# 17-HYDROXYLUPANINE AND 17-OXYLUPANINE[1]

By O. E. Edwards, F. H. Clarke,[2] and Bryce Douglas[3]

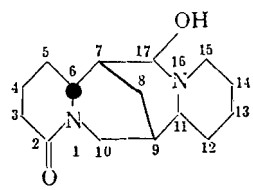
ABSTRACT

Silver oxide has been shown to oxidize lupanine to 17-hydroxylupanine. This base gives an anhydronium perchlorate identical with the "dehydrolupanine (NBS)" perchlorate of Marion and Leonard. 17-Oxylupanine is described, and, from the observation that it can be reduced catalytically to oxysparteine, the stereochemistry of aphylline and oxysparteine is deduced. The basic strength of tertiary carbinolamines is discussed.

Silver oxide has been observed to oxidize lycoctonine to hydroxylycoctonine (5, 8) and to dehydrogenate nicotine to nicotyrine (2). In an examination of the scope of the reaction of silver oxide with tertiary amines, we have now studied the action of the reagent on several lupine alkaloids.

Oxysparteine proved to be inert to silver oxide even at 90° in aqueous methanol. Sparteine was almost unattacked at room temperature but was oxidized at 60° giving products which have not been characterized. Lupanine is unaffected by the reagent at room temperature but is oxidized above 60° in aqueous methanol. From the mixture of products obtained in this reaction, a basic product was isolated as its perchlorate. This analyzed for $C_{15}H_{22}N_2O.HClO_4$ and proved identical (mixed melting point and comparison of infrared spectra) with the "dehydrolupanine (NBS)" perchlorate of Marion and Leonard (6). These workers treated lupanine with N-bromosuccinimide and obtained the above perchlorate in high yield from the product.

We have confirmed their observation that the new base is reduced to lupanine in the presence of platinum (Adams') in acetic acid solution. Since this reduction gave no change of configuration, Marion and Leonard concluded that the hydrogen on carbon 11 was not involved. On the assumption that N-bromosuccinimide introduced unsaturation $\alpha$-$\beta$ to the basic nitrogen, these authors suggested tentatively that their product was 14-dehydrolupanine. However, we have now been able to prove decisively that the new base is 17-hydroxylupanine.[4]




17-Hydroxylupanine

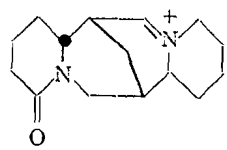
[1] *Manuscript received November 10, 1953.*
*Contribution from the Division of Pure Chemistry, National Research Council, Ottawa, Canada. Issued as N.R.C. No. 3168.*
[2] *Present address: Department of Chemistry, Columbia University, New York, N.Y., U.S.A.*
[3] *Present address: Department of Chemistry, Indiana University, Bloomington, Indiana, U.S.A.*
[4] *The authors are indebted to Dr. H. J. Vipond who first suggested this possibility in the course of discussion.*

The infrared spectrum (carbon disulphide solution) of the new base contained a hydroxyl band at 3380 cm.$^{-1}$ which was absent in the spectrum of lupanine in the same solvent. (Liquid films of this base and lupanine both showed bands near 3400 cm.$^{-1}$ and this confused the interpretation for a time.) An active hydrogen determination (Zerewitinoff) confirmed the presence of one hydroxyl group. Reduction of the base with sodium borohydride gave lupanine in high yield, which is consistent with the carbinolamine structure.

When the new base was oxidized with permanganate in acetone a neutral oxylupanine, $C_{15}H_{20}N_2O_2$, was obtained. Clemo and Leitch (3) described the oxidation of *dl*-lupanine to *dl*-oxylupanine. When this oxidation was repeated with *d*-lupanine an oxylupanine was obtained which was identical with that from the new base. Alkaline ferricyanide oxidation of lupanine also gave the same product.

Hydrogenation of this oxylupanine in 2 *N* hydrochloric acid with platinum catalyst (Adams') gave oxysparteine, identical with the product from ferricyanide oxidation of *l*-sparteine. These observations clearly locate the second lactam carbonyl in the above oxylupanine at position 17, and hence show the hydroxyl in the new base to be on that carbon atom.

The perchlorate and picrate of 17-hydroxylupanine analyze for anhydro salts. The infrared spectrum of the perchlorate has a band at 1682 cm.$^{-1}$ which can be assigned to a $\diagdown\!\!>C = \overset{+}{N}\!\!<\diagup$ group (9, 10). The pK's of lupanine and 17-hydroxylupanine in 50% aqueous methanol were found to be 8.4 and 10.5 respectively. This difference parallels the findings of Adams and Mahan (1) who showed that tertiary vinylamines which can form salts of quaternary ammonium character are stronger bases than the corresponding saturated amines. Thus the salts of 17-hydroxylupanine have the anhydronium salt form:

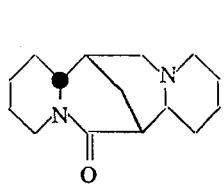



The carbinolamines hydrastinine and cotarnine form similar anhydronium salts. The former has a pK of 11, and the latter has been reported to be a strong base (4). However, pseudostrychnine, a carbinolamine which cannot give an anhydro salt (bridgehead double bond), is a weak base (7).

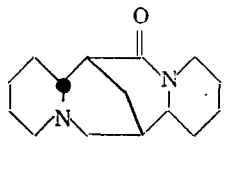
It appears that silver oxide can convert tertiary amines to the corresponding carbinolamines which in some cases can dehydrate to the vinylamine. The yield in the oxidation of lupanine with silver oxide was low when air was excluded, but in one run with exposure to air a high yield was obtained. It is possible that a silver catalyzed air oxidation was superimposed on the direct action of the reagent. N-Bromosuccinimide probably gives 17-bromolupanine which is later hydrolyzed to the carbinolamine.

Since the steric relation between lupanine and sparteine has been established (6), the preparation of oxysparteine from 17-oxylupanine is clear proof

of the stereochemistry of the former. Thus aphylline and oxysparteine are:



Aphylline



Oxysparteine

The ultraviolet absorption spectrum of 17-hydroxylupanine perchlorate (Fig. 1) is noteworthy. The normal hypsochromic shift in going from an aliphatic amine to its salt is reversed. This strong absorption above 250 mμ must be due to the $\rangle C = \overset{+}{N} \langle$ group. The intense end absorption due to the lactam function is illustrated in Fig. 2.

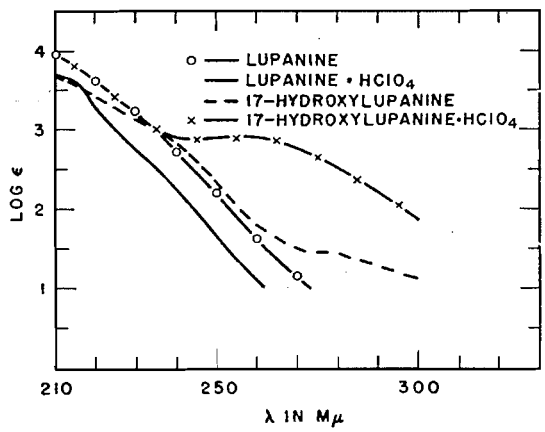



Fig. 1

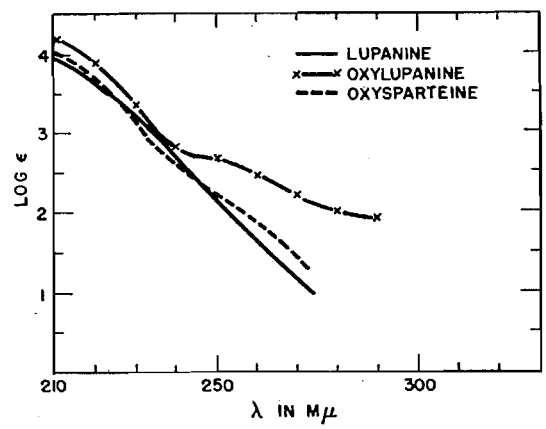



Fig. 2

## EXPERIMENTAL

Melting points are corrected to ±1° C. The infrared spectra were determined on a Perkin-Elmer double beam model 21 instrument. They are reported by citing the position of the main peaks in cm.$^{-1}$ followed by percentage absorption, in parentheses. The ultraviolet spectra were determined on solutions in 95% ethanol using a Beckman D.U. spectrophotometer.

### *d-Lupanine Perchlorate*

*d*-Lupanine perchlorate isolated in these laboratories from *Lupinus polyphyllus* L. and crystallized from methanol had m.p. 214–215° (immersed at 180°). $[\alpha]_D^{25} = +46.8 \pm 0.5°$ (*c*, 2.29 in water).

The pK of lupanine was found to be 8.4 (pH at half-titration) by titration of the perchlorate in 50% aqueous methanol. Calc. for $C_{15}H_{24}NO_2.HClO_4$: C, 51.61; H, 7.16; N, 8.02. Found: C, 51.54; H, 7.36; N, 7.84%. Infrared spectrum (nujol mull): 3500(31), 3240(42), 2680(35), 1617(91), 1455(77), 1425(68), 1377(31), 1346(44), 1334(38), 1314(51), 1281(31), 1250(52), 1225(20), 1192(25), 1170(68), 1100(98), 967(33), 929(25), 856(19), 820(11), 785(14), 725(15), 655(21), 607(24).

### *d-Lupanine*

*d*-Lupanine base was obtained by treatment of *d*-lupanine perchlorate with aqueous sodium hydroxide, extraction with methylene chloride, removal of solvent after drying (sodium sulphate), and distillation of the oil at 117–120° at 0.3 mm. Infrared spectrum (3 mgm./ml. in carbon disulphide, 1 mm. cell): 2930(64), 2840(36), 1644(77), 1359(32), 1345(38), 1335(48), 1309(37), 1279(40), 1250(38), 1185(23), 1165(40), 1137(38), 1119(42), 1099(26), 1071(21), 1025(18), 1013(17), 965(12), 916(14), 842(11), 785(16).

### *17-Hydroxylupanine*

Lupanine (1.614 gm.) dissolved in 50% aqueous methanol (40 cc.) was stirred for six hours at 60–70° with freshly prepared silver oxide (8.8 gm. dry weight) in a nearly closed system. Metallic silver was formed slowly. The solids were removed by filtration and washed thoroughly with hot methanol. The combined filtrate and washings were concentrated to remove solvent, made alkaline with aqueous sodium hydroxide, filtered, and extracted exhaustively with methylene chloride. The methylene chloride solution was extracted with 3 *N* sulphuric acid (twice) and once with water. The acid solution was made alkaline with sodium hydroxide, extracted with methylene chloride, the extract dried (sodium sulphate), and concentrated to yield an oil which was converted to perchlorate in methanol. The warm supernatant methanolic solution was removed from the deposited perchlorate (mainly *d*-lupanine perchlorate) and allowed to crystallize to yield crystals, m.p. 210–220°, which after three crystallizations from methanol had a melting point of 253° dec. (immersed at 210°) (100 mgm.). In other similar experiments yields of up to 15% of the theoretical were obtained. In one experiment in an open system (reflux condenser) a yield of 53% was obtained. Lupanine was nearly inert to air oxidation under similar conditions without a catalyst. A sample

of the perchlorate prepared by the method of Marion and Leonard (6) also melted at 253° (dec.). $[\alpha]_D^{27} = -135.6°$ (*c*, 2.91 in water). Found: C, 51.56; H, 6.81; N, 7.72. Calc. for $C_{15}H_{22}N_2O.HClO_4$: C, 51.94; H, 6.68; N, 8.08%. Infrared spectrum (nujol mull): 1682(33), 1635(86), 1434(55), 1416(53), 1371(40), 1350(35), 1335(36), 1312(41), 1295(22), 1271(57), 1243(34), 1215(22), 1175(48), 1149(36), 1103(90), 1182(90), 1130(29), 1111(26), 975(30), 949(24), 921(27), 907(17), 880(14), 851(12), 830(14), 686(22), 650(20).

17-Hydroxylupanine obtained from pure perchlorate was converted to picrate in methanol, recrystallized from methanol–ether, m.p. 172–174°. Found: C, 53.22, 53.45; H, 5.79, 5.73; N, 14.65. Calc. for $C_{21}H_{25}N_5O_8$: C, 53.05; H, 5.30; N, 14.73%.

The pK of 17-hydroxylupanine was found to be 10.5 (pH at half titration) by titration of the perchlorate in 50% aqueous methanol.

The base liberated from the perchlorate had $[\alpha]_D^{25}$ 38.7 ± 0.5° (*c*, 3.72 in ethanol).

Active hydrogen (Zerewitinoff). Found: 0.443%. Calc. for one active hydrogen: 0.378%. Infrared spectrum (7.6 mgm./ml. in carbon disulphide, 1 mm. cell): 3540(15), 3380(18), 2930(84), 2850(70), 2050(12), 1643(91), 1346(71), 1329(67), 1310(65), 1292(44), 1280(40), 1255(64), 1203(34), 1175(48), 1165(64), 1128(60), 1119(62), 1090(53), 1078(60), 1047(43), 1034(50), 1018(48), 1001(37), 980(25), 963(39), 910(45), 840(30), 795(28), 685(12), 648(21).

*Catalytic Reduction of 17-Hydroxylupanine*

17-Hydroxylupanine (65 mgm.) dissolved in absolute ethanol (10 cc.) was treated with hydrogen at atmospheric pressure and room temperature in the presence of Adams' platinum oxide catalyst (50 mgm.). One mole of hydrogen was absorbed. The catalyst was removed by filtration, the solution made acid to Congo red with 70% perchloric acid and allowed to crystallize to give prisms, m.p. 210–211°, which showed no depression on admixture with authentic *d*-lupanine perchlorate. $[\alpha]_D^{27.5} = +46.1$ (*c*, 1.92 in water). The infrared spectrum, as a liquid film, of the base from the perchlorate was superposable on that of authentic lupanine.

*Sodium Borohydride Reduction of 17-Hydroxylupanine*

17-Hydroxylupanine perchlorate (30 mgm.) was dissolved in water (4 cc.) and the solution made faintly alkaline with sodium hydroxide. Sodium borohydride (50 mgm.) was added and the solution maintained at room temperature with occasional shaking for one hour. The alkaline solution was extracted exhaustively with methylene chloride, the extract dried (sodium sulphate), concentrated, and the resulting oil converted to perchlorate in methanol.The salt crystallized from methanol as needles (30 mgm.), m.p. 209–210°, which showed no depression on admixture with a specimen of authentic *d*-lupanine perchlorate.

*d-Oxylupanine from 17-Hydroxylupanine*

17-Hydroxylupanine (107 mgm.) dissolved in acetone (10 cc.), glacial acetic acid (1 cc.), and water (1 cc.) was treated portionwise with pulverized po-

tassium permanganate (40 mgm.) during 40 min. The deposited manganese dioxide was filtered off and washed with acetone. The combined filtrate and washings were concentrated *in vacuo* to remove solvent, dissolved in methylene chloride (10 cc.), washed with dilute hydrochloric acid and water and dried (sodium sulphate). The solvent was removed to yield an oil which immediately crystallized. Sublimation at 170° at 0.4 mm. yielded a colorless crystalline product, m.p. 152–153°. Calc. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.58; H, 8.52; N, 10.77%. Infrared spectrum (8.7 mgm./ml. in carbon disulphide, 1 mm. cell): 2940(85), 2860(71), 1640(96), 1348(85), 1330(69), 1320(51), 1308(73), 1275(89), 1260(87), 1231(51), 1185(57), 1173(63), 1163(66), 1150(53), 1136(53), 1124(51), 1098(51), 1082(36), 1040(27), 1020(38), 985(28), 966(33), 916(31), 835(20), 815(21), 771(23), 707(16).

*d-Oxylupanine from Lupanine*

*d*-Lupanine (532 mgm.) dissolved in acetone (50 cc.), glacial acetic acid (5 cc.), and water (5 cc.) was treated as described for 17-hydroxylupanine with pulverized potassium permanganate (859 mgm.) during 35 min. The mixture was filtered, the solvent removed *in vacuo*, the oil dissolved in methylene chloride (15 cc.), and extracted with 3 *N* sulphuric acid (two 15 cc. portions) and once with water. The dried (sodium sulphate) methylene chloride solution was concentrated to yield a crystalline solid (319 mgm.) which was sublimed at 168–170° at 0.4 mm. After two recrystallizations from acetone–ether the compound melted at 154°. It showed no depression on admixture with *d*-oxylupanine obtained by oxidation of 17-hydroxylupanine. $[\alpha]_D^{23} = +138.9°$ (*c*, 2.86 in absolute ethanol).

*Oxidation of Lupanine with Alkaline Ferricyanide*

Lupanine (1.333 gm.) was shaken with potassium ferricyanide (10 gm.) and sodium hydroxide (1.75 gm.) in water (25 cc.) for 40 min. The solution was extracted with three portions of methylene chloride, the extracts washed twice with 3 *N* sulphuric acid and with water, dried (sodium sulphate), and concentrated to yield an oil (300 mgm.) which partially crystallized. This product was crystallized twice from boiling petroleum ether (b.p. 30–60°) to yield colorless needles, m.p. 150–151°, which showed no depression on admixture with specimens of oxylupanine prepared from lupanine or 17-hydroxylupanine.

The infrared spectrum in carbon disulphide was superposable with the corresponding spectrum of the oxylupanine prepared from lupanine or 17-hydroxylupanine.

*Catalytic Reduction of Oxylupanine*

Oxylupanine (200 mgm.) dissolved in 2 *N* hydrochloric acid (15 cc.) was treated with hydrogen at 26° and atmospheric pressure in the presence of platinum catalyst (200 mgm.) for 24 hr. The catalyst was removed by filtration and the filtrate extracted with methylene chloride. The acidic solution was made alkaline, extracted exhaustively with methylene chloride, dried (sodium sulphate), and concentrated to yield a crystalline product, m.p. 83–85°. After recrystallization from petroleum ether (b.p. 30–60°) it melted at 86°.

This showed no depression on admixture with authentic oxysparteine. The infrared spectra in carbon disulphide of the two specimens were superposable (10 mgm./ml. in carbon disulphide; 1 mm. cell): 2930(91), 2860(78), 2760(69), 1640(92), 1363(82), 1355(73), 1335(63), 1315(74), 1298(57), 1286(54), 1274(88), 1260(87), 1247(50), 1233(45), 1192(71), 1185(62), 1166(56), 1150(71), 1136(69), 1120(76), 1108(59), 1086(55), 1061(43), 1026(37), 1115(48), 985(18), 965(35), 932(20), 905(16), 842(25), 805(14), 769(22), 749(45), 690(15).

*Hydrastinine*

The pK of hydrastinine was found to be 11 by titration of the chloride with sodium hydroxide in 50% aqueous methanol.

ACKNOWLEDGMENT

The authors wish to thank Dr. Léo Marion for helpful discussions, for a sample of "dehydrolupanine (NBS)" perchlorate, and for the lupanine used in these experiments. They also wish to thank Mr. M. Lesage for helpful technical assistance, Mr. J. Eagen and Mr. H. Seguin for the analyses, and Dr. R. N. Jones and Mr. R. Lauzon for providing the infrared spectra.

REFERENCES

1. ADAMS, R. and MAHAN, J. E. J. Am. Chem. Soc. 64: 2588. 1942.
2. BLAU, F. Ber. 27: 2535. 1894.
3. CLEMO, G. R. and LEITCH, G. C. J. Chem. Soc. 1811. 1928.
4. DECKER, H. Ber. 33: 2273. 1900.
5. EDWARDS, O. E. and MARION, L. Can. J. Chem. 30: 627. 1952.
6. MARION, L. and LEONARD, N. J. Can. J. Chem. 29: 355. 1951.
7. PRELOG, V. and HÄFLIGER, O. Helv. Chim. Acta, 32: 1851. 1949.
8. SUGINOME, H. and OHNO, K. J. Fac. Sci. Hokkaido Univ. Ser. III. 4: 36. 1950. Chem. Abstracts, 46: 1008. 1952.
9. WITKOP, B. and PATRICK, J. B. J. Am. Chem. Soc. 75: 4474. 1953.
10. WITKOP, B., PATRICK, J. B., and KISSMAN, H. M. Ber. 85: 949. 1952.