temperature for 20 hr. The product was precipitated with water, filtered, and crystallized from methanol to give (VIII) (2.6 g.), m.p. 100–115° (bubbling). The analytical sample melted at 114–116° (after drying *in vacuo*) $[\alpha]_D$ −74°.

Anal. Calcd. for $C_{21}H_{31}BrCl_2O_2$: C, 54.09; H, 6.70; Br, 17.14; Cl, 15.21. Found: C, 53.98; H, 6.76; Br, 17.91; Cl, 14.68.

5α,6β-Dichloro-17α-bromopregnane-3,20-dione (IX). The preceding compound (2.26 g.) in acetone (60 ml.) was treated at 0° with a slight excess of 8*N* chromium trioxide–sulfuric acid solution and the product precipitated by the addition of ice water. Crystallization from methanol gave the 3-ketone (IX) (1.6 g.), m.p. 158–161°. The analytical sample melted at 161–162°, $[\alpha]_D$ −85°.

Anal. Calcd. for $C_{21}H_{29}BrCl_2O_2$: C, 54.32; H, 6.29; Br, 17.21; Cl, 15.27; O, 6.89. Found: C, 54.71; H, 6.09; Br, 17.29; Cl, 15.40; O, 6.75.

6β-Chloro-17α-bromoprogesterone (X). The preceding compound (500 mg.) in absolute ethanol (40 ml.) was refluxed with fused sodium acetate (1.2 g.) for 1.5 hr. Part of the solvent was evaporated and the product precipitated with ice water. Crystallization from aqueous acetone gave 6β-chloro-17α-bromoprogesterone (X) (103 mg.), m.p. 145–148°. The analytical sample melted at 154–155°, $[\alpha]_D$ −48°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 4.12.

Anal. Calcd. for $C_{21}H_{28}BrClO_2$: C, 58.91; H, 6.59; Br, 18.66; Cl, 8.24; O, 7.48. Found: C, 58.85; H, 6.69; Br, 18.41; Cl, 8.04; O, 7.61.

6α Chloro-17α-bromoprogesterone (XI). 5α,6β-Dichloro-17α-bromopregnane-3,20-dione (IX) (400 mg.) in glacial acetic acid (25 ml.) was treated with dry hydrogen chloride gas at 10° for 2 hr. Precipitation with water and filtration gave 320 mg. of crude product, $\lambda_{max}^{C_2H_5OH}$ 236–238 mμ, log ε 4.13. Crystallization from aqueous acetone gave an analytical sample of 6α-chloro-17α-bromoprogesterone, m.p. 157–158°, $[\alpha]_D$ +14°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.16.

Anal. Calcd. for $C_{21}H_{28}BrClO_2$: C, 58.91; H, 6.59; Br, 18.66; Cl, 8.24; O, 7.48. Found: C, 58.65; H, 6.44; Br, 18.38; Cl, 7.81; O, 7.34.

5α,6β,17α-Trichloropregnan-3β-ol-20-one acetate (XIII). To a solution of the crude enol acetate XII[9] (3 g.) in carbon tetrachloride (15 ml.) at 0° was added a solution of chlorine in carbon tetrachloride (1%; 120 ml.) during 5 min. After a further 10 min., the solution was washed with cold 5% sodium carbonate solution and water, dried, and evaporated *in vacuo*. The resulting oil was chromatographed on 90 g. of neutral alumina. Elution with hexane-benzene (1:1) gave material which on crystallization from methylene chloride–methanol afforded 5α,6β,17α-trichloropregnan-3β-ol-20-one acetate (XIII) (711 mg.), m.p. 175–180°. Recrystallization gave an analytical sample, m.p. 194–195°, $[\alpha]_D$ −70°.

Anal. Calcd. for $C_{23}H_{33}Cl_3O_3$: C, 59.54; H, 7.17; Cl, 22.95; O, 10.34. Found: C, 58.97; H, 7.26; Cl, 23.22; O, 10.46.

5α,6β,17α-Trichloropregnan-3β-ol-20-one (XIV). The trichloroacetate XIII (2.6 g.) dissolved in dioxane-methanol (1:1; 50 ml.) was treated with concd. hydrochloric acid (4 ml.) and allowed to stand at 25°, for 24 hr. The product was precipitated with ice water, filtered, and crystallized from methylene chloride–methanol, yielding the trichloroalcohol XIV (2.15 g.), double m.p. 92° and 152–156°. The analytical sample melted at 92° and 164–165°, $[\alpha]_D$ −67°.

Anal. Calcd. for $C_{21}H_{31}Cl_3O_2$: C, 59.78; H, 7.41; Cl, 25.23. Found: C, 60.28; H, 7.47; Cl, 25.30.

5α,6β,17α-Trichloropregnane-3,20-dione (XV). The foregoing compound (1.2 g.) in acetone (30 ml.) was treated at 0° with a slight excess of 8*N* chromium trioxide–sulfuric acid. The product started to crystallize and ice water was added and the material filtered to yield the 3-ketone XV (1 g.), m.p. 161–163°. Recrystallization from aqueous acetone gave the analytical sample, m.p. 171–172°, $[\alpha]_L$ −60.5°.

Anal. Calcd. for $C_{21}H_{29}Cl_3O_2$: C, 60.08; H, 6.76; O, 7.62. Found: C, 59.90; H, 6.98; O, 7.46.

6β,17α-Dichloroprogesterone (XVI). 5α,6β,17α-Trichloropregnane-3,20-dione (500 mg.) was refluxed in absolute ethanol (40 ml.) with fused sodium acetate (1.2 g.) for 90 min. Precipitation with water and filtration gave an amorphous material with $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 3.90, which was chromatographed on 15 g. of neutral alumina. Elution with benzene and crystallization from aqueous acetone gave 6β,17α-dichloroprogesterone (180 mg.), m.p. 182–185°. Two further crystallizations gave material of m.p. 192–193°, $[\alpha]_D$ −30°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 4.12.

Anal. Calcd. for $C_{21}H_{28}Cl_2O_2$: C, 65.79; H, 7.36; Cl, 18.50; O, 8.35. Found, C, 65.46; H, 7.50, Cl, 18.62; O, 8.54.

6α,17α-Dichloroprogesterone (XVII). 5α,6β,17α-Trichloropregnane-3,20-dione (700 mg.) in glacial acetic acid (50 ml.) was treated at 0° with a stream of dry hydrogen chloride gas for 2 hr. The product was precipitated with ice-water and collected. Chromatography over 20 g. of alumina elution with benzene, and crystallization from aqueous acetone yielded 6α,17α-dichloroprogesterone (310 mg.), m.p. 160–162°. Recrystallization gave material of m.p. 165–166°, $[\alpha]_D$ +29°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.16.

Anal. Calcd. for $C_{21}H_{28}Cl_2O_2$: C, 65.79; H, 7.36; Cl, 18.50; O, 8.35. Found: C, 65.80; H, 7.46; Cl, 18.31, O, 8.26.

RESEARCH LABORATORIES
SYNTEX, S. A.
APARTADO 2679
MEXICO, D.F., MEXICO

The Preparation of 19-Nortestosterone-17-propionate

P. NARASIMHA RAO

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Among the various esters of 19-nortestosterone (I) the 17-propionate (II) has been proved to be biologically the most efficient.[1,2] It has been shown previously that attempts to prepare II with propionyl chloride or propionic anhydride gave mixtures of mono and di (enol) propionates *even at room temperature*.[3] In contrast, the preparation of II was recorded in a patent[4] by first heating a solution of I in pyridine and propionic anhydride for three hours at 75° and then for sixteen hours at room temperature. In another patent[5] the preparation of II was mentioned using propionic anhydride and pyridine without giving any physical constants of II. However, a suitable method has been worked out in these laboratories to prepare II in excellent

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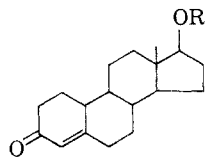
(3) A. L. Wilds and Norman A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

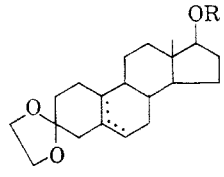
(4) R. A. Donis and A. C. Ott, U. S. Patent **2,798,879**; *Chem. Abstr.*, **51**, 15621a (1957).

(5) C. Djerassi, F. Sondheimer, and G. Rosenkranz, U. S. Patent **2,756,244**; *Chem. Abstr.*, **51**, 5852g (1957).

yield. The enolizable 3-keto function in 19-nortestosterone was first protected by the formation of 3-ethylenedioxy derivative (III).[6] The ethylenedioxy derivative (III) without further purification was treated with pyridine and propionic anhydride at room temperature to give 3-ethylenedioxy-19-nortestosterone-17-propionate (IV). The ethylenedioxy group from IV was then removed by acid-catalyzed exchange with acetone to give 19-nortestosterone-17-propionate (II). The overall yield of II without isolating the intermediates is 90–95%.



I. R = H
II. R = OC.CH_2CH_3



III. R = H
IV. R = OC.CH_2CH_3

EXPERIMENTAL

3-Ethylenedioxy-19-nortestosterone-17-propionate (III). A mixture of 19-nortestosterone (7 g.) benzene (525 ml.) ethylene glycol (52 ml.) and *p*-toluenesulfonic acid monohydrate (0.35 g.) was heated under reflux with stirring in a modified Dean-Stark phase separator until no more water phase separated (*ca.* 20–24 hr.). At the completion of this step the solution was washed with aqueous sodium bicarbonate, and then with water until neutral, and the solvent was then removed under reduced pressure under a stream of nitrogen. 3-Ethylenedioxy-19-nortestosterone (III) (8.3 g.) was obtained as a gum. Without further purification this was dissolved in pyridine (20 ml.) and propionic anhydride (8 ml.) was added and kept at room temperature for 18 hr. The excess pyridine was then removed under reduced pressure in a stream of nitrogen and the residue was dissolved in ether. The ether extract was washed with sodium bicarbonate solution, and then with water until neutral, and dried over sodium sulfate. After evaporating the solvent 3-ethylenedioxy-19-nortestosterone-17-propionate (IV) (10 g.) was obtained as a solid and no further purification was attempted.

19-Nortestosterone-17-propionate (II). The above solid (10 g.) was dissolved in anhydrous acetone (150 ml.) and *p*-toluenesulfonic acid monohydrate (0.4 g.) was added and the contents heated under reflux for 14 hr. After this time the reaction mixture was concentrated to a small volume (20 ml.) and then diluted with water. The precipitated 19-nortestosterone-17-propionate (8.3 g.) was filtered and washed with sodium bicarbonate solution and then with water until the washings were neutral.

This product melted at 60–65°. On further recrystallization from aqueous methanol, II was obtained with water of crystallization and melted at 71–73°. A sample dried in high vcauum over phosphorus pentoxide for 20 hr. at 35° melted at 50–51° and still contained half a molecule of water of crystallization. $[\alpha]_D^{23.5}$ +58.0° (in chloroform): $\lambda_{max}^{methanol}$ 240 mμ, ϵ = 17,280; ν_{max}^{KBr} 1727, 1668, and 1613 $cm.^{-1}$

Anal. Calcd. for $C_{21}H_{30}O_3$,$^1/_2H_2O$ (339.45): C, 74.29; H, 9.20. Found: C, 74.56; H, 9.09.

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DEPARTMENT OF PHYSIOLOGY AND BIOCHEMISTRY
SOUTHWEST FOUNDATION FOR RESEARCH
AND EDUCATION
SAN ANTONIO 6, TEX.

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Bisammonium Salts Related to 1,10-Decamethylenebisatropinium Diiodide[1,2]

HUGH B. DONAHOE, SAMUEL I. TROTZ,[3] AND KAZUO K. KIMURA[4]

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Studies concerned with the preparation of synthetic muscle paralyzing agents have often focused on structures in which two quaternary nitrogens are approximately 15 Å apart.[5,6] This distance corresponds to a methylene chain containing ten carbon atoms.

One of the more interesting compounds resulting from this approach is 1,10-decamethylenebisatropinium diiodide[7] (ID) which, in the rabbit, exhibited curariform activity twice that of *d*-tubocurarine (DTC) with a greater margin of safety. Unfortunately, this compound also possessed atropine-like activity greater than that of atropine itself and thus was unsatisfactory as a muscle paralyzing agent.

The potential pharmacological interest of this type of compound prompted an investigation into possible structural modifications which involved: 1) the removal of the two-carbon bridge between atoms 1 and 5 of the tropane ring system (Table I) to give the simpler piperidine system (Table II); 2) the substitution on the nitrogen atom; and 3) variations in the substituents on carbon 4 of the piperidine ring.

The tropane series. (Table I). Except for homatropine, which was commercially available, the tropane derivatives were obtained through the intermediate tropinone[8] which was prepared by

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(2) Taken in part from a dissertation submitted by Samuel I. Trotz in partial fulfillment of requirements for the degree of Doctor of Philosophy, Saint Louis University, 1956. Supported in part by Grant #44 from the American Medical Association Council on Pharmacy and Chemistry.

(3) Present address, Olin Mathieson Chemical Corporation, Niagara Falls, N. Y.

(4) Present address, Clinical Research Division, Medical Research Directorate, Army Chemical Center, Maryland.

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