[CONTRIBUTION FROM THE DOW CHEMICAL COMPANY, MIDLAND, MICHIGAN]

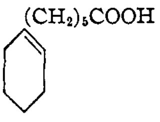
An Alkaline Fusion Product of Cyclohexanone

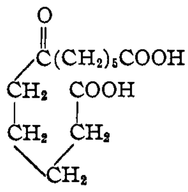
BY E. L. PELTON, C. J. STARNES AND S. A. SHRADER

Wallach[1] in a series of experiments on the alkaline fusion of alicyclic compounds heated cyclohexanone with potassium hydroxide and, among other products, was able to isolate an acid, $C_{12}H_{20}O_2$, of unknown structure. Recently Cairns, Joyce and Schreiber[2] have described the preparation of a $C_{12}H_{20}O_2$ acid by alkaline fusion of cyclohexanone. The carbon skeleton was proven by hydrogenation to cyclohexanecaproic acid but the double bond was not located.

Similar investigations here have shown[3] that if cyclohexanone or cyclohexanol is added to a molten caustic alkali (preferably a eutectic mixture of sodium and potassium hydroxides at 275–320°) the main product is an acid, or isomeric mixture of acids, of formula $C_{12}H_{20}O_2$, and containing one double bond.

The carbon skeleton of the acid (I) was shown by the hydrogenation of the refractionated ethyl ester to ethyl cyclohexane-caproate. The position of the double bond was determined by the production of a 12-carbon keto-dicarboxylic acid (II) either from permanganate oxidation or by ozonolysis of the unsaturated ethyl ester. The acid (II) was reduced to dodecanedioic acid. Since the 1-cyclohexene position is the only possible structure permitting the formation of II under the conditions stated, II is therefore 6-keto-dodecanedioic acid and the original acid (I) is 1-cyclohexene-1-caproic acid.


I


II

Although it is recognized that the possible reactions a compound may undergo on alkaline fusion are complex,[4] a mechanism similar to that of Cairns, Joyce and Schreiber[2] may be advanced. Condensation of cyclohexanone to a cyclohexenecyclohexanone[5] followed by ring scission in the alkaline melt would lead to the formation of 1-cyclohexene-1-caproic acid.

Experimental

Acid I (1-Cyclohexene-1-caproic Acid).—This compound, which was prepared and isolated as previously described,[3] was fractionated several times to give a water-white oily viscous liquid, b. p. 150° (2.2 mm.), 155° (3 mm.), 179° (10 mm.), n^{25}_D 1.4793, d^{25}_4 0.9828, f. p. −6.5 to −5.0°.

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.4; H, 10.2; neut. equiv., 196.3; *M*R, 56.50. Found: C, 73.4; H, 10.3; neut. equiv., 195.5; *M*R, 56.1.

The acid was further characterized by the preparation of the amide, m. p. 99.9–100.1°[6] and the anilide, m. p. 71.5–72.5°.

Ethyl Ester of Acid I.—Since the freezing point data indicated the above acid was still impure, the ethyl ester was prepared by refluxing in ethanol–benzene using an alkanesulfonic acid as catalyst, removing water azeotropically. The ester obtained was fractionated twice, the second time over a Podbielniak column of 100 theoretical plates. A cut (39% of charge) of 98.9 mole % purity was obtained. The clear fragrant ester had b. p. 137.5° (5 mm.), f. p. −43.86°, n^{25}_D 1.4633, d^{25}_4 0.937, *M*R 65.9, mol. wt. 226; calcd. *M*R 65.74, mol. wt. 224.3.

The unsaturated ester was hydrogenated using a 35% nickel on Super-Cel catalyst at 80–85° under 500 p. s. i. hydrogen for eight hours. An essentially quantitative (91% after fractionation) yield of ethyl cyclohexanecaproate was obtained, b. p. 119.5° (2.5 mm.), n^{20}_D 1.4522. The saturated ester was further saponified to give cyclohexanecaproic acid, m. p. 32.5–33.2°, neut. equiv. 199.1. The *p*-bromophenacyl ester had m. p. 62.0–62.5° and did not depress the melting point of known *p*-bromophenacyl cyclohexanecaproate (m. p. 62–62.5°, 20.0% Br; calcd. for $C_{20}H_{27}O_3Br$, 20.22% Br).

Acid II (6-Ketododecanedioic Acid): (a) By Oxidation of Acid I.—A solution of 19.7 g. of acid I dissolved in 60 ml. of 5% sodium hydroxide was added within five minutes to a well-stirred slurry of 32.2 g. of potassium permanganate in 500 ml. of water. After ten minutes of stirring the manganese dioxide was filtered off and the filtrate evaporated to half volume, acidified and extracted with ethyl ether to give 9.90 g. of solid. After three recrystallizations from water, white crystals were obtained, m. p. 110.4–111.0°. The acid gave positive Legal and 2,4-dinitrophenylhydrazine tests.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.0; H, 8.2; neut. equiv., 122.1. Found: C, 59.1; H, 8.0; neut. equiv., 123.0.

Semicarbazone of Acid II.—To a solution of 0.5 g. of semicarbazide hydrochloride and 0.4 g. of sodium acetate in 5 ml. of water was added a solution of 50 mg. of acid II in 3 ml. of water. After a few seconds the semicarbazone separated out as a white floc. The slurry was warmed to a clear solution, allowed to stand an hour, filtered, washed, and dried at 100° to give a white powder, m. p. 167.0–167.5°.

Anal. Calcd. for $C_{13}H_{23}O_5N_3$: C, 51.8; H, 7.7; neut. equiv., 150.7. Found: C, 51.9; H, 7.6; neut. equiv., 150.0.

Clemmensen Reduction of Acid II.—Acid II, 718 mg., was refluxed using mechanical stirring with 12 g. of zinc amalgam and 100 ml. of 1:2 hydrochloric acid for six hours, adding small amounts of fresh acid periodically. The product was isolated by ether extraction to give 510 mg. of white powder and recrystallized from 10% ethanol to give dodecanedioic acid,[7] white flakes, m. p. 129.0–129.5°,

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[1] Wallach and Behnke, *Ann.*, **369**, 99–101 (1909).

[2] THIS JOURNAL, **70**, 1689–1690 (1948).

[3] Pelton, U. S. Patent 1,961,623, June 5, 1934.

[4] H. Meyer, "Analyse und Konstitutionsermittlung organischer Verbindungen," 6th ed., Edwards Brothers, Ann Arbor, Mich., 1943, pp. 329–331.

[5] Reese, *Ber.*, **75** (B1), 384–394 (1942), gives considerable evidence that Wallach's stable liquid ketone has the structure of a cyclohexenecyclohexanone, and that cyclohexylidenecyclohexanone is partially isomerized at high temperatures to the 1-cyclohexene isomer.

[6] All melting points are uncorrected.

[7] English, Bonner and Haagen-Smit, THIS JOURNAL, **61**, 3434 (1939), give the melting point of dodecanedioic acid as 127° and its anilide 171°.

neut. equiv. 115.0 (calcd. for $C_{12}H_{22}O_4$, 115.2). The anilide, prepared by the thionyl chloride–aniline procedure and recrystallized from 90% ethanol, had m. p. 172–173°.

(b) **By Ozonization of Ethyl Ester of Acid I.**—A solution of 5.94 g. of refractionated unsaturated ester in 100 ml. of ethyl chloride was ozonized at −20 to −30° until excess ozone was present, 10 ml. of water added, and the ethyl chloride allowed to boil off. The gelatinous ozonide was refluxed with 10 ml. of 30% hydrogen peroxide and a few mg. of palladium sponge for sixteen hours, 20 ml. of 5 *N* sodium hydroxide added, and refluxing continued an hour longer. Distillation of the alkaline solution gave no cyclohexanone. Acidification and ether extraction gave 3.70 g. of tan solid which after three recrystallizations from water yielded white crystals, m. p. 109.3–110.0°, neut. equiv., 123.9. The mixed melting point of this saturated keto-acid with the acid II produced by permanganate oxidation was 110.0–110.5°. The semicarbazone was prepared and its melting point and mixed melting point with the previously obtained acid II semicarbazone were the same, 167.0–167.5°.

Summary

The physical properties of a $C_{12}H_{20}O_2$ acid obtained by alkaline fusion of cyclohexanone or cyclohexanol are listed and the amide and anilide recorded.

From the hydrogenation and ozonolysis products of the pure ethyl ester and the oxidation product of the original acid, the original acid is shown to be 1-cyclohexene-1-caproic acid.

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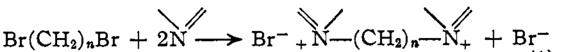
Some Quaternary Ammonium Salts of Heterocyclic Bases. III. Bis-Quaternary Ammonium Salts[1]

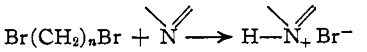
BY JONATHAN L. HARTWELL AND MILTON A. POGORELSKIN

In continuation of the study of the effect of quaternary ammonium salts on tumors in animals,[2] it was desired to prepare several series of bis-quaternary ammonium salts for bioassay. Seven series of compounds were chosen for synthesis, namely, the bis-salts derived from the normal α,ω-alkylene dibromides C_2 to C_5, C_{10}, from glycerol-α,γ-dibromohydrin, and from 2,5-dibromohexane (see Table I). The bases used were the seven tertiary heterocyclic bases utilized in previous papers.

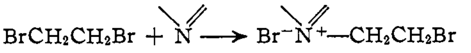
In the majority of cases, the reactions proceeded according to expectation and the alkylene dibromides added to two moles of the tertiary base to form the bis-quaternary ammonium salt (reaction 1). In those instances where the bromides were too hygroscopic for easy handling, analysis and the determination of melting points, they were converted into the corresponding perchlorates (in one case, the iodide).



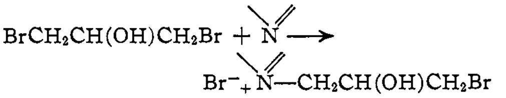
$$\mathrm{Br(CH_2)_nBr} + 2\overset{\diagdown\,\diagup}{\mathrm{N}} \longrightarrow \mathrm{Br^-}\ {}_{+}\overset{\diagdown\,\diagup}{\mathrm{N}}\mathrm{{-}(CH_2)_n{-}}\overset{\diagdown\,\diagup}{\mathrm{N}}{}_{+} + \mathrm{Br^-} \qquad (1)$$



$$\mathrm{Br(CH_2)_nBr} + \overset{\diagdown\,\diagup}{\mathrm{N}} \longrightarrow \mathrm{H{-}}\overset{\diagdown\,\diagup}{\mathrm{N}}{}_{+}\mathrm{Br^-} \qquad (2)$$



$$\mathrm{BrCH_2CH_2Br} + \overset{\diagdown\,\diagup}{\mathrm{N}} \longrightarrow \mathrm{Br^-}\overset{\diagdown\,\diagup}{\mathrm{N}}{}^{+}\mathrm{{-}CH_2CH_2Br} \qquad (3a)$$



$$\mathrm{BrCH_2CH(OH)CH_2Br} + \overset{\diagdown\,\diagup}{\mathrm{N}} \longrightarrow \mathrm{Br^-}{}_{+}\overset{\diagdown\,\diagup}{\mathrm{N}}\mathrm{{-}CH_2CH(OH)CH_2Br} \qquad (3b)$$

There were several exceptions, however. The reaction of ethylene dibromide with 3-methylisoquinoline, and of 2,5-dibromohexane with quinoline and with 3-methylisoquinoline, gave the hydrobromide of the base; since the fate of the alkylene dibromide is not known, the unbalanced equation (2) may be written for the reaction.

The reaction of ethylene dibromide with quinoline yielded two different crystalline products, depending on conditions, neither one identical with the bis-compound expected.[3] One product, m. p. 255–257° cor., gave an analysis unsatisfactory for a probable compound. The other product, m. p. 203–204° cor., had analytical figures and chemical properties corresponding to 1-(β-bromoethyl)-quinolinium bromide (reaction 3a); the nitrogen–bromine ratio showed that 1 mole of ethylene dibromide had reacted with 1 mole of quinoline, and only one-half of the bromine was ionically bound.

An interesting exception was found in the reaction between glycerol-α,γ-dibromohydrin and the tertiary bases. In several cases, this dibromide also combined with only one mole of base to form products containing two atoms of bromine of which only one atom was ionic. These products are represented by reaction (3b), and were formed with α-picoline, quinoline and 3-methylisoquinoline. With α-picoline and 3-methylisoquinoline, further reaction yielded the bis-salts, but with quinoline the bis-salt could not be formed under any conditions tried.

The reactions reported as being exceptional to the general reaction for the formation of bis-salts occurred only with the bases α-picoline, quinoline and 3-methylisoquinoline. Only these, of the bases used, have a substituent or a ring α- to the nitrogen atom. It would thus appear that steric hindrance plays a part in the course of the

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[1] Paper II, Hartwell and Kornberg, THIS JOURNAL, **68**, 1131 (1946).

[2] Hartwell and Shear, *Cancer Research*, **7**, 716 (1947).

[3] Rhoussopoulos, *Ber.*, **16**, 879 (1883), reported ethylene-α,β-bis-quinolinium bromide monohydrate on the basis of carbon and hydrogen analysis. No m. p. was given. Since the analytical values were almost equally valid for quinoline hydrobromide, and since the bis-salt was never obtained in the present work, it is considered doubtful that the bis-salt has ever been prepared.