

to confirm the presence of oxalic dihydrazide, so that it is doubtful whether oxalic acid is present. No. 2 gave a hydrazide melting at 165–170°. A mixture with *l*-malic dihydrazide melted at 171–174°, showing the product to be impure *l*-malic dihydrazide. No. 3 also gave impure *l*-malic dihydrazide. No. 4 gave a hydrazide which melted at 178–179°. A mixture with *l*-malic dihydrazide melted at the same temperature. The product is, therefore, *l*-malic dihydrazide. No. 5 gave a hydrazide melting at 172–174°, which is *l*-malic dihydrazide. The filtrate gave a small quantity of a benzylidene compound on treatment with benzaldehyde. No. 6 gave a hydrazide melting at 164–168° which is impure *l*-malic dihydrazide. The filtrate yielded a small quantity of a benzylidene compound without sharp melting point. No. 7 also gave *l*-malic dihydrazide and a benzylidene compound melting, not sharply, at about 160°. No. 8 gave a hydrazide which crystallized in clusters of prisms melting at 145°. Citric trihydrazide was prepared in the same way and a mixture of the two melted at 145°. The product is therefore citric trihydrazide.

The benzylidene compound prepared from this melted, not sharply, at 183–185°, the benzylidene compound of citric trihydrazide at 193–196°, and a mixture of the two at 185–187°.

Summary and Conclusion

The non-volatile acids of the dried apricot consist of a mixture of *l*-malic acid and citric acid, in the proportion of about 25 to 10, with traces of an unidentified acid which may be oxalic acid.

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A NEW LUPINE ALKALOID, SPATHULATINE, ISOLATED FROM LUPINUS SPATHULATUS (RYDB.)

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Our present knowledge of the lupine alkaloids is incomplete. Five European species of the genus *Lupinus* have been thoroughly examined; one American species has been examined in Germany, and five more have been investigated by American chemists. The available data that pertain to these alkaloids may be summarized as shown in Table I.

References to two other alkaloids, lupinidine and lupanidine, will be found in the literature. The former was the name that the sparteine from *L. luteus* bore for more than twenty years before it was recognized as identical with the base from *Spartium scoparium*. The name lupanidine was applied to an undetermined alkaloidal residue from *L. polyphyllus*, that has since been recognized as hydroxylupanine.

TABLE I
 LUPINE ALKALOIDS

Lupine	Lupinus	Alkaloids
Yellow ¹	<i>Luteus</i>	Lupinine, C ₁₀ N ₁₉ ON; and sparteine, C ₁₅ H ₂₆ N
Black ²	<i>Niger</i>	Lupinine sparteine
Blue ³	<i>Augustifolius</i>	<i>d</i> -Lupanine, C ₁₆ H ₂₄ ON ₂
White ⁴	<i>Albus</i>	<i>d</i> -Lupanine and <i>dl</i> -lupanine C ₃₀ H ₄₈ O ₂ N ₄
Perennial ⁵	<i>Polyphyllus</i>	<i>d</i> -Lupanine and hydroxy lupanine C ₁₆ H ₂₄ -O ₂ N ₂
Am. perennial ⁶	<i>Perennis</i>	<i>d</i> -Lupanine and hydroxylupanine
.....	<i>Leucopsis</i> ⁷	Unnamed, C ₁₆ H ₃₂ O ₂ N ₂ .HI
Silvery ⁸	<i>Argenteus</i>	Unnamed
.....	<i>Sericeus</i> ⁹	Unnamed
.....	<i>Leucophyllus</i> ⁹	Unnamed

Our interest in the lupines arises from the wide distribution of this genus upon the stock ranges of the Western States and from the food value and poisonous properties of many species.¹⁰ Lupines have caused many well authenticated cases of poisoning of sheep, cattle, horses, swine and goats which have been allowed to feed freely upon them. Some species, however, do not appear to poison animals under range conditions and it was with the object of determining which species are dangerous and which are valuable for forage plants that this investigation was begun by the Department of Agriculture.

The study reported in this communication has resulted in adding a new alkaloid to the list of lupine bases already known. This new substance has been named spathulatine. Its analytical and molecular-weight data indicate that it has the empirical composition C₃₃H₆₄N₄O₅. It melts sharply at 227° and is thus distinguished from all other known lupine alkaloids. Sparteine is a liquid, lupinine^{1b} melts at 68.5–69.2°, dextro-lupanine¹¹ melts at 44°, racemic lupanine melts at 99°,² and hydroxy-lupanine^{5b} melts at 172–174° (anhydrous).

The name spathulatine which has been applied to this base is derived

¹ Willstätter and Fourneau, (a) *Ber.*, **35**, 1910 (1902); (b) *Arch. Pharm.*, **240**, 335, (1902). (c) Schmidt, *ibid.*, **242**, 409 (1904). (d) Willstätter and Marx, *Ber.*, **37**, 2351 (1904).

² Gerhard, *Arch. Pharm.*, **235**, 342 (1897).

³ (a) Davis, *ibid.*, **235**, 218 (1897). (b) Beckel, *ibid.*, **249**, 329 (1911).

⁴ Ref. 3 a, p. 199.

⁵ (a) Ref. 2, p. 355. (b) Bergh, *Arch. Pharm.*, **242**, 416 (1904). (c) Beckel, *ibid.*, **248**, 451 (1910).

⁶ Callsen, *ibid.*, **237**, 566 (1899).

⁷ Black, *Science*, Nov. 30, **1917**, p. 546.

⁸ Beath, *Wyoming Expt. Sta. Bull.* No. 125, **1920**.

⁹ Sollmann, *U. S. Dept. Agr. Bull.* No. 405, **1916**.

¹⁰ Marsh, Clawson and Marsh, "Lupines as Poisonous Plants," *U. S. Dept. of Agr. Bull.*, No. 405, **1916**. Chestnut and Wilcox, *U. S. Dept. Agr., Div. Bot. Bull.*, **26**, **1901**.

¹¹ Soldaini, *Arch. Pharm.*, **231**, 321 (1893).

from the specific name of the plant "spathulatus." It was chosen because all feasible derivatives of the generic name *Lupinus* have been applied to other lupine alkaloids.

Material.—*Lupinus spathulatus* (Rydb.) is a perennial herbaceous plant which attains a height of 8 to 10 dm. The leaflets are seven in number and are about 4 cm. long with a short abrupt tip; the bracts are lanceolate, attenuate, deciduous and longer than the buds; the lower calyx lip is lanceolate and about twice as long as the upper; the corolla is bluish. The plant is native in Colorado and Utah, where it occurs in the mountains in the "pine belt."

The plant specimens used were collected in two neighboring localities in the Wasatch mountains about sixteen miles southeast of the city of Salina, Utah, and at an elevation of approximately 2.4 km. (8000 feet) above sea level. The species was determined by Mr. W. W. Eggleston of the Bureau of Plant Industry. Collection was begun in 1917 and was continued each year. In 1920 the climatic conditions were exceptionally favorable for the growth of this plant and a large amount of the mature seeds and pods was obtained. One hundred and twenty-seven kg. (280 pounds) of this material was spread out to dry under shade; when thoroughly air-dried the residue weighed 41.45 kg. (90.3 pounds); loss, 67%. Moisture determinations showed that the seeds and pods together lost from 64.97 to 68.87% of water during the drying. This collection provided the principal material for the investigation. It was divided into two portions, seeds alone and valves, which contained such mechanically enclosed seeds as were not readily to be separated from them. The separate portions were packed in cloth bags and were mailed to the laboratory at Washington for the detailed work. The seeds and valves are very bitter. Acid extracts from both readily gave positive tests with the ordinary alkaloidal reagents. A water extract was prepared which responded to tests for proteins and sugar. The latter was identified as dextrose.

Isolation of the Alkaloid

A lot of 21.94 kg. of the air-dried valves was ground to a coarse powder, moistened with an alcoholic solution of 220 g. of tartaric acid, packed into percolators and extracted with alcohol by percolation until it yielded no soluble substances to the menstruum. The percolate was collected in clean glass bottles and, from time to time, was concentrated by distilling the alcohol. The concentrated extracts so obtained were united, treated with enough glacial acetic acid to make the liquid contain 1% of acetic acid, and the whole was precipitated with an excess of 10% aqueous neutral lead acetate. A heavy, greenish precipitate appeared. The mixture was allowed to stand overnight to permit complete precipitation and was then filtered. The precipitate was thoroughly washed with water and the washings were added to the filtrate.

The washed precipitate was extracted with hot alcohol to obtain the fats. The fatty residue obtained by removing the solvent was tested for lead with negative results. It weighed 470.3 g. and constituted, therefore, 2.14% of the valves used.

The filtrate from the lead precipitation was acid and contained alkaloid. It was concentrated to convenient bulk, freed from lead by a current of hydrogen sulfide, filtered and concentrated to a small volume. The product of this treatment was a thick red-brown and very bitter sirup. On standing in the cold nothing could be made to crystallize from it. The sirup was then made strongly alkaline with potassium hydroxide, diluted to 2 liters with distilled water, and extracted with successive portions of chloroform.

After separation, the chloroform layer was drawn off through a filter into a flask; the chloroform was removed by distillation and returned to the alkaline solution in the separatory funnel to extract another portion of the alkaloid. Although the extraction was continued throughout a period of three weeks and involved the use of more than 50 separate portions of chloroform, it was found impossible to extract all of the alkaloid from the aqueous solution. It was assumed that there might be present either phenolic alkaloids, which are not generally removed from alkaline solutions by immiscible solvents, or that the remaining alkaloid is insoluble in chloroform. Accordingly, portions of the alkaline solution were taken and both of these assumptions were tested, with the result that it was found that the condition was due simply to the ready solubility of the alkaloid in water, which is so great that the distribution ratio of the alkaloid between water and chloroform is of the order of unity.

The material that remained when the chloroform was removed from the extract was a very viscous, red-brown sirup, with an odor resembling that of coniine. It weighed 161.2 g. In order to determine whether it was a mixture of several alkaloids it was treated with different solvents in succession, petroleum ether, ethyl ether and benzene, each of which dissolved a part of the mass. The portions extracted by petroleum ether and benzene were found, upon subsequent purification, to be identical. The ether-soluble alkaloid was obtained in small quantity and has not been sufficiently purified for identification. It is probably identical with the remainder of the alkaloid, although it presents some characteristics of its own.

Purification and Analysis of Spathulatine

The alkaloid soluble in petroleum ether and in benzene was purified by repeated crystallization from benzene, from which it separated in long needles which contain one molecule of benzene of crystallization and melt sharply at 86°. When dried in a desiccator over anhydrous calcium chloride, and then thoroughly dried in an electric oven at 85°, the crystals lose all of their benzene and fall to a white amorphous powder that melts at 227°. A portion of the alkaloid was crystallized from alcohol. Large, prismatic crystals were obtained which contained no alcohol of crystallization and melted sharply at 227°.

Anal. Subs., 0.1041, 0.2049, (III) 0.2063: CO₂, 0.2625, 0.4963, (III) 0.5045. H₂O, 0.1019, 0.1987. Subs., 0.2302, 0.1863, 0.2282, 0.3975: 19.1 cc. of N (over 30% KOH) (26°, 773 mm.), 17.4 (27°, 768 mm.), 19.3 (24°, 757 mm.), 33.4 (28°, 763.3 mm.). Calc. for C₃₃H₆₄O₂N₄: C, 66.39; H, 10.82; N, 9.39. Found: C, 66.41, 66.08, (III) 66.56; H, 10.95, 10.85; N, 9.43, 9.47, 9.49, 9.33.

Mol. wt. Subs., 0.2289, 0.2184: Δt 0.100, 0.096 in 14.009 g. of CHCl₃. Calc.: mol. wt., 596.51. Found: 585, 583.

The free base is soluble in water, alcohol, benzene, chloroform, carbon tetrachloride, acetone and acetic ether and sparingly soluble in petroleum ether and ethyl ether. The aqueous solution is weakly alkaline to litmus. The alkaloid combines with acids to form salts which are very soluble in water and tend to form supersaturated solutions with solvents so that, upon evaporation, either spontaneously or at higher temperatures, the residue is a thick sirup or a hard varnish that obstinately refuses to crystallize. On this account no pure salts of the alkaloid have been obtained for analysis. The alkaloid is sensitive to strong mineral acids. Sulfuric

acid rapidly resinifies it, even in dilute solution. Several attempts to determine the molecular weight of the alkaloid by titration with 0.1 *N* and with 0.02 *N* acids using different indicators were unsuccessful, no sharp end-point occurring.

Solutions of the alkaloid are slightly levorotatory.

Solutions in chloroform, alcohol and water were examined in a 1dm. tube using light from a sodium flame.

Solvent	Chloroform	Alcohol	Water
Subs., g. per 100 cc. of soln.	5.900	6.42	6.42
Obs. rotation	-1.109° (at 27°)	-1.49° (at 28.5°)	-1.57° (at 27.5°)
$[\alpha]_D$	-1.88°	-2.32°	-2.44°

The crystals obtained from benzene were unstable and readily effloresced. Dried in a desiccator for one day, they melted at 86°. Two samples were freshly prepared, separated as completely as possible from mother liquor by suction and pressing between filter papers and analyzed. The results showed that they had not been thoroughly freed from mother liquor and it was judged impossible to do this without losing some of the crystal benzene in the process.

Subs., 0.4934, 0.8737: loss at 100°, 0.0594, 0.1032. Calc. for base + 1 mol. of benzene: 11.56. Found: 12.04, 11.81.

When crystallized from water by very slow evaporation the base crystallized with solvent. A sample so prepared consisted of rhombic prisms, some of them 0.5 cm. long. Two samples were dried, first at 100° and then at 135°, to constant weight.

Subs., 0.5135, 1.1090: loss, 0.0292, 0.0618. Calc. for base + 2 mols. of water: H₂O, 5.60. Found: 5.67, 5.70.

A sample of the free base crystallized from alcohol was subjected to the Zeisel-Perkins process for the determination of alkoxy groups. After two hours' heating there was no precipitate of silver iodide in the receivers and consequently there are no alkoxy groups in the compound. Further experiments to determine the nature of the oxygen in spathulatine are in progress.

Reaction with Chloroform

The residue which remained after the crude alkaloid mixture had been extracted with organic solvents still contained much alkaloid and, upon examination, it was found that a portion of this was combined with hydrochloric acid. Bergh^{5b} has observed that hydroxylupanine reacts with chloroform at ordinary temperatures, forming the hydrochloride of the base, and it was thought possible that spathulatine might possess the same property. Investigation has shown that in the presence of alkalis there is a slow reaction between chloroform and spathulatine, but no crystalline compound of the base and hydrogen chloride could be isolated. Using very pure chloroform and the free base and carefully observing the temperature with a Beckmann thermometer, there was no evidence obtained

of any reaction after five hours' heating at the boiling point of chloroform. Considering the moderate instability of chloroform when exposed to light, it is possible that the effects that Bergh observed with hydroxylupanine were due to chloroform contaminated with decomposition products.

The Mercuric Iodide Compound

The unsatisfactory nature of the immiscible solvent method for the extraction of spathulatine from aqueous solutions led to a search for some other process that might be less tedious and wasteful. A satisfactory procedure was developed which involves the primary precipitation of the alkaloid with Mayer's solution and the subsequent separation of the mercury and iodine. During the investigation of this process a very interesting compound of the alkaloid with mercuric iodide was discovered. It was prepared by the following method. A suitable quantity of the alkaloid,

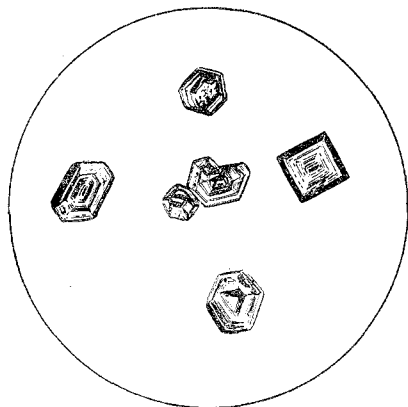


Fig. 1.—Spathulatine mercuric iodide, from a photomicrograph.

either pure or contaminated, in solution, is acidified with hydrochloric acid and treated with Mayer's solution. The voluminous, light brown precipitate is filtered off and carefully washed. The precipitate is somewhat soluble in water and, when freshly prepared, is soluble in 50% alcohol. It is intimately mixed with concd. sodium hydroxide solution or with powdered lime, and the mass is extracted with hot benzene on the water-bath, each portion of benzene being filtered hot from the residue. On cooling, the benzene deposits colorless crystals which have the appearance of dodecahedra, but are in reality derived from rhombic prisms. Their characteristic appearance under the microscope is shown in Fig. 1, a line drawing from a photomicrograph. A sample of the crystals was recrystallized from benzene and was preserved in a vacuum desiccator over anhydrous calcium chloride until it was thoroughly dry. It then melted sharply at 164°. Analyzed by the Carius method it was found to contain the alkaloid, mercury and halogen, most of which was iodine, and the remainder (which constituted a very small proportion) was chlorine.

Anal. Subs., 0.1819, 0.2305: HgS, 0.0650, 0.0820; Ag hal., 0.1230, 0.1555; AgCl equiv., 0.0794, 0.0997.

Subs., 0.6766, 0.9449: (Dumas method) moist N (over 30% KOH; corr. for aq. tens.) 17.2 cc. (28°, 764.4 mm.), 25.2 cc. (29°, 763.4 mm.).

Calc. for $C_{30}H_{34}N_4O_5 \cdot 3HgI_2$: N, 2.85; I, 38.50; Hg, 30.63. Found: N, 2.91, 3.0; I, 38.58, 38.26; Hg, 30.80, 30.66.

It is assumed that the compound either was contaminated with a small amount of a chloride, or that chlorine partly replaced the iodine in the molecule. The crystals of this substance have a characteristic appearance, especially under the microscope, and being readily prepared may serve as a basis for a convenient microchemical test for the alkaloid.¹²

The Seeds

A 25g. sample of the seeds was ground to a No. 40 powder and was extracted in a Soxhlet apparatus by several solvents in succession. Each extract was separately evaporated to constant weight in a tared dish and weighed.

Solvent	Petr. ether	C ₆ H ₆	(C ₂ H ₅) ₂ O	CHCl ₃	C ₂ H ₅ OH	Total
Extract, g.	2.3652	0.0190	0.0801	0.5083	1.5657	...
Extract, %	9.46	.076	.32	2.03	6.26	18.15

A lot of 977 g. of the air-dried seeds was ground to a coarse powder, packed into four Soxhlet apparatus and extracted with hot benzene which removed fats, waxes and phytosterols with but a trace of alkaloid. The weight of this fatty extract, when the solvent had been removed, was 90.18 g. or 9.23% of the weight of the seeds.

The marc from the benzene extraction was removed from the extraction apparatus, dried, made thoroughly alkaline with 5% sodium hydroxide solution, again dried, and extracted with hot alcohol in the Soxhlet apparatus. The solvent was distilled from the alcohol extract and the residue, which weighed 136.5 g., was dissolved in a liter of distilled water. The solution was acidified with hydrochloric acid, filtered and treated with Mayer's solution as long as a precipitate was produced. The mixture was allowed to stand overnight and was then filtered. The precipitate was washed with water which contained hydrochloric acid, allowed to drain and was then mixed with an excess of sodium carbonate by trituration in a mortar. The resulting mass was suspended in enough water to dissolve the alkaloid and the suspension was treated with hydrogen sulfide until all of the mercury was converted into sulfide. The solution was filtered and the filtrate was evaporated to dryness.

To separate the alkaloid from the admixed sodium carbonate and iodide the dry residue was extracted with alcohol, which dissolved the alkaloid and most of the sodium iodide. The alcohol was evaporated and the residue was extracted with chloroform, which dissolved the alkaloid alone. On evaporating, the alkaloid crystallized from the chloroform in long needles. These were collected and purified by recrystallization from water; yield 24.85 g. or 2.54% of the weight of the seeds. Dried in a desiccator

¹² Owing to the solubility of these crystals in the standard immersion media measurement of crystal faces and determination of optical constants were impracticable. A suitable mounting is still being sought for.

they melted at 227° and agreed in all other characteristics with the alkaloid obtained from the valves.

This procedure was much more satisfactory than the immiscible-solvent method used in isolating the alkaloid from the valves. It was carried out more quickly, was less wasteful, and yielded a crude alkaloid that was more easily purified. It should be especially useful in the isolation of alkaloids that are quite soluble in water and that are not reduced by hydrogen sulfide.

Summary

A new alkaloid has been isolated from *Lupinus spathulatus*, a plant that occurs in Utah and Colorado. The new base has been named spathulatine and has been assigned the formula $C_{33}H_{64}O_5N_4$. The properties of the free alkaloid and the preparation of its mercuric iodide compound which may serve as a microchemical test are described.

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THE CONDENSATION OF NORMAL BUTYRALDEHYDE WITH METHYLETHYL KETONE

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As *n*-butyl alcohol has become a common article of commerce, the hitherto difficultly obtainable *n*-butyraldehyde is now readily prepared in quantity. It, seemed, therefore, worth while to investigate the use of *n*-butyraldehyde as a starting material in various syntheses.

This paper describes the condensation of *n*-butyraldehyde with methylethyl ketone, and the preparation of various derivatives of the condensation products.

Weizmann¹ has shown that *n*-butyraldehyde reacts with acetone under the influence of solid sodium hydroxide to give the aldol, which loses water on distillation, yielding *n*-butylidene acetone. The aldol is not described. *n*-Butyraldehyde reacts with methylethyl ketone under the influence of solid or alcoholic potassium hydroxide in a similar manner, yielding 4-hydroxy-3-methyl-2-heptanone, $C_8H_{16}CHOH.CH(CH_3)CO.CH_3$. A small quantity of low-boiling substances is formed at the same time, consisting principally of the unsaturated ketone resulting from the dehydration of the aldol, although a small amount of α -ethyl- α -hexenal and some lower-boiling substances are also obtained. Similar lower-boiling substances were also found among the products of the condensation of *n*-butyraldehyde with acetone.¹ Practically no high-boiling, tarry products were obtained, the residue consisting of only a few cubic centimeters of material.

¹ Weizmann and Garrard, *J. Chem. Soc.*, 117, 334 (1920).