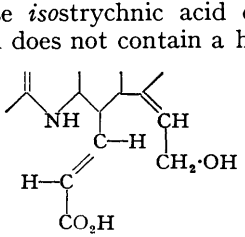
175. *Strychnine and Brucine. Part LII.* Conversion of the Wieland–Gumlich Aldehyde into* iso*Strychnic Acid.*

By Sir Robert Robinson and J. E. Saxton.

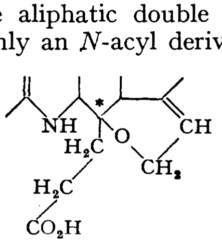
Condensation of the aldehyde, $C_{19}H_{22}O_2N_2$, obtained by the degradation of hydroxyiminostrychnine, with malonic acid in the presence of pyridine and piperidine, affords *iso*strychnic acid. This partial synthesis has a bearing on the problem of the constitution of *iso*strychnic acid.

*iso*Strychnic acid, $C_{21}H_{24}O_3N_2,H_2O$, was formerly regarded as a *trans*-β-substituted acrylic acid as shown in the partial structure (I) (Oesterlin and Imoudsky, *Ber.*, 1943, **76**, 172; Siddiqui, *J. Indian Chem. Soc.*, 1940, **17**, 152; Leuchs and Schulte, *Ber.*, 1943, **76**, 1038). Because *iso*strychnic acid contains only one aliphatic double bond (dihydro-derivative) and does not contain a hydroxyl group (only an *N*-acyl derivative is obtainable), Leuchs, Mengelberg, and Hemmann (*Ber.*, 1944, **77**, 737; cf. Leuchs and Mengelberg, *Ber.*, 1949, **82**, 250) suggested the structure (II) in which the configuration at the carbon atom marked * differs from that present in strychnine and strychnic acid and is

(I)



(II)



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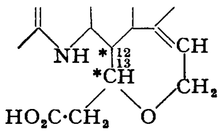
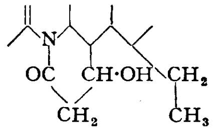
* Part LI, *J.*, 1950, 1585.

that which occurs in strychninolone-*c*. Finally, Boit (*Ber.*, 1951, **84**, 16) showed that the correct constitution must be (III), in which the configuration of either or both of the carbon atoms marked * (12, 13) is significant.

(III)





(IV)

The decisive argument concerned the *iso*tetrahydrostrychnine that Leuchs and Schulte had prepared (*loc. cit.*) by the reduction of *iso*strychnic acid in the presence of Adams's catalyst. These authors thought that its facile dehydration indicated a *tert.*-alcoholic structure, but Boit prepared the corresponding *iso*tetrahydrostrychnidine and proved that this was not easily dehydrated. It is therefore, in all probability, a secondary alcohol, and *iso*tetrahydrostrychnine is (IV). The easy dehydration is conditioned by the β-situation of hydroxyl with respect to the carbonyl group.

The structure (III) for *iso*strychnic acid was therefore preferred to (II). At the time of publication of Boit's paper we had independently reached the same conclusion as the result of experiments on the partial synthesis of strychnine. After the discovery of a reactive methylene group in strychnine (benzylidenestrychnine, Perkin and Robinson, *J.*, 1929, 997), Wieland and Gumlich prepared hydroxyiminostrychnine (*iso*nitrosostrychnine) (*Annalen*, 1932, **494**, 191) and degraded it to the aldehyde (or semi-acetal) (V).

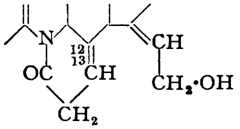
(V)

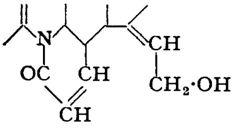
Our project was to reverse this process and build up strychnine from (V), obviously in the first stage by condensation of (V) with acetic acid or a reactive equivalent. This recalls a step in Woodward's theory of the biogenesis of strychnine (*Nature*, 1948, **162**, 155).

After several unsuccessful trials, for example, with acetic anhydride and sodium acetate, it was found that condensation occurred with malonic acid in pyridine solution with the addition of a little piperidine. The product was found to be *iso*strychnic acid, which is strong evidence of the correctness of the structure (III).

It should be pointed out that the term "*iso*strychnic acid" is a misnomer in that it suggests that the substance bears the relation to *iso*strychnine that strychnic acid bears to strychnine. Actually the hydrolysis of *iso*strychnine involves not only the opening of the lactam ring but also the closing of the oxide ring.

(VI)

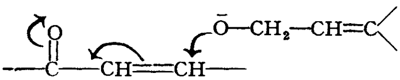




(VII)

Two isomeric *iso*strychnines are known, corresponding in constitution to strychninolones; *iso*strychnine-I ($[\alpha]_D$ +32°) is (VI) and is related to strychninolone-*b*, whilst *iso*strychnine-II ($[\alpha]_D$ −258°) is (VII) and is related to strychninolone-*c* (or, less probably, -*a*). Considering the experimental fact that (VI) yields (III) on treatment with hot alcoholic potassium hydroxide we note that there is no analogy or theoretical basis for the reaction unless it proceeds by initial conversion of *iso*strychnine-I into *iso*strychnine-II or a stereoisomeride of the same structure. The addition of the allylic alcohol to the αβ-unsaturated amide is then understandable; it resembles the transformation of a chalkone into a flavanone (see scheme on p. 984).

But this leads to a further deduction, namely, that in *iso*strychnic acid the configuration at position 12 must be inverted as compared with that in strychnine; for we know that the configuration of strychninolone-*a* (αβ-double bond) at position 12 is inverted in its transformation into strychninolone-*c* (αβ-double bond) by way of strychninolone-*b* (βγ-double bond).



The problem of the configuration at position 13 in (III) is more difficult. As this asymmetric centre is set up in an additive process to a double bond, adherence to the strychnine configuration would be groundless. A comparison of rotatory powers of relevant substances affords no sure guidance in this case, but inspection of the models suggests that inversion at position 13 should be a corollary of inversion at position 12. Moreover, inversion at position 13 supplies the best explanation of the failure of *iso*strychnic acid to lactamise under any conditions, and this is not only related to the use of models but also to the fact that dihydrostrychninolone-*c* is a stable cyclic amide.

We conclude that *both* centres, 12 and 13, of strychnic acid are inverted in *iso*strychnic acid.

The conversion of the Wieland–Gumlich aldehyde into *iso*strychnic acid is also a conversion into strychnine because Boit (*loc. cit.*) has effected the transformation of *iso*strychnic acid into *iso*strychnine-I and Prelog, Battegay, and Taylor (*Helv. Chim. Acta*, 1948, **31**, 2244) have obtained strychnine from *iso*strychnine-I. Under the condition of the experiment it is probable that three *iso*strychnines are equilibrated and only one of these is transformed into strychnine.

We have examined claims that *O*-acyl derivatives of *iso*strychnic acid can be prepared but have not been able to confirm them.

In connexion with the possibility that the Wieland–Gumlich aldehyde is a semi-acetal we place on record the formation of a methyl ether methiodide which probably contains the groups –CH(OMe)–O– and :N(*b*)Me}I.

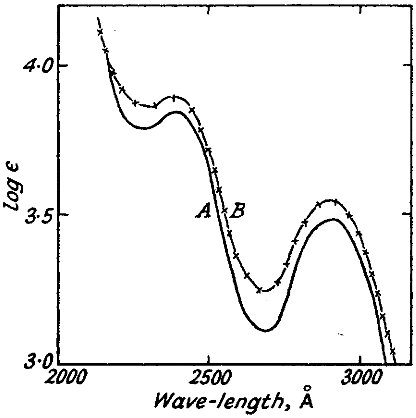
EXPERIMENTAL

The aldehyde, $C_{19}H_{22}O_2N_2$, was prepared according to the direction of Wieland and Gumlich (*loc. cit.*) and Wieland and Kaziro (*Annalen*, 1933, **506**, 70) and obtained as colourless plates, m. p. 215° (Found: C, 73·8; H, 7·3; N, 8·9. Calc. for $C_{19}H_{22}O_2N_2$: C, 73·6; H, 7·2; N, 9·0%). The *picrate* crystallised from acetone as yellow needles, decomp. 230° (Found: C, 56·0; H, 4·9. $C_{19}H_{22}O_2N_2,C_6H_3O_7N_3$ requires C, 55·7; H, 4·7%). The Wieland–Gumlich aldehyde afforded a hydroxamic acid derivative when heated in aqueous alcohol with benzenesulphohydroxamic acid and sodium carbonate. This gave an immediate deep reddish-purple colour with ferric chloride. The colour is easily distinguished from the strychnidine-type blood-red colour which ferric chloride develops as the result of oxidation of the aromatic amine system in the same molecule, and which requires a few seconds for development in the cold.

Reaction of the Wieland–Gumlich Aldehyde with Malonic Acid.—A mixture of the aldehyde $C_{19}H_{22}O_2N_2$ (3·2 g.), malonic acid (12 g.), pyridine (16 ml.), and piperidine (3 ml.) was heated on the steam-bath until evolution of carbon dioxide ceased. The solvents were removed on the steam-bath under reduced pressure, and the residual gum was taken up in water. The solution was made alkaline with sodium hydroxide, and the mixture of resin and unchanged aldehyde extracted with chloroform. The aqueous solution was neutralised exactly with acetic acid, and the solvent removed under reduced pressure until crystallisation of the amino-acid was observed. When crystallisation was complete, the amino-acid was separated, washed with a little water, and recrystallised from methanolic acetic acid (2·5% of acid). *iso*Strychnic acid (300 mg.) was obtained as colourless prisms, m. p. 244—245° (decomp.) with previous softening from 220°. The exact decomposition point observed depended on the rate of heating.

Authentic *iso*strychnic acid, prepared by Leuchs and Schulte's method (*Ber.*, 1943, **76**, 1038), was obtained from methanolic acetic acid as colourless prisms, decomp. 244—245° with previous softening. Leuchs and Schulte (*loc. cit.*) give m. p. 245—248° (vac.) (decomp.) and Siddiqui (*loc. cit.*) reports m. p. 240° (decomp.). A mixture of the acid prepared from the Wieland–Gumlich aldehyde and authentic *iso*strychnic acid decomposed at 245—250° with previous softening. The behaviour of the two specimens was identical in all respects; both were easily soluble in dilute acid and alkali, gave a positive ferric chloride reaction, but no Otto reaction; both were slightly soluble in hot water and almost insoluble in the usual organic solvents. The synthetic specimen had $[\alpha]_D^{18}$ −155° in dilute aqueous sodium hydroxide, and authentic *iso*strychnic acid had $[\alpha]_D^{18}$ −152·4°; Leuchs and Schulte (*loc. cit.*) report $[\alpha]_D^{20}$ −151°/d. The ultra-violet absorption spectra of the two specimens have also been compared (see Fig.); within the limits of experimental error they are identical, the small difference being attributable to a variation of concentration. Mrs. D. M. Hodgkin and Miss P. M. Cowan have kindly examined the two specimens by means of powder *X*-ray photographs, and report that they are identical.

Reaction of iso*Strychnic Acid with Benzoyl Chloride.*—The reaction was carried out according to the directions given by Siddiqui (*loc. cit.*). *iso*Strychnic acid (2 g.) was suspended in dry pyridine, and benzoyl chloride (0·9 g.) gradually added. The substance dissolved on shaking, and, on keeping, a crystalline hydrochloride was deposited, which was washed with ether and recrystallised from ethanol, being so obtained as colourless prisms, which softened at 170° and decomposed at 255—257°. After being dried at 100°/15 mm., the compound decomposed at 260° (Found: C, 61·7; H, 6·5; N, 6·8; Cl, 8·5, 8·6. Calc. for $C_{21}H_{26}O_4N_2$,HCl: C, 62·0; H, 6·6; N, 6·9; Cl, 8·7%). The behaviour on heating of authentic *iso*strychnic acid hydrochloride was identical, and the decomposition point was undepressed on admixture of the two specimens.



——— *Authentic* iso*strychnic acid.*
—×—×— iso*Strychnic acid prepared from the Wieland–Gumlich aldehyde.*

The corresponding base, obtained as colourless prisms from methanolic acetic acid, had m. p. 245—250° (decomp.), undepressed on admixture with authentic *iso*strychnic acid (Found: N, 7·5. Calc. for $C_{21}H_{26}O_4N_2$: N, 7·6%).

N-*Acetyl*iso*strychnic Acid.*—We followed the directions of Leuchs, Mengelberg, and Hemmann (*loc. cit.*) and converted the product into the perchlorate, which crystallised from water as colourless plates, m. p. 250° (decomp.) with previous frothing at 165—170° (Found: C, 53·5; H, 5·6; N, 5·5. $C_{23}H_{26}O_4N_2$,$HClO_4H_2O$ requires C, 53·8; H, 5·7; N, 5·5%). The free acetyl*iso*strychnic acid gave a positive Otto reaction, but no colour with ferric chloride. This preparation was also carried out according to the conditions given by Siddiqui (*loc. cit.*), but the only product isolated was identical with the above *N*-acetyl*iso*strychnic acid.

Methyl Ester of iso*Strychnic Acid.*—The *dihydrochloride* was prepared by the method of Leuchs, Mengelberg, and Hemmann (*loc. cit.*). It separated from methanol or ethanol as colourless prisms, which lose solvent when kept in an evacuated desiccator and decompose at 215—217° (Found, in dried material: C, 57·9; H, 6·6; N, 5·8; Cl, 15·7. $C_{22}H_{28}O_4N_2$,2HCl requires C, 57·8; H, 6·6; N, 6·1; Cl, 15·5%). The free ester could not be crystallised.

Action of Ethanolic Potassium Hydroxide on iso*Strychnic Acid.*—*iso*Strychnic acid (1 g.) was refluxed for 6½ hours with potassium hydroxide (1 g.) in ethanol (50 ml.). The solvent was removed under reduced pressure and the residue dissolved in an excess of dilute hydrochloric acid. The solution was heated on the steam-bath for an hour, then cooled and made alkaline. No precipitate was obtained, nor did chloroform extract any basic material from the aqueous layer. Under these conditions any strychnic acid produced should have cyclised to strychnine. On neutralisaton of the aqueous solution, *iso*strychnic acid was quantitatively recovered.

Methyl Ether of Wieland–Gumlich Aldehyde Methiodide.—The alkali-insoluble part of the product from the condensation of the Wieland–Gumlich aldehyde with malonic acid afforded no crystalline material directly. Its reactions suggested the presence of unchanged aldehyde.

A *methiodide*, decomposing above 215°, was obtained by treatment with methyl iodide in methanol and this crystallised from methanol in colourless prisms.

Also a *perchlorate* was prepared in methanolic solution. It was sparingly soluble in methanol and in water and was crystallised from aqueous acetic acid, being so obtained as colourless prisms, decomp. 250° (Found: C, 55·4; H, 5·9; N, 6·0; Cl, 7·7. $C_{20}H_{24}O_2N_2,HClO_4,0{\cdot}5C_2H_4O_2$ requires C, 55·4; H, 5·9; N, 6·2; Cl, 7·8%). These analyses suggested the possibility that the base concerned was the aldehyde methyl ether [–CH(OMe)–O–]. Hence the following experiment was made. A solution of the pure Wieland–Gumlich aldehyde (0·2 g.) in methanol (20 c.c.) containing a drop of 0·1N-hydrochloric acid was refluxed for 20 minutes and evaporated. The glassy residue could not be crystallised but addition of methyl iodide to its methanolic solution gave the above methiodide, decomposing above 215°, as was proved by a careful comparison of the crystals (Found: C, 54·4; H, 5·7; N, 6·0; I, 27·3. $C_{19}H_{22}O_2N_2,CH_3I$ requires C, 53·1. $C_{20}H_{24}O_2N_2,CH_3I$ requires C, 54·1; H, 5·8; N, 6·0; I, 27·3%). A mixture of the two specimens of the methiodide showed no change in the behaviour on heating.

The authors are grateful to the D.S.I.R. for a maintenance grant to one of them (J. E. S.).

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