0.4 g. of platinum oxide under atmospheric pressure. Slightly over 1 mole of hydrogen was absorbed. After the removal of the catalyst, the filtrate was poured into ice-water and the precipitate collected and washed thoroughly with water. The crude, dried solid was chromatographed over alumina and the fraction eluted with 5% methanol in ether crystallized from dilute aqueous ethanol, m.p. 70–73°.

Anal. Calcd. for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.91; H, 10.30.

Dihydrotigogenin-26-tosylate (V'a).—The acetate V' (1.01 g.) was tosylated as in the manner of V. A sample for analysis was chromatographed over Florisil.

Anal. Calcd. for $C_{36}H_{55}O_6S$: C, 70.20; H, 9.00; S, 5.21. Found: C, 70.37; H, 9.28; S, 5.09.

26-Deoxy-26-iododihydrotigogenin Acetate (V'b).—The tosylate V'a (1.15 g.) was iodinated and worked up in the same manner as Vb. A sample was distilled in high vacuum to yield an oil which crystallized from ether–methanol as slightly colored plates, m.p. 66–70°. Repeated crystallizations and chromatography failed to produce an analytically pure specimen.

A crystalline **26-deoxy-26-iododihydrotigogenin** of m.p. 118–122° was prepared by hydrolysis with potassium bicarbonate in methanol. As with Vb, the analysis was unsatisfactory.

26-Deoxy-26-N-ethyldihydrotigogenin (IVb).—A sealed tube containing 0.773 g. of V'b, 5 cc. of ethylamine and anhydrous potassium carbonate (*ca.* 0.1 g.) was allowed to stand at room temperature for 64 hr. After removal of the excess amine, water was added to the tube and the suspension extracted with ether. The ethereal extract yielded 0.794 g. of an oily residue which was hydrolyzed with 2% methanolic potassium hydroxide. Upon partial concentration and addition of water to the solution, 0.613 g. of a slightly colored crystalline mass was obtained. Recrystallization from acetone–hexane yielded white plates of m.p. 139–140.5°, $[\alpha]^{20}D$ +4.3° (chlf.). A mixture melting point with 26-N-ethyltetrahydrosolasodine of m.p. 139.5–141.5° was undepressed. The infrared spectrum (Nujol mull) was identical with the product derived from solasodine.

Anal. Calcd. for $C_{29}H_{51}O_2N$: C, 78.14; H, 11.53; N, 3.14. Found: C, 78.06; H, 11.69; N, 3.03.

The 26-N-ethyl-N-acetyl derivative, prepared as in the previous manner, agreed (m.p., mixture m.p., infrared spectra) with the N-acetylated derivative of the product (IVb) obtained from solasodine.

Hydrolysis of the Unsaturated Triacetyltomatidine[12] (VI) to N-Acetyltomatidine (VIa).—A solution of 1.27 g. of the so-called unsaturated triacetyltomatidine in 35 cc. of 2% methanolic potassium hydroxide was refluxed for 75 minutes. After partial concentration and addition of water 1.0 g. of crystals, m.p. 175–182°, was obtained. Recrystallization from methanol–water yielded plates of m.p. 186–190°; λ_{max}^{chlf} 2.77 μ (free hydroxyl); 2.89, 2.99 μ (N–H); 5.98, 6.61 μ (NH–acetyl).

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35. Found: C, 76.25; H, 10.15.

Isomeric N-Acetyldihydrotomatidine (VII).—The unsaturated alcohol VIa (0.92 g.) in 30 cc. of acetic acid was reduced with platinum oxide (0.36 g.) under atmospheric pressure. After an uptake of 1 mole of hydrogen the hydrogenation ceased. The filtrate, after the removal of the catalyst, was poured into ice-water containing excess dilute sodium hydroxide. The precipitate (0.839 g.) was washed thoroughly with water and crystallized from dilute methanol. Needles of m.p. 180–183° were obtained.

Anal. Calcd. for $C_{29}H_{49}O_3N$: C, 75.77; H, 10.75. Found: C, 75.69; H, 10.80.

Isomeric 26-N-Ethyldihydrotomatidine (VIIa).—The N-acetyl derivative VII (0.700 g.) was reduced with lithium aluminum hydride as in the previous manner. The semi-crystalline material (0.621 g.) obtained from this reduction was chromatographed on alumina. Elution with 1% methanol–ether afforded the isomeric amino alcohol of m.p. 119–123°. Recrystallization from dilute acetone yielded plates of m.p. 121–123°, $[\alpha]^{20}D$ −3° (chlf.).

Anal. Calcd. for $C_{29}H_{51}O_2N$: C, 78.14; H, 11.53. Found: C, 77.89; H, 11.27.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE JULIAN LABORATORIES, INC., AND THE GLIDDEN COMPANY]

Sterols. XVI.[1] Cortisone and Analogs. Part 2. 17α,21-Dihydroxy-4-pregnene-3,12,20-trione

BY PERCY L. JULIAN, CHAPPELLE C. COCHRANE,[2] ARTHUR MAGNANI AND WILLIAM J. KARPEL*

RECEIVED OCTOBER 15, 1955

The synthesis of the 12-keto analog of cortisone, namely, 17α,21-dihydroxy-4-pregnene-3,12,20-trione (XV) from 3α,12α-diacetoxypregnan-20-one (I) is described. The 17,21,21-tribromo derivative of I is converted into 3α,12α-diacetoxy-16-pregnen-20-one (III) by treatment with sodium iodide in glacial acetic acid. The 16α,17α-epoxy derivative of III is converted into 3α-acetoxy-17α-hydroxypregnane-12,20-dione (VIIIa) and the latter converted into XV by the well-known procedures of bromination and acetoxylation at C_{21}, followed by introduction of the double bond into ring A. Improvements in several reactions involved in this type of synthesis of cortisone analogs are recorded, including the Raney nickel dehalogenation of vicinal steroid bromohydrins and the oxidation at C_3.

Some years ago when the simpler analogs of cortisone were actively being sought for the first time, we devised a facile synthesis of 17α,21-dihydroxy-4-pregnene-3,12,20-trione (XV) from 3α,12α-diacetoxypregnan-20-one (I). The procedure was in great part made possible by four observations in our laboratories.

(a) Bromination of I with slightly more than 3 moles of bromine yields the corresponding 17,21,-21-tribromo-3α,12α-diacetoxypregnan-20-one (II), isolable pure in good yield.[3]

(b) II on treatment with sodium iodide in boiling glacial acetic acid solution gives 3α,12α-diacetoxy-16-pregnen-20-one (III), likewise in good yield.[3b,3c]

(c) Epoxidation of 16-pregnen-20-ones, like III, with hydrogen peroxide in alkaline medium, followed by opening the 16,17-epoxy ring with hydrogen bromide, and dehalogenation of the resulting bromohydrin with Raney nickel leads generally to 17α-hydroxypregnan-20-ones in yields as high as 90% or better.[1,3b,3c,4]

(d) Bromination of 17α-hydroxypregnan-20-ones,

* This talented young investigator, devoted friend and research assistant to the senior author for twelve years, died on February 12, 1956.

(1) For Sterols XV, see THIS JOURNAL, **77**, 4601 (1955).

(2) The Glidden Company, Chicago, Illinois.

(3) (a) P. L. Julian and W. J. Karpel, THIS JOURNAL, **72**, 362 (1950); (b) P. L. Julian, Abstracts of 118th Meeting, Amer. Chem. Soc., Chicago, September, 1950; (c) P. L. Julian in G. Pincus, "Recent Progress in Hormone Research," Vol. VI, Academic Press, Inc., New York, N. Y., 1951, p. 195.

(4) (a) P. L. Julian, E. W. Meyer, W. J. Karpel and I. Ryden, THIS JOURNAL, **71**, 3574 (1949); (b) **72**, 5145 (1950).

like VIII, followed by treatment with potassium acetate in acetone (with or without prior treatment with sodium iodide) leads to 21-acetoxy-17α-hydroxypregnan-20-ones, like XI, in excellent yield.[4,5]

We are reporting the experimental details of the work outlined above, as related to the synthesis of XV, although Petrow, *et al.*, have in the meantime reported its synthesis[6b] and likewise that of the 12α-hydroxy analog, namely, 12α,17α,21-trihydroxy-4-pregnene-3,20-dione.[6a] Not only does our synthesis of XV follow a different course from that of Petrow[6] with respect to most of the intermediates, but it also offers experimental clarification of some difficulties, and improvement in certain yields, encountered in their work.

The reaction I → II was first carried out, employing three moles of bromine, by Koechlin and Reichstein,[7] who did not isolate a pure compound from the bromination mixture, but instead employed the latter for a Faworski[8] rearrangement, explicitly assuming it to be a mixture of 3α,12α-diacetoxy-17-bromopregnan-20-one and 3α,12α-diacetoxy-17,21-dibromopregnan-20-one. With alcoholic alkali, these authors did isolate a 3% yield of 3α,12α-dihydroxy-17-pregnen-21-oic acid. That however, the bromination mixture consisted primarily of 3α,12α-diacetoxy-17,21,21-tribromopregnan-20-one (II) is attested by our isolation of the latter in 75% yield.[9] Appropriate dehalogenation of the mother liquors gives recovered starting material, so that by this procedure the over-all yield of I to III can be made very attractive indeed. For convenience and rapidity, the total crude tribromo product, prepared as described in the Experimental, could be used to give a 55% yield of III, based upon I.[6]

The 16,17-epoxy derivative of III is best isolated in the form of its 3α,12α-dihydroxy derivative IV which we obtained in 90% yield. Petrow separated the 3α,12α-diacetoxy derivative of IV directly from this epoxidation reaction without reacetylation. We have found it more feasible in this case to hydrolyze the entire reaction product and isolate IV itself since the latter melts at 204° and crystallizes beautifully while the corresponding diacetate, which Petrow isolated, melts at 77° and does not crystallize as well from the reaction mixture.

Partial succinoylation of IV to 3α,12α-dihydroxy-16α,17α-epoxypregnan-20-one 3-hemisuccinate (V), followed by chromic acid oxidation and hydrolysis of the crude oxidation product gave VI. The latter was then acetylated to yield 3α-acetoxy-16α,17α-epoxypregnane-12,20-dione (VIIa).

The conversion of the epoxide VIIa into the corresponding bromohydrin and the Raney nickel dehalogenation of the latter to 3α-acetoxy-17α-hydroxypregnane-12,-20-dione (VIIIa) proceeded in 94% yield. Since the early days following our discovery of this useful and now widely used[10] procedure for dehalogenating steroid bromohydrins, we have consistently obtained such yields. In view of conflicting results reported in the literature, a few comments on this reaction are deemed desirable.

The difficulties recently reported by Petrow,[6] by Rothman and Wall[11] and by Mueller, Stobaugh and Winniford[12] with this reaction can all be obviated by employing the simple and inexpensive Raney nickel preparation described in the Experimental, which preparation we unfortunately neglected to describe in our earlier papers.[1,3,4] Thus, using this nickel preparation, the conversion of 3β-acetoxy-16α,17α-epoxyallopregnane-12,20-dione (VIIb) into 3β-acetoxy-17α-hydroxyallopregnane-12,20-dione (VIIIb) proceeded in 90% yield.[11-13] A Raney nickel catalyst for this purpose has also been described by Barkley, Farrar, Knowles and Raffelson,[10] but we have found it to have no advantages over the preparation herein described.

The bromination of VIIIa to IX is one of the few comparatively low yield reactions occurring in the sequence in this paper, so far as the actual isolation of pure IX is concerned (53%). This was to be expected, inasmuch as bromination at C_{11} and C_{21} compete with each other. Indeed, the impetus to continued work in this area resided in our observations that the 11-bromo stereoisomeric mixture could not only be obtained from the 11,21-dibromo structures by the selective dehalogenation procedure devised by Julian and Karpel,[3a] but also the 11-bromo isomers could be readily separated by fractional crystallization. Although this is the subject matter of a later communication, it should be mentioned here that the 53% yield of isolable 3α,17α-dihydroxy-21-bromopregnane-12,20-dione 3-acetate (IX) is excellent in view of the fact that the debromination of mother liquors serves to regenerate most of the starting material.

Both the hydrolysis of IX to X and the conversion of X into XI proceed in excellent yield. The oxidation of XI with NBS in *t*-butyl alcohol and pyridine[14] resulted in a 91% yield of XII. The alternative route from X to XII *via* XVI was not as good, undoubtedly owing to the possibly disturbing reaction of the 21-bromo derivative with pyridine. Nevertheless, XVI could be isolated and characterized.

The introduction of the 4,5-double bond into

(5) The bromination of 17α-hydroxypregnan-20-ones at C_{21}, followed by treatment with potassium acetate for completing the introduction of the dihydroxyacetone side chain, was first reported almost simultaneously by Julian, *et al.*,[4a] and by Koechlin, Garmaise, Kritchevsky and Gallagher, THIS JOURNAL, **71**, 3263 (1949).

(6) (a) (Mrs.) W. J. Adams, D. K. Patel, V. Petrow and (Mrs.) I. A. Stuart-Webb, *J. Chem. Soc.*, 1825 (1954); (b) (Mrs.) W. J. Adams, D. K. Patel and V. Petrow, *ibid.*, 4688 (1954).

(7) B. A. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 562 (1944).

(8) A. Faworski, *J. Russ. Phys. Chem. Soc.*, **44**, 1358 (1913); *cf.* also A. Faworski, *J. prakt. Chem.*, [2] **88**, 641 (1914).

(9) It is odd that Koechlin and Reichstein even isolated a small amount of the Faworski rearrangement acid, expected from the 17,21-dibromopregnanone, in view of the successful application of the rearrangement by Wagner and Moore (THIS JOURNAL, **71**, 4160 (1949)) to 3β-hydroxy-17,21,21-tribromopregnan-20-one to yield 3β-hydroxy-20-bromo-17-pregnen-21-oic acid.

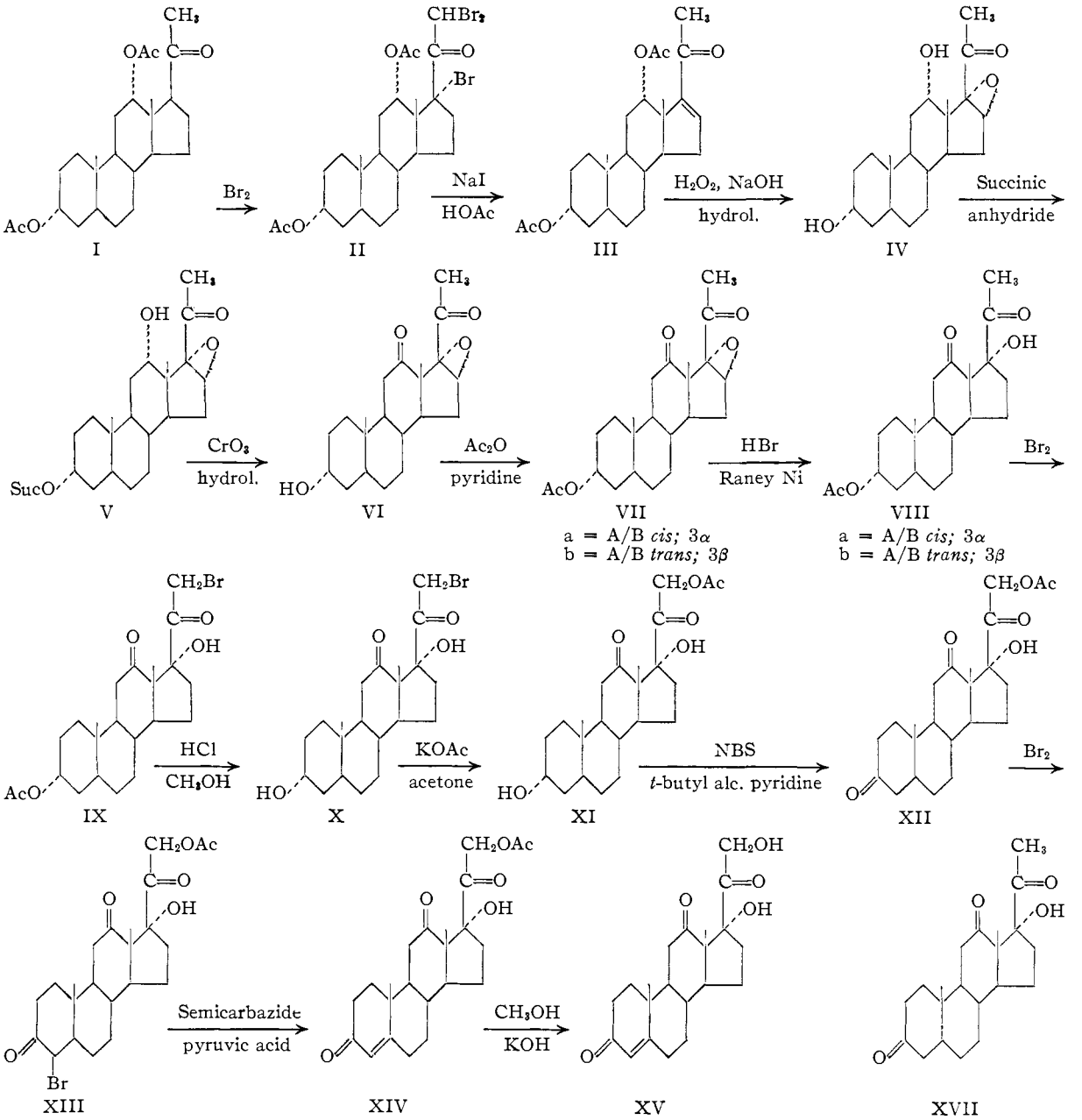
(10) Among others see J. Pataki, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 5615 (1952); L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, *ibid.*, **75**, 4110 (1953); **76**, 5104 (1954); *cf.* J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **36**, 1241 (1953).

(11) E. S. Rothman and M. E. Wall, THIS JOURNAL, **77**, 2229 (1955).

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

(13) We are indebted to Dr. B. A. Hems of Glaxo Laboratories, Ltd., for a generous supply of 3β-acetoxy-16-allopregnene-12,20-dione.

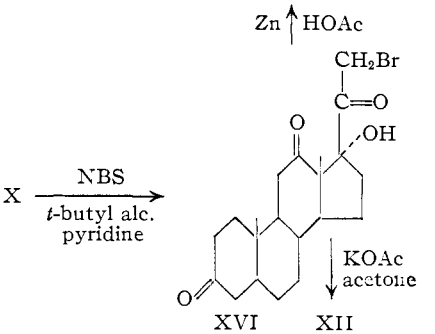
(14) *Cf.* L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **71**, 3935 (1949); **73**, 118 (1951).



XII was straightforward and followed the now classical procedure of Gallagher, *et al.*[15] Hydrolysis of the resulting XIV to XV offered no difficulties.

Experimental[16]

3α,12α-Diacetoxy-17,21,21-tribromopregnan-20-one (II). To 62.7 g. of 3α,12α-diacetoxypregnan-20-one (I) in 750 cc. of glacial acetic acid at 22°, 74 g. of bromine in 225 cc. of glacial acetic acid was gradually added. At the outset the bromination was catalyzed by addition of 2 cc. of 32% HBr in glacial acetic acid. After bromination started, the temperature of the reaction mixture was lowered to 15°, and after all bromine had been added, the mixture was let stand 1.5 hr. at room temperature. The reaction mixture was poured into 3 l. of cold water and filtered. The filtered cake was taken up in 1.5 l. of alcohol-free ether, the ether solution washed with water, with 3% sodium carbonate solution and finally with water to neutrality. The ether solution was then concentrated to a crystalline slush, 50 cc. of petroleum ether (b.p. 35–60°) was added and the crystals filtered and washed with 125 cc. of a 50-50 ether–petroleum ether mixture. The yield was 70.5 g., m.p. 172–173° dec.



(15) B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **184**, 393 (1950).

(16) All melting points are uncorrected. Analyses by Micro-Tech Laboratories, Skokie, Illinois.

A second crop of 4.3 g., m.p. 169–173°, was obtained, making a total yield of 75% of theory. The analytical sample was recrystallized from absolute ether, m.p. 175–176°. *Anal.* Calcd. for $C_{26}H_{35}O_5Br_3$: C, 45.82; H, 5.38; Br, 36.6. Found: C, 46.12; H, 5.39; Br, 36.4.

3α,12α-Diacetoxy-16-pregnen-20-one (III).—The crude tribromopregnan-20-one (II) (dried filter cake) from 86.3 g. of I above, in 1 l. of glacial acetic acid was added to a solution of 160 g. of sodium iodide in 1 l. of acetic acid and refluxed for 1.5 hr. The cooled mixture was diluted with water and extracted with ether. Successive washings of the ethereal extract with water, dilute sodium thiosulfate, 2% sodium carbonate and water to neutrality, followed by drying and concentration to a crystalline slush afforded 46.1 g. (55% based upon I) of 3α,12α-diacetoxy-16-pregnen-20-one, m.p. 188–192°. A second crop of 8.4 g., m.p. 165–175°, was obtained by concentration of the mother liquor. Since most of the remaining material is crystalline, it is probable that hydrogenation of the second crop and the mother liquors will give good recovery of starting material I. This has not been investigated.

Repeated recrystallization of the first crop material from ether gave colorless prisms, m.p. 199–201°, shrinking at 194°; $[\alpha]^{25}D$ +134.0° (1.0% in $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 238 mμ; E 10900 (lit.[17] reports m.p. 193–193.5°; λ_{max}^{alc} 238 mμ; E 11700; $[\alpha]^{25}D$ +113°). *Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 72.08; H, 8.71. Found: C, 71.94; H, 8.64.

3α,12α-Dihydroxy-16α,17α-epoxypregnan-20-one (IV).—Forty-six g. of 3α,12α-diacetoxy-16-pregnen-20-one was dissolved in 1500 cc. of methanol and chilled to 10°. The solution was treated with 92 cc. of 4 *N* sodium hydroxide and then with 185 cc. of 30% hydrogen peroxide, maintaining a temperature of 15–20°. After 18 hours at room temperature, the mixture was cold concentrated to a volume of 700 cc. After dilution with water, extraction with ether and successive washings with dilute sulfate, water, dilute permanganate and water, the dried extract was concentrated to a sirup and refluxed 2 hr. with 500 cc. of methanol containing 21 g. of potassium hydroxide. Concentration to 150-cc. volume and addition of water to turbidity afforded 34.8 g. (90%) of colorless needles, m.p. 203–204°; $[\alpha]^{25}D$ +83.7° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.19; H, 9.45.

3α,12α-Dihydroxy-16α,17α-epoxypregnan-20-one 3-Hemisuccinate (V).—A suspension of 20 g. of 3α,12α-dihydroxy-16α,17α-epoxypregnan-20-one (IV) in 100 cc. of carbon tetrachloride was distilled until 20 cc. of solvent had been removed. Ten grams of succinic anhydride and 20 cc. of dry pyridine were added and the mixture refluxed for 3 hr. The resultant orange solution was concentrated *in vacuo* to a sirup and extracted with ether. The extract was washed with dilute hydrochloric acid and the 3-hemisuccinate extracted with 10% sodium carbonate solution and acidified. Crystallization from ether yielded 15.6 g. (55%), m.p. 166–168°. Recrystallization from ether raised the melting point to 173–174°; $[\alpha]^{25}D$ +82.3° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{25}H_{37}O_7$: C, 66.79; H, 8.23. Found: C, 66.81; H, 8.25.

Hydrolysis of the mother liquor combined with the neutral extract gave 7.1 g. (35.5%) of recovered starting material IV.

16α,17α-Epoxypregnan-3α-ol-12,20-dione (VI).—A solution of 22.5 g. of 3α,12α-dihydroxy-16α,17α-epoxypregnan-20-one 3-hemisuccinate (V) in 225 cc. of glacial acetic acid was cooled to 20° and a solution of 5 g. of chromium trioxide in 10 cc. of water and 50 cc. of acetic acid added. The temperature was maintained at 20–25° for 2 hr. After pouring into 1 l. of cold water, the filtered solid was hydrolyzed by refluxing for 2 hr. in 200 cc. of 10% methanolic potassium hydroxide containing 10 cc. of water. Filtration through a pad of filter aid and addition of 800 cc. of cold water gave 13.6 g. (78%) of 16α,17α-epoxypregnan-3α-ol-12,20-dione, m.p. 223–226°. Recrystallization from methylene chloride–ether gave colorless plates, m.p. 224–225°; $[\alpha]^{25}D$ +145.8° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.23; H, 8.72.

(17) C. Djerassi and C. Scholz, *J. Org. Chem.*, **14**, 660 (1949). Numerous preparations of this compound and numerous recrystallizations gave material that always showed definite shrinking consistently at 194° but did not melt until 199–201°. The optical rotation has also been checked on numerous samples.

3α-Acetoxy-16α,17α-epoxypregnane-12,20-dione (VIIa).—A mixture of 13.6 g. of 16α,17α-epoxypregnan-3α-ol-12,20-dione (VI), 40 cc. of acetic anhydride and 55 cc. of pyridine was warmed on the steam-bath to effect solution. After 18 hr. at room temperature, it was concentrated *in vacuo* to a sirup and extracted with ether. The extract was washed with dilute hydrochloric acid and water to neutrality. After drying with sodium sulfate and concentration to a crystalline slush, there was obtained 15.1 g. (99%), m.p. 213–215°, of the 3-acetate. Recrystallization from methanol raised the melting point to 215–216°; $[\alpha]^{25}D$ +158° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.49; H, 8.70.

3α,17α-Dihydroxypregnane-12,20-dione 3-Acetate (VIIIa). To a solution of 16.5 g. of 3α-acetoxy-16α,17α-epoxypregnane-12,20-dione in 165 cc. of methylene chloride cooled to 15°, 17 cc. of 32% hydrogen bromide in acetic acid was added. The resultant dark brown solution was held at room temperature for 2 hr. and washed to neutrality with water. After removal of the solvent, under diminished pressure, the residue was dissolved in 400 cc. of methanol containing 15 cc. water, 85 g. of Raney nickel added and the mixture refluxed for 4 hr. The Raney nickel was prepared from commercial Raney nickel[18] (slurry) by neutralizing with acetic acid and washing by decantation three times with water, then with methanol and storing under methanol. The weight of Raney nickel used is the difference in weight between a given volume of methanol slurry of the nickel and the same volume of pure methanol. Cautious filtering and drying (to constant weight) of a methanol slurry of the nickel showed that the actual weight of dry Raney nickel is almost exactly equal to that obtained by the weighing by difference in methanol recorded above. Thus, the 85 g. employed represented for all practical purposes actually that weight of dry catalyst. The hot methanolic suspension was filtered through filter aid and concentrated to turbidity. Ether extraction, water washing and drying yielded, after crystallization from ether–petroleum ether, 15.7 g. (94.6%) of 3α,17α-dihydroxypregnane-12,20-dione 3-acetate, m.p. 165–166°. Recrystallization from acetone gave colorless plates, m.p. 167–169°; $[\alpha]^{25}D$ +99° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.80; H, 8.78. Found: C, 70.47; H, 8.83.

16α,17α-Epoxyallopregnan-3β-ol-12,20-dione 3-Acetate (VIIb).—To a solution of 18.62 g. (0.05 mole) of 3β-acetoxy-16-allopregnene-12,20-dione,[13] m.p. 176–178°, in 85 cc. of chloroform and 215 cc. of methanol cooled to 5°, 46.5 cc. of 27.5% hydrogen peroxide was added. After the addition of the peroxide, 28 cc. of 5 *N* sodium hydroxide was added over a period of 1 hr., keeping the temperature of the reaction below 15°. The resulting solution was then allowed to stand overnight at room temperature. It was then watered out, extracted with chloroform, the chloroform solution washed until neutral and concentrated to dryness *in vacuo*. The resulting solid was then dissolved in 16 cc. of pyridine and treated with 8 cc. of acetic anhydride for 30 minutes at steam-bath temperature. After cooling to room temperature, the solution was carefully watered out. After filtering, 18.17 g. of material, m.p. 229–233°, was obtained. Recrystallization from chloroform–ether raised the melting point to 234–235°, and the product was identical with that previously described in the literature.[11,12]

Allopregnane-3β,17α-diol-12,20-dione 3-Acetate (VIIIb).—Six ml. of 30% hydrogen bromide in acetic acid was added to a solution of 5.5 g. (0.014 mole) of 16α,17α-epoxyallopregnan-3β-ol-12,20-dione 3-acetate, m.p. 229–233°, in 55 cc. of methylene chloride cooled to 15°. The resultant solution was held at room temperature for 2 hr. and then washed with water until neutral. After removal of the solvent with gentle warming under reduced pressure, the crystalline residue was dissolved in 135 cc. of methanol containing 5 cc. of water, and 28.4 g. of Raney nickel (prepared as indicated above) was added. The resulting mixture was refluxed under agitation for 4 hr. The hot methanolic suspension was filtered through filter aid, concentrated to turbidity and extracted with ether. After water washing, drying and concentrating the solution, crystallization from ether–petroleum ether yielded in two crops, 4.97 g. (90%) of allopregnane-3β,17α-diol-12,20-dione 3-acetate, m.p. 129–131°.

(18) Purchased from Raney Catalyst Company, Chattanooga, Tennessee.

3-α-Acetoxy-17α-hydroxy-21-bromopregnane-12,20-dione (IX).—A solution of 11.7 g. of 3α,17α-dihydroxypregnane-12,20-dione 3-acetate (VIIIa) in 200 cc. of chloroform, to which 30 cc. of chloroform saturated with hydrogen bromide had been added, was cooled to 0°. At this temperature the solution was brominated with 4.8 g. of bromine in 50 cc. of chloroform over 45 minutes. After warming to room temperature, the solution was washed with sodium bicarbonate and water and concentrated *in vacuo* to a sirup. Crystallization from methylene chloride–methanol gave 12.3 g. of crystalline material, m.p. 165–181°. Several recrystallizations from methylene chloride–methanol yielded material of melting point 184–186° (53%). The analytical sample, crystallized again from methylene chloride–methanol as colorless prisms, m.p. 185–186°; $[\alpha]^{25}D$ +100° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{33}O_5Br$: C, 58.85; H, 7.09; Br, 17.01. Found: C, 59.33; H, 7.49; Br, 16.90.

During the recrystallizations, there was isolated 840 mg. (5%) of a crystalline dibromide. Debromination of the mother liquors gave 3.4 g. (29%) of starting material (VIIIa).

3α,17α-Dihydroxy-21-bromopregnane-12,20-dione (X).—A suspension of 7.5 g. of 3α-acetoxy-17α-hydroxy-21-bromopregnane-12,20-dione (IX) in 115 cc. of 3.5% methanolic hydrogen chloride was stirred at room temperature for 2 hr. After an additional hour at room temperature, the solution was diluted with water and extracted with methylene chloride. Concentration and crystallization from ether yielded 6.97 g. of solvated material, m.p. 90–100° (effervescence), resolidified and melted at 152–157° dec. A second crop of 460 mg. was obtained. A 1-g. sample, after drying *in vacuo* for 2 hr. at 100°, lost 13.7% of its weight (theory for one mole of ether of solvation, 15.9%), and melted at 153–157°. *Anal.* Calcd. for $C_{21}H_{31}O_4Br$: Br, 15.96. Found: Br, 16.30.

3α,17α,21-Trihydroxypregnane-12,20-dione 21-Acetate (XI).—A mixture of 5 g. of 3α,17α-dihydroxy-21-bromopregnane-12,20-dione (X), 10 g. of anhydrous potassium acetate and 80 cc. of alcohol-free acetone was stirred and refluxed for 18 hr. After dilution with water, extraction with ether and drying, crystallization from ether–petroleum ether yielded 3.67 g. (90%) of the 21-acetate, m.p. 180–184°. The material was slightly contaminated with halogen. Debromination with zinc–acetic acid and crystallization from methylene chloride–ether–petroleum ether elevated the melting point to 187–188°; $[\alpha]^{25}D$ +68° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.65; H, 8.56.

17α-Hydroxy-21-acetoxypregnane-3,12,20-trione (XII).—To a solution of 11.3 g. of 3α,17α-dihydroxy-21-acetoxypregnane-12,20-dione (XI) in 60 cc. of methylene chloride, 165 cc. of *t*-butyl alcohol and 10 cc. of pyridine, 9.25 g. (1.75 equivalents) of finely pulverized N-bromosuccinimide was added. After 18 hr. at room temperature in the dark, the orange colored solution was diluted with water, extracted with methylene chloride and washed successively with bisulfite, dilute hydrochloric acid and water to neutrality. Concentration and crystallization from ether–petroleum ether gave 8.95 g., m.p. 153–156°. A second crop of 1.35 g., m.p. 147–150°, was obtained by concentration of the mother liquor, total 91%. The analytical sample after two recrystallizations from ether–petroleum ether had m.p. 158–160°; $[\alpha]^{25}D$ +87° (0.4% in acetone). *Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.13; H, 8.18.

4β-Bromo-17α-hydroxy-21-acetoxypregnane-3,12,20-trione (XIII).—Two ml. of a solution of 1.33 g. of bromine in 40 cc. of acetic acid were added to a solution of 3.35 g. of 17α-hydroxy-21-acetoxypregnane-3,12,20-trione in 100 cc. of acetic acid. After decolorization had occurred, the solution was chilled to incipient crystallization, and the remainder of the bromine solution, in which 610 mg. of anhydrous sodium acetate had been dissolved, was added over a period of 30 minutes. The solution was diluted with water and extracted with methylene chloride. After washing with sodium bicarbonate in the usual procedure, 2.44 g. (61%) of the 4β-bromo derivative, m.p. 150–154° dec., was obtained, $[\alpha]^{25}D$ +105° (0.5% in acetone). Reworking the mother liquor gave a second crop, 700 mg. (17.5%), m.p. 145–152° dec. *Anal.* Calcd. for $C_{23}H_{31}O_6Br$: Br, 16.56. Found: Br, 16.20.

Debromination of the mother liquor by warming with zinc in acetic acid for 15 minutes yielded 570 mg. (19%) of recovered starting material.

17α-Hydroxy-21-acetoxy-4-pregnene-3,12,20-trione (XV).—Six hundred and eighty milligrams of 4β-bromo-17α-hydroxy-21-acetoxypregnane-3,12,20-trione was dissolved in 8.5 cc. of methylene chloride and 20 cc. of *t*-butyl alcohol. To the solution, under a nitrogen atmosphere, there was added a mixture of 393 mg. of semicarbazide hydrochloride, 296 mg. of sodium bicarbonate and 0.7 cc. of water previously warmed until evolution of carbon dioxide was complete. An orange color developed, which disappeared after 1 hr.

A solution comprising 0.85 cc. of pyruvic acid, 7 cc. of acetic acid and 1.4 cc. of water was added. While maintaining the nitrogen atmosphere, the mixture was let stand overnight (16 hr.). After dilution with water and extraction with methylene chloride, the organic layer was washed with bicarbonate and water and concentrated to crystallization from methylene chloride–ether to yield 385 mg., m.p. 180–185°. A second crop of 30 mg. could be obtained from the mother liquor, total yield 73.5%. Several recrystallizations from methylene chloride–ether raised the melting point to 190–191°; $[\alpha]^{25}D$ +135° (0.4% in acetone); +117° (0.5% in $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 238 mμ, *E* 16,773. *Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.19; H, 7.82.

17α,21-Dihydroxy-4-pregnene-3,12,20-trione (XV).—A solution of 1.25 g. of 17α-hydroxy-21-acetoxy-4-pregnene-3,12-20-trione in 30 cc. of methanol was cooled to room temperature under nitrogen. Addition of 3.5 cc. of 0.4 *N* methanolic potassium hydroxide was made and the nitrogen atmosphere maintained for 10 minutes. After acidification with acetic acid, 800 mg. of colorless needles, m.p. 244–246° dec., separated on standing. An additional crop of 140 mg., m.p. 242–245° dec., was obtained from the mother liquor, after extraction with methylene chloride and concentration and crystallization from ether, total yield 87%. The analytical sample crystallized from ether as a hemihydrate, m.p. 244–245° dec.; $[\alpha]^{25}D$ +132° (0.5% in $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 239 mμ, *E* 16,846. *Anal.* Calcd. for $C_{21}H_{28}O_5 \cdot {}^1/_2H_2O$: C, 68.27; H, 7.91. Found: C, 68.33; H, 8.02.

17α-Hydroxy-21-bromopregnane-3,12,20-trione (XVI).—A solution of 4.3 g. of 3α,17α-dihydroxy-21-bromopregnane-12,20-dione in 33 cc. of methylene chloride, 100 cc. of *t*-butyl alcohol and 4 cc. of pyridine was cooled to 5° and 3.2 g. (1.75 equivalents) of N-bromosuccinimide added. After 18 hr. at room temperature in the dark, the brown colored mixture was diluted with water, extracted with methylene chloride and worked up in the usual manner with bisulfite, dilute hydrochloric acid and crystallized from acetone to give 1.72 g., m.p. 195–202° dec. Recrystallization from acetone gave prisms, m.p. 202–203° dec.; $[\alpha]^{25}D$ +79° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{29}O_4Br$: Br, 18.78. Found: Br, 18.70.

A 200-mg. sample, dehalogenated with zinc and acetic acid, afforded 125 mg. of a substance melting at 215–218° and giving no depression with an authentic sample of 17α-hydroxypregnane-3,12,20-trione (XVII) prepared as in the sequel.

17α-Hydroxypregnane-3,12,20-trione (XVII).—From 3 g. of 3α,17α-dihydroxypregnane-12,20-dione 3-acetate (VIIIa) 2.42 g. of 3α,17α-dihydroxypregnane-12,20-dione was first prepared by hydrolysis in a mixture of 50 cc. methanol and 4 cc. of acetyl chloride at room temperature for 2 hr. Recrystallized from acetone it melted at 173–174°; $[\alpha]^{25}D$ +84° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.25. Found: C, 72.22; H, 9.34.

One gram of this 3α,17α-dihydroxypregnane-12,20-dione was oxidized in a mixture of 25 cc. of *t*-butyl alcohol, 8 cc of methylene chloride, 1 cc. of pyridine and 900 mg. of NBS. Working up in the usual manner and crystallizing from methylene chloride–acetone afforded colorless prisms of 17α-hydroxypregnane-3,12,20-trione (XVII), m.p. 217–219°; $[\alpha]^{25}D$ +77° (0.5% in $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.41; H, 8.74.

Conversion of XVI into XII. (A) **Treatment with Potassium Acetate in Acetone.**—A mixture of 500 mg. of 17α-hydroxy-21-bromopregnane-3,12,20-trione, 20 cc. of acetone and 1 g. of potassium acetate was refluxed for 12 hr. Working up in the usual manner and crystallizing from ether–petroleum ether gave 370 mg. of the 21-acetate, m.p. 149–151°, which on recrystallization from ether–petroleum ether

melted at 158–160° and was identical with the product (XII) secured via NBS oxidation of XI.

(B) **Alkaline Hydrolysis and Acetylation.**—To a solution of 400 mg. of the 21-bromotrione XVI in 60 cc. of methanol and 30 cc. of water, 6.3 cc. of a 3.7% methanolic potassium hydroxide solution was added under nitrogen. The solution which immediately turned yellow, was held at room temperature for 8 minutes and then acidified with acetic acid. The solution was then taken to dryness *in vacuo*, extracted with methylene chloride, washed with water and evaporated to dryness. The residue was warmed on the steam-bath for a few minutes with 1 cc. of acetic anhydride and 2 cc. of pyridine and then let stand for 0.5 hr. Working up in the usual manner and crystallizing from ether–petroleum ether afforded 215 mg. of substance, m.p. 148–152°, which after recrystallization melted at 158–160° and proved identical with XII secured from the NBS oxidation.

FRANKLIN PARK, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

Steroidal Amines. III. 16α-Amino-Substituted Pregnanes[1]

BY DAVID GOULD, ELLIOT L. SHAPIRO, LAWRENCE E. FINCKENOR, FRED GRUEN AND E. B. HERSHBERG

RECEIVED JANUARY 13, 1956

5,16-Pregnadien-3β-ol-20-one (II) and its acetate were treated with unhindered primary and secondary amines in the presence of a basic catalyst. The products are substituted 16α-amino-5-pregnen-3β-ol-20-ones, some of which were also reduced to the corresponding 5-pregnene-3β,20-diols and allopregnanediols. The derivatives most closely resembling steroidal alkaloids such as rubijervine (I) do, in fact, have pharmacological properties similar to these alkaloids.

In the process of saponification of 5,16-pregnadien-3β-ol-20-one acetate with methanolic potassium hydroxide, the major product was not pregnadienolone but 16α-methoxy-5-pregnen-3β-ol-20-one.[2] It was thus apparent that the Δ^{16}-20-ketone system is favorable for base-catalyzed additions to the 16-carbon of nucleophilic reagents with an active hydrogen.

Marker had observed[3a] that Grignard reagents attacked pregnadienolone acetate at both the 16-carbon and the 20-carbonyl. With the more hindered reagents, the only isolable products were 16-alkyl-pregnenolones. Similarly the nucleophilic carbon of diazomethane attacks the 16-position.[3b]

Recently, Romo, *et al.*,[4] found confirmation of this indication in the addition of benzylmercaptan to give 16-thiobenzyl derivatives.

In an approach to synthetics similar to the various steroidal alkaloids, *e.g.*, rubijervine[5] (I), having an amino substituent at C_{16}, we investigated the addition of various amino compounds to 5,16-pregnadienolone (II) and its acetate, usually using basic catalysis.[6] When steric factors were not involved, the reaction proceeded readily and, under the proper conditions, more or less to completion, to give 16α-aminopregnenolones (III). The preferred conditions varied somewhat for different amines, apparently depending on their water solubility and base strength. The catalysts used were aqueous alkali, quaternary ammonium hydroxides and quaternary ammonium resin bases. In a typical reaction the amine with solvent was warmed to dissolve the steroid and stirred at room temperature overnight in the presence of the catalyst. When amines were used without catalysis, the reaction either did not occur or was less than 25% complete. The use of at least one mole of base permitted concomitant saponification of the 3-acetate, but a greater excess did not make any further difference.

It was found that primary alkyl and cycloalkyl amines added in the presence of strong base, while aniline did not add readily. Of the secondary amines, however, only dimethylamine and the cyclic amines, pyrrolidine, piperidine, morpholine and β- and γ-pipecoline added. Diethylamine reacted only slightly with the pregnadienolone as shown by the decreased ultraviolet absorption, but the product was not isolated. Similarly, α-pipecoline did not react well. It was apparent that there are notable steric limitations imposed on amines which can add. In addition to secondary alkylamines, it was found that primary amines attached to a tertiary carbon, *e.g.*, *t*-butylamine, would not add. Furthermore, primary amines on a secondary carbon added with difficulty or only partially. This was particularly so when the resin base was used as catalyst. Thus *sec*-butylamine would add only with the non-polymeric catalysts. The extent of reaction in the crude product was easily determined by an examination of the remaining ultraviolet absorption due to the α,β-unsaturated carbonyl of the unreacted starting material. The properties of the 16α-aminopregnenolones prepared are given in Table II. Many products crystallized as solvates and frequently the solvent could not be removed completely.

Since they could not be prepared directly by addition, some quaternary amines were prepared by alkylation of the corresponding secondary and tertiary amino steroids. Thus 16-benzylaminopregnenolone was converted to the benzyl dimethylammonium iodide with methyl iodide and sodium hydroxide, and the methylpiperidinium

(1) Presented in part before the 128th Meeting of the American Chemical Society, Minneapolis, Minn., Sept. 15, 1955. Paper I, see ref. 6; paper II, H. L. Herzog, C. Payne and E. B. Hershberg, THIS JOURNAL, **77**, 5324 (1955).

(2) (a) D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951); (b) D. Gould, F. Gruen and E. B. Hershberg, *ibid.*, **75**, 2510 (1953).

(3) (a) R. E. Marker and H. M. Crooks, Jr., *ibid.*, **64**, 1280 (1942); (b) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944); A. Sandoval, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 2383 (1951).

(4) J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *ibid.*, **73**, 1528 (1951).

(5) Y. Sato and W. A. Jacobs, *J. Biol. Chem.*, **179**, 623 (1949).

(6) A preliminary announcement by D. Gould, E. L. Shapiro and E. B. Hershberg appeared in THIS JOURNAL, **76**, 5567 (1954).