CCCCXXXVII.—*Strychnine and Brucine. Part XIV. Oxidation of Hexahydrostrychnine.*

By Lindsay Heathcote Briggs and Robert Robinson.

Strychnine, $C_{18}H_{22}ON(C{:}C)(CO{\cdot}N)$, yields the so-called tetrahydrostrychnine, $C_{18}H_{22}ON(C{:}C)(CH_2{\cdot}OH\ NH)$, on electrolytic reduction (Tafel and Naumann, *Ber.*, 1901, **34**, 3291; Tafel, *Annalen*, 1898, **301**, 285) and the catalytic reduction of this base yields hexahydrostrychnine, $C_{18}H_{22}ON(CH{\cdot}CH)(CH_2{\cdot}OH\ NH)$ (Oxford, Perkin, and Robinson, J., 1927, 2403). We now find that the oxidation of hexahydrostrychnine by means of aqueous chromic acid affords an amino-acid, $C_{21}H_{22}O_4N_2$, in 22% yield. The substance is a base and if this function resided in N(a), which is attached to the aromatic nucleus, the absence of substituted alkylaniline character and the general stability to oxidising agents would be inexplicable; the basic centre is therefore N(b). The acid does not respond to reagents for the carbonyl group, but it condenses with benzaldehyde to form a benzylidene derivative, of which the *picrate* was analysed. It seems, therefore, that it must contain the original $:N(a){\cdot}CO{\cdot}CH_2{\cdot}$ group of strychnine.

The composition change representing the relation of the acid to dihydrostrychnine is that which would occur if a methyl group were oxidised to carboxyl. Thus the simple view is that hexahydrostrychnine, $C_{17}H_{19}ON(CH{\cdot}CH)(CH_2{\cdot}OH\ NH)(CH_3)$, is transformed on oxidation into the acid $C_{21}H_{22}O_4N_2$ or

$$C_{17}H_{19}ON(CH{\cdot}CH)(CO{\cdot}N)(CO_2H).$$

It appears to us that the only simple alternative is represented by the opening of the oxide ring of the base, but this must leave a carbonyl group in the molecule; and this we have so far been unable to detect. It will be seen that the changes, $R{\cdot}CH_3 \longrightarrow R{\cdot}CO_2H$ and $:CH{\cdot}O{\cdot}CH_2{\cdot} \longrightarrow :CO\ CO_2H{\cdot}$ are equivalent.

It is possible, however, that the changes involved are much more complex, because it is very remarkable that the acid does not exhibit the usual strychnine colour reaction with sulphuric acid and a dichromate.

It was apparent that the acid was not identical with an amino-acid obtained by Leuchs (*Ber.*, 1930, **63**, 3184) by the chromic acid oxidation of tetrahydrostrychnine, to which the formula $C_{21}H_{22}O_4N_2$ was attributed. Quite recently Leuchs has reduced this acid catalytically and considers that the product is $C_{21}H_{24}O_4N_2$. We have also prepared the latter substance and found it identical with the oxidation product of hexahydrostrychnine.

This observation suggested that the acid $C_{21}H_{22}O_4N_2$ of Leuchs might be $C_{21}H_{20}O_4N_2$, a hypothesis which is not refuted by recorded analyses. New careful analyses of the substance and its dihydro-derivative have convinced us that this view is correct.

Accordingly the oxidation of tetrahydrostrychnine and of hexahydrostrychnine take parallel courses and the ethylenic linkage of tetrahydrostrychnine cannot be involved in the process.

EXPERIMENTAL.

Hexahydrostrychnine.—An improvement of the yield and an economy in the use of palladium have been effected. Palladous chloride (1·25 g.) and animal charcoal (12·5 g.) were added to a solution of tetrahydrostrychnine (20 g.) in 10% acetic acid (475 c.c.), and the whole stirred in hydrogen at 75°. 1820 C.c. were absorbed in 2½ hours (calc., 1320 c.c.). The base isolated from the solution was crystallised from ethyl acetate–light petroleum (10 : 1) and the yield of material, m. p. 198—199°, was 65% of the theoretical.

Oxidation of Hexahydrostrychnine.—A solution of the base (11·57 g.) in water (440 c.c.) and sulphuric acid (34 c.c.) was cooled to 16°, and chromic anhydride (23·8 g.), dissolved in water (115 c.c.), added at once; a dense red precipitate was thrown down. The mixture was shaken for 40 minutes and gradually heated to 80° during 2½ hours; the solid then passed into the solution, which acquired a pure green colour.

The hot liquid was partly neutralised with aqueous ammonia (17 c.c., *d* 0·880, and 17 c.c. of water) and then treated with barium hydroxide (200 g.) dissolved in boiling water (150 c.c.). The sludge was collected, washed with hot dilute aqueous ammonia, and extracted with successive volumes of boiling water (500 c.c. and 300 c.c.). The filtrates were combined, and concentrated under diminished pressure to 20—30 c.c. and the solid that separated on cooling and keeping was collected, washed, and dried (2·52 g.). Several crystallisations from water (charcoal) gave colourless needles and prisms, m. p. 281—282° (decomp.) (Found: loss at 120°, 8·9. Found in anhydrous material: C, 68·8; H, 6·1. $C_{21}H_{22}O_4N_2,2H_2O$ requires $2H_2O$, 8·9%. $C_{21}H_{22}O_4N_2$ requires C, 68·9; H, 6·0%).

The substance has an acid reaction to litmus and is insoluble in the usual organic solvents. Dissolved in 1% hydrochloric acid, it has $[\alpha]_D^{20^\circ}$ + 10·73°.

Methosulphate. Attempts to prepare this derivative in non-hydroxylic solvents were fruitless and the following method was therefore adopted. The anhydrous acid (0·2 g.) was mixed with freshly distilled methyl sulphate (0·08 g.) and dry methyl alcohol (5 c.c.). No reaction occurred in the cold but, on heating, the solid passed into solution; after 15 minutes' refluxing, the liquid was evaporated under diminished pressure. The viscous residue was dissolved in hot ethyl alcohol and crystallised on the addition of light petroleum and on cooling (0·05 g.). The substance darkened on heating but did not melt below 318° (Found : N, 5·8. $C_{21}H_{22}O_4N_2,C_2H_6SO_4$ requires N, 5·7%).

The *methiodide* was obtained from the mother-liquor from the methosulphate by the action of sodium iodide. It crystallised from water containing sulphurous acid and had m. p. 280—287° (decomp.) with previous darkening (Found : N, 5·3. $C_{21}H_{22}O_4N_2,CH_3I$ requires N, 5·5%).

The *methochloride*, prepared from the iodide by means of silver chloride, crystallised from a solution in a very little water in pointed prisms, which darken at 280° and begin to melt at 320° (Found : N, 6·4. $C_{21}H_{22}O_4N_2,CH_3Cl$ requires N, 6·7%). This derivative is very readily soluble in methyl alcohol and sparingly soluble in cold ethyl alcohol.

Benzylidene derivative. A mixture of the acid, $C_{21}H_{22}O_4N_2$, from hexahydrostrychnine (0·2 g.), benzaldehyde (0·2 g.), and ethyl alcohol (5 c.c.) was heated to boiling, concentrated alcoholic sodium ethoxide (6 drops) introduced, and the mixture boiled for 10 minutes. The gummy residue, after removal of the solvent in a vacuum at the room temperature, was insoluble in ether and acetone but readily soluble in cold methyl alcohol. It was dissolved in hot ethyl alcohol (1·5 c.c.), and cold saturated alcoholic picric acid (3 c.c.) added with formation of a yellow precipitate. This was collected, washed with water and absolute alcohol (yield, 0·26 g.), and crystallised from 1000 parts of boiling water (Found : C, 59·5; H, 4·5; N, 10·2. $C_{34}H_{29}O_{11}N_5$ requires C, 59·7; H, 4·3; N, 10·3%).

The oxidation product of tetrahydrostrychnine (Leuchs, *loc. cit.*) was prepared and analysed (Found : loss at 105°, 15·6. Found in anhydrous material : C, 69·4; H, 5·7. $C_{21}H_{20}O_4N_2,4H_2O$ requires $4H_2O$, 16·5%. $C_{21}H_{20}O_4N_2$ requires C, 69·2; H, 5·5; N, 7·9%. $C_{21}H_{22}O_4N_2$ requires C, 68·9; H, 6·0; N, 7·7%). The analyses recorded by Leuchs agree well with the formula now suggested and were the following: H_2O, 16·6%, and in anhydrous material: C, 69·1; H, 5·8; N, 7·7%.

Catalytic Reduction of the Acid, $C_{21}H_{20}O_4N_2$.—We describe this experiment because our method was not the same as that recently reported by Leuchs and Beyer (*Ber.*, 1931, **64**, 2161). These authors employed platinum oxide and used an alkaline solution of the acid. The acid from tetrahydrostrychnine (1·0 g.) was dissolved in 25% acetic acid (20 c.c.) and hydrogenated in the presence of palladium (from 0·1 g. of palladous chloride) and animal charcoal (1·0 g.). The absorption of hydrogen was slow and the theoretically required volume was taken up in 6 hours. The filtered solution was rendered just alkaline by means of ammonia; on keeping, a colourless solid separated and the quantity was increased by exposure to a vacuum at the room temperature. The total solid (0·68 g.) crystallised from hot water (90 c.c.) in needles and prisms, which soften at 250° and then melt at 272°; the dehydrated material, however, has m. p. 280—285° (decomp.) (Found: loss at 110°, 7·1. Found in anhydrous material: C, 68·9; H, 6·1; N, 7·6. $C_{21}H_{22}O_4N_2,2H_2O$ requires $2H_2O$, 8·9%. $C_{21}H_{22}O_4N_2$ requires C, 68·9; H, 6·0; N, 7·6%. $C_{21}H_{24}O_4N_2$ requires C, 68·5; H, 6·5; N, 7·6%). In 1% hydrochloric acid solution this acid had $[\alpha]_D^{19°}$ +11·36°, in sufficiently good agreement with our finding for the acid from hexahydrostrychnine.

Leuchs and Beyer (*loc. cit.*) gave $[\alpha]_D^{20°}$ + 28·6°, + 30·6°, and + 27·8° for different preparations. They found: H_2O, 9·2, 9·2, 8·8, and in the anhydrous acid: C, 68·8; H, 6·3%. In this case also the results are in accord with the formulæ now proposed. The divergence of the rotatory power between our observations and those of Leuchs and Beyer is probably the result of different conditions of experiment.

A careful direct comparison has shown that the acid $C_{21}H_{22}O_4N_2$, derived from hexahydrostrychnine, is identical with that obtained by the hydrogenation of the oxidation product of tetrahydrostrychnine.

THE UNIVERSITY OF OXFORD.

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