Anal. Calcd. for $C_{11}H_{23}NO_2$: C, 65.6; H, 11.4. Found: C, 65.3; H, 11.3.

The chloroplatinate formed a light tan powder from dilute alcohol, m. p. 165–166° dec.

Anal. Calcd. for $C_{11}H_{23}NO_2 + H_2PtCl_6$: N, 2.6. Found: N, 2.5.

Summary

Several methods for the preparation of 3-substituted-4-methoxymethylpiperidines have been studied. The best one involves condensation of γ-methoxycrotononitrile with a monoalkylated malonic ester, where 36–50% yields are obtained. Subsequent steps, reductive cyclization, hydrolysis, decarboxylation and sodium–butyl alcohol reduction can be effected, without isolating intermediates, in yields of 43–46%.

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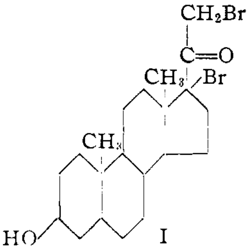
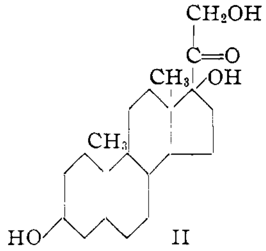
[CONTRIBUTION FROM THE WHITMORE LABORATORIES OF THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Some Metathetical Reactions of α,α'-Dibromomethyl Cyclohexyl Ketone

BY R. B. WAGNER AND JAMES A. MOORE[1]

The direct hydrolysis of 17,21-dibromopregnan-20-one compounds (I) to the corresponding diols (II) would represent a very valuable route in the elaboration of the side-chain of the cortical hormones.


I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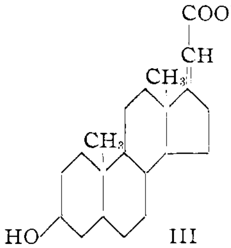
III

This dibromoketone system, however, exhibits a strong tendency toward rearrangement, when treated with alkali hydroxides, with the formation of the pregnenoic acid (III)[2]; hydrolysis to the dihydroxyketone has never been accomplished. An aliphatic α,α'-dibromoketone, 2,4-dibromo-2,4-dimethyl-3-pentanone, in which both bromine atoms are tertiary, has been converted to the dihydroxyketone in unstated yield by treatment with aqueous potassium carbonate.[3] In this case, no rearrangement products were reported.

In the present work, this problem of the hydrolysis and related metathetical reactions of an α,α'-dibromoketone has been further investigated. The compound chosen for this study was the α,α'-dibromo derivative of methyl cyclohexyl ketone. This compound was desirable from two standpoints; it had been synthesized by two independent routes[4] and its structure was thus positively known, and it represented a model compound for the dibromoketone of the steroid series (I). α,α'-Dibromomethylcyclohexyl ketone and several analogous ketones have been found previously to yield exclusively α,β-unsaturated esters upon treatment with sodium methylate in ether, *viz.*, $R_2CBrCOCH_2Br \rightarrow R_2C{=}CHCO_2CH_3$.[4]

Upon treatment with aqueous potassium hydroxide or potassium carbonate, however, this compound has been found to yield approximately equal amounts of the rearrangement product, cyclohexylideneacetic acid, and the metathesis product, α,α'-dihydroxymethyl cyclohexyl ketone. The yields of these compounds were quite low due to the difficulty of obtaining complete removal of the bromine atoms without causing serious decomposition of the products.

The reaction of the dibromoketone with sodium benzoate under two sets of conditions was also investigated. When a benzene–xylene mixture was employed as the medium, the only product which could be isolated (in very poor yield) was the benzoate of hydroxymethyl α-bromocyclohexyl ketone, thus only the primary bromine atom was attacked. When benzoic acid was used as a solvent, the product was the benzoate of hydroxymethyl 1-cyclohexenyl ketone, in which both bromine atoms had been abstracted.

These reactions and the interconversions which were made in order to characterize the products are summarized in the accompanying chart.

The behavior of this dibromoketone may be compared with the 17,21-dibromopregnan-20-one series. In addition to the contrasting effects of alkaline reagents, the action of sodium benzoate in benzoic acid in the present study is somewhat different from that of potassium acetate in acetic acid on the dibromo steroidal ketone.[5] In the latter case, the tertiary bromine atom is preferentially removed with the formation of the 21-bromo-16,17-unsaturated compound.

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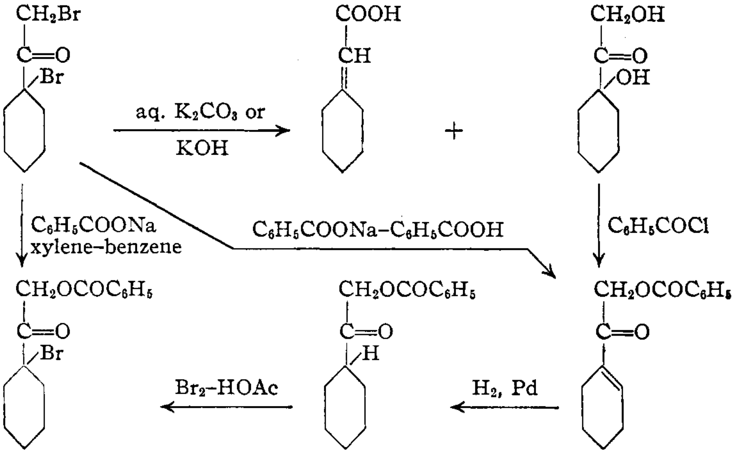
(2) Marker, Crooks and Wagner, THIS JOURNAL, **64**, 817 (1942).

(3) Favorskii, *J. prakt. Chem.*, [2] **88**, 681 (1913).

(4) Wagner and Moore, THIS JOURNAL, **72**, 974 (1950).

(5) Marker, Crooks and Wagner, *ibid.*, **64**, 213 (1942).



The course and extent of metathetical reactions of α,α′-dibromoketones thus appears to be significantly conditioned by the nature of the entire molecule and by the effects of the groups adjacent to the dibromo ketone system.

Experimental

α,α′-Dihydroxy Methyl Cyclohexyl Ketone from 1-(Bromoacetyl)-1-bromocyclohexane.—(a) By Potassium Carbonate Hydrolysis.—A solution of 142 g. (0.5 mole) of α,α′-dibromomethyl cyclohexyl ketone in 100 cc. of ether was stirred at room temperature with a solution of 69 g. (0.5 mole) of potassium carbonate in 625 cc. of water. After 120 hours, the aqueous layer was found to contain 0.74 eq. of bromide ion. An additional 20 g. of potassium carbonate was then added, and stirring was continued for another 120 hours. The aqueous solution then contained 0.81 eq. of bromide ion, and this amount was not increased by further stirring. The ether was then allowed to evaporate, and the oily upper layer crystallized. This material was removed by filtration, and the aqueous layer was continuously extracted with ether. Acidification of the aqueous solution yielded 5 g. (7% yield) of cyclohexylideneacetic acid, m. p. and mixed m. p., 90–90.5°. The combined neutral fraction yielded a total of 21 g. of material which crystallized from ethyl acetate or ether as white cubes, m. p. 86–87°. This represents a 26% yield of α,α′-dihydroxymethyl cyclohexyl ketone. The material reduced ammoniacal silver nitrate solution rapidly.

Anal. Calcd. for $C_5H_{14}O_3$: C, 60.7; H, 8.6; –OH, 21.5. Found: C, 60.5; H, 8.6; –OH (Zerewitinoff), 21.4.

This compound yielded a semicarbazone, m. p. 182–183 (dec.).

Anal. Calcd. for $C_9H_{17}O_3N_3$: N, 19.5. Found: N, 18.9.

(b) **By Potassium Hydroxide Hydrolysis.**—A solution of 13.7 g. (0.25 mole) of potassium hydroxide in 500 cc. of water was added in one portion to 21.3 g. (0.075 mole) of α,α′-dibromomethyl cyclohexyl ketone. The reaction was very vigorous, the temperature rising from 30 to 100°. After stirring at 75° for 1.5 hours, the reaction mixture was cooled and neutral compounds were extracted with ether. After drying and concentrating the ethereal solution, 1.5 g. (12% yield) of dihydroxymethyl cyclohexyl ketone was obtained, m. p. and mixed m. p., 87–88°. The aqueous layer, on acidification, yielded 2.1 g. (20%) of cyclohexylideneacetic acid.

Benzoate of Hydroxymethyl 1-Bromocyclohexyl Ketone.—(a) From α,α′-Dibromomethyl Cyclohexyl Ketone by Sodium Benzoate in Benzene–Xylene.—To a solution of 5 g. of the dibromoketone and 1 cc. of pyridine in 10 cc. of benzene and 10 cc. of xylene was added 4.33 g. of sodium benzoate. The mixture was maintained with stirring for 1.5 hours at a temperature of 100°. The reaction mixture was then cooled and water was added. The organic layer was separated, washed with acid and base, and the solvent was then evaporated in vacuum. The dark residue was refrigerated, and crystals formed overnight. After repeated crystallizations from aqueous methanol and ether–pentane, a very small amount of material (less than 400 mg.) was obtained which had m. p. 79–80°, and was unaltered by further crystallization.

Anal. Calcd. for $C_{15}H_{17}O_3Br$: C, 55.4; H, 5.3. Found: C, 55.4; H, 5.3.

(b) **From the Benzoate of Hydroxymethyl Cyclohexyl Ketone by Bromination.**—To a solution of 1.0 g. of the benzoate of the hydroxymethyl ketone (prepared from diazomethyl cyclohexyl ketone) in 15 cc. of glacial acetic acid was added 4.06 ml. of 1 *M* bromine in acetic acid solution. The reaction was carried out at 50°, at which temperature the bromine was rapidly consumed. The reaction mixture was then diluted with water and extracted with ether. The ether solution was washed free of acid, and then was evaporated. The residue crystallized completely to yield 1.1 g. of white needles, m. p. and mixed m. p. with material from (a), 79–80°.

Benzoate of Hydroxymethyl 1-Cyclohexenyl Ketone.—(a) From α,α′-Dibromomethyl Cyclohexyl Ketone by Sodium Benzoate in Benzoic Acid.—To a solution of 7.2 g. (0.05 mole) of sodium benzoate in 25 g. of benzoic acid at a temperature of 160°, was added 5.7 g. (0.03 mole) of the dibromoketone. The reaction mixture was heated at 200° with occasional shaking for two hours. The solution was then cooled and dissolved in ether and water. The ether solution was washed with dilute aqueous sodium hydroxide to remove all of the benzoic acid, and the ether was evaporated to yield 0.5 g. of white needles, m. p. 95–97°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.7; H, 6.6. Found: C, 73.7; H, 6.6.

(b) **From α,α′-Dihydroxymethyl Cyclohexyl Ketone by Benzoylation.**—Five grams of the dihydroxyketone was warmed with 8.4 g. of benzoyl chloride for fifteen minutes, and the solution was then cooled and processed in the usual manner to yield 2.3 g. of derivative, m. p. and mixed m. p. with above, 96–98°.

Hydrogenation of the Benzoate of Hydroxymethyl 1-Cyclohexenyl Ketone.—A solution of 200 mg. of the unsaturated hydroxy ketone benzoate in 50 cc. of purified dioxane was shaken with 1.0 g. of 5% palladium–barium sulfate catalyst in a hydrogen atmosphere for two hours at 45 pounds pressure. The contents of the bottle was then filtered through Celite and the solvent evaporated in vacuum. The residue was dissolved in a small volume of ether and cooled. After three days, the solution deposited a small amount of crystalline material, m. p. 42–45°. This was recrystallized from ether–pentane, m. p. and mixed m. p., 54.5–55°.

Summary

Some reactions of α,α′-dibromomethyl cyclohexyl ketone, an alicyclic analog of the 17,21-dibromo-20-keto-steroids, have been investigated and the behavior of the two dibromoketone systems has been compared.

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