Preparation of 7-Chloro Steroids

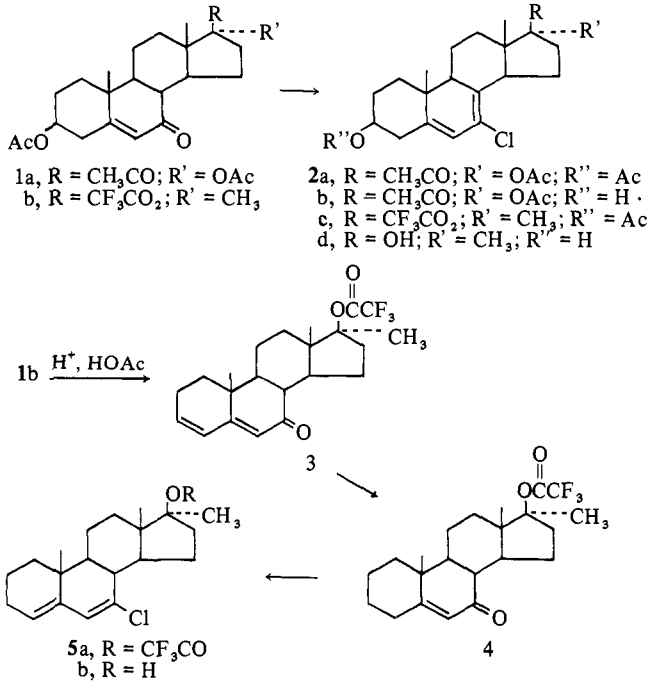
Robert W. Guthrie,* Alfred Boris, Francis A. Mennona, John G. Mullin, and Richard W. Kierstead

Chemical Reserach Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received July 10, 1972*

The reaction of 3β-acetoxy-Δ^5-7-keto steroids with oxalyl chloride gives rise to $\Delta^{5,7}$-7-chloro derivatives. In contrast, reaction of the corresponding 3-deoxy compound with oxalyl chloride leads to a $\Delta^{4,6}$-7-chloro derivative. The chemistry of these compounds is discussed, and their endocrinological properties are described.

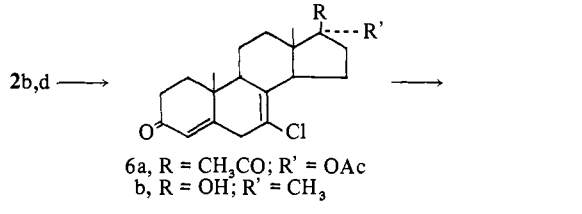
Over the past two decades significant biological activities have been imparted to the natural steroidal hormones through peripheral modifications at various positions throughout the steroid nucleus. One of these positions, however, that has received relatively scant attention has been C-7. Several 7α-thio,[1] 7α- and 7β-alkyl,[2-4] and Δ^6-7-alkyl[2,3] derivatives have been described and do show some promising activities. A steroid incorporating a 7-chloro-4,6-dien-3-one† system represents a novel series that might be expected to exhibit interesting biological activity.

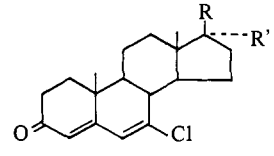
Chlorodiene systems are available through the action of oxalyl chloride[6] or $POCl_3$–DMF[7] on α,β-unsaturated ketones. Accordingly, convenient starting materials for this series of compounds were the Δ^5-7-ones **1a** and **1b** available *via* the allylic oxidation of the corresponding Δ^5 steroids using *tert*-butyl chromate.[8] Treatment of **1a** and **1b** with oxalyl chloride in boiling $PhCH_3$ gave fair yields (30–40%) of the 3β-acetoxy-$\Delta^{5,7}$-7-chlorodienes **2a** and **2c**, respectively, which were readily identified by their characteristic uv absorption. These conditions were significantly more vigorous than those required[6] to transform Δ^4-3-keto steroids into 3-chloro-3,5-dienes.



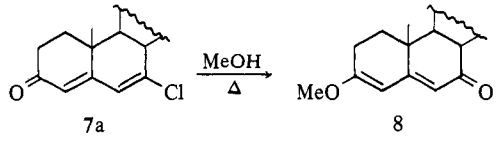
In the 3β-acetoxy series, the fact that homoannular chlorodienes **2a** and **2c** were produced in this reaction may be contrasted with the product obtained when the corresponding 3-deoxy-Δ^5-7-keto steroid **4** was treated under similar reaction conditions. The substrate **4** was obtained *via* acid-catalyzed elimination of the acetoxy group in **1b** and subsequent hydrogenation of the intermediate dienone **3** using a homogeneous catalyst. Treatment of **4** with oxalyl chloride in refluxing PhH furnished the $\Delta^{4,6}$-7-chlorodiene **5a**. The formation of the alternative $\Delta^{5,7}$-7-chlorodiene was not detected.

Mild alkaline hydrolysis of **2a** and **2c** furnished the corresponding 3β-hydroxy compounds **2b** and **2d**, respectively. Attempts to oxidize the 3β-hydroxyl function in **2b** and **2d** by a variety of methods, *e.g.*, Jones reagent,[9] Sarett reagent,[10] DCC–DMSO,[11] and DCC–Ac_2O,[12] either failed or caused overoxidation at C-6. However, a modified Oppenauer oxidation[13] could be used to efficiently transform the pregnene **2b** into the deconjugated chlorodienone **6a**. Only minor amounts (3–5%) of the 7-chloro-4,6-dien-3-one 7a were detected in the crude reaction mixture. In the androstene series, however, the reaction product was a mixture (2:1) of the chlorodienones **6b** and 7**b**. The conversion of **6a** and **6b** into 7a and 7**b** could be effected under mild acid catalysis.





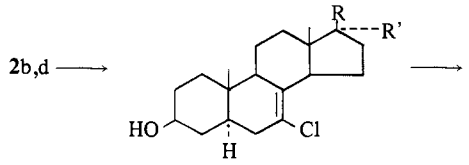
In an early experiment, an effort was made to purify **7a** by crystallization from methanol. However, it was noted that the hot solution evolved HCl gas. Examination of the resulting product by ir, uv, nmr, tlc, and mixture melting point showed it to be the known dienolone ether **8**.[14,15]



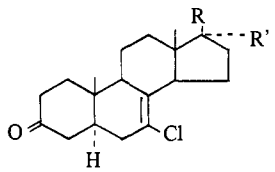
Since this product was formed under equilibrating conditions, its structure is consistent with the reported[16] relative stability of the 3-methoxy-3,5-dien-7-one system *vis a vis* the alternative 7-methoxy-4,6-dien-3-ones.

Hydrogenation of **2d** over Pd/C resulted in the uptake of 1 molar equiv of hydrogen to give **9b**. The structure of the dihydro derivative could be readily established by oxidation using Jones reagent to furnish the 3-ketone **10b**. The ORD curve of **10b** was positive in agreement with an A/B trans

†The corresponding 7-chloro-4-en-3-one is very unstable and has been observed only in solution. See ref 5.



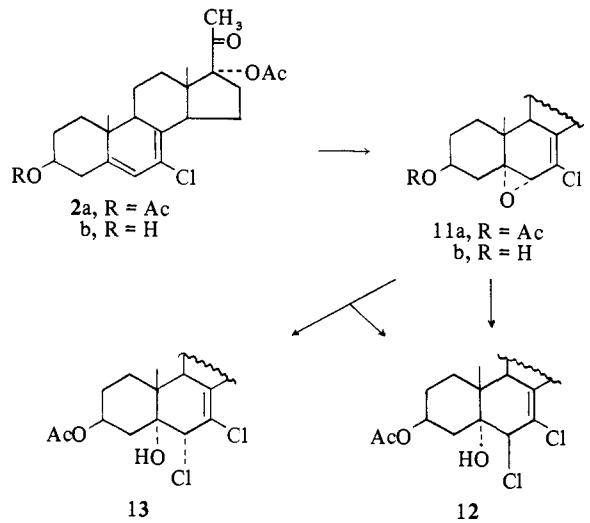
9a, R = CH_3CO; R' = OAc
b, R = OH; R = CH_3



10a, R = CH_3CO; R' = OAc
b, R = OH; R' = CH_3

junction. In the nmr, a lack of vinyl protons or protons attributable to a chloromethine group eliminated products that might have arisen through migration of the Δ^7 double bond. Using a similar sequence, **2b** was transformed into **9a** and **10a**.

Oxidation of the 3β-acetoxychlorodiene **2a** using *m*-chloroperbenzoic acid yielded the 5α,6α-epoxide **11a**. Treatment of **11a** with HCl (gas) using CCl_4 as solvent gave the expected 5α-hydroxy-6β-chloro derivative **12**. In contrast, when CH_2Cl_2 was used as the reaction medium, the predominant product (~50% isolated yield) was the epimeric 5α-hydroxy-6α-chloro compound **13**. The mother liquors of this reaction contained a fair proportion (~1:1 by tlc) of **12**. The chemical shifts of the C-19 methyl protons in **12** (1.23 ppm) and **13** (1.01 ppm) were the basis for the structural assignments of these compounds. The nonpolarity of CCl_4 evidently favors a "normal" SN2 opening of the epoxide to give **12**, while the use of more polar solvent (CH_2Cl_2) presumably promotes the formation of an allylic carbonium ion which then suffers attack from the less hindered α face of the molecule to give the 6α-chloro compound **13**. This participation of a Δ^7 double bond in the opening of 5,6-epoxides to give rise to anomalous products is well known.[17,18]



Biological Results. Progestational activity was determined in a modified Clauberg-McPhail assay which has been described previously.[19] Screening for antiuterotropic activity was performed in 21-day-old rats according to the method described by Boris.[20] The dosage level used was 0.5 mg/day of the test compound po and estradiol benzoate (0.1 μg/day sc) was used as standard uterine growth stimulator. Antigonadotropic activity was determined in 21-day-old rats at a level of 1 mg/day/rat po of test substance using the protocols outlined by Boris.[20] Andromyogenic activities were measured following the method of Hershberger, *et al.*,[21] at a dosage level of 1 mg/day/rat po. The only modification was that treatment began 7 days after castration of the 21-day-old rats used in the test.

Compounds **2a**, **2b**, **6a**, 7a, **10a**, 11a, 11b, 12, and 13 were screened for progestational activity. Compound 7a showed activity at a daily dose of 400 μg/day by both sc and po routes. In the test procedure used, this would indicate an effect weaker than that of progesterone, sc. The remainder of the compounds were inactive. **2a**, **2b**, **6a**, 7a, **11a**, **11b**, **12**, and **13** were also inactive when screened for antiestrogenic activity, while 2d, **5b**, **9b**, 7b, and **10b** showed no antigonadotropic, anabolic, or androgenic activity.

From these results it may be concluded that the incorporation of a Δ^7-7-chloro or a Δ^6-7-chloro moiety greatly diminishes the progestational activity of a hitherto active compound, *i.e.*, 17-acetoxyprogesterone. In addition, the inclusion of these groupings in 17α-methyltestosterone or its derivatives inactivates their andromyogenic properties.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are corrected. Where elemental analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The nmr spectra were determined using a Varian A-60 or HA-100 spectrometer and the chemical shifts (δ) are given in parts per million downfield from TMS. Only those resonance signals necessary for differentiating the various compounds are given. The optical rotations were measured on a Perkin-Elmer Model 141 polarimeter using a 1% solution of compound in $CHCl_3$ unless indicated otherwise.

7-Chloro-3β,17α-dihydroxypregna-5,7-dien-20-one 3,17-Diacetate (2a). Oxalic acid (0.4 g, 4.35 mmol) and oxalyl chloride (15 ml, 0.178 mol) were added to a stirred solution of 3β,17α-dihydroxypregn-5-ene-7,20-dione 3,17-diacetate (1a, 8.0 g, 18.6 mmol) in dry PhMe (150 ml). The reaction was heated at reflux temperature under N_2 for 36 hr and then was cooled and the solvent was evaporated under reduced pressure. The dark brown residue was taken up in 500 ml of PhH–hexane (1:1) and was washed with 5% $NaHCO_3$ solution (two times) and with H_2O. The dried ($MgSO_4$) organic layer was percolated through a short column of silica gel (70 g). The PhH–hexane fractions were discarded and the product was eluted with CH_2Cl_2. Evaporation of the eluent afforded a pale yellow solid which on crystallization from CH_2Cl_2–Et_2O furnished 2.5 g (30%) of **2a**, mp 223–225°. Concentration of the mother liquors yielded an additional 0.53 g (6%) of product, mp 219–223°. Recrystallization from Et_2O gave the analytical sample: mp 224–225°; $[\alpha]^{25}D$ −155.2°; uv (EtOH) 263 nm (ε 7250), 273 (9800), 283 (9600), and 295 (5450); ir ($CHCl_3$) 1735 and 1650 cm^{-1}; nmr ($CDCl_3$) δ 5.58 (br s, 1 H, C_6H). *Anal.* ($C_{25}H_{33}ClO_5$) C, H, Cl.

7-Chloro-3β,17α-dihydroxypregna-5,7-dien-20-one 17-Acetate (2b). A solution of KOH (1.7 g, 30 mmol) in H_2O (5 ml) was added to a solution of **2a** (11.7 g, 26 mmol) in MeOH (800 ml) and THF (600 ml). The mixture was stirred at room temperature for 30 min and then was poured into H_2O. The resulting precipitate was collected by filtration, washed (H_2O), and dried. Crystallization of the crude material from MeOH gave 10.3 g (96%) of **2b**, mp 227–229°. Recrystallization from MeOH gave the analytical sample: mp 230–232°; $[\alpha]^{25}D$ −194.2°; uv (EtOH) 263 nm (ε 7000), 273 (9300), 283 (9300), and 295 (5300); ir ($CHCl_3$) 3700, 1730, and 1710 cm^{-1}; nmr ($CDCl_3$) δ 5.58 (br s, 1 H, C_6H). *Anal.* ($C_{23}H_{31}ClO_4$) C, H, Cl.

7-Chloro-17α-methylandrosta-5,7-diene-3β,17β-diol (2d). To a stirred solution of 1b (100 g, 0.22 mol) in dry PhMe (1 l.) containing oxalic acid (5 g, 53 mmol) was added oxalyl chloride (120 ml, 1.4 mol). The reaction mixture was refluxed under N_2 for 16 hr and then was cooled and the solvent was removed *in vacuo*. The resulting dark brown residue was dissolved in PhH (700 ml) and washed with 5% $NaHCO_3$ solution and with brine. The dried (Na_2SO_4) organic

solution was diluted with an equal volume of hexane and adsorbed on a short column of silica gel (500 g). Elution with PhH–hexane (1:1) and PhH furnished the unstable chlorodiene **2c** as an oil (45 g, 43%).

The oil (45 g, 95 mmol) was dissolved in a mixture of MeOH (300 ml) and THF (50 ml) and a solution of KOH (14.8 g, 0.265 mol) in H_2O (120 ml) was added. After 30 min at room temperature, the fine yellow precipitate which had formed was collected by filtration, washed (H_2O), and dried. Crystallization from MeOH–EtOAc gave 25.1 g of the diol, mp 203–205.5° (34% from 1b). Recrystallization from EtOAc afforded the analytical sample: mp 200–201°; $[\alpha]^{25}D$ −157° (*c* 1.0, MeOH); uv (EtOH) 263 nm (ε 6700), 273 (9000), 283 (8900), and 295 (4750); ir (KBr) 3350 and 1645 cm^{-1}; nmr (DMSO) δ 5.42 (s, 1 H, C_6H). *Anal.* ($C_{20}H_{29}ClO_2$) C, H, Cl.

17β-Hydroxy-17α-methylandrosta-3,5-dien-7-one Trifluoroacetate (3). Concentrated HCl solution (18 ml) was added to a solution of 1b (36.4 g, 80 mmol) in AcOH (360 ml). The solution was allowed to stand at room temperature for 5 hr and then it was poured into an ice–water mixture (1.5 l.). The resulting precipitate was filtered, washed (H_2O), and then dissolved in CH_2Cl_2. The dried (Na_2SO_4) organic solution was evaporated under reduced pressure and the residue crystallized from MeOH to give 23.6 g (80%) of **3**, mp 150–150.5°. Recrystallization from the same solvent gave the analytical sample: mp 150–150.5°; $[\alpha]^{25}D$ −311.6°; uv (EtOH) 279 nm (ε 24,100); ir ($CHCl_3$) 1775, 1655, 1620, and 1595 cm^{-1}. *Anal.* ($C_{22}H_{27}F_3O_3$) C, H, F.

17β-Hydroxy-17α-methylandrost-5-en-7-one Trifluoroacetate (4). A solution of **3** (10 g, 25.2 mmol) in PhH (240 ml) and ethanol (60 ml) was hydrogenated using tris(triphenylphosphine)chlororhodium (3.0 g, 4.1 mmol) as catalyst. The absorption of H_2 stopped after 20 hr (650 ml, 760 mm, 23°). The solvent was evaporated and the residue was triturated several times with hot hexane. The combined extracts were concentrated to dryness *in vacuo* and crystallization of the resulting solid from MeOH afforded 7.6 g (75%) of **3**, mp 146–147°. An additional 600 mg (6%), mp 143–146°, was obtained from the mother liquors. Recrystallization from MeOH gave the analytical specimen: mp 146–147°; $[\alpha]^{25}D$ −165.4°; uv (EtOH) 237 nm (ε 13,350); ir ($CHCl_3$) 1775, 1665, and 1625 cm^{-1}; nmr ($CDCl_3$) δ 5.66 (s, 1 H, C_6H). *Anal.* ($C_{22}H_{29}F_3O_3$) C, H, F.

7-Chloro-17α-methylandrosta-4,6-dien-17β-ol Trifluoroacetate (5a). Oxalyl chloride (25 ml, 0.3 mol) and oxalic acid (0.4 g, 4.35 mmol) was added to a stirred solution of 4 (8.4 g, 21 mmol) in PhH (50 ml). The reaction mixture was refluxed in a N_2 atmosphere for 5 hr, then was cooled, and evaporated to dryness *in vacuo*. The resulting reddish brown residue was dissolved in CH_2Cl_2 and the solution was washed with 5% $NaHCO_3$ solution. The dried (Na_2SO_4) organic layer was percolated through a short column of silica gel (40 g) to remove most of the color. Evaporation of the solvent under reduced pressure gave a yellow oil which, when crystallized from MeOH containing a trace of H_2O, afforded the colorless chlorodiene **5a** (5.4 g, 62%), mp 100–108°. Further recrystallization from MeOH did not raise or sharpen the melting point: uv (EtOH) 239 nm (ε 20,500), 246 (24,200), and 255 (18,000); ir ($CHCl_3$) 1780 and 1610 cm^{-1}; nmr ($CDCl_3$) δ 5.41 (t, 1 H, C_4H) and 6.11 (d, 1 H, C_6H). *Anal.* ($C_{22}H_{28}ClF_3O_2$) Cl.

7-Chloro-17β-hydroxy-17α-methylandrosta-4,6-diene (5b). A solution of KOH (0.4 g, 7.2 mmol) in MeOH (3 ml) was added to a solution of **5a** (3.0 g, 7.2 mmol) in THF (10 ml). The reaction mixture was left at room temperature for 5 min and then was poured into an ice–H_2O mixture. The precipitate was collected by filtration, washed well with H_2O, and then dried. The crude material (2.1 g, 91%), mp 171–177°, was crystallized from MeOH to give the analytical sample: mp 172–178°; $[\alpha]^{25}D$ +98.9°; uv (EtOH) 240 nm (ε 19,000), 246 (22,500), and 253 (16,200); ir ($CHCl_3$) 3620 and 1605 cm^{-1}; nmr ($CDCl_3$) δ 5.45 (m, 1 H, C_4H) and 6.16 (d, 1 H, C_6H). *Anal.* ($C_{20}H_{29}ClO$) C, H, Cl.

7-Chloro-17α-hydroxypregna-4,7-diene-3,20-dione Acetate (6a). Solvent was allowed to distill slowly from a solution of **2b** (7.5 g, 18.2 mmol) in PhMe (190 ml) and cyclohexanone (22 ml). After 30 ml of distillate had been collected, a solution of aluminum isopropoxide (3.6 g, 17.6 mmol) in PhMe (20 ml) was added fairly rapidly. The slow distillation was continued for an additional 30 min, the reaction was then cooled, and saturated Rochelle salt solution (30 ml) was added. The organic layer was separated, washed with brine, and then steam distilled. The resulting yellow granular precipitate was filtered, washed (H_2O), dried, and then triturated with cold MeOH (20 ml) to remove most of the color to give 6.1 g (80%) of 6a, mp 196–199°. Several recrystallizations from MeOH and a final crystallization from EtOAc–hexane were required to give a colorless analytical sample: mp 199–200°; $[\alpha]^{25}D$ −85.2°; uv (EtOH) 235 nm (ε 16,700); ir ($CHCl_3$) 1735, 1675, and 1635 cm^{-1}; nmr ($CDCl_3$) δ 5.83 (s, 1 H, C_4H). *Anal.* ($C_{23}H_{29}ClO_4$) C, H, Cl.

7-Chloro-17α-hydroxypregna-4,6-diene-3,20-dione Acetate (7a). Six drops of concentrated HCl was added to a solution of **6a** (1.0 g, 2.25 mmol) in THF (50 ml). The reaction was allowed to stand at room temperature for 3 hr and was then diluted with H_2O. The resulting yellow precipitate was filtered, washed (H_2O), dried, and crystallized from CH_2Cl_2–Et_2O to give 0.4 g (40%) of 7a, mp 194–195°. A second crop (0.2 g, 20%), mp 193–195°, was collected from the mother liquors. Crystallization from Et_2O furnished the analytical sample: mp 194–195°; $[\alpha]^{25}D$ +130°; uv (EtOH) 291 nm (ε 23,800); nmr ($CDCl_3$) δ 6.34 (d, 1 H, C_6H) and 5.65 (s, 1 H, C_4H). *Anal.* ($C_{23}H_{29}ClO_4$) C, H, Cl.

Oppenauer Oxidation of 2d. A stirred solution of **2d** (9.55 g, 27.4 mmol) in $PhCH_3$ (600 ml) containing cyclohexanone (36 ml) was heated in a three-necked flask equipped for distillation. After 100 ml of distillate had been collected, a solution of aluminum isopropoxide (5.75 g, 27.4 mmol) in PhMe (23 ml) was added over 5 min. The distillation was allowed to continue at a slow rate during the addition and for 30 min thereafter. The reaction mixture was worked up as before and the resulting oily residue was extracted into Et_2O. The Et_2O solution was dried (Na_2SO_4) and evaporated under reduced pressure to give approximately 9.5 g of a yellow oil, shown by uv to be a mixture of 6b and **7b** (2:1).

7-Chloro-17β-hydroxy-17α-methylandrosta-4,6-dien-3-one (7b). The above crude mixture of 6b and 7b (~9.5 g, 27 mmol) was dissolved in THF (250 ml) containing concentrated HCl solution (1 ml). The solution was left at room temperature overnight, then was diluted with H_2O, and extracted with PhH. The dried (Na_2SO_4) organic layer was evaporated to a volume of ~250 ml. This concentrate was adsorbed on a column of silica gel (300 g) and chromatographed. Evaporation of fractions eluted with Et_2O–PhH (1:1) gave a residue which when crystallized from Et_2O–hexane afforded yellow crystals of the chlorodienone 7b (8.2 g, 81% from **2d**), mp 165–168°. The same solvent system gave the analytically pure material: mp 168–170°; $[\alpha]^{25}D$ +200.3°; uv (EtOH) 293 nm (ε 29,700); ir ($CHCl_3$) 3600, 1660, 1640, and 1620 cm^{-1}; nmr ($CDCl_3$) δ 5.68 (s, 1 H, C_4H) and 6.33 (d, 1 H, C_6H). *Anal.* ($C_{20}H_{27}ClO_2$) C, H, Cl.

3-Methoxy-17α-hydroxypregna-3,5-diene-7,20-dione Acetate (8). A solution of 7a (400 mg) in MeOH (20 ml) was heated to reflux. Fumes of HCl were immediately detected coming from the solution. After 5 min the solution was cooled and 320 mg of 8, mp 258–259°, was collected by filtration. The analytically pure material was obtained from the same solvent: mp 261–263°; $[\alpha]^{25}D$ −419°; uv (EtOH) 311 nm (ε 29,800); ir ($CHCl_3$) 1730, 1650, and 1610 cm^{-1}; nmr ($CDCl_3$) δ 5.57 (s, 1 H, C_6H), 5.29 (d, 1 H, C_4H), and 3.68 (s, 3 H, OCH_3). *Anal.* ($C_{24}H_{32}O_5$) C, H.

7-Chloro-3β,17α-dihydroxy-5α-pregn-7-en-20-one 17-Acetate (9a). A solution of **2b** (2.5 g, 6.2 mmol) in EtOAc (250 ml) was hydrogenated (760 mm, 23°) over 10% Pd/C (0.5 g). The reaction stopped abruptly within 30 min with the uptake of 150 ml of H_2 (1 mol equiv). Removal of the catalyst by filtration and concentration of the filtrate afforded 1.9 g (77%) of 9a, mp 184–188°. Additional crystallizations from EtOAc gave the analytical sample:‡ mp 187–190°; $[\alpha]^{25}D$ −103.4°; ir ($CHCl_3$) 3700 and 1730 cm^{-1}. *Anal.* ($C_{23}H_{33}ClO_4 \cdot 0.25C_4H_8O_2$) C, H, Cl.

7-Chloro-3β,17β-dihydroxy-17α-methyl-5α-androst-7-ene (9b). Hydrogenation of **2d** (6.2 g, 18.2 mmol) in EtOAc (150 ml) using 1.3 g of 10% Pd/C resulted in the uptake of 450 ml of H_2 (760 mm, 23°). Crystallization of the crude product from EtOAc furnished 4.5 g (74%) of 9b, mp 210–213°. Recrystallization afforded the analytical sample: mp 212–214°; $[\alpha]^{25}D$ −78.5° (*c* 1.0, MeOH); ir (KBr) 3350 and 1650 cm^{-1}. *Anal.* ($C_{20}H_{31}ClO_2$) C, H, Cl.

7-Chloro-17α-hydroxy-5α-pregn-7-ene-3,20-dione Acetate (10a). A solution of 9a (1.8 g, 4.4 mmol) in Me_2CO (170 ml) was cooled to 0°. To the stirred solution Jones reagent (1.8 ml) was added and the reaction mixture was allowed to stir at 0–5° for 10 min. Isopropyl alcohol (10 ml) was added to destroy excess oxidant and the reaction mixture was diluted with H_2O. The resulting precipitate was filtered, washed with H_2O, and dried. Crystallization of the crude material from Me_2CO–hexane afforded 1.3 g (73%) of **10a**, mp 227–228°. Further crystallizations from the same solvent system gave the analytical sample: mp 228–229°; $[\alpha]^{25}D$ −83.3°; ir ($CHCl_3$) 1735 and 1715 cm^{-1}. *Anal.* ($C_{23}H_{31}ClO_4$) C, H, Cl.

7-Chloro-17β-hydroxy-17α-methyl-5α-androst-7-en-3-one (10b). A similar oxidation of 9b (2.0 g, 5.9 mmol) using the Jones reagent furnished 1.49 g (75%) of 10b, mp 202–207°, after crystallization

‡0.25 mol of EtOAc present as solvent of crystallization.

of the crude product from Me_2CO–hexane. Recrystallization from EtOAc–hexane gave the analytical specimen: mp 209–212°; $[\alpha]^{25}D$ −78.9°; ir ($CHCl_3$) 3620 and 1720 cm^{-1}. *Anal.* ($C_{20}H_{29}ClO_2$) C, H, Cl.

7-Chloro-5α,6α-epoxy-3β,17β-dihydroxypregn-7-en-20-one 3,17-Diacetate (11a). A solution of **2a** (0.9 g, 2 mmol) and *m*-chloroperbenzoic acid (0.42 g) in CH_2Cl_2 (10 ml) was stirred at room temperature for 30 min, diluted with CH_2Cl_2, and washed in turn with 5% $NaHSO_3$ solution, 5% $NaHCO_3$ solution, and H_2O. The dried (Na_2SO_4) organic layer was evaporated *in vacuo* and crystallization of the resulting solid from CH_2Cl_2–Et_2O gave 0.68 g (72%) of 11a, mp 224–225°. Two additional crystallizations from the same solvent system afforded the analytical sample: mp 226–227°; [α]D −169.2°; nmr ($CDCl_3$) δ 3.20 (s, 1 H, C_6H). *Anal.* ($C_{25}H_{33}ClO_6$) C, H, Cl.

6β,7-Dichloro-3β,5α,17α-trihydroxypregn-7-en-20-one 3,17-Diacetate (12). A suspension of 11a (0.9 g, 1.93 mmol) in CCl_4 (20 ml) was cooled to 0°. HCl (g) was bubbled through the stirred mixture until the solid dissolved (~4 min). The solvent was removed at low temperature (<15°) under reduced pressure and the resulting solid was crystallized from Et_2O–hexane to give 0.629 g (65%) of 12, mp 197–198°. Recrystallization from the same solvent system gave the analytical sample: mp 198–199°; [α]D −124.0°; ir ($CHCl_3$) 3700 (sharp), 3400 (br), and 1735 cm^{-1}; nmr ($CDCl_3$) δ 4.33 (s, 1 H, C_6H) and 1.23 (s, 3 H, $C_{19}H_3$). *Anal.* ($C_{25}H_{34}Cl_2O_6$) C, H, Cl.

6α,7-Dichloro-3β,5α,17α-trihydroxypregn-7-en-20-one 3,17-Diacetate (13). A solution of 11a (1.0 g, 2.15 mmol) in CH_2Cl_2 (20 ml) was cooled to 0°. HCl (g) was bubbled through the solution for 4 min and the solvent was then removed *in vacuo*. The residue was crystallized from CH_2Cl_2–Et_2O to furnish (0.41 g, 37%) of 13, mp 209–210° (mmp with **12**, 183–185°). A second crop (0.1 g, 9%, mp 210–211°) was obtained from the mother liquors. Recrystallization from the same solvent mixture afforded the analytical specimen: mp 211–212°; $[\alpha]^{25}D$ −104.5°; ir ($CHCl_3$) 3650 and 1735 cm^{-1}; nmr ($CDCl_3$) δ 4.57 (t, 1 H, C_6H) and 1.01 (s, 3 H, $C_{19}H_3$). *Anal.* ($C_{25}H_{34}Cl_2O_6$) C, H, Cl.

7-Chloro-5α,6α-epoxy-3β,17α-dihydroxypregn-7-en-20-one 17-Acetate (11b). To a solution of **2b** (2.9 g, 7.2 mmol) in CH_2Cl_2 (30 ml) was added *m*-chloroperbenzoic acid (1.8 g). The solution was allowed to stand at room temperature for 1 hr and was worked up as before. The crude product was crystallized from CH_2Cl_2–Et_2O to give 1.9 g (63%) of 14. A second crop (0.4 g, 13%) was recovered from the mother liquors. Recrystallization from the same solvents furnished the analytical sample: mp 213° dec; $[\alpha]^{25}D$ −179.5°; ir ($CHCl_3$) 3700, 1730, and 1710 cm^{-1}; nmr ($CDCl_3$) δ 3.20 (s, 1 H, C_6H). *Anal.* ($C_{23}H_{31}ClO_5$) C, H, Cl.

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Antimalarials. 4. 4-Pyridinemethanols with Styryl and Benzoyl Substituents†

M. P. LaMontagne

Ash Stevens Inc., Detroit, Michigan 48202. *Received July 13, 1972*

A series of seven α-alkylaminomethyl-4-pyridinemethanols containing styryl substituents in the 2 and/or 6 positions of the pyridine ring has been synthesized. One compound was curative against *Plasmodium berghei* in mice at a dosage of 20 mg/kg, three were curative at 40 mg/kg, two were curative at 80 mg/kg, and one was inactive through 160 mg/kg. In addition, one compound bearing a 4-trifluoromethylbenzoyl substituent in the 2 position of the pyridine ring was prepared. It was curative at 80 mg/kg and showed marginal activity at 40 mg/kg.

In the two preceding papers[1,2] in this series, we reported the preparation and antimalarial activity against *Plasmodium berghei* in mice‡ of a series of α-alkylaminomethyl-2,6-bis(phenyl)-4-pyridinemethanols bearing Cl, Br, F, OCH_3, and CF_3 substituents on the phenyl rings. The very encouraging antimalarial activity demonstrated by several compounds in these series prompted us to investigate the effect of replacing one or both of the phenyl substituents with styryl and benzoyl groups.

Chemistry. The four structural types of compounds described in the present work are shown in Chart I. Compounds of type I were synthesized by the procedure shown in Scheme I.

Ethyl 2,6-dimethylisonicotinate was prepared from 4-cyano-2,6-lutidine[4] *via* hydrolysis and esterification under usual conditions. Condensation of the ester with excess aldehyde afforded the requisite 2,6-bis(styryl)isonicotinic acid esters in approximately 50% yield. Hydrolysis of the esters to the isonicotinic acid, followed by introduction of the amino alcohol side chain by the procedure developed

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‡The antimalarial tests were performed by Dr. Leo Rane of the University of Miami (see ref 3). See footnote *a*, Table III. Testing results were supplied through the courtesy of Drs. Thomas R. Sweeney and Richard E. Strube of the Walter Reed Army Institute of Research.