## 153. *Yohimbine (Quebrachine). Part IV. Harman, a Degradation Product.*

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ON resuming this investigation special attention has been given to the dimethyl- or ethyl-indole and the bases $C_{12}H_{10}N_2$ and $C_{13}H_{12}N_2$, derived from yohimbine by different types of degradation.

A substituted indole was obtained by Barger and Field (J., 1915, **107**, 1025), who heated yohimbine with soda-lime at ordinary pressure and characterised the indole as the picrate. It was also obtained by Warnat (*Ber.*, 1927, **60**, 1118) in much better yield, on dry distillation of yohimbic acid or *allo*-yohimbic acid by itself, and by Winterstein and Walter (*Helv. Chim. Acta*, 1927, **10**, 577) both on distillation of yohimbine with soda-lime or zinc dust and on treatment of the alkaloid with superheated steam at 300°.

Other degradation products, doubtless closely related to this indole, were isolated by Warnat (*Ber.*, 1926, **59**, 2391) on oxidation of yohimbine with potassium permanganate. These were *o*-hydroxyphenylcarbimide, an indolemonocarboxylic acid (m. p. 197—200°), and a dicarboxylic acid (m. p. 195°). The last has been identified by Späth (*Ber.*, 1930, **63**, 2997) as *N*-oxalylanthranilic acid. Further Hahn and Just (*Ber.*, 1932, **65**, 717) separated from the products of oxidation of diacetylyohimbine with nitric acid 6-nitroindazole-3-carboxylic acid, which is no doubt also derived from the indole part of the yohimbine molecule.

In the hope of identifying this dimethyl- or ethyl-indole, various isomerides were synthesised by Warnat (*Ber.*, 1927, **60**, 1121) and by Mendlik and Wibaut (*Rec. trav. chim.*, 1931, **50**, 109), but none was identical with the degradation product.

A consideration of other degradation products, of known constitution and mentioned above, leads to the conclusion that the alkyl is not attached to the benzene ring as Mendlik and Wibaut imagined, but to the pyrrole ring of the indole nucleus. The reaction of Herzig and Meyer showed us that the 1-position is unsubstituted. Although of limited evidential value, several colour reactions (pine-shaving, positive; *p*-dimethylaminobenzaldehyde, positive, red, on addition of dilute sodium nitrite solution, blue; chloroform with a trace of bromine, positive, violet; etc.) make it very probable that only the 3-position is substituted. Nevertheless, we have not yet been able to identify this particular indole derivative, which is very similar to skatole and 3-ethylindole, but much more labile.

We have, however, identified another indole derivative, obtained in small quantity in the potash fusion of yohimbic acid at 300°. It melted at 37° after distillation in a high vacuum and it did not depress the m. p. of 3-ethylindole, prepared by the method of E. Fischer (*Annalen*, 1886, **236**, 137) from phenylhydrazine and butaldehyde. In the same experiment we also isolated several acids, one of which, m. p. 198—200°, was proved to be identical with indole-2-carboxylic acid (prepared from 2-methylindole according to the method of Ciamician and Zatti, *Ber.*, 1888, **21**, 1930). We consider it almost certain that this is the acid (m. p. 200°) obtained by Barger and Field (J., 1915, **107**, 1028) on potash fusion of yohimbine nitrate and by Warnat (*Ber.*, 1926, **59**, 2392) on oxidation of

yohimbine hydrochloride with potassium permanganate in acetone suspension (m. p. 197—200°).*

The identification of these indole derivatives as degradation products of yohimbine makes it very likely that the bases $C_{12}H_{10}N_2$ and $C_{13}H_{12}N_2$—obtained simultaneously with the so-called dimethylindole by Barger and Field,† by Warnat, and by Winterstein and Walter (*locc. cit.*)—contain also the indole nucleus to which a pyrrole or a pyridine ring is attached in the 2 : 3-positions.

We lately followed the method of Warnat (*Ber.*, 1927, **60**, 1121) when preparing the base $C_{13}H_{12}N_2$, which he surmised to be a phenanthridine derivative, but our analyses fit the formula $C_{12}H_{10}N_2$ better than $C_{13}H_{12}N_2$. The manner of purification was slightly changed. The residues, which had not distilled up to 280° at atm. press., were extracted with boiling $H_2O$ containing a small amount of EtOH; most of the EtOH was allowed to evaporate and the solution was cooled. The cryst. ppt. was collected, dried, recrystallised from $C_6H_6$, and sublimed in a high vac. at 140—150°. The sublimate was crystallised from 80% MeOH and had m. p. 232° (softening at 227°) (Found: C, 79·5, 79·25, 79·2; H, 5·5, 5·4, 5·5; N, 15·35, 15·5. Calc. for $C_{12}H_{10}N_2$: C, 79·1; H, 5·5; N, 15·4%). Its cryst. form (from $C_6H_6$), its striking blue-violet fluorescence in dil. acid solution, its m. p., its ability to form a benzylidene compound, etc., made it very probable that this base is identical with harman. Harman was therefore prepared from tryptophan by method A of Kermack, Perkin, and Robinson (J., 1921, **119**, 1617). After purification the m. p. was 235·5° (softening at 233°); mixed m. p. 234° (softening at 230°).

The absorption spectra, the fluorescence spectra, and the influence of $p_H$ on the intensity of the latter were determined on both products by Dr. J. Eisenbrand of Berlin, who reports that they appear identical; for these further evidences we are greatly indebted to him.

The hydrochloride of the benzylidene compound was prepared according to Kermack, Perkin, and Robinson (J., 1921, **119**, 1620), both of the product from yohimbine and of that from tryptophan, and we then prepared the free base, not previously characterised, and recrystallised it from *ca.* 75% EtOH [Found for the product, m. p. 201·5° (softening at 200°), from yohimbine: C, 84·1; H, 5·3. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2%]. The *benzylideneharman* from tryptophan melted at 200° (softening at 198°). Mixed m. p. 201° (softening at 196°). The benzylidene compound exhibits strong violet fluorescence in neutral solvents and no difference in the colour could be observed between the specimens of either source.

Since it has been shown that the base $C_{12}H_{10}N_2$ obtained from yohimbine is identical with harman, we are disinclined to accept the view of Hahn and Just (*Ber.*, 1932, **65**, 720) that yohimbine contains a dihydroindole nucleus unsubstituted in position 3. The drastic methods of degradation, which have been chiefly employed so far, are indeed not entirely satisfactory and it is conceivable that harman is a secondary product formed by the destructive distillation of yohimbic acid, but we imagine this applies rather to the minute quantity of *iso*quinoline obtained by Winterstein and Walter (*loc. cit.*).

Harman is a base of biological importance, since it is readily formed from tryptophan (first obtained by Hopkins and Cole, *J. Physiol.*, 1903, **29**, 451), is identical with the alkaloids aribine (Späth, *Monatsh.*, 1919, **40**, 351) and loturine (Späth, *Monatsh.*, 1920, **41**, 401), and is present in modified form in the alkaloids harmaline, harmine (Robinson, J., 1922, **121**, 1872), evodiamine, and rutaecarpine (Asahina, *Acta phytochim. Tokyo*, **1**, 67).

The above experiments were chiefly carried out with a specimen of yohimbic acid and tryptophan presented to us by Messrs. Hoffman-La Roche, Basel. For this gift as well as for a grant from the Moray Research Fund of this University we desire to express our thanks.

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† Having only a small quantity of the yellow picrate, these authors omitted a nitrogen determination and concluded that the base was a quinoline derivative; as Winterstein and Walter point out, the C and H analysis fits even better the picrate of a base with two nitrogen atoms.