CXII.—*Yohimbine* (*Quebrachine*).

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THE identity of the alkaloid from Yohimboa-bark with quebrachine from Quebracho-bark has been established by Fourneau and Page (*Bull. Sci. Pharmacol.*, 1914, **21**, 7), and confirmed by Ewins (T., 1914, **105**, 2739), and strictly, therefore, the older name quebrachine should be applied to the alkaloid from either source, but since its chemical and physiological properties have mostly been recorded under the name yohimbine, we may retain this latter name also.

The chemistry of yohimbine has been investigated chiefly by Spiegel (*Ber.*, 1903, **36**, 169; 1904, **37**, 1759; 1905, **38**, 2825), who ultimately adopted the formula $C_{22}H_{28}O_3N_2$ for the anhydrous alkaloid; Fourneau and Page give the formula $C_{21}H_{26}O_3N_2$, but our own analyses of the alkaloid and of its derivatives all agree well with Spiegel's formula. For the base itself, crystallised from benzene and dried at 100°, we found:

0·2079 gave 0·5480 CO_2 and 0·1358 H_2O. C = 71·8; H = 7·3.
0·1202 „ 0·3156 CO_2 „ 0·0810 H_2O. C = 71·6; H = 7·5.
$C_{22}H_{28}O_3N_2$ requires C = 71·7; H = 7·6 per cent.

We further confirmed the presence of one methoxy-group:

0·1970 gave 0·1266 AgI. OMe = 8·5.

$C_{22}H_{28}O_3N_2$ requires for one methoxy-group OMe = 8·4 per cent.

The alkaloid sublimes below its melting point, with only slight decomposition. At 210—220°/8 mm. very thin needles were formed, melting at 220° (uncorr.).

According to Spiegel, yohimbine can also exist in a hydrated form, $C_{22}H_{30}O_4N_2$; the salts correspond with the anhydrous form. This is, to some extent, reminiscent of cotarnine and hydrastinine, where the free bases contain the elements of a molecule of water more than the salts. Winzheimer (*Ber. Deut. pharm. Ges.*, 1902, **12**, 391), who drew attention to this similarity, failed, however, to obtain compounds analogous to cyanocotarnine by treatment with potassium cyanide, or to hydro- and oxy-hydrastinine by treatment with potassium hydroxide. We now find that the analogy is supported by the composition of *yohimbine methiodide*, which, contrary to Spiegel's assumption (*Chem. Zeit.*, 1899, **23**, 59), contains the additional molecule of water, even when prepared from the anhydrous base and dried at 100°. When 0·1 gram of yohimbine is dissolved in 20 c.c. of acetone and 0·1 c.c. of methyl iodide is added, the methiodide slowly crystallises; it melts somewhat indefinitely at about 250°:

0·1184 gave 0·2278 CO_2 and 0·0671 H_2O. C = 52·4; H = 6·3.

0·2230 „ 0·1000 AgI. I = 24·2.

$C_{22}H_{30}O_4N_2,CH_3I$ requires C = 52·3; H = 6·25; I = 24·0 per cent.

Yohimbine, being a monacid tertiary base, unites with only one methyl group in the conditions employed, whereas the secondary bases, cotarnine and hydrastinine, unite with two methyl groups; the methiodides of all three contain an additional molecule of water.

Mono- and Di-bromoyohimbine.

Yohimbine, dissolved in chloroform, instantly combines with a molecular proportion of bromine without evolution of hydrogen bromide. One gram of the base in 40 c.c. of solvent, when treated with 0·44 gram of bromine, remained in solution, but, on adding dry ether, 1·2 grams of a white precipitate were obtained. On dissolving this in a little cold alcohol, and adding dry ether, the substance separated in micro-crystalline aggregates, melting and decomposing at 296—298°. These were moderately soluble in water, and represent the *hydrobromide* of monobromoyohimbine, for the solution gives a precipitate with silver nitrate. With ammonia, the free base separates, but as we were unable to

crystallise it, the hydrobromide was analysed, after drying in a vacuum:

0·1206 gave 0·0832 AgBr. Br = 29·3.

$C_{22}H_{29}O_4N_2Br,HBr$ requires Br = 29·3 per cent.

Monobromoyohimbine, again treated with a molecular proportion of bromine in chloroform solution, yields an immediate precipitate, the resulting *hydrobromide* of dibromoyohimbine being less readily soluble. It crystallises from a mixture of alcohol and ether in small needles, melting at 296°:

0·1114 gave 0·1730 CO_2 and 0·0484 H_2O. C = 42·3; H = 4·8.

0·1042 „ 0·1590 CO_2 „ 0·0441 H_2O. C = 41·6; H = 4·7.

$C_{22}H_{28}O_4N_2Br_2,HBr$ requires C = 42·2; H = 4·7 per cent.

It is noteworthy that both bromo-derivatives, like the methiodide, contain a molecule of water more than yohimbine itself.

Yohimbinesulphonic Acid.

In an attempt to hydrolyse the alkaloid by means of concentrated sulphuric acid, it was found that sulphonation took place instead. This points to the existence of a benzene nucleus in the molecule, as does the formation of the bromo-compounds (compare strychnine); the large hydrogen content of yohimbine appears to exclude the presence of a second benzene ring.

One gram of yohimbine was dissolved in 10 c.c. of cold concentrated sulphuric acid, and, after a few minutes, the solution was poured on ice. The white solid which separated was dissolved by means of ammonia in 250 c.c. of boiling water. On boiling off the excess of ammonia, 0·95 gram of crystals separated, melting at 292—295°. The acid can be recrystallised from water, in which it is very sparingly soluble at room temperature (1 : 6000). In boiling water, the solubility is 1 : 1400:

0·2042 gave 0·4378 CO_2 and 0·1103 H_2O. C = 58·8; H = 6·0.

0·2236 „ 0·1140 $BaSO_4$. S = 7·0.

$C_{22}H_{28}O_6N_2S$ requires C = 58·9; H = 6·2; S = 7·1 per cent.

At the suggestion of one of us, Dr. A. J. Ewins recently prepared the same sulphonic acid from quebrachine (T., 1914, **105**, 2739), thereby further proving the identity of this alkaloid with yohimbine.

Oxidation of Yohimbine.

Various reagents were tried without success, perhaps owing to the small quantities of material available.

Potassium permanganate yielded, under certain conditions, small quantities of crystalline degradation products. The reaction was better in aqueous than in acetone solution.

Nitric acid behaves in a somewhat similar way to its action on strychnine, yielding, finally, a crystalline nitro-compound. Boiling with concentrated nitric acid for some hours does not produce very extensive degradation, but with 25—30 per cent. acid at 200°, a pale yellow solution results, which, on evaporation, deposits six-sided crystals, insoluble in water, but readily soluble in cold alcohol. On a small scale, it was found impossible to recrystallise them or free them from the mother liquor.

Hydrogen peroxide in 30 per cent. solution dissolves yohimbine almost completely in the course of a few days. On filtration and evaporation in a vacuum desiccator, a syrup resulted, which was dissolved in alcohol. Acetone precipitated a white, amorphous solid, which could not be crystallised. It was purified, as far as possible, by repeated solution in alcohol and precipitation by dry ether, and was dried in a vacuum, and then at 100°:

0·1410 gave 0·2796 CO_2 and 0·0744 H_2O. C = 54·1; H = 5·9.

0·1272 „ 6·7 c.c. N_2 (moist) at 13·5° and 740 mm. N = 6·1.

$C_{21}H_{26}O_{10}N_2$ requires C = 54·1; H = 5·6; N = 6·0 per cent.

In spite of the good agreement of the analyses with the formula, the latter must be accepted with great reserve, since the substance was amorphous. It is evident, however, that hydrogen peroxide at room temperature greatly increases the oxygen content of yohimbine, without marked degradation. The oxidation product is unstable; at 120° it loses weight and darkens, becoming much less readily soluble in water.

By fusion of yohimbine nitrate with potassium hydroxide at 240—280°, we obtained a nitrogenous acid in a yield of 1—2 per cent. of the alkaloid employed. This acid crystallised from water, and subsequently from benzene, melted at 200°, and on titration showed an equivalent of about 100. It would therefore appear to be a dicarboxylic acid, probably of quinoline, but we had not sufficient material to prepare enough for analysis.

Degradation of Yohimbine by means of Soda-Lime.

This we carried out in two ways. The substance obtained by Spiegel by removal of a methyl group from yohimbine, and termed by him yohimbic acid (Yohimboasäure), might be made to lose carbon dioxide by heating with soda-lime and to yield a volatile product, particularly since the alkaloid itself is volatile. We prepared yohimbic acid by boiling yohimbine with alkali, as described by Spiegel, and obtained from the acid a crystalline barium salt:

0·8074 gave 0·1220 $BaSO_4$. Ba = 8·89.

$(C_{21}H_{25}O_3N_2)Ba,2C_{21}H_{25}O_3N_2$ requires Ba = 8·83 per cent.

The substance was therefore an acid salt.

Yohimbic acid was then heated with three times its weight of calcium oxide in a flask provided with a collar, to prevent the distillate flowing back. On heating the flask in a metal-bath to 320—360°, and exhausting to 4 mm., it was possible to collect from 0·5 gram of yohimbic acid 0·1—0·15 gram of a dark brown distillate. On dissolving in methyl alcohol and concentrating the solution, a small quantity of colourless platelets separated, which melted at 167° without decomposition. This still rather complex degradation product is a feeble base; its solution in hydrochloric acid gives alkaloidal reactions. The investigation of this substance is being continued.

As in the above distillation with lime part of the alkaloid is decomposed further, giving a fæcal odour, we also heated yohimbine with lime under atmospheric pressure in a current of hydrogen. Seven grams, mixed with 60 grams of soda-lime, were distilled in four lots. The distillate was extracted with ether, first from acid and then from alkaline solution. The extract from acid solution coloured red a pine shaving soaked in hydrochloric acid, and possessed the fæcal odour already noticed by Spiegel (*Ber.*, 1905, **38**, 2825).

After drying, the residue from the ether was dissolved in benzene, and yielded with picric acid a rather soluble, red, crystalline picrate, melting at 154—155°:

0·0642 gave 0·1213 CO_2 and 0·1970 H_2O. C = 51·4; H = 3·4.
$C_{10}H_{12}N,C_6H_3O_7N_3$ requires C = 51·3; H = 3·3 per cent.

The substance is therefore an ethyl- or a dimethyl-indole, possibly 2 : 3-dimethylindole, the picrate of which is stated to melt at 157°. The small quantity available did not enable us to crystallise the indole itself.

The ethereal extract from alkaline solution was dissolved in alcohol and mixed with alcoholic picric acid solution. A yellow picrate separated, and tarry matter. The picrate was purified by crystallisation from water, and then from alcohol. It was very sparingly soluble in either solvent:

0·1178 gave 0·2306 CO_2 and 0·0372 H_2O. C = 53·5; H = 3·5.
$C_{11}H_9N,C_6H_3O_7N_3$ requires C = 53·15; H = 3·15 per cent.
$C_{11}H_{11}N,C_6H_3O_7N_3$ „ C = 52·85; H = 3·6 „ „

On the supposition that the base, $C_{11}H_9N$, was 4-phenylpyridine, we prepared some of the picrate of this base, but found it to differ from the picrate from yohimbine. According to the second formula, the base might be a dimethylquinoline. Although this product has not been identified, its composition, and the properties

of its picrate, make it almost certain that it contains a pyridine ring associated with a benzene ring, and that it contains the basic nitrogen atom of yohimbine. The other nitrogen atom would be in an indole ring.

The above experiments were chiefly carried out in the chemical department of Goldsmiths' College in 1911—1912 with a specimen of the alkaloid presented to us by the firm of T. Teichgraeber, of Berlin. We are also indebted to Prof. R. Willstätter, of Berlin, for a quantity of the alkaloid. For both specimens we desire to express our hearty thanks.

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