

catalyst the xylene was stepwise evaporated giving two fractions (both gave negative Schiff tests) of small quantity which melted at 153.2–159° and 175–180° (partially). Complete evaporation afforded a pleasant-smelling mobile yellow oil which solidified under low pressure of nitrogen over phosphorus pentoxide and gave a strong aldehyde test with Schiff reagent. Extraction with hot dry ether removed a small amount of material responsible for the aldehyde test and left a residue (0.35 g.) which did not melt up to 360° but when placed in a sealed capillary in a previously heated bath melted at 210–220°. The material was insoluble in hot and cold, concentrated and dilute aqueous solutions of sodium bisulfite.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 76.39, 76.39; H, 5.00, 4.86.

When 0.0704 g. of the above dimer was heated for five minutes at 285° the loss in weight amounted to 0.0031 g. or 4.4%.

Anal. Calcd. for $C_{27}H_{20}O_4$: C, 79.39; H, 4.94. Found: C, 79.12; H, 4.91.

Attempted Reduction of *p*-Cyanoacetophenone.—To a solution of 3.1 g. (0.016 mole) of anhydrous stannous chloride in 35 ml. of anhydrous ether saturated with dry hydrogen chloride was added over a five-minute period a solution of 1.6 g. (0.011 mole) of *p*-cyanoacetophenone in 20 ml. of dry chloroform. The resulting light yellow solution was stirred and treated with hydrogen chloride for four hours at which time a light yellow colored solid had formed. This was removed, washed with ether and then added to 15 ml. of warm water. The dark brown oil which formed contained much inorganic salt and gave a negative Schiff test. It was therefore subjected to a series of hydrolyses and extractions with various solvents. In this way were obtained two solid fractions. One, which melted at 51.2–58.0° appeared to be impure nitrile and the other (also in small amount) melted mainly at 59–72° and may have been partially hydrolyzed nitrile. Most of the product persisted as an oil which did not give the strong immediate Schiff test characteristic of the aldehyde. It was therefore discarded.

***p*- α,α -Dibromoethylbenzal Bromide.**—*p*- α -Bromoethyltoluene was prepared from methyl *p*-tolylcarbinol in 70% yield by the action of phosphorus tribromide and pyridine in benzene solution (b. p. 101.6–103° at 12 mm.). To a solution of 25 g. (0.126 mole) *p*- α -bromoethyltoluene in 25 ml. of carbon tetrachloride (at 60°) was added, over a period of three hours, a solution of 60.5 g. (0.378 mole) of bromine in 185 ml. of dry carbon tetrachloride. Two 300-watt bulbs provided the radiation. Upon removal of the solvent there was obtained 51.9 g. (97%) of heavy brown oil, n_D^{25} 1.6496, d_4^{25} 2.1254.

Anal. Calcd. for $C_9H_8Br_4$: Br, 73.35. Found: Br, 73.11.

On standing for several months in the refrigerator the oil solidified and, after recrystallization from ether and then ether-petroleum ether mixture, melted at 133.2–134.3°.

Anal. Calcd. for $C_9H_8Br_4$: C, 24.80; H, 1.85. Found: C, 24.98; H, 2.43.

Attempted Hydrolysis of *p*-Ethyltoluene Tetrabromide.—The following is typical of the runs made. A mixture of 20.1269 g. (0.0461 mole) of tetrabromide, 100 ml. of water and 1 g. of hydroquinone was refluxed for ten hours during which time the mixture frequently was brought to the brom thymol blue end-point by titration with standard base. At the end of the reaction period, when base consumption had practically ceased, a total of 81.4 ml. of 1.7079 *N* sodium hydroxide had been consumed. This is equivalent to 0.1390 mole of hydrogen bromide as compared to the theoretical value of 0.1385 mole (on the basis of 3 moles of hydrogen bromide per mole of original tetrabromide). The product was a dark-brown polymeric substance which was only slightly soluble in saturated sodium bisulfite solution. It was not investigated further.

Summary

Of the methods tried the only practical synthesis of *p*-acetylbenzaldehyde is by means of the Rosenmund reduction of *p*-acetylbenzoyl chloride.

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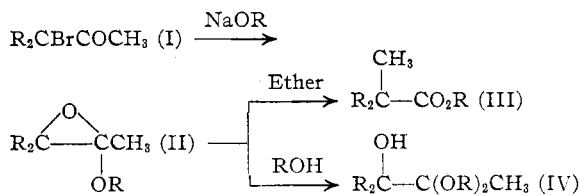
RECEIVED NOVEMBER 7, 1949

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

The Reaction of the Isomeric α -Bromomethyl Cyclohexyl Ketones with Sodium Methoxide

BY R. B. WAGNER AND JAMES A. MOORE¹

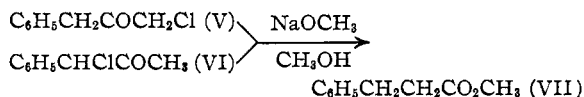
The conversion of an α -bromo- α -alkyl ketone (I) to a trisubstituted acetic ester (III) or a hydroxyl ketal (IV) has been recognized by Aston and Green² to be a general reaction, which was considered to proceed *via* an intermediate oxide (II), the latter precursor giving rise to the ester (III) when ether was employed as the medium, and to a hydroxyketal (IV) if alcohol was present, *viz.*



(1) Research Department, Parke, Davis and Company, Detroit 32, Michigan.

(2) Aston and Green, *THIS JOURNAL*, **62**, 2590 (1940).

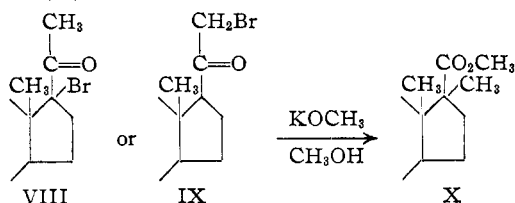
However, the postulation of an ethylene oxide intermediate appears inadequate to explain the formation of the same ester by rearrangement of isomeric chloroketones. This was shown to occur by McPhee and Klingsberg³ who treated the isomeric α -chlorophenylacetones (V and VI) with sodium methoxide in methanol and obtained methyl hydrocinnamate (VII) in each case, *viz.*



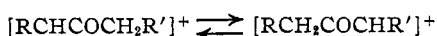
Recently, another example of this phenomenon was observed in the steroidal series, in which both the 17-bromo and 21-bromopregnenolones (VIII and IX) were transformed with potassium meth-

(3) McPhee and Klingsberg, *ibid.*, **66**, 1132 (1944).

oxide in methanol to the 17-methyl-etio-cholenic ester (X).⁴



It was considered³ that although the hydroxyketals could arise by an oxide intermediate, the formation of the same ester from the two isomeric haloketones occurs by the rearrangement of one of the carbonium ions of a synionic isomeric pair, *i. e.*

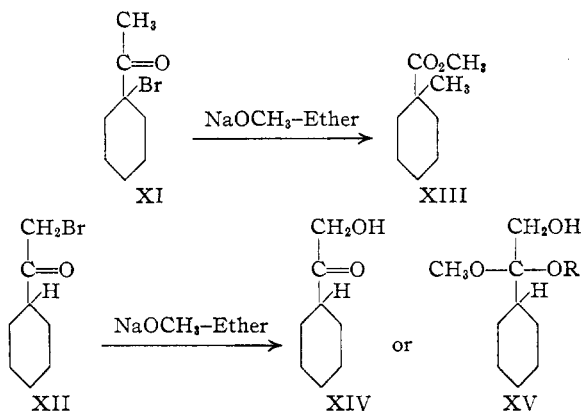


which results from either of the two haloketones. Thus, the ion which had the lower energy of activation would undergo the rearrangement.

Although this explanation appeared to have ample confirmation in the steroid series, it has been our experience^{5,6} that steroidal bromoketones do not invariably exhibit the same reactions as their aliphatic and simpler alicyclic analogs. We have therefore extended this study of isomeric α -bromoketones to methyl cyclohexyl ketone. Methyl α -bromocyclohexyl ketone (XI) and bromomethylcyclohexyl ketone (XII) have been prepared by the most straightforward methods available, and treated with sodium methoxide in ether under identical conditions. Ether, rather than methanol, was used as the solvent since it has been found^{6,7} that the former solvent with sodium methoxide leads exclusively to rearrangement products in the dibromoketone series.

It was of considerable interest to find that these two ketones underwent entirely different reactions. The methyl α -bromocyclohexyl ketone (XI) was converted in good yield to methyl 1-methylcyclohexanecarboxylate (XIII), thus exhibiting the expected rearrangement. The isomeric bromomethyl ketone (XII), however, showed no rearrangement. One of two metathesis products, the hydroxyketone (XIV) or hydroxyketal (XV), was obtained, depending upon whether water or alcohol was first added in processing the bromoketone-sodium methoxide mixture. A small amount of methyl cyclohexyl ketone was also obtained in the reactions of the bromomethyl ketone.

Bromomethyl cyclohexyl ketone was available by treatment of the diazomethyl ketone with hydrogen bromide. The structure of the bromoketone thus obtained was confirmed by its conversion, in excellent yield, to a crystalline pyri-

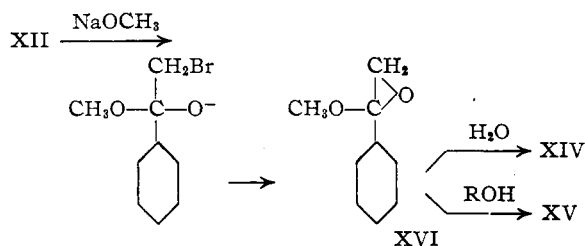


dinium salt and by subsequent degradation to cyclohexanecarboxylic acid. The isomeric methyl α -bromocyclohexyl ketone was prepared by direct bromination. Although this procedure is not uncomplicated, it has been widely used for the preparation of ketones of the type $\text{R}_2\text{CBrCOCH}_3$,^{2,8,9} since the tertiary hydrogen atom is replaced more readily than any of the primary ones. It will be noted that the properties of these two bromoketones were entirely different.

The products obtained from these bromoketone reactions were identified by the customary procedures. Authentic samples of hydroxymethyl cyclohexyl ketone and its benzoate were readily obtained from the diazoketone.

Whereas the rearrangement of the methyl α -bromocyclohexyl ketone to the tertiary ester has been seen to be an entirely normal reaction, the behavior of the isomeric bromomethyl ketone deserves some mention. The fact that two different compounds could be obtained from the reaction, depending upon the method of processing, strongly indicates the presence of a highly reactive intermediate compound in the reaction mixture.

The most probable precursor for both the hydroxy ketone and the hydroxyketal appears to be the methoxy epoxide (XVI). This type of intermediate has been postulated several times^{2,10} to account for the formation of ketal products from the reaction of a bromoketone with alkali alkoxide.



Although schemes based upon either an epoxide intermediate such as XVI or some equivalent

(4) Plattner and Heuser, *Helv. Chim. Acta*, **31**, 603 (1948); **32**, 275 (1949).

(5) Wagner, *This Journal*, **71**, 3214 (1949).

(6) Wagner and Moore, *ibid.*, **72**, 1873 (1950).

(7) Wagner and Moore, *ibid.*, **72**, 974 (1950).

(8) Favorskii, *J. prakt. Chem.*, [2] **88**, 658 (1913).

(9) Marker and Wagner, *This Journal*, **64**, 210, 216 (1942).

(10) Bergmann and Mieleky, *Ber.*, **64**, 802 (1931).

ionic intermediate may be proposed, no completely satisfactory explanation is available at present to account for these analogous sets of compounds, *i. e.*, V-VI or VIII-IX *vs.* XI-XII, undergoing different reactions. The former scheme appears to be operating in the formation of the metathesis products (XIV and XV) from bromomethyl cyclohexyl ketone (XII) and may even be involved in the formation of the rearrangement product (XIII) from the isomeric bromoketone (XI). On the other hand, an ionic intermediate, certainly indicated in previous work,^{3,4} appears to be lacking in the reaction of this isomeric pair.^{10a}

Experimental¹¹

Diazomethyl Cyclohexyl Ketone.—This compound was prepared in the usual manner¹² by the reaction of cyclohexanecarbonyl bromide with two equivalents of diazomethane. The diazoketone crystallized after removal of the ether to yield long yellow needles, m. p. 11–13°. The yield, in several experiments, was 80%. It was impossible to completely free this compound from traces of solvent.

Anal. Calcd. for $C_8H_{12}ON_2$: N, 18.4. Found: N, 17.1.

Bromoacetyl cyclohexane (Bromomethyl Cyclohexyl Ketone) (XII).—To a solution of 26.9 g. (0.176 mole) of the diazomethyl ketone in 300 cc. of pentane was added, with stirring at 20°, 45 cc. (theoretical amount + 10% excess) of aqueous 34% hydrogen bromide. After nitrogen evolution had completely stopped, the layers were separated and the pentane solution was washed with water until all of the hydrogen bromide had been removed. The solution was then evaporated *in vacuo* until the loss in weight was constant. The residual pale yellow, extremely lachrymatory oil amounted to 34.4 g., representing a 95.2% yield of bromoketone. Since preliminary preparations had indicated that this compound could not be distilled without very serious decomposition, this material was used directly for the determination of physical properties: n_D^{20} 1.5033; d_4^{20} 1.358; M_D (obs.) 44.91; M_D (calcd.) 44.73 m. p. –3.5 to –2°.

Anal. Calcd. for $C_8H_{13}OBr$: Br, 38.9. Found: Br, 38.5.

This bromoketone, on treatment with 2,4-dinitrophenylhydrazine in the usual manner, furnished a derivative containing bromine which crystallized from ethanol, m. p. 130–131°.

Pyridinium Salt of Bromomethyl Cyclohexyl Ketone.—To one cc. (1.385 g.) of the above bromoketone was added one cc. of purified pyridine (twice the theoretical quantity). The reaction mixture became very hot, and exceedingly viscous. The material was cooled and stirred thoroughly with twelve portions (5 cc.) of anhydrous ether. With each successive portion the solution became more tacky, until the mass solidified. The salt was then pulverized and thoroughly triturated with ether to remove all traces of pyridine. When dried, this material weighed 1.826 g., or 97.4% of the theoretical; m. p. 67–71°.

Anal. Calcd. for $C_{13}H_{15}ONBr$: Br, 28.1. Found: Br, 27.3.

A sample (0.80 g.) of this salt was dissolved in water, and the solution was warmed for 40 minutes with 3 cc. of

10% sodium hydroxide. The purple solution was cooled, and after extraction with ether, was acidified. The organic acid was extracted with ether, and the ether solution was concentrated. The residue was treated with *p*-bromophenacyl bromide, and the derivative was obtained as plates from aqueous dioxane, m. p. and mixed m. p. with the *p*-bromophenacyl ester of cyclohexanecarboxylic acid, 91–92°.

Anal. Calcd. for $C_{15}H_{17}OBr$: C, 55.4; H, 5.2. Found: C, 55.1; H, 5.2.

Methyl α -Bromocyclohexyl Ketone (XI).—To 61 g. (0.48 mole) of methyl cyclohexyl ketone and 1 cc. of 38% hydrobromic acid in a flask, equipped with a stirrer and surrounded by a salt-ice-bath, was added 76 g. (0.475 mole) of bromine at a temperature of 0°. The reaction mixture was then diluted with pentane, and the hydrogen bromide was removed by washing thoroughly with water. The pentane was removed *in vacuo* and the bromoketone was then fractionated rapidly in a 1.8 × 45 cm. column packed with 1/4 in. helices. The first fractions which were obtained contained mainly methyl cyclohexyl ketone. Six fractions, b. p. 58–65 (3 mm.), n_D^{20} 1.5019–1.5043, 52.6 g., were obtained which consisted of the monobromoketone. A sample from a middle fraction was removed for physical properties and analysis: n_D^{20} 1.5027; d_4^{20} 1.350; M_D (obs.) 44.88; M_D (calcd.) 44.73; m. p. –10 to –8°; a mixture with bromomethyl cyclohexyl ketone melted –32 to –20°.

Anal. Calcd. for $C_8H_{13}OBr$: Br, 38.9. Found: Br, 38.9.

A sample of this ketone was treated with 2,4-dinitrophenylhydrazine and the derivative of methyl cyclohexenyl ketone was obtained, m. p. and mixed m. p. 197–199°.

Reactions of Bromoketones with Sodium Methoxide.—These experiments were performed by adding the bromoketone to an ether suspension of sodium methoxide (Mathieson Alkali Works, 95% assay) contained in a three-necked flask equipped with a dropping funnel, mercury-sealed stirrer, and thermometer well. All of the equipment was stored in an oven at 110° for one hour prior to the run. The ether was distilled into the flask through a column packed with calcium hydride. All outlets of the system were protected by tubes containing this drying agent. The sodium methoxide was taken from a freshly opened bottle of the commercial material; its composition was checked. The bromoketone was stored over phosphorus pentoxide in an evacuated desiccator prior to use.

The bromoketone was added over a one to three hour period with the temperature maintained at 0° by means of a salt-ice-bath. The reaction mixture was then stirred for an additional two to eight hours under anhydrous conditions. For (a) and (c) below, water was added, the layers were separated, and the ether solution of the product was dried over sodium sulfate. The ether was removed through a three-foot helix-packed column and the residue was then distilled in a Claisen flask as rapidly as possible, and the volatile material was finally fractionated.

This method of processing the reaction mixture was varied as described under (b).

(a) **Bromomethyl Cyclohexyl Ketone (XII) to Hydroxymethyl Cyclohexyl Ketone (XIV).**—In a typical experiment, in which 0.8 mole of the bromomethyl ketone had been treated in the manner just described, fractionation of the first distillate in an 8-inch column packed with 1/8 in. helices yielded two compounds. The first fractions, 5 g., had the following properties: b. p. 48–50° (6 mm.); n_D^{20} 1.4487. This represents a 5% yield of methyl cyclohexyl ketone. The second compound amounted to 31 g. (28% yield) and had the following properties: b. p. 82° (3 mm.); n_D^{20} 1.4751; d_4^{20} 1.040; m. p. 29°; M_D (calcd.) 37.49; M_D (obs.) 36.46.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.6; H, 9.9. Found: C, 66.8; H, 9.6.

This material reduced ammoniacal silver nitrate solution, Fehling solution, and paraperiodic acid rapidly. It absorbed hydrogen in the presence of platinum catalyst to

(10a) ADDED IN PROOF: Stevens, Malik and Pratt, Abstracts of Papers, 117th Meeting, American Chemical Society, Philadelphia, April, 1950, p. 56L, report the isolation of an epoxy ether from the action of sodium methoxide on α -chloroacetophenone. Similarly, their substance yields a hydroxyketal with methanol and a ketobenzoate with benzoic acid.

(11) All melting points and boiling points are uncorrected.

(12) Eistert, in "Newer Methods of Preparative Organic Chemistry," 1st Am. Ed., Interscience Publishers, Inc., New York, N. Y., 1948, p. 513.

yield a product which reduced periodic acid but not ammoniacal silver nitrate. The compound furnished the following derivatives: semicarbazone, m. p. 160–162°; 2,4-dinitrophenylhydrazone, m. p. 183–185°; benzoate, m. p. 56–57°.

Authentic samples of hydroxymethyl cyclohexyl ketone and its benzoate were prepared from diazomethyl cyclohexyl ketone. The hydroxyketone thus obtained had properties identical with those of the above product, and a mixed melting point determination showed no depression.

The benzoate was obtained as needles from ether-pentane, m. p. and mixed m. p. with the benzoylation product from above, 56–57°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.2; H, 7.4. Found: C, 73.6; H, 7.4.

(b) **Bromomethyl Cyclohexyl Ketone to Ketal of Hydroxymethyl Cyclohexyl Ketone (XV).**—After the reaction of 95 g. (0.46 mole) of bromoketone with 28 g. (0.48 mole) of sodium methoxide, most of the ether was removed by distillation, and an equal volume (200 cc.) of absolute ethanol was distilled into the reaction mixture. Sodium methoxide, 2 g., was then added and the mixture was refluxed for two and a half hours, with moisture still excluded. The ethanol was then removed by distillation and the residue processed with water as usual; the organic material was extracted with ether, the ethereal solution was washed well with water, and then concentrated. The residue was distilled in a Claisen flask; 16 g. of distillate and 40 g. of resin were obtained. Fractionation of the volatile material in an 8-in. column packed with $1/8$ in. helices yielded a very small quantity of impure methyl cyclohexyl ketone and 14.1 g. (16% yield) of a compound having the following properties: b. p. 90° (3 mm.); n_D^{20} 1.4695; d_4^{20} 1.036. For the dimethyl ketal: M_D (calcd.) 51.00, M_D (obs.) 50.65; for the methyl ethyl ketal: M_D (calcd.) 55.62, M_D (obs.) 54.43.

Anal. Calcd. for $C_8H_{14}O(OCH_3)_2$: C, 63.8; H, 10.7; OCH_3 , 33.0. Calcd. for $C_8H_{14}O(OCH_3)(OC_2H_5)$: C, 65.3; H, 11.0; OR (as OCH_3), 30.7. Found: C, 64.3; H, 10.5; OCH_3 , 30.2.

Thus the ketal which arose from the alcoholysis of the oxide (XIV) is evidently a mixture of the dimethoxy- and methoxyethoxy-ketals; the oxide reacting preferentially with the residual methanol.

This material reduced paraperiodic acid, but did not reduce ammoniacal silver nitrate solution. On treatment with benzoyl chloride, a derivative was obtained, m. p. and mixed m. p. with the benzoate of hydroxymethyl cyclohexyl ketone, 56–57°.

For further characterization, a sample of the ketal (8.26 g.) was added to a solution of 10% sulfuric acid. The material dissolved in a few minutes, and the solution was then placed under a six-inch column packed with a

copper spiral and the alcohol was slowly distilled. A total of 2.25 g. of material was obtained, b. p. 64–66° (730 mm.), n_D^{20} 1.3289–1.3450. The last fraction of alcohol obtained, having n_D^{20} 1.3450, yielded on treatment with 3,5-dinitrobenzoyl chloride and pyridine the 3,5-dinitrobenzoate of methanol, m. p. and mixed m. p. 105–107°. This quantity of material is 70% of the theoretical for two equivalents of methanol per mole of ketal.

(c) **Methyl Bromocyclohexyl Ketone (XI) to Methyl 1-Methyl-1-cyclohexanecarboxylate (XIII).**—Fractionation of the reaction products from 42 g. (0.21 mole) of methyl α -bromocyclohexyl ketone and sodium methoxide yielded 25.9 g. (79% yield) of material having the following properties: b. p. 35° (3 mm.); n_D^{20} 1.4456; d_4^{20} 0.963; M_D (calcd.) 43.23; M_D (obs.) 43.30.

On treatment with anilino-magnesium bromide, the ester furnished, in excellent yield, an anilide which crystallized from methanol as large prisms, m. p. 111.5–112°.

Anal. Calcd. for $C_{14}H_{19}ON$: C, 77.4; H, 8.8. Found: C, 76.9; H, 8.6.

For saponification, 16 g. of the material was heated at 180° with a solution of 8 g. of potassium hydroxide in 50 cc. of aqueous ethanol in a sealed tube for twelve hours. After removal of the alcohol, acidification of the solution yielded 14 g. of a crystalline acid, m. p. 39–40°.

Anal. Calcd. for $C_8H_{14}O_2$: neut. equiv., 142.3. Found: neut. equiv., 143.5.

A sample of the acid was converted to an amide via the acid chloride. This derivative crystallized from pentane as needles, m. p. 65–66°.¹³

Summary

1. Two isomeric α -bromoketones, methyl α -bromocyclohexyl ketone and bromomethyl cyclohexyl ketone, have been prepared and subjected to identical treatment with sodium methoxide in ether. Entirely different reactions were observed; the former compound underwent rearrangement, whereas the latter compound gave metathesis products.

2. Evidence is given for the occurrence of an alkoxy-oxide in the reaction of bromomethyl cyclohexyl ketone with sodium methoxide in ether, giving further support to these postulated intermediates.

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RECEIVED OCTOBER 25, 1949

(13) Gutt, *Ber.*, **40**, 2069 (1907), reports for 1-methyl-1-cyclohexanecarboxylic acid, m. p. 38–39°; amide, m. p. 68–69°.