140. *Strychnine and Brucine. Part XLIX. A New Method for the Preparation of Pseudostrychnine.*

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It is found that strychnine *N*-oxide is changed into pseudostrychnine (hydroxystrychnine) by treatment with an aqueous solution of potassium chromate at 100°. This process is the best available for the preparation of the substance. In the brucine series the yield is less favourable, and one of Leuchs's brucones is obtained as a by-product.

FREUND and SPEYER (*Ber.*, **1911**, **44**, 2339) found that treatment of the *N*-oxide of codeinesulphonic acid with potassium chromate gave formaldehyde and a substance believed to be $C_{18}H_{23}O_8NS$ but which on de-sulphonation afforded $C_{17}H_{19}O_3N$, isomeric with morphine. Diels and Fischer (*Ber.*, 1916, **49**, 1721) showed that this base is norcodeine previously obtained by the ethyl azodicarboxylate method (*idem*, *Ber.*, **1914**, **47**, 2043), also that the Freund and Speyer product is $C_{17}H_{19}O_6NS$ and further that this *N*-demethylation procedure can be applied to codeine itself. Although advantage has been taken of these observations in the manufacture of *N*-allylnorcodeine, very few, if any, further applications of the method have been reported.

It occurred to us that it might well be generally available for the fission of tertiary amines, and that in a polycyclic system the result should be the formation of a carbinol-amine. Thus in the case of strychnine the product should be pseudostrychnine or an isomeride.

Actually, pseudostrychnine is obtained as the modification of higher melting point, convertible into that of lower melting point by the known methods. The formation of this modification is doubtless connected with the fact that it crystallises from a hot aqueous solution, and the plausible analogy with the separation of β-glucose under similar conditions is under examination.

The smooth reaction here realised leads us to suggest that the oxidation of strychnine by atmospheric oxygen in the presence of co-ordinated cupric derivatives (Leuchs, *Ber.*, 1937, **70**, 1543) takes a similar course. Indeed, strychnine *N*-oxide was actually isolated a by-product of the oxidation.

This view is supported by the fact that the action of potassium chromate on brucine *N*-oxide affords pseudobrucine together with that brucone which Leuchs and Boit (*Ber.*, 1940, **73**, 884) obtained as one of the products of the catalysed aerial oxidation of brucine. The potassium chromate may be replaced, but without advantage, by an equivalent amount of chromic acid or potassium dichromate.

EXPERIMENTAL.

Pseudostrychnine.—As usually prepared, strychnine *N*-oxide contains hydrogen peroxide which replaces a part of the water in the crystals. This affects the yield adversely and the following method was adopted.

A mixture of strychnine (50 g.), water (150 c.c.), and hydrogen peroxide (30 c.c. of 30%) was heated for 1 hour at 100°, boiled for 5 minutes, filtered, and cooled. The separated crystals were dissolved in hot water (120 c.c.) and the solution boiled for 5 minutes with platinum wire; 53 g. (88%) of the hydrated *N*-oxide separated; m. p. 205—207° (Pictet, *Ber.*, 1907, **40**, 1172, gives m. p. 207°).

A solution of this material (20 g.) in water (100 c.c.) was heated in boiling water, and potassium chromate (1 g.) in water (5 c.c.) added. After 5—10 minutes the solution clouded and soon filled with long needles; the reaction was completed in 45 minutes. The mixture was cooled, the solid collected, washed with water, and ether, and dried in a vacuum over phosphoric anhydride (yield, 15—17 g.) (Found: loss at 100° in a vacuum, 7·7. $C_{21}H_{22}O_3N_2,1{\cdot}5H_2O$ requires 7·2%). The water is lost at 180—190°, and the substance then had m. p. 253—257 (decomp.) with previous sintering (Leuchs, *loc. cit.*, gives m. p. 262°, and Warnat, *Helv. Chim. Acta*, 1931, **14**, 999, gives m. p. 268°). This product is sufficiently pure for many purposes. It was crystallised by addition of ether to its solution in chloroform, and was then dissolved in dilute hydrochloric acid and precipitated with ammonia. This treatment afforded the lower melting isomeride, m. p. 235—237° (decomp.), $[\alpha]_D^{18^\circ}$ − 63° (*c*, 1·63 in chloroform) (Leuchs, *loc. cit.*, gives m. p. 233°, $[\alpha]_D^{20^\circ}$ − 69°) (Found in material dried in high vacuum at 130°: C, 71·7; H, 6·5; N, 8·3. Calc. for $C_{21}H_{22}O_3N_2$: C, 72·0; H, 6·3; N, 8·0%).

The perchlorate crystallised from water in stout needles which in agreement with Blount and Robinson (*J.*, 1932, 2305) darkened at 235—240° but did not melt at 300° (Leuchs, *Ber.*, 1937, **70**, 1703, reports that the salt sinters at 250° and decomposes at 260—270°) (Found: loss at 100° in a vacuum, 0·9%; in dried material, C, 55·5; H, 5·2; N, 6·2; Cl, 7·8. Calc. for $C_{21}H_{22}O_3N_2,HClO_4$: C, 55·9; H, 5·1; N, 6·2; Cl, 7·9%).

The methyl ether was prepared from the crude reaction product in the usual manner; it crystallised from methanol in long needles, m. p. 196—198° (decomp.), $[\alpha]_D^{15^\circ}$ − 64° (*c*, 0·89 in chloroform) (Found: C, 72·0; H, 6·7. Calc. for $C_{22}H_{24}O_3N_2$: C, 72·5; H, 6·6%). Warnat (*loc. cit.*) gives m. p. 198—200°, $[\alpha]_D^{20^\circ}$ − 70°; Leuchs (*loc. cit.*) gives m. p. 190°, $[\alpha]_D^{20^\circ}$ − 75°; David (private communication, material prepared according to Leuchs) finds $[\alpha]_D^{20^\circ}$ − 69°.

The ethyl ether crystallised from ethanol in slender matted needles, m. p. 217—219° (decomp.), $[\alpha]_D^{16^\circ}$ − 51° (*c*, 0·92 in chloroform) (Found: C, 72·9; H, 6·9; N, 7·2. Calc. for $C_{23}H_{26}O_3N_2$: C, 73·0; H, 6·9; N, 7·4%). Its benzylidene derivative, fine yellow needles from ethanol, had m. p. 205—207° (decomp.) (Found: C, 76·9; H, 6·7; N, 5·6. Calc. for $C_{30}H_{30}O_3N_2$: C, 71·3; H, 6·7; N, 6·0%). For the ethyl ether Warnat (*loc. cit.*) cites m. p. 222—224°, $[\alpha]_D^{28^\circ}$ − 57° (David finds $[\alpha]_D^{20^\circ}$ − 53°), and Leuchs (*loc. cit.*) states that the benzylidene derivative has m. p. 202°, and m. p. 208—209° in an evacuated capillary. The *N*-nitroso-derivative crystallised from 80% alcohol as small prisms, m. p. 288—290° (decomp.) (Found: C, 66·3; H, 5·5; N, 10·7. Calc. for $C_{21}H_{21}O_4N_3$: C, 66·4; H, 5·6; N, 11·1%). Warnat (*loc. cit.*) reports m. p. 292—294°. The reduction of pseudostrychnine to strychnine (Blount and Robinson, *J.*, 1932, 2305, cf. Leuchs, *Ber.*, 1937, **70**, 1703) was confirmed with material made by the new process. The crude product (0·8 g. from 1 g.) was washed with ether and dried, m. p. 266—270°; after crystallisation from *n*-propanol it had m. p. 275—278°; a mixture with strychnine, m. p. 277—279°, had m. p. 276—278°.

Action of Potassium Chromate on Brucine N-*Oxide.*—Recrystallised brucine *N*-oxide (40 g.) (prepared from 50 g. of brucine, 100 c.c. of water, and 20 c.c. of 30% hydrogen peroxide) was dissolved in water (150 c.c.), potassium chromate (4 g.) in water (10 c.c.) was added, and the solution heated in a boiling water-bath. After 3 hours the solution had become dark red, and crystals began to separate slowly after 4—5 hours, a period not shortened by seeding. The liquid was heated for 10 hours, kept overnight, and the pale yellow solid then collected and washed with water (yield, *ca.* 9 g.). This material was partly soluble in dilute mineral acid, and was separated into neutral and basic components by boiling with N-hydrochloric acid (50 c.c.) and filtering hot (solution *A*, below); the solid was washed with ether and dried, yielding 3·0 g. of a pale cream-coloured powder, m. p. 305—308° (decomp.).

The product was insoluble in dilute acid or alkali, methanol, ethanol, ethyl acetate, or acetone, moderately soluble in chloroform. It gave the brucine reaction with 5N-nitric acid, and was best purified by dissolution in boiling acetic acid and addition of an equal volume of boiling water to the filtered solution; the substance then crystallised in small, well-formed prisms which darkened at 305° and melted to a clear brown liquid at 313—317° (the m. p. is very sensitive to the rate of heating; on rapid heating the substance had m. p. 322—325°), $[\alpha]_D^{15^\circ}$ − 20° (*c*, 1·4 in chloroform) (Found: C, 67·2; H, 5·8; N, 6·6. Calc. for $C_{23}H_{24}O_5N_2$: C, 67·6; H, 5·9; H, 6·9%). Leuchs and Boit (*loc. cit.*) report m. p. 300—310° in a closed tube, and $[\alpha]_D^{20^\circ}$ − 15° for the brucone isolated from the mother liquors of the catalysed aerial oxidation of brucine.

An attempted preparation of benzylidenebrucone in ethanolic sodium ethoxide afforded a yellow solid readily soluble in methanol and aqueous ethanol, but it could not be crystallised.

On addition of ammonia to the acid solution (*A*), 5·6 g. of a brown solid, m. p. 230—240° (decomp.), were precipitated. It was purified by crystallisation from chloroform–ether, followed by dissolution in dilute sulphuric acid and precipitation with ammonia, giving a solid which darkened at 240°, m. p. 255—258° (decomp.), $[\alpha]_D^{20^\circ}$ − 64° (*c*, 1·04 in chloroform) (Found: in material dried at 120° in a vacuum: C, 67·5; H, 6·4; N, 6·3. Calc. for $C_{23}H_{26}O_5N_2$: C, 67·3; H, 6·3; N, 6·8%). Leuchs and Tessmar (*Ber.*, 1937, **70**, 2359) give m. p. 258—268° and $[\alpha]_D^{20^\circ}$ − 65·6° for pseudobrucine.

N-Nitrosopseudobrucine was prepared like the corresponding strychnine derivative; it crystallised from ethanol–*n*-propanol in fine needles, m. p. 245—247° (decomp.) (Found: C, 62·4; H, 5·7; N, 9·8. Calc. for $C_{23}H_{25}O_6N_3$: C, 62·8; H, 5·7; N, 9·6%). Leuchs (*loc. cit.*) gives m. p. 248°.

Pseudobrucine was reduced with zinc and hydrochloric acid as described for pseudostrychnine, yielding brucine, m. p. and mixed m. p. 175—177°.

The mother liquors from several preparations were concentrated to one-third of their volume and thoroughly extracted with chloroform (6 × 50 c.c.). The dried (Na_2SO_4) solution was evaporated to a small bulk and ether added; the gum which separated soon solidified. The product contained chloroform, and was readily soluble in warm water, but only crystallised very slowly on long standing, the crystals melting at 68—73° to a cloudy liquid which lost water at 100—105° but did not appear to resolidify. Leuchs and Boit (*Ber.*, 1940, **73**, 884) state that a 1 : 1 molar mixture of brucine and brucine *N*-oxide has m. p. 72°. Reduction of the solid with sulphurous acid gave brucine, m. p. and mixed m. p. 175—178°.

Action of Potassium Chromate on Brucine N-*Oxide in Presence of Hydrogen Peroxide.*—Brucine (20 g.), water (60 c.c.), and 30% hydrogen peroxide (10 c.c.) were heated on a water-bath for an hour, and potassium chromate (2 g.) in water (5 c.c.) was cautiously added to the clear solution. Oxygen was evolved and the solution became deep red. After 45—60 minutes an oil separated which soon solidified. The solution was heated for 3 hours after the addition of the chromate, left overnight, the dark solid collected, and washed well with water and ether.

The product was separated into neutral and basic fractions, yielding the brucone of m. p. 315—320° (decomp.) (2·2—3·5 g.) (Found: C, 67·1; H, 5·9; N, 6·9. Calc. for $C_{23}H_{24}O_5N_2$: C, 67·6; H, 5·9; N, 6·9%).

The basic fraction was contaminated with more dark coloured material than in the previous preparation. After crystallisation from chloroform–ether followed by precipitation from sulphuric acid solution with ammonia, 4—5 g. of pseudobrucine were obtained, m. p. 255—257° (decomp.) (Found in material dried at 120° in a vacuum: C, 67·7; H, 6·5. Calc. for $C_{23}H_{26}O_5N_2$: C, 67·3; H, 6·3%).

Oxidation of Pseudobrucine to the More Fusible Brucone.—Following the directions of Leuchs, Tuschen, and Mengelberg (*Ber.*, 1944, **77**, 403), pseudobrucine (1·0 g.) was dissolved in a mixture of hydrogen peroxide (20 c.c. of 3%) and acetic acid (1 c.c.), and the mixture heated at 80° for 15 minutes. The solid which separated (0·4 g.) was collected and crystallised from methanol or water, yielding flat plates, m. p. 180—186°, $[\alpha]_D^{20^\circ}$ − 410° (*c*, 1·4 in chloroform) (Found in material dried at 100° in high vacuum: C, 67·2; H, 6·1; N, 6·8. Calc. for $C_{23}H_{24}O_5N_2$: C, 67·7; H, 5·9; N, 6·9%). Leuchs (*loc. cit.*) gives m. p. 180—187°, $[\alpha]_D^{20^\circ}$ − 393°. It was found that the substance, crystallised from methanol, retained solvent of crystallisation tenaciously.

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