1 mol of ether of crystallization, as shown by its nmr spectrum. The 1,6-anhydropenta-*O*-benzoylmaltouronic acid (**9**) has mp 152–153°, $[\alpha]^{20}D$ +46° (*c* 0.4 chloroform).

Anal. Calcd for $C_{47}H_{36}O_{16}\cdot O(C_2H_5)_2$: C, 65.66; H, 5.19. Found: C, 65.98; H, 4.90.

Treatment of **9** with diazomethane in the usual fashion gave the methyl ester (**10**), mp 169–171°.

4-*O*-(Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate)-tetra-*O*-acetyl-β-D-glucose (11).—The crystalline acid **9** (3.5 g) was debenzoylated in 0.05 *N* sodium methoxide solution (60 ml) for 2 hr. The solution, after neutralization with Amberlite IR-120 exchange resin, was freed from methyl benzoate. The deacetylated product was heated at 95–100° in 0.5 *N* aqueous sulfuric acid for 12 hr. After neutralization with barum carbonate, and removal of cations by ion exchange, the product was isolated by chromatography over cellulose, using ethyl acetate–acetic acid–water (18:7:8) as the eluent to yield 650 mg (48%) of 4-*O*-α-D-glucopyranuronosyl-D-glucose (maltouronic acid), $[\alpha]^{20}D$ +115° (*c* 0.17, water). Dutton and Slessor[18] have reported $[\alpha]^{20}D$ +116° for this acid. The derived 4-*O*-(methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate)tetra-*O*-acetyl-β-D-glucose (**11**), prepared by esterification of maltouronic acid with diazomethane followed by acetylation with sodium acetate and acetic anhydride and crystallization from ethanol, had mp 199–200°, $[\alpha]^{20}D$ +71° (*c* 0.72 chloroform).

Anal. Calcd for $C_{27}H_{36}O_{19}$: C, 48.80; H, 5.46. Found: C, 48.95; H, 5.58.

1,2,3,4,2′,3′,4′-Hepta-*O*-acetyl-6′-*O*-tritylgentiobiose (12).—Gentiobiose (8 g) was tritylated in pyridine solution and then acetylated *in situ* as described in the preparation of **2**. The hepta-*O*-acetyl-6′-*O*-tritylgentiobiose (**12**) (12.5 g) obtained had $[\alpha]^{20}D$ +38° (*c* 1.5, chloroform). The nmr spectrum showed the presence of both anomeric acetates.

Anal. Calcd for $C_{45}H_{50}O_{18}$: C, 61.50; H, 5.73. Found: C, 61.66; H, 6.03.

1,2,3,4,2′,3′,4′-Hepta-*O*-acetylgentiobiose (13).—In order to remove the trityl group from **12** (9 g) it was dissolved in acetic acid (60 ml) and treated with 1 equiv of hydrogen bromide exactly as described in the preparation of **3**. After purification by silica gel chromatography as described for **3**, the pure 1,2,3,4,2′,3′,4′-hepta-*O*-acetylgentiobioise (**13**), was crystallized from ethanol yielding 5.4 g (83%): mp 162–167°; $[\alpha]^{20}D$ +24.7° (*c* 1.0 chloroform).

Anal. Calcd for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 49.01; H, 5.81.

6-*O*-(Methyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)-tetra-*O*-acetyl-β-D-glucopyranose (14).—Gentiobiose heptaacetate **13** (4 g), was dissolved in acetic acid (40 ml) and oxidized with potassium permanganate (2.7 g) exactly as described in the preparation of **4**. Direct esterification of the acid with diazomethane in ether gave 1.91 g (50%) of the desired 6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)tetra-*O*-acetyl-D-glucopyranose after purification by silica gel chromatography (benzene–ether, 1:2): mp 200–201° (after crystallization from methanol); $[\alpha]^{20}D$ −1.5° (*c* 1, chloroform).

Anal. Calcd for $C_{27}H_{36}O_{19}$: C, 48.80; H, 5.46. Found: C, 48.52; H, 5.36.

The above methyl ester, albeit crystalline, was still a mixture of anomeric acetates. It was therefore treated with hydrogen bromide, followed by silver acetate in benzene, as described for **5** to give 6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)tetra-*O*-acetyl-β-D-glucose (**14**), in 50% yield: mp 200–202°, $[\alpha]^{20}D$ −11° (*c* 0.1, chloroform).

Registry No.—**2**, 15811-22-0; **3**, 15811-23-1; **5**, 15811-24-2; **7**, 15811-25-3; **8**, 15811-26-4; **9**, 15811-27-5; **10**, 15856-56-1; **11**, 4079-39-4; **12**, 15811-29-7; **13**, 15811-30-0; **14**, 15811-31-1.

Acknowledgment.—We wish to thank Mr. H. W. Diehl for assistance in the preparation of β-isomaltose octaacetate.

The Synthesis of 18,19-Dioxygenated Steroids by Intramolecular Radical Processes[1]

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Received October 10, 1967

By the application of known methods, especially intramolecular substitution reactions, pregnenolone has been converted into 18,19,20α- and 18,19,20β-trihydroxypregn-4-en-3-one. These compounds are possible metabolites from the perfusion of adrenal glands with progesterone.

The ability of adrenal tissue to oxygenate steroids at the angular methyl groups (C-18 and C-19) is well known.[2] Steroids functionalized at either of these positions have been isolated from adrenal tissue[2a–d] or formed by the action of adrenal preparations on exogenous steroidal substrates.[2e–g] These substances have been of considerable interest as a result of their intrinsic biological activity (aldosterone, for instance), their role in hormone biosynthesis (19-hydroxy steroids), and the chemical challenge inherent in their preparation. This challenge has been met by the development of several methods[3] for the selective functionalization of "unactivated" carbon atoms.

Although steroids substituted at either C-18 or C-19 are well known and now, for the most part, easily available, the occurrence of steroids functionalized at *both* angular methyls has not yet been reported. (Allusion has been made to functionalization at C-18 of a 19-substituted steroid. The nature of the products was not disclosed.[3g]) We now report the synthesis of the isomeric 18,19-disubstituted pregnanetriols **1a** and **1b**. This synthesis was undertaken as a portion of our continuing program of synthesis of 18- and 19-substituted steroids[4] and to provide standard materials for a program of adrenal perfusion. Compound

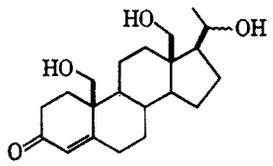
(1) Contribution No. 39 from the Research Institute for Medicine and Chemistry. For No. 38, see M. M. Pechet and H. F. Kohler, *J. Clin. Invest.*, in press. A preliminary description of this work was presented at the 149th National Meeting of the American Chemical Society, Chicago, April 1965, Abstract, p 4N.

(2) (a) S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. von Euw, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, **37**, 1163 (1954); (b) R. Neher and A. Wettstein, *ibid.*, **39**, 2062 (1956); (c) R. Neher, *Folia Endocrinologia* (Pisa), **8**, 55 (1960); (d) F. G. Peron, *Endocrinology*, **69**, 39 (1961); (e) H. Levy and S. Kushinsky, *Arch. Biochem. Biophys.*, **55**, 290 (1955); (f) P. S. Chen, H. P. Schedl, G. Rosenfeld, and F. C. Bartter, *Proc. Soc. Exptl. Biol. Med.*, **97**, 683 (1958); (g) F. G. Peron, *Endocrinology*, **70**, 386 (1962).

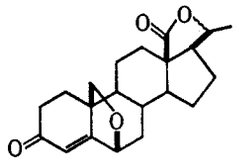
(3) (a) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, **82**, 2640 (1960); (b) P. Buchschacher, M. Cereghetti, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **42**, 2122 (1959); (c) G. Cainelli, M. L. Mihailovic, D. Arigoni, and O. Jeger, *ibid.*, **42**, 1124 (1959); (d) Ch. Meystre, K. Heusler, J. Kalvoda, P. Weiland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961); (e) E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.*, **80**, 2903 (1958); (f) M. Akhtar, *Advan. Photochem.*, **2**, 263 (1964); (g) K. Heusler and J. Kalvoda, *Angew. Chem. Intern. Ed. Engl.*, **3**, 525 (1964).

(4) R. H. Hesse and M. M. Pechet, *J. Org. Chem.*, **30**, 1723 (1965).

1 was chosen as a synthetic goal, since, in our experience, C-20-reduced metabolites are often isolated after lengthy perfusion of the adrenal gland.[5]

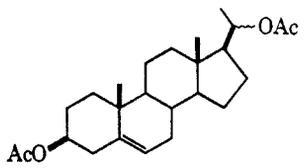


1a, 20α OH
b, 20β OH

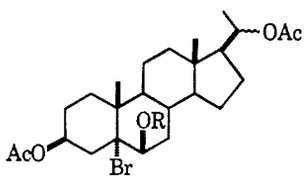


2a, 20α
b, 20β

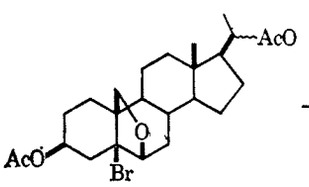
Scheme I



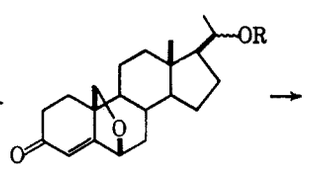
3a, 20α
b, 20β



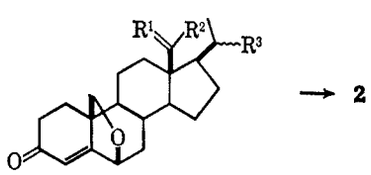
4a, 20α, R = H
b, 20β, R = H
5, 20β, R = NO



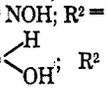
6a, 20α
b, 20β

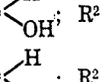


7a, 20α, R = Ac
b, 20β, R = Ac
8a, 20α, R = H
b, 20β, R = H
9a, 20α, R = NO
b, 20β, R = NO



10a, 20α, R′ = NOH; R² = H; R³ = OH
b, 20β, R′ = NOH; R² = H; R³ = OH

11a, 20α, R′ =  ; R² + R³ = –O⁻

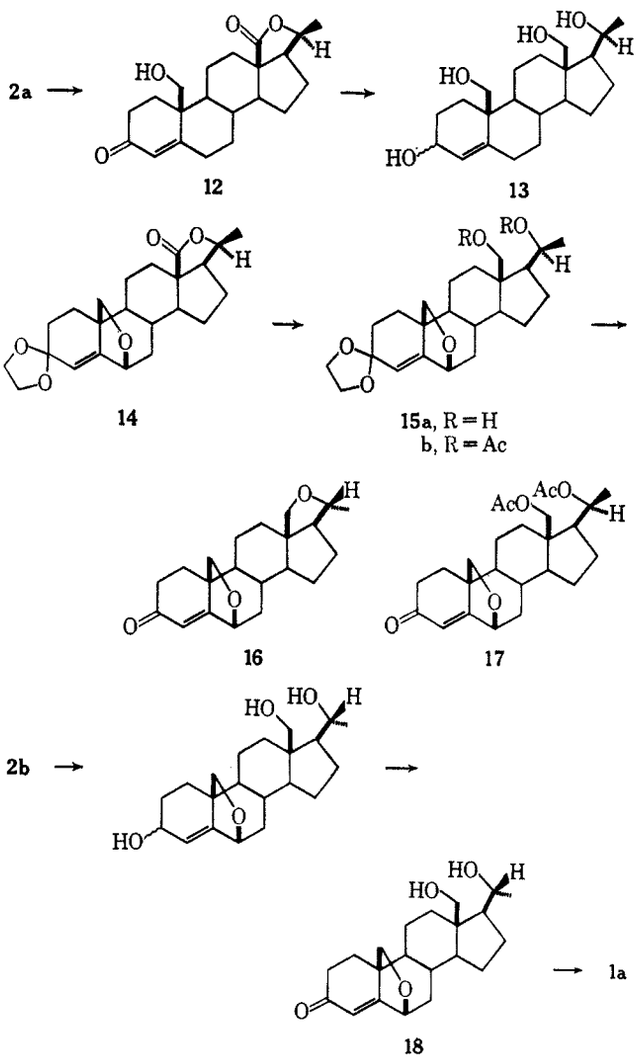
b, 20β, R′ =  ; R² + R³ = –O⁻

The key intermediate in each series was the corresponding 6,19-oxido-20-18-lactone 2, which contains the requisite Δ⁴-3-keto system as well as potential hydroxyl groups at 18, 19, and 20. This compound was prepared from the readily available diacetates **3a** and **3b**[6] by the application of methods developed in these and other laboratories. Reaction of the diacetate 3 with hypobromous acid[7] gave the bromo alcohol 4, which on irradiation in the presence of lead tetraacetate and iodine[3d] was converted into the epoxide 6 (Scheme I). The same epoxide was readily prepared by irradiation of the nitrite 5 in the presence of iodine.[8] Controlled saponification of 6 to remove the 3-acetate, followed by oxidation and β elimination,[7b] gave the Δ⁴-3-keto compound 7. Alkaline hydrolysis of 7 gave the alcohol 8, which on treatment with nitrosyl chloride afforded the nitrite 9. Irradiation[3a] of 9 afforded the oxime 10, which was treated with nitrous acid[9] to give the hemiacetal 11. This compound was, without isolation, oxidized with chromium trioxide in acetone[10] to give the desired intermediate 2.

It now remained to adjust the oxidation level of the substituents at C-6 and C-18. It is at this point that the synthesis of the isomeric triols **1a** and **1b** diverged.

Treatment of the oxidolactone **2a** with zinc and acetic acid[7b] gave the 19-hydroxy compound 12 (Scheme II). Reduction of this gave a material,

Scheme II



12
13
14
15a, R = H
b, R = Ac
16
17
18

(5) We attribute this to reductases present in the blood used for perfusion; *cf.* R. V. Short, *J. Endocrinology* (London), **16**, 415 (1958).

(6) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(7) (a) Y. Ueno, *J. Pharm. Soc.* (Japan), **72**, 1622 (1952); (b) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964).

(8) M. Akhtar, D. H. R. Barton, and P. G. Sammes, *ibid.*, **86**, 265 (1964); **87**, 4601 (1965).

(9) S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman, *J. Chem. Soc.*, 4614 (1958).

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 39 (1946).

presumably the tetrol **13**, which was difficult to isolate and purify because of inconvenient solubility properties. Oxidation of **13** with manganese dioxide[11] might have been expected to afford the desired triol **1a**. In practice, however, the reaction was extremely sluggish, and this approach was abandoned when it was found that model 3,19-dihydroxy-Δ^4 steroids were incompletely and only with great difficulty oxidized by manganese dioxide. As an alternative, **2a** was converted into the cyclic ethylene ketal **14** and reduced with lithium aluminum hydride to give the diol **15a**. Treatment of **15a** with toluene-*p*-sulfonic acid removed the protecting group but apparently effected a concomitant cyclodehydration to give a nonhydroxylic compound formulated as **16**. The diacetate **15b**, however, underwent an uncomplicated deketalization to give the Δ^4-3-keto diacetate **17**, which on treatment with zinc and acetic acid gave the 18,21-diacetate of the desired triol **1a**. Hydrolysis under mild conditions proceeded cleanly to give the unprotected triol **1a**.

The observation in these laboratories that 3-hydroxy-Δ^4-6,19-oxido steroids are slowly[12,13] but cleanly converted into the 3-keto compounds by dichlorodicyanoquinone (DDQ)[14] made it possible to shorten this somewhat circuitous route (*vide supra*) during the preparation of the remaining triol **1b**. Reduction of the appropriate oxidolactone **2b** with lithium aluminum hydride gave a mixture of triols, which on oxidation with DDQ afforded the oxidodiol **18**. Happily, this compound was stable to acetic acid (*vide supra*) and upon reduction with zinc in that medium gave the desired triol **1b**.

Experimental Section

All melting points were obtained on the Kofler hot stage. Optical rotations are reported for 0.5–1% solutions in chloroform unless otherwise stated. Microanalyses were performed in the laboratories of Dr. Alfred Bernhardt, Max Planck Institute, Mülheim (Ruhr), Germany. All compounds had appropriate and unexceptional infrared spectra.

5α-Bromopregnane-3β,6β,20α-triol 3,20-Diacetate (4a).—A stirred solution of 3β,20α-dihydroxypregn-5-ene 3,20-diacetate (**3a**) (1 g) in dioxane (12 ml) containing aqueous perchloric acid (0.5 ml, 3%) was treated with N-bromoacetamide (950 mg, added in three portions at 10-min intervals). The reaction mixture was stirred for a further 30 min in the dark and then poured into ice water and treated with aqueous sodium sulfite (10%). The product was extracted into methylene chloride, which was then washed with sodium bicarbonate and water, dried, and concentrated *in vacuo*. Crystallization from petroleum ether (bp 30–40°) and methylene chloride gave the title compound (500 mg), mp 160–166°. The analytical specimen had mp 160–166°, $[\alpha]D$ −49.5°.

Anal. Calcd for $C_{25}H_{39}O_5Br$: C, 60.12; H, 7.81; O, 16.03; Br, 16.04. Found: C, 60.24; H, 7.62; O, 15.94; Br, 16.14.

5α-Bromopregnane-3β,20α-diol 6β,19-Epoxide 3,20-Diacetate (6a).—A stirred solution of the bromohydrin **4a** (1 g) in dry benzene (75 ml) containing lead tetraacetate (2.5 g) and iodine (1.14 g) was irradiated for 17.5 hr using a 200-W lamp. After irradiation, the mixture was poured into water and the product extracted into ether. The organic extract was washed with aqueous sodium thiosulfate (10%) and water, dried, and evaporated to dryness. The title compound **6a** was crystallized from methanol (730 mg), mp 193–205°. The analytical sample had mp 203.5–206°, $[\alpha]D$ −7.5°.

Anal. Calcd for $C_{25}H_{37}O_5Br$: C, 60.36; H, 7.46; O, 16.10. Found: C, 60.36; H, 7.69; O, 16.33.

5α-Bromopregnane-3β,20α-diol 6β,19-Oxide 20-Acetate.—A solution of the 3,20-diacetate **6a** (7.6 g) in ethanol–water (3.9 l., 3:1) containing sodium hydroxide (630 mg) and methanol (63 ml) was allowed to stand at 5° for 16 hr. After the addition of acetic acid, the mixture was concentrated to dryness *in vacuo*, partitioned between methylene chloride and water, and the organic phase filtered and taken to dryness. The residual solid was recrystallized from cyclohexane–methylene chloride to give the title compound in two crops: (i) 3 g, mp 198–204°, and (ii) 2.3 g, mp 192–204°. The analytical sample had mp 202–206°, $[\alpha]D$ −10°.

Anal. Calcd for $C_{23}H_{35}O_4Br$: C, 60.66; H, 7.69; O, 14.07; Br, 17.78. Found: C, 60.68; H, 7.67; O, 14.11; Br, 17.70.

20α-Hydroxypregn-4-en-3-one 6β,19-Oxide 20-Acetate (7a).—A solution of 5α-bromopregnan-3β,20α-diol 6β,19-oxide 20-acetate (5.3 g) in acetone (300 ml) was treated with an excess of Jones reagent.[10] After 5 min, the excess oxidant was decomposed with methanol and the mixture partitioned between methylene chloride and half-saturated salt solution. After the usual work-up, a crude product was obtained which was dissolved in a solution of potassium acetate in methanol (500 ml) and heated under reflux for 0.5 hr. The solution was cooled, taken to dryness, and the residue partitioned between methylene chloride and water. The organic layer was worked up as usual to afford the title compound **7a** in two crops: (i) 1.4 g, mp 133–138°, and (ii) 2.7 g, mp 132–138°. The analytical sample crystallized from methanol had mp 142–143°, $[\alpha]D$ −107°, λ_{max}^{MeOH} 239 mμ (ε 13,900).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.19; H, 8.60; O, 17.20. Found: C, 73.83; H, 8.55; O, 17.33.

20α-Hyroxypregn-4-en-3-one 6,19-Oxide (8a).—A solution of the 20-acetate **7a** (3.6 g) in methanol (175 ml) containing potassium hydroxide (5 g) was allowed to stand at room temperature for 2.5 hr. The mixture was then concentrated *in vacuo* at 50° and partitioned between methylene chloride and water. The usual work-up afforded the title compound **8a**, which crystallized from cyclohexane–methylene chloride (2.4 g), mp 146–151°. The analytical sample had mp 154–155°, $[\alpha]D$ −110°, λ_{max}^{MeOH} 240 mμ (ε 13,500).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.36; H, 9.09. Found: C, 76.26; H, 9.18.

20α-Hydroxypregn-4-en-3-on-18-oic Acid 6β,19-Oxide 20→18-Lactone (2a).—A solution of the 20-hydroxy compound **8a** (500 mg) in pyridine (15 ml) was treated with an excess of nitrosyl chloride. The solution was then poured into ice water and extracted with methylene chloride. The organic extract was washed exhaustively with water, filtered, and taken to dryness to afford the 20-nitrite **9a** as a crystalline solid. This compound was not further characterized but was processed immediately as below.

The crude nitrite **9a** was dissolved in dry toluene and irradiated (200-W lamp) at room temperature for 2 hr. The solvent was then removed and the crude product redissolved in acetic acid (68 ml) and water (12 ml). The solution was heated to 70° and treated with sodium nitrite (500 mg) for 2 min. Ice was then added and the mixture partitioned between half-saturated salt solution and methylene chloride. The organic phase was washed with saturated sodium bicarbonate, dried, and concentrated to dryness. The crude hemiacetal **11a** was then dissolved in acetone (80 ml) and treated with an excess of Jones reagent.[10] After 5 min, the excess oxidant was decomposed with methanol and the reaction mixture partitioned between methylene chloride and water. After the usual work-up, the product **2a** was obtained from methanol (176 mg), mp 230–285°. An analytical specimen had mp 282–288° (crystal change at 250°), $[\alpha]D$ −129°, λ_{max}^{MeOH} 237.5 mμ (ε 14,900).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.68; H, 7.60. Found: C, 73.89; H, 7.75.

5α-Bromopregnane-3β,6β,20β-triol 3,20-Diacetate (4b).—A solution of 3β,20β-dihydroxypregn-5-ene 3,20-diacetate (**3b**, 1 g) in dioxane (12 ml) containing perchloric acid (0.5 ml as above) was treated with N-bromoacetamide (950 mg, added in four portions at 10-min intervals). The reaction mixture was stirred at room temperature for an additional 30 min and then worked up as above to afford the title compound **4b** which was crystallized

(11) F. Sondheimer and G. Rosenkranz, *Experientia*, **9**, 62 (1953).

(12) The reaction carried out in *t*-butyl alcohol was incomplete after 24 hr; compare with ref 13.

(13) S. H. Burstein and H. J. Ringold, *J. Amer. Chem. Soc.*, **86**, 4952 (1964).

(14) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Lett.*, No. 9, 14 (1960).

from cyclohexane–methylene chloride (570 mg): mp 162–165°; $[\alpha]D$ −23.1° (lit.[15] mp 163–164°; $[\alpha]D$ −23°).

5α-Bromopregnane-3β,20β-diol 6,19-Oxide 3,20-Diacetate (6b).—A stirred solution of the bromohydrin **4b** (1 g) in dry benzene (77 ml) containing iodine (1.2 g) and lead tetraacetate (2.5 g) was irradiated (200-W lamp) overnight at room temperature. After the usual work-up (*vide supra*), the title compound **6b** was obtained from methanol (500 mg): mp 169.5–171.5°, $[\alpha]D$ +20.8° (lit.[15] mp 164–165°, $[\alpha]D$ +21°).

Alternate Preparation of 6b.—A solution of the bromohydrin **4b** (1 g) in pyridine (25 ml) was treated with excess nitrosyl chloride at 0°. Ice was added to decompose excess nitrosyl chloride. On dilution of the reaction mixture with water the nitrite separated as a solid. It was collected, washed with water, dissolved in benzene (500 ml), and the solution dried over sodium sulfate. Iodine (0.24 g) and pyridine (0.1 ml) were added and the mixture was irradiated (500-W lamp) for 1 hr. The usual work-up (*vide supra*) afforded **6b** (375 mg) identical in all respects with the material described above.

5α-Bromopregnane-3β,20β-diol 6,19-Oxide 20-Acetate.—A solution of the diacetate **6b** (2.5 g) in ethanol–water (625 ml, 3:1) containing sodium hydroxide (1.9 g) was allowed to stand overnight at 5°. Acetic acid was then added and the mixture worked up as usual to afford the title compound crystallized from methanol (2.4 g). The analytical specimen had mp 60, 100, 191–195°; $[\alpha]D$ +16.3°.

Anal. Calcd for $C_{23}H_{35}O_4Br$: C, 60.66; H, 7.69; Br, 17.58. Found: C, 60.66; H, 7.63; Br, 17.67.

20β-Hydroxypregn-4-en-3-one 6β,19-Oxide 20-Acetate (7b).—A solution of the monoacetate from above (2.15 g) in acetone (150 ml) was treated with excess Jones reagent.[10] After 15 min, the excess oxidant was decomposed with methanol and the reaction mixture worked up as usual. The crude product was dissolved in methanol (250 ml) containing potassium acetate (12.5 g) and the solution heated under reflux for 0.5 hr. The usual work-up afforded the title compound **7b**, which was crystallized from methanol (1.1 g), mp 200–207°. The analytical specimen had mp 205–206°, $[\alpha]D$ −39°.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.19; H, 8.60; O, 17.20. Found: C, 74.06; H, 8.76; O, 17.51.

20β-Hydroxypregn-4-en-3-one 6,19-Oxide (8b).—A solution of the monoacetate **7b** (1 g) in a mixture of methanol (15 ml), ethanol (15 ml), and tetrahydrofuran (10 ml) containing potassium hydroxide (1.5 g) was allowed to stand at room temperature overnight. The usual work-up afforded the title compound **8b**, which was recrystallized from cyclohexane–methylene chloride (720 mg), mp 202–211°. The analytical specimen had mp 207–211°, $[\alpha]D$ −116°.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.36; H, 9.09. Found: C, 76.23; H, 9.21.

20β-Hydroxypregn-4-en-3-on-18-oic Acid 6β,19-Oxide 20→18-Lactone (2b).—A solution of the alcohol from above (**8b**, 1 g) in pyridine (10 ml) was treated at 5° with an excess of nitrosyl chloride. The product crystallized on addition of water and was recrystallized from hexane to give the crude nitrite **9b** (0.8 g), mp 150–162°. The solution of this nitrite (0.75 g) in toluene (200 ml) was irradiated (200-W lamp) for 1 hr. The solvent was then removed *in vacuo* and the crude product chromatographed on alumina. Elution with 1% methanol in methylene chloride gave the crude oxime **10b**. The oxime was, without further purification, dissolved in acetic acid (5 ml) and the solution treated with sodium nitrite (200 mg) in water (2.5 ml). After 5 min, the reaction mixture was worked up as usual and the crude product redissolved in acetone (3 ml). The acetone solution was treated with an excess of Jones reagent.[10] After 5 min, the excess oxidant was decomposed with methanol and the reaction mixture worked up in the usual way to afford the title compound **2b** crystallized from ether (190 mg), mp 255–258°. The analytical specimen had mp 255–258°, $[\alpha]D$ −158°.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.65; H, 7.65; O, 18.64. Found: C, 73.87; H, 7.59; O, 18.68.

19,20α-Dihydroxypregn-4-en-3-on-18-oic Acid 20→18-Lactone (12).—A solution of the oxidolactone **2a** (360 mg) in acetic acid (70 ml) was heated under reflux and treated with zinc dust (5 g, added in three portions at 5-min intervals). The zinc dust was removed by filtration and washed with methylene chloride. The combined organic portions were taken to dryness and partitioned between water and methylene chloride. The methylene chloride was then washed with sodium bicarbonate, dried, and concentrated *in vacuo*. The title compound **12** was obtained on crystallization from methanol (256 mg), mp 205–240°. An analytical sample had mp 243–248°, $[\alpha]D$ +85.2°, λ_{max} 242 mμ (ε 17,000).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.25; H, 8.14. Found: C, 73.01; H, 8.27.

20α-Hydroxypregn-4-en-3-on-18-oic Acid 6β,19-Oxide 20→18-Lactone 3-Ethylene Ketal (14).—A mixture of the oxidolactone **2a** (575 mg), *p*-toluenesulfonic acid (26 mg), and ethylene glycol (16 ml) was slowly distilled under vacuum (2 mm) until 8 ml of distillate had been collected. The reaction mixture was then cooled, treated with 7% aqueous sodium bicarbonate, and partitioned between methylene chloride and water. The organic phase was dried and evaporated. The residual solid was recrystallized from methanol to give the title compound **14** (350 mg), mp 198–215°. An analytical sample had mp 206–220°; $[\alpha]D$ −35.5°.

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.50; H, 7.77. Found: C, 71.41; H, 7.67.

18,19,20α-Trihydroxypregn-4-en-3-one 18,20-Diacetate.—A solution of the ketal **14** (620 mg) in tetrahydrofuran (10 ml) was added slowly to a stirred slurry of lithium aluminum hydride (700 mg) in tetrahydrofuran (20 ml). The mixture was heated under reflux for 0.5 hr after addition was complete. Water was then cautiously added and the product isolated with methylene chloride. The crude product was allowed to stand overnight in acetic anhydride (20 ml) and pyridine (26 ml). The mixture was then taken to dryness and the residue partitioned between methylene chloride and water. The methylene chloride was dried and concentrated to afford an oil (760 mg), which resisted attempts at crystallization.

A solution of the above crude material (760 mg) in acetone (40 ml) containing *p*-toluenesulfonic acid (40 mg) was allowed to stand at room temperature for 2 hr. The reaction mixture was then treated with aqueous sodium bicarbonate and concentrated to dryness. The crude product was partitioned between methylene chloride and water. The organic phase was removed, dried, and evaporated. The resultant oil, which resisted attempts at crystallization, was chromatographed on alumina (35 g). Elution with 2% acetone in methylene chloride afforded an oil (431 mg), the infrared spectrum of which revealed a band at 1660 cm^{-1} (α,β-unsaturated ketone). This crude material was dissolved in acetic acid (100 ml). The solution was heated under reflux and treated with zinc dust (7.0 g, added in six portions at 2.5-min intervals). After the usual work-up, the crude product was chromatographed on alumina (35 g). Elution with acetone and methylene chloride gave the title compound (260 mg). An analytical sample had mp 183–186°, $[\alpha]D$ +117°, λ_{max}^{MeOH} 242 mμ (ε 15,500).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.44; H, 8.33. Found: C, 69.60; H, 8.42.

18,19,20α-Trihydroxypregn-4-en-3-one (1a).—A solution of the 18,20-diacetate of the title compound (200 mg) in methanol (45 ml) containing potassium hydroxide (1 g) was allowed to stand at room temperature for 3 hr. The reaction mixture was then neutralized with dilute acetic acid, concentrated to small bulk, and partitioned between half-saturated salt solution and ethyl acetate. The organic portion was dried and evaporated to afford the crude product. An aliquot (85 mg) was then chromatographed on silica gel (15 g). Elution with 8–15% methanol in methylene chloride gave the title compound **1a** (64 mg), mp 235–250°. The analytical sample had mp 241–250°, $[\alpha]D$ +131°, λ_{max}^{MeOH} 243 mμ (ε 14,400).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.37; H, 9.25; O, 18.36. Found: C, 72.04; H, 9.52; O, 18.28.

18,20β,Dihydroxypregn-4-en-3-one 6,19-Oxide (18).—A solution of the oxidolactone **2b** (400 mg) in dry, freshly distilled tetrahydrofuran (25 cc) was treated with lithium aluminum hydride (400 mg). The suspension was heated under reflux for 2.5 hr and then worked up as usual. The crude mixture of triols was, without further purification, dissolved in *t*-butyl alcohol (30 cc) and treated with dichlorodicyanoquinone (310 mg). After storage for 24 hr at room temperature, the reaction mixture was worked up as usual[14] to afford the title compound **18** (210 mg). An analytical specimen had mp 99–100, 158–160, 175–176°; $[\alpha]D$ −162°; λ_{max}^{MeOH} 238 mμ (ε 12,700).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.79; H, 8.73; O, 18.47. Found: C, 73.14; H, 8.71; O, 17.99.

(15) J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1361 (1963).

18,19,20β-Trihydroxypregn-4-en-3-one (1b).—Zinc dust (75 g) and sufficient 3 *N* HCl to make a paste were heated on the steam bath for 30 min. The zinc was filtered off, washed with water and ethanol, and the resulting cake ground in a mortar under ethanol. The powdered zinc was then suspended in dilute acetic acid, filtered, and washed with water and acetic acid.

A solution of the 6,19-oxido compound (350 mg) in acetic acid (10 cc) was heated with vigorous agitation on the steam bath. Zinc, prepared as above, was then added (7 g, in portions over 13 min). The reaction mixture was cooled, filtered, and worked up as usual to afford the crude product, which was chromatographed on silica gel (30 g). Elution with 8–16% methanol in methylene chloride gave the title compound **1b** recrystallized from methylene chloride–ether (220 mg), mp 194–197°. An analytical sample had mp 198–204°, $[\alpha]D$ +78°, λ_{max}^{MeOH} 243 mμ (ε 14,000).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.37; H, 9.25; O, 18.36. Found: C, 72.32; H, 9.35; O, 18.22.

Registry No.—**1a,** 15833-26-8; **1b,** 15833-27-9; **2a,** 15833-28-0; **2b,** 15833-29-1; **4a,** 15833-30-4; **6a,** 15833-31-5; 5α-bromopregn-3β,20α-diol 6β,19-oxide 20-acetate, 15833-32-6; **7a,** 15833-33-7; **7b,** 15833-34-8; **8a,** 15833-35-9; **8b,** 15856-42-5; **12,** 15833-40-6; **14,** 15833-37-1; 18,19,20α-trihydroxypregn-4-en-3-one 18,20-diacetate, 15833-38-2; **18,** 15833-39-3.

A Rearrangement Reaction of 17-α-Hydroperoxypregnan-20-ones

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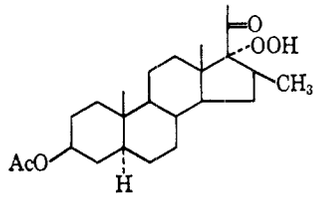
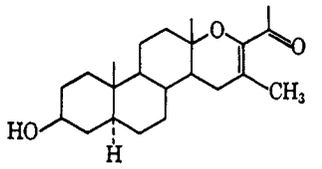
17α-Hydroperoxy-16β-methylpregnan-20-ones have been found to rearrange to 17a-oxa-D-homopregnan-20-ones upon acetylation or treatment with mineral acid. The structure, stereochemistry, and mode of formation of the products are discussed.

Although the preparation of 17α-hydroperoxypregnan-20-ones has been described,[2] their acylation has not been reported. While attempting the acetylation of 17α-hydroperoxy-16β-methyl-5α-pregnan-3β-ol-20-one 3-acetate (I) with a pyridine–acetic anhydride mixture, we were surprised to find that the crude product absorbed in the ultraviolet, having a band at λ_{max} 278 mμ.



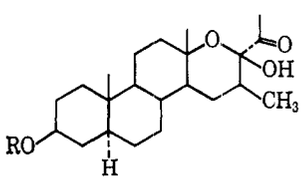
I



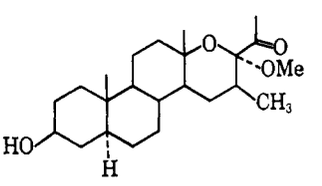
II

Chromatographic analysis revealed the presence of several materials and an investigation of their nature was undertaken.

Chromatography of the mixed acetates failed to resolve the mixture into its components and it was therefore subjected to hydrolysis with excess potassium hydroxide in aqueous methanol at room temperature. From the resulting mixture of alcohols three crystalline materials, II, III, and IV, were readily obtained by partition chromatography. Their structures were assigned on the basis of the following evidence.

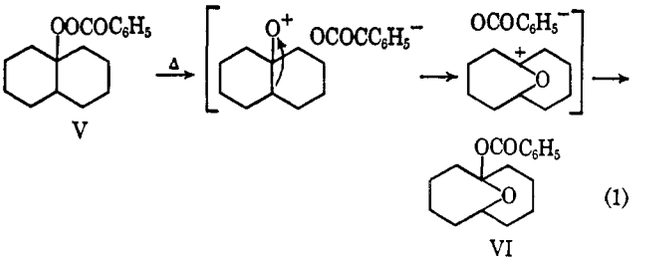


III, R = H
VII, R = $COCH_3$



IV

The major product (II), obtained in *ca.* 25% yield, had an ultraviolet absorption maximum at 278 mμ (ε 5900) and analyzed for $C_{22}H_{34}O_3$, whereas infrared maxima at 1700 and 1620 cm^{-1} indicated the presence of a conjugated carbonyl group. As the Criegee rearrangement of hydroperoxide esters is a well-documented reaction,[3] a typical example being the conversion of the decalin hydroperoxide benzoate V into the isomeric compound VI (eq 1), it was apparent early in the investigation that structure II was mechanistically



V → VI (1)

logical and fitted much of the available evidence. Although no good model could be found for the chromophore in II, the observed absorption did not seem inconsistent with such a structure. The nmr spectrum of II (see Table I) was also in agreement with the pro-

TABLE I
NMR DATA[a]

Compd	Chemical shift C-16 Me	C-18 Me	C-19 Me	C-21 Me	17-OH	17-OMe	3-OAc	C-6 Me
II	1.90	1.02	0.77	2.14				
XVIII	1.98	1.06	0.98	2.22			2.04	1.64
III	0.66	1.25	0.77	2.20	4.15			
	0.77							
XIX	0.68	1.25	0.95	2.20	4.15		1.98	1.58
	0.77							
IV	0.93	1.08	0.75	2.13		3.22		
	1.04							
XV	0.77	1.25	0.77	2.13		3.12		
	0.90							

[a] Expressed in parts per million.

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(2) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, p 633.