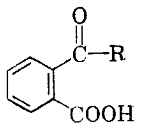
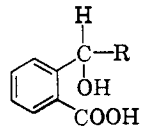
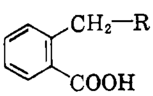


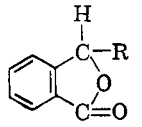
Ia. R = CH_3
Ib. R = $-CH_2-$



IIa. R = CH_3
IIb. R = $-CH_2-$



IVa. R = CH_3
IVb. R = $-CH_2-$



IIIa. R = CH_3
IIIb. R = $-CH_2-$

Huisgen and Rauenbusch[1] reported that the catalytic reduction of Ia does not proceed beyond the hydroxy stage (IIa) which then cyclizes into the lactone (IIIa), which is not easily amenable to further reduction. We found that the desired reduction can be easily accomplished by working in neutral or slightly alkaline medium, this means in fact the reduction of a salt of Ia instead of Ia itself. The formation of the lactone (IIIa) is thus prevented. When Ia in the form of its sodium salt in water is hydrogenated with palladium on charcoal catalyst at 80° and a pressure of 40 p.s.i. two moles of hydrogen are absorbed in eight hours to afford IVa. The results are similar with 2-phenylacetylbenzoic acid (Ib). The hydroxy acid (IIb) can be also reduced into IVb under analogous conditions. The yields are in the range of 83–92%.

Experimental

2-Ethylbenzoic Acid (IVa).—A 16.4-g. sample of *o*-acetylbenzoic acid (Ia; 0.100 mole; from Aldrich Chemical Co.) was dissolved in a mixture of 100 ml. of 1.0 *N* sodium hydroxide solution and 70 ml. of water (pH 7). It was hydrogenated after the addition of 10 g. of Pd–Darco catalyst (10% palladium) at 40 p.s.i. starting pressure. After the uptake of 0.1 mole of hydrogen in 2 hr. further uptake ceased, therefore it was heated to 80° and hydrogenated for 6 hr. at 40 p.s.i. until another 0.1 mole of hydrogen was consumed. After filtration through Supercel and acidifying with hydrochloric acid 12.4 g. of IVa was obtained (83% yield) m.p. 62–63° (lit.,[1] m.p. 60–62°).

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.9; H, 6.75. Found: C, 72.02; H, 6.95. Equiv. wt. (by titration) 149; theory 150.08.

2-Phenylethylbenzoic Acid (IVb). A. From 2-Phenylacetylbenzoic Acid (Ib).—A 22.2-g. sample of 3-benzalphthalide (0.100 mole) was transformed into the sodium salt of 2-phenylacetylbenzoic acid by saponification with a solution of 5 g. of sodium hydroxide in 100 ml. of water (20 min. at 90–95°). Fifty milliliters of water was added and the pH of the solution adjusted to 8.5 by the addition of hydrochloric acid. After cooling to room temperature the solution was filtered to remove a small amount of by-product; it was then hydrogenated after the addition of 7 g. of Pd–Darco catalyst (10% palladium) at 80° with a starting pressure of 40 p.s.i. In 8 hr. 0.2 mole of hydrogen was taken up and the uptake practically ceased. Acidification of the filtered solution gave 20.71 g. of IVb, m.p. 128–130° (lit., 130–131°; mixed m.p., the same; over-all yield 91.6%.

B. From 2-(1-Hydroxy-2-phenylethyl)benzoic Acid (IIb).—A solution of the sodium salt of 2-(1-hydroxy-2-phenylethyl)benzoic acid was prepared by saponifying 22.4 g. (0.100 mole) of 3-benzylphthlide[3] by refluxing for a short time with 5 g. of sodium hydroxide in 150 ml. of water. The solution of IIb then obtained was buffered to pH 8–9 by the addition of 14.2 g. of disodium phosphate and 1.1 ml. of 85% phosphoric acid. It was hydrogenated for 8 hr. at 120° at 40 p.s.i. with 3.5 g. Pd–Darco catalyst (5% palladiun). By acidification of the filtrate 19.7 g. of 2-phenylethylbenzoic acid was obtained (85% of theory); m.p. 125–128°; did not depress the melting point of an authentic sample of IVb.

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[3] S. Natilson and S. P. Gottfried, *J. Am. Chem. Soc.*, **58**, 1432 (1936).

A Reinvestigation of the Hydrogenolysis of Hydroxyl Groups of the Stereoisomeric 3-Phenylcholestanols

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Recently Zderic, Rivera, and Limón found that Raney nickel hydrogenolysis of the hydroxyl groups of the epimeric 3-phenylcholestanols led to the common product, 3β-phenylcholestane.[2] Reportedly, the Raney nickel hydrogenolysis of 3α-phenylcholestan-3β-ol was the first instance in which a hydroxyl group was reduced with inversion of configuration.[3] A mechanism was proposed.[2]

Observations from work now underway have led to a reinvestigation of the hydrogenolysis of the 3-phenylcholestanol system.[2] The series of experiments summarized below demonstrate that W-2 Raney nickel hydrogenolysis of the hydroxyl groups of the stereoisomeric 3-phenylcholestanols indeed proceeded with a high degree of retention of configuration (probably > 90%), and that 3α-phenylcholestane was rapidly equilibrated to the thermodynamically more stable 3β-phenylcholestane by Raney nickel in refluxing ethanol.

In accordance with earlier reports,[2] the treatment of 3α-phenylcholestan-3β-ol (I) with Raney nickel in refluxing ethanol led to 3β-phenylcholestane (IV). Likewise, the hydroxyl group of 3β-phenylcholestan-3α-ol (II) was hydrogenolyzed to give pure IV.[4] The proton magnetic resonance spectrum of IV exhibits absorptions at 7.58τ and 2.89τ for the C-3 proton and phenyl protons, re-

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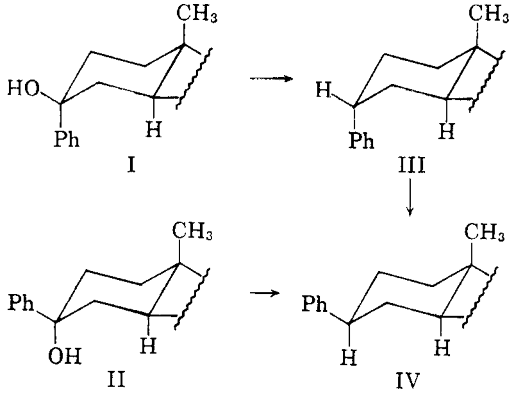
[1] N. S. F. Postdoctoral Fellow, 1961–1962. Present address: Department of Chemistry, University of Chicago, Chicago 37, Illinois.

[2] J. A. Zderic, Ma. E. C. Rivera, and D. C. Limón, *J. Am. Chem. Soc.*, **82**, 6373 (1960).

[3] See Ref. 1 for background references. See also: D. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954); D. Curtin and S. Schmukler, *ibid.*, **77**, 1105 (1955); and S. Mitsui and S. Imaizumi, *Bull. Chem. Soc. Japan*, **34**, 774 (1961).

[4] As little as 5% of III in IV or vice versa could be detected reliably in the infrared using the absorptions between 13.1 μ and 14.3 μ.

spectively.[5] However, when I was stirred with Raney nickel at room temperature, pure 3α-phenylcholestane (III) was obtained.[4] The proton magnetic resonance spectrum of III exhibits absorptions at 6.95τ and 2.80τ for the C-3 proton and phenyl protons, respectively. Under refluxing ethanol hydrogenolysis conditions, III was gradually converted to IV. Hydrogenolysis of II proceeded slowly at room temperature (as compared with I) to give IV. Under comparable conditions, I was converted to III with < 5% of IV. By modifying the catalyst through the addition of small amounts of sodium methoxide, the rate of equilibration was apparently reduced relative to the rate of hydrogenolysis, and higher temperatures could be employed to further demonstrate the stereospecificity of the hydrogenolysis which now proceeded at a convenient rate. Using this procedure, I was hydrogenolyzed to a mixture of 85% of III and 15% of IV in refluxing ethanol–Raney nickel. Likewise, II was converted to pure IV.[4]



Experimental

3α-Phenylcholestan-3β-ol (I) and 3β-phenylcholestan-3α-ol (II) were prepared as described previously[2] and melted at 109.5–110° and 164–165°, respectively; reported,[2] m.p. 100–103° and 163–165°, respectively.

Hydrogenolysis at 78°.—A mixture of 50 mg. of I, 2 g. of W-2[6] Raney nickel and 4 ml. of ethanol was refluxed for 20 min. The ethanol solution then was decanted into a mixture of 10 ml. of pentane and 10 ml. of water. The catalyst was washed twice with 10-ml. portions of pentane and the washings were added to the water–pentane mixture. The pentane layer was washed with water and the pentane then evaporated. Infrared analysis of the residue (37 mg.) gave approximately 85% of IV and 15% of III.[4] After one recrystallization from acetone, pure 3β-phenylcholestane (IV), m.p. 113–114.5°, was obtained; infrared spectrum (CS_2), 13.16 (s) μ and 14.25 (s) μ; reported,[2] m.p. 113–114°. The hydrogenolysis of II as described above led to 42 mg. of pure IV.[4]

Hydrogenolysis at Room Temperature.—A mixture of 100 mg. of I, 3 g. of Raney nickel, and 10 ml. of ethanol was stirred for 10 min. at room temperature. The reaction mixture was processed as previously described to give 84 mg. of pure 3α-phenylcholestane (III), m.p. 82–85°.[4] Several recrystallizations from acetone raised the melting point to 86.5–88.5°; infrared spectrum (CS_2), 13.51 (m) μ, 13.77 (m) μ, and 14.25 (s) μ.

Anal. Calcd. for $C_{33}H_{52}$: C, 88.32; H, 11.68. Found: C, 88.51, H, 11.48.

A mixture of 40 mg. of III, 4 ml. of ethanol, and 3 g. of Raney nickel was refluxed for 15 min. The crude product of this reaction analyzed for 35% of III and 65% of IV (infrared).

A mixture of 30 mg. of II, 4 ml. of ethanol, and 3 g. of Raney nickel was stirred for 2 hr. The infrared spectrum of the crude hydrogenolysis product showed about a 50% conversion of II to IV and no detectable amount of III.[4] A comparable treatment of I led to III contaminated with < 5% of IV.

Hydrogenolysis at 78° with Added Sodium Methoxide.—Treatment of 50 mg. of I with 2 g. of Raney Nickel and 10 mg. of sodium methoxide in 4 ml. of ethanol at reflux for 7 min. led to the isolation of 36 mg. of a mixture of 85% of III and 15% of IV (by infrared analysis).

The treatment of 50 mg. of II in the same manner as above led to 37 mg. of pure IV.

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[5] The proton magnetic resonance spectra were determined by Dr. W. B. Schwabacher.

[6] R. Mozingo, *Org. Syntheses*, Vol. III, John Wiley & Sons, Inc., New York, 181 (1955). The Raney nickel used in this work was freshly prepared and of the same batch.

Synthesis of 3-Substituted 3-Phenylphthalides[1]

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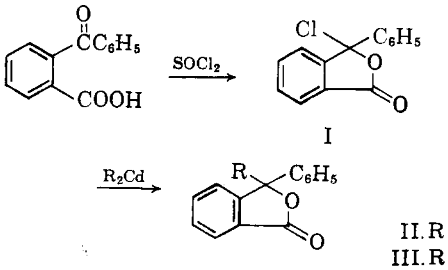
In connection with other work, we have found that the pseudo chloride of o-benzoylbenzoic acid, 3-chloro-3-phenylphthalide (I), reacts with organocadmium reagents to give 3-substituted 3-phenylphthalides in excellent yields (equation 1). The reaction is effected by the technique recommended by Cason[2] for preparation of ketones from acid chlorides.



(1)

II. R = CH_3
III. R = n-C_4H_9
IV. R = C_6H_5

Three examples of the reaction were effected. Treatment of I with dimethylcadmium, prepared from methylmagnesium bromide, gave 3-methyl-3-phenylphthalide (II) in 88% yield, based on o-benzoylbenzoic acid. Similarly, di-n-butylcadmium

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[1] Supported by the Army Research Office (Durham).

[2] J. Cason, *Chem. Rev.*, **40**, 15 (1947).