THE OXYMERCURATION OF 4-METHYLENECYCLOHEXANEMETHANOL

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ABSTRACT

The oxymercuration of 4-methylenecyclohexanemethanol in *tert*-butyl alcohol yields 1-chloromercurimethylnorcineole which may be converted to 1-methylnorcineole by borohydride reduction or to 4-chloromercurimethyl-4-↑-hydroxycyclohexane-↓-carboxylic acid. This may be deoxymercurated to 4-methylenecyclohexanecarboxylic acid and reduced with borohydride to 4-↓-methyl-4-↑-hydroxycyclohexane-↓-carboxylic acid.

The oxymercuration of alkenols has been accomplished before. Sand and Singer (1, 2), as well as others (3), found that the hydroxyl group in 2,6-dimethylheptene-5-ol and in α-terpineol (1, 2, 4) is involved in the reaction with the consequences that cyclic ethers are formed. The same type of reaction has now been carried out with 4-methylenecyclohexanemethanol to ascertain the effect of a terminal double bond in this reaction.

When mercuric acetate in an excess of 4-methylenecyclohexanemethanol, I, is stirred for 3 days according to the method used for preparation of chloromercuricineole (4), the results are unpleasant. An unworkable gum is formed which is probably a mixture of the geoisomers of 4-acetoxymercurimethyl-4-acetoxycyclohexanemethanol, II. However, the expected product, chloromercurimethylnorcineole (III, 4-chloromercurimethyl [2,2,2,]-bicyclo-8-oxaoctane) can be obtained in 33% yield with difficulty. Dilution of the reaction system with 2,5-dioxahexane does not improve the situation, but the yield of III is doubled when *tert*-butyl alcohol is used to dilute the reaction system.

The reduction of the gum by use of sodium borohydride leads only to 4-methylenecyclohexanemethanol but reduction of III to 1-methylnorcineole, IV, occurs smoothly. The correspondence of the infrared spectrum of IV with that of 1,8-cineole which it resembles in odor leaves little doubt about its [2,2,2] bicyclic structure but it does not designate the position of the chloromercuri group in III.

This group might be linked to C-2 or C-9, depending on whether the double bond does or does not shift during oxymercuration. Two pieces of evidence show that chloromercuri is on C-9. First the substance III is recovered configurationally unchanged when it is subjected to reaction with hydrazine hydrate under conditions (5) to promote epimerization, which would be possible only at C-2. Secondly it undergoes permanganate oxidation, not to give a norcineolic acid V comparable with the cineolic acid from 2-chloromercuricineole, but instead 4-chloromercurimethyl-4-hydroxyhexanecarboxylic acid, VI. This acid can be deoxymercurated to 4-methylenecyclohexanecarboxylic acid VII and the latter may be re-oxymercurated to VI. Since VII has been characterized by ozonization to formaldehyde and the known 4-ketocyclohexanecarboxylic acid, VIII (6), it seems to be highly probable that oxymercuration of I leads to the primary chloromercurial.

Evidently the alkaline permanganate oxidation of III is accompanied by prototropic rearrangement of the carboxyl group in the product VI, probably during saponification of the lactone that is formed initially. This rearrangement is revealed when VI undergoes reduction with sodium borohydride reduction. The reduction product seems to be 4-↑-hydroxy-4-↓-methylcyclohexane-↓-carboxylic acid, IX, which is also the product when

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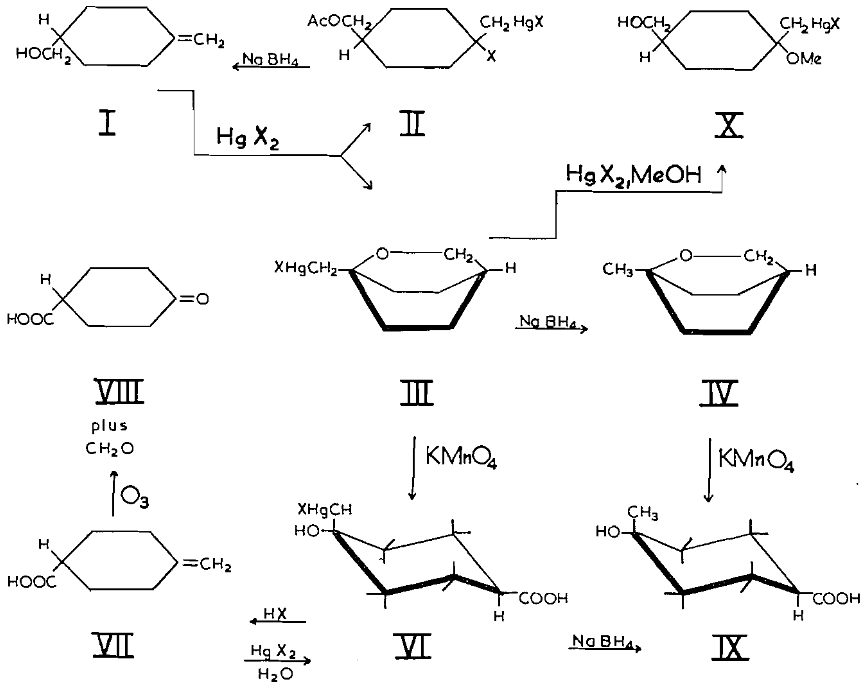

1-methylnorcineole, IV, is oxidized by means of potassium permanganate. This acid corresponds with that defined by Vila and Coll (7) as the *cis*-geoisomer. Like their acid of slightly lower melting point ours will not form a lactone (6, 8) but, instead, is dehydrated to 4-methyl-Δ^3-cyclohexanecarboxylic acid.

Besides the chemical evidence for the structure of III there is confirmation from the proton magnetic resonance spectrum. The simple spectrum of Fig. 1 shows clearly that band 3 is due to the methylene group attached to the 4-chloromercuri group because the spin interaction with ^{199}Hg gives rise to the side bands 2 and 6 spaced equally at 1.5 p.p.m. The chemical shift of the methylene portions represented by band 3 is somewhat greater (5.1 p.p.m. relative to benzene) than the values of 4.3 and 4.5 p.p.m. quoted by Cotton and Leto (9) for the chloromercurimethyl group in β-hydroxyethylmercuric acetate and the analogous anhydride respectively; this upfield shift must be attributed to the greater electrofelicity of the chlorine substituent. The 3.4 p.p.m. shift for oxymethylene (band I) and 5.3 p.p.m. for ring methylene are within the ranges 3.4–3.9 and 5.3–5.8 quoted by Chamberlain (10) for bicylic systems, while the 5.5 p.p.m. shift upfield from benzene for tertiary hydrogen is higher, probably in consequence of the cyclic distortion, than that specified (11) for this linkage in isobutane and 2,3-dimethylbutane.

It is of interest that treatment of the acetate analogue of III (X = OAc) with mercuric acetate in methanol leads to a single geoisomer of the methoxy derivative VIII rather than the expected mixture of two isomers.

EXPERIMENTAL

Physical Constants

Melting points have been corrected against reliable standards. The infrared spectra have been determined by use of a Beckman IR-4 spectrometer using polyethylene wax wafers (12 000 p.s.i.) and in carbon tetrachloride in the 900 – 3 000 cm^{-1} region and absorptions are recorded in cm^{-1} at extinctions (E) calculated from peak heights. Nuclear magnetic resonance (n.m.r.) spectra in carbon tetrachloride were determined by use of a Varian HR-60 spectrometer with the aid and advice of Professor S.S. Danyluk.

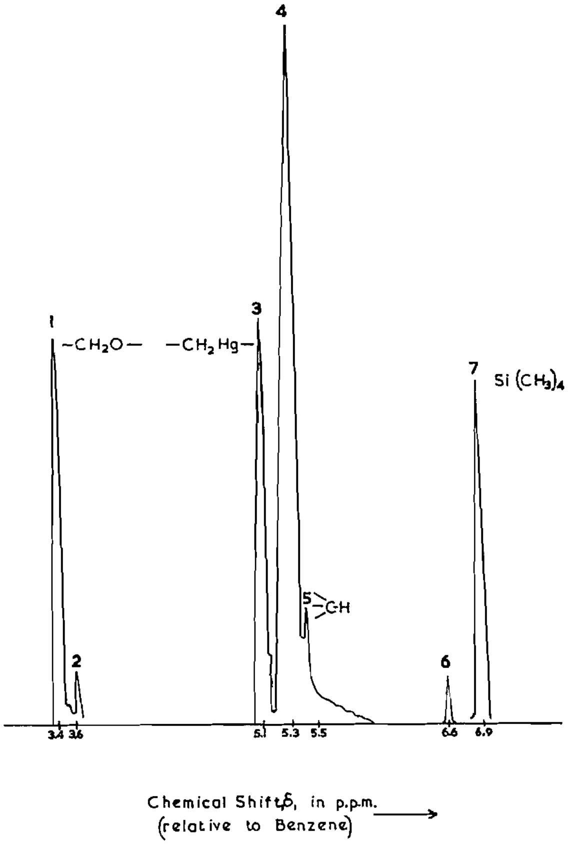

FIG. 1.

Reagents

Tertiary butyl alcohol was twice distilled from sodium wire under nitrogen (40), b.p. 82.8° at 760 mm, m.p. 25.5°. Glycol ether was distilled, after a positive benzophenone test under nitrogen, b.p. 85.5°, n_D^{20} 1.3792. Reagent grade B.D.H. mercuric acetate was recrystallized from glacial acetic acid, washed with 95% ethanol on a suction funnel, and dried at room temperature at 15 mm for 48 h. The alkene, 4-methylenecyclohexanemethanol, I, courtesy of Tennessee Eastman Company, was distilled at 40–41 °C at 0.001 mm. A heart-cut was taken, m.p. 19.5–18.5°, n_D^{20} 1.48275.

1-Chloromercurimethylnorcineole, III

(a) Use of Excess 4-Methylenecyclohexanemethanol I

Following the method of Brook and Wright (4) for the preparation of α-2-chloromercuricineole, a suspension of 82 g (0.65 mole) of 4-methylenecyclohexanemethanol I and 21 g (0.065 mole) of mercuric acetate was shaken at room temperature for 3 days. The system on filtration yielded 0.08 g of mercurous salt. Distillation of the filtrate at 0.001 mm, 28–40°, yielded 66 g (about 0.5 mole) of excess 4-methylenecyclohexanemethanol contaminated with acetic acid. The residue was suspended in 200 ml of petroleum ether (60–70°) in a separatory funnel and, on shaking, a gummy layer separated and was removed. The petroleum ether layer was then extracted with 1 × 200 and 3 × 50 ml portions of 10% aqueous sodium hydroxide, followed by 3 × 50 ml water. To the combined filtered aqueous extracts was added 12.0 g (0.2 mole) of sodium chloride, and carbon dioxide was bubbled into this solution for 12 h at 4°. Filtration by suction gave 9 g (0.25 mole), 38%, of chloromercurimethylnorcineole III, m.p. 95–97°. After three crystallizations from 95° ethanol (6 ml/g) followed by treatment with Darco, a white solid melting at 101.1–102 °C was obtained.

Anal. Calcd. for $C_8H_{13}ClHgO$: C, 26.6; H, 3.63, Found: C, 26.7; H, 3.82.

The infrared spectrum (10% in P.E. wax) is (306) 15.3, (316) 15.9, (394) 9.28, (419) 8.94, (512) 9.37, (531) 9.19, (578) 9.18, (623) 9.33, (749) 10.3, (783) 9.22, (813) 9.48.

The gum produced in this reaction seems to be a mixture. Treatment of its ether solution with an excess of mercuric chloride or with aqueous sodium chloride failed to produce a crystalline product. When 50 g was added to 50 ml of concentrated hydrochloric acid this system underwent complete solution within 2 min. After 15 min the system was neutralized by means of 40% aqueous sodium hydroxide and the mercuric oxide was filtered off into a celite bed in a tared Buchner funnel, water washed, and air dried, weight 32 g, 0.148 mole.

The filtrate from the removal of mercuric oxide was steam distilled and the distillate was extracted 4 times with 50 ml portions of chloroform. The combined extract, dried over magnesium sulfate was distilled, finally at 8 mm, to yield 190 g (0.151 mole) b.p. 90–91°. The infrared spectrum showed that this distillate was 4-methylenecyclohexanemethanol, I, in high purity. The same compound was obtained when II was treated with sodium borohydride.

The use of 500 ml of 2,5-dioxahexane as a diluent did not diminish the formation of gum, and 11 g of mercurous salt was formed during the otherwise comparable reaction.

(b) Use of tert-Butyl Alcohol as Reaction Medium

To 19.1 g (0.06 mole) of mercuric acetate in 400 ml (4.4 mole) of tertiary butyl alcohol was added 7.7 g (0.061 mole) of 4-methylenecyclohexanemethanol, I. After stirring for 48 h at room temperature, the milky suspension was filtered giving 1.0 g of mercurous salt. The filtrate was added to 200 ml of 3% (0.1 mole) aqueous sodium chloride solution. After evaporation of the *tert*-butyl alcohol at 30–35° and 20 mm, the mercurial was filtered off by suction and dried at 40° and 15 mm, for 24 h to yield 14.4 g (0.04 mole, 67%) of chloromercurimethylnorcineole III, m.p. 98–99.5°. Two crystallizations from 95% ethanol raised the m.p. to 101–102°. A mixture melting point with a sample from part (*a*) was not depressed.

The mercurial III was deoxymercurated by treatment of 3.69 g (0.01 mole) with 25 ml of 10% hydrochloric acid. When solution was complete after 5 min the system was extracted with three 25 ml portions of petroleum ether (b.p. 60–70°). The combined extract, washed with 30 ml of water, was dried over magnesium sulfate. Evaporation of the solvent left 1.2 g (96%) which was converted to the dinitrobenzoate, m.p. 97–98°, identified by mixture melting point with an authentic sample (12).

When the mercurial III in alkaline solution was heated with an excess of 100% hydrazine hydrate an oil was formed. This oil is evidently a 40% yield of the bis-mercurial because it may be converted quantitatively to III, m.p. 98.5–99°, by treatment with an equivalent of mercuric acetate in diethyl ether and then with aqueous sodium chloride.

4-↓-Chloromercurimethyl-4↑-hydroxycyclohexane-↓-carboxylic Acid, VI

A solution of 7.6 g (0.02 mole) of chloromercurimethylnorcineole, III, in 30 ml of 10% aqueous sodium hydroxide was added to 3.2 g (0.02 mole) of potassium permanganate in 200 ml of water. After 1 day at 20–25° the excess permanganate was destroyed by addition of 5 ml of ethanol. After 1 h the system was filtered. The filtrate was vacuum evaporated to a volume of 140 ml, then treated with 1 g (0.02 mole) of sodium chloride. This solution cooled to 0° was slowly acidified by means of 1.8% hydrochloric acid until precipitation was complete. The product, filtered, water washed, and dried at 35° (15 mm), weighed 3.0 g (38%) m.p. 145° (decomp.) when the sample was inserted at 130°.

Anal. Calcd. for $C_8H_{13}ClHgO_3$: C, 24.4; H, 3.33. Found: C, 24.7; H, 3.59.

The infrared spectrum of a sample 10% in polyethylene wax is 311 (1.6), 390 (2.9), 413 (2.9), 432 (2.0), 498 (1.8), 521 (5.2), 594 (1.6), 628 (0.2), 645 (1.5), 756 (3.4), 181 (1.9), 844 (3.2).

This acid may be obtained also by treatment of 0.5 g (0.0036 mole) of 4-methylenecyclohexanecarboxylic acid, VII, with 1.29 g (0.0036 mole) of mercuric acetate in 50 ml of water for 12 h at 20–25°. Then the milky suspension was treated with 2 ml of saturated aqueous sodium chloride. The product was filtered and crystallized from 50 ml of 1:1 methanol–acetone, 0.8 g, (56%) m.p. 141–143°. The mixture melting point with the oxidation product was not lowered and the infrared spectrum was identical.

4-Methylenecyclohexanecarboxylic Acid, VII

A quantity of 7.86 g (0.02 mole) of 4-chloromercurimethyl-4-hydroxycyclohexanecarboxylic acid was dissolved in 20 ml of 6% hydrochloric acid and then was extracted 5 times with 50 ml portions of chloroform. The combined extract, washed twice with 50 ml portion of water was dried with magnesium sulfate and vacuum evaporated to leave 2.69 g (93%) of vile-smelling 4-methylenecarboxylic acid, VII, m.p. 56°. Crystallization from 16 ml of 1:7 ethanol–water raised this m.p. to 57.5–58°; Neutralization equivalent: calcd. 140; found, 141.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.6; H, 8.63. Found: C, 68.4; H, 8.65.

The infrared spectrum, 4% in carbon tetrachloride is 890 (41.4), 905 (10.6), 930 (broad, 9.85), 995 (1.24), 1 085 (3.88), 1 180 (9.76), 1 230 (30.2), 1 305 (214), 1 410 (21.1), 1 440 (16.1), 1 635 (11.3), 1 700 (74.8), 1 740 (6.59), 2 650 (broad, 15.1), 2 950 (broad, 46.0).

4-Ketocyclohexanecarboxylic Acid, VIII

Into 20 ml of sodium-dried *tert*-butyl alcohol was dissolved (0.231 g, 0.00165 mole) of 4-methylenecyclohexanecarboxylic acid XIII. Ozone (9%) was passed into this solution for 60 min at room temperature and then the ozonide was reduced with solid sodium borohydride (added pinchwise until no more oxidizing materials were present). The solution was then steam distilled into 20 ml of 95% ethanol containing 0.5 g (0.0036 mole) of dimethyldihydroresorcinol. After standing for 2 h the organic solvents were evaporated off, leaving a solid which was filtered by suction, washed with a little methanol, and dried; weight of solid 0.11 g (0.0038 mole, 23% yield), m.p. 190°. A mixed melting point with an authentic sample of formaldehyde-dimedone was not lowered.

The steam distillation residue was examined for the other product of the ozonolysis, 4-ketocyclohexanecarboxylic acid, VIII. The solution was acidified to pH 2 and extracted with 8 × 25 ml diethyl ether. These combined ether extracts were then washed with 2 × 10 ml water and dried over magnesium sulfate. On filtration and subsequent evaporation of the ether, an oil was obtained as residue. An oxime was prepared from it and crystallized from benzene, weight 20 mg (0.00013 mole, 8% yield), m.p. 146–147° (6).

1-Methylnorcineole

A solution of 10.8 g (0.030 mole) of chloromercurimethylnorcineole, III, in 20 ml of 10% aqueous sodium hydroxide was stirred at room temperature. A second solution consisting of 0.3 g (0.006 mole) of sodium borohydride in 50 ml of 10% aqueous sodium hydroxide was added dropwise over 30 min. After 1 h, the aqueous supernatant liquid was extracted with 5 × 25 ml of diethyl ether, and the combined ether extracts washed with 3 × 10 ml water and then dried over calcium chloride for 12 h. Filtration with subsequent evaporation of the diethyl ether at 20° (15 mm) left 3.0 g (0.024 mole, 80%) of a colorless oil having an odor similar to 1,8-cineole but more penetrating. The oil was distilled at 31° (8 mm) or 155° (750 mm); n_D^{20} 1.42685; d_4^{26} 0.962.

Anal. Calcd. for $C_8H_{14}O$: C, 76.2; H, 11.2. Found C, 76.0; H, 11.3.

The infrared spectrum of this 1-methyl-1,8-norcineole is shown in Table I in comparison with the spectrum of 1,8-cineole, both 0.128 *M* in carbon tetrachloride. The parenthetical values are extinction coefficients for the indicated wave numbers.

TABLE I

Infrared spectra of methylnorcineole and cineole

Methylnorcineole	2 940 (177),	2 860 (123),	2 700 (13)	—	
Cineole	2 890 (167),	2 860 (96),	1 800 (6),	168 (15),	1 450 (75)
Methylnorcineole	1 435 (43),	1 368 (66),	1 345 (33),	1 305 (13),	—
Cineole	1 432 (45),	1 368 (96),	1 348 (72),	1 329 (14),	1 295 (35)
Methylnorcineole	1 240 (27),		1 200 (52),	1 170 (31),	1 110 (32)
Cineole	1 262 (25),	1 223 (49),	1 205 (86),	1 165 (64),	1 110 (30)
Methylnorcineole		1 032 (172),	1 010 (33),	—	935 (94)
Cineole	1 072 (105),	1 045 (69),	1 009 (27),	975 (3),	922 (8)
Methylnorcineole	913 (9),	872 (10),	855 (55),	—	
Cineole	915 (22),	880 (8),	857 (8),	835 (45)	

4-↓-Methyl-4↑-hydroxycyclohexane-↓-carboxylic Acid, IX

(a) From 1-Methylnorcineole, IV

To a solution of 2.5 g (0.016 mole) of potassium permanganate in 150 ml of water was added 0.5 g (0.004 mole) of methylnorcineole, IV. After 1 day at 20–25° the system was treated with 2 ml of ethanol. When the pink color had disappeared the mixture was filtered. The filtrate, concentrated to a volume of 50 ml by evaporation, was chilled to 0° and acidified by means of 16% hydrochloric acid. The precipitated acid weighed 0.4 g (63%), m.p. 156–156.5°. Crystallization from hot water raised this m.p. to 156.2–156.5°.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.92. Found: C, 60.6; H, 8.95.

When this acid was heated at 90° for 30 min (8) the lactone, m.p. 60–70°, was not formed. Instead 4-methyl-Δ^3-cyclohexenecarboxylic acid, m.p. 99–100°, was obtained by chloroform extraction. It formed a dibromide, m.p. 104°.

(b) From 4-Chloromercurimethyl-4-hydroxycyclohexanecarboxylic Acid, VI

A solution of 0.8 g (0.002 mole) of VI in 10 ml of 1% aqueous sodium hydroxide was heated with 0.10 g (0.0026 mole) of solid sodium borohydride during 15 min. One hour later 0.35 g (0.0018 atom) of metallic mercury was filtered off. The filtrate was evaporated to a volume of 3 ml and then was acidified by use of 5% aqueous sulfuric acid. With cooling to 0°, the crude acid 0.3 g (94%), m.p. 149–155°, was crystallized from water for mixture melting point (not depressed) with IX from the oxidation procedure.

4-Chloromercurimethyl-4-methoxycyclohexanemethanol, X

To a solution of 4.45 g (0.012 mole) of chloromercurimethylnorcineole, III, in 100 ml of pure, dry, oxygen-free methanol was added 2.0 g (0.012 mole) of silver acetate. After stirring for 0.5 h under nitrogen, the silver chloride was filtered off and 2 ml of glacial acetic acid was added along with 3.8 g (0.0012 mole) of mercuric acetate. The solution was shaken for 95 h at room temperature, but still tested positive for mercuric salt with 10% sodium hydroxide solution. Then the solution was basified with 10% aqueous sodium hydroxide and filtered by suction, using Celite, to remove mercuric oxide. On addition of 5 ml of saturated aqueous sodium chloride solution, carbon dioxide was bubbled into the system. After 1 h, 2.3 g of fluffy white solid was filtered off, m.p. 156–158°. The solid was recrystallized from 50 ml of 50% aqueous ethanol and dried over KOH pellets for 24 h at 65°(10 mm), m.p. 157–158°.

This methoxymercurial was soluble but stable in 10% aqueous sodium hydriodide. It was recovered almost completely after 0.30 g was dissolved in 10 ml acetic anhydride although 12 mg of mercurous chloride precipitated during the process.

Anal. Calcd. for $C_9H_{17}ClHgO_2$: C, 27.3; H, 4.36. Found: C, 27.3; 4.45.

The infrared spectrum, 3% in potassium bromide, was 2 925 (220), 2 850 (200), 2 925 (220), 2 850 (200), 1 625 (58.2), 1 450 (77.5), 1 430 (86.4), 1 320 (87.6), 1 265 (76.0), 1 220 (46.8), 1 200 (49.3), 1 170 (77.5), 1 145 (71.8), 1 135 (71.8), 1 097 (80.4), 1 060 (284), 1 045 (250), 997 (48.0), 970 (86.4), 950 (104), 925 (83.3), 877 (134), 798 (29.2), 755 (63.5), 705 (64.8).

The formation of this single methoxymercurial from acetoxymercurimethylnorcineole is in contrast to the pair of methoxymercurials obtained from I and mercuric acetate in methanol. One of the pair melted at 157–158 and the other at 118–119°, after separation by crystallization from methanol.

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