[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOMINION RUBBER CO., LTD.]

The Alkaloids of Fumariaceous Plants. XLIX. Thalictricavine, A New Alkaloid from *Corydalis tuberosa* DC.

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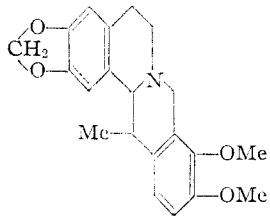
A new alkaloid, now named thalictricavine, from *Corydalis tuberosa*, is isomeric with thalictrifoline and is shown to be 2,3-methylenedioxy-9,10-dimethoxy-6-methyltetrahydroprotoberberine.

Corydalis tuberosa DC. (*C. cava* (L.) Schweigg. et Körte) is a much investigated plant. Nearly twenty alkaloids of known structure as well as several whose structures are not known, have been isolated from this plant in the last ten decades. The relevant chemical literature is so extensive that reference to it is confined to a forthcoming publication.[1] The writer was fortunate to obtain a concentrated mother liquor from which the bulbocapnine and a number of other alkaloids had been separated. The material originated with Merck of Darmstadt, Germany, but was made available through the interest and kindness of Dr. R. T. Major of Merck & Co., Inc., Rahway, N. J.

It was possible to separate many of the known alkaloids from this material but several new ones were also obtained. In as much as it was possible to determine the structure of one of these, it is now reported upon.

The procedure repeatedly used by the writer[2] was satisfactory in this separation. The mother liquors from the corydaline fraction yielded a base, now named *thalictricavine*, which was slightly less basic than the corydaline and which on analysis gave values indicating $C_{21}H_{23}O_4N$ with two methoxyls. This new alkaloid is isomeric with thalictrifoline[3] and could be a stereoisomer of it or it could have the two methoxyls and the methylenedioxy group in reversed positions. The former possibility was disposed of when it was shown that the racemized form of the alkaloid was not identical with *dl*-thalictrifoline. That the annexed formula is correct was strongly indicated when it was found possible to convert thalictricavine into corydaline by demethylenation followed by methylation, and final proof was forthcoming when permanganate oxidation of the alkaloid furnished hydrastic acid.



Experimental[4]

***d*-Thalictricavine.**—The alkaloid mother liquors were received in the form of very soluble sulfates which were dissolved in hot water and treated with a solution of ammonium chloride in excess. The sparingly soluble hydrochloride which then separated proved to be that of *d*-tetrahydropalmatine and was readily obtained in a pure condition by recrystallizing from hot water. A small amount of a less soluble fraction proved to be the hydrochloride of *dl*-tetrahydropalmatine.

The combined aqueous filtrates were then exhausted with chloroform and the chloroform removed from the extract. The residue on dissolution in hot water and cooling deposited another crop of *d*-tetrahydropalmatine hydrochloride.

The free bases were then prepared from the soluble hydrochlorides by shaking the solution with a large volume of ether in the presence of ammonia. Removal of the solvent from the ether extract and dissolution of the residue in methanol served to yield a copious crop of corydaline. The methanolic mother liquor was then neutralized with concentrated nitric acid, and the base nitrate which crystallized in the course of several days separated by filtration. This nitrate proved to consist of a portion very sparingly soluble in hot water which was shown to be that of corycavine and a more soluble one. The base, regenerated from the more soluble nitrate, was converted to acid oxalate. There was then obtained a very sparingly soluble oxalate as well as the more soluble and characteristic oxalate of corycavine. The base, regenerated from the less soluble oxalate, proved to be *d*-canadine.

The bases in the methanol filtrate from the nitrates were regenerated and shaken, while in ether solution, with 40% potassium hydroxide solution. This served to remove a mixture of phenolic bases, one of which was identified as corybulbine. The clear ether solution, now free of phenolic bases, was shaken with dilute hydrochloric acid in five successive and equal portions, the last of which was adequate to extract all of the alkaloids. The bases were separately regenerated from the extracts and allowed to crystallizate from somewhat concentrated ether solutions. The base that separated from the first two extracts proved to be substantially pure corydaline. The bases which were obtained from the last three extracts proved to be a mixture from which warm methanol readily dissolved some corydaline. The less soluble portion was easily recrystallized from chloroform–methanol and then consisted of colorless well developed prisms, which when rapidly heated melted sharply at 149°. When slowly heated, this alkaloid, now named *thalictricavine*, sintered at 148–149° and then only darkened and became semi-liquid as the temperature was raised. It showed $[\alpha]^{23}D$ +291.9° (*c* 0.555 in chloroform).

Anal. Calcd. for $C_{21}H_{23}O_4N$: C, 71.39; H, 6.52; N, 3.97; 2 OMe, 17.56. Found: C, 71.12, 71.20; H, 6.50, 6.51; N, 4.27, 4.15; OMe, 17.99, 17.42.

DL-Thalictricavine.—A small amount of the alkaloid was dissolved in chloroform–methanol, treated with iodine in excess, and heated on the steam-bath with a little sodium acetate. The solvent and excess iodine were then removed and the residue heated on a steam-bath with zinc and dilute hydrochloric acid until all of it had dissolved to a colorless solution. An excess of ammonia was added and the liberated base extracted with ether. The residue from the washed and evaporated extract crystallized rapidly from methanol in colorless stout prisms, which in an open tube melted at 204° and at 209° in an evacuated tube.

Anal. Calcd. for $C_{21}H_{23}O_4N$: N, 17.56. Found: N, 17.85.

Corydaline from *d*-Thalictricavine.—A solution of the alkaloid (0.5 g.) in 20 cc. of a solution made by diluting 21 cc. of sulfuric acid with 25 cc. of water was treated with 1.2 g. of phloroglucinol, boiled for 2 min., and then heated on a steam-bath for 6 hr.[5] The diluted, cooled and filtered solu-

(1) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. IV, Academic Press, Inc., New York, N. Y.

(2) R. H. F. Manske, *Can. J. Research*, **8**, 210 (1933).

(3) R. H. F. Manske, *ibid.*, **21B**, 111 (1943).

(4) All melting points are corrected.

(5) E. Späth and H. Holter, *Ber.*, **60**, 1891 (1927).

tion was basified with ammonia and extracted with 250 cc. of ether in three successive portions. The washed ether solution deposited a sparingly soluble base while it was being evaporated. The colorless prisms, after washing with ether and then with methanol melted sharply at 246° in an evacuated tube. In an open tube this base, which is evidently 2,3-dihydroxy-9,10-demethoxy-6-methyltetrahydroprotoberberine, melted with decomposition at 200–210°.

Anal. Calcd. for $C_{20}H_{23}O_4N$: N, 4.10. Found: N, 4.27.

The crystalline base was dissolved in hot methanol (sparingly soluble) and the rapidly cooled solution treated with an ethereal solution of diazomethane. The brisk evolution of nitrogen ceased after several hours and the non-phenolic base, which was readily isolated from the reaction mixture, crystallized from methanol in the characteristic stout prisms of *d*-corydaline. Either alone or in admixture with an authentic specimen it melted sharply at 135°.

Oxidation of Thalictricavine.—A small amount of the base was dissolved in very dilute hydrochloric acid and the solution then treated with aqueous sodium carbonate until the turbidity was just permanent. An excess of aqueous potassium permanganate was added. After 5 to 6 hr. the excess reagent was destroyed with sulfur dioxide and the acidified mixture then extracted with ether. The residue from the ether extract was dissolved in a small volume of water, the solution filtered to remove a turbidity, treated with excess ethylamine, and evaporated to dryness. The residue thus obtained was sublimed *in vacuo* and the crystalline sublimate washed with ether–hexane, and then recrystallized from dilute methanol. The colorless fine needles thus obtained melted at 168–169° either alone or in admixture with an authentic specimen (m.p. 170°) of the N-ethylimide of hydrastic acid.

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[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

The Structure of Jervine. III. Degradation to Nitrogen-free Derivatives

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The degradation of jervine by means of acetic anhydride and zinc chloride to a nitrogen-free substance is described. Evidence is presented, on the basis of which structure III is assigned to this substance. The structure of jervine is discussed in the light of this and other available evidence and found to be most satisfactorily expressed by formula II.

Jervine, the main alkaloid of *Veratrum viride*, first isolated by Wright and Luff[1] has recently been the subject of a number of important investigations by Jacobs and his collaborators,[2–5] as a result of which the steroidal structure I was proposed for this interesting alkaloid. This structure if correct would render jervine a valuable starting material in the synthesis of corticoids carrying oxygen in position 11, and it is mainly for this reason that a thorough investigation of this alkaloid has been undertaken in this Laboratory.

The most important arguments advanced by Jacobs and his collaborators in favor of structure I shall be summarized briefly. Jervine has the composition $C_{27}H_{39}O_3N$.[6] Its three oxygen atoms were demonstrated to be present as (1) an acylable secondary hydroxyl group, (2) a keto group, which is inert toward carbonyl reagents but is readily reduced to an acylable hydroxyl group by sodium and butanol (β-dihydrojervinol)[3] and (3) a cyclic ether group cleaved by acids to form an acylable hydroxyl group (isojervine).[3,7] Jervine contains two double bonds demonstrable by catalytic hydrogenation (dihydro- and tetrahydrojervine).[3] The more easily reduced double bond is in conjugation with the keto group as evidenced by the characteristic ultraviolet absorption spectrum of jervine (λ_{max}^{alc} 252 and 360 mμ, ε 14,000 and 70). The second double bond is an isolated double bond, which readily enters into conjugation with the keto group formed by Oppenauer oxidation of the secondary hydroxyl group (Δ^4-jervone).[3] In this and other reactions of the secondary hydroxyl group and of the isolated double bond, jervine closely resembles cholesterol and it is for this reason that rings A and B of jervine were formulated as shown in formula I.[4] This latter conclusion in conjunction with the finding that rubijervine, a companion alkaloid of jervine, possesses a steroidal ring system[8] led Jacobs and his collaborators to postulate the existence of such a ring system in jervine also. The unreactive keto group was then logically placed into the hindered 11-position and the conjugated double bond between carbon atoms 8 and 9, the only position available for conjugation with the keto group. The formulation of the heterocyclic rings E and F the former containing the secondary nitrogen atom[9] is based on the formation of 2-ethyl-5-methylpyridine and 2-ethyl-5-methyl-3-hydroxypyridine in the dehydrogenation with selenium,[2,5] and patterned after the proved attachment of the octahydropyrrocoline system in the tertiary alkaloids rubijervine[8] and solanidine.[10] The attachment of the oxidic oxygen atom at carbon 16 is purely speculative.

Evidence casting doubt on the correctness of structure I was presented by Wintersteiner, *et al.*,[11] who described 7-keto derivatives of jervine and dihydrojervine, the ultraviolet spectra of which, while lending support to the formulation of rings A and B militated against the location assigned by Jacobs to the α,β-unsaturated ketone group. On the basis of the studies reported in this and the subsequent paper,[12] we wish to propose formula II[13]

(1) C. R. A. Wright and A. P. Luff, *J. Chem. Soc.*, **35**, 421 (1879).

(2) W. A. Jacobs, L. C. Craig and G. I. Lavin, *J. Biol. Chem.*, **141**, 51 (1941).

(3) W. A. Jacobs and C. F. Huebner, *ibid.*, **170**, 635 (1947).

(4) W. A. Jacobs and Y. Sato, *ibid.*, **175**, 57 (1948).

(5) W. A. Jacobs and Y. Sato, *ibid.*, **181**, 55 (1949).

(6) W. A. Jacobs and L. C. Craig, *ibid.*, **148**, 51 (1943).

(7) W. A. Jacobs and L. C. Craig, *ibid.*, **155**, 565 (1944).

(8) Y. Sato and W. A. Jacobs, *ibid.*, **179**, 623 (1949).

(9) K. Saito, H. Suginome and M. Takaoka, *Bull. Chem. Soc. Japan*, **11**, 172 (1936).

(10) F. Uhle and W. A. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945).

(11) O. Wintersteiner, M. Moore, J. Fried and B. M. Iselin, *Proc. Nat. Acad. Science*, **37**, 333 (1951).

(12) O. Wintersteiner and M. Moore, THIS JOURNAL, **75**, 4938 (1953).

(13) Part of this material has already been presented in a Communication to the Editor by J. Fried, O. Wintersteiner, M. Moore, B. M. Iselin and A. Klingsberg, *ibid.*, **73**, 2970 (1951).