[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE]

The Aconite Alkaloids. XXXI. A Partial Synthesis of Atisine, Isoatisine and Dihydroatisine[1]

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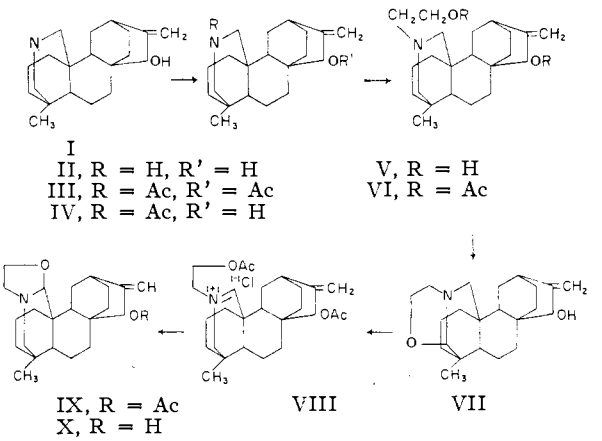
A partial synthesis of atisine (X), isoatisine (VII) and dihydroatisine (V) from the $C_{20}H_{29}NO$ unsaturated base (I) is described.

Atisine[2] and isoatisine have been assigned structures X and VII, respectively, on the basis of analogy to the reactions of the Garrya alkaloids[3] and on dehydrogenation, oxidation and infrared studies.[4] The presence of an oxazolidine ring in these structures[3,4] made it desirable to test the correctness of this assignment by reconstruction of this feature of the molecules from an appropriate degradation product. This paper describes such a partial synthesis of atisine and isoatisine from the $C_{20}H_{29}NO$ unsaturated base (I)[1] obtained earlier by mild permanganate oxidation of atisine.[5]

Reduction of I with excess sodium borohydride in aqueous methanol proceeded smoothly to give the secondary base II, m.p. 151–153°, in 85% yield; ν^{KBr} (OH) 3384; (NH) 3242; (>C=CH_2) 3081, 1657, 894 cm.$^{-1}$. This base was characterized by an O,N-diacetate III, m.p. 167–170° (infrared spectrum showed the absence of any hydroxyl or –NH bands; ν^{Nujol} (OAc) 1735, 1238 cm.$^{-1}$; (NAc) 1643 s. cm.$^{-1}$), and an N-acetate IV, m.p. 222–225°; ν^{Nujol}(OH) 3421 cm.$^{-1}$; (NAc) 1639 cm.$^{-1}$. Treatment of II with ethylene chlorohydrin and sodium and sodium carbonate in absolute methanol gave dihydroatisine (V),[6] identical with an authentic sample[7] in melting point, mixture melting point and infrared spectrum (KBr disk). Furthermore the diacetate VI of V, prepared in acetic anhydride and dry pyridine, was identical in all respects (m.p. and infrared spectrum in Nujol) with authentic dihydroatisine diacetate.

Cyclization of the hydroxyethyl group of dihydroatisine was accomplished by oxidation of V with exactly one equivalent of osmium tetroxide in ether.[8] Decomposition of the resulting osmium ester with boiling alkaline mannitol solution gave a mixture which afforded isoatisine (VII) when chromatographed in benzene over alumina. The isoatisine was identified by a mixed melting point and by its infrared spectrum in KBr. Since it already has been shown that isoatisine may be isomerized to atisine (X) *via* the diacetate chloride VIII[9–11] and monoacetate IX[9,10] the sequence of reactions described constitutes a partial synthesis of atisine.



Experimental[12]

The $C_{20}H_{31}NO$ Base (II).—A solution of 156 mg. of the $C_{20}H_{29}NO$ base (I) in 5 ml. of 80% methanol was treated with 300 mg. of sodium borohydride at room temperature and let stand for one hour. The mixture was evaporated to dryness *in vacuo*, taken up in water and extracted with chloroform. The extract yielded a resin which crystallized from acetone to give 131 mg. of prisms melting at 148–153°. Recrystallization furnished 100 mg. of pointed prisms melting at 151–153°; infrared spectrum ν^{KBr}(OH) 3384; (NH) 3242; (>C=CH_2) 3081, 1657, 894 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{31}NO$: C, 79.67; H, 10.37. Found: C, 79.90; H, 10.54.

O,N-Diacetate III.—A solution of 63 mg. of the $C_{26}H_{31}NO$ base (II) in a mixture of 4 ml. of acetic anhydride–dry pyridine (1:1) was left at room temperature for three days. The mixture was evaporated to dryness with benzene several times, taken up in water and neutralized with sodium bicarbonate. Extraction with chloroform yielded a resin which crystallized on long standing in petroleum ether.

(1) Presented at the Gordon Research Conference on Steroids and Related Natural Products, New Hampton, N. H., August 24, 1955. For the preceding article in this series, see S. W. Pelletier and W. A. Jacobs, THIS JOURNAL, **78**, 4139 (1956).

(2) E. S. Stern, The Aconitum and Delphinium Alkaloids in "The Alkaloids, Chemistry and Physiology," Vol. IV, edited by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York, N. Y., 1954, p. 280.

(3) K. Wiesner, *et al.*, *Ber.*, **86**, 800 (1953); *Chemistry and Industry*, 132 (1954); *Experientia*, **11**, 255 (1955). The elucidation of the structures of the Garrya alkaloids provided the clue to the correct skeleton for the Atisine alkaloids which was first suggested in the second of these papers.

(4) For leading references see reference 1.

(5) The pattern of synthesis up to isoatisine parallels that described by Wiesner, *et al.* [*Chemistry and Industry*, 323 (1953); *Ber.*, **86**, 800 (1953)] for the partial synthesis of garryine from a $C_{20}H_{29}NO$ base obtained from the selenium dehydrogenation of veatchine.

(6) A referee kindly informs us that a partial synthesis of dihydroatisine by this method is described in a thesis summary by J. A. Edwards (Univ. of New Brunswick, October, 1955). We have not seen this summary.

(7) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **147**, 567 (1943).

(8) K. Wiesner, *et al.* [*Ber.*, **86**, 800 (1953)] used this method of cyclization in the analogous case of the partial synthesis of dihydroveatchine.

(9) O. E. Edwards and T. Singh, *Can. J. Chem.*, **33**, 448 (1955).

(10) Edwards and Singh have assigned a triacetate formulation to these intermediates but we have shown [*Chemistry and Industry*, 1385 (1955)] that their triacetate hydrochloride is in fact identical with our diacetate chloride VIII and their triacetate with our atisine monoacetate (IX). In a communication[11] which appeared while the above paper was in press, Wiesner first proposed a diacetate structure for Edwards "triacetate."

(11) K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955).

(12) Melting points are corrected. They were taken on a hot-stage under a microscope equipped with a polarizer. Samples were placed on the stage about 15° below the melting point and the temperature raised rapidly to within 5° of the melting point. The temperature was then raised 2° per minute.

Two recrystallizations from ether yielded 32 mg. of crystals melting at 167–170°. The infrared spectrum showed the absence of any hydroxyl bands; ν^{Nujol} (OAc) 1735, 1238 cm.$^{-1}$; (NAc) 1643 s. cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{35}NO_3$: C, 74.76; H, 9.15; OAc, 11.16.[13] Found: C, 75.10, 74.76; H, 9.10, 9.24; Ac, 12.05.[13]

N-Acetate IV.—A solution of the O,N-diacetate III in 60% ethanol containing 0.5 g. of sodium hydroxide was left at 50° for one hour. After evaporation to dryness the residue was taken up in water and extracted with chloroform. The chloroform extract yielded a resin which crystallized from ether. Recrystallization from acetone gave material melting at 222–225°. The infrared spectrum in Nujol showed the presence of a hydroxyl band at 3421 cm.$^{-1}$ and an N-acetate band at 1639 s. cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.88; H, 9.36.

Condensation of the $C_{20}H_{31}NO$ Base (II) with Ethylene Chlorohydrin.—A solution of 70 mg. of II in 3 ml. of dry ethylene chlorohydrin and 10 ml. of dry methanol containing 300 mg. of anhydrous sodium carbonate was boiled under reflux for 18 hours. After evaporation to dryness *in vacuo* the residue was taken up in water and extracted repeatedly with chloroform. The chloroform extract yielded a resin which was dissolved in methanol and treated with Norite. When concentrated to 3 ml., diluted to incipient turbidity and seeded, the solution yielded 53 mg. of feathery needles of dihydroatisine, m.p. 155–159°. Recrystallization from aqueous methanol gave 44 mg. of pure dihydroatisine, m.p. 156–159°, undepressed with an authentic sample. The infrared spectrum in Nujol was identical with that of authentic dihydroatisine.

Dihydroatisine Diacetate (VI). A.—The above dihydroatisine (35 mg.) in 3 ml. of acetic anhydride was boiled under reflux for 13 minutes. After evaporation to dryness *in vacuo*, the residue was taken up in water, treated with sodium bicarbonate and extracted with chloroform. The extract yielded a residue which crystallized from ether as heavy prisms. Recrystallization gave material melting at 122–123°, undepressed with a sample of the authentic diacetate described below. The infrared spectra (Nujol) of the two samples were also identical.

B.—Dihydroatisine prepared by the sodium borohydride reduction of atisine was acetylated in acetic anhydride as described above. The diacetate crystallized from ether as heavy prisms, m.p. 123.5–124°, $[\alpha]^{27}D$ −84° (*c* 1.5 in chf.). The infrared spectrum showed the absence of hydroxyl bands; ν^{Nujol} (OAc) 1739 cm.$^{-1}$; (>C=CH$_2$) 1660, 907 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{39}NO_4$: C, 72.69; H, 9.15; OAc, 19.99. Found: C, 72.76; H, 9.27; OAc, 20.30.

Conversion of Dihydroatisine (V) to Isoatisine (VII).—To a solution of 665 mg. of dihydroatisine in 100 ml. of absolute ether was added 486 mg. of osmium tetroxide.[3] After standing for three days at 0° the black mixture was filtered and the filtrate concentrated to dryness. The residue (290 mg.) crystallized from ether as unchanged dihydroatisine, m.p. 154–157°. The precipitate of osmium ester was decomposed by boiling for 90 minutes in 100 ml. of 50% ethanol containing 3 g. of potassium hydroxide and 1.5 g. of mannitol. After evaporation to dryness *in vacuo* the residue was taken up in water and extracted with chloroform. The extract yielded 340 mg. of a brown resin which was chromatographed in benzene over 7 g. of alumina. The material obtained from the first eight 50-ml. fractions was combined (172 mg.) in benzene, filtered from insoluble material, and rechromatographed over 3 g. of alumina. The material eluted with the first 50 ml. of benzene (140 mg.) was crystallized twice from dilute acetone to give 98 mg. of prisms. Two more recrystallizations from acetone gave pure isoatisine, m.p. 145–149°. The infrared spectrum in KBr was identical with that of an authentic sample of isoatisine.

Infrared spectra were determined in the appropriate phase without compensation on a Perkin-Elmer model 21 double beam spectrometer, with sodium chloride optics, set at resolution 927, response 2, gain 6, suppression 2 and a scanning speed of 0.2 μ per minute.

Acknowledgment.—Analytical data have been obtained by Mr. D. Rigakos of this Laboratory. The technical assistance of Miss Vera Bohan is also gratefully acknowledged.

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(13) The sample was rather insoluble in the *p*-toluenesulfonic acid solution. Under the conditions of the hydrolysis only the O-acetate was cleaved.

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Alkaloids of the Amaryllidaceae. VIII. The Structures of Narcissamine, Pseudolycorine and Methylpseudolycorine[1]

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The bulbs of the King Alfred daffodil (*Narcissus pseudonarcissus* L.) have been found to contain a new alkaloid named methylpseudolycorine, as well as the known alkaloids galanthamine, galanthine, lycorenine, homolycorine, haemanthamine and narcissamine. Narcissamine has been shown to be N-demethylgalanthamine. Structures are proposed for pseudolycorine and methylpseudolycorine.

In spite of the availability of horticultural varieties of daffodils, the first comprehensive report on the alkaloids in the common daffodil (*Narcissus pseudonarcissus* L.) was published this year by Boit and Ehmke.[2] While our results are essentially in agreement with their findings, we wish to record the occurrence of a new alkaloid in the King Alfred daffodil not mentioned by these authors and assign a structural formula to it. Incidental to this research, it was possible to assign a structure to the known alkaloid pseudolycorine.

The preparation of a crude alkaloid fraction from the bulbs followed the method used in our earlier work. Isolation of the pure alkaloids was accomplished by chromatography on alumina. Lycorenine[3] and haemanthamine[4] had been isolated previously in this Laboratory, and the specimens obtained from *N. pseudonarcissus* were identified by melting points, mixed melting points and infrared spectra. Galanthamine was identified by its melting point, rotation, analysis and the preparation of two derivatives that agreed well

(1) Paper VII, Carol K. Briggs, Patricia F. Highet, R. J. Highet and W. C. Wildman, THIS JOURNAL, **78**, 2899 (1956).

(2) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 163 (1956).

(3) R. J. Highet and W. C. Wildman, THIS JOURNAL, **77**, 4399 (1955).

(4) W. C. Wildman and Carol J. Kaufman, *ibid.*, 1248 (1955).