Anal. Calc'd for $C_{34}H_{46}N_2O_7$: N, 4.71. Found: N, 4.77.

16,22-Epoxycholestan-3β-ol (IV). A solution of 0.162 g. of slightly impure III (from I) in 6 cc. of acetic acid was hydrogenated with 0.052 g. of Adams' catalyst at atmospheric pressure. After a rapid consumption of 1 mole equivalent of hydrogen, the uptake ceased. The catalyst was removed and the solution was made alkaline with dilute alkali. The precipitate was extracted with ether and after solvent removal the product was crystallized from dilute ethanol, m.p. 150–153.5°. Recrystallization from dilute acetone gave needles of m.p. 152–153.5°, $[\alpha]^{20}_D$ −5.8° ($CHCl_3$).

Anal. Calc'd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.77; H, 11.53.

Reduction of III obtained from II gave the identical product IV.

The *benzoate* of IV, after several recrystallizations from methanol-ether, formed rods of m.p. 154.5–156°.

Anal. Calc'd for $C_{34}H_{50}O_3$: C, 80.58; H, 9.95. Found: C, 80.86; H, 10.03.

16,22-Epoxycholestan-3β-ol (IV) *from the lithium aluminum hydride reduction of dihydrotigogenin 26-tosylate.* The oily dihydrotigogenin 26-tosylate prepared in the manner of Scheer, *et al.*[2] was reduced directly with lithium aluminum hydride according to their directions. The crude product (228 mg.) then was chromatographed over alumina and the fraction eluted with benzene-ether (4:1) was crystallized from dilute ethanol to form rods of m.p. 148–152°. Recrystallization from dilute acetone raised the m.p. to 152–153°. The compound was identical in every respect with IV, obtained from the reduction of III.

A compound of m.p. 95–97° (35 mg. crystallized from abs. ethanol) was obtained from the fraction eluted earlier with benzene-hexane (1:1). It is presumably the 3-deoxy derivative, 16,22-epoxycholestane, formed by the reduction of the 3,26-ditosylate (by-product in the tosylation). Its infrared spectrum showed no hydroxyl band.

Anal. Calc'd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.97; H, 11.95.

National Institute of Arthritis and Metabolic Diseases
National Institutes of Health
Bethesda 14, Maryland

Preparation of a Crystalline 22-Bromo-24,24-diphenylchol-23-ene

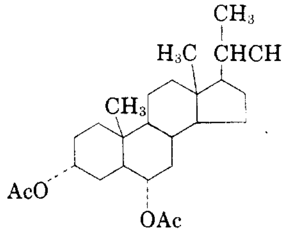
Emil Kaiser and Thomas Maudsley

Received February 6, 1956

The 22-bromo-24,24-diphenylchol-23-ene derivatives are intermediates in the degradation of the side chain of bile acids.[1] They are very unstable compounds and usually dehydrobrominate immediately after being formed in the reaction between 24,24-diphenylchol-23-ene and N-bromosuccinimide. The only 24,24-diphenylchol-23-ene derivative reported is the 3α,12α-diacetoxy-22-bromo-24,24-diphenylchol-23-ene.[2] This compound was obtained only in a crude form and decomposed when further purification was attempted.

In the course of their studies on the side chain degradation of hyodesoxycholic acid, Hoehn and coworkers reacted 3α,6α-diacetoxy-24,24-diphenyl-23-ene and N-bromosuccinimide in carbon tetrachloride solutions.[3] The reaction mixture was illuminated with a 150-watt floodlight while being refluxed 15 minutes.

Re-investigating this process we found by using a pure 3α,6α-diacetoxy-24,24-diphenylchol-23-ene and a petroleum ether fraction boiling from 60–80° (Skellysolve B) as solvent that illumination of the reaction mixture was not necessary. The bromination proceeded smoothly and the 22-bromo derivative was stable even after several hours of refluxing. A crude bromo compound was isolated from the petroleum ether solution. It was crystallized from cyclohexane and ether and a pure, crystalline 3,6-diacetoxy-22-bromo-24,24-diphenylchol-23-ene[1] was obtained. To confirm the 22 position of the bromine the crystalline compound was dehydrobrominated by refluxing it with sodium acetate in acetic acid. The dehydrobromination product was found to be pure 3α,6α-diacetoxy-24,24-diphenylchol-21,23-diene by absorption spectra measurements.[4] This finding indicates that the bromine was a substituent on the 22 carbon atom of the crystalline bromo derivative.



I

EXPERIMENTAL

3α,6α-Diacetoxy-24,24-diphenylchol-23-ene[3] (20 g.) was dissolved in 500 ml. of Skellysolve B, 7.2 g. of N-bromosuccinimide and 3.6 g. of sodium bicarbonate were added, and the mixture was refluxed for 1.5 hours with constant stirring. The reaction mixture was cooled to room temperature, filtered, and the residue (succinimide) was washed with 80 ml. of Skellysolve B. The combined filtrates were kept overnight in the cold. A precipitate was formed which was removed by filtration. The filtrate was evaporated under reduced pressure from a water-bath at 25°. The brown residue weighed 10 g. and had a bromine content of 9.95% (Calc'd for I: 11.83%).

Five g. of this product was dissolved by heating in 30 ml. of cyclohexane. The solution was filtered and the filtrate was kept overnight in the cold; needles were formed which were

---

(1) Ch. Meystre, H. Frey, A. Wettstein, and K. Miescher, *Helv. Chim. Acta*, **27**, 1815 (1944).

(2) Ch. Meystre, L. Ehmann, N. Neher, and K. Miescher, *Helv. Chim. Acta*, **28**, 1252 (1945).

(3) R. B. Moffett, J. E. Stafford, J. Linsk, and W. H. Hoehn, *J. Am. Chem. Soc.*, **68**, 1857 (1946).

(4) 3α,6α-diacetoxy-24,24-diphenylchol-21,23-diene was prepared by L. Rubin, Research Department, Canada Packers, Ltd. by repeated recrystallizations of the dehydrobrominated reaction product of 3α,6α-diacetoxy-24,24-diphenylchol-23-ene and N-bromosuccinimide until a constant extinction coefficient ($E^{1\%}_{1\,cm.}$ 464 at 360 mμ) was obtained. The authors wish to thank Dr. Rubin for communicating to them the value of this extinction coefficient.

separated by filtration. They were still impure, m.p. 116–134°. This material was dissolved in boiling ether (80 ml. per gram of substance), and the solution was filtered while hot, and concentrated to one-fifth of its original volume. Crystallization was started by chilling. After 24 hours in the cold the crystals were filtered and dried in a vacuum at room temperature; m.p. 151–154°; *Anal.* Calc'd for I: Br, 11.83. Found: Br, 11.8.

Research Division
Armour and Company
Chicago 9, Illinois

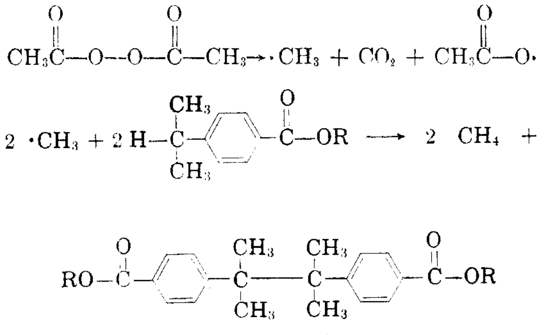
The Comparative Reactivities of *p*-Isopropylbenzoic Acid and Acetic Acid Toward the Methyl Free Radical

Henry C. McBay and Paul T. Groves

Received January 27, 1956

Previous studies[1] have indicated that the primary *beta* hydrogens in trimethylacetic acid are cleft by methyl free radicals with more difficulty (poorer yields) than are the *alpha* hydrogens in acetic acid. Preliminary studies made in our laboratories of reactions of methyl radicals in mixed solvents show that an equimolar mixture of isobutyric acid and isopropylbenzene reacts with the methyl free radical to produce the crossed dimer.[2] A crossed dimer is also obtained when an equimolar mixture of isopropylbenzene and methyl dichloroacetate is reacted with methyl free radicals.[2] These data suggest that the *tertiary alpha* hydrogens in isopropylbenzene, methyl dichloroacetate, and isobutyric acid are to a first approximation equally reactive toward hydrogen abstraction by methyl free radicals.

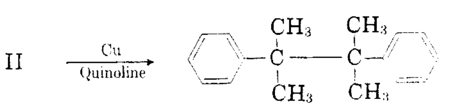
We have had need to synthesize 2,3-dimethyl-2,3-di-*p*-carboxyphenyl-*n*-butane. This synthesis has been accomplished by decomposing diacetyl peroxide in methyl *p*-isopropylbenzoate and subsequently saponifying the dimeric ester.



$$CH_3\overset{\overset{O}{\|}}{C}—O—O—\overset{\overset{O}{\|}}{C}—CH_3 \rightarrow \cdot CH_3 + CO_2 + CH_3\overset{\overset{O}{\|}}{C}—O\cdot$$

I, R = CH$_3$
II, R = H

This free unesterified dimeric acid (II) cannot be obtained directly from *p*-isopropylbenzoic acid, m.p. 113°, by this method without modification because the technique[3] requires that the solvent in which the diacetyl peroxide is decomposed must be a liquid at room temperature. We have overcome this difficulty by dissolving crystalline *p*-isopropylbenzoic acid in a mixture of acetic acid, acetic anhydride, and benzene. Thermal decomposition of diacetyl peroxide dissolved in this mixture produces pure 2,3-dimethyl-2,3-di-*p*-carboxyphenyl-*n*-butane. The methyl free radical attacks selectively from this mixture the *tertiary alpha* hydrogen from the *p*-isopropylbenzoic acid to give methane and the dimeric acid. This dimeric acid (II) and the dimeric ester (I) just described have by orthodox methods been converted each into the other. The structure of the dimeric acid (II) has been established by conversion to the well-known 2,3-dimethyl-2,3-diphenyl-*n*-butane through decarboxylation with copper powder in quinoline.[4]



These results demonstrate that the hydrogens in benzene, and more significantly, the *alpha* hydrogens in acetic acid are sufficiently more difficult to cleave with the methyl free radical than is the *alpha tertiary* hydrogen in *p*-isopropylbenzoic acid as to allow for complete selectivity in such a competitive system as is here described.

EXPERIMENTAL

Reagents. Eastman's white-label *p*-isopropylbenzoic acid, m.p. 112–114°, was used without further treatment. Methyl *p*-isopropylbenzoate was obtained through exhaustive esterification of this acid, b.p. 72°/0.5 mm., n_D^{20} 1.5113. The benzene was scrubbed with conc'd H_2SO_4 and doubly distilled from sodium. The acetic anhydride was Eastman's white-label product, and the acetic acid was Baker's C.P. grade. The preparation, isolation, analysis, and decomposition of the diacetyl peroxide in organic solvents has been described elsewhere.[3]

Thermal decomposition of diacetyl peroxide in methyl p-isopropylbenzoate. The preparation of 2,3-di-p-carbomethoxyphenyl-2,3-dimethyl-n-butane. A solution containing diacetyl peroxide, (14.2 g., 0.118 mole), dissolved in methyl *p*-isopropylbenzoate, (153.8 g., 0.80 mole), was introduced in single drops beneath the surface of methyl *p*-isopropylbenzoate, (79.0 g., 0.41 mole), held at 130°. The volatile products obtained and identified were carbon dioxide, (7.6 g., 0.17 mole), methane, (3.40 l., STP., 0.15 mole), and methyl acetate, (0.6 g., 0.009 mole), b.p., 54–56°. The material remaining in the reaction vessel was distilled at reduced pressure, and unreacted methyl *p*-isopropyl benzoate, (201.7 g., 1.0 mole), was collected at 76.5–79°/1 mm.; n_D^{20} 1.5082. The residual oil remaining in the distilling flask crystallized upon cooling to room temperature. These white crystals, (12.0 g.), were recrystallized from absolute methanol and melted at 210–211°.

---

(1) Kharasch and Gladstone, *J. Am. Chem. Soc.*, **65**, 15 (1943); Kharasch, Jensen, and Urry, *J. Org. Chem.*, **10**, 386 (1945); Kharasch, Zimmerman, Zimmt, and Nudenberg, *J. Org. Chem.*, **18**, 1046 (1953); McBay and Tucker, *J. Org. Chem.*, **19**, 869 (1954).

(2) McBay, Unpublished results.

(3) Kharasch, McBay, and Urry, *J. Org. Chem.*, **10**, 394, 406 (1945).

(4) Shepard, Winslow, and Johnson, *J. Am. Chem. Soc.*, **52**, 2087 (1930).