377. *The Alkaline Degradation of Strychnine.*

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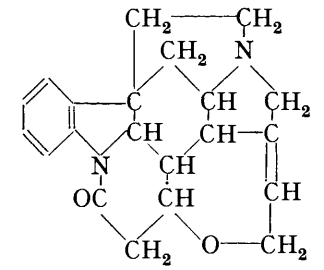
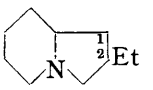
In the earlier work in which indole and carbazole were obtained from strychnine (Clemo, Perkin, and Robinson, J., 1927, 1589) no attempt was made to isolate all the products of decomposition in a pure state. In the interval many formulæ have been advanced for the alkaloid, such as the Robinson representation (I) (J., 1932, 780) and similar ones by Leuchs (*Ber.*, 1932, **65**, 1230) and Kotake (*Inst. Phys. Chem. Res. Tokyo*, 1934, 119).

(I.)





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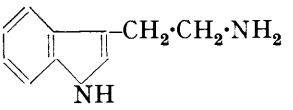

(III.)

A feature of all these formulæ is that they contain the basic nitrogen atom in either the octahydropyridocoline or the octahydropyrrocoline system. For some years past these bases have been studied here in connection with the lupin alkaloids and a year ago the time was considered ripe to examine the alkaline degradation products of strychnine in detail in order to see if any of the products were identical with our synthetic bases. Although two of the degradation bases herein described have not yet been identified, it is desirable to record the results already obtained in view of the statement by Kotake (*Proc. Imp. Acad., Tokyo*, 1936, **12**, 99) that he has obtained tryptamine by the action of potassium hydroxide on strychninolone. No experimental details are given in his paper, however, nor does he discuss the question of the identification of this tryptamine (compare p. 1696).

Strychnine has been degraded with potassium hydroxide under as mild conditions as possible, and the products distilled from the reaction mixture by steam and separated into basic and non-basic compounds. The mixed bases have been converted into picrates, and these separated to give the yellow compounds $C_8H_{11}N,C_6H_3O_7N_3$ (m. p. 143—144°) and $C_{10}H_{11}N,C_6H_3O_7N_3$ (m. p. 192°) and a bright red one, $C_{10}H_{12}N_2,C_6H_3O_7N_3$ (m. p. 254° decomp.). The relative amounts of the three bases (denoted by A, B, and C respectively) depend on the amount of potassium hydroxide and the temperature, elevation of temperature diminishing the proportion of A and increasing that of C.

The non-basic materials have not been as fully separated as the basic fraction, but indole and 3-ethylindole have been isolated.

The base (A) is easily reduced by platinum and hydrogen to $C_8H_{17}N$ and thus appears to be monocyclic. It has no diazotisable amino-group, and the properties of its picrate and the fact that it is slightly alkaline to litmus also rule out the possibility of its being ethylaniline, which could result from fission of the indole ring of (I). Furthermore, the base does not give the usual pyrrole colour reactions and is not 2-*n*-butylpyridine.

Base (B) is readily reduced by the addition of eight atoms of hydrogen to give the strong base $C_{10}H_{19}N$. This easily forms a crystalline methiodide and, assumed to be fully reduced, it must be dicyclic. The properties of (B), and more especially the stability of its picrate, seem to rule out the possibility of its being either an *N*-methyl methylindole or *N*-methyl-1 : 2-dihydroquinoline and it would therefore appear to contain the nitrogen as a common member of the two ring systems. The reduced base $C_{10}H_{19}N$, however, has not the characteristic odour and low boiling point of any of the octahydropyridocolines or octahydropyrrocolines prepared here. On the basis of (I), however, it might be 2 ethyl-octahydropyrrocoline, which would explain the elevation of boiling point and possibly the different odour.

The base (C) is particularly interesting in that it contains both the nitrogen atoms of strychnine, and a remarkable feature of its brilliant red picrate is that it is not decomposed by a short boiling with concentrated hydrochloric acid and crystallises from the solution on cooling. The free base, obtained by decomposing the picrate with potassium hydroxide, melts at 101—102° and gives a deep red-purple colour when the alcoholic solution is boiled in the Ehrlich colour reaction. The colour is discharged on addition of alcohol, and the crystalline hydrochloride of the base gives in the same reaction a port-wine colour which rapidly fades on cooling but is repeatedly reproducible on boiling. This suggests 3-β-aminoethylindole (tryptamine) for (C), since the α-compounds generally give an immediate intense purple colour in the Ehrlich indole test in the cold. The descriptions of tryptamine in the literature, however, are conflicting, as shown in the following table :

Ewins (J., 1911, **99**, 271) :	m. p. of base 145°	hydrochloride 246°	red picrate 242—3°
Majima (*Ber.*, 1925, **58**, 2042)	,, ,, ,, 114—5	,, 246 , ,,	,, 242—3
Manski (*Centr.*, 1932, i, 2474)	,, ,, ,, 118	,, 246 , ,,	,, 242—3
M. p. of base (C)	101	,, 249 , ,,	,, 254 (decomp.)

Although 2-β-aminoethylindole does not appear to have been synthesised, Asahina (*Centr.*, 1923, iii, 248) claims to have obtained it (m. p. of base 120°, of hydrochloride 246°, of red picrate 242—243°) in the degradation of rutaecarpine.

I am indebted to Mr. T. P. Metcalfe, who, repeating Majima's preparation of tryptamine, obtained the compound after three crystallisations from ether as a faintly brown, poorly crystalline solid, m. p. 114°, mixed m. p. with (C) 102—112°. When, however, it is converted into a picrate and recrystallised from alcohol, it corresponds to the picrate of (C) in crystalline form and decomp. point. Furthermore, the base regenerated from the picrate forms prisms (from ether), m. p. 101°, unchanged by admixture with (C), and gives well-formed prisms, m. p. 101°, on vacuum sublimation.

It is suggested that this difference in physical properties may be due to the two bases being the indole and the indolenine form of (III). It is true there does not appear to be any record of the isolation of two such tautomeric forms, but nevertheless a model shows that in the indolenine, but not in the indole form, either of the hydrogen atoms of the amino-group may be so situated that it could easily co-ordinate with the indolenine nitrogen atom to give a strain-free molecule. Lowry and Lloyd (J., 1929, 1771) ascribed the physical properties of nicotine to such a " dative " bond between one of the hydrogen atoms of the pyridine ring and the nitrogen atom of the pyrrolidine ring and furthermore a statement in *Annual Reports* (1935, 330) appears to show that the position of the double bond in certain pyrrolines depends on the substituents present and the method of preparation.

The indolenine structure claimed admits of being tested by resolution of the compound into optically active forms. It is intended to examine this point.

The results so far obtained indicate that the C atom of (I) is attached to the 3-position of the indole nucleus, and not to the 2-position as in some of the formulæ which have been advanced for strychnine, but it is necessary to settle the nature of (A) and (B) before discussing the structural question.

Experimental.

Four lots each of strychnine (2 g.), alcohol (30 c.c.), and potassium hydroxide (7 g.) were refluxed gently on a water-bath for 9 hours in a glass bulb with a 6″ neck drawn out at the top and bent down so that test-tube receivers could be attached. The alcohol was then removed, and water (3 c.c.) added and gradually distilled into a receiver during an hour by heating the bulb in a metal-bath at 230°. The addition and removal of the water were repeated similarly five times and the combined milky distillates, which smelt strongly of indole, were acidified and shaken with ether. The acid solution was evaporated to dryness under reduced pressure, the residue made alkaline with potassium hydroxide solution (25%) and extracted three times with ether, and the extracts dried and added to a hot solution of picric acid (0·15 g.) in benzene. After standing at least 24 hours, the benzene was decanted from nine such batches and the separated picrates were stirred with a little cold acetone and filtered off. The acetone was removed, and the residue crystallised from alcohol, giving 0·25 g. of yellow plates, m. p. 125—

130°, tinged with some of the red picrate (below). Two recrystallisations from ethyl acetate, in which the red picrate is sparingly soluble, raised the m. p. to 143—144° (Found : C, 48·2, 48·6, 48·3; H, 4·3, 4·35, 4·3. $C_8H_{11}N,C_6H_3O_7N_3$ requires C, 48·0; H, 4·0%).

Base A.—The above picrate (0·9 g.) was ground with cold hydrochloric acid (10 c.c. of 1 : 1) and filtered off, and the filtrate evaporated to dryness under reduced pressure. Excess of potassium hydroxide solution (40%) was added, and the liberated base extracted by ether and dried over potassium carbonate. On fractionation a colourless sweet-smelling *oil* (0·3 g., b. p. 48°/1 mm.) passed over (Found : C, 79·3, 79·2, 79·0; H, 9·5, 9·6, 9·3; N, 11·6, 11·0. $C_8H_{11}N$ requires C, 79·3; H, 9·1; N, 11·6%). The base is slightly soluble in water, giving a solution which turns red litmus blue, and it does not give a crystalline methiodide with methyl iodide in cold acetone. The base (0·2 g.) in acetic acid (5 c.c.) was shaken with platinum oxide (0·2 g.) in hydrogen (100 lb./sq. in.) for 18 hours. Hydrochloric acid (1 c.c.) was added to the filtrate, which was then evaporated to dryness, and the base liberated, extracted with ether, and obtained as a colourless *oil* (0·15 g.), b. p. $< 40°/1$ mm., with a strong basic smell (Found : C, 74·8; H, 14·1. $C_8H_{17}N$ requires C, 75·6; H, 13·4%). The *picrolonate* separated from alcohol in irregular yellow prisms, m. p. 233—234° (decomp.) (Found : C, 55·3, 55·8, 55·2; H, 6·5, 6·8, 6·7. $C_8H_{17}N,C_{10}H_8O_5N_4$ requires C, 55·2; H, 6·4%).

Base B.—The solid left undissolved by the cold acetone was dissolved in boiling acetone; yellow prisms of a sparingly soluble *picrate*, m. p. 192°, separated (Found : C, 51·5; H, 3·9. $C_{10}H_{11}N,C_6H_3O_7N_3$ requires C, 51·3; H, 3·7%). The free *base* was obtained by decomposing the picrate with hot hydrochloric acid (1 : 1) as a colourless oil with a sweet smell, b. p. 90°/1 mm. (Found : C, 82·9; H, 7·6; N, 9·6. $C_{10}H_{11}N$ requires C, 82·8; H, 7·6; N, 9·6%). Its aqueous solution was slightly alkaline to litmus. When the base (0·25 g.) in acetic acid (15 c.c.) was shaken for 18 hours with platinum oxide (0·15 g.) in hydrogen (100 lb./sq. in.), and the reaction mixture worked up in the usual way, 0·24 g. of a colourless, strongly basic *liquid* was obtained, b. p. 65°/1 mm. (Found : C, 78·0; H, 13·0. $C_{10}H_{19}N$ requires C, 78·4; H, 12·4%). The *picrate* was obtained as pale yellow prisms easily soluble in alcohol, m. p. 147—148° (Found : C, 50·3, 50·7; H, 6·0, 6·0. $C_{10}H_{19}N,C_6H_3O_7N_3$ requires C, 50·3; H, 5·8%); the *picrolonate* as irregular yellow prisms sparingly soluble in alcohol, m. p. 243—244° (decomp.) (Found : C, 57·4, 57·6; H, 6·6, 6·6. $C_{10}H_{19}N,C_{10}H_8O_5N_4$ requires C, 57·6; H, 6·5%); and the *methiodide* as colourless prisms from acetone, m. p. 263—264° (Found : C, 44·9; H, 7·4. $C_{10}H_{19}N,CH_3I$ requires C, 44·8; H, 7·5%).

Base C.—The red picrate of this base was obtained as mentioned in the purification of the picrate of base (A) and also by removing the acetone from the filtrate in the crystallisation of the picrate of (B) and crystallising the residue from alcohol. It was easily soluble in acetone, but sparingly so in alcohol, from which it separated in bright red prisms, m. p. 253—254° (decomp.) after darkening from 245° (Found : C, 49·5, 49·6; H, 4·4, 4·3. $C_{10}H_{12}N_2,C_6H_3O_7N_3$ requires C, 49·3; H, 3·8%). The powdered picrate (0·7 g.) was stirred with 40% potassium hydroxide solution (40 c.c.) for 10 minutes in the water-bath, and the deep red solution cooled and extracted four times with ether. The extract was dried, and the ether removed, leaving 0·25 g. of a nearly colourless, crystalline solid. It was sparingly soluble in light petroleum (b. p. 80—100°) and separated in thin hair-like prisms, but was best recrystallised from ether, giving faintly brown prisms, m. p. 100—101°. The base was obtained in colourless prisms, m. p. 101—102°, when sublimed in a high vacuum at 180° [Found : C, 74·6, 74·6; H, 7·3, 7·7; N, 17·4; *M* (Rast), 154, 157, 152. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·5; N, 17·5%; *M*, 160]. The *hydrochloride* formed stout colourless prisms from alcohol, m. p. 248—249° (Found : N, 14·45. $C_{10}H_{12}N_2,HCl$ requires N, 14·3%),and the base regenerated from it had m. p. 101—102° after crystallisation from ether or hexane.

Non-basic Material.—The ethereal extract from several experiments was dried and fractionated, giving (*a*) 4·37 g., up to 100°/1 mm., (*b*) 5 g., b. p. 110—120°/1 mm., and (*c*) 0·6 g., b. p. up to 160°/1 mm. On standing, (*a*) deposited 0·7 g. of a crystalline solid, which was recrystallised from light petroleum (b. p. 60—80°) and gave colourless plates, m. p. 52°, not depressed by admixture with indole. Fraction (*b*) was steam-distilled, the distillate extracted with ether, and the extract dried and fractionated, giving 0·65 g., b. p. 100—103°/1 mm., 0·9 g., b. p. 103—105°/1 mm., 1·34 g., b. p. 105—110°/1 mm., and 0·55 g., b. p. up to 120°/1 mm. On cooling, the 1·34 g. fraction set to a buttery mass of plates, which were collected (0·4 g.), m. p. 32—33°, and redistilled (Found : C, 83·1; H, 7·7. Calc. for $C_{10}H_{11}N$: C, 82·8; H, 7·6%). The literature records the m. p. of 2-ethylindole as 32—33°, and that of the 3-isomer is given values from 37° to 43° (compare Barger and Scholz, J., 1933, 614). That the compound is 3-ethylindole is shown by the fact that it liquefies when mixed with synthetic 2-ethlyindole,

but does not depress the m. p. of 3-ethylindole, and, further, its picrate, made in and crystallised from benzene, has m. p. 114—115° in agreement with that of 3-ethylindole.

I am indebted to Mr. F. E. Charlton for carrying out a large number of the degradation experiments.

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