Anal. Calcd. for $C_{29}H_{38}N_2O_6S_2$: C, 60.60; H, 6.66; N, 4.87; S, 11.15. Found: C, 60.92; H, 7.19; N, 4.40; S, 11.19.

17β-(2-Amino-4-thiazolyl)-9α-fluoro-11β,17α-dihydroxy-4-androsten-3-one p-toluenesulfonate (*see* XIX). A solution of 3 g. of 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-androsten-3-one and 468 mg. of thiourea in 60 cc. of absolute alcohol was treated as described above for the preparation of 17β-(2-amino-4-thiazolyl)-4-androsten-3-one *p*-toluenesulfonate to give 1.14 g. (34%) of product, m.p. 214–216° dec.

In another experiment using crude 9α-fluoro-11β,17α-dihydroxy-21-tosyloxy-4-androsten-3-one there was obtained 2.7 g. (15%) of product, m.p. 218° dec.; $[\alpha]_D^{25}$ +38.2° (*c*, 1.05%, dimethylformamide); $\lambda_{max}^{CH_3OH}$ 222, 227 (shoulder), 242 mμ; (ε 21,000; 20,700; 19,800); λ_{max} 2.95, 3.16, 5.99, 6.20, 6.28, 8.50, 8.90, 9.64, 9.87, 12.25, 14.70 μ.

Anal. Calcd. for $C_{29}H_{37}FN_2O_6S_2$: C, 58.76; H, 6.29; F, 3.21; N, 4.73; S, 10.82. Found: C, 59.44; H, 6.66; F, 3.21; N, 5.10; S, 10.56.

17α,21-Epoxy-3,20-bisethylenedioxy-11β-hydroxy-5-pregnene (XXI). A suspension of 500 mg. of 11β,17α-dihydroxy-3,20-bisethylenedioxy-21-tosyloxy-5-pregnene (XX)[19] in 50 cc. of methanol saturated with ammonia was kept in a steel bomb at 90–95° for 18 hr. Evaporation of the solution afforded a semi-solid. Recrystallization from acetone–petroleum ether afforded 284 mg. (79%) of crystalline material, m.p. 236–238°. Several recrystallizations from acetone gave white crystals, m.p. 253–255°; $[\alpha]_D^{25}$ 0° (chloroform), ν_{max} 3450, 1102, and 1055 cm.$^{-1}$ Reported[19] values are m.p. 252–255°; $[\alpha]_D^{25}$ 0°; ν_{max} 3500, 1102, and 1055 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.18; H, 8.52.

Acknowledgment. We wish to thank Dr. G R. Allen, Jr., and Dr. A. S. Tomcufcik for helpful discussions; Mr. W. Fulmor for assistance in the spectral interpretations; Mr. L. Binovi of the Preparations Laboratory for the large scale preparation of certain intermediates; and Mr. L. Brancone and staff for microanalyses.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, KYÔTO UNIVERSITY AND FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO]

The Preparation of Synthetic Estrogens.
IX. 3,3′-Disubstituted Derivatives of Hexestrol[1]

KEIITI SISIDO, YÔKO UDÔ, HITOSI NOZAKI, AND ELWOOD V. JENSEN

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3,3′-Dihalohexestryl dimethyl ethers were prepared from the corresponding *m*-halo-*p*-methoxypropiophenones through reduction to the carbinol, bromination and the subsequent condensation of the Wurtz type. 3,3′-Difluoro- and 3,3′-dichlorohexestryl dimethyl ethers were demethylated smoothly by hydriodic acid, but similar treatment of 3,3′-dibromohexestryl dimethyl ether resulted in dehalogenation to give hexestrol. 3,3′-Dihalogenated butestrols were synthesized similarly. The Friedel-Crafts reaction of hexestryl dimethyl ether with various acids chlorides furnished the corresponding 3,3′-diacylhexestryl dimethyl ethers which were reduced to the respective 3,3′-dialkylhexestrols. Certain other derivatives of nuclear substituted hexestrols are described.

This paper comprises the preparation of heretofore unknown 3,3′-dihalohexestrols and -butestrols, which are of interest in their relation to 16α-chloro- and 16α-iodoestrone methyl ether, compounds reported[2] to be potent blood lipid-shifting agents of low estrogenic potency and thus of potential value in the treatment of atherosclerosis.

These halohexestrols and butestrols were synthesized according to the procedure of Bernstein and Wallis[3] as modified by Sisido and Nozaki,[4] which was summarized in the accompanying flow sheet. Treatment of 3,3′-dibromohexestryl dimethyl ether (IVc) with hydriodic acid gave a bromine-free diphenol which was identified as hexestrol. Apparently, the bromine atoms in the positions *ortho* to the methoxy groups are eliminated by the reducing action of hydriodic acid. Attempted demethylation of the dibromo ether (IVc) with hydrobromic acid yielded a reaction product from which no analytically pure compound could be isolated.[5] The action of a Grignard reagent or of pyridine hydrochloride also failed to afford any demethylation product. The 3,3′-dihalohexestrols and -butestrols are listed in Table I.

Other classes of hexestrol derivatives herein reported are 3,3′-dialkylhexestrols and related compounds. Though Buu-Hoï, Hoán, and Xuong[8] have reported the monoacylation of hexestryl dimethyl ether, the diacylated products have not

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(1) For the previous paper in this series see K. Sisido, K. Okano, M. Sindô, and H. Nozaki, *J. Am. Chem. Soc.*, **79**, 3591 (1957).

(2) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958). For the preparation of 3-fluoro-3′-hydroxyhexestrol see R. J. Pratt and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 4430 (1956).

(3) S. Bernstein and E. S. Wallis, *J. Am. Chem. Soc.*, **62**, 2871 (1940).

(4)(a) K. Sisido and H. Nozaki, *J. Am. Chem. Soc.*, **70**, 778 (1948). (b) K. Sisido, H. Nozaki, and H. Kuyama, *J. Org. Chem.*, **14**, 1124 (1949). (c) Ng. Ph. Buu-Hoï and Ng. Hoán, *J. Org. Chem.*, **14**, 1023 (1949). (d) For the mechanism of the dehalogenation condensation in the presence of iron powder in water-suspension see K. Sisido, Y. Udô, and H. Nozaki, *J. Am. Chem. Soc.*, **82**, 434 (1960).

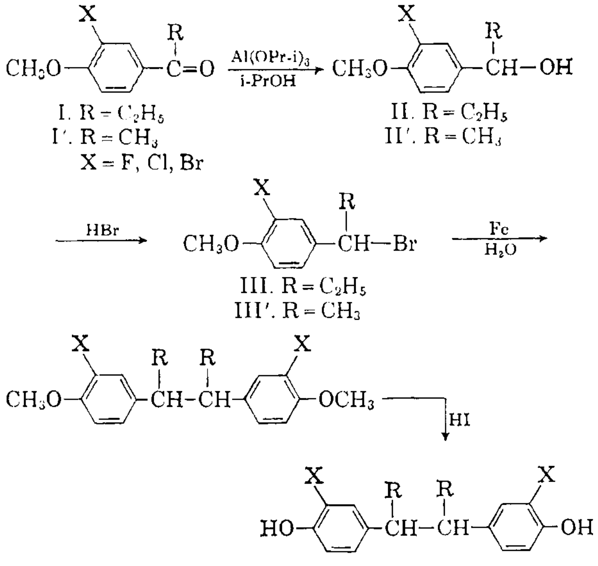
(5) For examples of shift and partial elimination of bromine atoms in the demethylation of bromo ethers with hydrobromic acid see T. Tomita and T. Kugô, *J. Pharm. Soc. Japan*, **75**, 1354 (1955); T. Tomita, Y. Kondo, and S. Tanaka, *J. Pharm. Soc. Japan*, **76**, 1119 (1956).

TABLE I

3,3′-DIHALOHEXESTROLS AND 3,3′-DIHALOBUTESTROLS

Compound	Formula	M.p.	Calcd.		Found	
			C, %	H, %	C, %	H, %
IVa[a]	$C_{20}H_{24}F_2O_2$	162	71.83	7.24	71.60	6.75
			(F% 11.36)		(F% 11.74)	
IVa[a,b]	$C_{20}H_{24}F_2O_2$	92.5–93	71.83	7.24	71.51	7.30
			(F% 11.36)		(F% 11.69)	
Va[a]	$C_{18}H_{20}F_2O_2$	198	70.57	6.58	70.41	6.57
			(F% 12.40)		(F% 12.61)	
IVb[c]	$C_{20}H_{24}Cl_2O_2$	159	65.40	6.59	65.33	6.55
Vb[d]	$C_{18}H_{20}Cl_2O_2$	146–147	63.72	5.94	63.43	6.11
IVc[e]	$C_{20}H_{24}Br_2O_2$	184.5	52.65	5.30	52.91	5.38
IV′a[f]	$C_{18}H_{20}F_2O_2$	114	70.57	6.58	70.68	6.54
			(F% 12.40)		(F% 12.19)	
V′a[g]	$C_{16}H_{16}F_2O_2$	202	69.05	5.80	69.18	5.57
			(F% 13.65)		(F% 13.52)	
IV′b[h]	$C_{18}H_{20}Cl_2O_2$	160	63.72	5.94	63.24	5.91
V′b[i]	$C_{16}H_{16}Cl_2O_2$	116–117	61.75	5.18	62.08	5.56
VI′b[j]	$C_{20}H_{20}Cl_2O_4$	169	60.77	5.10	60.87	5.24
IV′c[k]	$C_{18}H_{20}Br_2O_2$	155	50.49	4.71	50.72	4.85

[a] Details are given in the Experimental. [b] The lower melting isomer of presumably racemic form has been isolated in this case. Other compounds herein described are considered to be the *meso*-form. [c] IVb was prepared in the same way as IVa from *m*-chloro-*p*-methoxypropiophenone[6] in an overall yield of 13%. Recrystallized from benzene. [d] Demethylation was carried out with hydriodic acid, yield 86%. Recrystallized from ligroin. [e] IVc was prepared in the same way as IVa using *m*-bromo-*p*-methoxypropiophenone[6] in an overall yield of 14%. Recrystallized from benzene. [f] IV′a was prepared from *m*-fluoro-*p*-methoxyacetophenone,[7] in an overall yield of 12%. Recrystallized from ligroin. [g] Demethylation with hydriodic acid gave a quantitative yield of V′a. Recrystallized from a mixture of benzene and alcohol. [h] IV′b was prepared from *m*-chloro-*p*-methoxyacetophenone[8] in an overall yield of 8.5%. [i] The product of demethylation with hydriodic acid formed a dark colored oil, which did not crystallize. The crude oil was treated with acetic anhydride in the presence of a small amount of pyridine to give the diacetate, VI′b, which was then heated under reflux with 2*N* methanolic potassium hydroxide for a half hour. The solid which separated upon acidification with hydrochloric acid was recrystallized from ligroin to give V′b. [j] This is the diacetate of V′b (see footnote[i]). Recrystallized from ethanol. [k] IV′c was prepared from *m*-bromo-*p*-methoxyacetophenone[6] in an overall yield of 7.7%. Recrystallized from benzene.



IVa. R = C_2H_5, X = F
IVb. R = C_2H_5, X = Cl
IVc. R = C_2H_5, X = Br
IV′a. R = CH_3, X = F
IV′b. R = CH_3, X = Cl
IV′c. R = CH_3, X = Br

Va. R = C_2H_5, X = F
Vb. R = C_2H_5, X = Cl

V′a. R = CH_3, X = F
V′b. R = CH_3, X = Cl

been described. The reaction of the hexestryl dimethyl ether with two moles each of the acyl chloride and aluminum chloride proceeded smoothly to give the 3,3′-diacylhexestryl dimethyl ethers. Treatment with hydroxylamine furnished the corresponding dioximes, and Wolff-Kishner reduction and subsequent demethylation with hydriodic acid produced the 3,3′-dialkylhexestrols. These compounds are listed in Table II. Attempted formylation of the 3,3′-positions of hexestryl dimethyl ether by means of the Gattermann-Koch synthesis or of hexestrol itself by the Reimer-Tiemann reaction was unsuccessful.

The dioxime of 3,3′-diacetylhexestryl dimethyl ether was subjected to the Beckmann rearrangement by the action of phosphorus pentachloride to give 3,3′-diacetamidohexestryl dimethyl ether. Treatment of the amide with boiling hydrochloric acid gave the hydrochloride of 3,3′-diaminohexestryl dimethyl ether as a hygroscopic solid, m.p. 201°, but the free base was too unstable to be isolated.

On attempted oxidation of 3,3′-diacetylhexestryl dimethyl ether with sodium hypobromite to yield the 3,3′-dicarboxy compound, the starting ketone was recovered unchanged.

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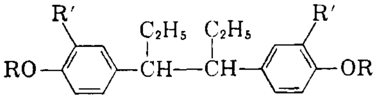
(6) Ng. Hoán and Ng. Ph. Buu-Hoï, *Compt. rent.*, **224** 1363 (1947).

(7) Ng. Ph. Buu-Hoï, Ng. D. Xuong, and D. Lavit, *J. Org. Chem.*, **18**, 910 (1953).

(8) Ng. Ph. Buu-Hoï, Ng. Hoan, and Ng. D. Xuong, *J. Am. Chem. Soc.*, **72**, 3992 (1950).

TABLE II

3,3′-DIACYLHEXESTRYL DIMETHYL ETHERS, AND DIOXIMES, 3,3′-DIALKYLHEXESTRYL DIMETHYL ETHERS, AND 3,3′-DIALKYLHEXESTROLS



R	R′	M.P.	Formula	Calcd.		Found	
				C, %	H, %	C, %	H, %
CH_3	$COCH_3$[a]	172	$C_{24}H_{30}O_4$	75.36	7.91	75.21	8.08
CH_3	$C(CH_3)NOH$[a]	228	$C_{24}H_{32}N_2O_4$	69.88	7.82	69.70	7.81
CH_3	C_2H_5[a]	108	$C_{24}H_{34}O_2$	81.31	9.67	81.04	9.54
H	C_2H_5[a]	127.5–128.5	$C_{22}H_{30}O_2$	80.93	9.26	81.10	9.41
CH_3	COC_2H_5[b]	157	$C_{26}H_{34}O_4$	76.06	8.34	75.75	8.47
CH_3	$C(C_2H_5)NOH$[c]	231–232	$C_{26}H_{36}N_2O_4$	70.88	8.24	70.82	8.27
CH_3	n-C_3H_7[d]	71	$C_{26}H_{38}O_2$	81.62	10.01	81.88	10.17
CH_3	n-COC_3H_7[e]	130–131	$C_{28}H_{38}O_4$	76.67	8.73	76.39	8.73
CH_3	$C(n\text{-}C_3H_7)NOH$[f]	213	$C_{28}H_{40}N_2O_4$	71.76	8.60	71.34	8.84
CH_3	n-C_4H_9[g]	145	$C_{28}H_{42}O_2$	81.90	10.31	81.58	10.33
H	n-C_4H_9[h]	138–139	$C_{26}H_{38}O_2$	81.62	10.01	81.13	10.39
CH_3	$COCH(CH_3)_2$[i]	153	$C_{28}H_{38}O_4$	76.67	8.73	76.80	9.02
CH_3	$C(i\text{-}C_3H_7)NOH$[j]	195–196	$C_{28}H_{40}N_2O_4$	71.76	8.60	71.76	8.90
CH_3	$CH_2CH(CH_3)_2$[k]	89	$C_{28}H_{42}O_2$	81.90	10.31	81.85	10.32
H	$CH_2CH(CH_3)_2$[l]	161.5–162	$C_{26}H_{38}O_2$	81.62	10.01	81.40	10.18

[a] Details are given in the Experimental. [b] Prepared from hexestryl dimethyl ether and propionyl chloride in the same way as 3,3′-diacetylhexestryl dimethyl ether. Recrystallized from a mixture of methanol and benzene; yield 91%. [c] Recrystallized from benzene. Quantitative yield. [d] Recrystallized from methanol; yield 89%. Demethylation with hydriodic acid gave 3,3′-dipropylhexestrol, m.p. 124–124.5°, after recrystallizations from petroleum ether containing a small amount of benzene. This diphenol has been prepared by Kaiser and Svarz[9] from hexestryl diallyl ether. The recorded m.p. is 123.5–124.5°. [e] Friedel-Crafts reaction with n-butyryl chloride. Recrystallized from ethanol containing a small amount of benzene; yield 48%. [f] Recrystallized from benzene; quantitative yield. [g] Recrystallized from ligroin; yield 32%. [h] Recrystallized from ligroin. [i] Friedel-Crafts reaction with isobutyryl chloride. Recrystallized from ethanol; yield 67%. [j] Recrystallized from benzene. [k] Recrystallized from ethanol; yield 64%. [l] Recrystallized from a mixture of benzene and petroleum ether.

EXPERIMENTAL[10]

3,3′-Difluorohexestryl dimethyl ether (IVa). A solution of 14.5 g. (0.08 mole) of m-fluoro-p-methoxypropiophenone (m.p. 84°, reported[7] 86°) in 60 ml. of anhydrous isopropyl alcohol was added to a solution of aluminum isopropoxide prepared from 2.7 g. (0.1 g.-atom) of aluminum foil, 54 ml. of anhydrous isopropyl alcohol containing 0.2 g. of mercuric chloride and 0.5 ml. of carbon tetrachloride. The mixture was heated under reflux for 2.5 hr., while the acetone was removed by fractional distillation as it was formed. After 50 ml. of distillate had been collected, the residue was treated with ice and hydrochloric acid and extracted with benzene; the benzene solution was washed, dried, and concentrated to afford 14 g. of crude 1-(m-fluoro-p-methoxyphenyl)-1-propanol as an orange, viscous oil.

Dry hydrogen bromide was passed into 14 g. of this crude carbinol for 3 hr., the reaction temperature being kept at 0–2° by an ice bath. A mixture of 100 ml. of ligroin and 100 g. of crushed ice was added, and the organic layer was separated and washed thoroughly with ice water.

This ligroin solution of crude 1-bromo-1-(m-fluoro-p-methoxyphenyl)propane was added immediately to a suspension of 12 g. of reduced iron in 120 ml. of ice water. The resulting mixture was heated slowly with stirring, while the ligroin was removed by distillation. When most of the ligroin had been removed, the reaction mixture was heated under reflux with vigorous stirring for an additional 3 hr. After cooling, the reaction mixture was extracted with benzene and the benzene solution was washed with water, dried, and evaporated. Recrystallization of the residue from petroleum ether gave 2.2 g. of 3,3′-difluorohexestryl dimethyl ether of presumably *meso*-form as colorless prisms, m.p. 157–160°. A single recrystallization from ligroin furnished a pure product, m.p. 162° unchanged by further recrystallization.

The combined mother liquors were concentrated and the residue distilled under reduced pressure to give a fraction (3.1 g.) boiling at 189–210 (6 mm.). Fractional crystallization of this distillate from a mixture of ligroin and petroleum ether gave 1.0 g. of the lower melting, presumably racemic, isomer of 3,3′-difluorohexestryl dimethyl ether, m.p. 92.5–93°, along with 0.3 g. of crystals melting at 162°, not depressed by admixture with the specimen mentioned above. The total yield of the higher melting 3,3′-difluorohexestryl dimethyl ether amounts to 18.7% based on m-fluoro-p-methoxypropiophenone.

Other 3,3′-dihalohexestryl and -butestryl dimethyl ethers listed in Table I were prepared in essentially the same way, starting from appropriately substituted propiophenones or acetophenones.

3,3′-Difluorohexestrol (Va). A mixture of 2.0 g. of the higher melting 3,3′-difluorohexestryl dimethyl ether (m.p. 162°), 30 ml. of glacial acetic, acid and 7 ml. of hydriodic acid (d. 1.7) was heated under reflux for 1 hr.; during this time the crystals dissolved gradually to give a dark brown solution. Removal of the solvent followed by single recrystallization of the residue from benzene containing a small amount of alcohol gave 3,3′-difluorohexestrol, m.p. 198°.

The demethylation of other 3,3′-dihalohexestryl and -butestryl dimethyl ethers was carried out similarly. Attempted demethylation of 3,3′-dibromohexestryl dimethyl ether failed to give the desired diphenol. A mixture of 1.8 g. (0.004 mole) of 3,3′-dibromohexestryl dimethyl ether (m.p. 184°), 20 ml. of acetic acid and 7 ml. of hydriodic acid (d. 1.7) was refluxed for 1.5 hr. Recrystallizations of

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[9] E. Kaiser and J. J. Svarz, *J. Am. Chem. Soc.*, 68, 636 (1946).

[10] All temperatures are uncorrected.

the reaction product from a mixture of benzene and alcohol afforded 0.8 g. of hexestrol, m.p. and mixed m.p. 186°, which gave correct analyses for carbon and hydrogen.

3,3'-Diacetylhexestryl dimethyl ether. A solution of 4.5 g. (0.015 mole) of hexestryl dimethyl ether, m.p. 144°,[11] 5.9 g. (0.075 mole) of acetyl chloride and 60 ml. of nitrobenzene was cooled in an ice bath, and 10.5 g. (0.079 mole) of finely powdered aluminum chloride was added in small portions with stirring. After 4 hr. stirring at room temperature, the reaction mixture was poured onto crushed ice, acidified with hydrochloric acid, and the nitrobenzene was removed by steam distillation. The remaining solid was collected, dried, and recrystallized from a mixture of methanol and benzene to yield colorless prisms of 3,3'-diacetylhexestryl dimethyl ether, 5.4 g. (93%), m.p. 172°.

Other 3,3'-diacylhexestryl dimethyl ethers listed in Table II were prepared analogously by use of appropriate acyl chloride.

Dioxime of 3,3'-diacetylhexestryl dimethyl ether. A solution of 3.0 g. (0.008 mole) of 3,3'-diacetylhexestryl dimethyl ether, 1.5 g. (0.022 mole) of hydroxylamine hydrochloride and 2.0 g. of anhydrous sodium acetate in 15 ml. of ethanol was heated under reflux for 2 hr. on a water bath. After cooling, the mixture was diluted with cold water, whereupon 3.3 g. (100%) of crystals separated. Three recrystallizations from a mixture of ethanol and benzene gave colorless prisms melting at 228°.

3,3'-Diethylhexestryl dimethyl ether. The reduction was carried out according to the Wolff-Kishner method as modified by Huang-Minlon.[12] A mixture of 3.1 g. (0.008 mole) of 3,3'-diacetylhexestryl dimethyl ether, 7.0 g. (0.125 mole) of potassium hydroxide, 7 ml. of 85% hydrazine hydrate, and 70 ml. of diethyleneglycol was heated under reflux for 1.5 hr. After removal of the water formed, the mixture was heated at 195° for an additional 4 hr. The solution was diluted with cold water and poured into hydrochloric acid. After a few hours the resulting dark oil solidified, and the solid, 2.8 g., (98%), was recrystallized from a mixture of methanol and benzene to give colorless prisms melting at 108°.

3,3'-Diethylhexestrol. A mixture of 1.5 g. of 3,3'-diethylhexestryl dimethyl ether, 20 ml. of glacial acetic acid, and 7 ml. of 48% hydriodic acid was heated under reflux for 1.5 hr. The solution was poured into an aqueous solution of sodium bisulfite. The resulting crystals were collected by filtration and washed with water and then with a small amount of cold ethanol. Several recrystallizations from ligroin gave colorless prisms melting at 127.5–128.5°.

Other 3,3'-dialkylhexestrols listed in Table II were prepared by the similar reduction and demethylation processes.

3,3'-Diacetamidohexestryl dimethyl ether. To a suspension of 2.7 g. (0.007 mole) of the dioxime of 3,3'-diacetylhexestryl dimethyl ether in 50 ml. of absolute ether, 4.5 g. (0.022 mole) of phosphorus pentachloride was added gradually with stirring and cooling in an ice bath. After 10 min., the ice bath was removed, and the stirring was continued for an additional 20 min. at room temperature. The mixture was poured onto crushed ice and the ether layer separated and washed with water. After removal of the solvent, the crystalline residue was recrystallized from ethanol to yield 2.6 g. (96%) of product, m.p. 252°.

Anal. Calcd. for $C_{24}H_{32}N_2O_4$: C, 69.87; H, 7.82. Found: C, 69.58; H, 7.91.

A mixture of this product with the dioxime of 3,3'-diacetylhexestryl dimethyl ether showed a marked depression.

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[11] Hexestryl dimethyl ether was supplied by the Chugai Pharmaceutical Co., Ltd., Tokyo, Japan.

[12] Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2487 (1946).

[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA]

Investigations on Steroids. XXXIII. Conversion of Strophanthidin into 19:8-Lactone Analogs of Progesterone and Cortexone[1,2]

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Received July 7, 1960

By oxidative procedures, strophanthidin (I) may be converted into 3β,5,14-trihydroxy-21-nor-5β,14β,17α-pregnane-19,20-dioic acid (VII) or 3β,5,14-trihydroxy-21-nor-5β,14β-pregnane-19,20-dioic acid (IV), which differ only regarding their configurations at carbon atom 17. Treatment of VII with concentrated hydrochloric acid gave 3β,5,8-trihydroxy-21-nor-5β,17α-pregnane-19,20-dioic acid 19:8-lactone (IX), whereas with IV the same reaction yielded 3β,5,8-trihydroxy-21-nor-5β-pregnane-19,20-dioic acid 19:8-lactone (XVIII). The latter compound was also obtained by a different pathway, utilizing strophanthidinic acid (II) which on treatment with concentrated hydrochloric acid gave strophanthidinic acid 19:8-lactone (XX). The latter by ozonization yielded 3β,5,8,21-tetrahydroxy-20-oxo-5β-pregnan-19-oic acid 19:8-lactone (XXI), which by degradation with periodic acid furnished XVIII. Oxidation with chromium trioxide of IX and XVIII, and subsequent treatment of the reaction products with Girard's reagent T gave 8-hydroxy-3-oxo-21-nor-Δ^4-17α-pregnene-19,20-dioic acid 19:8-lactone (XI) and 8-hydroxy-3-oxo-21-nor-Δ^4-pregnene-19,20-dioic acid 19:8-lactone (XXII) respectively. The reaction of the acid chloride of XI with diazomethane gave 21-diazo-8-hydroxy-3,20-dioxo-Δ^4-17α-pregnen-19-oic acid 19:8-lactone (XIII). By treatment with concentrated hydriodic acid, XIII was converted into 19:8-lacto-17α-progesterone (XIV), whereas with acetic acid 19:8-lacto-17α-cortexone acetate (XV) (amorphous) resulted which by saponification yielded 19:8-lacto-17α-cortexone (XVI). In identical fashion, XXII was converted into 21-diazo-8-hydroxy-3,20-dioxo-Δ^4-pregnen-19-oic acid 19:8-lactone (XXIII) which was transformed into 19:8-lactoprogesterone (XXIV) and 19:8-lactocortexone acetate (XXV). By saponification, the latter was converted into 19:8-lactocortexone (XXVI). The infrared absorption spectra of the terminal products XIV and XXIV, as well as XVI and XXVI have been compared. The results of the bioassays on these four compounds are also presented. XIV and XXIV produce only little, if any, progestational action. Both XVI and XXVI are devoid of mineralocorticoid activity.

In studies dealing with the degradation of strophanthidin, we encountered some time ago an etio acid which was first considered to possess a $\Delta^{8,14}$-double bond,[3] but was later[4,5] interpreted to contain a 19:8-lactone bridge (IX). In subsequent publications it was shown that 3β,5,8-trihydroxy-