of saturated aqueous Rochelle salt solution was added, and the mixture was steam distilled to remove nonaqueous solvents. The solid precipitate was collected, washed with water, dried, and recrystallized from ethyl acetate to yield 620 mg of **21b**: mp 129–134°; $\lambda_{max}^{CHCl_3}$ 6.00, 6.19 μ.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.15; H, 9.48.

Following the above procedure identically, 1.0 g of **17** was oxidized and the crude reaction product was recrystallized from ethyl acetate to yield 480 mg of **16b**: mp 144–150°; nmr, 68 (17-CH_3), 72 (19-CH_3), 225 (multiplet, 21-CH_2), 344 (4-H) cps.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.21; H, 9.37.

17α-(3-Hydroxypropyl)-3-methoxy-17β-methylgona-1,3,5(10),-13-tetraene (9b) and 13,17[3]-Epoxy-3-methoxy-17β-methyl-17α-propyl-13α-gona-1,3,5(10)-triene (13b).—A reaction mixture of 25 g of 17α-(3-hydroxypropyl)-3-methoxy-1,3,5(10)-estratrien-17β-ol (**6d**),[11] 100 ml of ethanol, and 25 ml of concentrated HCl was stirred and refluxed for 45 min with solution being complete after 10 min. It was cooled and stirred, and 350 ml of cold H_2O was added producing an oil which congealed when cooled to 5°. The oil was collected, washed with H_2O, dried, and recrystallized from ethyl acetate to give 8.0 g of **9b**. A sample was recrystallized from acetone for analysis: mp 85–90°; $\lambda_{max}^{CHCl_3}$ 2.76 μ; nmr, 61 (17-CH_3), 216 (triplet, 22-CH_2), 226 (OCH_3) cps.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.74; H, 8.92.

The mother liquors from **9b** were chromatographed and the first fractions eluted with 1% ethyl acetate–benzene were combined and recrystallized twice from ethyl acetate to yield **1.1** g of **13b**: mp 93–95°; nmr, 44 (17-CH_3), *ca.* 225 (multiplet, 22-CH_2), 227 (OCH_3) cps.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.23; H, 9.22.

17α-(3-Hydroxypropyl)-3-methoxy-17β-methylgona-2,5(10),-13-triene (11) and 17α-(3)-Hydroxypropyl)-17β-methylgona-4,-13-dien-3-one (10b).—Lithium wire (1.6 g) was added over a 10-min period to a stirred solution of 2.5 g of **9b** in 75 ml of THF, 75 ml of *t*-butyl alcohol, and 150 ml of liquid NH_3. After 2.5 hr, 6 ml of methanol was added dropwise over 15 min with decolorization of solution after 3 hr. NH_3 was allowed to evaporate for 2 hr and then 150 ml of H_2O was added. Nonaqueous solvents were removed by vacuum distillation and the precipitate was collected, washed with H_2O, dried, and recrystallized from ethyl acetate containing 1 drop of pyridine to yield 1.3 g of **11**: mp 83–89°; $\lambda_{max}^{CHCl_3}$ 2.74, 5.88, 6.00 μ.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.69; H, 10.00.

A solution of 800 mg of **11** in 8 ml of methanol with 0.6 ml of concentrated HCl, and 0.6 ml of H_2O was held at room temperature for 2 hr and then diluted with 40 ml of H_2O. The precipitate was collected, washed with H_2O, dried, and recrystallized from ethyl acetate to yield **10b** (550 mg): mp 135–141°; $\lambda_{max}^{CHCl_3}$ 2.74, 6.00, 6.18 μ; λ_{max} 238.5 mμ (ε 16,000).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.15; H, 9.59.

13,17[3]-Epoxy-10,17β-dimethyl-17α-propyl-13α-gon-4-en-3-one (16c) and 17α-(3-Hydroxypropyl)-10,17β-dimethylgona-4,3-dien-3-one (10c).—A reaction mixture of 15 g of 17α-(3-hydroxypropyl)-4-androsten-17β-ol-3-one,[3] 60 ml of ethanol, and 15 ml of concentrated HCl was stirred and refluxed for 50 min during which time solution became complete. Water (300 ml) was added and the precipitate was extracted with benzene and chromatographed. The fraction eluted with 15% ethyl acetate–benzene was recrystallized from hexane to yield 2.35 g of **16c**. An analytical sample was obtained by a second recrystallization from hexane; mp 100–105°; $\lambda_{max}^{CHCl_3}$ 5.98, 6.18 μ; nmr, 45 (17-CH_3), 72 (19-CH_3), 222 (multiplet, 22-CH_2), 343 (4-H) cps.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.63; H, 9.89.

The oily peak fractions eluted with 40% ethyl acetate–benzene (8.44 g) were crude **10c** contaminated with a small amount of the acetate ester of the C-22 hydroxyl group (from transesterification with ethyl acetate). A 2-g sample was dissolved in 20 ml of warm methanol, 5 ml of 2% aqueous $KHCO_3$ was added, and after 5 hr at room temperature 100 ml of H_2O was added. The separated oil was extracted with ether and the ether solution was washed with H_2O, dried (Na_2SO_4), and evaporated to yield 1.7 g of **10c**: $\lambda_{max}^{CHCl_3}$ 2.73, 2.88, 5.98, 6.18 μ; λ_{max} 239 mμ (ε 17,100); nmr, 49 (17-CH_3), 59 (19-CH_3), 216 (triplet 22-CH_2), 345 (4-H) cps.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.33; H, 9.72.

Acknowledgment.—The author wishes to thank Dr. E. F. Nutting and Mr. Roger Bergstrom of the Division of Biological Research for the biological data and Dr. Roy H. Bible, Jr., for interpretation of nmr spectra.

6-Chloro-6-dehydro-A-nor Steroids with Progestational Activity. 7α-Chloro-A-nor Steroids

PATRICK A. DIASSI, SEYMOUR D. LEVINE, AND RAYMOND M. PALMERE

The Squibb Institute for Medical Research, New Brunswick, New Jersey

Received January 21, 1967

The synthesis of several 6-chloro-6-dehydro-A-nor steroids is described. Two of these compounds, 6-chloro-6-dehydro-17α-acetoxy-A-norprogesterone (**16**) and 6-chloro-6-dehydro-16α,17α-dimethylmethylenedioxy-A-norprogesterone (**14**), are potent progestational agents. These represent the first examples of A-nor steroids having this hormonal activity. Reaction of Δ^3-2-keto-A-nor steroids with 2,3-dichloro-5,6-dicyanobenzoquinone and HCl results in the formation of 7α-chloro compounds as well as the 6-dehydro derivatives. The mechanism of this reaction is discussed.

Previously reported A-nor analogs of sterodial hormones have shown little or none of the biological properties of the parent hormones. Thus A-norprogesterone (**1**)[1] does not exhibit progestational properties but is a potent antiandrogenic compound;[2] A-nortestosterone (**2**)[1] is weakly androgenic,[3] and A-norhydrocortisone and A-norcortisone[4] do not show the glucocorticoid or antiinflammatory properties of hydrocortisone or cortisone.

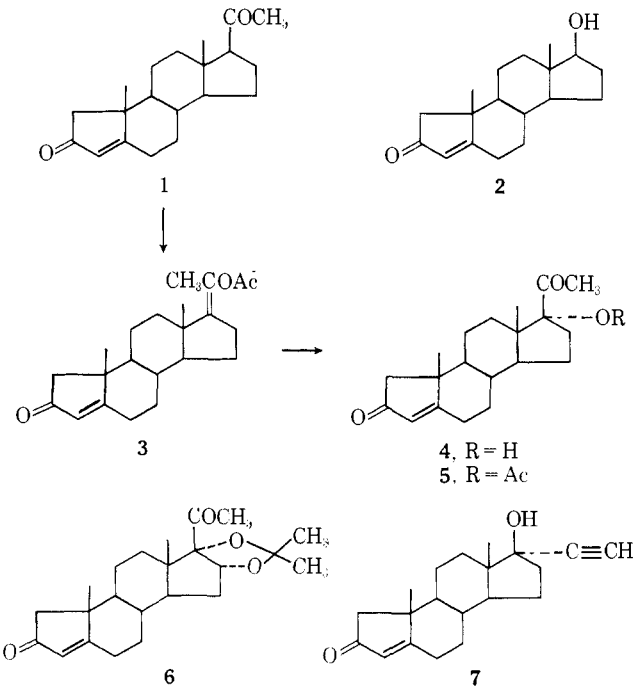
The chemical modification of steroid structures designed to enhance progestational activity has been the subject of much interest in recent years. In certain

(1) F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959).

(2) L. J. Lerner, A. Bianchi, and A. Borman, *Proc. Soc. Exptl. Biol. Med.*, **103**, 172 (1960).

(3) L. J. Lerner, A. Bianchi, M. Dzelzkalns, and A. Borman, *Proc. Soc. Exptl. Biol. Med.*, **115**, 924 (1964).

(4) R. Hirschmann, G. A. Bailey, R. Walker, and J. M. Chemerda, *J. Am. Chem. Soc.*, **81**, 2822 (1959).



instances, the esterification of 17α-hydroxyprogesterone,[5] the formation of acetals and ketals of 16α,17α-dihydroxyprogesterone,[6] and the introduction of chlorine and/or unsaturation at position 6,[7] as well as the ethynylation of testosterone[8] have been among the modifications leading to compounds with potentiated progestational activity. Our object was to incorporate these structural features into A-nor steroids to determine whether this hormonal activity could be observed.

We therefore set out to synthesize 6-chloro-6-dehydro-A-norprogesterone (**12**), 6-chloro-6-dehydro-16α,17α-dimethylmethylenedioxy-A-norprogesterone (**14**), 6-chloro-6-dehydro-17α-acetoxy-A-norprogesterone (**16**), and 6-chloro-6-dehydro-17α-ethynyl-A-nortestosterone (**18**).

The synthesis of 17α-acetoxy-A-norprogesterone (**5**) from A-norprogesterone (**1**) required as the initial step selective enol acetylation at C-20 in preference to C-2. It was encouraging to us that the preparation of the enol acetate of A-norcholestenone had not been realized even under forcing conditions.[9] Room temperature enol acetylation[10] of **1** afforded a mixture of geometric 17(20)-enol acetate isomers which could not be separated by chromatography. Fractional crystallization from isopropyl ether gave a small amount of one isomer, whose analysis and spectral properties were in agreement with an enol acetate structure (**3**). The mixture of enol acetate isomers was used in subsequent reactions.

(5) K. Junkmann, *Arch. Exptl. Pathol. Pharmakol.*, **223**, 244 (1954); M. E. Davies and G. Wied, *J. Clin. Endocrinol. Metab.*, **15**, 923 (1955).

(6) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **80**, 2338 (1958).

(7) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *ibid.*, **81**, 3485 (1959).

(8) H. H. Inhoffen, W. Logemann, W. Hohlweg, and A. Serini, *Ber.*, **71**, 1024 (1938).

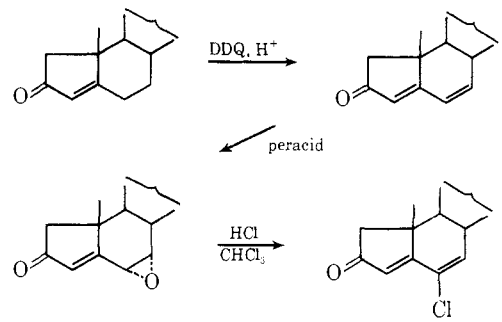
(9) W. G. Dauben and G. A. Boswell [*J. Am. Chem. Soc.*, **83**, 5003 (1961)] obtained an oily product the ultraviolet spectrum of which showed the presence of the $\Delta^{2,4}$-dienol acetate contaminated with starting material.

(10) D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones, and T. Walker, *J. Chem. Soc.*, 747 (1954).

Since the next step required peracid treatment of **3** to form the 17,20-oxide, the susceptibility of ring A to peracid oxidation was determined by treatment of A-nortestosterone (**2**) with *m*-chloroperbenzoic acid. Even after 1 day, no reaction had taken place as evidenced by tlc and the ultraviolet spectrum of the reaction mixture. Thus treatment of **3** with peracid in $CHCl_3$ at room temperature for 2–3 hr followed by methanolic KOH solution gave 17α-hydroxy-A-norprogesterone (**4**). Acetylation of **4** afforded 17α-acetoxy-A-norprogesterone (**5**).

The preparation of the 6-chloro-6-dehydro-A-nor steroids was then carried out by the sequence of reactions shown below (Scheme I) starting from **1**, **2**, **5**, 16α,17α-dimethylmethylenedioxy-A-norprogesterone (**6**)[11] and 17α-ethynyl-A-nortestosterone (**7**).[12]

SCHEME I



Treatment of **1** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and HCl[13] in dioxane at room temperature for 16 hr gave a crude product whose ultraviolet spectrum indicated the presence of a 6-dehydro compound (λ 277 mμ) and material with a maximum at 232 mμ. Chromatography of the resultant mixture followed by fractional crystallization afforded a halogen-containing compound (Beilstein) which has been assigned the 7α-chloro structure (**8**) on the basis of its elemental analysis and the following. The ultraviolet spectrum [λ_{max}^{alc} 232 mμ (ϵ 16,900)] and infrared spectrum (λ_{max}^{Nujol} 5.84 and 6.12 μ) indicated an α,β-unsaturated ketone system. The nmr spectrum showed a multiplet at τ 5.59 ($W_{1/2} \sim 7$ cps) which could be assigned to the 7β-proton since there was no large coupling constant as would be expected for a 7α-(axial) proton.[14] Furthermore, the multiplet which appeared at τ 7.03 ($W_{1/2} \sim 6$ cps) could be assigned to the protons at C-6 and likewise showed no large coupling constant.

Indeed, collidine dehydrohalogenation of **8** gave the known 6-dehydro-A-norprogesterone (**9**).[15] Similar treatment of **2** and **5**–**7** also gave mixtures (ultraviolet, nmr, and Beilstein) of 7α-chloro and 6-dehydro products. However, only in the cases of **2** and **7** could the 7α-chloro products **10** and **11** be isolated in pure form. In subsequent experiments the crude reaction products from the DDQ–HCl reaction were treated with collidine to obtain the 6-dehydro compounds exclusively.

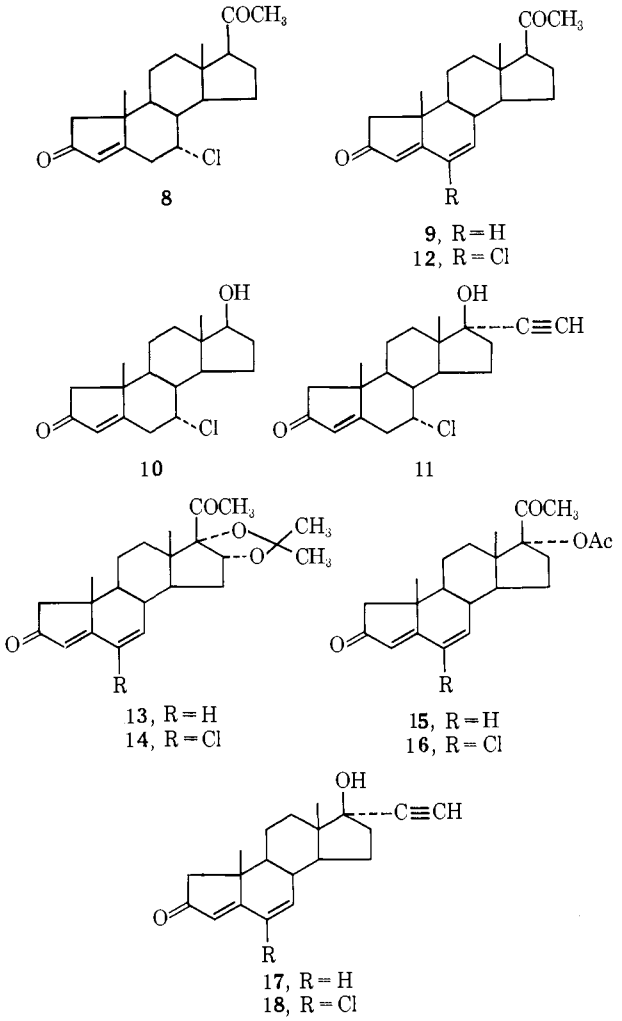
(11) F. L. Weisenborn, U. S. Patent 3,213,142 (1965).

(12) S. D. Levine, *Steroids*, **7**, 477 (1966).

(13) H. J. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962).

(14) Y. Kawazoa, Y. Sato, I. Okamora, and K. Tsuda [*Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963)] reported a $W_{1/2}$ of >16 cps for the 7α-proton in a series of 7β-hydroxy steroids and a $W_{1/2}$ of <12 cps for the 7β-proton of the epimeric 7α-hydroxyl compounds.

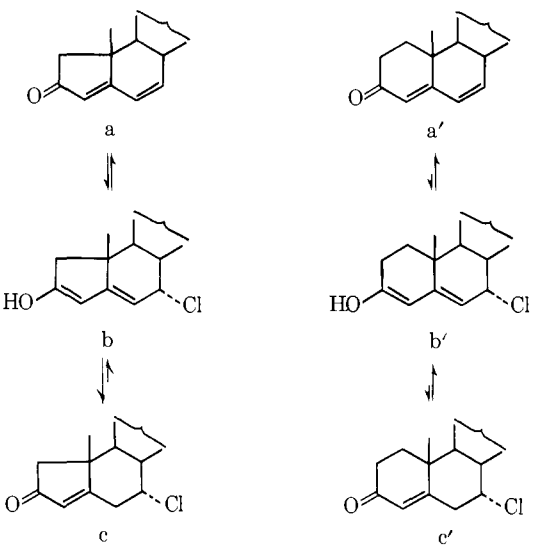
(15) F. L. Weisenborn, U. S. Patent 3,141,044 (1964).



It was apparent that the rate of dehydrogenation of A-nor steroids was slower than that of normal steroids as evidenced by the delayed precipitation of the 2,3-dichloro-5,6-dicyanohydroquinone during the reaction. With normal steroids this hydroquinone begins to separate as HCl is bubbled into the solution,[13] while in the case of A-nor steroids, precipitation does not begin for *ca.* 15 min. That this is a reflection of the difficulty of enolization of Δ^3-2-keto-A-nor steroids as compared to Δ^4-3-keto normal steroids is supported by the failure to obtain a $\Delta^{2,5}$-dienol acetate[9] and the failure of formation of the Δ^5-2-ketal during ketalization.[16] Under similar conditions the $\Delta^{3,5}$-dienol acetate[17] and Δ^5-3-ketal form readily in the normal series.[18] Although formation of the $\Delta^{2,5}$-dienol in the A-nor series is not as facile a process as in the normal series, once any dienol forms, the 7α-proton is irreversibly removed by the DDQ and the 6-dehydro product accumulates.

The unique formation of a 7α-chloro compound from the DDQ–HCl reaction is postulated to occur by Michael addition of HCl[19] to the 6-dehydro derivative and, indeed, reaction of **9** with HCl in dioxane gave an equilibrium mixture of **8** and **9** in approximately the same ratio as had been observed in the DDQ–HCl reaction. No 7α-chloro compounds have been reported to be obtained by either DDQ–HCl treatment of Δ^4-3-ketones or by Michael addition of HCl to $\Delta^{4,6}$-3-ones. Reaction of testosterone or 16α,17α-dimethylmethylenedioxyprogesterone[20] with DDQ and HCl gave the 6-dehydro derivatives as the only isolable products. That some 1:6 addition of HCl actually does occur in the reaction mixture under these conditions is suggested by the ultraviolet spectrum of 6-dehydrotestosterone[21] in dioxane containing HCl which indicated an equilibrium mixture of 7α-chloro (λ 238 mμ, ~40%) and 6-dehydro (λ 277 mμ, ~60%) components.[22] The ultraviolet spectrum of **11** taken in dioxane containing HCl showed just the presence of the 7α-chloro derivative (λ 238 mμ). We attribute the fact that the 7α-chloro compound can be isolated in the A-nor series to the difficulty of formation of the 7α-chloro-2,5-dienol b from c, while in the normal series the 7α-chloro-3,5-dienol b′ forms easily from c′ and leads to dehydrochlorination upon work-up of the reaction mixture (Scheme II).

Scheme II



Epoxidation of the 6-dehydro compounds with *m*-chloroperbenzoic acid gave the 6α,7α-oxides which on treatment with excess HCl in $CHCl_3$ were converted to the desired 6-chloro-6-dehydro derivatives.

Biological Activity.—Table I lists the approximate oral and subcutaneous progestational activity in the Clauberg assay of several of these A-nor steroids and the corresponding normal steroids. Compounds **14** and **16** represent the first examples of A-nor steroids having this hormonal activity. Compounds **8** and **15** have no significant activity in this assay by both the oral and subcutaneous routes.

(16) S. D. Levine and P. A. Diassi, *J. Org. Chem.*, **30**, 1325 (1965).

(17) See J. F. W. Keana in "Steroid Reactions," C. Djerassi, Ed., Holden Day, Inc., San Francisco, Calif., 1963, pp 37–42, for references in this area.

(18) (a) E. F. Fernholz and H. E. Stavely, Abstracts, 102nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1941, p 39M; (b) R. Antonocci, S. Bernstein, R. Littel, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952); (c) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(19) R. T. Rapala and M. F. Morray, Jr. [*J. Med. Chem.*, **5**, 1049 (1962)], have reported on the Michael addition of HCl to a Δ^{16}-20-one steroid to give the 16α-chloro derivative.

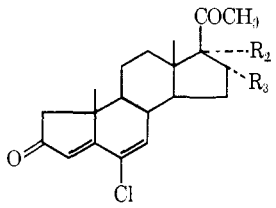
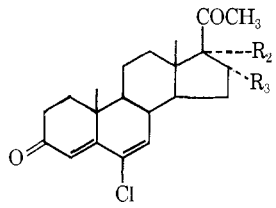
(20) G. Cooley, B. Ellis, F. Hartley, and V. Petrow, *J. Chem. Soc.*, 4373 (1955).

(21) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(22) The spectra of 6-dehydrotestosterone in dioxane containing either 0.5 *N* H_2SO_4 or concentrated HCl only exhibited absorption at 277 mμ indicating the exclusive presence of the $\Delta^{4,6}$-3-one system.

TABLE I

BIOLOGICAL ACTIVITY

R_2	R_3	Progestational activity (Clauberg assay) Oral[a]	Sc[b]
			
H	H		0.125–0.25
16α,17α-Dimethylmethylenedioxy		0.5–1	0.5–1
OAc	H	4	4
			
16α,17α-Dimethylmethylenedioxy		2–4	2
OAc	H	64	64

[a] 16α,17α-(β-Methyl-α-phenylmethylenedioxy)progesterone = 1. [b] Progesterone = 1.

Experimental Section

Melting points are uncorrected. Values of $[\alpha]D$ have been approximated to the nearest degree. Ultraviolet spectra were determined on a Cary II spectrometer in 95% ethanol, infrared spectra on a Perkin-Elmer 21 spectrometer (KBr pellets), and nmr spectra on a Varian A-60 spectrometer ($CDCl_3$, Me_4Si as internal standard). All evaporations were carried out *in vacuo* on a rotatory evaporator and Na_2SO_4 was used as the drying agent.

20-Acetoxy-A-norpregna-3,17(20)-dien-2-one (3).—An ice-cold solution of acetic anhydride (1.5 ml) containing 3 drops of perchloric acid was added to a solution of **1** (250 mg) in CCl_4 (8 ml) and benzene (20 ml) and left at room temperature for 1 day. The reaction mixture was poured into ice–water and additional CCl_4 was added. The organic layer was separated, washed with a saturated $NaHCO_3$ solution and 8% salt solution, dried, and evaporated to give 280 mg of residue. Plate chromatography of the residue using silica gel as the adsorbent and $CHCl_3$ containing 1% methanol as the developing solvent gave a major band at about R_f 0.4, which was detectable by ultraviolet. Elution with ethyl acetate and evaporation gave a 232-mg residue. Crystallization of the residue from ether–hexane gave **3** (21 mg, mp 131–132°). Recrystallization from isopropyl ether gave the analytical sample: mp 131–132°; $[\alpha]^{29}D$ −5° (EtOH); λ 5.75, 5.92, 6.17 μ; λ 234 mμ (ε 19,400); τ 9.11 (s, 18-Me), 8.83 (s, 19-Me), 8.21 (s, 21-Me), 7.90 (s, 20-$OCOCH_3$), and 4.27 (s, 3-H).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.20; H, 8.79.

17α-Hydroxy-A-norpregn-3-ene-2,20-dione (4).—A mixture of *m*-chloroperbenzoic acid (150 mg) and **3** (225 mg) in $CHCl_3$ (4 ml) was stirred at room temperature for 2 hr. The $CHCl_3$ solution was washed wih 5% NaOH solution, 8% salt solution, dried, and evaporated to give a gum. The gum was treated with a hot solution of KOH (280 mg) in methanol (5 ml) and stirred at room temperature for 35 min and diluted with H_2O. The precipitate was collected by filtration and washed with H_2O and dried overnight at 45° *in vacuo* to afford **4** (100 mg mp 210–212°). The analytical sample was prepared by recrystallation from $CHCl_3$–ether; mp 233–234°; $[\alpha]^{26}D$ +5° (EtOH); λ 2.90, 5.87, 5.95, 6.17 μ; λ 234 mμ (ε 15,800), 300 (143); τ 9.24 (s, 18-Me), 8.82 (s, 19-Me), 7.72 (s, 21-Me); 7.15 (s, 17-OH), and 4.25 (s 3-H).

Anal. Caled for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.09; H, 8.74.

17α-Acetoxy-A-norpregn-3-ene-2,20-dione (5). A.—A mixture of **4** (61 mg) and *p*-toluenesulfonic acid monohydrate (61 mg) in acetic anhydride (0.6 ml) and glacial acetic acid (3 ml) was left at room temperature for 22 hr, diluted with H_2O, and neutralized (K_2CO_3). The reaction mixture was extracted with ether, and the extracts were washed with 8% salt solution, dried, and evaporated. Crystallization of the residue from isopropyl ether gave 5 (50 mg, mp 182–184°). The analytical sample was prepared by recrystallization from isopropyl ether: mp 186.5–187.5°; $[\alpha]^{26}D$ −47° (EtOH); λ 5.78, 5.85, 5.94 (sh), 6.17 μ; λ 234 mμ (ε 16,300), 292 (154); τ 9.31 (s, 18-Me), 8.81 (s, 19-Me), 7.95 (s, 17-$OCOCH_3$), 7.90 (s, 21-Me), and 4.26 (s, 3-H).

Anal. Caled for $C_{23}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.75; H, 8.34.

B.—A solution of 70% $HClO_4$ in acetic anhydride (1:100, 3 ml) was added to a stirred suspension of **4** (4.79 g) in acetic anhydride (110 ml). The reaction mixture was stirred at room temperature for 30 min, and then poured into ice–water and stirred until the oil, which separated initially, solidified. The precipitate was collected by filtration, and dried overnight at 45° *in vacuo* to give **5** (4.76 g, mp 186–187°).

7α-Chloro-A-norpregn-3-ene-2,20-dione (8).—Hydrogen chloride was passed into a solution of **1** (305 mg) and DDQ (254 mg) in dioxane (10 ml) for 30 sec. The reaction mixture was then left at room temperature for 16 hr. The mixture was filtered and washed with dioxane, and the filtrate was evaporated. The residue was dissolved in $CHCl_3$ and plate chromatographed using neutral alumina (activity V) as adsorbent and $CHCl_3$ as the developing solvent. Detection of the band at about R_f 0.6 by ultraviolet light and elution with ethyl acetate followed by evaporation gave a residue which on crystallization from acetone–hexane yielded **8** (108 mg): mp 124–126°; $[\alpha]^{25}D$ +36° ($CHCl_3$); λ 232 mμ (ε 16,900); τ 9.30 (s, 18-Me), 8.81 (s, 19-Me), 7.87 (s, 21-Me), 7.72 (s, 1-CH_2), 7.03 (m, $W_{1/2}$ ~ 6 cps, 6-CH_2), 5.59 (m, $W_{1/2}$ ~ 7 cps, 7β-H), 4.12 (s, 3-H).

Anal. Caled for $C_{21}H_{27}ClO_2$: C, 71.65; H, 8.12. Found: C, 71.62; K, 8.16.

A-Norpregna-3,6-diene-2,20-dione (9).—A solution of **8** (1.15 g) in collidine (25 ml) was refluxed for 1 hr, cooled, diluted with $CHCl_3$, and washed with 2 *N* HCl, H_2O, 5% $NaHCO_3$ solution, and H_2O again. It was evaporated and the residue was plate chromatographed on neutral alumina (activity V) using $CHCl_3$ as the developing solvent. The ultraviolet-absorbing band at about R_f 0.2 was eluted with ethyl acetate and evaporated, and the residue crystallized from acetone–hexane to give **9** (540 mg): mp 153–154°; $[\alpha]^{25}D$ +89° ($CHCl_3$); λ 277 mμ (ε 22,100); τ 9.26 (s, 18-Me), 8.88 (s, 19-Me), 7.86 (s, 21-Me), 7.76 (s, 1-CH_2), 4.28 (s, 3-H), 3.85 (d, d, J = 10, 2 cps, 6-H), 3.50 (d, d, J = 10, 2 cps, 7-H).

7α-Chloro-A-norandrost-3-en-17β-ol-2-one (10).—HCl was bubbled into a solution of **2** (271 mg) and DDQ (250 mg) in dioxane (10 ml) for 30 sec and the reaction mixture was left at room temperature for 3.5 hr. The mixture was filtered, and the filtrate was evaporated. Plate chromatography of the residue on neutral alumina using $CHCl_3$ as the developing solvent gave six bands. Elution of the two major bands (R_f ~0.3 and 0.4) gave a residue (176 mg) which was a mixture of the 7α-chloro and $\Delta^{5,6}$ components (uv). Retreatment as above with DDQ and HCl gave after chromatography on alumina a major band which was eluted with ethyl acetate and evaporated. Several recrystallizations from acetone–hexane gave **10**: mp 212–214°; $[\alpha]^{22}D$ −34° ($CHCl_3$); λ 232 mμ (ε 16,400); τ 9.19 (s, 18-Me), 8.81 (s, 19-Me), 7.03 (m, $W_{1/2}$ ~7 cps, 6-CH_2), 6.33 (m, 17α-H), 5.62 (m, $W_{1/2}$ ~ 9 cps, 7β-H), 4.10 (s, 3-H).

Anal. Caled for $C_{18}H_{25}ClO_2$: C, 70.00; H, 8.16; Cl, 11.48. Found: C, 70.65; H, 8.39; Cl, 12.0.

7α-Chloro-17α-ethynyl-A-norandrost-3-en-17β-ol-2-one (11).—HCl was bubbled into a solution of **7** (490 mg) and DDQ (750 mg) in dioxane (25 ml) for 10 min and the reaction mixture was left at room temperature for 67 hr. The precipitate was removed by filtration, and the filtrate was evaporated. Plate chromatography of the residue on neutral alumina (activity V) using $CHCl_3$ as the developing solvent gave three bands detectable in the ultraviolet. The least polar band was eluted with ethyl acetate and evaporated, and the residue was crystallized from ethyl acetate–isopropyl ether to give **11** (140 mg, mp 166–167° (effervescent)). The analytical sample was prepared by recrystallization from ethyl acetate–isopropyl ether: mp 172–173° (effervescent); λ 2.97, 3.07, 5.97, and 6.13 μ; λ 233 mμ (ε 14,500); τ 9.08 (s, 18-Me), 8.80 (s, 19-Me), 7.41 (s, 17α-C≡CH), 5.62 (m, $W_{1/2}$ ~ 6 cps, 7β-H) and 4.10 (s, 3-H).

Anal. Caled for $C_{21}H_{25}ClO_2$: C, 72.19; H, 7.57. Found: C, 72.16; H, 7.54.

6-Chloro-A-norpregna-3,6-diene-2,20-dione (12).—A solution of **19** (502 mg) in a $CHCl_3$ solution (25 ml) saturated with HCl was kept at 40–45° for 22 hr. The mixture was washed with H_2O and evaporated. Plate chromatography of the residue on neutral alumina (activity V) using ethyl acetate–$CHCl_3$ (1:9) as the developing solvent gave an ultraviolet-absorbing band at about R_f 0.1 which on elution with ethyl acetate, evaporation, and crystallization of the residue from acetone–hexane gave **12** (195 mg): mp 138–140°; $[\alpha]^{22}D$ +98° ($CHCl_3$); λ 279 mμ (ε 20,400); τ 9.26 (s, 18-Me), 8.86 (s, 19-Me), 7.87 (s, 21-Me), 7.67 (s, 1-CH_2), 3.95 (s, 3-H), 3.78 (d, J = 2.5 cps, 7-H).

Anal. Calcd for $C_{20}H_{25}ClO_2$: C, 72.19; H, 7.57. Found: C, 72.20; H, 7.70.

16α,17α-Dimethylmethylenedioxy-A-norpregna-3,6-diene-2,20-dione (13).—HCl was bubbled into a mixture of **6** (2.0 g) and DDQ (1.5 g) in dioxane (60 ml) for 10 min and the reaction mixture was left overnight at room temperature. The precipitate was removed by filtration and the dioxane was evaporated. The residue was dissolved in $CHCl_3$ (75 ml) and passed through a neutral alumina column (activity I, 90 g) to remove polar colored material. Elution with $CHCl_3$ (350 ml) gave upon evaporation a slightly yellow residue (2 g). The residue was refluxed in collidine (25 ml) for 1 hr. The reaction mixture was diluted with $CHCl_3$, washed with 2 N HCl and 8% salt solution, dried, and evaporated. The residue was dissolved in $CHCl_3$ (50 ml) and passed through a neutral alumina column (activity I, 90 g) to remove polar colored material. Elution with $CHCl_3$ (300 ml) gave after evaporation a residue which was crystallized from acetone–hexane to give **13** (1.0 g, mp 211–213°). The analytical sample was prepared by crystallization from acetone–hexane; mp 213–215°; $[\alpha]^{22}D$ +36° ($CHCl_3$); λ 277 mμ (ε 22,500); τ 9.29 (s, 18-Me), 8.89 (s, 19-Me), 8.81 (s, β-Me, ketal), 8.53 (s, α-Me, ketal), 7.76 (s, 1-CH_2), 4.94 (d, J = 4 cps, 16β-H), 4.26 (s, 3-H), 3.89 (d, d, J = 10, 2 cps, 6-H), 3.47 (d, d, J = 10, 2 cps, 7-H).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.64; H, 8.10.

6-Chloro-16α,17α-dimethylmethylenedioxy-A-norpregna-3,6-diene-2,20-dione (14).—A solution of **20** (200 mg) in $CHCl_3$ (10 ml saturated with HCl at 0°) was left overnight at 45°. The reaction mixture was diluted with additional $CHCl_3$ and washed with 5% $NaHCO_3$ solution and H_2O, dried, and evaporated. Plate chromatography of the residue on neutral alumina (activity V) using $CHCl_3$ as the developing solvent and elution of the least polar band with ethyl acetate gave after evaporation **14** (32 mg, mp 203–205°). The analytical sample was prepared by recrystallization from methanol; mp 203–205°; $[\alpha]^{22}D$ +13° ($CHCl_3$); λ 278 mμ (ε 21,400); τ 9.31 (s, 18-Me), 8.85 (s, 19-Me), 8.81 (s, β-Me, ketal), 8.52 (s, α-Me, ketal), 7.76 (s, 1-CH_2), 4.93 (d, J = 4 cps, 16β-H), 3.92 (s, 4-H), 3.80 (d, J = 2 cps, 7-H).

Anal. Calcd for $C_{23}H_{29}ClO_4$: C, 68.21; H, 7.22; Cl, 8.75. Found: C, 68.15; H, 7.15; Cl, 8.97.

17α-Acetoxy-A-norpregna-3,6-diene-2,20-dione (15).—HCl was bubbled into a solution of **5** (1.40 g) and DDQ (1.0 g) in dioxane (30 ml) for 5 min and the reaction mixture was left at room temperature overnight. The precipitate was filtered and the filtrate was evaporated. The residue was treated with $CHCl_3$ and the additional precipitate was filtered. The filtrate was diluted with additional $CHCl_3$ to a total volume of 80 ml and passed through a 40-g neutral alumina (activity I) column. The column was eluted with $CHCl_3$ (420 ml) and the eluate was evaporated to give a residue (1.42 g), which was refluxed in collidine (30 ml) for 75 min, cooled to room temperature, and diluted with $CHCl_3$. The $CHCl_3$ solution was washed with 2 N HCl, saturated $NaHCO_3$ solution, and 8% salt solution, dried, and evaporated. Plate chromatography of the residue using neutral alumina (activity V) as the adsorbent and $CHCl_3$ containing 10% hexane as the developing solvent gave a major band at about R_f 0.5, which was detectable by ultraviolet. Elution with ethyl acetate, afforded a residue which was crystallized from isopropyl ether to give **15** (764 mg, mp 175–176°). The analytical sample was prepared by recrystallization from isopropyl ether; mp 178–179°; $[\alpha]^{26}D$ −45° (EtOH); λ 5.78, 5.87, 6.18, and 6.35 μ; λ 277 mμ (ε 22,600); τ 9.31 (s, 18-Me), 8.88 (s, 19-Me), 7.94 (s, 17-OCOCH$_3$), 7.92 (s, 21-Me), 4.25 (s, 3-H), 3.83 (d, d, J ~ 1, 9.5 cps, 6-H), 3.46 (d, d, J = 2–3, 9.5 cps, 7-H).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.09; H, 7.83.

6-Chloro-17-α-acetoxy-A-norpregna-3,6-diene-2,20-dione (16).—HCl was passed into a solution of **21** (335 mg) in $CHCl_3$ (30 ml) for 3 min. The reaction mixture was left at room temperature for 2 hr, and then at 45° for 1 day. It was washed (H_2O, saturated $NaHCO_3$, and 8% salt solution), dried, and evaporated. Plate chromatography of the residue using neutral alumina (activity V) as the adsorbent and $CHCl_3$ containing 20% hexane as the developing solvent gave a major band at about R_f 0.8, which was detectable by ultraviolet light. Elution with ethyl acetate gave a residue which was crystallized from isopropyl ether–ethyl acetate to give **16** (177 mg, mp 183–184°). The analytical sample was prepared by recrystallization from isopropyl ether–ethyl acetate; mp 195.5–196.5°, $[\alpha]^{25}D$ −75° (EtOH); λ 5.78 (sh), 5.87, 6.18, and 6.33 μ; λ 280 mμ (ε 19,700); τ 9.26 (s, 18-Me), 8.84 (s, 19-Me), 7.95 (s, 17-OCOCH$_3$), 7.91 (s, 21-Me), 3.95 (s, 3-H), 3.78 (d, J = 2 cps, 7-H).

Anal. Calcd for $C_{22}H_{27}ClO_4$: C, 67.66; H, 6.96; Cl, 9.07. Found: C, 67.42; H, 7.00; Cl, 9.09.

17α-Ethynyl-A-norandrosta-3,6-dien-17β-ol-2-one (17).—A mixture of **11** and **17** (375 mg) obtained as described for the preparation of **11** was refluxed for 1 hr in collidine (8 ml), cooled, and diluted ($CHCl_3$). The $CHCl_3$ solution was washed (2 N HCl, saturated $NaHCO_3$, and 8% salt solution), dried, and evaporated. Plate chromatography of the residue on neutral alumina (activity V) using $CHCl_3$ as the developing solvent gave a major band detectable by ultraviolet light. Elution with ethyl acetate, evaporation, and crystallization from acetone–hexane afforded **17** (58 mg, mp 206–208°). The analytical sample was prepared by recrystallization from $CHCl_3$–isopropyl ether; mp 206–208°; $[\alpha]^{25}D$ −141° (EtOH); λ 2.97, 3.05, 5.88, 6.00, 6.22, and 6.33 μ; λ 278 mμ (ε 22,600); τ 9.03 (s, 18-Me), 8.88 (s, 19-Me), 7.44 (s, 17α-C≡CH), 4.27 (s, 3-H), 3.87 (d, d, J ~ 2, 10.5 cps, 6-H), and 3.49 (d, d, J ~ 1, 10.5 cps, 7-H).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.04; H, 8.14.

6-Chloro-17α-ethynyl-A-norandrosta-3,6-dien-17β-ol-2-one (18).—HCl was passed into a solution of **22** (218 mg) in $CHCl_3$ (20 ml) for 5 min. The reaction mixture was left at room temperature for 2 hr and then at 45° for 19 hr. The reaction mixture was washed (saturated $NaHCO_3$, 8% salt solution), dried, and evaporated. Crystallization of the residue from $CHCl_3$–isopropyl ether gave **18** (122 mg, mp 214.5–216.5°). The analytical sample was prepared by recrystallization from $CHCl_3$–isopropyl ether; mp 227.5–228.5°; $[\alpha]^{24}D$ −122° ($CHCl_3$); λ 2.88, 3.00, 5.93, 6.22, and 6.35 μ; λ 280 mμ (ε 20,200); τ 9.05 (s, 18-Me), 8.86 (s, 19-Me), 7.43 (s, 17α-C≡CH), 3.80 (d, J = 2 cps, 7-H), and 3.94 (s, 3-H).

Anal. Calcd for $C_{20}H_{23}ClO_2$: C, 72.63; H, 7.08; Cl, 10.72. Found: C, 72.67; H, 7.03; Cl, 10.94.

6α,7α-Oxido-A-norpregn-3-ene-2,20-dione (19).—A solution of **9** (400 mg) in CH_2Cl_2 (50 ml) was cooled to 0° and m-chloroperbenzoic acid (900 mg) was added in small portions. The reaction was then left at room temperature for 40 hr. The solution was washed (5% $NaHCO_3$, 5% Na_2SO_3, H_2O) and then evaporated. The residue on plate chromatography using neutral alumina (activity V) as adsorbent and $CHCl_3$ as the developing solvent gave a major band at about R_f 0.5 detectable by uv light. Elution with ethyl acetate followed by evaporation and crystallization from acetone–hexane gave **19** (151 mg): mp 168–170°; $[\alpha]^{22}D$ +95° ($CHCl_3$); λ 234 mμ (ε 13,100); τ 9.27 (s, 18-Me), 8.89 (s, 19-Me), 7.86 (s, 21-Me), 7.78 (s, 1-CH_2), 6.57 (d, d, J = 3.5, <1 cps, 7β-H), 6.14 (d, J = 3.5 cps, 6β-H), 3.73 (s, 3-H).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.37; H, 8.34.

6α,7α-Oxido-16α,17α-dimethylmethylenedioxy-A-norpregn-3-ene-2,20-dione (20).—A solution of **13** (500 mg) and m-chloroperbenzoic acid (1 g) in CH_2Cl_2 (50 ml) was left at room temperature for 20 hr. The reaction mixture was washed (saturated $NaHCO_3$, 5% Na_2SO_3, 8% salt solution), dried, and evaporated. Plate chromatography of the residue on neutral alumina (activity V) using $CHCl_3$–hexane (2:1) as the developing solvent, gave a major band detectable in the ultraviolet. Elution with ethyl acetate gave after evaporation a residue which was crystallized from methanol to give **20** (246 mg, mp 246–248°). Recrystallization from methanol gave the analytical sample: mp 251–252°; $[\alpha]^{26}D$ +41° ($CHCl_3$); λ 233 mμ (ε 16,300); τ 9.31 (s, 18-Me), 8.89 (s, 19-Me), 8.81 (s, β-Me, ketal), 8.50 (s, α-Me, ketal), 7.76 (s, 21-Me), 6.63 (d, J = 3.5 cps, 7β-H), 6.19 (d, J =, 3.5 cps, 6β-H), 4.93 (d, J = 4.5 cps, 16β-H), 3.78 (s, 3-H).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.76; H, 8.02.

6α,7α-Oxido-17α-acetoxy-A-norpregn-3-ene-2,20-dione (21).—A mixture of **15** (320 mg) and *m*-chloroperbenzoic acid (600 mg) in CH_2Cl_2 (40 ml) was left at room temperature for 66 hr. The CH_2Cl_2 solution was washed (saturated $NaHCO_3$, 5% Na_2SO_3, 8% salt solution), dried, and evaporated. Crystallization of the residue from ether–$CHCl_3$ gave **21** (191 mg, mp 202–204°). The analytical sample was prepared by recrystallization from acetone–hexane; mp 232–233°; $[\alpha]^{30}D$ −15° (EtOH); λ 5.78, 5.86, and 6.13 μ; λ 235 mμ (ε 11,700); τ 9.28 (s, 18-Me), 8.88 (s, 19-Me), 7.94 (s, 17-OCOCH$_3$), 7.88 (s, 21-Me), 6.61 (d, d, J < 1, 3.5 cps, 7β-H), 6.18 (d, J = 3.5 cps, 6β-H), 3.78 (s, 3-H).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.97; H, 7.57.

6α,7α-Oxido-17α-ethynyl-A-norandrost-3-en-17β-ol-2-one (22).—A mixture of **17** (1.8 g) and *m*-chloroperbenzoic acid (3.1 g) in CH_2Cl_2 (150 ml) was left at room temperature for 65 hr. The CH_2Cl_2 solution was washed (saturated $NaHCO_3$, 5% Na_2SO_3, 8% salt solution), dried, and evaporated. Plate chromatography of the residue on neutral alumina (activity V) using $CHCl_3$ as the developing solvent gave a major band detectable in the ultraviolet. Elution with ethyl acetate, evaporation, and crystallization from ethyl acetate afforded **22** (302 mg, mp 222–224°). The analytical sample was prepared by recrystallization from ethyl acetate: mp 241.5–243.5°; $[\alpha]^{25}D$ −79° ($CHCl_3$); λ 2.97, 3.05, 5.82, 5.97 and 6.17 μ; λ 234 mμ (ε 14,300); τ 9.06 (s, 18-Me), 8.89 (s, 19-Me), 7.43 (s, 17α-C≡CH), 6.63 (d, J = 3.5 cps, 7β-H), 6.19 (d, J = 3.5 cps, 6β-H), and 3.79 (s, 3-H).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 76.80; H, 7.74. Found: C, 76.43; H, 7.58.

Acknowledgment.—We wish to thank Mr. E. Yiacas and Dr. L. Lerner for the biological results, Mr. J. Alicino and his staff for analytical results, and Dr. A. I. Cohen for the nmr data.

The Synthesis of Hydroxylamine Derivatives Possessing Hypocholesteremic Activity

B. J. LUDWIG, F. DÜRSCH, M. AUERBACH, K. TOMECZEK, AND F. M. BERGER

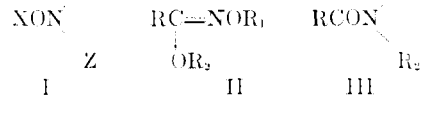
Wallace Laboratories, Division of Carter-Wallace, Inc., Cranbury, New Jersey

Received March 3, 1967

The preparation of a variety of O-aralkyl- and O,N-diaralkylhydroxylamine compounds is reported. These include, in addition to the amines, acyl- and aroylhydroxamates, carbalkoxy- and carbaryloxyhydroxamates, and various urea compounds derived from the hydroxylamines. Many of these compounds show significant hypocholesteremic activity upon oral administration to rats. Aralkylation of acetohydroxamic acid is shown to lead to the O,N-diaralkylated rather than O,O′-diaralkylated reaction product. O,N substitution (III) is therefore assumed for the series of analogous acyl- and aroylhydroxamates described.

The biological and pharmacological properties of a large variety of hydroxylamine derivatives have been evaluated in the past. Discovery of the antibacterial properties of canavanine[1] and of cycloserine[2] stimulated the search for antimicrobials containing the oxyamino group. Hydroxylamine derivatives have been reported to possess antibacterial, herbicidal, enzyme inhibiting, and antitumor activities and to have anticonvulsant, analgesic, antirheumatic, diuretic, local anesthetic, hypoglycemic, and CNS stimulating and depressing properties. These reported activities are apparently not necessarily dependent on the hydroxylamine moiety since the corresponding amino analogs frequently exhibit similar activities. In other cases the hydroxylamine function seems to be essential for biological activity. In many investigations these aminooxy compounds have been found to bear little, if any, biological resemblance to their amine counterparts.[3]

We now wish to report the preparation and the results of preliminary pharmacological evaluation of a number of hydroxylamine derivatives that significantly lower the serum cholesterol concentration of warm blooded animals.[4] These compounds consist of aralkoxyamines (I, X = aralkyl; Y = Z = H), N-aralkylaralkoxyamines (I, X = Y = aralkyl; Z = H), a number of the corresponding acyl- and aroylhydroxamates (I, Z = RCO), carbalkoxy- and carbaryloxyhydroxamates (I, Z = ROCO), and urea derivatives (I, Z = $CONH_2$, CONHR, CONHCOR). Also included in this study are several related compounds of these types having aryloxyalkyl rather than aralkyl substitution.



The preparation of these compounds followed in general well-established routes of synthesis (Chart I). Aralkylation of N-hydroxyurethan A with the appropriate aralkyl halides[3a,5,6] furnished good to excellent yields of the aralkyl carbethoxyhydroxamates B or of the corresponding aralkyl N-aralkylcarbethoxyhydroxamates C depending on the ratio of the reactants (reactions 1 and 2). These aralkylations were usually performed in anhydrous ethanol using sodium ethoxide or KOH as acid acceptors. The reactions were exothermic when substituted benzyl bromides were employed, and it was usually possible to obtain good con-

(1) B. E. Volcani and E. E. Snell, *J. Biol. Chem.*, **174**, 893 (1948).

(2) (a) F. A. Kuehl, F. J. Wolf, N. R. Trenner, R. L. Peck, E. Howe, B. D. Hunnewell, G. Downing, E. Newstead, and K. Folkers, *J. Am. Chem. Soc.*, **77**, 2344 (1955); (b) P. H. Hidy, E. B. Hodge, V. V. Young, R. L. Harned, G. A. Brewer, W. F. Phillips, W. F. Runge, H. E. Stavely, A. Pohland, H. Boaz, and H. R. Sullivan, *ibid.*, **77**, 2346 (1955).

(3) (a) For a comprehensive review of the literature on O-substituted oxyamines, see A. O. Ilvespää and A. Marxer, *Chimia* (Aarau), **18**, 1 (1964); (b) P. Mamalis, L. Jeffries, S. A. Price, M. J. Rix, and D. J. Outred, *J. Med. Chem.*, **8**, 684 (1965), have summarized the literature dealing with the biological and pharmacological activities of these compounds.

(4) (a) The effect of one of these compounds, benzyl N-benzylcarbobenzoxyhydroxamate, on experimental atherosclerosis and hypercholesterolemia has been described; see F. M. Berger, J. F. Douglas, B. J. Ludwig, and S. Margolin, *Proc. Soc. Exptl. Biol. Med.*, **114**, 337 (1963); J. F. Douglas, B. J. Ludwig, S. Margolin, and F. M. Berger, *J. Atherosclerosis Res.*, **6**, 90 (1966); J. F. Douglas, *Proc. Soc. Exptl. Biol. Med.*, **117**, 190 (1964). (b) F. M. Berger and B. J. Ludwig, U. S. Patents 3,245,878 (April 12, 1966) 3,278,583 (Oct 11, 1966), 3,280,171 (Oct 18, 1966).

(5) A. T. Fuller and H. King, *J. Chem. Soc.*, 963 (1947).

(6) (a) L. W. Jones, *Am. Chem. J.*, **20**, 1 (1898); (b) L. W. Jones and E. E. Fleck, *J. Am. Chem. Soc.*, **50**, 2018 (1928).