35 cc. of 50% acetic acid, and 0.4 g. of xanthydrol in 8 cc. of methanol was added. After standing overnight, the dixanthylurea was filtered off, washed with 50% acetic acid and dried; 0.25 g., m.p. 270–274°. A mixed melting point determination with an authentic sample was not depressed.

1,2-Dihydro-6,7-dimethyl-2-keto-1-D-ribityl-3-quinoxalinecarboxylic Acid (II).—The sodium salt was dissolved in about ten volumes of hot water and an excess of dilute sulfuric acid was added. After cooling in ice, the yellow colored solid was filtered off and then recrystallized from 95% alcohol. After drying *in vacuo* at 60° and then at 100° to constant weight, the product melted at 183–183.5° dec. (cor.).

Anal. Calcd. for $C_{16}H_{20}N_2O_7$: C, 54.54; H, 5.72; N, 7.95. Found: C, 54.68; H, 5.64; N, 7.90.

Acknowledgment.—The authors are indebted to Dr. F. P. Luduena and Miss Estelle Ananenko of the Pharmacology Department of this Institute for the pharmacological data, and to Mr. M. E. Auerbach and Mr. K. D. Fleischer for the analyses reported, and to Miss Catherine M. Martini for the spectrophotometric determinations.

RENSSELAER, N. Y. RECEIVED NOVEMBER 7, 1950

[CONTRIBUTION FROM THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

Bromination of Allopregnane-3,20-dione[1,2]

BY MARTIN RUBIN, HENRY WISHINSKY[1] AND FRANCA BOMPARD

The stepwise bromination of allopregnane-3,20-dione has been shown to proceed on carbons 2, 17 and finally 4. The direct tribromination yielded the 2,4,17-tribromide which on dehydrobromination gave the corresponding triene, a suitable intermediate for selective Ring A thermal aromatization to aromatic analogs of progestational and cortical steroids.

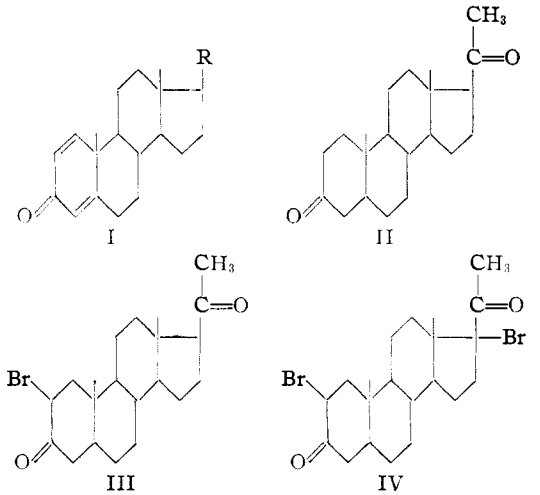
The conversion of steroidal sapogenins to estrogenic hormones and phenolic analogs of the progestational and cortical hormones[3] by the selective thermal aromatization procedure developed by Inhoffen, *et al.*,[4] and recently improved by us[5] required the preparation of Ring A dienones, I. Structures of this type have been formed by the 2,-4-dibromination and dehydrobromination of 3-ketoallosteroids.[6] The usual course of the bromination of allopregnane-3,20-dione (II), the readily available 3-ketoallosteroid derived from the sapogenins, may be expected to be complicated by the presence in the molecule of a second active center at the C-20 carbonyl group. Marker, *et al.*, have shown[7] that the hydrogen at C-17 in pregnane-3β-ol-20-one and allopregnane-3β-ol-20-one is replaceable by bromine in acetic acid at room temperature, and that the C-21 hydrogen can be replaced by bromine at 40°. It is of interest, therefore, that Butenandt and Mamoli have reported[8] that the monobromination of (II) resulted in the formation of the 2-bromo derivative (III). This compound was characterized by its dehydrobromination to Δ^1-pregnane-3,20-dione, ultraviolet absorption maximum at 230 mμ (ethanol).

We have extended the study of the monobromination of (II) to include the dehydrobromination of the products remaining in the mother liquors after removal of the crystalline 2-bromo fraction. By comparison of the yields of the Δ^1-fraction and the Δ^4-fraction formed in the course of the collidine dehydrobromination from pure 2-bromoallopregnane-3,20-dione it has been possible to estimate that at least 90% of the monobromination occurs at the 2-position. This calculation is based on the reasonable assumption that the only precursor of the Δ^1-allopregnane-3,20-dione is the 2-bromo derivative in the mother liquor material.

The introduction of a second bromine atom in (III) takes place at C-17 primarily with the formation of (IV). Proof of this fact has been obtained by preparation of the identical compound by further bromination of 17-bromoallopregnane-3,20-dione (V).[7]

The direct dibromination of (II) under the present conditions has been found to be a complicated reaction. Depending on the molar relation of bromine and (II), on the concentration of hydrogen bromide in the reaction mixture, and on other unknown factors it has been possible to isolate two dibromides, (IV) and its 2,4-isomer (VI), as well as two tribromides, the 2,4,17-compound, (VII) and a third tribromide of unknown structure.

Proof of the structure of the 2,4-dibromo compound (V) has been obtained by its independent synthesis from allopregnane-3-one-20β-ol (VIII), by dibromination in the 2,4-positions and subsequent oxidation to the dione (VI). The preparation of (VIII)[9] has been improved by utilization



(1) From the Ph.D. Thesis of Henry Wishinsky to the Graduate School of Georgetown University.

(2) Supported by grants-in-aid from Chemical Specialties Co., Inc., and the Geschickter Fund for Medical Research, Inc.

(3) C. Djerassi, G. Rosenkranz, *et al.*, THIS JOURNAL, **73**, 1523 (1951).

(4) H. Inhoffen, *Angew. Chem.*, **59**, 207 (1947).

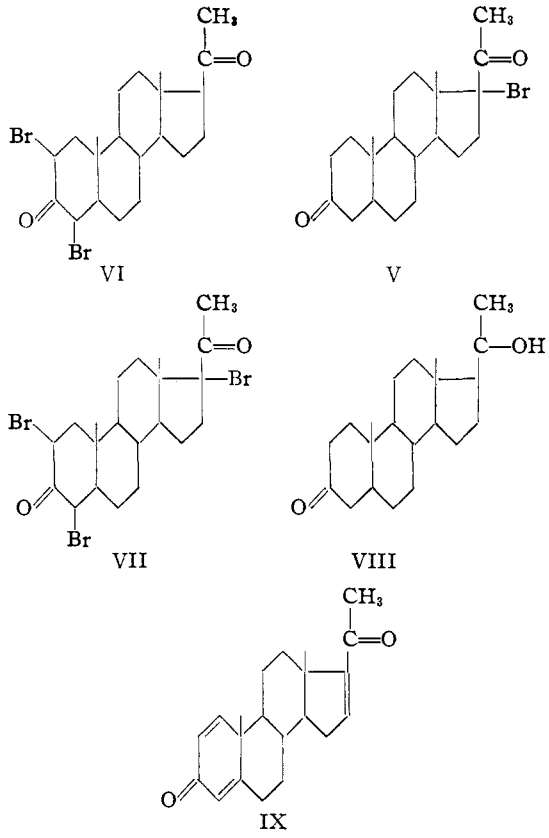
(5) E. Hershberg, M. Rubin and E. Schwenk, *J. Org. Chem.*, **15**, 292 (1950).

(6) H. Inhoffen, *Naturwissenschaften*, **26**, 756 (1938).

(7) R. Marker, *et al.*, THIS JOURNAL, **64**, 210, 2089 (1942).

(8) A. Butenandt and L. Mamoli, *Ber.*, **68**, 1850 (1935).

(9) R. Marker, *et al.*, THIS JOURNAL, **59**, 164 (1937).



of the mixed ester synthesis[10] starting with allopregnane-3β,20β-diol-3-acetate.

Stepwise bromination of the 2,17-dibromide (IV) gave a tribromide (VII). The identical product was obtained in good yield by the direct tribromination of (II). The structure of this tribromide was established by dehydrobromination to a triene (IX). The triene on dien-phenol rearrangement[11] yielded a reaction product with the ultraviolet absorption characteristics of a "hetero" phenol.

Experimental

2-Bromoallopregnane-3,20-dione(III).[8]—To a solution at 25° of 3.16 g. of (II) in 125 ml. of glacial acetic acid containing some hydrogen bromide was added rapidly with shaking a solution of 1.6 g. of bromine in 15 ml. of acetic acid. Decolorization was immediate. The product was precipitated by dilution and recrystallized three times from ethanol–chloroform; yield 2.0 g., 55%, m.p. 198–200° (dec.), $[\alpha]^{24}D$ 104.2°. The mother liquors were combined, concentrated to dryness *in vacuo* and utilized for subsequent dehydrobromination study.

Δ¹-Allopregnane-3,20-dione.—A mixture of 0.44 g. of (III) and 4 ml. of 2,4,6-collidine was refluxed in an oil-bath for one hour. After the usual workup the crude yellow gummy reaction product was purified by chromatography over 3 g. of alumina. The petroleum ether–benzene eluate, 0.20 g., 60%, ultraviolet max. 230–232 mμ, on repeated crystallization from methanol gave 0.15 g. of product, 43%, m.p. 201–203°, ultraviolet max. 230–230.5 mμ (log *E* 4.10 (ethanol)). The benzene eluate, 0.03 g., 9.9%, m.p. 130–160°, ultraviolet max. 232–236 mμ was evidently a mixture with the Δ⁴-isomer. The ether eluate gave 0.05 g. of product, 14%, m.p. 120–130°, ultraviolet max. 238–241 mμ, which did not depress the melting point of a sample of Δ⁴-progesterone.

(10) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).

(11) C. Djerassi and C. Scholz, *J. Org. Chem.*, **13**, 697 (1948).

Dehydrobromination of the Mother Liquor Fraction.—The dried material, 1.80 g., obtained by concentration of the mother liquor of the reaction above was dehydrobrominated and fractionated in the manner described. There were obtained 0.79 g., 55%, of Δ¹-fraction, ultraviolet *max.* 230–232 mμ from the petroleum ether–benzene eluate, 0.21 g., 15% of product, ultraviolet max. 232–237 mμ and 0.07 g., 5% of product, ultraviolet max. 237–241 mμ in the ether eluate. Formation of these products accounts for over 90% of the initial bromination product as the 2-bromo derivative.

2,17-Dibromoallopregnane-3,20-dione (IV). A.—A solution of 1.98 g. of (II) in 200 ml. of glacial acetic acid containing some hydrogen bromide was treated with 0.8 g. of bromine in 10 ml. of acetic acid. The solution decolorized after five minutes at room temperature. After standing for one hour the product was precipitated by dilution and recrystallized from methanol to constant melting point and rotation. There was obtained 0.95 g. (40%) of material, m.p. 187–188, $[\alpha]^{24}D$ 28.8°. *Anal.* Calcd. for $C_{21}H_{30}O_2Br_2$: Br, 33.8. Found: Br, 33.0.

B. **From 17-Bromoallopregnane-3,20-dione.**—A solution of 1.98 g. of (V) in 200 ml. of glacial acetic acid containing some hydrogen bromide was brominated with 0.8 g. of bromine in 10 ml. of acetic acid. The reaction mixture, when worked up as described above, gave 1.42 g. (IV), 60%, of product identical with that above.

17-Bromoallopregnane-3,20-dione(V).[7]—A solution of 9.3 g. of allopregnane-3β-ol-20-one in 225 ml. of glacial acetic acid containing some hydrogen bromide was treated with 4.8 g. of bromine in 30 ml. of acetic acid. After decolorization (15 minutes) the product was precipitated by dilution, the oil separated by decantation and redissolved in 200 ml. of acetic acid. To this solution at 20–22° was added 6 g. of chromic acid in 15 ml. of water. After two hours the product was obtained by dilution and filtration. After three recrystallizations from ethanol 4.5 g., 38%, of product, m.p. 121–123°, $[\alpha]^{24}D$ 39.6°, was obtained. *Anal.* Calcd. for $C_{21}H_{31}O_2Br$: Br, 20.3. Found: Br, 20.1.

2,4-Dibromoallopregnane-3,20-dione(VI).—A solution of 3.18 g. of (VIII), in 250 ml. of glacial acetic acid containing some hydrogen bromide was treated with a solution of 3.2 g. of bromine in 10 ml. of acetic acid. The progress of the rearrangement of the 2,2- to the 2,4-dibromide was followed by the change in rotation of the solution as a function of time. The curve, Fig. 1, has the typical characteristics of this reaction. At the end of 70 minutes the reaction product was precipitated by dilution and the oil redissolved in 200 ml. of acetic acid. To this solution was added 1.5 g. of chromic acid in 5 ml. of water. After two hours the solution was diluted, the product filtered and stirred with methanol. The insoluble residue, 2.6 g., 55%, was recrystallized from ethanol–chloroform to constant melting point, 193–195° and rotation $[\alpha]^{24}D$ 54.1°. *Anal.* Calcd. for $C_{21}H_{30}O_2Br_2$: Br, 33.8. Found: Br, 33.4.

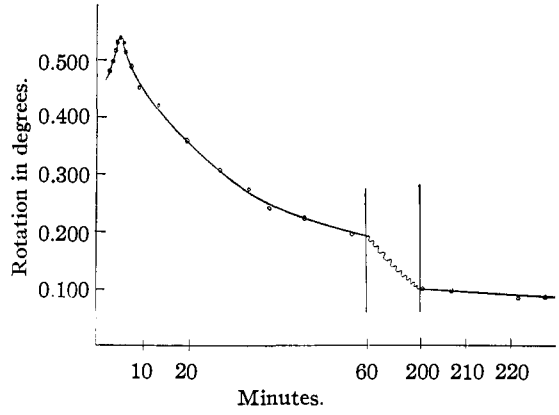


Fig. 1.—Dibromination of allopregnane-3-one-20β-ol (VIII).

Allopregnane-3β,20β-diol 3-Acetate.[12]—The procedure described for the preparation of this compound by catalytic reduction of Δ⁵-pregnen-3β-ol-one-20 acetate served equally well for its preparation from Δ¹,¹⁶-pregnadien-3β-ol-one-

(12) W. Klyne and D. Barton, THIS JOURNAL, **71**, 1501 (1949).

20 acetate.[13] The product, m.p. 168–169°, $[\alpha]^{24}D$ −6 was obtained in 85% yield.

Allopregnane-3β,20β-diol 3-Acetate, 20-Benzoate.—Benzoylation in the usual way with benzoyl chloride in pyridine gave 80% of product m.p. 163–165° on recrystallization from methanol, $[\alpha]^{24}D$ −12°. *Anal.* Calcd. for $C_{30}H_{41}O_4$: C, 77.3; H, 9.4. Found: C, 77.2; H, 9.4.

Allopregnane-3β,20β-diol 20-Benzoate.—To a refluxing mixture of 12.1 g. of the diester above in 670 ml. of methanol was added 13.4 g. of potassium carbonate in 67 ml. of water. Reflux was continued for one hour. The solution was then neutralized by the addition of acetic acid, concentrated to half its volume *in vacuo* and diluted with water. The product was an amorphous solid which was very difficult to purify being readily soluble in most oxygenated organic solvents and forming solid gels from petroleum hydrocarbons. By ice cooling of a concentrated methanol solution, a sample, m.p. 148–149°, $[\alpha]^{24}D$ −17.8°, was obtained for analysis. *Anal.* Calcd. for $C_{28}H_{38}O_3$: C, 79.2; H, 9.6. Found: C, 79.2; H, 9.4. To test the selectivity of this partial hydrolysis, a sample of the amorphous product described above was reconverted to the acetate-benzoate by two-hour reflux with acetic anhydride. There was obtained 95% of the acetate-benzoate, m.p. 163–165°, which did not depress the melting point of the material described previously.

Allopregnane-3-one-20β-ol Benzoate.—The amorphous product obtained above was dissolved in 150 ml. of acetic acid and treated with a solution of 5 g. of chromic acid in 15 ml. of water at 18–20°. After standing for two hours the product was precipitated by dilution, filtered and recrystallized from ethanol. There was obtained 8.2 g. of needles, 74%, m.p. 184–185°, $[\alpha]^{24}D$ 8.86°. *Anal.* Calcd. for $C_{28}H_{38}O_3$: C, 79.6; H, 9.0. Found: C, 79.8; H, 9.5.

Allopregnane-3-one-20(β)-ol(VIII).—A solution of 5.5 g. of the benzoate in 500 ml. of methanol containing 3.0 g. of potassium hydroxide was refluxed for six hours. After neutralization with acetic acid the solution was concentrated to one-third its volume, diluted with water and filtered. The product was recrystallized from heptane to constant m.p. 187–189°, $[\alpha]^{24}D$ 18.5°. *Anal.* Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.6. Found: C, 79.5; H, 10.4.

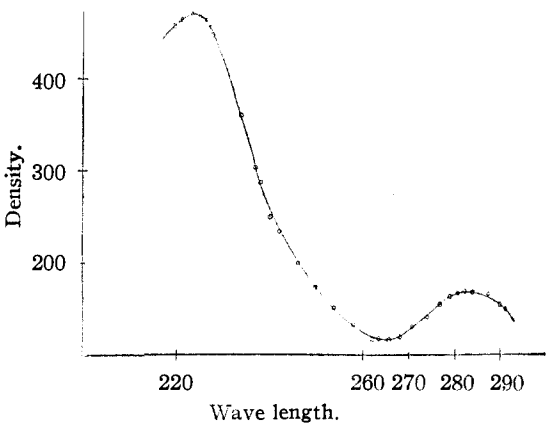


Fig. 2.—Ultraviolet absorption of "heterophenol" (X).

The acetate, prepared by two-hour reflux with acetic anhydride melted at 148–149°, $[\alpha]^{24}D$ 56.4°, after two recrystallizations from heptane. *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.7; H, 10.0. Found: C, 76.8; H, 10.1.

Direct Dibromination of Allopregnane-3,20-dione.—To a solution of 2.0 g. of (II) in 100 ml. of glacial acid was added 2.0 g. of bromine in 10 ml. of acetic acid. Decolorization was immediate. After one hour the product was obtained by dilution and filtration. Fractional crystallization from methanol and ethanol–chloroform yielded 0.4 g. of the least soluble fraction, m.p. 195–197°, $[\alpha]^{24}D$ −16.3°. *Anal.* Calcd. for $C_{21}H_{29}O_2Br_3$: Br, 43.4. Found: Br, 44.5. This product was identical with the 2,4,17-tribromide described below. A second fraction, m.p. 185–187°, $[\alpha]^{24}D$ 28.8° was shown to be the 2,17-dibromide; yield 1.2 g. *Anal.* Calcd. for $C_{21}H_{30}O_2Br_2$: Br, 33.8. Found: Br, 34.2.

When the above reaction was conducted under more dilute conditions, in a total volume of 350 ml. of acetic acid there were obtained two additional fractions. One was a dibromide, m.p. 193–195°. *Anal.* Calcd. for $C_{21}H_{30}O_2Br_2$: Br, 33.8. Found: Br, 32.5 identical with the 2,4-dibromide described above. The second product was a tribromide, m.p. 187–189°, $[\alpha]^{25}D$ −4.5°. *Anal.* Calcd. for $C_{21}H_{29}O_2Br_3$: Br, 43.4. Found: Br, 44.1.

2,4,17-Tribromoallopregnane-3,20-dione(VII). A. From (IV).—A solution of 2.4 g. of (IV) in 350 ml. of glacial acetic acid containing some hydrogen bromide was treated with 0.8 g. of bromine in 10 ml. of acetic acid. After the usual workup there was obtained 1.6 g. of product, 57%, m.p. 196–197°, $[\alpha]^{24}D$ −16.3°. *Anal.* Calcd. for $C_{21}H_{29}O_2Br_3$: Br, 43.4. Found: Br, 44.4.

B. **By Direct Tribromination.**—A solution of 6.3 g. of (II) in 200 ml. of glacial acetic acid containing some hydrogen bromide was treated with 9.6 g. of bromine in 30 ml. of acetic acid. After the usual workup there was obtained 7.9 g., 71% of tribromide, m.p. 195–197°, $[\alpha]^{24}D$ −16.3°. *Anal.* Calcd. for $C_{21}H_{29}O_2Br_3$: Br, 43.4. Found: Br, 44.6.

$\Delta^{1,16}$-Allopregnadien-3,20-dione.—A solution of 6.0 g. of (IV) and 25 ml. of 2,4,6-collidine was refluxed for one hour. After the usual workup and chromatographic fractionation there was obtained 2.2 g. of product, m.p. 196–202°, 59%, which after three recrystallizations from methanol showed a m.p. 215–216°, $[\alpha]^{24}D$ 112.6° (log *E* 4.17) ultraviolet max. 241 mμ. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.8; H, 9.0. Found: C, 81.0; H, 9.2.

$\Delta^{1,4,16}$-Allopregnatriene-3,20-dione(IX).—Dehydrobromination of 11.0 g. of (VII) with 50 ml. of 2,4,6-collidine for one hour gave 3.0 g., 49%, of triene, m.p. 200–210°, which on recrystallization from methanol gave a m.p. 210–213°, $[\alpha]^{24}D$ 117° (log *E* 4.17), ultraviolet max. 240–241 mμ. *Anal.* Calcd. for $C_{21}H_{26}O_2$: C, 81.3; H, 8.4. Found: C, 81.3; H, 8.7.

Heterophenol(X).—A solution of 100 mg. of $\Delta^{1,4,16}$-allopregnatriene-3,20-dione in 5 ml. of acetic anhydride and 30 mg. of *p*-toluenesulfonic acid was heated on a steam-bath for 4.5 hr. After the usual workup the crude gummy reaction product was dissolved in 12 ml. of methanol containing 600 mg. of potassium hydroxide and refluxed for one hour. After the usual workup we were unable to isolate a pure crystalline sample for analysis. The reaction product, however, had the ultraviolet absorption characteristic of a heterophenol (Fig. 2).

WASHINGTON 7, D. C. RECEIVED OCTOBER 27, 1950

(13) We wish to thank Dr. G. Rosenkranz, Syntex S. A., Mexico City, for a generous supply of this material.