When 8 mg. of starting material were added, the transformation appeared to go to completion in the 96-hr. period. Chromatographic analysis of a 17-day aliquot indicated that the transformation at the 10-mg. level had gone to completion and that further changes had not occurred.

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Synthesis of 1,4-Pregnadiene-17α,20α,21-triol-3,11-dione

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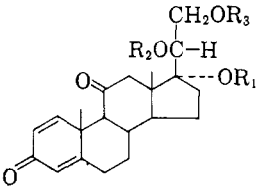
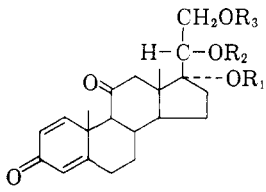
In the metabolism of adrenocortical hormones reduction of the C_{20}-ketone to a 20α- and (or) 20β-ol is frequently encountered.[1-5] After administration of prednisone or prednisolone to humans, the 20-dihydro derivatives (Δ^1-Reichstein's Substance U and E) appear to be important metabolites.[6-8] In addition A-ring reduced compounds may be produced.[8]

We have been interested in the synthesis of these 17,20,21-triols because of their metabolic significance and because of their glycogen deposition properties.[9,10] Like Szpilfogel and co-workers we also had found the *20β-ols* to have glucocorticord activity. For this reason we undertook the synthesis of a *20α-ol* such as 1,4-pregnadiene-17α,20α,21-triol-3,11-dione, which was suggested to be one of the urinary metabolites isolated after administration of prednisone to humans.[5]

Selective reduction of prednisone with sodium borohydride[9,11] yielded Δ^1-Reichstein's U 21-monoacetate (Ia). The general method of Fukushima *et al.*[12] was used to invert the configuration at C_{20} from β to α as follows: mesylation gave the 20-mesylate (Ib); acid-catalyzed acetylation formed the 17,21-diacetate-20-mesylate (Ic); internal displacement of the 20-mesylate by the 17-acetate function *with inversion at* C_{20} yielded a 20,-21-diacetate in the 20α-series (IIa); alkaline hydrolysis of the acetate groups afforded 1,4-pregnadiene-17α,20α,21-triol-3,11-dione (IIb).



Ia. R_1 = R_2 = H, R_3 = CH_3CO
b. R_1 = H, R_2 = CH_3SO_2, R_3 = CH_3CO
c. R_1 = R_3 = CH_3CO, R_2 = CH_3SO_2



IIa. R_1 = H, R_2 = R_3 = CH_3CO
b. R_1 = R_2 = R_3 = H

An attempt to apply this method to the preparation of the 11β-hydroxy analog of IIb failed due to acetylation of the 11-hydroxyl group during the acid-catalyzed C_{17}-acetylation stage. We were not able to remove this 11-acetate even with sodium methoxide.

In contrast to the reported[9] glucocorticoid activity of the corresponding 20β-ol, compound IIb was inactive in the liver glycogen test.[13]

EXPERIMENTAL[14]

1,4-Pregnadiene-17α,20β,21-triol-3,11-dione-20-mesylate-21-acetate (Ib). One gram of 1,4-pregnadiene-17α,20β,21-triol-3,11-dione-21-acetate (Ia)[9] was dissolved in 3.0 ml. of pyridine and cooled in an ice bath. To this solution was added 1.5 ml. of methanesulfonyl chloride. After standing at room temperature for 2 hr. the reaction mixture was poured into water. The resultant solid was filtered and recrystallized from methanol to give 920 mg. of the desired 20-mesylate (Ib), m.p. 173–178° (dec.).

Anal. Calcd. for $C_{24}H_{32}O_8S$: C, 59.99; H, 6.71. Found: C, 60.52; H, 6.61.

1,4-Pregnadiene-17α,20β,21-triol-3,11-dione-20-mesylate-17,21-diacetate (Ic). To 920 mg. of the mesylate (Ib) was added 16 ml. of acetic acid, 8 ml. of acetic anhydride, and 160 mg. of *p*-toluenesulfonic acid. After standing at room temperature for 3 days the mixture was poured into ice and water which contained 1.0 ml. of pyridine. It was then extracted 4 times with ethyl acetate, washed with 5% hydrochloric acid, water, and saturated sodium bicarbonate solution. The extract was dried and evaporaged under reduced pressure to yield 1.06 g. of an oil (Ic) suitable for the next step.

1,4-Pregnadiene-17α,20α,21-triol-3,11-dione-20,21-diacetate (IIa). To 1.0 g. of Ic above, 150 ml. of 96% acetic acid, and 7.5 ml. of acetic anhydride was added 15 g. of potassium acetate. This reaction mixture was heated under reflux for 3 hr. and then poured into ice water containing 1 ml. of pyridine. This was extracted thrice with ethyl ace-

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(13) Determined by C. C. Porter of the Merck Institute for Therapeutic Research.

(14) Melting points were determined on a Kofler hot stage. Rotations were determined at approximately 1% concentration.

tate, washed with 5% hydrochloric acid, water, saturated sodium bicarbonate, dried, and evaporated to yield 650 mg. of oil which crystallized when triturated with acetone-ether. After recrystallization from acetone, the resultant diacetate (IIa) melted at 255–259°.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26; acetyl, 18.95. Found: C, 67.75; H, 7.40; acetyl, 19.61. λ_{max}^{Nujol} 2.88, 5.72, 5.79, 5.85, 5.94, 6.09, 6.18μ. $[\alpha]_D^{24}$ +92° ± 2° ($CHCl_3$); M_D = +408°. $[\alpha]_D^{23}$ +71° ± 2° (dioxane); M_D +315°.

1,4-Pregnadiene-17α,20α,21-triol-3,11-dione (IIb). To 150 mg. of IIa dissolved in 5 ml. of methanol was added 2 ml. of water containing 150 mg. of potassium bicarbonate. The reaction mixture was allowed to reflux for 2 hr., evaporated to a small volume under reduced pressure, and extracted several times with ethyl acetate. After distillation of the ethyl acetate there was obtained 100 mg. of crystals which were recrystallized from methanol to yield 70 mg. of IIb with a double melting point, 225–227° and 238–240°. Another recrystallization from methanol gave 46 mg. of analytically pure material, m.p. 225–227°, 240–242°.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.03; H, 7.82. λ_{max}^{MeOH} 239 mμ, E 14,900. λ_{max}^{Nujol} 3.0, 5.88, 6.01, 6.15, 6.21μ. $[\alpha]_D^{23}$ +132° ± 2° (dioxane); M_D +477°.

ΔM_D (diacetate) $-_A M_D$ (free alcohol) = +315° − (+477°) or ΔM_D = −162°. Since the ΔM_D is negative, the configuration at C_{20} is α.[15]

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Disubstituted Tetrazoles as Analogs of Esters[1]

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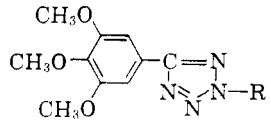
Following the elucidation of the structure of reserpine[4] and its confirmation by unequivocal synthesis,[5] efforts to determine the active portion of the molecule took a variety of courses. Of particular interest to us was the report that dialkylaminoalkyl 3,4,5 - trimethoxybenzoates exhibited certain features of the reserpine activity.[6]

In view of the acidic character of 5-substituted tetrazoles,[7] it was of interest to prepare a number of derivatives of 5-(3′,4′,5′-trimethoxyphenyl)-tetrazole (I) in which the ring was alkylated with dialkylaminoalkyl groups (II–IV). The possibility that the disubstituted tetrazoles might bear some similarity to the comparable esters, at least in the pharmacological responses evoked, was attractive.



I. R = H
II. R = —$(CH_2)_2N(C_2H_5)_2$
III. R = —$(CH_2)_3N(CH_3)_2$
IV. R = —$(CH_2)_3N(C_2H_5)_2$

Using the general procedure for preparation of 5-aryltetrazoles involving interaction of nitriles with sodium azide and acetic acid in boiling *n*-butyl alcohol,[8] 3,4,5-trimethoxybenzonitrile was converted into I in 93% yield. A general procedure involving interaction of nitriles with lithium or ammonium azides in dimethylformamide[9] which permitted shorter reaction periods was described after conclusion of this work. Ring alkylation was accomplished by interaction of I with appropriate dialkylaminoalkyl halides in aqueous acetone in the presence of sodium hydroxide. Studies on alkylation of 5-aryltetrazoles with a number of alkylating agents have shown that the 2,5-disubstituted derivatives are the major products,[10,11] although treatment of 5-phenyltetrazole with methyl iodide and sodium hydroxide in aqueous acetone gave appreciable amounts of the 1,5-disubstituted product.[10] Pharmacological screening of compounds II–IV is under way in the Schering Corp. research laboratories.

EXPERIMENTAL[12]

3,4,5-Trimethoxybenzonitrile was prepared from the acid by conversion successively to the acid chloride and amide,[13] followed by dehydration of the latter with sodium metabisulfite and phosphorus oxychloride, m.p. 93–94.5°, previously reported[14] m.p. 95°.

5-(3′,4′,5′-Trimethoxyphenyl)tetrazole (I). A mixture of 29.8 g. of 3,4,5-trimethoxybenzonitrile, 14.9 g. of sodium azide and 13.8 g. of glacial acetic acid in 100 ml. of *n*-butyl alcohol was boiled under reflux for 4 days when further 5 g. of sodium azide and 10 g. of glacial acetic acid were added; refluxing was continued for 2 days. The mixture was diluted with 250 ml. of water and distilled to remove *n*-butyl alcohol. The residual aqueous solution was cooled, acidified with hydrochloric acid (Caution: hydrazoic acid liberated), and the precipitated product filtered off. The product was recrystallized from aqueous isopropyl alcohol, yield 33.9 g. (93%), m.p. 199–200°.

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.8; H, 5.1; N, 23.7. Found: C, 51.1; H, 5.2; N, 23.6.

2-(Diethylaminoethyl)-5-(3′,4′,5′-trimethoxyphenyl)tetrazole (II) *hydrochloride.* A suspension of 11.8 g. of I and 8.6 g.

(1) Based on part of the doctoral thesis submitted to Michigan State University in 1958 by James M. McManus.
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