THE ACONITE ALKALOIDS

IX. THE ISOLATION OF TWO NEW ALKALOIDS FROM ACONITUM HETEROPHYLLUM, HETERATISINE AND HETISINE

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In the course of the isolation of atisine from the roots of Aconitum heterophyllum of commercial origin, as presented in Paper VIII (1), it was noted that further concentration of the final mother liquors from atisine hydrochloride yielded a thick solution which on longer standing gave an additional crystalline fraction. It was then found that this fraction (10 gm. from 24 kilos of root) consisted essentially of a mixture of the hydrochlorides of two additional alkaloids. As far as it has been possible to ascertain, it appears that these alkaloids have not been previously described.1 One of these formed the major portion of the above mixture and most of it was readily separated from its companion alkaloid by virtue of its sparing solubility in benzene. It crystallized very readily from alcohol as stout prisms which melted at 262–267° with decomposition and was optically active, \([\alpha]_D = +40^\circ\) in methanol. The trivial name heteratisine is suggested for this alkaloid.

The analytical data all conformed to the formulation \(C_{22}H_{33}O_6N\). The alkaloid contains one methoxyl group and an N-methyl group. No unsaturated linkage could be detected by hydrogenation. The presence of a lactone group was shown by its behavior towards alkali. On reacidification relactonization occurred. Aside from saponification of the lactone group the alkaloid did not appear to be affected by alkali. The presence of two hydroxyl groups was indicated by the Tschugaeff-Zerewitinoff determination. The hydrochloride of heteratisine was also prepared.

From the above data heteratisine, like atisine, appears to be pentacyclic and this fact along with the apparent occurrence of these alkaloids in the same plant makes it probable that they are derivatives of a common pentacyclic ring system. The formulation of heteratisine and its possession of a lactone group recall in some respects observations which have been recorded with alkaloids obtained from Stemona species; viz., the

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1 Lawson and Topps (2) were of the opinion that, "Atisine appears to be the only base [alkaloid] in A. heterophyllum." The high yield of atisine which we have obtained is suggestive of the good quality of the commercial root with which we have worked and there appears to be no reason to believe that the new alkaloids owe their presence to a contaminating plant source. However, it is desirable to confirm our observations with botanically identified Aconitum heterophyllum.
stemonine C_{22}H_{33}O_{4}N of Lobstein and Grumbach (3), the tuberostemonine C_{22}H_{33}O_{4}N of Kondo, Suzuki, and Satomi (4), and the unnamed alkaloid C_{22}H_{33}O_{2}N obtained from Stemona sessilifolia by Schild (5). In the last two cases the alkaloids were found to contain a lactone group and could be reduced, however, to dihydro derivatives, C_{22}H_{33}O_{4}N.

The second alkaloid, which was obtained in very small amount and which can be called hetisine, was separated from residual heteratisine most satisfactorily by chromatographic fractionation. It was more slowly eluted from the column than heteratisine and was isolated first as the hydrochloride. The base itself which crystallized readily from dilute alcohol melted at 253–256° and was also optically active, [α]_D = +13.7° in alcohol. The analytical data from both the alkaloid and its hydrochloride suggested a formulation of C_{20}H_{27}O_{2}N. It contained no methoxyl group and the N-methyl determination appeared also to exclude the presence of an N-methyl group. The Tschugaeff-Zerewitinoff determination indicated the presence of 3 active H atoms. Whether all of these were due to three hydroxyl groups has not been directly determined. The alkaloid appeared to be unaffected by heating with alkali under conditions which should have permitted the detection of ester linkages. The presence of at least one double bond in hetisine was shown by hydrogenation of the hydrochloride to the hydrochloride of dihydrohetisine.

Our data with hetisine present a close analogy with those given recently for the new alkaloid kobusine, C_{26}H_{27}O_{2}N, described by Suginome and Shimanouti (6). The latter was shown to contain two hydroxyl groups, a tertiary N atom, and two unsaturated linkages. In the last respect a difference was shown, since hetisine appeared to yield only dihydrohetisine on hydrogenation. This is a point among others which will be studied further when opportunity is presented.

**EXPERIMENTAL**

*Heteratisine*—The mother liquors from which the final crops of atisine hydrochloride had been obtained as described in the previous paper (1) were concentrated further to a syrup. When allowed to stand for several weeks an additional crop of crystals gradually formed. After collection with cold 95 per cent alcohol roughly 10 gm. were obtained from 24 kilos of atis root. This proved to be a mixture of alkaloid salts. 7.9 gm. of this mixture were decomposed in aqueous solution with excess alkali and the precipitated alkaloid was extracted with chloroform. The extract on concentration yielded a residue which when dissolved in benzene readily

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2 The N(CH_3) determinations gave results, viz. 1.01 and 1.28, which were far too low for the calculated 4.1. While such results cannot be ignored, they may have been due to a C(CH_3) rather than an N(CH_3) group.
crystallized. After collection with benzene 3.2 gm. of the new alkaloid were obtained.

After recrystallization from 95 per cent alcohol it formed short, stout, often rhombic or trapezoidal prisms, which melted gradually at 262–267° to a colorless mass which slowly effervesced. The alkaloid is rather sparingly soluble in the usual organic solvents.

\[ \alpha_D^{2\ell} = +40^\circ \quad (c = 1.07 \text{ in methyl alcohol}) \]

C_{24}H_{33}O_4N. Calculated. C 67.47, H 8.50, N 3.58, OCH_3 7.93, N(CH_3) 3.84

Found. (a) " 67.57, " 8.40, OCH_3 8.14, N(CH_3) 3.08
" (b) " 67.30, " 8.51, N 3.56
" (c) " 67.58, " 8.57

The molecular weight was determined in camphor by the Rast method. Molecular weight calculated, 391.27; found, 394.

The Tschugaeff-Zerewitinoff determination showed the presence of 2 active H atoms. Calculated, 2H 0.515; found at 25°, 0.521; at 95°, 0.532.

0.1 gm. of the alkaloid was boiled in a 10 per cent methyl alcoholic solution of NaOH for 1 hour. The colorless solution remained clear on dilution and yielded nothing on extraction with chloroform. However, when the solution was acidified with an excess of H_2SO_4 for relactonization and then again made alkaline, a turbidity followed by crystallization occurred. The crystalline base was extracted with chloroform. The extract gave a residue which crystallized from alcohol in the form characteristic of the alkaloid used. It is apparent that relactonization of a saponified lactone group occurred. The product melted gradually from 261–266° with slow effervescence.

\[ \alpha_D^{2\ell} = +40^\circ \quad (c = 1.00 \text{ in methyl alcohol}) \]

For analysis it was dried at 110° and 2 mm.

C_{22}H_{34}O_5NCl. Calculated, C 61.72, H 8.01; found, C 61.38, H 7.91

The benzene mother liquor from which the above alkaloid had crystallized was brought to a volume of 50 cc. and chromatographed through 150 gm. of Al_2O_3 (Merek and Company, Inc.). An attempt was first made to elute with benzene but even after 550 cc., collected in 50 cc. fractions, had passed through, no appreciable material was eluted from the column. On changing to 1 per cent methanol in benzene again no appreciable effect was noted. 4 per cent methanol was then employed. This eluent soon removed a band from the column which consisted essentially of more of the
above alkaloid. 0.5 gm. of the latter crystallized readily from benzene in characteristic form. It gradually melted at 262–265° with slow effervescence after preliminary softening. Found, C 67.80, H 8.39.

_Hetisine_—On continued elution of the column with 4 per cent methanol in benzene no further sharp band was obtained but a very gradually diminishing amount of material continued to be eluted. Following the above sharp band succeeding volumes of 50 cc. of eluent at first yielded about 70 mg. of solid residue and after about twenty additional fractions had been collected this dropped to about 30 mg. When finally 10 per cent methanol was used, a sharp band was again eluted which was found to have practically exhausted the column.

Since the alkaloid in these fractions did not appear to crystallize directly, a number of succeeding fractions were combined for conversion into the hydrochlorides which were found to crystallize. Thus Fractions 35 to 39 were combined. The residue obtained on concentration was dissolved in a minimum of 95 per cent alcohol and converted into the _HCl_ salt. The latter, 0.1 gm., formed small flat needles or prisms which decomposed at 300° after preliminary sintering.

\[ \text{C}_{30}\text{H}_{15}\text{O}_{2}\text{NCl. Calculated. C 65.63, H 7.72, N 3.83, Cl 9.70} \]
\[ \text{Found. " 65.56, " 7.37, " 3.91} \]

The combined Fractions 42 to 47 yielded 0.14 gm. of hydrochloride which melted with decomposition at 306–308° after preliminary softening. Found, C 65.55, H 7.46.

Finally Fractions 51 to 56 which consisted of the sharper band eluted with 10 per cent methanol in benzene gave 0.3 gm. of a hydrochloride which melted with decomposition at 307–308°. Found, C 65.37, H 7.63, N 3.85, Cl 9.37.

The second and third of these hydrochlorides were combined for isolation of the free base. On treatment of the aqueous solution with dilute NaOH a pasty mass precipitated. When extraction with benzene was attempted, crystallization rapidly occurred and the material proved to be too insoluble in benzene. Even a relatively large volume of chloroform was required to extract the alkaloid. The concentrated chloroform extract was dissolved in a small volume of 95 per cent alcohol. On careful dilution the alkaloid crystallized readily as broad flat needles or platelets which sintered above 245° and gradually melted at 253–256°.

\[ [\alpha]_D^{20} = +13.7^\circ \ (c = 1.02 \text{ in 95 per cent alcohol}) \]
\[ \text{C}_{30}\text{H}_{27}\text{O}_{2}\text{N. Calculated. C 72.90, H 8.27, N 4.26} \]
\[ \text{Found. " 72.80, " 8.04, " 4.50; C 72.86, H 8.26} \]

The sparing solubility of the alkaloid in camphor made unreliable the attempts at a molecular weight determination. The active hydrogen de-
termination was as follows: 13.980 mg. of substance gave 3.05 cc. of CH₄ (25°, 734.5 mm.); at 95° there was no change. Found, 0.87; calculated for 3H, 0.918.

As a control a portion of the crystalline alkaloid was reconverted into the hydrochloride. This now melted with decomposition at 325° (uncorrected). Found, C 65.80, H 7.72.

The alkaloid did not appear to be affected by alkali. A solution of 0.15 gm. of the hydrochloride in 4 cc. of 10 per cent methyl alcoholic NaOH was refluxed for 1 hour. The colorless mixture after dilution was extracted with chloroform. The residue obtained after concentration of the extract was reconverted into the hydrochloride. This melted with decomposition at 315° (uncorrected). Found, C 65.52, H 7.72.

Dihydrohetisine—0.1 gm. of the hydrochloride of the above alkaloid was hydrogenated in methyl alcoholic solution with 50 mg. of platinum oxide catalyst under 3 atmospheres pressure. Absorption was prompt and practically completed within 10 to 15 minutes. After several hours the absorption of H₂ was about 8 cc. in excess of that required by the catalyst, calculated for 1 mole, about 6 cc. The product crystallized readily from alcohol-ether as needles which after recrystallization decomposed at 333° (uncorrected) after preliminary softening and darkening.

C₂₅H₂₉O₂NCl. Calculated, C 65.27, H 8.22; found, C 65.30, H 8.16

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