CLVIII.—*The Constitution of Sinactine (*1*-Tetrahydro-epiberberine).*

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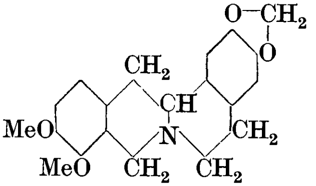
SINACTINE, the natural occurrence of which was prophesied by W. H. Perkin and his co-workers (Perkin, J., 1918, **113**, 494; Haworth, Koepfli, and Perkin, J., 1927, 2261), is present in *Sinomenium acutum*, Reht and Wills, in minute quantities and has been isolated from the root as a sub-alkaloid of sinomenine by Goto and Sudzuki (*Bull. Chem. Soc. Japan*, 1929, **4**, 220). These authors assigned to it the formula $C_{19}H_{21}O_4N$ and suggested that it might contain the tetrahydropapaverine skeleton. We have now found that its formula is $C_{20}H_{21}O_4N$ and that it contains the tetrahydroberberine skeleton.

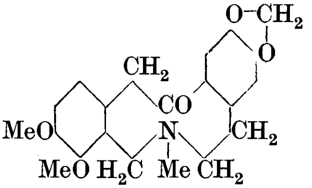
Sinactine contains two methoxy-groups and one methylenedioxy-group. Its absorption spectra resemble closely those of tetrahydroberberine and tetrahydropapaverine (*loc. cit.*), an *M*/1000-alcoholic solution producing an absorption band at a frequency of about 3500 : this similarity suggests a very close structural relation between these compounds (compare Dobbie and Lauder, J., 1903, **83**, 614; Kitasato, *Acta Phytochim.*, 1927, **3**, 229).

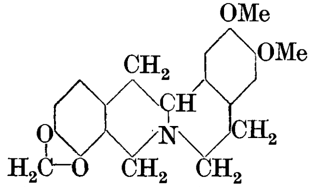
By the action of mild oxidising agents, such as iodine in alcoholic solution, on sinactine a base is produced which forms an intensely orange chloride, $C_{20}H_{18}O_4NCl$, corresponding to the berberinium salt. From this base, by reduction, *r*-sinactine is obtained. This melts at 168° and has properties very similar to those of tetrahydro*epi*berberine (III), m. p. 169—170° (Perkin, J., 1918, **113**, 512; Haworth and Perkin, J., 1926, 1777) : direct comparison of *r*-sinactine with a specimen of synthetic tetrahydro*epi*berberine, kindly sent to us by Dr. R. D. Haworth, and the melting point of a mixture of the two substances definitely established their identity.

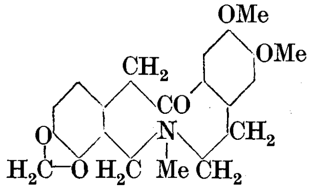
From the foregoing, it appears that sinactine is *l*-tetrahydro*epi*berberine (III), that is, the positions of the methylenedioxy-group and the two methoxy-groups in sinactine are the reverse of their positions in tetrahydroberberine (I).

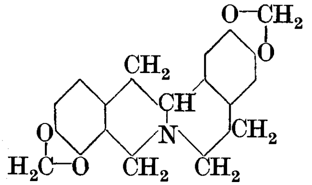
The relationship of the ten-membered ring alkaloids is still more clearly brought out when their formulæ are compared :

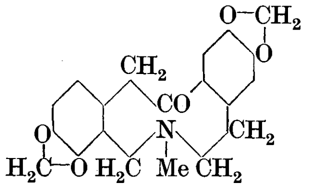

(I) Tetrahydroberberine (*r*-canadine).


(II) *β*-Homochelidonine (*a*-*allo*cryptopine).


(III) Tetrahydro*epi*berberine (*r*-sinactine).


(IV) Cryptopine.


(V) Tetrahydrocoptisine.


(VI) Protopine.

EXPERIMENTAL.

The roots of *Sinomenium acutum* are digested three times with 0·5% hydrochloric acid at the ordinary temperature and the combined extracts are made alkaline with sodium carbonate and shaken thrice with chloroform. The chloroform solution is treated with dilute hydrochloric acid to remove alkaloids (sinomenine, etc.) other than sinactine. Sinactine hydrochloride accumulates in chloroform when this is repeatedly used in the extraction of the alkaloids without evaporation; it is so sparingly soluble in water (0·74%) that it can easily be purified from sinomenine.

Sinactine, m. p. 175°, is obtained in needles from a solution of its hydrochloride by means of ammonia or in colourless slender prisms by crystallisation from alcohol. It is sparingly soluble in cold methyl or ethyl alcohol, almost insoluble in water, and readily soluble in chloroform. The solution of a crystal in a drop of acetic acid gives at first no coloration on the addition of sulphuric acid, but gradually a violet tint develops [Found by microanalysis: C, 71·0, 70·5, 71·05; H, 6·4, 6·3, 6·3; N, 4·4; OMe, 18·9. $C_{18}H_{15}O_2N(OMe)_2$ requires C, 70·8; H, 6·2; N, 4·2; OMe, 18·3%]. The alkaloid has $[\alpha]_D$ − 312° in chloroform ($c = 1$; $l = 1$). It contains a methylenedioxy-group, as it gives a copious precipitate on treatment with phloroglucinol–sulphuric acid; it has no phenolic hydroxyl group, since it does not react with ferric chloride, potassium ferricyanide, or a diazo-solution; and it has no methylimino-group, since after being heated for 2 hours at about 300° with hydriodic acid and ammonium iodide it gives no precipitate with silver nitrate.

The hydrochloride separates from water in colourless needles, m. p. about 272° (decomp.). The chloroplatinate forms crystals which begin to darken at 240° and melt at 245—247°.

r-*Sinactine.*—Sinactine (0·5 g.) is dissolved in boiling alcohol, and a 2% alcoholic solution of iodine added in portions. The colour of the iodine disappears rapidly and an orange crystalline precipitate separates (compare Perkin, J., 1918, **113**, 514). After ½ hour's boiling, the precipitate is collected, treated with sulphurous acid to remove a trace of iodine, and recrystallised from boiling water; orange-yellow needles are obtained which darken at 275° and decompose at about 300°. This iodide is suspended in water and digested with freshly precipitated silver chloride for an hour. After removal of silver compounds, the filtrate and washings are concentrated considerably and treated with hydrochloric acid. The dehydrosinactine chloride that separates after a few hours is recrystallised from hot water by addition of hydrochloric acid:

the orange needles obtained have all the properties of *epi*berberinium chloride described by Perkin (*loc. cit.*, p. 516).

Dehydrosinactine chloride (1 g.) is reduced for 5 hours with glacial acetic acid (10 c.c.), 15% sulphuric acid (100 c.c.), and zinc dust. When sodium chloride is added to the filtered solution, a pale yellow precipitate separates : this is collected, washed with dilute sodium chloride solution, dissolved in boiling alcohol, and decomposed by very dilute aqueous ammonia. The base obtained is optically inactive and crystallises from much alcohol in colourless needles, m. p. 168° (Found : C, 71·0; H, 6·2. Calc. : C, 70·8; H, 6·2%). Mixed with synthetic tetrahydro*epi*berberine (m. p. 166—167°), it melts at 166°. Moreover, a solution of the base in glacial acetic acid, on addition of concentrated sulphuric acid, gives a colourless solution which gradually turns deep violet : tetrahydro*epi*berberine shows the same reaction. The hydrochloride of *r*-sinactine separates from much water in fine needles, which decompose at about 286°. The methosulphate, prepared in the same way as tetrahydro*epi*berberine methosulphate (Perkin, *loc. cit.*), crystallises from methyl alcohol in large colourless prisms, m. p. 257° (decomp.). The iodide melts at 275°.

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