with tetrahydrofuran. The combined filtrates were dried with magnesium sulfate and the solvent was removed. The residue was twice crystallized from aqueous acetic acid and yielded light yellow plates, m.p. 181–182.5°, wt. 1.07 g. The inorganic salts were dissolved in dilute hydrochloric acid, combined with the acetic acid filtrates above, and the solution was extracted with chloroform. After drying the extracts the chloroform was evaporated. The residue was twice crystallized from acetic acid and gave pale yellow plates, m.p. 180.5–182.6°, wt. 0.20 g., plus filtrates (A). The total yield of pure *N*-desylcarbazole was 1.27 g. (63%). An analytical sample was prepared by recrystallizing this material first from aqueous acetic acid, and then from a mixture of tetrahydrofuran and hexane, and was obtained as colorless needles, m.p. 184–184.5°. The infrared spectrum in chloroform showed a strong band at 5.85μ.

Anal. Calcd. for $C_{26}H_{19}NO$: C, 86.41; H, 5.30; N, 3.88; mol. wt., 361. Found: C, 86.29; H, 5.45; N, 3.93; mol. wt., (Rast) 342.

Filtrates (A) were neutralized with potassium hydroxide and the solution was extracted with chloroform. The chloroform extracts were dried, the solvent was evaporated, and the residue was chromatographed on alumina with chloroform-hexane. There was thus obtained 55 mg. (4%) of *N*-benzylcarbazole (IV) which was identified by mixture melting point and infrared comparison with an authentic sample.

Degradation of N-desylcarbazole. *N*-Desylcarbazole (II), 0.71 g., was dissolved in 40 ml. of diethylene glycol containing 0.11 g. of potassium hydroxide, and the resulting solution was heated under reflux for 3.5 hr. under an atmosphere of nitrogen. The cooled solution was diluted with water and the precipitated solid was collected and washed with water.

The dried solid was crystallized from petroleum ether at 0°, and gave colorless needles, m.p. 117–118°, wt. 0.23 g. (45%). This material gave no melting point depression with an authentic sample of *N*-benzylcarbazole (IV) (prepared according to Buu-Hoï and Royer[15]). The two samples also gave identical infrared spectra.

The aqueous filtrate from above was acidified and extracted with ether. The ether solution was extracted with *N* sodium hydroxide solution, and the latter was acidified and extracted with ether. The ethereal solution was dried and the solvent was evaporated which yielded a light brown crystalline solid. The solid was recrystallized from water (Norit), m.p. 122–123°. A mixture melting point with benzoic acid (m.p. 122–124°) was 123–124°. The infrared spectra of the isolated solid and benzoic acid were identical. The yield was 0.08 g. (33%).

N-Desylcarbazole (II). Several unsuccessful attempts were made to prepare this compound from carbazole itself, and from its salts as formed from potassium hydroxide, sodamide, phenyllithium, and ethyl Grignard with desyl chloride. In each case carbazole was recovered.

In a flask equipped with condenser with drying tube were placed 4.15 g. of the potassium salt of carbazole, 4.59 g. of 1,2-diphenyl-1-methoxy-1,2-epoxyethane (V),[7] and 80 ml. of dry dimethylformamide. The solution was heated under reflux 15 hr. After cooling the mixture was poured into ice water and the resulting mixture was extracted with chloroform. The chloroform solution was washed with water, dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was adsorbed on a neutral alumina column and eluted with hexane-chloroform (4:1). A yellow oil was first eluted, followed by *N*-desylcarbazole, and then carbazole. The *N*-desylcarbazole was recrystallized twice from aqueous acetic acid forming pale yellow plates, m.p. 179–182°. The yield was 1.52 g. (21% of the theoretical). This synthetic material gave no depression in melting point when mixed with the *N*-desylcarbazole obtained from I. The ultraviolet and infrared spectra of the two samples were identical.

DETROIT 2, MICH.

(15) N. P. Buu-Hoï and R. Royer, *J. Org. Chem.*, 16, 1198 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DE PAUL UNIVERSITY]

Compounds Related to 22-Ketocholesterol

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22-Ketocholesterol[2] (I) and one form of 3β-chloro-22-keto-5-cholestene (III) were prepared by alkylation with diisoamylcadmium of acid chlorides prepared from 3β-acetoxy-5-bisnorcholenic acid. These steroids were converted, respectively, into 6β-methoxy-3,5-cyclocholestan-22-one (methyl 22-keto-*i*-cholesteryl ether) (VIII) and 3,5-cyclocholesta-6,22-dione (*i*-cholesta-6,22-dione) (VI). Preparation of 3β-chloro-22-keto-5-cholestene (III) by chlorination of 22-ketocholesterol (I) or by rearrangement of 6β-methoxy-3,5-cyclocholestan-22-one (VIII) gave two similar isomeric products isolable because of different adsorptions on alumina. Attempted reduction of 6β-methoxy-3,5-cyclocholestan-22-one (VIII) by Wolff-Kishner procedure appeared to fail.

This study of the properties of compounds prepared from 22-ketocholesterol (I) was part of a plan to prepare side-chain labeled cholesterol. 22-Ketocholesterol (I)[2] was prepared by hydrolysis of the keto ester furnished by the reaction of 3β-acetoxy-5-bisnorcholenyl chloride with diisoamylcadmium. The 3β-chloro-22-keto-5-cholestene (III) (form B) was prepared most satisfactorily by the action of diisoamylcadmium on crude 3β-chloro-5-bisnorcholenyl chloride. Chloroketone III prepared this way contained a single isomer and was more satisfactory than chloroketone produced either from 22-ketocholesterol (I) or 6β-methoxy-3,5-cyclocholestan-22-one (VIII).

The 3β-chloro-22-keto-5-cholestene (III) prepared by action of thionyl chloride on 22-ketocholesterol (I) or from 6β-methoxy-3,5-cyclocholestan-22-one (VIII) was shown to exist as two very similar isomers. These were probably the two epimers that can exist at C-20. These isomers were separated by chromatography on alumina: A,

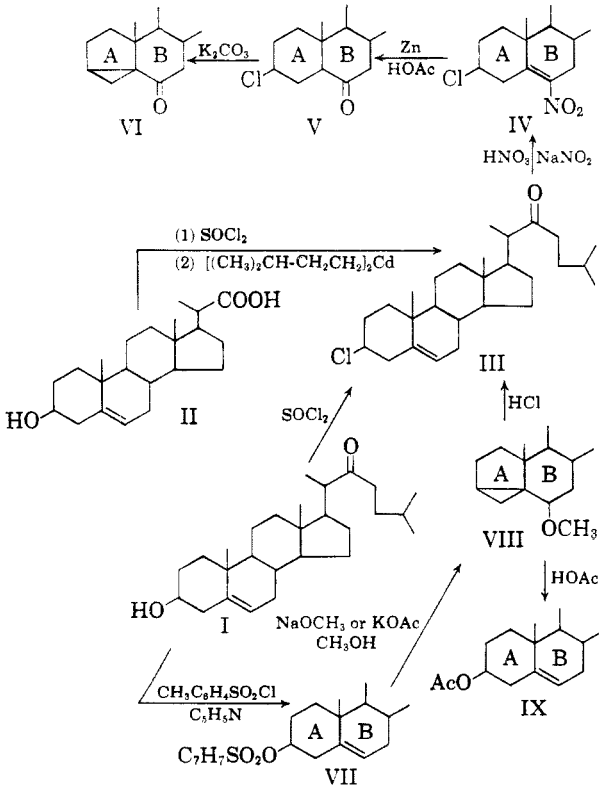
(1) Part of this work was abstracted from the Master of Science thesis of Z. F. Chmielewicz submitted to the faculty of De Paul University, 1952.

(2) W. Cole and P. L. Julian, *J. Am. Chem. Soc.*, 67, 1369 (1945).

weakly adsorbed, m.p. 115.5–116°, $[\alpha]_D$ −50.0° and B, strongly adsorbed, m.p. 111–113°, $[\alpha]_D$ −49.6°; a mixture had m.p. 88–101°. The one isomer obtained in the alkylation of 3β-chloro-5-bisnorcholenyl chloride was form B, based on mixed melting point, and was the purest chloroketone obtained: m.p. 115.5–116°, $[\alpha]_D$ −53.2°.

3β-Chloro-22-keto-5-cholestene (III) (form B) was treated with sodium nitrite in nitric acid to produce the 3β-chloro-6-nitro-22-keto-5-cholestene (IV).[3] This product (IV) was reduced with zinc and acetic acid[3] to give the 3β-chloro-6,22-cholestadione (V). The chlorodione (V) was treated with potassium carbonate[4] to give 3,5-cyclocholesta-6,22-dione (VI). In the intermediate steps each product was chromatographed carefully on alumina to demonstrate the absence of an isomeric form.

In another sequence, 22-ketocholestrol (I) was converted to 22-ketocholesteryl *p*-toluenesulfonate (VII).[5] 6β-Methoxy-3,5-cyclocholestan-22-one (VIII) was prepared from the tosylate using sodium methoxide or potassium acetate.[6] Liquid fractions of high positive rotation appeared to be pure *i*-ether. These pure fractions were converted into 22-ketocholesteryl acetate (IX) and 3β-chloro-22-keto-5-cholestene (III). Attempts made to reduce the 22-keto group in the *i*-ether (VIII) using Wolff-Kishner procedures[7,8] failed to produce crystalline 6β-methoxy-3,5-cyclocholestane or, upon rearrangement with acetic acid, cholesteryl acetate.



EXPERIMENTAL

All melting points were uncorrected. The expression 'hexane' refers to 'Skellysolve B' (b.p. 60–70°) produced by the Skelly Oil Company, Kansas City, Mo. The alumina was Merck's 'Suitable for Chromatography.' Ultraviolet absorption spectra were taken on a Beckman Model DU spectrophotometer. Infrared spectra were taken on a Baird Associates infrared spectrophotometer. Elemental analyses were by (a) Clark Laboratories, Urbana, Illinois, (b) Micro-Tech Laboratories, Skokie, Ill. or by (c) Robert E. Meyer.

3β-Chloro-5-bisnorcholenyl chloride. Five grams of 3β-acetoxy-5-bisnorcholenic acid (The Glidden Company) was saponified to furnish 4.40 g. (99%) of hydroxy acid; m.p. 289–291°. Fernholz[9] reported m.p. 295°.

3β-Hydroxy-5-bisnorcholenic acid (II) (4.40 g.) was suspended in 50 ml. of dry ether and 100 ml. of benzene; and 6.60 g. (4.0 ml.) of thionyl chloride was swiftly added. The mixture was heated under reflux until the solution became homogeneous. The solvent was removed, an additional 50 ml. of benzene was added and was removed. A sample of the product was crystallized from benzene-hexane, m.p. 170–172°. The crude acid chloride was used for further reactions.

The acid *amide* was prepared from the acid chloride with aqueous ammonia in ethanol.[2] Recrystallization from ethanol-water gave a product having a melting point of 245–247°, $[\alpha]_D^{29}$ −21° (conc. 1.4 mg. per ml. of chloroform, α_D^{29} −0.06° in a 2-dec. tube).

Anal. Calcd. for $C_{22}H_{34}ClON$: C, 72.59; H, 9.42. Found. C, 72.65 (b); 9.49 (b).

3β-Chloro-5-cholesten-22-one (III). *A. Alkylation of 3β-chloro-5-bisnorcholenyl chloride.* Diisoamylcadmium was prepared under nitrogen with 36.5 g. of isoamyl bromide, 6.0 g. of magnesium and 24 g. of cadmium chloride in 125 ml. of ether.[2,10] A solution of 3β-chloro-5-bisnorcholenyl chloride prepared from 12.4 g. of 3β-hydroxy-5-bisnorcholenic acid (II) in 20 ml. of ether and 50 ml. of benzene was added. The mixture was stirred at 0° for 4 hr. and allowed to stand at room temperature overnight.

The reaction mixture was hydrolyzed with 10% hydrochloric acid. The organic layer was separated and washed with water and saturated sodium chloride. After drying with sodium sulfate the solvent was distilled and a residue of 12.9 g., m.p. 95–105°, was obtained. Crystallization from methanol and methanol-water gave several fractions totaling 7.73 g., m.p. 100–106°. (An additional 3.29 g. of less-pure, higher-melting product was also obtained.) To effect further purification the product was chromatographed on alumina, eluting with hexane and hexane-benzene solution, to give fractions melting at 106–111°. (Exhaustive chromatography on several fractions gave no evidence of the existence of the isomeric chloroketone.) Crystallization of this material from methanol gave 5.91 g. (39.1%) of the chloroketone, m.p. 113–115°, suitable for the subsequent reactions.

Four additional crystallizations from methanol gave the purest chloroketone obtained in this work: m.p. 115.5–116°, $[\alpha]_D^{24}$ −53.2° (39.3 mg. dissolved to 2 ml. in chloroform, α_D^{24} −1.044° in a 1 d. tube). This chloroketone was the more strongly adsorbed form B as shown by mixed melting points: mixed with A, m.p. 87–112° and mixed with B, m.p. 115–117°.

(3) *Cf.* A. Windaus and O. Dalmer, *Ber.*, **52**, 168 (1919).
(4) *Cf.* E. G. Ford, P. Chakravorty, and E. S. Wallis, *J. Am. Chem. Soc.*, **60**, 413 (1938).
(5) *Cf.* K. Freundenburg and H. Hess, *Ann.*, **148**, 128 (1926).
(6) W. Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).
(7) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 248 (1946).
(8) B. Riegel and I. A. Kaye, *J. Am. Chem. Soc.*, **66**, 723 (1944).
(9) E. Fernholz, *Ann.*, **507**, 128 (1933).
(10) J. Cason and F. S. Prout, *Org. Syntheses*, **Coll. Vol. III**, 601 (1955).

The ultraviolet absorption spectrum shows the maximum at 285 mμ, log ε 1.88. The infrared spectrum had a peak at 5.9 microns characteristic of a ketone.[11]

The less-pure crystallization fractions (3.29 g., above) were chromatographed on alumina. Elution with ether-acetic acid (20:1) furnished an acid fraction: 1.49 g., m.p. 205–208°. Crystallization from cyclohexane gave 1.025 g., m.p. 215–217°, of 3β-chloro-5-bisnorcholenic acid; $[\alpha]_D^{25}$ −67° (10.5 mg. dissolved up to 5.0 ml. in chloroform, α_D^{25} −0.28° in a 2 dec. tube).

Anal. Calcd. for $C_{22}H_{33}O_2Cl$: C, 72.40; H, 9.11. Found: C, 71.95 (b); H, 9.24 (b).

This alkylation when attempted with the Grignard reagent gave a 19% yield of crude chloroketone.

B. Rearrangement of 6β-Methoxy-3,5-cyclocholestan-22-one (VIII). One hundred forty milligrams of 6β-methoxy-3,5-cyclocholestan-22-one (VIII) ($[\alpha]_D^{21}$ +30.1°, see below) was heated under reflux for 4 hr. with 10 ml. of dry acetone and 0.5 ml. of concentrated hydrochloric acid. The chloroketone precipitated upon dilution with water to give 101 mg. of crude product, m.p. 88–97°. This material was chromatographed on 15 g. alumina. Elution with 100 ml. of 1:9 benzene–hexane gave 48 mg. of isomer A, m.p. 100–108°, $[\alpha]_D^{25}$ −53° (chloroform). Elution with 1:4 benzene–hexane gave 22 mg. of a mixture (m.p. 80–101°) in the first 25 ml., but gave 28 mg. of isomer B, m.p. 111–113°, $[\alpha]_D^{25}$ −57° (chloroform), in the next 75 ml. Crystallization of A from alcohol gave 30 mg., m.p. 115–116.5°; and crystallization of B gave 13 mg., m.p. 112.5–114°. A mixture of the two melted at 87–97°.

Later samples of both A and B were prepared by careful chromatography of fractions of chloroketone from several runs. After chromatography and four crystallizations from ethanol the pure, weakly adsorbed A-fraction resulted as soft, short needles: m.p. 115.5–116° (softened at 113°); $[\alpha]_D^{22}$ −50.0° (58.0 mg. dissolved up to 1.96 ml. in chloroform, α_D^{22} −1.48° in 1 d. tube).

Anal. Calcd. for $C_{27}H_{43}OCl$. C, 77.36; H, 10.34. Found: C, 77.36 (b); H, 10.38 (b).

The more strongly adsorbed chloroketone, fraction B, resulted in pure heavy needles after three crystallizations from ethanol: m.p. 111–113° (softened at 109.5°); $[\alpha]_D^{22}$ −49.6° (47.0 mg. dissolved up to 1.96 ml. in chloroform, α_D^{22} −1.19° in a 1 d. tube).

Anal. Calcd. for $C_{27}H_{43}OCl$: C, 77.36; H, 10.34. Found: C, 77.07 (a); H, 10.10 (a).

A mixture of these two purified compounds had m.p. 88–101°.

C. Thionyl chloride on 22-ketocholesterol (I). 22-Ketocholesterol (I) (528 mg.) and 0.5 ml. of thionyl chloride was allowed to stand at 23° for 90 min. and heated at 40–60° for 90 min. The thionyl chloride was removed, 2 ml. of benzene was added and also removed *in vacuo*. The resulting oil was chromatographed on alumina. Elution with benzene-hexane mixtures gave three crude fractions totaling 439 mg. Fractional crystallization from alcohol led to 242 mg. of chloroketone, probably B-form, m.p. 110–116.5°. (Chloroketone prepared this way was also used to prepare the purified A- and B-forms, above.)

3β-Chloro-6-nitro-5-cholesten-22-one (IV). A suspension of 5.5 g. of 3β-chloro-5-cholesten-22-one (III) (B-isomer, prepared by alkylation of 3β-chloro-5-bisnorcholenyl chloride) in 70 ml. of glacial acetic acid was stirred while 15 ml. of fuming nitric acid (Merck, sp. gr. 1.50) was added in 20 min. After stirring for 30 min., 5.5 g. of sodium nitrite was added over a 30 min. period. After an additional hr. the mixture was poured into ice water, the solid was collected; 6.08 g. (107%); m.p. 172–180°. The chromatography of this product on 120 g. of alumina furnished 3.50 g. upon elution with benzene. Recrystallization from cyclohexane gave 2.4 g. (42%) of 3β-chloro-6-nitro-5-cholesten-22-one; m.p. 183–189°. Rechromatography of 100 mg. and crystallization from acetonitrile gave 52 mg. of pure product: m.p. 192–192.5°; $[\alpha]_D^{26}$ −52.0° (39.5 mg. dissolved up to 2 ml. in chloroform, α_D^{26} −1.027° in a 1 d. tube).

Anal. Calcd. for $C_{27}H_{42}ClO_3N$: C, 69.87; H, 9.12. Found: C, 69.88 (b); H, 8.98 (b).

The ultraviolet spectrum showed a maximum at 260 mμ; log ε 3.39. The infrared spectrum indicated the presence of a keto (5.9μ) and a nitro group (6.6μ).

3β-Chlorocholestane-6,22-dione (V). 3β-Chloro-6-nitro-5-cholesten-22-one (IV) (2.3 g.) in 55 ml. of glacial acetic acid was stirred while 4.3 g. of zinc dust was added over a 90 min. period. The mixture was stirred while heating under reflux for 2 hr. After filtering to remove the zinc, 20 ml. of water was added. The product which solidified upon cooling was collected; 1.40 g. (65%); m.p. 168–179° (darkens at 160°). After two chromatographs on alumina (eluting with 1:1 hexane–benzene) and crystallization from methanol, the purified chlorodione was obtained: m.p. 184.5–186°; $[\alpha]_D^{25}$ −14.3° (42 mg. dissolved up to 2 ml. in chloroform, α_D^{26} −0.301 in a 1 d. tube).

Anal. Calcd. for $C_{27}H_{43}O_2Cl$: C, 74.53; H, 9.96. Found. C, 74.67 (b); H, 10.04 (b).

The ultraviolet spectrum showed a maximum absorption at 290 mμ (log ε 1.98), characteristic of a ketone and no peak near 260 mμ as would be expected if the nitro group had persisted. The infrared spectrum showed an intensified band at 5.9μ (i.e., a ketone). No band at 6.6μ characteristic of the nitro group was evident.

3,5-Cyclocholestane-6,22-dione (VI). A mixture of 165 mg. of 3β-chlorocholestan-6,22-dione (V), 650 mg. of potassium carbonate, 30 ml. of 95% alcohol, and 1.5 ml. of water was heated under reflux for 2 hr. Water was added to precipitate the product which was then extracted with chloroform. After drying the chloroform solution with sodium sulfate and removing the solvent, 140 mg. (97%) of the *i*-dione was obtained; m.p. 127–130°. Crystallization from methanol gave 125 mg. (86.5%) of product: m.p. 128.5–130°; $[\alpha]_D^{27}$ +17.3° (36.5 mg. dissolved up to 2 ml. in chloroform; α_D^{26} +0.327° in a 1 d. tube).

Anal. Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.52 (b); H, 10.66 (b).

The ultraviolet absorption spectrum showed a maximum at 282.5 mμ (log ε 2.14), indicative of the keto group. The infrared spectrum revealed a carbonyl band at 6μ, slightly displaced from 5.9μ expected for the carbonyl group.

22-Ketocholesteryl p-toluenesulfonate (VII). 22-Ketocholesterol (I) was prepared from 3β-acetoxy-5-bisnorcholenic acid in 72% yield using the three-step procedure of Cole and Julian.[2] This sterol (2.077 g.), 1.98 g. *p*-toluenesulfonyl chloride and 5 ml. of pyridine were mixed and allowed to stand 22 hr. at room temperature. The mixture was diluted with 35 ml. of water, was precipitated, and was collected: 2.84 g., m.p. 140–143°. After two crystallizations from acetone-hexane 1.289 g. (45.7%) resulted; m.p. 143–144.5°; $[\alpha]_D^{26}$ −52.0° (42.4 mg. dissolved up to 1.96 ml. in chloroform, α_D^{26} −1.139° in a 1 d. tube).

Anal. Calcd. for $C_{34}H_{50}O_4S$: C, 73.60; H, 9.08; S, 5.78. Found: C, 73.42 (a); H, 9.16 (a); S, 5.62 (c).

6β-Methoxy-3,5-cyclocholestan-22-one (VIII). *A. Sodium methoxide method.* Sodium (0.25 g.) was dissolved in 25 ml. of methanol and then 536 mg. of 22-ketocholesteryl tosylate (VII) was added. The mixture was heated under reflux for 4.5 hr., was diluted with water, and extracted with ether. After washing the ether and drying with sodium sulfate, the solvent was removed furnishing 395 mg. of crude oil. This oil was chromatographed on alumina. Elution with 1:1 hexane–benzene gave 361 mg. of oil (88.4%) that appeared homogeneous; $[\alpha]_D^{29}$ +32° (12.4 mg. dissolved up to 1.96 ml. with chloroform, α_D^{29} +0.20° in a 1 d. tube).

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.51 (a); H, 11.35 (a).

(11) H. M. Randall, N. Fuson, R. G. Fowler, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Co., Inc., New York, New York, 1949.

B. Potassium acetate method. A mixture of 1.049 g. of 22-ketocholesteryl tosylate (VII), 1.5 g. of fused potassium acetate and 50 ml. of methanol was heated under reflux for 4.5 hr. After working up as described for procedure *A*, above, the crude oil was chromatographed on alumina. Elution with 1:4 benzene–hexane furnished 605 mg. (77%) of the *i*-ether as an oil, $[\alpha]_D$ +26° to +30° (chloroform). Further elution with 1:1 benzene–hexane and benzene gave 128 mg. of oil that was probably the normal ether, $[\alpha]_D$ −29° (chloroform).

22-Ketocholestery acetate (IX). A sample of 6β-methoxy-3,5-cyclocholestan-22-one (107 mg., $[\alpha]_D$ +26°) and 10 ml. of glacial acetic acid were heated under reflux for 5 hr. The mixture was diluted with water to give 108 mg. of material having m.p. 144–150°. Crystallization from ethanol gave 71 mg.; m.p. 150.5–152.5°; $[\alpha]_D^{31}$ −61° (chloroform). There was no depression upon mixing with an authentic sample of 22-ketocholesteryl acetate.

Attempted conversion of 6β-methoxy-3,5-cyclocholestan-22-one to 6β-methoxy-3,5-cyclocholestane. Two grams of sodium was dissolved in 10 ml. of methanol and 15 ml. of 85% hydrazine hydrate and 1.041 g. of the keto *i*-ether ($[\alpha]_D^{21}$ +30.1°) in 20 ml. of methanol were sealed in a tube.[8] The mixture was heated at 200° ± 10° for 12 hr. The product was extracted with ether-hexane, the solvent was removed, and the resulting oil was chromatographed on alumina. Elution with hexane gave 167 mg. of oil, $[\alpha]_D^{21}$ +43° (chloroform). (An additional 812 mg. of oil was obtained in subsequent elutions.)

The first eluate (167 mg., above) was heated under reflux for 5 hr. with 15 ml. of acetic acid. The 156 mg. of precipitate recovered was chromatographed on alumina and eluted with hexane. One fraction of 91 mg. had a specific rotation, $[\alpha]_D^{27}$ −52° (chloroform) and a following fraction of 36 mg. had a rotation of $[\alpha]_D^{25}$ −47°. Both fractions were oils and their structure is uncertain, since cholesteryl acetate has the m.p. 115–116° and $[\alpha]_D$ −47.4°.[12]

Essentially the same results were obtained when the Huang-Minlon procedure was used.[7]

Stability of the *i*-ether structure was shown by subjecting 1.0 g. of 6β-methoxy-3,5-cyclocholestane to the reduction conditions of Huang-Minlon.[7] Chromatography and crystallization from acetone-methanol furnished 485 mg. of purified starting material, m.p. 78–79°, $[\alpha]_D^{30}$ +54.0° (chloroform). Stoll[6] reported m.p. 79°, $[\alpha]_D$ +51.8°.

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CHICAGO 14, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S.A.]

Steroids. CXIII.[1] 6-Methyl Estrogens

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17-Ethylenedioxy-6α,7α-oxidoestrone acetate (IV) was transformed into 6β-methyl-7α-hydroxyestrone (VI) and thence by collidine treatment of its 3-benzoate-7-mesylate (VIII) into 6-methyl-6-dehydroestrone (X). Catalytic hydrogenation provided 6β-methylestrone (XIII) while reduction with sodium borohydride led to 6β-methylestradiol (XV). Introduction of a 6β-methyl group into estrone or estradiol was found to be associated with a drastic decrease in estrogenic activity.

Introduction of a methyl group in position 6 of steroids belonging to the androgenic, progestational, and cortical hormone series[3] usually results in an increase in biological activity. The only group of hormones which have so far not been investigated in this respect are the estrogens and the present paper deals with the preparation of some 6-methylated estrogenic hormones.

The most commonly employed route to 6-methyl steroids has been the conversion of a Δ^5-olefin to the corresponding 5α,6α-epoxide followed by opening with a methylmagnesium Grignard reagent.[3,4] The ready availability of 6-dehydroestrone (I)[5] and 6-dehydroestradiol (II)[6] led us to employ the same path, the key intermediate being, 17-ethylenedioxy-6α,7α-oxidoestrone 3-acetate (IV); its preparation (I→II→III→IV) and stereochemistry (by transformation to 7α-hydroxyestrone) have already been reported in an earlier paper from this Laboratory.[7] Treatment of the ketal-epoxide IV with methylmagnesium bromide provided 17-ethylenedioxy-6β-methyl-7α-hydroxyestrone (V),[8] while cleavage of the ketal to 6β-methyl-7α-hydroxyestrone (VI) was accomplished

(1) Paper CXII, J. A. Zderic, D. Chávez, H. J. Ringold, and C. Djerassi, in press.

(2) This material represents part of the professional thesis submitted by Srta. Esperanza Velarde to the Facultad de Química, Universidad Motolinia.

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(8) The product of normal diaxial opening (see A. Fürst and P. Plattner, 12th Internat. Congress Pure and Appl. Chem., New York 1951, Abstracts, p. 405), which is still further favored because of benzylic activation.