

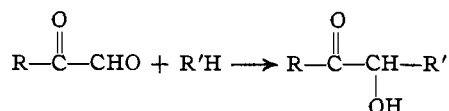
and was continued until the residual solution was reduced to a volume of 30 cc. To this was added 30 cc. of low-boiling petroleum ether, and the solution kept cold overnight. The precipitate was separated by filtration with suction and washed with four 25-cc. portions of cold, low-boiling petroleum ether. The material weighed 10.2 g. (70.2% of the theoretical amount), and melted at 105–106°. After one recrystallization from ethyl alcohol, the benzoin melted at 108–109°.

The general procedure involves the use of the hydrocarbon reactant as the solvent; in some cases, however, carbon disulfide has been found to give very satisfactory results.

The Structure of the Benzoin

In every case where the resulting benzoin is known, our product showed perfect agreement with the published descriptions of the compound anticipated. In cases where both benzoin isomers

were prepared, both were oxidized by iodine¹⁴ to give identical diketones. Most of these diketones are known substances.¹⁰ It is important to note that in each instance only one benzoin was obtained, and that in every case the structure of the benzoin corresponded to that to be expected on the basis of the general equation



Summary

Twelve benzoin isomers have been prepared by condensation of arylglyoxals with aromatic hydrocarbons or their derivatives. The structures of the mixed benzoin isomers have been shown to be those which would be predicted on the basis of the general equation as indicated above.

(14) Carson and McAllister, *THIS JOURNAL*, **51**, 2822 (1929).

URBANA, ILLINOIS

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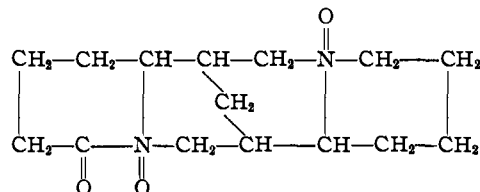
[CONTRIBUTION FROM THE PATHOLOGICAL DIVISION, BUREAU OF ANIMAL INDUSTRY]

Lupine Studies. XI. The Alkaloids of *Lupinus Barbiger* S. Wats.

BY JAMES FITTON COUCH

In a previous communication¹ the occurrence of sparteine in *Lupinus barbiger* was announced. At that time the presence of two other alkaloids of undetermined identity was indicated. This paper describes the isolation and identification of these alkaloids. *L. barbiger* is a perennial species ranging from Colorado, Utah, Arizona, and California.² Two lots of material, one from northern Arizona and one from Utah were examined in the course of this study and no significant differences between them were found.

Three well-defined alkaloids were isolated from this species: sparteine and two hitherto undescribed bases which have been named dilupine and trilupine. Lupinine and lupanine were sought for and found not to be present. The new alkaloids are of unusual interest. Trilupine, C₁₅H₂₄O₃N₂, proved to be an amine oxide derived from *d*-lupanine of which it is the di-N-oxide corresponding to the structure



By the action of hydrogen dioxide on sparteine the di-N-oxide of that base has been prepared³ by a number of workers. Polonovski⁴ has shown that geneserine is the amine oxide of eserine and analogous compounds have been prepared synthetically from other bases.⁵ This is, however, the first instance in which amine oxides have been discovered in a lupine species. It was found that while gold chloride and platinum chloride would yield the corresponding double salts of trilupine if the mixtures were not heated for more than a short time, other acids and longer heating resulted

(3) F. B. Ahrens, *Ber.*, **20**, 2218 (1887); Wackernagel and Wolfenstein, *ibid.*, **37**, 2220 (1904); A. Valeur and E. Luce, *Compt. rend.*, **168**, 1276 (1919).

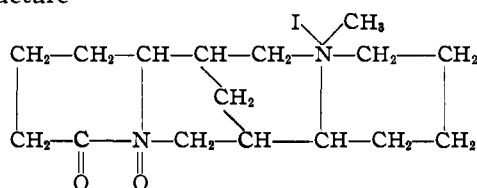
(4) Max Polonovski, *Bull. soc. chim.*, **21**, 191 (1917).

(5) (a) Max and Michel Polonovski, *Compt. rend.* **180**, 1755 (1925); (b) M. Freund and E. Speyer, *Ber.*, **43**, 3310 (1910); (c) R. Wolfenstein, *ibid.*, **25**, 2777 (1892).

(1) J. F. Couch, *THIS JOURNAL*, **54**, 1691 (1932).

(2) W. W. Eggleston, in I. Tidestrom, "Flora of Utah and Nevada," *Contr. U. S. Nat. Herbarium*, **25**, 297 (1925), Govt. Printing Office, Washington.

in the formation of salts of *d*-lupanine, the reaction involving removal of the oxide oxygen atoms. Freund and Speyer^{5b} were able to prepare crystalline salts of the oxides of morphine, thebaine, codeine and ethylmorphine with mineral acids. When trilupine reacted with methyl iodide in the cold a compound was obtained that contains one oxygen atom less than is required from trilupine methiodide and which appears to be the methiodide of *d*-lupanine mono-N-oxide of the probable structure



Trilupine was converted into *d*-lupanine by treating the dihydrochloride, which is identical with *d*-lupanine dihydrochloride, with alkali, and shaking out the liberated base with chloroform, which yielded an alkaloid identical with *d*-lupanine. The latter was converted into trilupine by the action of calcium dioxide on *d*-lupanine dihydrochloride and the synthetic base agreed with the natural alkaloid in all respects.

The optical activity of trilupine might be expected to throw some light on the problem of the possible asymmetry of the nitrogen atoms in lupanine. The crystallized base had a specific rotation of 63.76° as compared with 84.35° for *d*-lupanine. Correcting for the content of water of crystallization and for the difference in molecular weight the comparable figure for trilupine is 83.12° or sufficiently close to the figure for *d*-lupanine to furnish no support for the view that the nitrogen atoms are asymmetrical.

Dilupine was not obtained in sufficient quantities to permit a thorough study. The analytical figures agree with the formula $C_{16}H_{26}O_2N_2$ for the free base while the analyses of the methiodide and the hydrobromide require a base of the formula $C_{16}H_{26}ON_2$, suggesting that dilupine may be the amine oxide of a C-methyl-lupanine. The base recovered from the hydrobromide was not identical with dilupine but had the nitrogen content required by a methyl-lupanine which supports this view. The question, however, must await further study for complete clarification.

The presence of the di-amine oxide of lupanine in the plant suggested that lupanine should also have been found if only as a decomposition prod-

uct of trilupine. Careful search failed to reveal that alkaloid even in the residues from vacuum distillations.

Experimental

Material.—The plant material consisted of two lots of plants, one collected on the Kaibab Forest, Arizona, and the second at Hilltop, 10 miles north of Fairview, Utah. The first collection was made during the summer of 1928 and the second on July 11 and August 11, 1931. The plants had not formed seeds at the time of collection. The material was dried, shipped to Washington and ground to a coarse powder for use. The air-dried plant had moisture contents of 8.47 and 7.62% for the two collections. It was identified by W. W. Eggleston as *Lupinus barbiger* S. Wats.

Isolation of the Alkaloids.—The method used in extracting the alkaloids has previously been described;⁶ 16.45 kg. of the first collection yielded 1.67% of alkaloid, freed from resinous impurities and calculated to moisture-free plant; 58.09 kg. of the second yielded 1.86%. The alkaloids were treated with an equal volume of ether which dissolved nearly half. The dissolved alkaloids, freed from ether, were then dissolved in petroleum ether, which took up all but a trace of resinous matter. The alkaloidal residue obtained by distilling off the solvent will be referred to as fraction A. The material not dissolved by ether was extracted with benzene which dissolved the larger portion of it. On distilling off the solvent fraction B was obtained. The material not dissolved by benzene was extracted with boiling ethyl acetate and, freed from solvent, the extract furnished fraction C. The undissolved matter was insoluble in a mixture of boiling acetone and 10% alcohol and consisted of resinous substances.

Fraction A was a brownish sirup of strong burnt-wool odor. It weighed 441 g. and gave a strong reaction for sparteine in the modified Grant test. It was submitted to distillation under reduced pressure but could not be separated into its constituents by that method. Fractions were obtained that had nearly the correct index of refraction and optical activity for sparteine, but were evidently contaminated with some other base. Separation was effected by dissolving the fractions that distilled below 195° at 1 mm. in dilute hydrochloric acid and adding aqueous mercuric chloride when the double chloride of sparteine and mercury crystallized and could be purified by recrystallization from hot 20% hydrochloric acid. The alkaloid was recovered from this compound by treating it with ammonia and extracting with chloroform. On distilling off the solvent the base remained as a light yellow sirup which distilled at 185° and 7 mm. with a small residue. It had n_D^{20} 1.5256, $(\alpha)_D^{20}$ 5.95° , and depressed the freezing point of benzene conformably to the molecular weights 241, 244 and 240. The substance was positive to the Jorissen⁷ and modified Grant⁸ tests for sparteine.

Anal. Calcd. for $C_{22}H_{26}N_2$: C, 76.86; H, 11.19. Found: C, 76.51; H, 11.40.

Salts of Sparteine.—Picrate, m. p. $205-206^\circ$, did not depress the melting point of authentic sparteine picrate.

(6) J. F. Couch, *THIS JOURNAL*, **56**, 2434 (1934).

(7) Jorissen, *Ann. chim. anal.*, **16**, 412 (1911).

(8) Couch, *Am. J. Pharm.*, **97**, 38 (1925).

Calcd.: N, 16.18. Found: N, 16.00. The platinum chloride melted at 248° (dec.) and did not depress the melting point of authentic sparteine platinum chloride.

The Dihydrobromide.—Five grams of the base, dissolved in 100 cc. of acetone, was treated with an excess of hydrobromide acid solution. Two layers formed and 1 volume of alcohol was added which produced a homogeneous solution. On standing overnight in an ice box the solution deposited a mass of colorless prisms. Recrystallized from alcohol these melted at 197°.

Anal. Calcd. for $C_{16}H_{26}N_2 \cdot 2HBr \cdot H_2O$; Br, 38.63; H_2O , 4.35. Found: Br, 38.51, 38.50; H_2O , 4.40, 4.54. $(\alpha)^{25D} -18.33^\circ$ in water, $c = 1.2770$, $l = 4$, $a = 0.93^\circ$. The free alkaloid regenerated from this salt showed $n^{27D} 1.5259$ and formed a picrate that melted at 206°. The methiodide readily separated from a mixture of the base with methyl iodide without warming. Recrystallized from alcohol it melted at 239–240°.

Anal. Calcd. for B, CH_3I : I, 33.75; N, 7.45. Found: I, 33.72, 33.63; N, 7.51.

The Zinc Chloride.—Sparteine dissolved in 10% hydrochloric acid (2 moles) treated with excess of saturated zinc chloride solution within a few minutes begins to deposit crystals of the double chloride with zinc.⁹ Recrystallized from water and dried in a desiccator these were free from water of crystallization and melted at 316–317°.

Anal. Calcd. for $B2HCl \cdot ZnCl_2$: Cl, 32.09. Found: Cl, 32.01, 31.84. $(\alpha)^{30D} -19.57$ in water; $c = 0.9912$, $l = 1$, $a = 0.194^\circ$.

Isolation of a New Lupine Alkaloid, Dilupine.—The highest boiling fraction of the original fraction A distilled at 190–222° and 1 mm. It consisted of a thick reddish oil of strong burnt-wool odor, $(\alpha)^{26D} 69.50^\circ$, $n^{24D} 1.5395$. It contained some sparteine which was removed by distillation with steam. The non-volatile alkaloid was recovered by shaking the water solution with chloroform and on distilling the chloroform a sirup was obtained that did not react to the modified Grant test for sparteine. On standing the sirup deposited a small quantity of needles which were filtered off and proved to be a third alkaloid which is described in detail below. The sirupy alkaloid was redistilled under reduced pressure several times until it was obtained as light yellow, very thick sirup. It has not been crystallized. The analytical figures agree best with a formula for a C-methyl-lupanine oxide and this is tentatively accepted. Further study of the base is in progress.

Anal. Calcd. for $C_{16}H_{26}O_2N_2$: C, 69.01; H, 9.41; N, 10.07. Found: C, 69.38, 69.31, 69.45; H, 9.81, 9.66, 9.75; N, 10.05, 10.08. $(\alpha)^{26D} 65.59^\circ$, in water, $c = 6.5028$, $l = 1$, $a = 4.26^\circ$, $n^{27D} 1.5440$.

The Methiodide.—A mixture of equal volumes of the alkaloid and methyl iodide began to deposit crystals within thirty minutes and in twenty hours the mixture had solidified. Recrystallized from boiling alcohol several times the m. p. was 253°. The analytical figures for this compound do not agree with those calculated for a methiodide of a base of the composition assigned to the free alkaloid but require a base with one less oxygen atom. This would indicate that dilupine is an amine oxide.

Anal. Calcd. for $C_{16}H_{26}ON_2 \cdot CH_3I$: C, 50.47; H, 7.17; N, 6.94; I, 31.40. Found: C, 50.47; H, 7.19; N, 6.80, 6.94; I, 31.32, 31.13. $(\alpha)^{32D} 51.10^\circ$, in water, $c = 1.409$, $l = 1$, $a = 0.72^\circ$.

The Hydrobromide.—The base, dissolved in alcohol and treated with a slight excess of hydrobromic acid, deposited cubical crystals after several days' standing in an ice box. Recrystallized from alcohol and dried at 115° these crystals melted at 233–234°. As in the case of the methiodide the analytical figures agree better for a less oxygenated base.

Anal. Calcd. for $C_{16}H_{26}ON_2 \cdot HBr$; Br, 23.31. Found: Br, 23.86, 23.83.

Three grams of the hydrobromide was dissolved in water, alkalinized with sodium hydroxide, and the liberated base shaken out with chloroform. The solvent was removed and the residual sirup was dissolved in methanol and the solvent boiled off three times to remove chloroform. The base was a reddish sirup.

Anal. Calcd. for $C_{16}H_{26}ON_2$: N, 10.68. Found: N, 10.62. $(\alpha)^{25D} 49.78^\circ$, in water, $c = 1.832$, $l = 1$, $a = 0.91$. $n^{25D} 1.5454$.

Isolation of a New Lupine Alkaloid, Trilupine.—Fraction B was freed from benzene by warming on the water-bath. An attempt to separate the constituents of this fraction by distillation under reduced pressure resulted in considerable decomposition. On standing several weeks the fraction deposited a mass of prismatic crystals embedded in thick sirup. The crystals were collected by filtering the mass through a porous plate under suction. The sirupy filtrate proved to consist of a small quantity of sparteine, much dilupine, and some of the crystalline alkaloid. The crystals were washed with small quantities of cold acetone in which they were slowly soluble and then were recrystallized from boiling ethyl acetate several times, finally with addition of charcoal. By this means the melting point was raised from 112 to 127° where it was constant. The product was colorless efflorescent needles, soluble in water, alcohol, and chloroform, less soluble in cold acetone and ethyl acetate, and nearly insoluble in ether. They contained 2 moles of crystal water and, when anhydrous, melted at 252°. The aqueous solutions are neutral to litmus.

Anal. Calcd. for $C_{15}H_{24}O_3N_2 \cdot 2H_2O$: C, 56.93; H, 8.92; N, 8.85; $2H_2O$, 11.38. Found: C, 56.71, 56.85, 56.42; H, 9.02, 9.05, 9.15; N, 8.88, 8.79; H_2O 11.07, 11.25. $(\alpha)^{30D} 63.76^\circ$, in water, $c = 1.7252$, $l = 1$, $a = 1.10^\circ$.

Certain salts could be prepared from trilupine if the reaction mixtures were not heated for more than a very short time. Heating mixtures of trilupine and acids resulted in salts of *d*-lupanine.

Trilupine Platinum Chloride.—A solution of trilupine (1 g.) and a few drops of dilute hydrochloric acid in 5 cc. of water was treated with platinum chloride solution. No precipitation occurred. The solution was evaporated to dryness in a desiccator over concentrated sulfuric acid. The dried mass was freed from excess platinum chloride by extraction with alcohol and the residue was dried. It melted at 224° (dec.).

Anal. Calcd. for $C_{15}H_{26}O_3N_2 \cdot H_2PtCl_6 \cdot 4H_2O$: Pt, 25.61; Cl, 27.95. Found: Pt, 25.66, 25.66; Cl, 27.78, 27.86.

(9) E. J. Mills, *J. Chem. Soc.*, 15, 1–8 (1862).

Trilupine Gold Chloride.—A solution of the alkaloid in dilute hydrochloric acid treated with gold chloride solution yielded a yellow flocculent precipitate which was redissolved in the mother liquor by gentle warming and set aside. Golden needles were deposited on standing which were collected, washed and dried. The melting point was 188–189° (dec.). The mother liquors on standing deposited much metallic gold.

Anal. Calcd. for $C_{15}H_{24}O_3N_2 \cdot 2HAuCl_4 \cdot 4H_2O$: Au, 38.19; H_2O , 6.97. Found: Au, 38.18; H_2O , 6.91.

Trilupine Methiodide.—To a cold solution of trilupine (1 g.) in ethyl acetate (5 cc.) was added 2 cc. of methyl iodide. On standing octahedral crystals slowly separated. These were collected and dried, m. p. 127°. Analysis indicated that this substance contains one atom of iodine and that one oxide oxygen had been replaced by methyl iodide. The substance is, therefore, the methiodide of the mono-N-oxide of *d*-lupanine.

Anal. Calcd. for $C_{15}H_{24}O_2N_2 \cdot CH_3I$: I, 31.25. Found: I, 31.47, 31.50.

Conversion of Trilupine into *d*-Lupanine.—Five grams of trilupine dissolved in acetone (100 cc.) and treated with 4 cc. of hydrochloric acid in 4 cc. of alcohol evolved heat. On cooling there was a scanty deposition of colorless crystals. These were collected, washed with acetone and dried. They melted at 163–164°. When mixed with *d*-lupanine dihydrochloride there was no depression of the melting point. This substance lost 16.32% in weight when dried at 120° corresponding to one mole each of hydrochloric acid and water of crystallization. The anhydrous monohydrochloride melted at 252–254° as does anhydrous *d*-lupanine hydrochloride.

Anal. Calcd. for $C_{15}H_{24}ON_2 \cdot 2HCl \cdot H_2O$: 2Cl, 20.95; 1 HCl and 1 H_2O , 16.06, 1 Cl, 10.47. Found: Cl_2 , 20.46; "moisture" 16.30, 16.34; Cl, 10.43.

Recovery of *d*-Lupanine from (Trilupine) Dihydrochloride.—Four grams of dihydrochloride prepared from trilupine was dissolved in 25 cc. of water and alkalinized with sodium hydroxide. The precipitated oil was shaken out with chloroform which was separated, evaporated off and the residue was three times treated with methanol and evaporated to remove traces of chloroform. The alkaloid so obtained was a light brown oil with the characters of *d*-lupanine.

Anal. Calcd. for $C_{15}H_{24}ON_2$: N, 11.28. Found: N, 11.27. (α)²⁵_D 79.20°, in alcohol, $c = 5.404$, $l = 1$, $a = 4.28$ °; n^{25}_D 1.5470. Dextro-lupanine prepared from *L. albus* had (α)²⁵_D 84.35 in alcohol and n^{25}_D 1.5444.

***d*-Lupanine Gold Chloride.**—Trilupine in dilute hydrochloric acid treated with excess of gold chloride solution gave a heavy flocculent precipitate which was redissolved in boiling dilute hydrochloric acid and crystallized on cooling; yellow needles, m. p. 206°. *Anal.* Calcd. for $C_{15}H_{24}ON_2 \cdot HAuCl_4$: Au, 33.52. Found: Au, 33.33, 33.25.

***d*-Lupanine Perchlorate.**—The dihydrochloride prepared from trilupine (1 g.) dissolved in 5 cc. of water, was treated with 0.5 cc. of perchloric acid and 2 cc. of saturated sodium acetate solution. An immediate crystalline pre-

cipitate fell which was recrystallized twice from water, dried, and then melted at 207–209° and did not depress the melting point of *d*-lupanine perchlorate.

***d*-Lupanine Dihydrochloride.**—Since this compound had not been reported it was necessary to prepare it from authentic *d*-lupanine for comparison with the salt derived from trilupine. Seven grams of *d*-lupanine hydrochloride from *L. albus* was dissolved in 30 cc. of alcohol, 3 cc. of hydrochloric acid was added and then enough acetone to produce a slight cloud. The mixture was filtered and set in an ice box. Crystallization began within an hour. After twenty-four hours the crystals were collected, washed, redissolved in 10 cc. of alcohol and treated with 30 cc. of acetone. On standing the substance crystallized. Washed and dried the crystals melted at 161–162° and did not depress the melting point of the dihydrochloride obtained from trilupine. On drying at 120° their behavior was similar to the trilupine derivative.

Anal. Calcd. for $C_{15}H_{24}ON_2 \cdot 2HCl \cdot H_2O$: 2Cl, 20.95; 1 HCl and 1 H_2O , 16.06; 1 Cl, 10.47. Found: Cl_2 , 20.72; "moisture" 16.05, 16.12; Cl, 10.50, 10.44.

Conversion of *d*-Lupanine into Trilupine.—To 10 g. of *d*-lupanine dihydrochloride dissolved in 50 cc. of water was added in small portions 4 moles of calcium dioxide (8.4 g.) with frequent shaking. When the calcium dioxide had all been added hydrochloric acid was added a few drops at a time until the calcium dioxide was nearly all dissolved. The solution was then alkaline to litmus. It was warmed for four hours on the water-bath, let cool and shaken out with chloroform. On distilling off the chloroform after separating it from the aqueous layer there remained a light brown sirup that soon crystallized to a mass of needles embedded in a dark sirup. The mixture was treated with ether, which dissolved the sirup, and the crystals were recrystallized from hot ethyl acetate with a little charcoal; colorless needles, m. p. 125–126°. Mixed with trilupine, m. p. 127°, the mixture melted at 126–127°.

Examination of Fraction C.—The portion of the original crude alkaloid that was not dissolved in ether or benzene proved to contain small amounts of sparteine, some dilupine which was recovered and added to fraction B, trilupine worked up with that alkaloid, much resinous matter, and a quantity of basic matter from which nothing definite has yet been obtained.

Summary

Lupinus barbiger S. Wats. from Arizona and Utah contains three alkaloids, sparteine, dilupine and trilupine, the last two of which were previously undescribed. Dilupine, provisionally $C_{15}H_{26}O_2N_2$, appears to be the amine oxide of a C-methyl-lupanine. Trilupine, $C_{15}H_{24}O_3N_2$, is the di-amine oxide of *d*-lupanine into which it may be converted by the action of acids and heat. It may be prepared by oxidizing *d*-lupanine with calcium dioxide.

WASHINGTON, D. C.

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