condensing agent such as hydrochloric acid is well known. In this particular case it can be explained by the presence of methoxyl groups in positions 3 and 5 which activate the 6-position in the ring. It must be remembered that phenethylamine,[3] hordenine[4] and 2,5-dimethoxyphenethylamine[5] give the dimethyl tertiary amines in good yields.

The usual technique has been followed[6] and after alkalinization and extraction with ether, a new base was obtained in a 51% yield. Under more drastic conditions the yield was increased to 80%.

The base was isolated as its hydrochloride which was not identical with that of trichocereine. Since the structure of this last compound is well established, this fact suggested that the reaction had led to a tetrahydroisoquinoline derivative.

A definite proof was provided by the oxidation of the hydrochloride which gave N-methyl-3,4,5-trimethoxyphthalimide, identical with a synthetic sample.[7]

Experimental

Pure mescaline (1.95 g.), 97.5% by weight formic acid (2.20 g.) and 40% "formalin" (1.53 ml.) were heated on the steam-bath for 12 hours. The reaction mixture was diluted with 70 ml. of water and strongly alkalinized with 20 ml. of 20% sodium hydroxide solution. After 4 extractions with ether the aqueous solution was exhausted of alkaloid. The collected extracts were dried over anhydrous sodium sulfate and the ether removed. An oily, slightly yellowish base (1.12 g.) was obtained (yield 51.2%).

It was taken up in 18 ml. of acetone, filtered and 0.45 ml. of concentrated hydrochloric acid added. On cooling to 0° and scratching, a colorless hydrochloride crystallized. It was collected, washed three times with 5 ml. of cold acetone and dried, weight 0.67 g. A second crop of less pure hydrochloride was obtained from the mother liquors. The first crop was recrystallized twice from absolute alcohol, m.p. 215–216° (cor.); mixed with trichocereine hydrochloride m.p. 180°.

Anal. Calcd. for $C_{13}H_{19}O_3N\cdot HCl$: C, 57.03; H, 7.36; OCH_3, 34.01; CH_3, 22.0. Found: C, 57.04; H, 7.49; OCH_3, 33.81; CH_3, 22.5.

Another experiment was carried out with a mixture of mescaline (0.86 g.), 93% in weight formic acid (1.81 g.) and 40% "formalin" (1 ml.) which was refluxed for eight hours in the oil-bath. Under these conditions 0.77 g. of the base was obtained (79.7%).

Methiodide.—The free base (0.19 g.), prepared from the hydrochloride, was dissolved in acetone (2 ml.) and methyl iodide added (0.1 ml.). A spontaneous exothermic reaction followed, and after 24 hours standing, the methiodide was filtered and washed 6 times with 1 ml. of acetone each time. Dry, it weighed 0.25 g., m.p. 210° (cor.). After three recrystallizations from alcohol a constant m.p. 215° (cor.), in agreement with that given by Späth,[8] (211.5–212.5°) who prepared this compound from anhalinine, was reached.

Anal. Calcd. for $C_{14}H_{22}O_3NI$: C, 44.34; H, 5.84; OCH_3, 24.54. Found: C, 44.87; H, 5.57; OCH_3, 25.18.

The **picrate** was precipitated from the hydrochloride (0.20 g.) and picric acid (0.17 g.) in alcohol. When recrystallized three times from the same solvent, it had m.p. 135–137° (cor.).

Anal. Calcd. for $C_{13}H_{19}O_3N\cdot C_6H_3O_7N_3$: N, 12.01. Found: N, 12.22.

Oxidation.—The hydrochloride (0.16 g.) was dissolved in water (50 ml.) and alkalinized with 2 ml. of 1 *N* sodium hydroxide. Permanganate solution (1.8%) was then added in small portions, finally with heating on the steam-bath. The total volume used up was 38 ml. The clear solution obtained after passing in sulfur dioxide was acidified with sulfuric acid and extracted thoroughly with chloroform. After evaporating the solvent, the residue (30 mg.) was taken up in hot water and filtered. This solution was concentrated to 1 ml. and the crystalline precipitate which separated was sublimed at 5 mm. pressure. A few milligrams of colorless needles melting at 125° (cor.) were collected. Mixed with an authentic sample of N-methyl-3,4,5-trimethoxyphthalimide, m.p. 127° (cor.), it melted at 126° (cor.).

RESEARCH LABORATORIES
"ATANOR" CÍA. NACIONAL PARA LA INDUSTRIA QUÍMICA S. A. M.
BUENOS AIRES, ARGENTINA

RECEIVED MAY 5, 1951

(3) R. N. Icke, B. B. Wisegarver and G. A. Alles, "Organic Syntheses," Vol. XXV, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 89.

(4) Y. Raoul, *Compt. rend.*, **204**, 74 (1937).

(5) B. Baltzly and J. S. Buck, THIS JOURNAL, **62**, 161 (1940). Dr. R. Baltzly, in a private communication, kindly revealed to us the conditions used in their work, which were essentially those of Eschweiler (heating with formalin in a bomb). The Eschweiler-Clarke was tried by Baltzly and Buck on β-(2,5-dimethoxyphenyl)-propylamine and was found to give a product different from β-(2,5-dimethoxyphenyl)-propyl dimethylamine. It was also found that the Eschweiler-Clarke method gave tetrahydroisoquinolines in varying amounts and purity from homoveratrylamine.

(6) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *ibid.*, **55**, 4571 (1933).

(7) R. H. F. Manske and H. L. Holmes, *ibid.*, **67**, 95 (1945).

(8) E. Späth, *Monatsh.*, **42**, 113 (1921).

Steroid Tetrahydropyranyl Ethers

BY WILLIAM G. DAUBEN AND H. LEON BRADLOW

In connection with other studies in this Laboratory[1] the synthesis and cleavage of tetrahydropyranyl ethers[2] of steroids have been investigated. This work was substantially completed before we learned of the similar work of Ott and co-workers.[3] It has been found that the tetrahydropyranyl ether of cholesterol can be prepared in good yield by employing an excess of dihydropyran as the solvent. Following the same procedure, the tetrahydropyranyl ether of methyl Δ^5-homocholenate was obtained in fair yield but the preparation of the ether of 3β-hydroxy-Δ^5-norcholesten-25-one gave erratic results. Good yields, in this latter case, could be obtained only when careful attention was paid to the addition of the acid catalyst (see Experimental). The yield was not improved in this instance by applying the procedure of Ott.[4]

Both dilute hydrochloric acid and catalytic amounts of *p*-toluenesulfonic acid in alcohol effected cleavage of the ether to the free sterol, though better yields were obtained when the sulfonic acid procedure was employed. It was found that when cholesteryl tetrahydropyranyl ether was refluxed with acetic acid or acetic anhydride as solvent for four hours, a mixture of cholesteryl acetate and the original ether was obtained. This mixture which had a constant melting point could not be separated by fractional crystallization. Treatment of the ether with boiling acetic acid or acetic anhydride for 24 hours or with acetic acid plus 1% hydrochloric acid gave the pure acetate in good yield.

In addition cyclohexyl tetrahydropyranyl ether was prepared in an orientating run.

(1) W. G. Dauben and H. L. Bradlow, THIS JOURNAL, **72**, 4248 (1950).

(2) (a) G. F. Woods and D. N. Kramer, *ibid.*, **69**, 2246 (1947); (b) W. E. Parham and E. L. Anderson, *ibid.*, **70**, 4187 (1948).

(3) A. C. Ott, M. E. Murray, R. L. Pederson and M. H. Kuizenga, Abstract of the 117th Meeting of the American Chemical Society, Philadelphia, Penna., 1950, p. 9K.

(4) We are indebted to Dr. Ott for details of their method.

Experimental[5]

Cholesteryl Tetrahydropyranyl Ether.—A slurry of 5.00 g. (13 mmoles) of cholesterol and 20 ml. of dihydropyran was treated with two drops of concentrated hydrochloric acid and shaken vigorously for five minutes. At the end of this time all of the steroid had dissolved. After standing 12 hours at room temperature, the semi-solid mass was diluted with ether and processed as previously described.[2b] The solid residue was recrystallized from ethanol to give 5.01 g. (82%) of the ether, m.p. 151.5–152.5°. Recrystallization raised the melting point to 154.5–155.5°, $[\alpha]^{23}D$ −35.9° in chloroform.

Anal. Calcd. for $C_{32}H_{54}O_2$: C, 81.62; H, 11.56. Found: C, 81.80; H, 11.56.

3β-Hydroxy-Δ⁵-homocholenic Acid.—A solution of 1.00 g. (2.40 mmoles) of 3β-acetoxy-Δ⁵-cholenic acid in 10 ml. of dry benzene and 4 ml. of oxalyl chloride was heated at 50° for two hours. The solution was then concentrated to dryness at 50° *in vacuo*. Two 10-ml. portions of dry benzene were added and distilled under reduced pressure to remove the last traces of oxalyl chloride. The acid chloride, in 10 ml. of dry benzene, was added dropwise to a stirred solution of diazomethane (prepared from 1.1 g. of nitrosomethylurea) in 60 ml. of methylene chloride. After standing 12 hours, the solution was filtered, concentrated at reduced pressure and the residue treated with 100 ml. of methanol and freshly precipitated silver oxide (prepared from 10 ml. of 10% silver nitrate solution). The solution was slowly brought to reflux temperature, refluxed for one hour, treated with Norit, filtered and concentrated. The residue was refluxed with 5.00 g. of potassium hydroxide in 50 ml. of methanol and 40 ml. of water under a nitrogen atmosphere. The solution was filtered and acidified with concentrated hydrochloric acid. The suspension after standing for 12 hours, was centrifuged and dried overnight at 60°. The crude product weighed 0.72 g. (72%). After two recrystallizations from methanol–water, the acid melts from 197.6–199.2°. Hattori[6] reported a m.p. of 210–215°.

Anal. Calcd. for $C_{25}H_{40}O_3$: C, 77.23; H, 10.38. Found: C, 77.52; H, 10.53.

For conversion to the methyl ester the crude acid may be used.

Methyl 3β-Hydroxy-Δ⁵-homocholenate.—An ethereal solution of the crude acid was added slowly to an excess of diazomethane in ether at 0°. The solution was allowed to come to room temperature and the excess diazomethane removed with a slight excess of formic acid. The ethereal solution was washed with dilute sodium bicarbonate solution and water, dried and concentrated. The crude ester was chromatographed on alumina. After developing with benzene, the ester was eluted with 1% methanol in benzene. Recrystallization from methanol gave 80% of white plates, m.p. 85.6–87.0°.

Anal. Calcd. for $C_{26}H_{42}O_3$: C, 77.32; H, 10.52. Found: C, 77.04; H, 10.24.

Methyl 3β-Hydroxy-Δ⁵-homocholenate Tetrahydropyranyl Ether.—Concentrated hydrochloric acid (two drops) was added to a solution of 0.63 g. of the methyl homocholenate in 10 ml. of dihydropyran with vigorous shaking. The reaction solution was allowed to stand for 24 hours and then processed in the usual fashion.[2b] The crude material was recrystallized from ethanol–water, yield 0.20 g. (30%), m.p. 92.5–93.0°, $[\alpha]^{25}D$ −36.6° in chloroform.

Anal. Calcd. for $C_{31}H_{48}O_4$: C, 76.81; H, 9.98. Found: C, 76.93; H, 10.40.

3β-Hydroxy-Δ⁵-norcholesten-25-one Tetrahydropyranyl Ether.—A solution of 1.00 g. (2.6 mmoles) of norolone in 20 ml. of dihydropyran was prepared by gentle warming and then carefully cooled to room temperature. Concentrated hydrochloric acid (0.4 ml.) was added dropwise to this solution over a period of four minutes with vigorous agitation. After the addition of each drop of acid, the solution was shaken until the blackish precipitate, which formed, redissolved. The solution was allowed to stand for 48 hours and then processed in the usual fashion.[2b] The first recrystallization gave a sirupy mixture which was best separated by centrifugation. After two more recrystallizations from alcohol–water, the product melted at 104.9–106.2°. The yield was 0.71 g. (57%), $[\alpha]^{28}D$ −28.6° in chloroform.

Anal. Calcd. for $C_{31}H_{50}O_3$: C, 79.11; H, 10.69. Found: C, 79.45; H, 10.85.

Hydrolysis of Cholesteryl Tetrahydropyranyl Ether.—A solution of 1.00 g. (2.12 mmoles) of cholesteryl tetrahydropyranyl ether and 0.05 g. of *p*-toluenesulfonic acid in 15 ml. of ethanol was refluxed for one hour, concentrated to half volume, diluted with water and cooled. Filtration gave 0.80 g. (97%) of lustrous plates, m.p. 146.0–147.5°. Concentrated hydrochloric acid may also be used as catalyst, though the yield is somewhat lower.

Acetolysis of the Ether to Cholesteryl Acetate.—A solution of 4.00 g. (8.15 mmoles) of the pyranyl ether in 25 ml. of acetic acid was refluxed for 24 hours, concentrated under reduced pressure and the residue dissolved in ether. The ethereal solution was washed with dilute sodium carbonate solution and saturated sodium chloride solution, dried and concentrated. The solid acetate was recrystallized twice from methanol to give 2.57 g. (70.5%) of cholesteryl acetate, m.p. 113.1–113.8°, undepressed upon admixture with an authentic sample. Acetic anhydride as solvent gave almost identical results. When the reaction time was cut to three or four hours, a mixture of unchanged ether and cholesteryl acetate was obtained, which melted at 95.5–97.0° after sintering at 92° (unchanged by repeated recrystallization), $[\alpha]^{23}D$ −40.9° in chloroform. The optical rotation was intermediate between that of the ether, −35.9°, and that of the acetate, −47.5°. An equimolar mixture of the ether and the acetate, thrice recrystallized from methanol, melted at 95.0–97.1°, $[\alpha]^{21}D$ −38.0° in chloroform.

Cyclohexyl Tetrahydropyranyl Ether.—Three drops of concentrated hydrochloric acid were added dropwise to a solution of 20.0 g. (0.2 mole) of cyclohexanol in 35 ml. of dihydropyran and the reaction allowed to stand overnight. The solution was then diluted with ether and worked up as usual. After 2.07 g. of forerun, 30.68 g. (82.5%) of the ether was obtained, b.p. 94–95° (5 mm.), $n^{25}D$ 1.4642.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.68; H, 10.95. Found: C, 71.83; H, 10.80.

CHEMICAL LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIFORNIA

RECEIVED AUGUST 9, 1951

(5) All melting points are corrected. All boiling points are uncorrected. All analyses are by the Microanalytical Laboratory of the Dept. of Chemistry, Univ. of California

(6) J. Hattori, *J. Pharm. Soc. Japan*, **58**, 548 (1938).

Reaction of Wijs Iodine Number Reagent with the *exo*-Isomer of Endomethylenetetrahydrophthalic Anhydride

BY C. H. HELBING

In connection with research on cyclopentadiene, *endo*-3,6-endomethylenetetrahydrophthalic anhydride was converted to the *exo*-isomer by a process which in its essential details followed that reported by Alder and Stein, *et al.*[1] The *endo*-isomer was prepared from cyclopentadiene and maleic anhydride in methyl ethyl ketone at 20–40°.

The iodine number determined by the Wijs method,[2] which utilizes iodine monochloride, on the *exo*-isomer was substantially the theoretical value as calculated for 3,6-endomethylenetetrahydrophthalic anhydride (154.7). The iodine number determined in the same manner on the *endo*-isomer was substantially zero. A determination on a known mixture gave about the expected result with the assumption that the *exo*-form reacts with iodine monochloride and the *endo*-form does not. This information should be useful in determining the isomers present in cyclopentadiene adducts.

(1) K. Alder, G. Stein, Wolfgang Eckardt, Rudolf Freiherr v. Buddenbrock and Stephan Schneider, *Ann.*, **504**, 216 (1933); *C. A.*, **27**, 5311 (1933).

(2) ASTM: D 555-41-9.