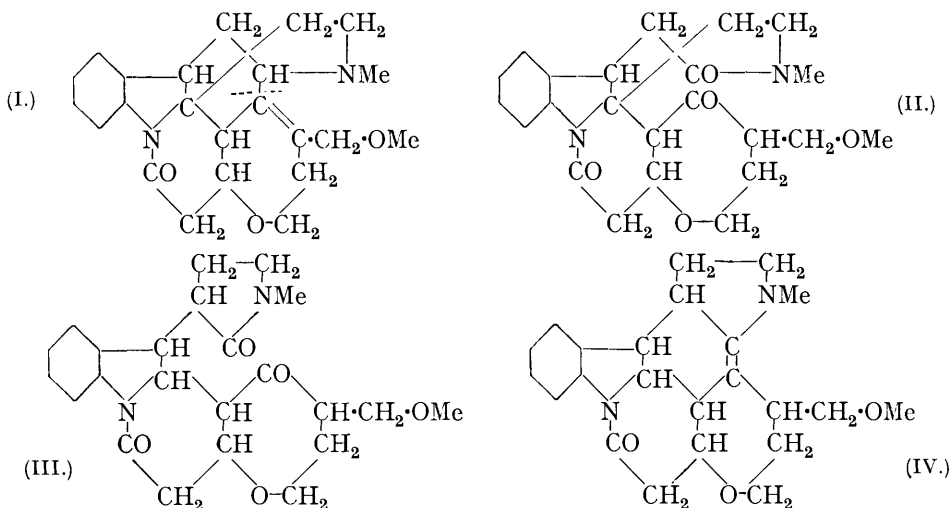


212. *Strychnine and Brucine. Part XXXIII. Methoxymethylchanodihydrostrychnanic Acid and its Resistance to Facile Dehydrogenation.*

By (Miss) T. M. REYNOLDS and ROBERT ROBINSON.

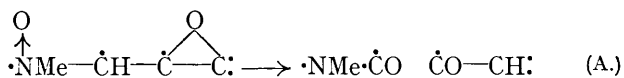
THE smooth oxidation of methoxymethyldihydro*neo*strychnine (I, containing the double bond in the position hitherto preferred for the *neo*-series of bases) (Achmatowicz, Clemo, Perkin, and Robinson, J., 1932, 767) by perbenzoic acid with formation of methoxymethylchanodihydrostrychnone (II) (Briggs and Robinson, J., 1934, 590) has recently been the subject of comment by Leuchs (*Ber.*, 1935, **68**, 292), who accepts the view that the product is a keto-amide, suggesting the usual modification of the ethylene-bridge (III) as the only variation from our formulæ.

Leuchs considers, however, that the formation of (III) proves that the double bond in the *neo*-bases is in the position shown in (IV) for methoxymethyl-dihydro-*neo*strychnine.

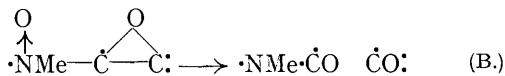


This is admittedly the direct and natural interpretation of the oxidation process when taken by itself, but there are other circumstances which must be considered. The double bond in (IV) has moved two steps from its original position; it seems more likely that only one step would be taken. Secondly, we have frequently contrasted the lability of the methoxy-group in the *neo*-series of bases with its stability in their dihydro-derivatives, in both cases towards acids. It seems likely, therefore, that the double bond is in the $\beta\gamma$ -position (allyl methyl ether type) to the methoxy-group. Thirdly, the $:C=C\cdot NMe$ system in (IV) might become $\cdot C\cdot\dot{C}\cdot NMe$ when the hydrochloride is formed and we do not know of any evidence of the formation of such quaternary salts from *neo*strychnine, *neo*strychnidine, or the methoxylated bases. To take one example, *neo*strychnidine forms a normal methiodide (not a *C*-methyl derivative which would be a possibility for the system $C=C\cdot N$) and it is immediately precipitated from solutions of its salts by ammonia.

These arguments are inconclusive, but we adhere to our original explanation, as a possibility to be investigated along with Leuchs's alternative, and we cannot admit that it can be ruled out on theoretical grounds. Such analogies as are available tend, in fact, to support our hypothesis that the process is indirect whatever the position of the double bond. We cannot find an instance of the fission of an olefin by perbenzoic acid in the sense $:C:C: + 2O \rightarrow :CO\ OC:$. The points of attack would be the tertiary nitrogen atom and the double bond and we think that the rearrangement (A) is a no more improbable event



than the rearrangement (B). So we are unable to accept the suggestion that oxidative

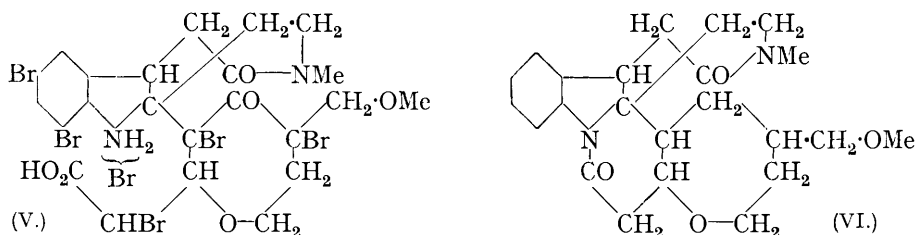


scission at the dotted line in (I) is incredible.

The further difficulties which Professor Leuchs finds depend on the acceptance of his point of view in regard to the mechanism of the oxidation and therefore no reply to the points raised is called for beyond a reaffirmation of the consistency of our position on the basis of the original conception of the structure of the *neo*-bases.

As the result of further investigations, the possibility (Reynolds and Robinson, J., 1934, 592) that methoxymethyl-*chanodihydrostrychnone* might be an aldehyde is not now

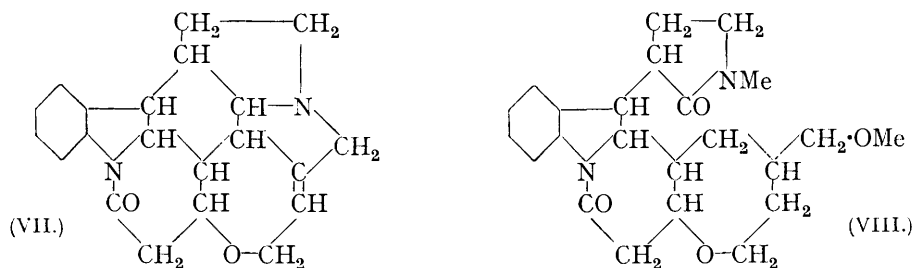
entertained. It was recovered quantitatively after being refluxed in aqueous solution with yellow mercuric oxide for one hour, and attempts to oxidise it with bromine and hydrobromic acid yielded a substance which reacted with sodium hydroxide and Fehling's solution in the manner characteristic of the original substance and appeared to be *penta-bromomethoxymethylchanodihydrostrychnonic acid hydrobromide* (V). Since the method of



preparation of methoxymethylchanodihydrostrychnone by means of perbenzoic acid in ether, where the ether-insoluble product separates immediately, precludes the possibility of further action by the oxidising agent, the process was carried out in chloroform solution at 40–50°; no heat was evolved after two molecular proportions of perbenzoic acid had been added, and (II) appeared to be the sole product of the reaction. As already stated (Briggs and Robinson, *loc. cit.*), (II) is stable to permanganate under usual conditions and owing to the ease with which it undergoes auto-condensation other oxidising agents have yielded only amorphous unidentified products.

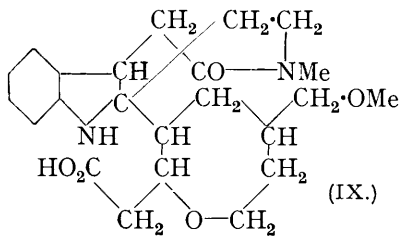
In view of the probable analogy between methoxymethylchanodihydrostrychnone and the substances obtained by the permanganate oxidation of *neostrychnidine* (Clemo, Perkin, and Robinson, J., 1927, 1589; cf. Briggs and Robinson, *loc. cit.*), *neobrucidine*, methoxymethylidihydroneobrucidine (Gulland, Perkin, and Robinson, J., 1927, 1627), and methoxymethylidihydroneostrychnidine (Leuchs, Beyer, and Schulte-Overberg, *Ber.*, 1933, 66, 1384), it seemed desirable to make further attempts to isolate a crystalline product from a similar oxidation of methoxymethylidihydroneostrychnine, and an experiment is now described from which methoxymethylchanodihydrostrychnone has been obtained in 10% yield. It is highly probable that the yield can be increased and the reaction is being further investigated, but a mixture of substances is obtained, whereas oxidation with perbenzoic acid yields a remarkably pure product.

We have frequently expressed the view that strychnine and its derivatives must contain a blocked dihydro-indole nucleus because the formation of aromatic indole derivatives in oxidation processes has not been observed. Against this it may be held that the stereochemistry of the complex ring system of strychnine stabilises the reduced indole nucleus, but, if our interpretation of the experimental evidence is correct, this resource is not available in the case of methoxymethylchanodihydrostrychnane (VI), the product of the Clemmensen reduction of (II) (Reynolds and Robinson, *loc. cit.*). On the basis of the formula (VII) for strychnine this compound would have the structure (VIII) and there



does not seem to be any reason why it should not be easily oxidised to an indole derivative. Nevertheless we find that it can be recovered after being heated at 100° in glacial acetic acid solution with an excess of mercuric acetate for four hours and

after being heated in boiling naphthalene with sulphur for thirty minutes. In confirmation of these results we have also prepared *methoxymethylchanodihydrostrychnanic acid* (IX) and compared its behaviour towards dehydrogenating agents with that of *cis*-hexahydrocarbazole. Conditions have been found whereby hexahydrocarbazole may be converted into tetrahydrocarbazole by means of mercuric acetate in dilute acetic acid solution in the cold or by means of sulphur in quinoline solution at 175–180°; in parallel experiments methoxymethylchanodihydrostrychnanic acid was recovered unchanged.



Methoxymethylchanodihydrostrychnanic acid was obtained from methoxymethylchanodihydrostrychnane by the action of hot 12% methyl-alcoholic barium hydroxide in an atmosphere of nitrogen; the reverse process could be effected by refluxing a solution of the acid in 5% hydrochloric acid for thirty minutes or by heating it at 180–185° in naphthalene, showing that no structural change had occurred. The stability of the -N(b)CO- group is noteworthy; its presence is, however, confirmed, because the strychnanic acid is acid to litmus and it yields a *nitrosoamine* which does not form a hydrochloride. The colour reactions of the acid show that the group :N(a)CO is the one that is hydrated.

EXPERIMENTAL.

Pentabromomethoxymethylchanodihydrostrychnonic Acid Hydrobromide (V).—A mixture of methoxymethylchanodihydrostrychnone (0.5 g.), water (12 c.c.), and 2*N*-bromine in hydrobromic acid (6 c.c.) was gently refluxed and after 10 minutes a further quantity (4 c.c.) of 2*N*-bromine in hydrobromic acid was added. The mixture was heated again for 10 minutes, the excess of bromine was removed under diminished pressure, and the brown tar which separated on cooling was triturated with water, giving a brownish-yellow solid insoluble in chloroform, benzene, and ether, almost insoluble in water, but freely soluble in acetone and hot alcohol. It separated from methyl alcohol in an apparently microcrystalline form when concentrated hydrobromic acid was added to the hot solution just before the solid began to separate: it was recrystallised twice in this way, giving an orange-yellow solid which softened and darkened at 152° and decomposed at 157° [Found: loss in a high vacuum at 105°, 3.6. Found in dried material: C, 30.1; H, 2.5; Br, 53.2; Me(MeO + MeN), 3.1. $\text{C}_{23}\text{H}_{26}\text{O}_6\text{N}_2\text{Br}_6$ requires C, 30.5; H, 2.9; Br, 53.0; 2Me, 3.3%]. The substance was soluble in cold 5% aqueous sodium hydroxide to a brown solution, but a yellow amorphous precipitate was thrown down on heating; it dissolved in hot aqueous sodium carbonate, reduced Fehling's solution, and gave no ferric reaction in dilute acid solution; with 60% sulphuric acid and a drop of potassium dichromate solution an intense stable crimson coloration was developed.

Permanganate Oxidation of Methoxymethyldihydrostrychnine.—A solution of methoxymethyldihydrostrychnine (3.75 g.) in pure acetone (150 c.c.) was maintained at -10° while powdered sieved (80-mesh) potassium permanganate (4.5 g.) was added with mechanical stirring during 90 minutes. After a further 2 hours' stirring, the excess of permanganate in the filtered solution and washings (cold acetone) was removed by sulphur dioxide and the clear yellow solution was concentrated to a syrup under diminished pressure at room temperature. The residue was dissolved in chloroform (50 c.c.), and the solution washed thrice with 7% hydrochloric acid, once with water, dried over magnesium sulphate, and evaporated to a syrup, which solidified when triturated with ether (2 g.). This amorphous material became syrupy in air or in contact with solvents; it was dissolved in a little warm ethyl acetate, ether added to produce a turbidity, and the crystals which separated on cooling were recrystallised in the same way and found to consist of methoxymethylchanodihydrostrychnone (0.3 g.) (m. p. and undepressed mixed m. p.).

Methoxymethylchanodihydrostrychnanic Acid (IX).—Anhydrous barium hydroxide (18 g.) was dissolved as far as possible in boiling methyl alcohol (100 c.c.) and air was excluded by means of a stream of nitrogen (washed with alkaline pyrogallol). A solution of methoxymethylchanodihydrostrychnane (4.5 g.) in methyl alcohol (40 c.c.) was introduced, and the mixture refluxed for 4 hours. The light reddish-brown solution was cooled, just acidified with acetic acid, and concentrated under diminished pressure; water was added to the residue, and the solution extracted thrice with chloroform. The combined extracts were washed twice

with 5% sodium hydroxide solution and once with water, dried, and evaporated; the residue gave after recrystallisation pure methoxymethylchanodihydrostrychnane (1.5 g.). The alkaline aqueous solution was acidified with acetic acid and shaken with chloroform; the chloroform layer was washed with water, dried, and concentrated to a syrup, which crystallised when triturated with a little aqueous alcohol. The solid, recrystallised from 50% alcohol, formed clusters of needles consisting of almost pure *methoxymethylchanodihydrostrychnanic acid* (1 g., m. p. 199—200° after softening at 197°). Further recrystallisation from the same solvent raised the m. p. to 205—206°, with slight darkening and the evolution of gas, after softening at 203° [Found: C, 66.4; H, 7.6; N, 6.8; MeO, 8.1; Me(MeO + MeN), 8.4; no loss in a high vacuum at 80°. $C_{23}H_{32}O_5N_2$ requires C, 66.3; H, 7.7; N, 6.7; 1MeO, 7.5; 2Me, 7.2; 2.33Me, 8.4%]. The high value obtained for MeO must be attributed to a partial liberation of MeI from MeN, and the low value for Me(MeO + MeN) is evidently due to further decomposition of the molecule under the drastic conditions employed (under the same conditions methoxymethylchanodihydrostrychnane gave Me, 7.5. Calc. for $C_{23}H_{30}O_4N_2$: 2Me, 7.5%). Methoxymethylchanodihydrostrychnanic acid is readily soluble in acetone, chloroform, and hot alcohol, very slightly soluble in hot water and hot benzene, and almost insoluble in ether and light petroleum. It dissolves easily in cold hydrochloric acid (0.1—10%) and in aqueous sodium hydroxide and sodium bicarbonate; it is acid to litmus; it gives a stable orange-red coloration in 60% sulphuric acid on the addition of a drop of potassium dichromate solution. The ferric reaction is best shown in aqueous solution—a faint pink in the cold, becoming an intense red on heating and then fading in about 2 seconds to pale yellow with the separation of a pale yellow precipitate; similar but more transient reactions are observed in 0.1% and 1% hydrochloric acid and in the latter case very little precipitate is formed.

Regeneration of Methoxymethylchanodihydrostrychnane from (IX), including an Attempt to dehydrogenate the Acid.—(A) A solution of methoxymethylchanodihydrostrychnanic acid (0.1 g.) in 5% hydrochloric acid (4 c.c.) was refluxed for 30 minutes, cooled, and basified with 40% aqueous sodium hydroxide. The pink syrup which separated was triturated with water and then with ether; it was dissolved in benzene, and light petroleum added drop by drop until all the coloured material had been precipitated. The solution was decanted and crystals of methoxymethylchanodihydrostrychnane were obtained by the addition of ether and identified by m. p. and mixed m. p. with an authentic specimen.

(B) A mixture of methoxymethylchanodihydrostrychnanic acid (0.7 g.), sulphur (0.06 g.), and naphthalene (6 g.) was heated at 185° for 10 minutes and cooled, and the naphthalene dissolved as far as possible in light petroleum. The residue was dissolved in dilute hydrochloric acid, the solution extracted with light petroleum and then with chloroform, and the chloroform layer washed with water, dried, and evaporated, yielding methoxymethylchanodihydrostrychnane (0.3 g.) (m. p. and mixed m. p.).

N(a)-Nitrosomethoxymethylchanodihydrostrychnanic Acid.—Methoxymethylchanodihydrostrychnanic acid (0.1 g.) was dissolved in 5% hydrochloric acid (2 c.c.) by gentle heating, the solution cooled in ice, and sodium nitrite (0.2 g.) in water (0.5 c.c.) added. The mixture immediately became a semi-solid, pale yellow mass and, after dilution with a little water, the semicrystalline product was collected and rubbed with alcohol, inducing crystallisation. It was recrystallised from alcohol, forming pale yellow needles, decomp. 190° after softening and darkening at 187° (Found: C, 62.0; H, 7.1; N, 9.5. $C_{23}H_{31}O_6N_3$ requires C, 62.0; H, 7.0; N, 9.4%). The *nitrosoamine* was soluble in aqueous sodium carbonate and was very faintly acid to litmus; with aqueous ferric chloride it gave a pink coloration in the cold, becoming a stable red on warming, but it gave only a pale yellow with ferric chloride in 0.1% or 1% hydrochloric acid; it gave in 60% sulphuric acid a pinkish-orange solution, deepening to red on addition of potassium dichromate.

Methoxymethylchanodihydrostrychnane.—In describing the preparation of this compound (Reynolds and Robinson, *loc. cit.*) no mention was made of the strychnidine compound which was formed. Repeated efforts to isolate this substance have failed, but its presence is indicated by the intense ferric reaction in dilute hydrochloric acid exhibited by the mother-liquors and sometimes by the crude crystalline strychnane. Repeated crystallisation is required for the elimination of the last traces of this strychnidine derivative, the ferric reaction in hot hydrochloric acid being a better guide than the m. p.

Electrolytic reduction of methoxymethylchanodihydrostrychnane under the conditions used for the preparation of strychnidine from strychnine gave no new crystalline compound. The syrups obtained gave a strong reaction with *p*-dimethylaminobenzaldehyde indicative of an indole derivative with a free β -position; they also gave a ferric reaction, not, however,

of the usual strychnidine type, since it was of equal intensity in 1% and 15% hydrochloric acid.

Attempts to dehydrogenate Methoxymethylchanodihydrostrychnane.—It has been shown (Perkin and Plant, J., 1921, 119, 1825; 1923, 123, 676) that tetrahydrocarbazole may be oxidised to carbazole by the action of mercuric acetate in acetic acid solution at 100°, or of sulphur in boiling quinoline, and similar conditions were therefore employed in the present experiments.

(A) A solution of methoxymethylchanodihydrostrychnane (0.25 g.) in glacial acetic acid (2 c.c.) was mixed with one of mercuric acetate (0.25 g.) in the same solvent (2 c.c.) and heated in a boiling water-bath for (1) 15 minutes, (2) 4 hours, with the addition of a further quantity of mercuric acetate (0.2 g.) after 2 hours in the second case. In both experiments the light brown solutions obtained were diluted with water, saturated with hydrogen sulphide, filtered, and extracted with chloroform. The chloroform layer yielded a solid, which was recrystallised from benzene-light petroleum and proved to be methoxymethylchanodihydrostrychnane by m. p. and mixed m. p. (yield, 0.1—0.2 g.).

(B) Methoxymethylchanodihydrostrychnane (0.75 g.) and sulphur (0.25 g.) were dissolved by heating in naphthalene (10 g.), and the solution then refluxed for 30 minutes; it darkened and a little hydrogen sulphide was evolved, but on cooling and extraction with light petroleum a dark solid remained which yielded only methoxymethylchanodihydrostrychnane (0.3 g.).

Oxidation of cis-Hexahydrocarbazole to Tetrahydrocarbazole.—(A) Mercuric acetate (4 g.), added to a solution of hexahydrocarbazole (0.5 g.) in 50% acetic acid (14 c.c.), dissolved in the cold on shaking; a solid began to separate immediately and after 24 hours the liquid had become yellow with a green fluorescence and was half-filled with a colourless sticky precipitate. The solid was isolated, washed with 50% acetic acid, and suspended in a mixture (approximately 3 : 2) of hot 50% acetic acid and acetone, which was then saturated with hydrogen sulphide and filtered hot. On evaporation of some of the acetone and addition of water, almost pure tetrahydrocarbazole (0.2 g.) separated, and a further quantity was obtained by concentrating the filtrate.

(B) Hexahydrocarbazole (1 g.) and sulphur (0.5 g.) were dissolved in quinoline (8 c.c.) and heated at 175—180° for 10 minutes. The cooled solution was added to an excess of dilute hydrochloric acid and the solid which separated was collected and washed with water. It consisted of a mixture of tetrahydrocarbazole and a substance formed by the action of sulphur on quinoline. The former was obtained by extraction with a little hot alcohol, filtration, and addition of a little water to the filtrate (yield, 0.2—0.3 g.). Hexahydrocarbazole is not oxidised at lower temperatures under the above conditions.

Attempts to oxidise Methoxymethylchanodihydrostrychnanic Acid.—(A) Mercuric acetate (0.2 g.) was dissolved in a cold solution of methoxymethylchanodihydrostrychnanic acid (0.1 g.) in 50% acetic acid (2 c.c.). Crystals began to separate slowly after about 30 minutes and a mass of rosettes of colourless needles was formed over-night; after 24 hours the solid was collected and the colourless filtrate was diluted with acetone, warmed, saturated with hydrogen sulphide, filtered, and evaporated; there was no residue. The solid was suspended in a mixture of 50% acetic acid and acetone and treated in the usual way, giving unchanged methoxymethylchanodihydrostrychnanic acid, recovered quantitatively.

When the substance was heated at 100° with mercuric acetate in glacial acetic acid solution, considerable decomposition occurred and it was not possible to determine whether oxidation of the normal type had taken place.

(B) Methoxymethylchanodihydrostrychnanic acid (0.4 g.) and sulphur (0.03 g.) were dissolved in quinoline (4 c.c.) by warming and the solution was heated at 175—180° for 10 minutes and then cooled and poured into an excess of 10% acetic acid. The brown solution was extracted with chloroform, the chloroform layer washed with 5% sodium hydroxide solution, and the alkaline extract acidified with acetic acid and treated in the usual way, giving unchanged methoxymethylchanodihydrostrychnanic acid (0.2 g.). No other substance could be isolated from the residual chloroform or aqueous solution.

As stated above, methoxymethylchanodihydrostrychnanic acid was converted into methoxymethylchanodihydrostrychnane at higher temperatures.

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