water and evaporated to dryness under reduced pressure. To the yellow solid residue there was added 200 ml of methanol, 16 g of $NaOAc \cdot 3H_2O$, 40 ml of water, and 16 ml of AcOH; the resulting solution was refluxed for 4 hr. The methanol was evaporated and 200 ml of 4 *N* HCl was added to the residual mixture of oil and water, which was then extracted (CH_2Cl_2). The extract was washed with dilute base and water and was then dried and evaporated. Chromatography of the residual oil over silica gel (elution with 1:1 ether–pentane) followed by two crystallizations from acetonitrile gave 4.25 g of pure **15**, mp 162.5–163.5°, λ_{max} 242 mμ (ε 16,700), $[\alpha]^{25}D$ +70.2° [lit.[2] mp 158–159°, $[\alpha]^{22}D$ +62.2° (*c* 0.98), λ_{max} 241 mμ (ε 16,500)].

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.27; H, 9.93.

Steroids Possessing Nitrogen Atoms. III. Synthesis of New Highly Active Corticoids. [17α,16α-*d*]Oxazolino Steroids[1]

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The preparation of [17α,16α-*d*]-2′-methyloxazolino analogs of prednisone, prednisolone, and 9α-fluoroprednisolone, from 17α-azido-5α-pregnane-3β,16α-diol-11,20-dione 3,16-diacetate, is described. Preliminary pharmacological data show that the oxazolino analogs of prednisolone and 9α-fluoroprednisolone are significantly active when tested for neoglycogenetic and antiinflammatory activity in the rat.

In our previous paper[2] we described the preparation and demonstrated the structure of 5α-pregnan-3β-ol-11,20-dione[17α,16α-*d*]-2′-methyloxazoline (IIa). Due to the chemical stability of the oxazoline ring, this compound represented an excellent material for continuing our studies aimed at obtaining 17-nitrogen derivatives of steroid hormones. The present paper describes in detail the synthesis of the oxazoline analogs of prednisone, prednisolone, and 9α-fluoroprednisolone.

Starting from IIa which was prepared from the azide I by an improved method compared to that previously described,[2] we obtained excellent yields of pregnanetrione IIIa by oxidation with chromic acid in acetone. The introduction of a bromine atom followed by dehydrobromination led to the 1,2-dehydro derivative IV. Subsequent treatment with SeO_2 in *t*-butyl alcohol gave the diene V. This compound was more easily obtained from the 2,4-dibromo derivative IIIc by heating in dimethylformamide (DMF) with Li salts.

Attempts to introduce a bromine atom at C_{21} in the oxazoline II, under various experimental conditions, have failed. This absence of reactivity is not unusual in 16,17-disubstituted pregnane derivatives and is reported, for instance, for 17α-bromo-3β,16β-diacetoxy-5α-pregnan-20-one[3] and 16α,17α-dihydroxypregn-4-ene-3,20-dione 16,17-acetonide.[4] Allen and Weiss[4a] reported further that 16α,17α-isopropylidenedioxypregnan-20-one derivatives failed to give both 20-semicarbazones and 21-iodo compounds.

By contrast, good results were obtained in our 21-iodination of V according to the Ringold–Stork method modified by Rothman, *et al.*[5] The 21-iodo derivative reacted regularly with triethylammonium acetate to give the oxazoline analog of prednisone acetate (VI).

Conversion of VI into the 11β-hydroxy derivative *via* the 3,20-bis(semicarbazone), reduction with complex metal hydrides, and hydrolysis of the bissemicarbazone did not give appreciable yields of the required compound XII. It was found to be much more convenient to reduce the 20-semicarbazone VII, obtained from IIa, with $NaBH_4$. The facile conversion of IIa to the semicarbazone VII, when compared with the lack of reactivity of 20-ketopregnane-16α,17α-dihydroxyacetonides, suggests that other factors, and not merely steric hindrance, must intervene in order to explain the noteworthy different chemical behavior between the D-ring-fused oxazoline- and dioxolidine-pregnanes. The 11β-hydroxy derivative VIII was hydrolyzed to IX by merely boiling with HCl in aqueous methanol. This process has given better yields than other methods[6] which necessitate the use of pyruvic or nitrous acid. Selective oxidation of the 3-hydroxyl of IX, according to Oppenauer, led to the 3-keto derivative X, and the diene XI was obtained from this, by dibromination in dioxane and dehydrobromination with Li salts and DMF. 21-Acetoxylation performed as described for VI furnished the oxazoline analog of prednisolone (XII).

The synthesis of the 9α-fluoro derivative XV was performed in a routine manner, dehydrating[7] the 11β-hydroxy steroid XII to $\Delta^{1,4,9(11)}$-triene XIII; on adding HOBr to the 9,11 double bond and treating the bromohydrin with alkali the 9β,11β-epoxide XIV was obtained. Reaction of XIV with anhydrous HF supplied the required [17α,16α-*d*]-2′-methyloxazoline of 9α-fluoroprednisolone (XV).[8,9]

Biological Results.[10]—The compounds have been examined for neoglycogenetic[11] and antigranulomatous

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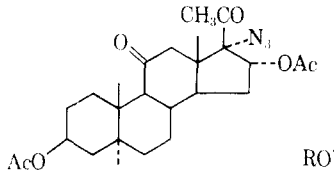

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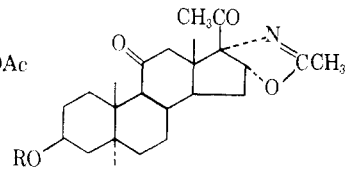
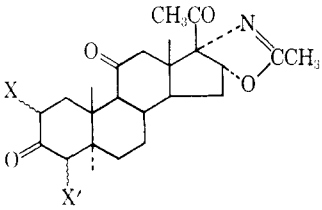
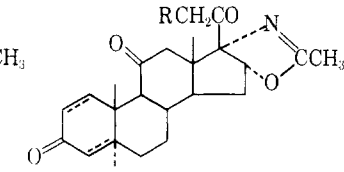


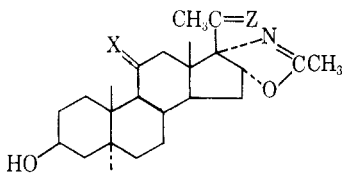
IIa, R = H
b, R = Ac



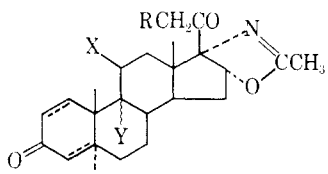
IIIa, X = X′ = H
b, X = Br; X′ = H
c, X = X′ = Br



IV, R = H; Δ^1
V, R = H; $\Delta^{1,4}$
VI, R = OAc; $\Delta^{1,4}$



VII, X = O; Z = NNHCONH$_2$
VIII, X =  ; Z = NNHCONH$_2$
IX, X =  ; Z = O



X, R = H; X = OH; Y = α-H
XI, R = H; X = OH; Y = α-H; $\Delta^{1,4}$
XII, R = OAc; X = OH; Y = α-H; $\Delta^{1,4}$
XIII, R = OAc; X, Y = double bond; $\Delta^{1,4}$
XIV, R = OH; X, Y = β-epoxyde; $\Delta^{1,4}$
XV, R = OH; X = OH; Y = α-F; $\Delta^{1,4}$

activities[12] in Wistar male rats. Compound XII revealed an activity 10 and 35 times greater than that of hydrocortisone in the two tests mentioned, while the 9α-fluoro derivative XV was 180 and 250 times more potent, respectively, than hydrocortisone. As far as we know, this is the first example of highly active corticoids in which the oxygen group at C_{17} is replaced by a nitrogen atom which in turn forms part of a fused heterocyclic ring at C_{16}–C_{17}.

Experimental Section[13]

5α-Pregnan-3β-ol-11,20-dione[17α,16α-*d*]-2′-methyloxazoline (IIa).—A solution of 72 g of 17α-azido-5α-pregnane-3β,16α-diol-11,20-dione 3,16-diacetate (I)[2] in methanol (3100 ml) was hydrogenated (PtO_2, 5 g) at normal pressure. After 2.5 hr the solution was filtered from the catalyst and evaporated to dryness *in vacuo*. The residue, consisting of a mixture of a product already cyclized to oxazoline and of 17α-acetamide (both in the form of the 3-acetate), was suspended in 250 ml of 10% HCl and heated on a boiling-water bath. After 15 min the clear solution of the hydrochloride of IIa was cooled and the free base precipitated with 10% NaOH; yield 58 g of IIa, mp 210–212°.

5α-Pregnane-3,11,20-trione[17α,16α-*d*]-2′-methyloxazoline (IIIa).—A solution of IIa (13.5 g) in acetone (620 ml) was oxidized at 20° with approximately 12 ml of 8 *N* chromic acid (Jones' reagent). The product separated on dilution with water and evaporation of the acetone: mp 222–224° (9.4 g). A further 2.2 g was obtained on adding excess aqueous NaOH to the mother liquor until $Cr(OH)_3$ redissolved. The triketone IIIa crystallized from CH_2Cl_2–hexane: mp 223–226°; $[\alpha]D$ +127.1° (*c* 0.5); ir, ν 1710 (C_3=O, C_{11}=O), 1660 (C=N) cm^{-1}; nmr, τ = 9.37 (18-CH_3), 8.78 (19-CH_3), 7.96 and 7.77 ppm (21-CH_3 and CH_3-C=N–).

Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.65; H, 8.1; N, 3.63. Found: C, 71.40; H, 8.14; N, 3.80.

2ξ-Bromo-5α-pregnane-3,11,20-trione[17α,16α-*d*]-2′-methyloxazoline (IIIb).—A solution of IIIa (11.3 g) in dioxane (200 ml) containing 6 ml of 32% HBr in AcOH was brominated with a solution of Br_2 (4.88 g) in dioxane (48 ml). The reaction mixture was then poured into 1500 ml of ice–water containing KOAc (20 g). The product was extracted with ethyl acetate, and the solvent was washed with saturated NaCl solution and then concentrated to a small volume. The 2-bromo derivative IIIb (8.9 g) crystallized; mp 275–287° dec; $[\alpha]D$ +93.3° (*c* 0.5); nmr, τ = 9.37 (18-CH_3), 8.82 (19-CH_3), 7.94 and 7.76 (21-CH_3 and CH_3C=N–).

Anal. Calcd for $C_{23}H_{30}BrNO_4$: C, 59.5; H, 6.51; Br, 17.2. Found: C, 59.31; H, 6.61; Br, 17.4.

5α-Pregn-1-ene-3,11,20-trione[17α,16α-*d*]-2′-methyloxazoline (IV).—A suspension of IIIb (8.6 g) in DMF (100 ml) was treated with LiBr (2.6 g) and Li_2CO_3 (2.6 g). The mixture was heated, with stirring, at 140° for 4 hr and then poured into 100 ml of ice–water and extracted with ethyl acetate. The solvent was washed with saturated NaCl and evaporated *in vacuo*, leaving crude IV which crystallized from acetone–hexane yielding 5.6 g, mp 204–210°. A sample recrystallized from methanol melted at 211–212°; $[\alpha]D$ +153° (*c* 0.5); λ_{max} 225–226 mμ ($E^{1\%}_{1cm}$ 327) (CH_3OH); ir, ν 1710 (C_{11}=O, C_{20}=O), 1670 (C_3=O, C=N) cm^{-1}; nmr, τ = 9.35 (18-CH_3), 8.75 (19-CH_3), 7.96 and 7.77 (21-CH_3 and CH_3C=N–).

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.0; H, 7.62; N, 3.65. Found: C, 72.11; H, 7.66; N, 3.84.

Pregna-1,4-diene-3,11,20-trione[17α,16α-*d*]-2′-methyloxazoline (V). A. From IIIa.—To a solution of IIIa (14.1 g) in dioxane (254 ml) was added 12 ml of 32% HBr in AcOH and bromination was performed at room temperature with a solution of Br_2 (11.82 g) in dioxane (112 ml). Thirty minutes after completing the addition of the Br_2, the crude 2,4-dibromo derivative was isolated by pouring the reaction mixture into ice–water (3500 ml) containing KOAc (50 g). The product (19 g) was dried and then dissolved in anhydrous DMF (275 ml) and heated for 4 hr at 140° with LiBr (7.2 g) and Li_2CO_3 (7.2 g). The mixture was poured into ice–water and extracted with ethyl acetate, yielding 13.2 g of crude product. Column chromatography on 220 g of silica gel and crystallization from methanol gave pure V (6.8 g): mp 229–231°; $[\alpha]D$ +170.3° (*c* 0.5); λ_{max} 238 mμ ($E^{1\%}_{1cm}$ 403) (CH_3OH); ir, ν 1715 (C_{11}=O, C_{20}=O), 1670 (C_3=O, C=N) cm^{-1}, typical band of the $\Delta^{1,4}$-3-keto group at 891 cm^{-1}; nmr, τ = 9.30 (18-CH_3), 8.56 (19-CH_3), 7.98 and 7.78 ppm (21-CH_3 and CH_3C=N–).

Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.4; H, 7.14; N, 3.67. Found: C, 72.25; H, 7.00; N, 3.63.

B. From IV.—To a solution of IV (5 g) in *t*-butyl alcohol (250 ml) and acetic acid (3.3 ml), 1.6 g of SeO_2 was added in two portions and the solution boiled for 18 hr, after each addition. Selenium was removed by filtering, the liquid evaporated to dryness, and the residue was taken up in ethyl acetate. The solvent was washed with $NaHCO_3$, $(NH_4)_2S$, and saturated NaCl solution, dried, and evaporated to dryness, leaving 4.85 g of

(12) R. Meier, W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950).

(13) Melting points were obtained on a Büchi–Tottoli apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer and nmr spectra with a Varian A-60 spectrograph, using Me_4Si as internal reference (τ = 10 ppm). The nmr and ir spectra and the specific rotations have been determined in $CHCl_3$, except in the cases expressly mentioned.

crude substance. Purification by column chromatography on SiO_2 and crystallization from acetone–hexane yielded 2.38 g of V, mp 230–232°, identical on ir analysis to the product obtained according to A, but still contaminated with the Δ^1 derivative IV recognized by ultraviolet analysis and thin layer chromatography.

Pregna-1,4-dien-21-ol-3,11,20-trione[17α,16α-d]-2′-methyloxazoline 21-Acetate (VI).—Ground CaO (9.9 g) and α,α′-azabisisobutyronitrile (330 mg) were added to a solution of V (6.6 g) in 100 ml of tetrahydrofuran (THF)–methanol (1:1). The suspension was treated dropwise under vigorous stirring with a solution of iodine (6.6 g) in THF (33 ml) and methanol (19.2 ml). The colorless suspension was diluted with CH_2Cl_2 (100 ml) and filtered from inorganic salts. The filtrate was washed with 3% aqueous $Na_2S_2O_3$ and water and evaporated at low temperature. The residue (8.5 g) dissolved in acetone (36 ml) was added to a mixture of triethylamine (60 ml), acetone (60 ml), and glacial acetic acid (36.2 ml) and boiled for 45 min. After concentration to a small volume, dilution with water, and extraction with ethyl acetate, crude 21-acetate (VI, 6.9 g) was obtained. Purification by column chromatography on SiO_2 and recrystallization from CH_2Cl_2–isopropyl ether gave 3.43 g of pure VI: mp 172–174°; $[\alpha]D$ +152° (*c* 0.5); λ_{max} 238 mμ ($E^{1\%}_{1cm}$ 353.9) (CH_3OH); ir, ν 1750 (C_{21}=O), 1735 (C_{20}=O), 1713 (C_{11}=O), 1665 (C_3=O, C=N) cm^{-1}, characteristic band of the 3-keto-$\Delta^{1,4}$ group, 890 cm^{-1}; nmr, τ = 9.22 (18-CH_3), 8.56 (19-CH_3), 7.98 and 7.83 ppm (CH_3COO and CH_3C=N–).

Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.20. Found: C, 68.44; H, 6.80; N, 3.11.

5α-Pregnan-3β-ol-11,20-dione[17α,16α-d]-2′-methyloxazoline 20-Semicarbazone (VII).—A solution of semicarbazide hydrochloride (8.3 g) in water (50 ml) and pyridine (5.75 ml) was added, over 10 min, to a boiling solution of IIa (10 g) in methanol (350 ml). After boiling for 5 hr, the liquid was concentrated *in vacuo* until it became pasty, and the product precipitated by adding 300 ml of water. The semicarbazone VII (11.5 g), mp 255–258°, was obtained. It was difficult to crystallize and was used as such for the next step without further purification; ir (Nujol), ν 3450 and 3250 (OH and NH), 1690 (C_{11}=O, amide I), 1655 (C=N), 1575 (amide II) cm^{-1}; nmr (pyridine-d_5), τ = 9.26 (18-CH_3), 8.87 (19-CH_3), 7.93 and 7.73 ppm (21-CH_3 and CH_3C=N–).

5α-Pregnane-3β,11β-diol-20-one[17α,16α-d]-2′-methyloxazoline 20-Semicarbazone (VIII).—A solution of VII (9 g) in 95% ethanol (230 ml) was treated first with $KHCO_3$ (3.6 g), dissolved in water (36 ml), and then, on boiling, with $NaBH_4$ (2.34 g). After 30 min a second portion of $NaBH_4$ (2.34 g) was added and heating was continued for 90 min. After cooling, the solution was neutralized with aqueous 5% AcOH and most of the alcohol was removed *in vacuo;* dilution with water gave crude VIII (8.5 g): mp 277–281°; in this case also the semicarbazone was not purified; ir (Nujol), ν 3300 (OH and NH) broad, 1680 (amide I), 1655 (C=N), 1575 (amide II) cm^{-1}; nmr (pyridine-d_5), τ = 8.73 (18-CH_3), 8.67 (19-CH_3), 7.97 and 7.68 ppm (21-CH_3 and CH_3C=N–).

5α-Pregnane-3β,11β-diol-20-one[17α,16α-d]-2′-methyloxazoline (IX).—Crude VIII (7.7 g) was refluxed for 1 hr with 75 ml of methanol and 75 ml of 10% HCl. The solution was decolorized with charcoal and the methanol was evaporated *in vacuo.* On neutralization with 10% NaOH, a bulky precipitate of IX (6.3 g) melting at 240–250° was obtained. The product for analysis, crystallized from methanol, melted at 254–259°; $[\alpha]D$ +103.8° (*c* 0.5, dioxane); ir (Nujol), ν 3380 and 3280 (OH), 1700 (C_{20}=O), 1640 (C=N) cm^{-1}; nmr (pyridine), τ = 8.79 (18-CH_3), 8.68 (19-CH_3), 7.99 and 7.67 ppm (21-CH_3 and CH_3C=N–).

Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.92; H, 9.06; N, 3.60. Found: C, 71.00; H, 9.13; N, 3.65.

5α-Pregnan-11β-ol-3,20-dione[17α,16α-d]-2′-methyloxazoline (X).—A solution of IX (6 g) in anhydrous toluene (230 ml) and cyclohexanone (45 ml) was treated with aluminum isopropoxide (3 g) dissolved in toluene (60 ml). The mixture was refluxed, with stirring, for 2 hr, and most of the solvent was then removed by distillation *in vacuo.* The last traces of solvent were removed by steam distillation. The suspended product[14] was collected and washed with water, and the steroid was extracted from the aluminum hydroxide with boiling methanol (130 ml). On evaporating the methanol 5.4 g of crude X was obtained. After purification by column chromatography on silica gel, 5.05 g of a homogeneous product was isolated. Crystallization from acetone–hexane afforded pure X (3.04 g): mp 196–200°; $[\alpha]D$ +108° (*c* 0.5); ir, ν 3450 (OH), 1700 (C_3=O, C_{20}=O), 1650 (C=N) cm^{-1}; nmr, τ = 9.08 (18-CH_3), 8.72 (19-CH_3), 8.01 and 7.73 ppm (21-CH_3 and CH_3C=N–).

Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58. Found: C, 71.37; H, 8.63.

Pregna-1,4-dien-11β-ol-3,20-dione[17α,16α-d]-2′-methyloxazoline (XI).—A solution of X (6.84 g) in anhydrous dioxane (123 ml) containing 8.2 ml of 25% HBr in AcOH was treated dropwise with Br_2 (5.65 g) dissolved in 50 ml of dioxane. Twenty minutes after completing the addition, the 2,4-dibromo derivative was isolated by pouring the reaction mixture into 1000 ml of ice–water containing KOAc (35 g). The dry product (9.15 g) was dissolved in DMF (120 ml) and heated under N_2 for 4 hr at 140°, stirring vigorously, in the presence of LiBr (2.88 g) and Li_2CO_3 (5.76 g). On pouring in water and extracting with ethyl acetate, crude XI (5.96 g) was obtained. Chromatography on 100 g of SiO_2 and crystallization from methanol, gave pure XI (2.35 g): mp 279–280°; $[\alpha]D$ +103.3° (*c* 0.5); λ_{max} 240–242 mμ ($E^{1\%}_{1cm}$ 402) (CH_3OH); ir, ν 3580 and 3400 (OH), 1700 (C_{20}=O), 1650 (C_3=O, C=N) cm^{-1}, characteristic band of the 3-keto-$\Delta^{1,4}$ group, 886 cm^{-1}; nmr, τ = 9.02 (18-CH_3), 8.52 (19-CH_3), 8.06 and 7.75 ppm (21-CH_3 and CH_3C=N–).

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62; N, 3.65. Found: C, 71.93; H, 7.78; N, 3.72.

Pregna-1,4-diene-11β,21-diol-3,20-dione[17α,16α-d]-2′-methyloxazoline 21-Acetate (XII).—XI (2 g) was converted into the 21-iodo derivative according to the method of example V → VI. On evaporation of CH_2Cl_2, the residue was taken up in alcohol to give 0.54 g of 21-iodo derivative melting at 226–228°. This was acetylated with triethylammonium acetate as described for VI; yield of crude 21-acetoxy derivative 0.27 g. Recrystallization from acetone–hexane gave 0.20 g of XII: mp 255–256.5°; $[\alpha]D$ +62.3° (*c* 0.5); λ_{max} 241–242 mμ ($E^{1\%}_{1cm}$ 352.5) (CH_3OH); ir, ν 3600 and 3400 (OH), 1738 (C_{21}=O), 1720 (C_{20}=O), 1650 (C_3=O, C=N) cm^{-1}, characteristic band of the $\Delta^{1,4}$-3-ketone group at 886 cm^{-1}; nmr, τ = 8.97 (18-CH_3), 8.54 (19-CH_3), 8.05 and 7.92 ppm (CH_3COO and CH_3C=N–).

Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.0; H, 7.08; N, 3.18. Found: C, 67.83; H, 7.08; N, 3.09.

Pregna-1,4,9(11)-trien-21-ol-3,20-dione[17α,16α-d]-2′-methyloxazoline 21-Acetate (XIII).—A solution of XII (500 mg) in DMF (2.7 ml) and collidine (1 ml) was treated at 10° with methanesulfonyl chloride (0.3 ml). Then 0.25 ml of 6% SO_2 in DMF was added, and the temperature was brought to 30–35° for 10 min. On dilution with 30 ml of ice–water, XIII (420 mg), mp 191–194°, was obtained. A sample for analysis, crystallized from methanol melted at 198–199°; $[\alpha]D$ −27.1° (*c* 0.5); ir, ν 1742 (C_{21}=O), 1725 (C_{20}=O), 1660 (C_3=O, C=N) cm^{-1}, characteristic band of the 3-keto-$\Delta^{1,4}$ group at 887 cm^{-1}; nmr, τ = 9.25 (18-CH_3), 8.60 (19-CH_3), 8.03 and 7.83 ppm (CH_3COO and CH_3C=N–).

Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.9; H, 6.9; N, 3.31. Found: C, 71.07; H, 7.2; N, 3.34.

9β,11β-Epoxypregna-1,4-dien-21-ol-3,20-dione[17α,16α-d]-2′-methyloxazoline (XIV).—N-Bromoacetamide (1.1 g) was added to a solution of XIII (2.4 g) in THF (24 ml) and 0.46 *N* $HClO_4$ (12.8 ml) protecting the flask from light. The mixture was stirred at room temperature for 4 hr, cooled to 10°, and saturated $NaHSO_3$ was added until the color was discharged. The clear solution was poured into 120 ml of ice–water, and 9α-bromo-11β-hydroxy derivative (2.75 g) was collected. It was dissolved in 128 ml of a methanol–chloroform mixture (3:2 v/v), cooled to 0 to 5°, and 1 *N* NaOH (5.5 ml) was added dropwise under N_2. After 5 min, a further 5.5 ml of 1 *N* NaOH was added over 30 min. The mixture was stirred at 0° for 2 hr, adjusted to pH 7–8 with AcOH, and then concentrated *in vacuo* to approximately 20 ml diluted with 130 ml of ice–water. The crude epoxide XIV (1.6 g) separated, mp 204–210°. On recrystallization from methanol 1.07 g melting at 227–230° was obtained; $[\alpha]D$ +39.7° (*c* 0.5): λ_{max} 248 mμ ($E^{1\%}_{1cm}$ 401.9) (CH_3OH); ir, ν 3500 (OH), 1710 (C_{20}=O), 1660 (C_3=O, C=N) cm^{-1}, characteristic band of the 3-keto-$\Delta^{1,4}$ group at 889 cm^{-1}; nmr, τ = 9.13 (18-CH_3), 8.57 (19-CH_3), 8.05 ppm (CH_3C=N–).

Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.70; H, 6.60; N, 3.42.

(14) It is impossible to follow the usual technique which involves final acidification of the oxidized mixture, because of the solubility in acids of this class of steroids containing a basic nitrogen.

9α-Fluoropregna-1,4-diene-11β,21-diol-3,20-dione[17α,16α-*d*]-2′-methyloxazoline (XV).—Gaseous HF (4.67 g) was passed into anhydrous THF (8.45 ml). Epoxide XIV (1 g) was added to 9.4 ml of this solution at 0° and the mixture was stirred for 1 hr at 0° and then for 6 hr at room temperature. The reaction mixture was diluted with THF (20 ml) and neutralized, cooling externally with salt and ice, by gradual addition of $NaHCO_3$ (24 g) and Na_2SO_4 (1 g). The inorganic salts were filtered off and the cake was washed with 75 ml of boiling ethyl acetate. The filtrate was concentrated *in vacuo* to dryness and the residue crystallized from acetone affording XV (0.61 g): mp 241–244°; $[\alpha]D$ +83.5° (*c* 0.5); λ_{max} 238 mμ ($E^{1\%}_{1cm}$ 373) (CH_3OH); ir, ν 3500 (OH), 1705 (C_{20}=O), 1664 (C_4=O, C=N) cm^{-1}, characteristic band of the 3-keto-$\Delta^{1,4}$ group at 890 cm^{-1}; nmr, τ = 9.02 (18-CH_3), 8.45 (19-CH_3), 8.04 ppm (CH_3C=N).

Anal. Calcd for $C_{24}H_{28}FNO_5$: C, 66.18; H, 6.71; N, 3.35. Found: C, 66.18; H, 6.86; N, 3.40.

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Nonsteroidal Hypocholesteremic Agents. I. The Synthesis and Serum Sterol Lowering Properties of Substituted 4-(2-Dialkylaminoethoxy)diphenylamines and Related Compounds[1]

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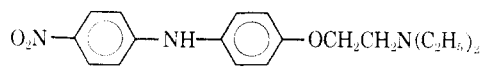
The preparation and serum sterol lowering properties of a series of 4,4′-disubstituted diphenylamines and related compounds are discussed. Initial screening data indicate that several of these compounds, synthesized by conventional means, possess oral activity greater than most nonsteroidal hypocholesteremic agents reported to date.

Our interest in the possible synthesis of hypocholesteremic agents began several years ago when the Biochemical Research Section of this laboratory observed the effective lowering of serum sterols by 4-(2-diethylaminoethoxy)-4′-nitrodiphenylamine (**1**) in both rats and mice. This discovery was timely in view of



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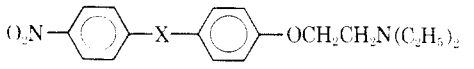
the increasing interest in the use of orally active, nonsteroidal hypocholesteremic agents[2,3] and offered a logical beginning for this investigation.

Results and Discussion

The results of a preliminary structure–activity study listed in Tables I and II point out the following very specific structural requirements for high activity in the diphenylamines: (a) as exemplified in **1**, an "electron-withdrawing" group must be in the 4 position of one ring and a basic ether residue in the 4′ position of the opposite ring; (b) maximum hypocholesteremic effects are observed when one of the aromatic rings of the diphenylamine system is a 4-nitrophenyl, a 2,4-dinitrophenyl, or a 2-nitro-4-aminophenyl group; and (c) the basic ether moiety must be comprised of an O and a tertiary amine N separated by a two-carbon chain. The marked changes in serum sterol lowering due to slight variations in the $-OCH_2CH_2N<$ portion of several hypocholesteremic agents is an interesting discovery and will be discussed in more detail later.

Having established the importance of functional groups and their relative positions in the aromatic rings of the active diphenylamines, we next considered isosteres[4] of **1** where the "bridging" –NH– group is replaced by divalent –O– and –S–. The ability of bridging atoms to promote "through conjugation" in



1, X = –NH–
2, X = –O–
3, X = –S–

derivatives such as **1**, **2**, and **3** can be ruled out because of the noncoplanarity of the aromatic systems; spectral data[5] obtained from a study of diphenyl sulfides also support this idea. Actually, compounds **1**, **2**, and **3** can be considered *para*-substituted nitrobenzenes in which the X atom conjugates through a p orbital. In this sense the –NH– group is the strongest electron donor; however, there is no reason to attribute the high activity of the diphenylamines to this property.

Although in medicinal chemistry it is not unusual for isosteres of an active compound to retain some amount of activity, the results listed in Table III indicate no retention of activity in **2** or **3**. This finding once again emphasizes the specific structural requirements in diphenylamines.

An extension of our initial research is described in Table IV where several interesting points should be noted: (a) a nitrophenyl group can be effectively replaced by 3- and 5-nitropyridyl groups; (b) the 5-nitropyridyl analog (**17**) of **1** is a potent hypocholesteremic agent; (c) within the 5-nitropyridyl series complete

(1) Portions of this paper were presented before the Division of Medicinal Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 13–17, 1965, Abstracts of Papers, p 11I.

(2) See, for example, the following references: (a) M. Friedman, S. O. Byers, and R. H. Rosenman, *Progr. Cardiovascular Diseases*, **4**, 419 (1962); (b) L. G. Humber, M. Kraml, J. Dubuc, and R. Gaudry, *J. Med. Chem.*, **6**, 210 (1963).

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(4) As defined by V. B. Schatz in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp 72–88.

(5) (a) A. Mangini and R. Passerini, *J. Chem. Soc.*, 1168 (1952); (b) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p 481.