16. *Strychnine and Brucine. Part XLVI. The Preparation of* neo*Strychnine and* neo*Brucine.*

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Strychnine and brucine are converted into the respective *neo*-isomerides by treatment with Raney nickel in boiling xylene. The process provides a convenient method of preparation of the bases and indicates that the isomeric change is essentially a dehydrogenation–hydrogenation.

When methylstrychnine or strychnine methosulphate is heated with methanolic sodium methoxide, or methanol and sodium amalgam, it is converted into methoxymethyldihydro-*neo*strychnine. Reconstitution of the quaternary salt with elimination of methanol occurs under the influence of hot 20% sulphuric acid and, after conversion into the methochloride by way of the methiodide, careful pyrolysis affords *neo*strychnine. The methiodide of this base is identical with the salt obtained as already mentioned and is convertible to methoxymethyldihydro*neo*strychnine in the same way as strychnine methosulphate (Part XVI, Achmatowicz, Clemo, Perkin, and Robinson, *J.*, 1932, 767).

These changes paralleled earlier observations in the strychnidine series and, since *neo*strychnidine and *neo*strychnine can be reduced to dihydrostrychnidine-A and dihydrostrychnine respectively, it was clear that the conversion into the *neo*isomerides involved no change in the carbon–nitrogen–oxygen skeleton, but only a new position of the double bond. Furthermore, the unsaturation of the methoxymethyldihydro-bases is already in this new position.

As the shift occurred under the influence of a strong base, the usual migration to an adjacent position was postulated. In Part XLII, however, it has been indicated that *neo*strychnine contains the group $:C{=}\dot{C}{-}N(b):$ and therefore the ethylene linkage of strychnine moves at least two steps in the formation of *neo*strychnine. There is no sign of the formation of intermediate products and hence we came to regard the transformation as a dehydrogenation–hydrogenation. It is perhaps analogous to that which occurs when oleic acid is heated with potassium hydroxide and palmitic acid is formed. In one sense the idea is a truism because all shifts of double bonds are necessarily oxidation–reduction processes.

From this point of view the interesting observation of Kotake and Yokohama (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 321) that strychnine is convertible into *neo*strychnine by heating with selenium, is readily understood. Consideration of the mechanism of the reaction suggested the probable formation of dehydrostrychnine and hydrogen selenide, followed by reduction of the former by the latter. The method is more convenient than the indirect one mentioned above, but it is not so satisfactory as the new process described in the present communication.

It occurred to us that a cleaner preparation might be based on the use of a hydrogenating catalyst. It was found that strychnine and brucine could be converted into the *neo*-bases by refluxing their xylene solutions with Raney nickel; the yields were almost theoretical and about 85% was readily obtained in a pure condition. *neo*Strychnine and *neo*brucine are now very readily accessible and a comprehensive study of their properties and transformations is in progress.

EXPERIMENTAL.

neo*Strychnine.*—Under the conditions of Kotake and Yokohama (*loc. cit.*) the yield of *neo*strychnine obtained by heating strychnine with selenium was found to be 15%. Using a quarter of the prescribed amount of selenium and a lower temperature the yield was increased to 50%.

Strychnine (50 g.) and selenium (25 g.) were powdered together and the mixture was heated at 260° until it melted, and then at 235° for an hour. The product was worked up as described by the Japanese chemists and gave 24 g., m. p. 228°.

In our first experiment with Raney nickel (prepared according to *Org. Synth.*, **21**, 15), 90% alcohol was used as solvent and although some conversion occurred at the boiling point, and *neo*strychnine could be isolated, other products were formed, purification was difficult, and the yield was unfavourable.

Raney nickel (about 1 c.c. of the sediment stored under alcohol) was thoroughly washed with dry xylene, drained, and dry xylene (400 c.c.) and powdered strychnine (50 g.) added. The whole was refluxed for 20 hours; the strychnine disappeared in 5—6 hours and the process is probably completed after 10 hours, but the longer period is advisable as contamination with strychnine hinders the purification of the product. The hot filtered solution deposited *neo*strychnine mixed with a little finely divided nickel; the solid was dissolved in chloroform, filtered through a fine paper, and the solution mixed with an equal volume of ether. Pure *neo*strychnine crystallised in transparent hexagonal plates, m. p. 228° (43 g.), and about 4—5 g. of less pure material could be obtained from the xylene mother liquors.

Success depends on the use of fresh Raney nickel and the exclusion of water and alcohol.

The *neo*strychnine crystallised from alcohol in glistening hexagonal plates or from aqueous alcohol in long needles. The m. p. was not depressed by mixture with a specimen obtained by the selenium process. For confirmation of identity it was converted into the *N*-oxide (Part XVI, *loc. cit.*), m. p. 179—180°, and by the action of methyl iodide in hot acetone into the methiodide, m. p. 325° in agreement with Part XVI (Kotake and Yokohama, *loc. cit.*, give m. p. 315°). The characteristic reaction with *p*-nitrobenzenediazonium chloride described in Part XLII was observed and this affords a distinction from strychnine that could doubtless be developed into a method of analysis of mixtures. We are unable to confirm the statement of Kotake and Yokohama (*loc. cit.*) that *neo*strychnine is changed by 6N-hydrochloric acid. The base dissolves in N-hydrochloric acid but the hydrochloride rapidly crystallises from the solution. Many experiments on the action of hydrochloric acid, dilute and concentrated, hot and cold, on the base left it unchanged. It was also recovered after treatment with boiling dilute acetic acid, glacial acetic acid, alone or mixed with pyridine, and boiling *iso*amyl alcohol containing a little acetic acid. It exhibits therefore no tendency to hydrolyse at the C=C–N group, or to undergo the theoretically possible transformation to dihydro-ψ-strychnine, or a derivative thereof.

Action of Perbenzoic Acid on neo*Strychnine.*—The result of this experiment exemplifies the general proposition that the double bond in *neo*strychnine is far less reactive than that in methoxymethyldihydro*neo*strychnine. The latter is converted by perbenzoic acid into methoxymethyl*chano*dihydrostrychnone by addition of two oxygen atoms (Briggs and Robinson, *J.*, 1934, 590) but *neo*strychnine gives only the *benzoate* of its *N*-oxide.

A solution of *neo*strychnine (3·34 g.) in pure dioxan (100 c.c.) was treated at 35—40° with a solution of perbenzoic acid (cf. Kötz and Steche, *J. pr. Chem.*, 1927, **107**, 203; Lewin, *ibid.*, 1930, **127**, 81) in ether (80 c.c.). After 5 minutes the product separated as snow-white crystals which were collected, washed with ether, and dried (3·62 g.). The substance is soluble in chloroform and dilute aqueous sodium hydroxide, but is insoluble in dilute acids. It crystallises from water in colourless plates, m. p. 183—184° (Found in material dried in a vacuum at the room temperature: C, 69·3, 69·9, 69·6; H, 5·9, 5·9, 6·0; N, 5·9. $C_{21}H_{22}O_3N_2,C_6H_5{\cdot}CO_2H,\frac{1}{2}H_2O$ requires C, 69·8; H, 6·0; N, 5·8%). The substance loses benzoic acid on heating and hence the content of water could not be determined in this way. It is retained after crystallisation from chloroform–ether. This salt can be obtained by mixing hot aqueous solutions of *neo*strychnine *N*-oxide and benzoic acid (1 mole), and on treatment with sulphurous acid it is reduced to *neo*strychnine. The action of perbenzoic acid on strychnine itself was found by Kotake and Mitsuwa (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 217) to be similar. The product was a benzoate of the *N*-oxide, $C_{21}H_{22}O_3N_2,C_6H_5{\cdot}CO_2H,H_2O$, a substance earlier made from its components by Polonovski and Polonovski (*Bull. Soc. chim.*, 1926, **39**, 1165), whose memoir was not cited by Kotake and Mitsuwa.

neo*Brucine*.—A mixture of powdered brucine (50 g.), Raney nickel (1 c.c. of the alcohol-moist sediment), and xylene (300 c.c.) was distilled. After 15 c.c. had been collected, boiling was continued under reflux for 12 hours. The base was isolated exactly as described for *neo*strychnine and 42 g. of transparent prismatic needles, m. p. 227°, obtained after crystallisation from chloroform–ether (Found: C, 69·7, 69·7; H, 6·6, 6·5. Calc. for $C_{23}H_{26}O_4N_2$: C, 70·0; H, 6·6%). A further few g. could be obtained by concentration of the xylene mother liquor. Addition of *p*-nitrobenzenediazonium chloride to an acid solution gave a yellow precipitate.

The *methosulphate* was prepared from the base (4 g.) and methyl sulphate (1·6 c.c.) in warm methanol (10 c.c.). It crystallised from the cold solution and was recrystallised from water and obtained as colourless, well-defined needles, and from methanol as glistening leaflets, m. p. 252° (decomp.) (Found in material dried at 130°: C, 57·0, 57·3; H, 6·3, 6·3. $C_{23}H_{26}O_4N_2,Me_2SO_4$ requires C, 57·6; H, 6·1%). Double decomposition with sodium iodide gave the methiodide, m. p. 305° (decomp.) [Achmatowicz, Perkin, and Robinson, *J.*, 1932, 775, give m. p. 302—306° (decomp.) and m. p. 225—226° for *neo*-brucine], which was also obtained directly from *neo*brucine and methyl iodide.

This methiodide afforded methoxymethyldihydro*neo*brucine, m. p. 205°, when it was treated with methanolic sodium methoxide as described by Achmatowicz, Perkin, and Robinson for methylbrucine; the m. p. 204—205° was given by these authors. As the yield from methylbrucine was only 15% and this substance was previously the only source of *neo*brucine, the advantage of the new method is clear.

*Benzylidene*neo*brucine*.—Potassium hydroxide (0·2 g.) in water (1 c.c.) was added to a boiling solution of *neo*brucine (1 g.) and benzaldehyde (1 c.c.) in alcohol (10 c.c.). The clear orange solution was concentrated somewhat under diminished pressure and diluted with water. The flocculent precipitate was collected and crystallised from methanol; canary yellow, silky needles of the *compound* were thus obtained, m. p. 211° (decomp.) (Found: C, 74·2, 74·4; H, 6·3, 6·3. $C_{30}H_{30}O_4N_2$ requires C, 74·6; H, 6·2%).

neo*Brucine* N-*Oxide*.—*neo*Brucine (2 g.) was heated on the steam-bath with hydrogen peroxide (20 c.c. of 6%) with occasional shaking; a clear solution was obtained in an hour. The filtered solution was concentrated under diminished pressure; the N-*oxide* then crystallised. It separated from water in glistening plates, m. p. 168°, which lost solvent of crystallisation at 100° (Found: loss at 130°, 8·6, 7·7. $C_{23}H_{26}O_5N_2,2H_2O$ requires H_2O, 8·1%). The anhydrous *base*, m. p. 222° (decomp.), is hygroscopic and is also obtained as glistening plates, m. p. 222° (decomp.), by crystallisation from methanol (Found in material dried at 130° with little loss: C, 67·4; H, 6·1. $C_{23}H_{26}O_5N_2$ requires C, 67·3; H, 6·3%). The *N*-oxide is reduced to *neo*brucine by hot aqueous sulphurous acid. It gives the brucine–nitric acid reaction.

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