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TIEMANN'S "ISOCAMPHORPHORONE"[1]

EDWIN R. BUCHMAN AND HERBERT SARGENT

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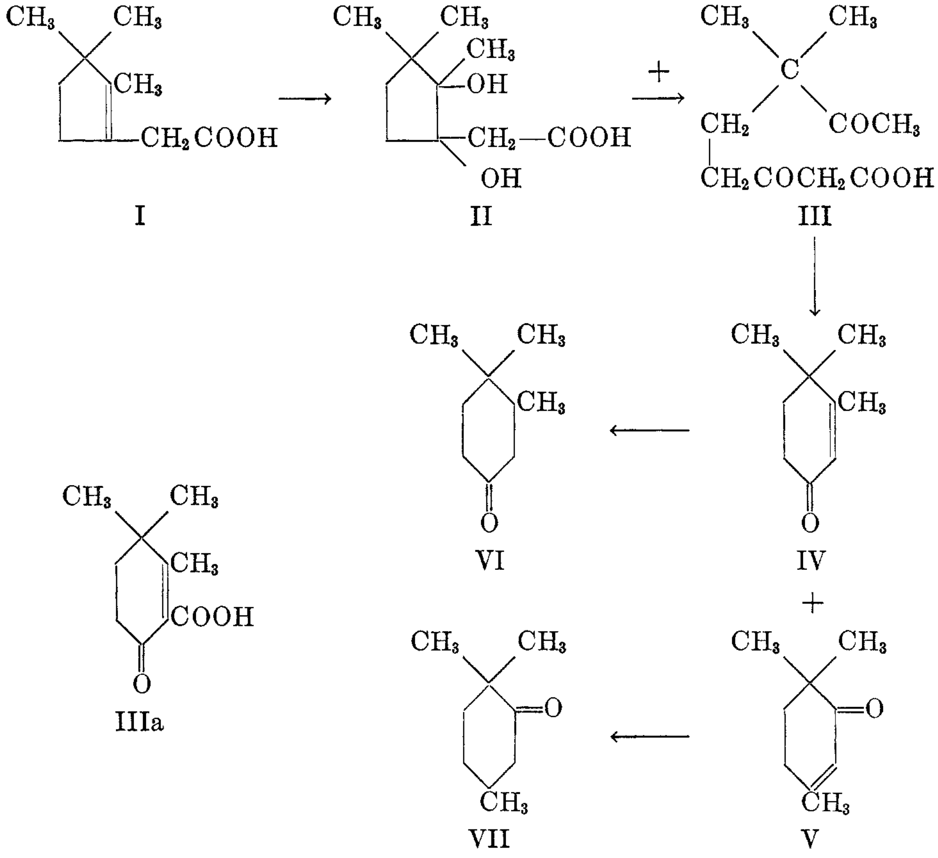
In 1897 Tiemann reported (3) that the permanganate oxidation of β-campholenic acid (I) yielded dihydroxydihydro-β-campholenic acid (II), small amounts of a ketonic acid ("campholonic acid") and a syrupy aliphatic acid which was not isolated in pure form. Under the conditions employed, this latter constituted 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 ("isocamphorphorone"). To this ketone, Tiemann assigned the structure (IV) based on a careful study of its oxidation products.



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[1] The "β-camphorphorone" of Kerp and Müller (1) has also been referred to (2) as "isocamphorphorone."

At the time of these experiments, the structure of (I) was not known; it was impossible therefore correctly to interpret[2] 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) postulated[3] 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 smoothly[5] 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

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[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

	"ISOCAMPHORPHORONE" TIEMANN (3)	IV[a]	V[b]	REDUCED "ISOCAMPHORPHORONE" 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 *p*-nitrobenzaldehyde				m.p. 226°	di-*p*-nitrobenzal derivative m.p. 223.0–223.2°	mono-*p*-nitrobenzal derivative m.p. 117.5–118.0°
Reaction with bisulfite		none	none		reacts readily	none

[a] The data in this column do not fit the $C_9H_{14}O$ 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 refractionated 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 hydrazide (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 refractionation 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 $C_9H_{15}NO$: 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 $C_9H_{17}N_3O_3$, 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-dimethylhexanon-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*-menthandione (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^{20}_D 1.4798, n^{25}_D 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-trimethylcyclohexanonoxime 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^{20}_D 1.4552, n^{25}_D 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^{20}_D 1.4442, n^{25}_D 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 $C_{16}H_{19}NO_3$:	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 fractioned. 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 "isocamphorphorone" is a mixture of the two above-named isomeric unsaturated cyclic ketones.

Pasadena, Calif.

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