CCCCXXXVI.—*Strychnine and Brucine. Part XIII. Note on Dihydroindolylpropionic and Dihydroindolylbutyric Acids.*

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THE oxidation of tetrahydrostrychnine and of some of its derivatives by means of chromic acid has recently been investigated by Leuchs (*Ber.*, 1930, **63**, 3184) with results which appeared to possess significance in relation to the constitutional problem.

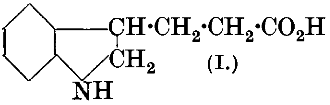
N-*O*-Diacetyltetrahydrostrychnine and *N*-acetyltetrahydrostrychnine furnished *N*-acetylstrychnic acid, so that, as would be anticipated, the group $\cdot CH_2\cdot OH$ (or $\cdot CH_2\cdot OAc$) in the base was the point of attack by the oxidising agent.

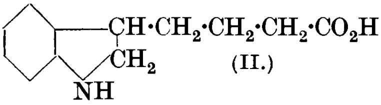
Tetrahydrostrychnine itself, however, yielded an acid $C_{21}H_{22}O_4N_2$ which was also a base and did not respond to reagents for the hydroxyl and carbonyl groups.

The explanation suggested was that tetrahydrostrychnine might be formulated as $C_{19}H_{20}ON(NH[a]\cdot CH_2\cdot)\cdot CH_2\cdot OH$ and that the oxidation product could then be $C_{19}H_{20}ON(NH[a]\cdot CO\cdot)\cdot CO_2H$.

This involves the assumption that the lactam ring of strychnine is in some way formed by a bridge connecting the nitrogen atom and the β-position in a dihydroindole derivative.

We have accordingly attempted to test this hypothesis by an examination of the properties of dihydroindolylpropionic acid (I) and dihydroindolylbutyric acid (II).


(I.)


(II.)

Neither of these acids shows any tendency to form a cyclic amide, and the related esters can be distilled without decomposition. In view of the extreme ease of closure of the lactam ring in strychnine, it seems highly improbable that strychnic acid can be regarded as a substituted derivative of (I) or of (II).

EXPERIMENTAL.

Ethyl β-3-Dihydroindolylpropionate.—A solution of β-3-indolylpropionic acid (Kalb, Schweizer, and Schimpf, *Ber.*, 1926, **59**, 1858; Manske and Robinson, J., 1927, 240) (6 g.) in absolute alcoholic hydrogen chloride (40 c.c. of 3%) was boiled for 3 hours and poured into water. The resulting solid ethyl ester was collected, dissolved in alcohol (100 c.c.), and hydrogenated in the usual way after the addition of platinic oxide (0·1 g.) and concentrated hydrochloric acid (1 c.c.). The rate of hydrogenation varied in different experiments, and was always slow. The solution was filtered from platinum catalyst, concentrated to a small bulk, mixed with ether, and extracted successively with sodium bicarbonate solution and with dilute sulphuric acid. Any unreduced ester remained in the ethereal solution. *Ethyl* β-3-*dihydroindolylpropionate* was liberated from the sulphuric acid extract by means of alkali, isolated by ether extraction, and purified by distillation in a high vacuum. It formed a colourless liquid, b. p. 145°/0·1 mm. (Found: C, 71·2; H, 7·8. $C_{13}H_{17}O_2N$ requires C, 71·2; H, 7·7%).

β-3-*Dihydroindolylpropionic Acid* (I).—The above ester (1 g.) was dissolved in sulphuric acid (10 c.c. of 2*N*) and heated for 4 hours on the water-bath. The brown liquid was then diluted, a little charcoal added, and, after being heated for a further 15 minutes, the solution filtered. Sulphuric acid was exactly precipitated by means of baryta, and the filtrate evaporated. The acid remained as a pale brown, viscous oil, readily and completely soluble in acids and alkalis; it resisted attempts to crystallise it and decomposed on distillation in a high vacuum. Its *benzoyl* derivative was prepared by shaking a solution of the acid in dilute alkali with benzoyl chloride and acidifying the product. The crude substance separated as a gum which crystallised on being stirred with ether. After removal of benzoic acid by extraction with hot water, the derivative was crystallised twice from toluene, forming rosettes of small white prisms, m. p. 152° (Found: N, 4·7. $C_{18}H_{17}O_3N$ requires N, 4·7%). Dissolved in sulphuric acid (50 vol. %) and treated with a drop of potassium dichromate solution, this substance gave the transient violet-blue colour reaction characteristic of *N*-acyldihydroindole derivatives and of strychnine.

Methyl γ-3-*Dihydroindolylbutyrate.*—This substance was prepared in a similar way by the reduction of methyl γ-3-indolylbutyrate (Jackson and Manske, *J. Amer. Chem. Soc.*, 1930, **52**, 5032) and was obtained as a colourless oil, b. p. 160°/0·1 mm. (Found: C, 70·8; H, 7·9. $C_{13}H_{17}O_2N$ requires C, 71·2; H, 7·7%).

γ-3-*Dihydroindolylbutyric Acid* (II).—The methyl ester was hydrolysed with dilute sulphuric acid, the latter removed by means of just sufficient baryta, and the filtrate evaporated. γ-3-Dihydroindolylbutyric acid remained as a brownish resin, soluble in acids and alkalis, and in this case the benzoyl derivative also was uncrystallisable. A solution of the acid in dilute caustic soda was shaken with ether and *p*-nitrobenzoyl chloride, the aqueous layer separated and acidified, and *p*-nitrobenzoic acid removed from the resulting sticky precipitate by extraction with boiling water. Two crystallisations from aqueous alcohol gave γ-1-p-*nitrobenzoyl*-3-*dihydroindolylbutyric acid* as pale yellow, diamond-shaped plates, m. p. 163—164° (Found : N, 8·4. $C_{18}H_{18}O_4N_2$ requires N, 8·6%). This compound also gave the colour reaction with sulphuric acid and a dichromate.

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