TABLE I

N-SUBSTITUTED AMIDES OF 5-CARBOXYDEHYDROACETIC ACID

Substituent	Yield, %	Recryst'd[a] from	M.P., °C.	Analysis Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
C_6H_5		B or T	189						
p-$C_6H_5C_6H_4$[b]	58	EA-T	235	69.41	4.72		69.36	4.66	
p-$O_2NC_6H_4$[b]	55	T	203–204	54.22	3.64		54.78	3.55	
p-$CH_3OC_6H_4$	90	B	210	60.56	4.77		60.63	4.89	
o-$CH_3OC_6H_4$			178	60.56	4.77		60.77	5.02	
p-$(CH_3)_2NC_6H_4$	62	B	198	61.81	5.49	8.48	62.22	5.52	8.52
p-$(C_2H_5)_2NC_6H_4$	60	B	176			7.82			7.90
2,5-$(CH_3O)_2C_6H_3$	90	M	161	68.79	4.93		59.17	5.07	
—CH_2CH_2—[c]	90	[d]	132			5.91			5.83

[a] B, benzene; T, toluene; EA, ethyl acetate; M, methanol. [b] Prepared in bromomesitylene. [c] From ethyleneimine. [d] Analyzed after washing with benzene. Not recrystallized.

TABLE II

INFRARED ABSORPTION CHARACTERISTICS OF DEHYDROACETIC ACID DERIVATIVES[a]

DHA[b]	TAL[c]	CDHA[d]	PCDHA[e]
3.40 n	3.40 br	3.30 n	3.30 br
		5.66	
5.80	5.85	5.78	5.77
	6.05	6.00 w	6.05 s
6.18	6.18	6.26	6.27
6.25	6.30	6.47 w	6.48 s
6.50	6.52		
6.92	6.95	6.81	6.82
7.45	7.45	7.35	7.36

[a] n, narrow; br, broad; w, weak; s, strong. [b] Dehydroacetic acid. [c] Triacetic lactone. [d] 5-Carboxydehydroacetic acid (I). [e] 5-Phenylcarbamyldehydroacetic acid (II).

procedure previously described[5] for the preparation of the 3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones. The crude product was obtained in 45% yield. Recrystallization from chloroform gave the pure product characterized as golden needles, m.p. 175°.

Anal. Calc'd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 59.8; H, 4.62.

The anilides listed in Table I were prepared by heating the appropriate aniline with the acid in benzene following the procedure outlined above for the dimethylaminophenylcarbamyl derivative. The ethylene imine reaction mixture was not heated. After filtration and evaporation the imide precipitated.

The infrared data were obtained using potassium bromide pellets and a Baird double beam recording infrared spectrophotometer.

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11-Oxygenated Steroids. XVII. 1,4-Pregnadien-21-al-17α-ol-3,11,20-trione Hydrate

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It has been observed that 4-pregnene-21-al-17α-ol-3,11,20-trione, the 21-aldehyde derived from cortisone, is an active cortical substance.[1,2] With this in mind we have converted 1,4-pregnadiene-17α,21-diol-3,11,20-trione (I),[3,4] a recently discovered, potent, anti-inflammatory agent, to 1,4-pregnadien-21-al-17α-ol-3,11,20-trione hydrate (IV) by the procedure of Leanza and coworkers.[2] Reaction of I with *p*-toluenesulfonyl chloride in pyridine afforded 1,4-pregnadien-17α-ol-3,11,20-trione-21-pyridinium chloride (II) in good yield. Displacement of the pyridine moiety in II with *p*-nitrosodimethylaniline yielded 1,4-pregnadien-17α-ol-3,11,20-trione-21-(*p*-dimethylaminophenyl)nitrone (III) smoothly. The nitrone III was hydrolyzed with aqueous hydrochloric acid to the desired aldehyde hydrate, IV.

The adrenocortical activities of III and IV were assessed by the eosinophile test[5] and these compounds were found to be at least as active as cortisone. The biological results will be reported in greater detail elsewhere. We are indebted to Drs. Sibylle Tolksdorf, P. L. Perlman, and their associates for the results of the biological tests.

EXPERIMENTAL

All melting points are corrected. Analyses and optical data were obtained by the Physical Chemistry Department of these laboratories and by the Galbraith Laboratories, Knoxville, Tenn.

1,4-Pregnadien-17α-ol-3,11,20-trione-21-pyridinium chloride (II). The procedure of Leanza and coworkers[2] was followed. From 6 g. of I there resulted 5.45 g. of II, m.p. 304–305° (dec.). Reprecipitation from methanol with ether did

(1) J. J. Schneider, *J. Am. Chem. Soc.*, **75**, 2024 (1953).
(2) W. J. Leanza, J. P. Conbere, E. F. Rogers and K. Pfister, 3rd, *J. Am. Chem. Soc.*, **76**, 1691 (1954).
(3) Meticorten (brand of prednisone, formerly metacortandracin).
(4) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman, and M. M. Pechet, *Science*, **121**, 176 (1955); A. Nobile, *et al.*, *J. Am. Chem. Soc.*, **77**, 1484 (1955).
(5) R. S. Speirs and R. K. Meyer, *Endocrinology*, **48**, 316 (1951); E. Rosemberg, *et al.*, *Endocrinology*, **54**, 363 (1954).

not change the m.p.; $[\alpha]_D^{25}$ +254° (CH_3OH); $\lambda_{max}^{CH_3OH}$ 241 mμ (ε = 18,600).

Anal. Calc'd for $C_{26}H_{30}ClNO_4 \cdot {}^1/_2CH_3OH$: C, 67.43; H, 6.83. Found: C, 67.79; H, 6.75.

1,4-Pregnadien-17α-ol-3,11,20-trione-21-(p-dimethylaminophenyl)nitrone (III). The reaction was carried out according to Leanza and coworkers.[2] From 4.52 g. of II there was obtained 3.78 g. of dark red plates of III, m.p. 182–183° (dec.). Recrystallization from aqueous methanol did not change the m.p.

Anal. Calc'd for $C_{29}H_{34}N_2O_5$: C, 70.99; H, 6.99; N, 5.71. Found: C, 71.26; H, 7.37; N, 5.62.

1,4-Pregnadien-21-al-17α-ol-3,11,20-trione Hydrate (IV). The procedure of Leanza and coworkers[2] was followed. Just prior to the crystallization of IV an orange oil precipitated and the latter was separated by decantation. From 2.88 g. of nitrone (III) there resulted 0.80 g. of IV as yellow needles, m.p. 220–230° (dec.) (capillary); $[\alpha]_D^{25}$ +166° (CH_3OH); λ_{max}^{EtOH} 238 mμ (ε = 15,800).

Anal. Calc'd for $C_{21}H_{24}O_5 \cdot 2H_2O$: C, 64.27; H, 7.19. Found: C, 64.55; H, 7.06.

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Conversion of Tigogenin and Neotigogenin into 16,22-Epoxycholest-25-en-3β-ol and 16,22-Epoxycholestan-3β-ol

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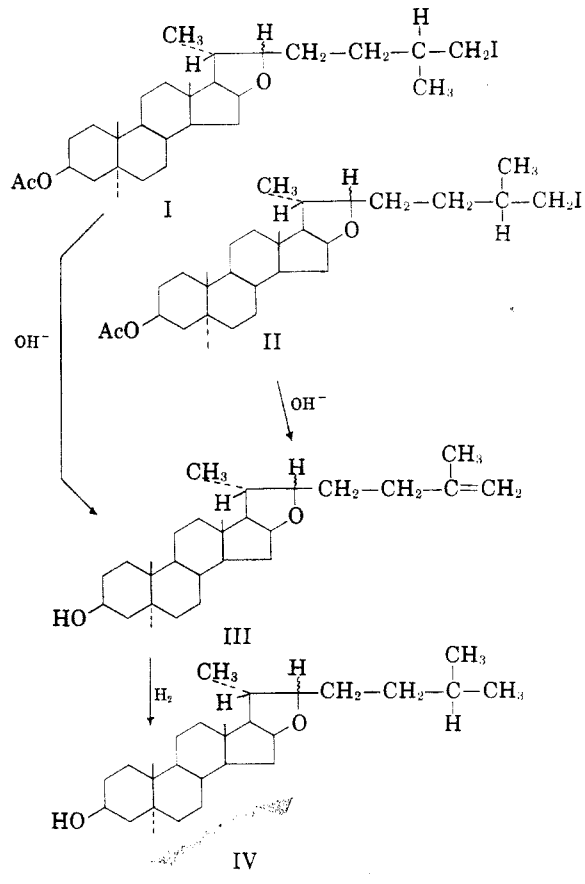
During the course of studies on the synthesis of some amino derivatives of dihydrotigogenin and dihydroneotigogenin, the 26-deoxy-26-iodo derivatives[1] of these dihydrosapogenins were prepared as intermediates. These compounds, 26-deoxy-26-iododihydrotigogenin acetate (I) and 26-deoxy-26-iododihydroneotigogenin acetate (II), were found to be extremely sensitive to base, readily undergoing simultaneous deacetylation and dehydrohalogenation to yield the common 26-deoxy-Δ^{25}-dihydro derivative (16,22-epoxycholest-25-en-3β-ol), III. Catalytic hydrogenation of III led to 16,-22-epoxycholestanol, IV. The epoxycholestanol (IV) was also obtained by the lithium aluminum hydride reduction of dihydrotigogenin 26-tosylate.

Scheer, *et al.*[2] have transformed the $C_5\beta$-sapogenin derivatives, dihydrosarsasapogenin and dihydrosmilagenin into 16,22-epoxycoprostanol by the lithium aluminum hydride reduction of the 26-tosylates of the respective dihydrosapogenins, but conversion of the $C_5\alpha$, C_{25}-epimeric sapogenins, tigogenin and neotigogenin into 16,22-epoxycholest-25-en-3β-ol and 16,22-epoxycholestan-3β-ol has hitherto been unreported.



EXPERIMENTAL[3]

16,22-Epoxycholest-25-en-3β-ol (III). 26-Deoxy-26-iododihydrotigogenin acetate[1] (I) (200 mg.) was dissolved in 20 cc. of methanolic potassium hydroxide (5%) and refluxed for 1 1/2 hours. The solution was partially concentrated *in vacuo* and water was added to the residue. The resulting crystalline precipitate (145 mg.), m.p. 134–138° was purified by chromatography over alumina. Elution with 0.5% methanol in ether yielded 112 mg. of III, which, after crystallization from dilute methanol and recrystallization from ether-hexane, yielded needles of m.p. 138–140°, $[\alpha]_D^{20}$ +3.7° (CH_3OH) λ_{max}^{Nujol} 2.90, 3.08 μ (hydroxyl); 6.05, 11.30 μ ($R_1R_2C{=}CH_2$).

Anal. Calc'd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.64; H, 10.88.

Treatment of 26-deoxy-26-iododihydroneotigogenin acetate (II) in the same manner afforded III of m.p. 138–140°. The substance agreed in all properties (m.p., mixture m.p., infrared spectra, derivatives) with the compound obtained from I.

When I and II respectively were refluxed with methanolic potassium hydroxide (2%) for 75 minutes, each gave III in about 70% yield. Some dehydrohalogenation occurs also with potassium bicarbonate in methanol.

The *benzoate* of III crystallized from ether-methanol, m.p. 137–140°.

Anal. Calc'd for $C_{34}H_{48}O_3$: C, 80.90; H, 9.59. Found: C, 80.68; H, 9.65.

The *3,5-dinitrobenozate* crystallized from benzene-methanol, m.p. 201–205°.

(1) Sato and Latham, Jr., *J. Am. Chem. Soc.*, in Press.

(2) Scheer, Kostic, and Mosettig, *J. Am. Chem. Soc.*, **77**, 641 (1955).

(3) All melting points were taken on the Kofler block and are uncorrected. We are indebted to Dr. W. C. Alford and his associates for the microanalyses and to Mr. H. K. Miller, all of this Institute, for the spectrophotometric measurements.