199. *Strychnine and Brucine. Part XLIII. Cuninecarboxylic Acid.*

By H. L. Holmes, H. T. Openshaw, and Sir Robert Robinson.

The oxidation of dihydrostrychninone (I) by means of barium peroxide affords cuninecarboxylic acid (II) which, on heating, gives a neutral *lactam*.

Publication of a paper by Prelog and Szpilfogel (*Helv. Chim. Acta,* 1946, **28**, 1669) prompts us to submit an account of experiments completed before the war and necessarily set aside during the past six years. The investigation has now been resumed with the object of effecting a meeting between degradation and synthesis on lines adumbrated in 1937 (Part XXXVI, *J.*, 941). The stage reached on the synthetical side is exposed in the following communications.

Dihydrostrychninolone-a (Leuchs, Diels, and Dornow, *Ber.*, 1935, **68**, 106) was oxidised to dihydrostrychninone (I) following Kotake and Mitsuwa (*Bull. Chem. Soc. Japan*, 1936, II, 238) and thence by means of barium hydroxide and hydrogen peroxide to *cuninecarboxylic acid* (II); the process is modelled on Leuchs's similar oxidation of strychninonic acid.

On heating at 210° and then at 260°, II loses water and yields the lactam (III) which is devoid of acidic and basic properties. Although cuninecarboxylic acid shows little tendency to lactamise under other conditions, and the temperature employed was high, this result favours the arrangement IV as against V in III. The possibility of a ring transformation is now being studied.

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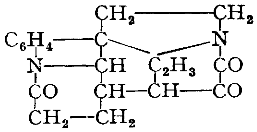
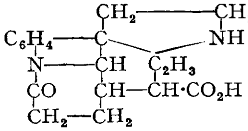
* (*Added, September 20th,* 1946).—An attempt made in the last few months to distinguish by a decisive experiment between II and III has given results, not yet free from all dubiety, but strongly supporting II. This statement applies only to the structural feature in regard to which II differs from III, and the full implications cannot be discussed until the work is completed.

Prelog and Szpilfogel (*loc. cit.*) hydrolysed dihydrostrychninone to a hydrated keto-acid which lost carbon dioxide and water on heating with pyridine. The resulting aldehyde formed semi-acetals [-CH(OR)-N:] with methanol and ethanol and therefore the ring containing N(b) is apparently at least six-membered. Here again, a ring transformation is not excluded, although it is less probable than in our case.


(I.)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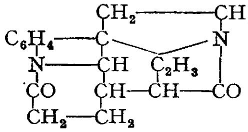
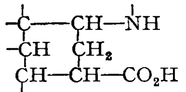

(III.)

Incidentally, if II had the constitution V we would anticipate scission of the β-amino-acid with formation of an αβ-unsaturated acid. There is no sign of such a process either on pyrolysis or, as has recently been observed by Mr. R. A. Hancock, on vigorous treatment with methyl sulphate and sodium hydroxide.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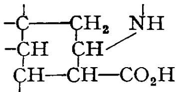
(V.)

Experimental.

Strychninonic Acid (cf. Leuchs and Schwaebel, *Ber.*, 1913, **46**, 3695).—Strychnine (7·5 g.) suspended in acetone (50 c.c.) and then finely powdered potassium permanganate (15 g.) were added to a vigorously stirred mixture of acetone (2500 c.c.) and chloroform (500 c.c.). At intervals of 30 minutes nine further similar additions of strychnine in acetone and permanganate were made and the mixture was finally stirred for an hour. The manganese precipitate was collected and washed with acetone (400 c.c.). It was then stirred with crushed ice (500 g.), saturated ammonium chloride solution (500 c.c.), and water (1200 c.c.) for 15 minutes and after filtration this extraction was twice repeated. Each extract was stirred with chloroform (200 c.c.) and acidified with hydrochloric acid, and the chloroform was separated and the solution extracted twice with fresh chloroform (300 c.c.). The whole chloroform solution (2700 c.c.) was concentrated to 300 c.c. and water (75 c.c.) added. The aqueous solution was then made alkaline by means of potassium hydrogen carbonate and stirred to ensure complete extraction. The aqueous layer was washed with chloroform (50 c.c.), just acidified with acetic acid, boiled to remove chloroform, and then made strongly acid with acetic acid. The product crystallised and was recrystallised from 160 parts of hot water as colourless plates (15·2 g.) (0·23 g. in 5·86 c.c. of N/10-NaOH made up to 25 c.c. with water; $[\alpha]_{\text{D}}^{20^\circ}$ − 46·7°). Ten lbs. of strychnine were so worked up and the chloroformic solutions from which the strychninonic acid was extracted were combined and concentrated, when a white crystalline powder (55·0 g.) separated. This neutral *product* is sparingly soluble in alcohol and acetone, moderately readily soluble in acetic acid. It is soluble in 500 parts of hot water and crystallises on cooling in white, elongated prisms, m. p. 332° (vac.) (Found: C, 67·45, 67·40, 67·41; H, 5·28, 5·26, 5·35; N, 8·39, 8·26. $C_{19}H_{18}O_4N_2$ requires C, 67·41; H, 5·36; N, 8·28%) (0·10 g. in 25 c.c. of acetic acid; $[\alpha]_{\text{D}}^{20^\circ}$ − 14·2). Leuchs and Schwaebel (*loc. cit.*) describe the substance as browning at 290°, m. p. 320° (decomp.), and assign the composition $C_{19}H_{20}O_4N_2$ (C, 66·7, 66·8, 67·0; H, 5·7, 5·7, 5·5; N, 8·0, 8·3. Calc.: C, 67·1; H, 5·9; N, 8·2%). It is almost certain that the substances are identical. Our compound gives a typical Otto reaction and is soluble in concentrated hydrochloric acid. On addition of water a new substance separates, m. p. 350—354°, and this also gives an Otto reaction.

A crystallographic examination of strychninonic acid was kindly undertaken by Dr. D. P. Riley who reports as follows.

" The crystals consisted mainly of orthorhombic plates {010} elongated along [100]. *X*-Ray oscillation photographs were taken with the crystal set up about [100] firstly with the *X*-rays shining parallel to (010) and secondly parallel to (001). From these photographs the unit-cell dimensions were measured as approximately: *a*, 7·2 A.; *b*, 8·45 A.; *c*, 14·5 A.

" The density of the crystals as determined by flotation in a mixture of carbon tetrachloride and toluene was 1·462 ± 0·002 at 20° C. Hence if it is assumed that there are two molecules in the unit-cell, the molecular weight of the compound can be calculated to be 392 ± 5 ($C_{21}H_{20}O_6N_2$ requires *M*, 396)."

Methyl strychninonate, m. p. 247—249°, was obtained from the acid by Leuchs and Reich (*Ber.*, 1910, **43**, 2420) by short treatment with methanolic hydrogen chloride (2·5%).

We employed a 25% excess of diazomethane and an ethereal suspension of the acid. The product crystallised from methanol in slender needles, m. p. 246·4—246·7° (0·015 g. in 25 c.c. of methanol; $[\alpha]_{\text{D}}^{20^\circ}$ − 166·6°).

Catalytic Reduction of the Neutral Product, $C_{19}H_{18}O_4N_2$.—The substance (0·75 g.) was reduced at 16°/760 mm. in acetic acid (100 c.c.) in the presence of platinum oxide (0·05 g.).

The theoretical volume of hydrogen (1 H_2) was absorbed in 45 minutes. The filtered solution was evaporated and the residue crystallised from water (0·70 g.). It was twice recrystallised from water (250 parts) and obtained as long, white needles, m. p. 244—245° (Found: C, 67·16, 67·01; H, 6·02, 5·90; N, 8·16. $C_{19}H_{20}O_4N_2$ requires C, 67·04; H, 5·92; N, 8·23%) (0·10 g. in 25 c.c. of acetic acid; $[\alpha]_{\text{D}}^{20^\circ}$ + 18·5°).

Catalytic Reduction of Strychninonic Acid.—The acid (1·66 g.) in acetic acid (120 c.c.) with platinum oxide (0·1 g.) absorbed the theoretical volume of hydrogen in 2¼ hours at 17°/740 mm. The product was crystallised from water and found to be pure dihydrostrychninonic acid (1·50 g.). The long glistening needles lost water of crystallisation at 100°/9 mm., m. p. 312° (decomp.) (0·30 g. in 7·6 c.c. N/10-NaOH made up to 25 c.c.; $[\alpha]_{\text{D}}^{20^\circ}$ − 4·9°) (Found in anhydrous material: C, 63·2; H, 5·6; N, 7·2. Calc. for $C_{21}H_{22}O_6N_2$: C, 63·3; H, 5·6; N, 7·0%). Leuchs (*Ber.*, 1908, **41**, 1711) gives decomp. 315° and $[\alpha]_{\text{D}}^{20^\circ}$ + 4·3° in 3·5% solution.

Dihydrostrychninone.—Strychninolic acid and strychninolone-a (Leuchs and Schneider, *Ber.*, 1909, **42**, 2495) were obtained by small modifications of the known methods in 82% and 93% yields respectively. The acid, long needles from water, lost solvent at 100°/9 mm. and had m. p. 238°; strychninolone-a formed elongated prisms from alcohol, m. p. 228° (0·59 g. in 25 c.c. of acetic acid; $[\alpha]_{\text{D}}^{20^\circ}$ − 115·3).

Dihydrostrychninolone-a (Leuchs, Diels, and Dornow *loc. cit.*), formed long needles, m. p. 271—272° (0·925 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20^\circ}$ − 11·3°) (Found : C, 70·6, 70·5; H, 6·3, 6·2; N, 8·8, 8·7. Calc. for $C_{19}H_{20}O_3N_2$: C, 70·4; H, 6·2; N, 8·6%). On oxidation according to Kotake and Mitsuwa (*loc. cit.*) a 70% yield of a product crystallised from alcohol was obtained. This crystallised from alcohol in elongated prisms that consistently had m. p. 263—264° (Found : C, 70·6, 70·7; H, 5·8, 5·8; N, 8·7, 8·8. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·8; H, 5·6; N, 8·7%) (0·099 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20^\circ}$ − 29·8°). The Japanese chemists gave m. p. 314° but it is not clear from the description that their starting point was pure strychninolone-a. However, the probability is that the lower-melting material was a labile stereoisomeride (dependent on :CH–CO—) because we, also, have recently observed the m. p. 314° and Prelog and Szpilfogel give the m. p. 318°, $[\alpha]_D^{20^\circ}$ − 49° in chloroform.

Dihydrostrychninone, m. p. 263—264° (1·0 g.), in acetic acid (50 c.c.), along with platinic oxide (0·05 g.), was shaken with hydrogen at 17°/743 mm. The theoretical volume (95 c.c.) was absorbed in 24 minutes and absorption then ceased. The product crystallised from ethanol in long, colourless needles (0·95 g.), m. p. 271—272°, alone or mixed with dihydrostrychninolone-a (0·1 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20^\circ}$ − 10·6°). This is a rather curious result in view of the reduction of strychninonic acid to dihydrostrychninonic acid (*v. supra*).

Cuninecarboxylic Acid (II).—Dihydrostrychninone (2·5 g.) was dissolved by gentle heating in aqueous barium hydroxide (60 c.c. of 5%); the cooled solution was treated with perhydrol (1·7 g.) in water (20 c.c.).

Barium carbonate was quickly precipitated and the reaction was completed by heating for 2 minutes on the steam bath. The mixture was made faintly acid with sulphuric acid, filtered, and extracted thrice with chloroform. The aqueous solution was then concentrated under reduced pressure to about 5 c.c. when 1·5 g. of a pale brown solid separated. The *substance* crystallised from water in dense, colourless prisms, that softened at 215°, hardened again, and then melted at 265—270° (Found : C, 69·2, 69·3; H, 6·6, 6·6; N, 8·9, 9·1. $C_{18}H_{20}O_3N_2$ requires C, 69·3; H, 6·5; N, 9·0%) (0·07 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20^\circ}$ − 22°). The substance shows the characteristic behaviour of an amino-acid and exhibits a normal Otto reaction.

This acid (1·5 g.) was refluxed for 3 hours with methanol (30 c.c.) and sulphuric acid (0·5 c.c.). After addition of water and basifying, the *methyl* ester was isolated by extraction with chloroform. The derivative crystallised from methanol in prismatic needles, m. p. 167—168° (Found : C, 69·9; H, 6·7; N, 8·3. $C_{19}H_{22}O_3N_2$ requires C, 69·9; H, 6·8; N, 8·6%) (0·07 g. in 25 c.c. of methanol; $[\alpha]_D^{20^\circ}$ − 25°).

Cuninecarboxylic acid was heated under nitrogen at 210°, when it softened, and then at 260°. During 30 minutes the product sublimed, m. p. 290—291°. It crystallised from methanol in large plates, m. p. 296—297° (Found : C, 73·3, 73·4; H, 6·1, 6·1; N, 9·4. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·1; N, 9·5%) (0·1 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20^\circ}$ − 220°). This neutral *lactam* (III) exhibits the Otto reaction. An attempt to hydrogenate this lactam (0·4 g.) in the presence of platinic oxide (0·05 g.) was made but the hydrogen absorbed corresponded to the volume taken up by the catalyst. Consequently it does not appear to be unsaturated, but the experiment will be repeated.

Oxidation of Strychninolone-a by means of Chromic Acid.—Our results diverge from those of Kotake and Mitsuwa (*loc. cit.*).

A solution of chromic anhydride (1·0 g.) in water (4 c.c.) and acetic acid (100 c.c.) was slowly added to one of strychninolone-a (5·0 g.) in acetic acid (60 c.c.) with vigorous stirring. Half an hour after the last addition the solution was poured into water (2000 c.c.) and extracted with chloroform (3 × 150 c.c.), and the extract washed with water and aqueous sodium bicarbonate. The pale green solid residue, after removal of the solvent, was dissolved in alcohol (charcoal) and, on concentration of the solution, 4·3 g. of colourless crystals were obtained. After two recrystallisations the beautiful plates had m. p. 246—247° (corr.) (Found : C, 68·8, 68·7; H, 6·2, 6·1; N, 7·9, 7·6. $C_{21}H_{22}O_4N_2$ requires C, 68·8; H, 6·1; N, 7·7%) (1·0 g. in 25 c.c. of acetic acid; $[\alpha]_D^{20^\circ}$ − 127·3°).

The Otto reaction was characteristic and the *substance* is clearly $C_{19}H_{16}O_3N_2 + C_2H_6O$, containing the groups :NH(b) and $\cdot CO\cdot CO_2Et$.

Kotake and Mitsuwa (*loc. cit.*) did not use alcohol but they manipulated the product with methanol and ethyl acetate and obtained strychninone, $C_{19}H_{16}O_3N_2$, m. p. 273°. Contamination with the methanol adduct is not indicated by the carbon content which was even 0·6% high.

On catalytic reduction under the conditions used in the case of dihydrostrychninone, the ring closed again, and, after absorption of a volume of hydrogen corresponding to $2H_2$, dihydrostrychninolone-a was obtained (m. p., mixed m. p., and rotation).

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