cipitate formed. After three reprecipitations from ethanol induced by the addition of ether, the methiodide melted at 187–188° dec.

*Anal.* Calcd. for $C_{13}H_{19}N_2I$: C, 47.58; H, 5.76; N, 8.49. Found: C, 47.30; H, 5.53; N, 8.68.

**Ozonolysis of the Product from the Reaction of 1,2-Dimethylhydrazine Dihydrochloride with Formaldehyde and Benzyl Methyl Ketone.**—A stream of oxygen containing about 3% ozone was bubbled through a cooled solution (0°) of 1.0 g. of the product in 60 ml. of absolute ethanol. The stream of oxygen leaving the reaction vessel was bubbled through a 40% solution of potassium iodide. The ethanolic solution completely absorbed the ozone from the steam of gas for about 45 minutes, after which the solution of potassium iodide suddenly became colored. The stream of ozone and oxygen was bubbled through the reaction mixture for an additional half-hour at the same moderate rate. The solution was then concentrated to about 15 ml. by removing most of the ethanol under reduced pressure. The concentrate was heated under reflux for about an hour with 50 ml. of a 10% solution of sodium hydroxide. After cooling, the mixture was acidified with excess concd. hydrochloric acid. The product was extracted with three 30-ml. portions of ether. Evaporation of the ether left a residue of 0.25 g. of phenylacetic acid (35% yield based on 1,2-dimethyl-3-benzyl-$\Delta^3$-pyrazoline). After recrystallization from ethanol and water the melting point was 75–77°; mixed melting point with an authentic sample was unchanged.

**Reaction of Ethyl Benzoylacetate with Formaldehyde and 1,2-Dimethylhydrazine Dihydrochloride.**—A solution of 25.0 g. (0.13 mole) of ethyl benzoylacetate, 9.0 g. of paraformaldehyde (0.15 mole of formaldehyde) and 13.3 g. (0.10 mole) of 1,2-dimethylhydrazine dihydrochloride in 250 ml. of 95% ethanol was heated under reflux for 24 hours. The mixture was concentrated by evaporation under reduced pressure. The residual oil was poured into 300 ml. of water, and the excess ethyl benzoylacetate was extracted with ether. The aqueous mixture was made alkaline by the addition of an excess of sodium bicarbonate, and the product was then extracted with three 100-ml. portions of ether. The combined extracts were dried over anhydrous sodium sulfate, the ether was removed by evaporation under reduced pressure, and the residue was distilled. About 3 ml. of distillate was collected at 70–90° (1.2 mm.) and about 3 ml. at 120–140° (1.2 mm.).

(a) **Lower-boiling Fraction.**—From the ultraviolet spectrum ($\lambda_{max}$ 229, 278 m$\mu$) this appeared to be mostly 1,2-dimethyl-3-phenyl-$\Delta^3$-pyrazoline. The product formed a methiodide, m.p. 150°, and a picrate, m.p. 122°. Mixed melting points of the methiodide and picrate with authentic samples were unchanged.

(b) **Higher-boiling Fraction.**—From the ultraviolet spectrum ($\lambda_{max}$ 238, 327 m$\mu$) this appeared to contain 1,2-dimethyl-3-phenyl-4-carbethoxy-$\Delta^3$-pyrazoline.

**Saponification and Decarboxylation.**—The higher-boiling fraction was heated under reflux for 2 hours in 50 ml. of a solution of 10% sodium hydroxide in 50% ethanol. The reaction mixture was acidified with a slight excess of concd. hydrochloric acid and heated for an additional hour and then concentrated under reduced pressure. The residue was poured into about 200 ml. of water, and a small excess of a 20% solution of sodium hydroxide was added. The product was then extracted with three 75-ml. portions of ether, which were combined and dried over anhydrous sodium sulfate. The ether was removed by distillation under reduced pressure, and the residual oil was distilled. About 1.2 ml. of distillate was collected at 71° (1.2 mm.). The ultraviolet spectrum of this liquid resembled closely that of 1,2-dimethyl-3-phenyl-$\Delta^3$-pyrazoline. The distillate formed a methiodide, m.p. 150°, and a picrate, m.p. 122°, whose m.p.'s were not depressed when mixed with the corresponding derivatives from an authentic specimen of 1,2-dimethyl-3-phenyl-$\Delta^3$-pyrazoline.

**Reaction of $\beta$-Dimethylaminopropiophenone with Methylhydrazine.**—A solution of 32 g. (0.15 mole) of $\beta$-dimethylaminopropiophenone hydrochloride, 15 g. (0.33 mole) of methylhydrazine and 32 g. (0.39 mole) of sodium acetate in 300 ml. of 50% acetic acid was heated on a steam-bath for 48 hours. The cooled mixture was made basic with 20% sodium hydroxide. The product was then extracted with four 100-ml. portions of ether, which were combined and dried over anhydrous sodium sulfate. Dry hydrogen chloride was bubbled into the ether solution, and a crystalline solid precipitated. After three recrystallizations from a mixture of ethanol and ether the m.p. was 162°. Additional recrystallizations did not alter the m.p. Mixed melting point with an independently prepared sample of 1-methyl-3-phenyl-$\Delta^2$-pyrazoline hydrochloride[12] (m.p. 162°) was not raised or depressed.

*Anal.* Calcd. for $C_{10}H_{13}N_2Cl$: C, 61.01; H, 6.66; N, 14.25; Found: C, 58.60, 59.12; H, 6.72, 6.14; N, 14.24.

A sample of the hydrochloride was sublimed at 140° (1.2 mm.). The m.p. rose to 197°.

*Anal.* Found with sublimed sample: C, 60.94; H, 6.75; N, 14.00. (No analytical data were reported by Mannich and Heilner[12] for this hydrochloride; the melting point was reported as 162°.)

A sample of the hydrochloride was treated with a 5% solution of sodium hydroxide. The organic base was extracted with ether, and the ether was evaporated. The residue melted at 36–37°. Mixed m.p. with a sample of 1-methyl-3-phenyl-$\Delta^2$-pyrazoline prepared by the method of Mannich and Heilner[12] was not raised or depressed.

IOWA CITY, IOWA

---

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE AND CO.]

# Azasteroids. II[1,2]

BY ROBERT H. MAZUR

RECEIVED NOVEMBER 7, 1959

The degradation of hecogenin acetate lactam (I) to 3$\beta$-acetoxy-12a-aza-C-homo-5$\alpha$-pregn-16-ene-12,20-dione (II) is described. Further transformations of II to various azasteroids are shown.

In the first paper of this series,[1] we described a scheme for the introduction of nitrogen into ring C of a steroid, specifically the conversion of hecogenin to 3$\beta$-acetoxy-12a-aza-C-homo-5$\alpha$,22a-spirostan-12-one (I). We also suggested that compound I could be the precursor of modified steroid hormones, and we now report some experiments along these lines.

It was found that Mueller's modification[3] of the sapogenin side-chain degradation worked satisfactorily with hecogenin acetate lactam I and yielded 3$\beta$-acetoxy-12a-aza-C-homo-5$\alpha$-pregn-16-ene-12,20-dione (II). This product had the

(1) Part I, R. H. Mazur, THIS JOURNAL, **81**, 1454 (1959).

(2) R. H. Mazur, U. S. Patent 2,806,029 (September 10, 1957).

(3) G. P. Mueller, *Nature*, **181**, 771 (1958).

unusually low ultraviolet absorption maximum (225 mμ) also shown by the $\Delta^{16}$-12,20-dione derived from hecogenin acetate[4] and attributed[5] to interaction between the 12- and 20-carbonyl groups. The similar ultraviolet spectra suggested that compound II might have the alternative 12-aza-C-homo-12a-one structure. However, we were able to demonstrate[1,6] that the arrangement depicted in the figures is correct.

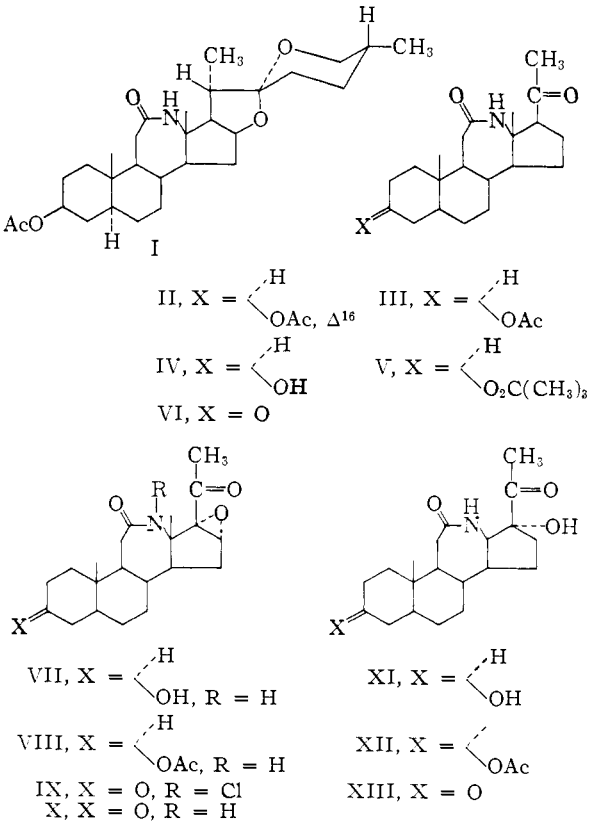
Compound II proved to be a suitable starting material for further reactions well known for ordinary steroids except that considerable effort was necessary to find the proper conditions. In particular, the complicating effect of the lactam group in oxidations was noted, perhaps through labilization of the 16-double bond and 20-ketone. Products containing alcoholic functions tended to solvate badly, necessitating drying at elevated temperatures while esters often had higher melting points than the coresponding alcohols.

Hydrogenation of II in acetic acid over a palladium catalyst yielded 3β-acetoxy-12a-aza-C-homo-5α-pregnane-12,20-dione (III). Saponification of the latter gave the corresponding 3β-ol IV. An additional derivative, the trimethylacetate V, was prepared. Oxidation of IV proved difficult. The usual chromium reagents, even chromic acid in acetone[7] or pyridine,[8] resulted in water-soluble products, possibly through overoxidation to acids. However, *t*-butyl hypochlorite[9] was highly satisfactory even though the lactam nitrogen was chlorinated and subsequently had to be reduced. Thus, treatment of IV with *t*-butyl hypochlorite in *t*-butyl alcohol gave, after sodium bisulfite reduction, 12a-aza-C-homo-5α-pregnane-3,12,20-trione (VI) and a small amount of an α-chloroketone. Resolution of the 3- and 20-carbonyl bands in the infrared spectrum of the chloroketone indicated α-chlorination (5.79 and 5.85 μ)—the unsubstituted ketone VI showed only a single band in this region (5.84 μ). Although usually the first position halogenated in 5α-pregnane-3,20-diones[10] is C-2, it seems possible that in the present case, chlorination may have occurred first at C-17 since *t*-butyl hypochlorite oxidation of 17-substituted materials did not give chlorinated by-products in isolable amounts.

The $\Delta^{16}$-20-ketone II was epoxidized in the two-phase system *t*-butyl alcohol–aqueous potassium hydroxide–30% hydrogen peroxide to give 16,17α-epoxy-3β-hydroxy-12a-aza-C-homo-5α-pregnane-12,20-dione (VII) also characterized as the acetate VIII. The usual conditions using hydrogen peroxide–aqueous methanolic alkali[11] were markedly inferior. Oxidation of VII with *t*-butyl hypochlorite gave the slightly soluble 12a-chloro-16,17α-epoxy-12a-aza-C-homo-5α-pregnane-3,12,20-trione (IX) in good yield which subsequently was reduced with sodium bisulfite to the desired 16,17α-epoxy-12a-aza-C-homo-5α-pregnane-3,12-20-trione (X).

The epoxide ring of VII was opened with hydrogen bromide in acetic acid[11] to yield the bromohydrin acetate which was reduced directly (palladium-on-calcium carbonate) and then saponified to 3β,17α-dihydroxy-12a-aza-C-homo-5α-pregnane-12,20-dione (XI), also characterized as the acetate XII. The usual conditions[11] for epoxide ring opening failed completely with compound VII and it was found necessary to heat the reaction solution at an elevated temperature for several hours to obtain conversion to the bromohydrin. Oxidation of XI with *t*-butyl hypochlorite gave 17α-hydroxy-12a-aza-C-homo-5α-pregnane-3,12-20-trione (XIII). The infrared spectra of XI, XII and XIII were particularly helpful as each OH and NH group showed distinctly as a separate band or shoulder.

Some question as to the stereochemistry at C-17 of the present compounds might arise. Although models[1] indicate no great change in the steric requirements of the 16,17-double bond due to the presence of the C-ring lactam, there is, nevertheless, a clear interaction as evidenced by the striking hypsochromic shift in the ultraviolet maximum,




(4) R. B. Wagner, J. A. Moore and R. F. Forker, THIS JOURNAL, **72**, 1856 (1950).

(5) G. P. Mueller, R. E. Stobaugh and R. S. Winniford, *ibid.*, **75**, 4888 (1953).

(6) R. H. Mazur, *J. Org. Chem.*, **25**, in press (1960).

(7) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch and G. W. Wood, *ibid.*, 2402 (1951).

(8) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(9) G. S. Fonken, J. L. Thompson and R. H. Levin, *ibid.*, **77**, 172 (1955).

(10) M. Rubin, H. Wishinsky and F. Bompard, *ibid.*, **73**, 2338 (1951).

(11) P. L. Julian, E. M. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

the sensitivity of the side-chain to over-oxidation (probably), the lowered yield on epoxidation of the $\Delta^{16}$-20-ketone and the lessened reactivity toward nucleophilic attack of the resulting epoxide. Molecular rotatory changes in reactions of our azasteroids, while internally consistent, did not agree with changes in corresponding reactions of either 11-keto, 12-keto or C-ring unsubstituted steroids (either 17$\alpha$ or 17$\beta$). The assignment of configuration at C-17, therefore, rests on consideration of the models.

## Experimental[12]

**3$\beta$-Acetoxy-12a-aza-C-homo-5$\alpha$-pregn-16-ene-12,20-dione** (II).—Hecogenin acetate lactam (I) (146.1 g., 0.3 mole) and 35 g. (0.3 mole) of pyridine hydrochloride were dissolved in one liter of acetic anhydride and the solution heated under reflux for 6 hours. Water (200 ml.) was added and the stirred solution kept below 50° during the decomposition of acetic anhydride. The solution was cooled to 10° and 50 g. (0.5 mole, 25% excess) of chromic acid in 100 ml. of water added over 20 min. The temperature rose to 15°. The solution was stirred at room temperature for 3 hours and the excess chromic acid decomposed by adding 12.5 ml. (0.15 mole) of 36% formaldehyde. Anhydrous sodium acetate (150 g.) was added and the solution stirred and heated at 100° for one hour.

After dilution with a large volume of water, the product was extracted into 1:1 ether–benzene and the organic layer washed four times with 5% sodium sulfate and once with 10% potassium bicarbonate. The residue from distillation of the ether–benzene was chromatographed on silica gel. Elution with ethyl acetate and subsequent crystallization from benzene–cyclohexane yielded the desired product, 65.1 g. (56%), m.p. 189–193°. Recrystallization from benzene–cyclohexane gave thick prisms, m.p. 199–200°, $[\alpha]_D$ +30°, $\lambda_{max}^{MeOH}$ 225 m$\mu$, $\epsilon$ 9660; $\lambda_{max}^{KBr}$ 2.96(w), 5.78(s), 6.12(s), 6.22(m) $\mu$.

*Anal.* Calcd. for $C_{23}H_{33}NO_4$: C, 71.28; H, 8.58; N, 3.62. Found: C, 71.36; H, 8.62; N, 3.74.

**3$\beta$-Acetoxy-12a-aza-C-homo-5$\alpha$-pregnane-12,20-dione** (III).—Compound II (2.02 g., 0.0052 mole) in 20 ml. of acetic acid was hydrogenated over 0.3 g. of 5% palladium-on-carbon at atmospheric temperature and pressure. Hydrogen uptake stopped after one molar equivalent had been absorbed (2 hours). The catalyst was removed by filtration, the filtrate diluted with water and extracted with chloroform. The residue from distillation of the chloroform was dissolved in 100 ml. of 50% ethanol and the solution concentrated to the cloud point. Compound III crystallized as plates, 1.79 g. (88%), m.p. 187–192°. Recrystallization from aqueous ethanol raised the m.p. to 192–194°, $[\alpha]_D$ −16°, $\lambda_{max}^{KBr}$ 2.98 (m), 5.77(s), 5.93(shoulder), 6.04(s) $\mu$.

*Anal.* Calcd. for $C_{23}H_{35}NO_4$: C, 70.92; H, 9.06; N, 3.60. Found: C, 70.84; H, 9.20; N, 3.94.

**3$\beta$-Hydroxy-12a-aza-C-homo-5$\alpha$-pregnane-12,20-dione** (IV).—The alcohol was best prepared by saponifying the crude acetate. The product from reduction of 7.8 g. (0.02 mole) of II was dissolved in 80 ml. of 95% ethanol, 8 g. of potassium hydroxide in 25 ml. of water added and the solution allowed to stand at room temperature for 3 hours. The solution was neutralized with acetic acid and concentrated to the cloud point. Slow cooling gave alcohol IV as long needles, 6.3 g. (91%), m.p. 187–190°. The analytical sample had m.p. 192.5–193.5° (aqueous ethanol). $[\alpha]_D$ −6°; $\lambda_{max}^{KBr}$ 2.93 (m), 2.96 (m), 5.94 (s), 6.06 (s) $\mu$.

*Anal.* Calcd. for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.38; H, 9.46; N, 4.05.

**3$\beta$-Pivalyloxy-12a-aza-C-homo-5$\alpha$-pregnane-12,20-dione** (V).—The ester was prepared by reaction of alcohol IV (1.0 g., 0.0029 mole) with 0.5 g. (0.004 mole) of pivalyl chloride in 10 ml. of pyridine overnight at room temperature. The solution was poured into water, precipitating the ester V, 1.1 g. (90%), m.p. 218–220°. Recrystallization from acetone–cyclohexane gave small needles, m.p. 223–226°, $[\alpha]_D$ −16.5°; $\lambda_{max}^{KBr}$ 3.05(w), 5.77(s), 6.02(s)$\mu$.

*Anal.* Calcd. for $C_{26}H_{41}NO_4$: C, 72.35; H, 9.58; N, 3.25. Found: C, 72.37; H, 9.48; N, 3.60.

**12a-aza-C-homo-5$\alpha$-pregnane-3,12-20-trione** (VI).—Alcohol IV (3.0 g.) was dissolved in 60 ml. of hot *t*-butyl alcohol, the solution cooled rapidly in an ice-bath and 3 ml. of *t*-butyl hypochlorite added. After standing in the dark for 4 hours, excess reagent was decomposed with aqueous sodium bisulfite, the solution extracted with chloroform and the residue from distillation of the chloroform chromatographed on silica gel. Elution with 50% ethyl acetate–benzene yielded 0.72 g. (22%) of a mono-chloroketone, long needles from benzene–chloroform, m.p. 260–262°, $[\alpha]_D$ +23°; $\lambda_{max}^{KBr}$ 2.94(w), 5.79(s), 5.85(s), 6.02(s) $\mu$.

*Anal.* Calcd. for $C_{21}H_{30}ClNO_3$: C, 66.38; H, 7.96; N, 3.69; Cl, 9.33. Found: C, 66.08; H, 8.31; N, 3.46; Cl, 9.14.

Elution of the column with ethyl acetate gave 1.31 g. (43%) of the ketone VI, tiny prisms from benzene–cyclohexane, m.p. 177–178°, $[\alpha]_D$ +10°; $\lambda_{max}^{KBr}$ 2.93(w), 5.84(s), 6.04(s)$\mu$.

*Anal.* Calcd. for $C_{21}H_{31}NO_3$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.08; H, 8.94; N, 3.75.

**16,17$\alpha$-Epoxy-3$\beta$-hydroxy-12a-aza-C-homo-5$\alpha$-pregnane-12,20-dione** (VII).—Compound II (10.0 g., 0.026 mole) was dissolved in 200 ml. of *t*-butyl alcohol and 5 g. of potassium hydroxide in 40 ml. of water added. The mixture was stirred very rapidly, cooled to 15° and 30 ml. of 30% hydrogen peroxide added at such a rate that the temperature remained at 15–16°. The mixture then was stirred overnight at room temperature. The mixture was neutralized with acetic acid, the product extracted into chloroform and the chloroform washed thoroughly with water. Distillation of the chloroform gave the desired product, needles from aqueous methanol, 6.3 g. (67%), m.p. 256–257°, $[\alpha]_D$ +14°; $\lambda_{max}^{KBr}$ 2.91 (m), 5.90 (s), 6.09 (s) $\mu$.

*Anal.* Calcd. for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.44; H, 8.39; N, 4.19.

The acetate VIII, needles from benzene–cyclohexane, had m.p. 267–268.5°, $[\alpha]_D$ +8°; $\lambda_{max}^{KBr}$ 2.96(w), 5.80 (s), 5.83 (shoulder), 6.02 (s) $\mu$.

*Anal.* Calcd. for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.63; H, 8.40; N, 3.65.

**12a-Chloro-16,17$\alpha$-epoxy-12a-aza-C-homo-5$\alpha$-pregnane-3,12,20-trione** (IX).—Epoxyalcohol VII (5.0 g., 0.014 mole) was dissolved in 100 ml. of boiling *t*-butyl alcohol, the solution cooled to room temperature and 15 ml. of *t*-butyl hypochlorite added. The desired product began to crystallize in a few minutes as long needles. After 2 hours in the dark, the solid was removed by filtration and washed with 50% methanol to yield IX, 4.5 g. (82%), m.p. 188–190° dec., $[\alpha]_D$ +36°; $\lambda_{max}^{KBr}$ 5.84(s), 6.04 (s)$\mu$.

*Anal.* Calcd. for $C_{21}H_{28}ClNO_4$: N, 3.56; Cl, 9.00. Found: N, 3.56; Cl, 9.32.

**16,17$\alpha$-Epoxy-12a-aza-C-homo-5$\alpha$-pregnane-3,12-20-trione** (X).—N-Chlorolactam IX (3.8 g., 0.0097 mole) was suspended in 80 ml. of acetic acid, the mixture heated to 100° and 2 g. of sodium bisulfite added in small portions with good stirring. After *ca.* 0.5 hour, the starting material had dissolved and finely divided sodium chloride separated. The mixture was diluted with chloroform, the chloroform washed throughly with water and distilled. The residue was chromatographed on silica gel. Elution with 40% ethyl acetate–benzene and crystallization from aqueous methanol gave 1.82 g. (52%) of X, small needles, m.p. 236–239°, $[\alpha]_D$ +42°; $\lambda_{max}^{KBr}$ 3.00 (w), 5.84 (s), 6.05 (s) $\mu$.

*Anal.* Calcd. for $C_{21}H_{29}NO_4$: C, 70.16; H, 8.13; N, 3.90. Found: C, 69.92; H, 7.97; N, 4.14.

**3$\beta$,17$\alpha$-Dihydroxy-12a-aza-C-homo-5$\alpha$-pregnane-12,20-dione** (XI).—Epoxyalcohol VII (5.0 g., 0.014 mole) was dissolved in 100 ml. of acetic acid, 10 ml. of 32% hydrogen bromide in acetic acid added and the solution heated at 55° for 6 hours. The solution was poured into water to give the 16,17-bromohydrin-3-acetate as a light tan powder, 6.1 g. (91%), m.p. 175–180° dec.

*Anal.* Calcd. for $C_{23}H_{34}BrNO_6$: Br, 16.50. Found: Br, 16.35.

(12) We wish to thank R. T. Dillon, H. W. Sause and their associates for analyses (samples dried under high vacuum at 118° for 3 hours), rotations (25 ± 3°, 1% in chloroform unless otherwise indicated) and spectra (ultraviolet in methanol, infrared at 0.5% in potassium bromide). Melting points are uncorrected

It was found advantageous to carry the 16-dehydroacetate II to the above bromohydrin acetate without purification of intermediates. In a typical example, 11.6 g. (0.03 mole) of II yielded 11.3 g. (78% over-all) of good quality bromohydrin acetate.

Bromohydrin acetate (6.1 g., 0.013 mole) in 75 ml. o 95% ethanol was hydrogenated over 5 g. of 5% palladium-on-calcium carbonate. Hydrogen uptake stopped after 36 hours. The filtrate after removal of the catalyst was treated with 5 g. of potassium hydroxide in 35 ml. of water and allowed to stand for 3 hours at room temperature. The solution was neutralized with acetic acid, diluted with water, extracted with chloroform and the residue from chloroform distillation crystallized from aqueous methanol to give XI, thick needles, 3.4 g. (74%), m.p. 260–261°, $[\alpha]D$ −6° (MeOH); $\lambda_{max}^{KBr}$ 2.89 (m), 2.96 (shoulder), 3.01 (s), 5.83 (s), 6.04 (s) μ.

*Anal.* Calcd. for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.09; H, 9.57; N, 3.99.

The acetate XII, clusters of needles from aqueous methanol, had m.p. 231–233°, $[\alpha]D$ −14°, $\lambda_{max}^{KBr}$ 2.96 (w), 3.00 (w), 5.75 (s), 5.83 (shoulder), 6.05 (s) μ.

*Anal.* Calcd. for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.46. Found: C, 67.90; H, 8.83; N, 3.65.

**17α-Hydroxy-12a-aza-C-homo-5α-pregnane-3,12,20-trione (XIII).**—Alcohol XI (1.6 g., 0.0044 mole) was dissolved in 50 ml. of *t*-butyl alcohol and 2.1 g. of *t*-butyl hypochlorite added. After 2 hours in the dark at room temperature, the solution was diluted with 25 ml. of water, stirred in an ice–water-bath and sodium bisulfite added until the yellow color had disappeared. The mixture was diluted with water, extracted with chloroform, the chloroform washed well with water and distilled. The residue was crystallized from aqueous ethanol to give the desired ketone XIII, small needles, 1.2 g. (75%), m.p. 274–277°, $[\alpha]D$ +8° (MeOH); $\lambda_{max}^{KBr}$ 2.99 (w), 3.16 (w, broad), 5.82 (s), 6.09 (s) μ.

*Anal.* Calcd. for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.59; H, 9.04; N, 3.60.

SKOKIE, ILL.

---

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

# The Partial Synthesis of 12α-Methyl-11-dehydrocorticosterone

BY B. G. CHRISTENSEN, R. G. STRACHAN, N. R. TRENNER, B. H. ARISON, RALPH HIRSCHMANN AND J. M. CHEMERDA

RECEIVED NOVEMBER 21, 1959

The partial synthesis of 12α-methyl-11-dehydrocorticosterone is described. The addition of methylmagnesium iodide to a steroidal 11β,12β-oxide resulted in rearrangement to a C-nor-11ξ-(α-hydroxy-α-ethyl)-pregnane derivative while the action of dimethylmagnesium resulted in the desired 12α-methyl-11β-hydroxy functionality. The chemistry of the latter reaction derives strong support from the use of n.m.r. spectroscopy. The influence of 12-oxygenated functions upon the positions of the C-18 and C-19 proton resonances is discussed in detail. A reproducible procedure for the preparation of dimethylmagnesium is also described.

The quest for anti-inflammatory steroids possessing increased activity or lacking side-effects has included several modifications[1] of the hydrocortisone molecule. Of these, the introduction of 6α- or 16-methyl substituents[2] has been particularly rewarding. Also the demonstrated enhancement of activity[3,4] due to the 12α-halogen substituent provided further impetus to the synthesis of a steroidal derivative methylated at position 12.

Although several procedures for the insertion of the 12α-methyl functionality might be envisioned, the addition of a methyl organometallic to an 11β,-12β-epoxide appeared to be the method of choice. The known diaxial opening of 5,6-epoxides with methyl Grignard reagents[5] suggested that the desired 11β-hydroxy-12α-methyl grouping would be the expected product of such an addition. Furthermore, the anticipated conversion *via* the 11-ketone to the equatorial 12β-epimer, which was expected to be the thermodynamically more stable isomer, also would make the 12β-methyl derivatives readily available. Accordingly, 11β,12β-epoxypregnane-3,20-dione 3,20-bis-(ethylene ketal) was prepared by the following route.

12α-Bromopregnane-3,11,20-trione[6] was converted to the corresponding 3,20-bis-(ethylene ketal) with ethylene glycol and *p*-toluenesulfonic acid.[7] Because of the loss of bromine during reduction of steroidal bromo-ketones with certain other hydrides,[4,8] lithium borohydride was the reagent of choice[4] in the preparation of the bromohydrin. This compound was not isolated as a crystalline intermediate, but was transformed immediately to the desired 11β,12β-epoxide IV.

The action of methyl Grignard reagents in opening 5,6-epoxides has been the subject of several investigations,[5] but their action upon other steroidal epoxides has remained largely unexplored. When IV was treated with methylmagnesium iodide in refluxing benzene, a crystalline product was obtained which gave the correct analysis for the desired bisketal VIII. However, since this product formed an acetate under conditions which do not normally effect acetylation of an 11β-hydroxyl group and

(1) For an excellent recent summary see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 682.

(2) For references demonstrating the effect of methyl substitution see R. E. Beyler, F. Hoffman and L. H. Sarett, *J. Org. Chem.*, **25**, *in press* (1960).

(3) J. E. Herz, J. Fried and E. F. Sabo, *ibid.*, **78**, 2017 (1956); J. Fried, J. E. Herz, E. F. Sabo and M. H. Morrison, *Chemistry & Industry*, 1232 (1956). See, however, J. Fried and A. Borman in "Vitamins and Hormones," Vol. XVI, Academic Press, Inc., New York, N. Y., 1959, p. 342.

(4) D. Taub, R. D. Hoffsommer and N. L. Wendler, THIS JOURNAL, **78**, 2912 (1956); **79**, 452 (1957).

(5) See ref. 1, pp. 199 and 692.

(6) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **26**, 726 (1943).

(7) R. A. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

(8) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **36**, 1241 (1953); J. N. Cornforth, J. M. Osbond and G. H. Phillips, *J. Chem. Soc.*, 970 (1954).