TABLE I
5-AMINO-N-SUBSTITUTED 4-PYRIMIDINECARBOXAMIDES

Compd	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
4a	112–114	A	90	$C_{14}H_{16}N_4O_2$	61.75	5.92	20.58	62.09	5.99	20.30
5b	141–143	B	89	$C_{15}H_{19}N_5O$	63.14	6.71	24.55	63.19	6.78	24.73
4c	137–139	C	74	$C_{15}H_{18}ClN_5O$	56.33	5.67	21.90	56.29	5.28	21.89

[a] A = absolute ethanol, B = cyclohexane, C = ethanol + water.

(2.5 g) was added in small portions to trifluoroacetic anhydride (30 ml). The resulting mixture was refluxed for 7.5 hr and set overnight at room temperature, during which time a precipitate separated. The precipitate was collected on a filter and washed with trifluoroacetic anhyride to give 3.2 g of product, mp 210–212°.

Anal. Calcd for $C_{13}H_6F_3N_3O_2$: C, 53.25; H, 2.06; N, 14.33. Found: C, 53.33; H, 2.03; N, 14.55.

6-(*m*-Chlorophenyl)-2-trifluoromethyl-4H-pyrimido[5,4-*d*][1,3]-oxazin-4-one (2b) was prepared similarly from **1b** and trifluoroacetic anhydride: yield 94%, mp 176–178°.

Anal. Calcd for $C_{13}H_5ClF_3N_3O_2$: C, 47.65; H, 1.54; N, 12.82. Found: C, 47.79; H, 1.45; N, 12.77.

2-Phenyl-5-(2,2,2-trifluoroacetamido)-4-pyrimidinecarboxylic Acid Ethyl Ester (3a).—To a refluxing mixture of **2a** (7.0 g) and absolute EtOH (70 ml) was added a catalytic amount of sodium ethoxide, and the resulting solution was refluxed for 10 min. Concentration of the reaction mixture under reduced pressure and chilling in ice caused separation of a precipitate which was collected on a filter to give 7.5 g of product: mp 136.5–138.5°, ir 5.80 (CF_3CO) and 5.87 μ (ester CO).

Anal. Calcd for $C_{15}H_{12}F_3N_3O_3$: C, 53.10; H, 3.57; N, 12.39. Found: C, 53.52; H, 3.33; N, 12.29.

2-(*m*-Chlorophenyl)-5-(2,2,2-trifluoroacetamido)-4-pyrimidinecarboxylic acid ethyl ester (3b) was prepared similarly from **2b**: yield 85%, mp 172–174°.

Anal. Calcd for $C_{15}H_{11}ClF_3N_3O_3$: C, 48.20; H, 2.97; N, 11.24. Found: C, 48.49; H, 2.93; N, 11.50.

5-Amino-2-phenyl-4-pyrimidinecarboxylic Acid Ethyl Ester (5a). From 2a.—A mixture obtained by adding 19.3 g of **2a** to 200 ml of absolute EtOH containing a catalytic amount of sodium ethoxide was refluxed for 15 min. After the reaction mixture was cooled to room temperature, dry HCl gas was introduced for 1 hr, and then the reaction material was chilled. The precipitate that was deposited was collected on a filter and transferred to a separatory funnel containing 1 *N* aqueous NaOH solution and ether. After the mixture was shaken vigorously, the ether layer was collected, dried ($MgSO_4$), and evaporated to give 12.5 g of product, mp 78–80°.

Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.22; H, 5.36; N, 17.50.

From 3a.—A slow stream of dry HCl gas was introduced into a mixture of **3a** (3.0 g) and absolute EtOH (100 ml), with stirring for 15 min. Chilling of the resulting mixture caused separation of a precipitate, which was collected on a filter. Working up as described above afforded 1.2 g of product, mp 80–82°. A mixture melting point with the authentic sample prepared from **2a** was not depressed.

5-Amino-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic Acid ethyl ester (5b) was prepared from **3b** and absolute EtOH and recrystallized from absolute EtOH, mp 130–132°.

Anal. Calcd for $C_{13}H_{12}ClN_3O_2$: C, 56.22; H, 4.36; N, 15.13; Cl, 12.87. Found: C, 56.22; H, 4.05; N, 15.37; Cl, 12.95.

5-Amino-2-phenyl-4-pyrimidinecarboxylic acid methyl ester (5c) was prepared from **2a** and absolute methanol in 65% yield and recrystallized from cyclohexane, mp 119.5–122°.

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.56; H, 4.62; N, 18.24.

5-Amino-N-(2-methoxyethyl)-2-phenyl-4-pyrimidinecarboxamide (4a) exemplifies the preparation of 5-amino-N-substituted 2-aryl-4-pyrimidinecarboxamides (**4a–c**) (Table I).

From 2a.—To 15 ml of 2-methoxyethylamine was added 2.5 g of **2a** in small portions, and the resulting mixture was heated on a steam bath for 0.5 hr. The excess amine was removed under reduced pressure, and the solid residue was recrystallized from absolute ethanol, giving 2.1 g of product (see Table I).

From 5a.—A mixture of **5a** (1.5 g) and 2-methoxyethylamine (20 ml) was refluxed for 7 hr and then the solution was concentrated under reduced pressure. Chilling caused separation of crystals which were collected on a filter and washed with EtOH to give 1.3 g of product, mp 113–115°. A mixture melting point with the authentic sample prepared from **2a** was not depressed.

Registry No.—5-Amino-2-(*m*-chlorophenyl)pyrimidine, 23788-75-2; **2a**, 23788-76-3; **2b**, 23788-77-4; **3a**, 23788-78-5; **3b**, 23877-35-2; **4a**, 23788-79-6; **4b**, 23843-57-4; **4c**, 23788-80-9; **5a**, 23788-81-0; **5b**, 23788-82-1; **5c**, 23788-83-2.

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Preparation of 16-Unsaturated Steroids by Elimination of 17α-Acyloxyl

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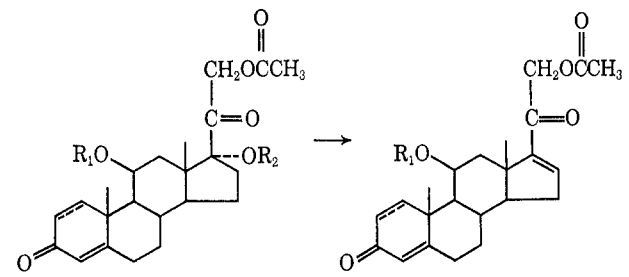
Two methods are known for elimination of the 17α-hydroxyl from the dihydroxyacetone side chain of the corticoids. Allen and Bernstein[1] have reported 16,17 dehydration of 20-dioxolane derivatives using thionyl chloride in pyridine at −5°. The dehydration yield is ~45%; the dioxolane must be subsequently converted into the 20 ketone. Slates and Wendler,[2] *et al.*, reported an improved procedure involving activation of the 17α-hydroxyl by the 20-semicarbazone. Almost quantitative dehydration is effected and conversion into the 20 ketone is facile. Both methods are unsatisfactory, however, when the 11β-hydroxyl is present. Thionyl chloride causes 9,11 dehydration. In the semicarbazone method, C-18 methyl migration[2b] takes place when an 11β-hydroxyl is present and little Δ^{16} steroid is isolated.

We wish to report the removal of a 17α-hydroxyl, in good yield, by reacting a 17α-acyloxy derivative with potassium acetate in dimethylformamide. Thus prednisolone 17,21-diacetate (**1**), when heated for 8 hr at 105° with potassium acetate in dimethylformamide, is almost quantitatively converted into 16,17-anhydroprednisolone 21-acetate (**5**). Prednisolone 17-caproate 21-acetate also gives **5** but in lesser yield, 52.6%. The

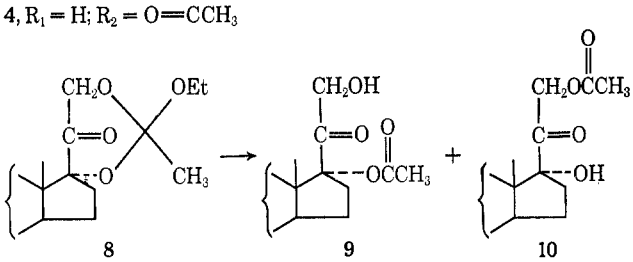
(1) W. S. Allen and S. Bernstein, *J. Amer. Chem. Soc.*, **77**, 1028 (1955).
(2) (a) H. L. Slates and N. L. Wendler, *J. Org. Chem.*, **22**, 498 (1957); (b) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *ibid.*, **29**, 3486 (1964).

11β-acetate, if present, is retained, as shown by conversion of prednisolone 11,17,21-triacetate (**3**) into 16,17-anhydroprednisolone 11,21-diacetate (**6**), a new compound. The method is also applicable in the 4-en-3-one series, and cortisol 17,21-diacetate (**4**) gave 16,17-anhydrocortisol 21-acetate (**7**).



1, Δ^1; $R_1 = H$; $R_2 = O{=}CCH_3$
2, Δ^1; $R_1 = H$; $R_2 = O{=}C(CH_2)_4CH_3$
3, Δ^1; $R_1 = R_2 = O{=}CCH_3$
4, $R_1 = H$; $R_2 = O{=}CCH_3$

5, Δ^1; $R_1 = H$
6, Δ^1; $R_1 = O{=}CCH_3$
7, $R_1 = H$



8 **9** **10**

Sodium acetate was not so effective as potassium acetate. Sodium formate, calcium carbonate, and calcium acetate in dimethylformamide failed. Potassium acetate in dimethyl sulfoxide and simple pyrolysis were also ineffective.

The 17α-acylates are conveniently prepared through the 17α,21 ortho esters[3] by heating the ortho ester at 45–50° with oxalic acid–water–methanol for 5 min.[4] However, a major weakness of this reported method is formation of the isomeric 17-hydroxy-21-acylate. Gardi, *et al.*,[3] attribute formation of the isomer to acyl migration from the 17 to the 21 position after cleavage of the ortho ester. We have found that hydrolysis can be effected in a pH 3 phthalate buffer without acyl migration, even on prolonged exposure. Thus hydrolysis of prednisolone 17,21-orthoacetate (**8**), with pH 3 phthalate buffer in aqueous methanol was complete in 8 hr at 25°. The ratio of 17α-acetate to 21-acetate (**9** to **10**) was estimated to be 9:1 by thin layer chromatography. The ratio did not change in an additional 64 hr. Using the oxalic acid–aqueous methanol procedure the isomer ratio was 8:2 after 5 min of reaction.

Experimental Section

All melting points were taken in open-end glass capillary tubes and are uncorrected. Thin layer chromatograms were visualized by charring, after spraying with sulfuric acid.

1,4,16-Pregnatriene-11β-,21-diol-3,20-dione 21-Acetate (16,17-Anhydroprednisolone 21-Acetate, 5). A. From 1,4-Pregnadiene-11β,17α,21-triol-3,20-dione 17,21-Diacetate (1).—A mixture of **1** (21 g, 0.0472 mol), anhydrous potassium acetate (10.5 g, 1.07 mol), and dimethylformamide (140 ml) was stirred at 105° for 7.5 hr in an atmosphere of nitrogen. After cooling to 25°, the mixture was poured into ice water (1.2 l.) with stirring. After 15 min of stirring, the precipitated solid was collected by filtration, washed with water, and dried to constant weight *in vacuo*. The yield of 16,17-anhydroprednisolone 21-acetate (**5**) was 16.8 g (92.8%), mp 197–200°, uv max (MeOH) 242 mμ (ε 23,100), indicating 97% purity. Tlc using either chloroform–acetone (7:3) or ethyl ether–benzene (9:1) showed only a single spot.

Recrystallization from isopropyl alcohol (81.2% recovery) raised the melting point to 205–207° (lit.[5] mp 208–209°), uv max (MeOH) 242 mμ (ε 23,800).

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.86; H, 7.25.

B. From 1,4-Pregnadiene-11β,17α,21-triol-3,20-dione-17-caproate 21-Acetate (Prednisolone-17-caproate 21-Acetate, 2).—Dehydrocaproxylation of **2**, prepared by the method of Gardi, *et al.*, as above, proceeded to **5** in 52.6% yield.

1,4,16-Pregnatriene-11β,21-diol-3,20-dione 11,21-Diacetate.—16,17-Anhydroprednisolone 11,21-diacetate (**6**) was obtained by dehydroacetoxylation of prednisolone 11,17,21-triacetate (**3**, 2 g). The yield of **6** was 1.72 g (92%), mp 225–230°. Tlc on silica gel G using ethyl acetate–chloroform (1:1) showed one spot with a trace of material at the origin. Charcoaling and recrystallization from isopropyl alcohol gave 1.09 g (62.4% recovery), mp 236–238°, tlc single spot. Further recrystallization increased the melting point to 238–241°; ir (KBr) 1735, 1745 (ester C=O), 1685 (16-ene, 20-C=O), 1665 (3-C=O), 1610, and 1625 cm^{-1} (1,4-diene); uv max (MeOH) 242 mμ (ε 24,950).

Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.40; H 7.09. Found: C, 70.38; H, 7.20.

4,16-Pregnadiene-11β-21-diol-3,20-dione 21-Acetate (16,17-Anhydrocortisol 21-Acetate, 7).—4-Pregnene-11β,17α,21-triol-3,20-dione 17,21-diacetate (**4**, 5.0 g) was dehydroacetoxylated as above. The yield of **7** was 3.42 g, (80%), and the melting point after further purification was 145–147° (lit.[1] mp 148–149°).

1,4-Pregnadiene-11β,17α,21-triol-3,20-dione 17-Acetate (Prednisolone 17-Acetate, 9).—To a solution of prednisolone 17,21-ethyl orthoacetate (**8**, 2.0 g, 0.0046 mol) in methanol (12 ml) was added pH 3 acid phthalate buffer (3.0 ml) prepared by mixing 0.1 *N* HCl (20.32 ml) and 0.1 *N* potassium biphthalate (50.0 ml). After 6.5 hr at 25°, tlc on silica gel G using chloroform–acetone (7:3) showed a 9:1 ratio of **9** to **10**. Stirring for an additional 64 hr did not change the ratio.

Registry No.—**5**, 3044-42-6; **6**, 23825-05-0; **7**, 21720-47-8.

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The Isolation and Structure Elucidation of Oxoxylopine, a New Oxoaporphine Alkaloid from *Stephania abyssinica*

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Stephania abyssinica Walp. is a creeping plant, native to southern and eastern Africa, which has been reported to have use as a purgative and emetic.[2] The roots are used in the treatment of roundworm, menorrhagia, and boils.[2] An examination of *S. abyssinica*

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