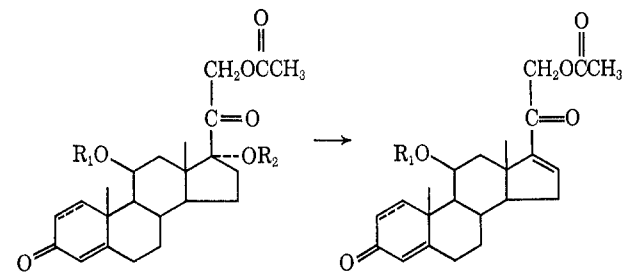
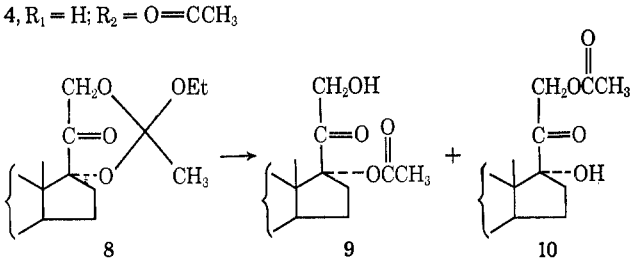
11β-acetate, if present, is retained, as shown by conversion of prednisolone 11,17,21-triacetate (**3**) into 16,17-anhydroprednisolone 11,21-diacetate (**6**), a new compound. The method is also applicable in the 4-en-3-one series, and cortisol 17,21-diacetate (**4**) gave 16,17-anhydrocortisol 21-acetate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

(3) R. Gardi, R. Vitali, and A. Ercoli, *Gazz. Chim. Ital.*, **93**, 413 (1963).
(4) R. Gardi, R. Vitali, and A. Ercoli, *ibid.*, **93**, 431 (1963).
(5) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, U. S. Patent 3,068,251 (1962); *Chem. Abstr.*, **58**, 10285c (1963).

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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(2) J. M. Watt and M. G. Breyer-Brandwijk, "The Medicinal and Poisonous Plants of Southern and Eastern Africa," E. and S. Livingstone Ltd., London, 1962, p 458.

TABLE I
NMR SIGNALS OF OXOAPORPHINE ALKALOIDS[a]

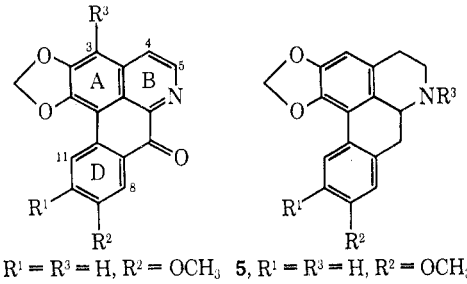
Compd	OCH_2O	C-3 H	C-3 OCH_3	C-4 H	C-5 H	C-8 H	C-9 OCH_3	C-10 H	C-11 H
Oxoxylopine (1)	3.35 (s)	2.47 (s)		1.55 (d)	1.22 (d)	1.93 (d)	5.88 (s)	2.33 (dd)	1.22 (d)
Liriodenine[b] (2)	3.28 (s)	2.37 (s)		C-4 H to C-11 H, 1.1 to 2.3 (6 H, aromatic, m)					
Atherospermidine[b] (3)	3.28 (s)		5.45 (s)	C-4 H to C-11 H, 1.1 to 2.3 (6 H, aromatic m)					
Lanuginosine[c]	3.25 (s)	2.33 (s)		2.30 (d)	1.30 (d)	1.74 (d)	5.92 (s)	2.03 (dd)	0.97 (d)

[a] All values are in τ units for CF_3COOH solutions at 60 MHz relative to tetramethylsilane. [b] Reference 4. [c] Reference 14.

from Natal revealed the presence of an alkaloid,[3] which was subsequently characterized as metaphanine,[4] originally isolated from *S. japonica*.[5]

The present communication concerns an investigation of a sample of roots and rhizomes of *S. abyssinica*, collected in Ethiopia in April 1965.[6] Examination of the alkaloidal fraction revealed the presence of a complex mixture. We report herein the isolation and structure elucidation of oxoxylopine (**1**), a new alkaloid of the oxoaporphine series.

A concentrated ethanolic extract of *S. abyssinica* roots and rhizomes was triturated with dilute hydrochloric acid. The acid solution was partially basified to pH 5 with ammonium hydroxide and extracted with chloroform to give a fraction designated as "weak bases." The weakly acidic solution (pH 5) was then further basified to yield a "strong base" fraction. The weak base fraction was chromatographed on silicic acid to yield a fraction rich in the new alkaloid. Rechromatography on alumina gave material which was crystallized from chloroform to yield oxoxylopine (**1**): mp 319–321° dec; $\lambda_{max}^{CHCl_3}$ 246 mμ (ε 28,650), 271 (21,800), 314 (5960); $\lambda_{max}^{0.1\,N\,HCl}$ 257 mμ (ε 20,570), 284 (15,500); λ_{max}^{KBr} 3.37, 6.02 μ (conjugated ketone); *m/e* 305 (M^+, 100%).



1, $R^1 = R^3 = H$, $R^2 = OCH_3$
2, $R^1 = R^2 = R^3 = H$
3, $R^1 = R^2 = H$, $R^3 = OCH_3$
4, $R^2 = R^3 = H$, $R^1 = OCH_3$
5, $R^1 = R^3 = H$, $R^2 = OCH_3$
6, $R^1 = H$, $R^2 = OCH_3$, $R^3 = Ac$
7, $R^1 = OH$, $R^2 = H$, $R^3 = CH_3$, methiodide

The analytical data supported assignment of the molecular formula $C_{18}H_{11}NO_4$. The compound's limited solubility, high melting point, fluorescence in solution, cherry-red coloration upon treatment with dilute mineral acid, and failure to show NH absorption in the infrared suggested that this highly conjugated ketone was a member of the oxoaporphine series. Comparison of the infrared and ultraviolet spectra of **1** with those reported for liriodenine (**2**)[7,8] showed them to be very similar and suggested that the new alkaloid also possessed a 1,2-methylenedioxy group.

The nmr spectrum of oxoxylopine showed signals for a methylenedioxy group at τ 3.35 (2 H, s), a methoxyl group at 5.88 (3 H, s), and six aromatic protons in the region of 1.22–2.47. A comparison of these data with the recorded nmr data for liriodenine (**2**) and atherospermidine (**3**)[9] (see Table I) suggested that C-3 is unsubstituted, since a one-proton singlet analogous to that found in liriodenine was observed in the spectrum of oxoxylopine at τ 2.47. The signals for the C-4 and C-5 protons appeared as doublets ($J_{4,5}$ = 6 Hz) at τ 1.55 and 1.22, respectively, indicating that the methoxyl group is not located in ring B. Analyses of the signals for the remaining free protons showed them to constitute a 1,2,4 aromatic hydrogen system. The signal for one proton at τ 1.22 (d, J = 9 Hz) showed *ortho* coupling to a second proton with a signal at 2.33 (dd, J = 3,9 Hz) which was *meta* coupled to the third proton with a signal at 1.93 (d, J = 3 Hz). The presence of a 1,2,4 pattern for the ring-D protons restricted placement of the methoxyl group to C-9 or C-10, and oxoxylopine could then be represented by either structure **1** or **4**.

The ultraviolet spectra of aporphines are known to vary with the location of oxygen substituents[10] and the specific ultraviolet spectra of the aporphines corresponding to **1** or **4** are sufficiently different to enable ready differentiation between these isomers. Oxoxylopine was therefore reduced with zinc–hydrochloric acid,[11] to afford a compound whose ultraviolet spectrum corresponded to that reported for the 1,2-methylenedioxy-9-methoxy isomer, xylopine (**5**).[12] Acetylation afforded (±)-N-acetylxylopine (**6**), with ultraviolet and infrared spectra and thin layer chromatographic properties indistinguishable from those of an authentic sample of (−)-N-acetylxylopine.[13] The cited facts established that oxoxylopine possesses structure **1**.

Recently another new oxoaporphine, lanuginosine,[14] has been isolated from *Michelia lanugionosa* Wall (*Magnoliaceae*) and structure **1** has also been assigned to this compound. However, a comparison of the melting point and infrared and nmr spectral data[14] with those of oxoxylopine clearly showed these compounds to be different. The assignment of structure **1** to lanuginosine was based largely upon nmr spectral arguments, and lanuginosine has yet to be interrelated with a known compound. The signals for the ring-D

(3) H. L. de Waal and E. Weideman, *Tydskr. Natuurwet.*, **2**, 12 (1962).
(4) H. L. de Waal, B. J. Prinsloo, and R. R. Arndt, *Tetrahedron Lett.*, 6169 (1966).
(5) M. Tomita, I. Ibuka, Y. Inubushi, and K. Takeda, *ibid.*, 3605 (1964).
(6) The authors acknowledge with thanks the receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture, Beltsville, Md., in accordance with the program developed with the U. S. Department of Agriculture by the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, National Institutes of Health.
(7) M. A. Buchanan and E. E. Dickey, *J. Org. Chem.*, **25**, 1389 (1960).
(8) W. I. Taylor, *Tetrahedron*, **14**, 42 (1961).
(9) I. R. C. Bick and C. K. Douglas, *Tetrahedron Lett.*, 1629 (1964).
(10) M. Shamma and W. A. Slusarchyk, *Chem. Rev.*, **64**, 59 (1964).
(11) T.-H. Yang, *J. Pharm. Soc. Jap.*, **82**, 804 (1962).
(12) J. Schmutz, *Helv. Chim. Acta*, **42**, 335 (1959).
(13) The authors cordially thank Dr. Jean Schmutz, Dr. A. Wander Research Institute, Bern, Switzerland, for the authentic sample of (−)-N-acetylxylopine.
(14) S. K. Talapatra, A. Patra, and B. Talapatra, *Chem. Ind.* (London), 1056 (1969).

protons in lanuginosine show a 1,2,4 pattern with the same coupling constants as those for oxoxylopine, although the chemical shifts are significantly different (see Table I). In view of the considerations discussed above, it appears likely that lanuginosine is the 10-methoxy isomer of xylopine and should be represented by structure **4** rather than structure **1**. It is noteworthy that michepressine iodide (**7**), an aporphine corresponding in substitution pattern to structure **4**, has been isolated from *Michelia compressa*.[15] Since oxoaporphine alkaloids are probably formed in the plant *via* oxidation of the corresponding aporphines,[16,17] the isolation of michepressine iodide from a *Michelia* species supports assignment of the revised structure **4** for lanuginosine.

Experimental Section

Melting points were determined on a Thomas–Hoover Unimelt apparatus and are corrected. Ir spectra were determined on a Beckman IR-9 double-beam recording spectrophotometer. Uv spectra were determined on a Beckman DK-2A recording spectrophotometer. Nmr spectra were determined on a Varian Associates A-60A spectrometer. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Mass spectra were measured on a Hitachi RMU-6A spectrometer. We thank the Purdue Mass Spectrometry Center, supported under U. S. Public Health Service Grant FR-00354, for the mass spectral data.

Extraction and Preliminary Fractionation.—The dried ground roots and rhizomes (7 kg) of *Stephania abyssinica* were extracted continuously with ethanol until the extract returning to the pot was nearly colorless. Evaporation of the ethanolic extract gave a mobile semisolid residue (901 g) which was triturated three times with 1.6 *N* hydrochloric acid (3-l. total) to leave a gummy residue (143 g). The aqueous solution was partially basified with concentrated ammonium hydroxide solution to pH 5 and extracted with chloroform (four 1-l. portions) to yield, after evaporation, the weak base fraction (28.7 g). The remaining aqueous solution was decanted from insoluble residue (70 g), basified to pH 8 with concentrated ammonium hydroxide solution, and extracted with chloroform (four 1-l. portions) to give, after evaporation, the strong base fraction (10.4 g).

Oxoxylopine (**1**).—The weak base fraction was chromatographed over silicic acid (900 g), eluting with chloroform, 1% methanol–chloroform, 2.5% methanol–chloroform, and 5% methanol–chloroform. The fraction eluted with 2.5% methanol–chloroform (6 g) was rechromatographed over acid-washed alumina, eluting with benzene–chloroform mixtures. A fraction eluted with 2:1 benzene–chloroform (150 mg) crystallized on standing to give orange prisms (108 mg). Two recrystallizations from chloroform yielded oxoxylopine (**1**, 70 mg): mp 319–321° dec; $\lambda_{max}^{CHCl_3}$ 246 mμ (ε 28,650), 271 (21,800), 314 (5960); $\lambda_{max}^{0.1\,N\,HCl}$ 257 mμ (ε 20,570), 284 (15,500); λ_{max}^{KBr} 3.37, 6.02, 6.24, 6.36, 6.67, 6.86, 7.06, 7.66, 7.92, 8.17, 9.57, 9.84 μ; *m/e* 305 (M^+, 100%), 275 ($M^+ - CH_2O$, 15%).

Anal. Calcd for $C_{18}H_{11}NO_4$: C, 70.81; H, 3.63; N, 4.59. Found: C, 70.88; H, 3.76; N, 4.63.

Oxoxylopine was found to be nearly insoluble in ethanol, methanol, benzene, ethyl acetate, ether, cyclohexane, and acetone, and only sparingly soluble in chloroform. Its chloroform solution exhibited a strong green-yellow fluorescence in visible light. Oxoxylopine showed a cherry-red coloration upon treatment with dilute hydrochloric or sulfuric acid, as observed earlier for other oxoaporphine alkaloids.

Conversion of Oxoxylopine (**1**) **into** (±)-**N-Acetylxylopine** (**6**).—A solution of oxoxylopine (22 mg) in acetic acid–water (2:1, 2 ml) was treated with powdered zinc (3 g) and 10 *N* hydochloric acid (6 ml). The reaction mixture was heated with stirring at 100° for 18 hr, after which time the zinc had been consumed and the reaction mixture turned red, indicating the presence of unreduced oxoaporphine. Additional zinc dust (1 g) and concentrated hydrochloric acid (3 ml) was added and the reaction was stirred at 100° for an additional 24 hr, after which time the zinc had again been consumed and the reaction mixture was colorless. The acidic solution was made strongly basic with a large excess of concentrated ammonium hydroxide solution and was extracted with chloroform (five 150-ml portions). The combined, dried (Na_2SO_4) chloroform extracts were evaporated to give crude (±)-xylopine (18 mg; λ_{max}^{MeOH} 217, 237, 280, 320 mμ) (*cf.* 12), which was acetylated without further purification. Treatment of the (±)-xylopine with acetic anhydride (1 ml) and pyridine (1 ml) at 70° for 0.5 hr, followed by standing at room temperature for an additional 3 hr and evaporation under reduced pressure, gave a light brown gummy residue. This material was dissolved in ether–chloroform (3:1, 50 ml) and washed successively with 50 ml of 0.5 *N* hydrochloric acid, 1 *N* sodium hydroxide, and water. The organic phase was dried (Na_2SO_4) and the solvent was evaporated to give a residue which was crystallized twice from acetone–ether to give colorless needles (9 mg), mp 216–218°. The product was chromatographed over silicic acid (5 g) in chloroform to give (±)-N-acetylxylopine (5 mg): λ_{max}^{EtOH} 216.5 mμ (ε 32,200), 283 (16,700); $\lambda_{max}^{CHCl_3}$ 3.32, 3.41, 3.45, 3.52, 6.12, 6.33 μ. The spectra were indistinguishable from those of an authentic sample.

Registry No.—**1**, 23740-25-2; **2**, 475-75-2; **3**, 3912-57-0; **6**, 23740-28-5.

(15) K. Ito, *J. Pharm. Soc. Jap.*, **81**, 703 (1961).

(16) J. Cohen, W. Von Langenthal, and W. I. Taylor, *J. Org. Chem.*, **26**, 4143 (1961).

(17) NOTE ADDED IN PROOF.—Subsequent to submission of the manuscript, Dr. A. J. Liepa has isolated and characterized xylopine from the weak base fraction from *S. abyssinica*.

Selective O-Demethylation of Papaverine[1]

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Prior art has shown that papaverine (**1**) can be O-demethylated partially to the diphenol **6** by refluxing concentrated HCl[2] and completely to the tetraphenol papaveroline (**8**) by refluxing 48% HBr.[3] In connection with our interest in the partial O demethylation of polymethoxylated alkaloids,[4] we investigated the acid-catalyzed ether cleavage of **1** in more detail.

Thin layer chromatography using authentic samples of the various phenols as standards provided an excellent tool for this purpose. The monophenols **2**–**5** and papaveroline (**8**) were prepared according to literature procedures,[3,5] whereas the diphenol **6** and the triphenol **7** were synthesized by the conventional methods outlined in Schemes I and II, respectively. Analysis of the reaction mixture obtained by refluxing papaverine (**1**) with concentrated HCl for several hours showed the presence of starting material and the five phenols **2**, **3**, **6**, **7**, and **8**. The two monophenols **4** and **5** were not detected. The major component in this reaction mixture proved to be the diphenol **6**, which could be isolated in good yield but whose physical properties differed considerably from those reported.[2]

The interrelationship of the cleavage products follows. Treatment of papaverine (**1**) with liquid HBr gave a 1:1 mixture of the two monophenols **2** and **3**, as

(1) Presented in part by A. Brossi at the 13th Symposium on the Chemistry of Natural Products, Sapporo, Japan, Sept 25–27, 1969, Symposium Papers, pp 177–186.

(2) A. Boucherle and J. Alary, *Bull. Soc. Chim. Fr.*, 1222 (1960).

(3) J. V. Burba and M. F. Murnaghan, *Biochem. Pharm.*, **14**, 823 (1965).

(4) A. Brossi and S. Teitel, *Helv. Chim. Acta*, **52**, 1228 (1969).

(5) E. Brochmann-Hanssen and K. Hirai, *J. Pharm. Sci.*, **57**, 940 (1968).