CCCLVII.—*The Oxidation of Narcotine by Hydrogen Peroxide.*

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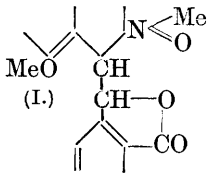
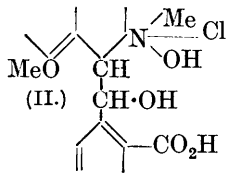
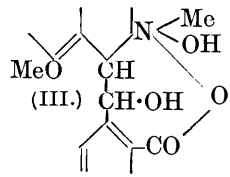
The formation of amine oxides by the action of hydrogen peroxide on alkaloids containing a nitrogen atom linked to three different carbon atoms is now well established. Pictet (*Ber.*, 1905, **38**, 2786) states that this nitrogen-linking is essential to the production of such substances (compare, however, Meisenheimer, *Ber.*, 1925, **58**, 2334). Amine oxides have been prepared from strychnine, brucine, quinine, and morphine (Pictet and Mathieson, *Ber.*, 1905, **38**, 2782; Freund and Speyer, *Ber.*, 1910, **43**, 3310; Speyer and Becker, *Ber.*, 1922, **55**, 1321). Among these, differences in the reactivity of the amine-oxidic oxygen atoms are found, as shown by their action on aqueous potassium iodide.

The oxidation of *l*-narcotine with hydrogen peroxide involved

considerable difficulty and only when the conditions described below were rigidly followed was a crystalline product, $C_{22}H_{23}O_8N$, m. p. 229°, obtained. This substance, which we represent as *narcotine oxide* (I), is feebly basic and optically active, being dextrorotatory. From its insolubility in aqueous sodium carbonate it appears that the lactonic structure, which is present in narcotine, is unaffected, as otherwise a carboxyl group would undoubtedly be produced. Whilst oxidation of narcotine by other means has resulted in the fission of the molecule between the *iso*quinoline and benzenoid nuclei, with hydrogen peroxide the complexity of the molecule is preserved. Oxidation of the amine oxide with nitric acid yielded hemipinic acid.







With concentrated hydrochloric acid, narcotine oxide yielded a crystalline *hydrochloride* (II), $C_{22}H_{25}O_9N$,HCl, m. p. 191°. The formation of this substance must be accompanied by some change such as the rupture of the lactone ring, as the hydrochloride contains a carboxyl group. It is readily hydrolysed to an optically inactive *acid*, $C_{22}H_{25}O_9N$, m. p. 212°, and reconversion into the hydrochloride is easily effected. The stability of this substance as a hydroxy-acid appears remarkable, but a parallel is found in the case of the hydroxy-acid from gnoscopine. Rabe and McMillan (*Annalen*, 1910, **377**, 242) have shown this substance to be much more stable than the corresponding compound from narcotine. The stability of the former is probably due to its greater insolubility. We suggest that the amine hydroxy-acid may be a betaine (III).

EXPERIMENTAL.

Oxidation of Narcotine by Hydrogen Peroxide.—To 20 g. of *l*-narcotine (1 mol.), dissolved in 50 c.c. of glacial acetic acid, were added in the cold, at the rate of 1 c.c. per day, 12 c.c. of 30% aqueous hydrogen peroxide (2 mols.). The yellow liquid was almost neutralised with sodium carbonate, sufficient acid being left to retain any unchanged narcotine in solution; and the sticky mass, which separated, was extracted with chloroform. From this extract, after shaking with sodium carbonate followed by water to remove acidity, a viscous material was obtained which, when stirred with 150 c.c. of dry acetone and cooled in ice, left a yellow solid (5 g.).

This substance, presumably *narcotine oxide*, separated from hot acetone in small, white needles, m. p. 229°, $[\alpha]_D$ + 139° for a 3% solution in chloroform (Found: C, 61·2; H, 5·2; N, 3·1. $C_{22}H_{23}O_8N$ requires C, 61·1; H, 5·4; N, 3·3%).

This compound does not liberate iodine from aqueous potassium iodide and is unaffected by the usual reducing agents (sulphur dioxide in chloroform solution or alkaline sodium sulphite). It is only sparingly soluble in the ordinary organic solvents, readily soluble in concentrated acids, and is unaffected by alkali. It has no marked physiological properties, which is in agreement with the recent results obtained by Polonovski (*Compt. rend.*, 1925, **181**, 887) in connexion with other alkaloidal *N*-oxides.

Oxidation of Narcotine Oxide with Nitric Acid.—The oxide (3 g.) was treated with a solution of 8 c.c. of concentrated nitric acid in 30 c.c. of water at 50°. Oxidation was slow on account of the sparing solubility, and after 14 days the unchanged material was filtered off. Hemipinic acid was isolated from the nearly neutralised solution, and was identified by its equivalent (found, 112; calc., 113), m. p., and mixed m. p. with an authentic specimen (177°).

Action of Hydrochloric Acid on Narcotine Oxide.—The oxide, dissolved in chloroform, was unaffected by hydrogen chloride; but from a solution of 5 g. of the oxide in 100 c.c. of concentrated hydrochloric acid a solid began to separate after 24 hours, and the amount increased on addition of water. This substance readily crystallised (m. p. 191°) from absolute alcohol and was soluble in aqueous sodium carbonate (Found: C, 55·0; H, 5·5; Cl, 7·1. $C_{22}H_{25}O_9N$,HCl requires C, 54·7; H, 5·4; Cl, 7·3%). It is regarded as the *hydrochloride* of the hydroxy-acid produced from narcotine oxide. It is stable in the presence of hydrochloric acid, but repeated crystallisation from aqueous alcohol or exposure to air gradually converts it into the *hydroxy-acid* itself, m. p. 212°, which is insoluble in all ordinary organic solvents. This change is accelerated by warming with water (Found: C, 58·8; H, 5·5; N, 3·3. $C_{22}H_{25}O_9N$ requires C, 59·1; H, 5·6; N, 3·1%).

Excess of concentrated hydrochloric acid was added to a solution of this acid in aqueous sodium hydroxide. A crystalline solid rapidly separated, and was identified as the hydrochloride, m. p. 191°.

The addition of lead acetate to a solution of the ammonium salt in water precipitated a yellow *lead* salt [Found: Pb, 18·2. $(C_{22}H_{24}O_9N)_2Pb$ requires Pb, 18·8%].

Dilute sulphuric acid precipitated from a solution of the sodium salt a viscous oil, which dissolved on being gently warmed. From

this solution there separated a *sulphate* in small, white needles, m. p. 148° [Found : SO_4, 9·1. $(C_{22}H_{25}O_9N)_2,H_2SO_4$ requires SO_4, 9·7%].

The authors desire to express their indebtedness to the Royal Society for a grant which enabled them to carry out this work.

UNIVERSITY OF GLASGOW. [*Received, July 14th,* 1926.]