4,6} from crude distilled (X). Such ester (104 g.) was mixed with 650 cc. of 20% methyl alcoholic ammonia and the solution allowed to stand for two days at room temperature. After removal of solvent, the

residue was recrystallized from dioxane³¹, yield 71 g. (80%) m.p. 137.2-

31) A small amount (2.5 g.) of dioxane insoluble material was also obtained, colorless crystals from methanol, m.p. 140.8-141.8° dec., readily soluble in water, less so in methanol and difficultly in ethanol. The substance arises from an impurity in crude (X). Anal. Calcd. for $C_2H_{10}N_4O_3S_2$: C, 11.88; H, 4.98; N, 27.70; S, 31.70. Found: C, 12.05; H, 4.98; N, 27.21; S, 30.80.

137.7°^{4,6} (analysis).

4-Methyl-5-(aminomethyl)-thiazole (XII)³².- To a solution of 10.8 g.

32) Various modifications of the Hofmann reaction were tried; the above procedure (compare ref. 5) seemed to give the best consistent results. The instability of the thiazole ring under these conditions was demonstrated by tests made with 4-methylthiazole and with 2,4-dimethylthiazole. These substances react readily (with production of sulfate ion) at room temperature with aqueous or aqueous alkaline N-bromoacetamide.

of bromine in 150 g. of 2.5 N potassium hydroxide was added 10.5 g. of (XI) with cooling in an ice bath. After solution was complete, 22 g. of potassium hydroxide pellets was added and the mixture heated at 95° for one and one-half hours. (XII) was isolated by continuous extraction with ether and distillation in vacuo; 1.4 g. (16%) was obtained almost all of which boiled at 94-95° at 5 mm.

Anal. Calcd. for $C_5H_8N_2S$: C, 46.84; H, 6.29; N, 21.85. Found: C, 47.29; H, 6.20; N, 21.10.

(XII) is stable in a sealed container, dihydrochloride (analysis) m.p. 259.5-260.0° dec. from methanol-ether, monopicrate (analysis) m.p. 213-214° dec. from 90% ethanol.

Action of Nitrous Acid on (XII).— (XII) (0.95 g.) was dissolved in 10 cc. of an aqueous solution containing 4.17 cc. of concentrated sulfuric acid. The solution was cooled to ca. -40° , 0.55 g. of sodium nitrite in 2 cc. of water was added and the reaction mixture allowed to warm gradually to room temperature (one hour) and to stand for an additional three hours after which gas evolution had ceased. After neutralization by gradual addition of potassium carbonate and making strongly alkaline with 6N sodium hydroxide, the product was rapidly extracted with ether and the extracts evaporated, yield 0.3 cc. of oil not readily soluble in ether. This oil was converted with ethereal picric acid to the picrate, yellow pearly flakes from water, m.p. 220.5° dec. (rapid heating; $213-214^{\circ}$ dec. on slow heating), yield 0.1 g.; no (I) picrate could be detected³³.

33) Compare Pyman, J. Chem. Soc., 109, 190 (1916).

Anal. Calcd. for $C_{16}H_{17}N_7O_{10}S_2 \cdot H_2O$ (tentative formula): C, 34.97; N, 17.84; S, 11.67; loss in weight, 3.28. Calcd. for $C_{16}H_{17}N_7O_{10}S_2$: C, 36.16; H, 3.22; N, 18.45. Found (dried at room temperature in vacuo): C, 35.49; H, 3.54; N, 18.26; S, 11.86; loss in weight on drying at 80° in vacuo, 3.56. Found (dried at 80° in vacuo): C, 37.29; H, 3.46; N, 18.63.

Reaction³⁴ between 3,4-Dibromobutanone-2 (XIV) and Thioformamide.—

34) Dibromoacrolein was found (in experiments carried out by Dr. E. M. Richardson) to react with thioformamide in alcohol with almost explosive violence. Although the reactants were brought together under a variety of conditions only insoluble products were obtained and there was no indication that any monomeric thiazole derivative was formed. When dibromoacrolein was mixed with an equimolar amount of

thiourea in the presence of absolute alcohol, no reaction (other than acetal formation) took place at room temperature. On warming on the steam bath, however, an apparently crystalline precipitate formed, only sparingly soluble in water. On treatment with aqueous potassium carbonate this solid was converted to an amorphous material insoluble in the usual solvents but soluble in acids. Hubacher (Ann., 259, 243 (1890)) had reported that dibromoacrolein does not react with thiourea.

Methyl vinyl ketone (XIII) was prepared by dehydration³⁵ of (III),

35) Decombe, Compt. rend., 202, 1685 (1936).

yield 75%, b.p. 75-78°. (XIV)³⁶ was prepared by adding bromine diluted

36) Schlotterbeck, Ber., 42, 2563 (1909).

with petroleum ether to a solution of (XIII) in the same solvent until color persisted, keeping the temperature at about -15° (below this temperature the reaction rate was slow). After removal of solvent in vacuo, (XIV) remained as an almost colorless oil, yield 92%.

Ethanol solutions of (XIV) and of thioformamide were mixed at -50° allowed to warm slowly to 5° and kept at this temperature for three days; a substantial crystalline deposit had formed. The basic products were taken up in acid, liberated with potassium carbonate and converted directly to picrates; no halogen containing picrate could be detected. The products³⁷

37) One condensation (carried out at 5°) gave 9.0 g. (from 40 g. of (XIV) and 17 g. of thioformamide) of viscous ether soluble oily bases. On fractionation, 0.3 g. of material b.p. ca. 70° at 2 mm. was obtained which gave a halogen-free picrate, m.p. 154.5-154.8° from ethanol; the rest was considerably higher boiling. Another condensation carried out at room temperature gave a product which behaved in a similar

fashion on distillation. The picrate however (also halogen-free) melted at 184.1-184.6° from water. Anal. (152° picrate): C, 35.97; H, 2.93; N, 14.71; S, 19.99. Anal. (184° picrate): C, 36.23; H, 2.78; N, 14.86; S, 19.94.

were not identified; however it seems reasonably certain that (XV) (see above) was not formed by this reaction.

Acknowledgment: The authors are indebted to Dr. E. M. Richardson for preliminary studies in this field, to Dr. James Bonner for biological assays, to Dr. R. T. Major of Merck and Co., Inc. for his continued support of this research, to his associates, Messrs. W. L. Sampson and D. F. Hayman, for bioassays and microanalyses and to the Research Foundation for financial aid in carrying out the investigation.

Summary

The preparation of 4-methyl-5-(hydroxymethyl)-thiazole by several different methods has been investigated. It may conveniently be obtained by a two-step synthesis starting from chloroacetone.

The thiamin analog was prepared from 4-methyl-5-(hydroxymethyl)-thiazole and found to be completely devoid of vitamin activity when tested with *Phycomyces Blakesleeanus* and with rats.

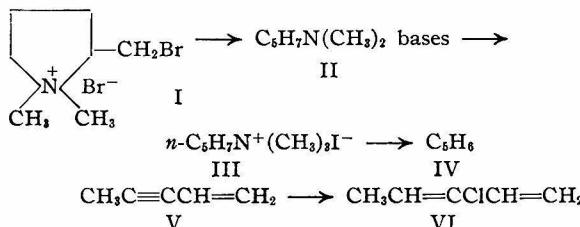
[Reprinted from the Journal of the American Chemical Society, **64**, 2692 (1942).]

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 903]

The Constitution of Pirlylene: Chemical Evidence

BY HERBERT SARGENT, EDWIN R. BUCHMAN AND JOHN P. FARQUHAR

The C_5H_6 hydrocarbon pirlylene (IV) was first prepared by Ladenburg¹ starting from piperidine and following essentially the path here indicated over the intermediates (I) to (III). The structure of these intermediates was but imperfectly known in Ladenburg's time,² so that a correct formulation of the pirlylene molecule was out of the question. In 1928, von Braun and Teuffert³ reinvesti-



gated the subject, and concluded that pirlylene must possess a doubly unsaturated ring structure. A number of possibilities were cited; that of methylenecyclobutene⁴ seemed most in accord with their observations. Because of our interest in cyclobutane derivatives the present study was undertaken.

It was found that degradation of (I) led to a mixture of bases (II), a fact which had been overlooked by previous investigators,^{1,3,5} who had assumed the homogeneity of their $C_5H_7N(\text{CH}_3)_2$ base. From (II), a methiodide (III) was obtained which is without doubt the parent substance from which pirlylene was formed. The straight-chain nature of the C_5H_7 radical in this quaternary salt was demonstrated by catalytic reduction of the corresponding chloride to n -amyltrimethylammonium chloride. From (III) pirlylene (IV) was made in the usual way^{1,3}; its properties, which agreed with the previous descriptions, were those of a pure substance.

A sample of this hydrocarbon has been submitted to Dr. V. Schomaker and Dr. R. Spurr of these Laboratories who have been able to work

(1) Ladenburg, (a) *Ber.*, **15**, 1024 (1882); (b) *Ann.*, **247**, 56 (1888).
 (2) It was not until 1900 that Willstätter, *Ber.*, **33**, 365 (1900), elucidated the structure of the N,N -dimethyl- α -(bromomethyl)-pyrrolidiniumbromide (I).

(3) von Braun and Teuffert, *ibid.*, **61**, 1092 (1928).

(4) Stevens and Richmond, *THIS JOURNAL*, **63**, 3133, Footnote 14 (1941), have pointed out that it is difficult to explain the formation of this hydrocarbon.

(5) See also (a) Ladenburg, *Ber.*, **14**, 1347 (1881); (b) Merling, *ibid.*, **17**, 2139 (1884); (c) Willstätter, ref. 2.

out its structure from the electron diffraction pattern.⁶ Their investigation indicates that (IV) is not a ring compound, but possesses the structure (V) of 1-methyl-2-vinylacetylene, a known substance,⁷ the physical properties of which agree well with those of pirlylene.

The results of our chemical investigation are in full conformity with this conclusion. On catalytic reduction pirlylene readily took up three moles of hydrogen; the reduced product was shown to be n -pentane. It also added one mole of hydrogen chloride, as has been demonstrated⁸ for (V), giving 3-chloro-1,3-pentadiene (methylchloroprene) (VI).

Experimental

$C_5H_7N(\text{CH}_3)_2$ Bases (II).—The pyrrolidinium bromide (I)^{6c} was degraded according to directions in the literature.^{1b,3} From 136.5 g. (0.5 mole) of (I), 39 g. (70%) of mixed bases (II) was obtained, b. p. *ca.* 56–70° at 50 mm.; the exact composition of this mixture⁹ was not determined due to its unstable nature. Fractionation through a precision column at 50 mm. gave 7.5 g. (13%) of material boiling constantly at 66.5°; examination of this fraction disclosed that it represented a substantially pure substance. It was used directly for conversion to the quaternary salt (III).

A portion of this base was further purified over the diluturate¹⁰ which crystallized from alcohol in well-formed narrow rectangular crystals; m. p. 161–162°. The regenerated base, b. p. 65° at 49 mm., d^{25}_{40} 0.800, n^{25}_{D} 1.4430, entirely stable for months in an atmosphere free from carbon dioxide, was obtained by distilling the diluturate with excess aqueous alkali.

Anal. Calcd. for $C_7H_{13}N$: C, 75.60; H, 11.79. Found: C, 75.89; H, 12.10.

The picrate was prepared from the components in ether, cube-like crystals from ethanol-isopropyl ether, m. p. 100.5–101.0°.

Anal. Calcd. for $C_{13}H_{16}N_4O_7$: N, 16.47. Found: N, 16.25.

With methyl iodide the methiodide (III) described below was obtained.

n - $C_5H_7N(\text{CH}_3)_3I$ (III).—To 54.3 g. of base (from fractionation of (II), b. p. *ca.* 66.5° at 50 mm.), in 250 cc. of ethanol, 76.4 g. of methyl iodide (10% excess) was added slowly, keeping the temperature at below 35° by cooling in an ice-bath. The crystalline product started to separate

(6) Spurr and Schomaker, *THIS JOURNAL*, **64**, 2693 (1942).

(7) Jacobson and Carothers, *ibid.*, **55**, 1622 (1933).

(8) Jacobson and Carothers, *ibid.*, **55**, 1624 (1933).

(9) A fuller account of the constituents will be published in another connection.

(10) Compare Redemann and Niemann, *ibid.*, **62**, 590 (1940).

almost immediately; after recrystallization from aqueous alcohol, the yield of (III) was 104 g. (84%), m. p. 259° d. (lit.³ m. p. 257°), entirely stable when heated with water at 100° (compare ref. 3).

Anal. Calcd. for C₈H₁₆IN: C, 37.96; H, 6.36; N, 5.53. Found: C, 38.33; H, 6.60; N, 5.57.

The same methiodide (III) was obtained when the mixed bases (II) were methylated according to directions¹ in the literature. As a characteristic derivative, the picrate was prepared from concentrated aqueous solutions of (III) and of sodium picrate, needles from ethanol, m. p. 112.5–113.0°.

(III) was not amenable to catalytic reduction; it was converted to the corresponding chloride³ which was hydrogenated in aqueous solution under two atmospheres pressure using a palladium–charcoal catalyst. Two moles of hydrogen was taken up; the product was characterized by conversion to the picrate, prisms, m. p. 93.2–94.0°, from ethanol–isopropyl ether, and to the bromide, needles, m. p. 181.0–181.5°,¹¹ from ethanol. These derivatives gave no depression when mixed with authentic samples of the corresponding *n*-amyltrimethylammonium salts made from *n*-amyl bromide and trimethylamine.

Pirylene (IV).—Quaternary iodide (III) (57.5 g.) was introduced together with 27 g. of potassium hydroxide and 70 cc. of water into a flask, and the mixture distilled from an oil-bath into a receiver immersed in a bath at –15°. A smooth decomposition took place (bath temperature 120–135°); the distillate was acidified with 6 N hydrochloric acid, and the hydrocarbon separated and dried over potassium carbonate, and over sodium. After distillation through a precision column, 8.9 g. (59%) of (IV) was obtained which boiled constantly; in

(11) von Braun and Murjahn, *Ber.*, **59**, 1205 (1926), reported the m. p. 175–176°.

a second similar experiment the yield was 11.0 g. (73%) of material having a 0.3° range. The constants observed were: b. p. 59.4° at 744 mm., d^{25}_4 0.7339, n^{25}_D 1.4467 (lit. pirylene²; b. p. 60°, d^{19}_4 0.7443, n^{19}_D 1.4505; methylvinylacetylene (V)⁷; b. p. 59.2° at 760 mm., d^{20}_4 0.7401, n^{20}_D 1.4496); the material polymerized slowly (much less rapidly than (VI)) on standing (compare refs. 3, 7).

The hydrocarbon (IV) (2.140 g.) was hydrogenated in ethanol solution using a palladium–charcoal catalyst. The hydrogen adsorbed (2.415 l. at 23° and 745 mm.) corresponded to 3 double bonds. The reduced hydrocarbon was distilled from the reduction mixture, treated with concentrated sulfuric acid and redistilled through a precision column; the sole product detected was *n*-pentane, yield 1.0 g., b. p. 36.3–36.5° (lit.¹² 36.1°).

Methylchloroprene (VI) was prepared from 3.7 g. of (IV) according to directions in the literature.⁸ Two and two-tenths grams of (VI) b. p. 98.5–101°, n^{25}_D 1.4745 (lit.⁸ b. p. 99.5–101.5°, n^{20}_D 1.4785) was obtained, and 1.5 g. of hydrocarbon was recovered. (VI) was identified by condensing with α -naphthoquinone; the derivative⁸ melted at 180.7–181.0° cor. (lit.⁸ 181°). When excess of (IV) and α -naphthoquinone were heated for two hours in a sealed tube at 100° no reaction¹³ was observed.

Summary

The conclusion, first arrived at as a result of the electron diffraction investigation,⁶ that pirylene and 1-methyl-2-vinylacetylene are identical, is supported by the chemical evidence.

(12) Egloff, "Physical Constants of Hydrocarbons," Vol. I, Reinhold Publishing Corp., New York, N. Y., 1939, p. 33.

(13) Compare Butz and Joshel, *THIS JOURNAL*, **63**, 3344 (1941). Under the same conditions, piperylene gave an adduct which was oxidized to 1-methylanthraquinone, m. p. 170–171°.

PASADENA, CALIF.

RECEIVED JULY 7, 1942

This Report is Submitted in Partial
Fulfillment of the Minor Department Requirements

Schultz-Dale Technique Applied to the Detection of Antigen-
Antibody Response in the Pacific Coast Lobster and in the
Long Muscles of the Sea Cucumber

I wish to state that this research would not have been
possible without the help of Dr. Dan H. Campbell who
suggested the problem and also aided in numerous ways
to bring the research to a sucessful conclusion.

Schultz-Dale Technique Applied to Detection of Antigen-Antibody Response in the Long Muscle of the Sea Cucumber and in the Lobster Intestine

Before conducting anaphylactic experiments on the long muscle of the Sea Cucumber it was considered desirable to determine the reactivity of this type of muscle towards the drugs acetyl choline, histamine, adrenaline and atropine. The apparatus used and the general method of muscle testing is ^{and} described by Schultz¹ and by Dale².

- 1) Schultz, W. H., J. Pharmacol., 2, 221 (1910).
- 2) Dale, H. H., J. Pharmacol., 4, 167 (1913).

Acetyl choline produced a violent contraction when the concentration was as low as one part in 10^7 . Concentrations as low as one part in 10^8 of sea water caused a slight contraction. The contracted state exists as long as acetyl choline is present. Additions of histamine to form concentrations of one part in 10^8 to one part in 10^5 had no effect whatever, either directly or as an inhibitor of the effect of acetyl choline.

Adrenaline caused a mild contraction followed by relaxation within a few minutes to the original state of the muscle. This behavior is repeated as often as further additions of adrenaline are made.

Atropine had no effect on the reactivity of the muscle towards acetyl choline.

Passive sensitization experiments were conducted by soaking the long muscles of the sea cucumber for several hours in rabbit antiovalbumin serum

which had been brought up to sea water ionic strength by the addition of concentrated sea water. The muscle was then transferred to the Schultz-Dale cell and the antigen ovalbumin added. In none of the numerous attempts was there any noticeable reaction of the muscle upon the addition of the antigen.

Before conducting immunological experiments with lobsters the reactivity of its gut towards acetyl choline, histamine, eserine, adrenaline, pilocarpine and atropine was determined. Filtered sea water was satisfactory as the liquid medium in the Schultz-Dale cell.

Acetyl choline in concentrations of the order of one part in 10^6 causes a mild sustained contraction while at the same time the gut becomes much more irritable than normally. This irritability is partially inhibited by histamine, but histamine does not cause relaxation of this partially contracted lobster gut. Histamine alone on lobster gut causes partial inhibition of the normal rhythmic contractions. Acetyl choline and histamine are antagonistic insofar as irritability of the muscular contractions go; however, acetyl choline and histamine are not antagonistic in the matter of muscular tone.

Eserine does not cause a contraction of lobster gut and it does not increase the sensitivity of the muscle towards acetyl choline or histamine. These tests were conducted at a temperature of 21°C . Elevated temperature of 30° does not alter the guts' response to acetyl choline nor to histamine.

Adrenaline causes a temporary contraction with irritability except when added after acetyl choline in which case it causes a sharp relaxation.

Atropine has no direct effect; however, acetyl choline added after atropine causes a sharp relaxation of the gut.

Pilocarpine has no effect on lobster gut.

Passive sensitization experiments were best carried out by injecting a 300-600 g. lobster with 3-5 ml. of purified rabbit anti-ovalbumin serum. The purified serum was prepared by adding to the rabbit antisera an equal volume of saturated ammonium sulfate solution. After allowing the slurry to stand for 5 minutes it was centrifuged. The precipitate was then dissolved in the minimum quantity of distilled water and dialyzed against sea water whereby one obtains a solution of a volume roughly the same as the starting volume of crude rabbit antisera. It was necessary to purify the rabbit antisera since an injection of crude rabbit antisera of the volume used would kill the lobster in a few hours. After allowing the lobster to circulate the antisera through itself for about 4 hours, the gut was removed and placed in the Schultz-Dale cell. Upon addition of 10 mg. of ovalbumin partial or in some cases complete inhibition of rhythmic contraction occurs. This inhibition does not occur if rabbit antisera alone or ovalbumin alone is added to the gut of an untreated lobster.

Since lobster gut is not overly sensitive to histamine and since the passive sensitization experiments on lobster gut indicated definitely that acetyl choline was not produced and that histamine might be,

it was decided to use guinea pig small intestine as a means of testing the blood of shocked lobsters for histamine or histamine-like substances.

The effect of histamine on lobsters and the stability of it in their blood stream was investigated. An injection of 15 mg. of histamine per kilo of lobster produced no noticeable effect. It was shown by withdrawing portions of blood over a period of several hours that the concentration of histamine in the lobster blood stream does not materially diminish. The concentration of histamine was roughly measured by the magnitude of the contraction produced in a guinea pig small intesting section when a 0.5 ml. portion of lobster blood diluted to guinea pig serum salt concentration was added to the Schultz-Dale cell. A dilution of 3 ml. of lobster blood with 7 ml. of distilled water was isotonic with guinea pig intestine. The liquid medium used in the Schultz-Dale cell for use with guinea pig intestine was obtained by mixing 3 parts filtered sea water with 7 parts of distilled water.

Passive sensitization and subsequent anaphylactic shock experiments were conducted by giving a lobster an injection of several milliliters of purified rabbit antiovalbumin and 4 hours later an injection of approximately 20 mg. of ovalbumen. One hour following the ovalbumen injection, 3 ml. of lobster blood was withdrawn, diluted to guinea pig serum strength, and added to the guinea pig gut in the Schultz-Dale cell. A contraction of the gut occurred. In the several passive sensitization experiments conducted, the contraction of the gut that occurred corresponded to that produced by 0.3-0.5 μ histamine. Controls were run

in which 3 ml. of lobster serum, 7 ml. of water, 0.3 ml. of purified rabbit antiovalbumin serum, and 3 mg. of ovalbumen were mixed in vitro and then added to guinea pig gut; only a very slight contraction occurred.

Lobsters were actively immunized to ovalbumen by injecting them with 5 mg. of ovalbumen every third day over a period of two weeks. A total of 5 injections was made. Four, eleven and eighteen days after the last ovalbumen injection a lobster was given an injection of 30 mg. of ovalbumen; one hour later, 5 ml. of blood was withdrawn, diluted to guinea pig serum strength and added to guinea pig small intestine sections mounted in the Schultz-Dale cell. The blood from the shocked lobster, four days after the last injection, caused no contraction of guinea pig gut, whereas the blood from the lobsters shocked eleven and eighteen days after the last of the immunizing injections caused strong contractions. The magnitude of the contraction corresponded to that produced by the addition of 0.5% histamine to the Schultz-Dale cell. Controls were run by mixing lobster blood from the lobster to be shocked with ovalbumen in vitro and adding this mixture, after proper dilution, to guinea pig intestine; a slow contraction occurred, but it was not comparable in magnitude or pattern to the sharp, vigorous contraction that occurred when the blood from the shocked lobster was added to the guinea pig intestine. From this we may conclude that lobsters in undergoing anaphylactic shock produce a chemical that causes guinea pig intestine to contract.

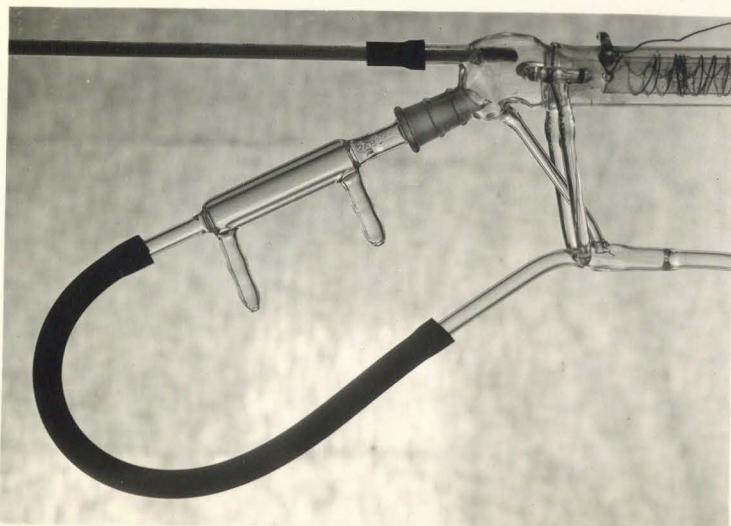
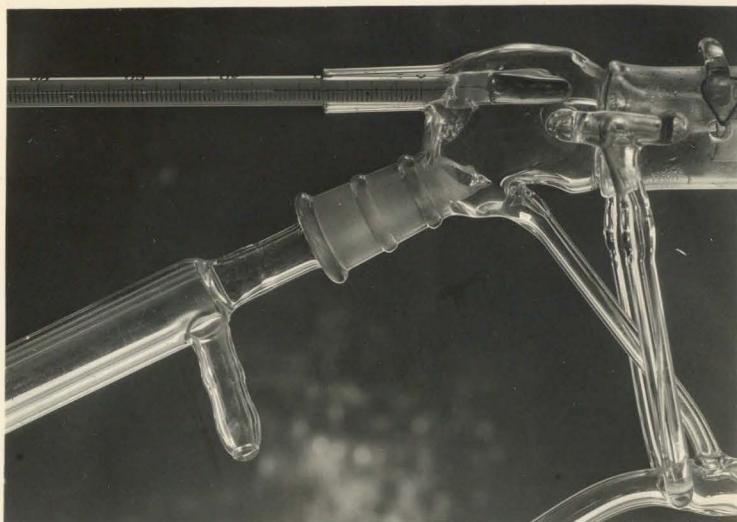
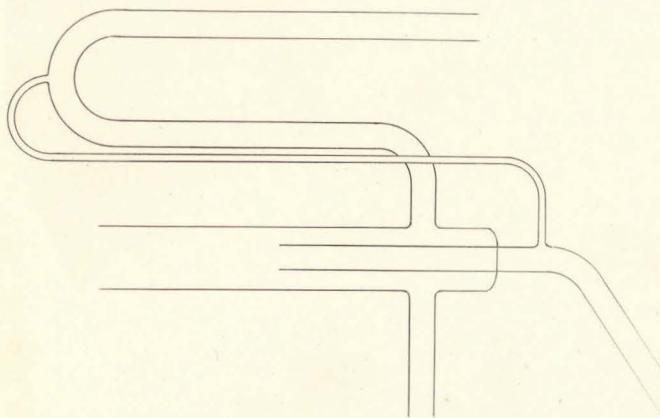
A duplicate experiment was conducted wherein fish glycogen was used as the immunizing antigen. A total of 4 mg. of fish glycogen was injected over a period of two weeks. These lobsters were tested for anaphylactic shock reactions four and eleven days after the last of the series of immunizing injections, exactly as were the lobsters actively immunized to ovalbumen. No evidence of shock reaction could be observed.

Acknowledgment: The authors wish to thank Dr. Scheer of the William G. Kerckhoff Marine Laboratories for his numerous helpful suggestions.

Summary

The effects of acetyl choline, histamine, atropine and adrenaline on the long muscles of the Sea Cucumber and on lobster intestine were investigated.

Lobsters can be passively and actively sensitized to ovalbumen and upon anaphylaxis a substance is given off into their blood stream that causes guinea pig small intestine to contract. This substance could very well be histamine.



Propositions

(1) A. I propose the design of a new type of still head that is capable of maintaining a constant reflux ratio under widely varying rates of distillation.

B. I propose the design of a constant level water bath device, the siphon arm of which is not broken by the air given off when water is heated.

(2) It is known that diketones (1,4; 1,5; 1,6) are easily cyclized giving cyclopentenones or cyclohexenones. Wherever two isomers are predicted by theory, one should expect to encounter both forms and this has not been generally recognized.
 Buchman and Sargent, J. Org. Chem., 7, 141 (1942)
 Sargent, J. Org. Chem., 7, 154 (1942)
 Willstatter and Clarke, Ber., 47, 295.

(3) Von Braun obtained from naphthenic acids a cyclic ketone of the type $\text{R} \begin{array}{c} \diagup \text{CH}_2 \\ \diagdown \text{CH}_2 \end{array} \text{CO}$ the structure of which he unsuccessfully attempted to elucidate by degradation. The problem could successfully have been attacked in another manner.
 Von Braun and co-workers, Ber., 66, 1500 (1933)
 Ruzicka et al, Helv. Chim. Acta, 23, 935 (1940)
 Ruzicka et al, Helv. Chim. Acta, 25, 190 (1942).

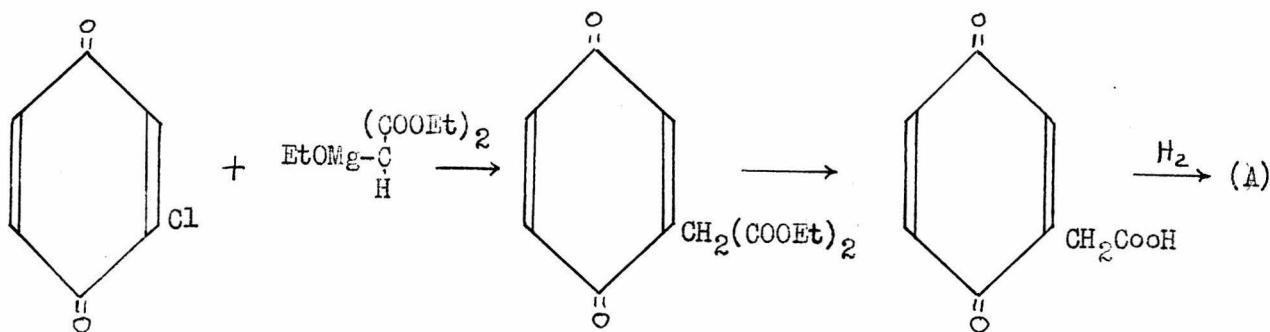
Propositions

(4) I propose 3,5-dinitrobenzoic acid as a reagent with properties similar to and in some respects superior to those of picric acid.

(5) I propose a convenient manner of storing Adams' platinic oxide catalyst by which the catalyst retains its activity for an indefinite length of time.

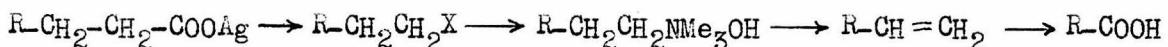
Organic Syntheses, Collective Vol. I, p. 452.

(6) I propose that homogentisic acid (A) be synthesized by the following series of reactions:



McElvain and Cohen, J. Am. Chem. Soc., 64, 260
 Hahn and Stenner, Z. Physiol. Chem., 181, 88 (1929)
 Lund and Voigt, Organic Syntheses, Collective Vol. II,

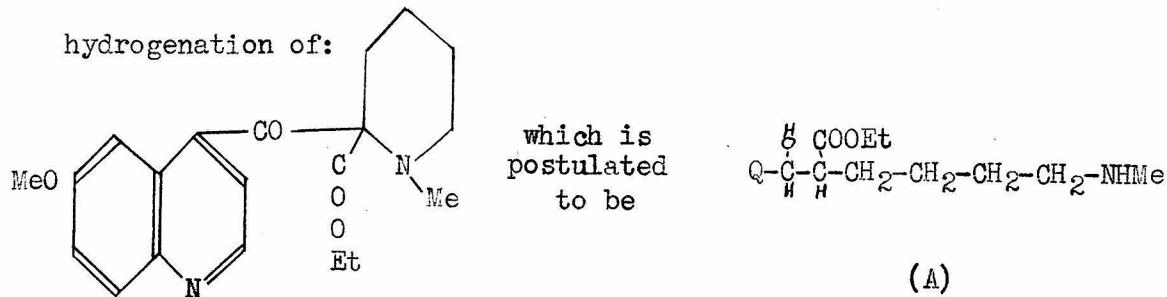
(7) I propose that naphthenic acids be degraded by the Oldham and Ubbelohde silver salt reaction with iodine or bromine:



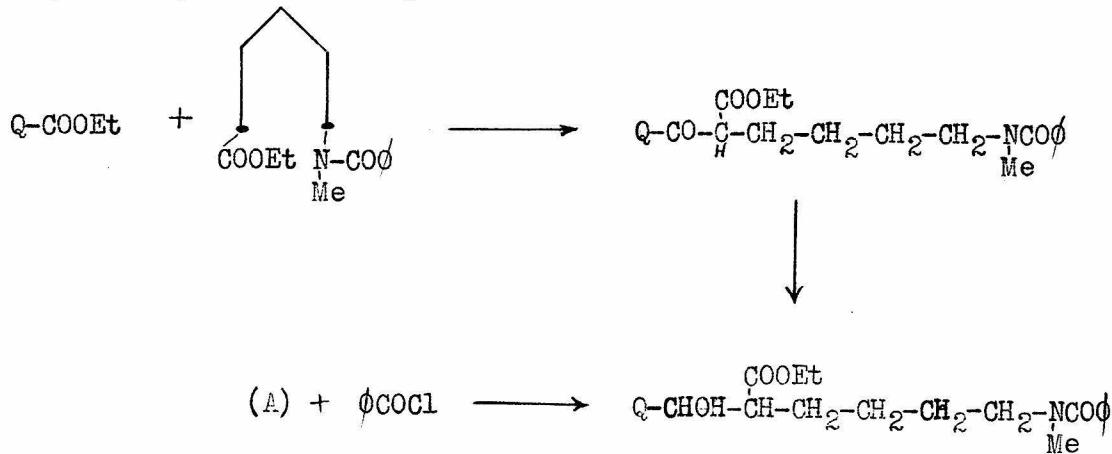
Von Braun, Ann., 490, 100 (1931)
 Luttinghaus and Schade, Chem. Abstr., 37, 74 (1943).
 Oldham and Ubbelohde, J. Chem. Soc., 1941, 368-75.

Propositions

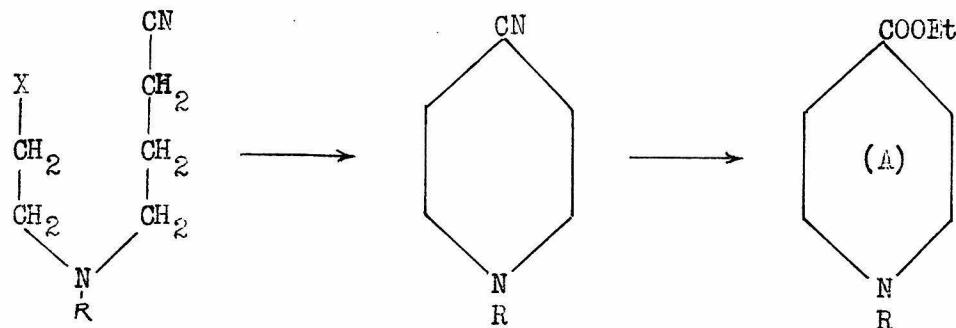
(8) I propose that the structure of a compound obtained by the hydrogenation of: 



be proved by the following series of reactions:



(9) I propose that an intermediate (A) needed in research be synthesized by the following series of reactions:



(10) I propose that histamine or a histamine-like substance is formed in lobsters by anaphalactic shock.