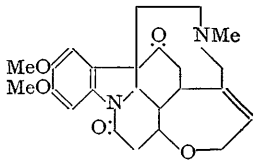
687. *The Isolation of Novacine, an Alkaloid from* Strychnos Nux-vomica, *L. and its Identification as* N-*Methyl*-sec.-pseudo*brucine.*

By W. F. Martin, H. R. Bentley, J. A. Henry, and F. S. Spring.

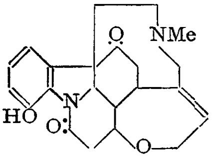
N-Methyl-*sec.*-*pseudo*brucine (novacine) has been identified as a minor alkaloid of *Strychnos Nux-vomica*, L.

From residues obtained during the purification of crude brucine sulphate from *Strychnos Nux-vomica* seeds, a new alkaloid has been isolated for which the name novacine is proposed. Novacine occurs together with vomicine in a fraction separated from strychnine and brucine by taking advantage of the solubility of the hydrochlorides of the two last-named alkaloids in chloroform. Thereafter novacine and vomicine can be conveniently separated as their hydrogen tartrates which have markedly different solubilities in water.

Analyses of novacine and of several of its crystalline derivatives established the formula $C_{24}H_{28}O_5N_2$ for the alkaloid and this led to its identification as *N*-methyl-*sec.*-*pseudo*brucine (I) previously obtained by Leuchs and Tessmar (*Ber.*, 1939, **72,** 965) from *pseudo*brucine by the action of methyl iodide.



(I)



(II)

The relation between *N*-methyl-*sec.*-*pseudo*brucine (I) and vomicine (II) has recently been established by Robinson (cf. Robinson, "Progress in Organic Chemistry," Vol. I, p. 15, Butterworth's Scientific Publns., London, 1952; Bailey and Robinson, *Nature*, 1948, **161,** 433). Novacine is thus a second alkaloid of the vomicine type. It occurs to an approximately equal extent with the latter in the residues we have examined and its isolation suggests that further search may reveal the presence of other alkaloids related to vomicine.

Experimental

Isolation of Novacine Hydrochloride.—The alkaloid mixture from nux-vomica beans from which most of the strychnine had been removed gave a crude brucine sulphate. Purification of this gave pure brucine sulphate, a small quantity of strychnine, and a dark resinous alkaloidal residue, which contained brucine, a small amount of strychnine, and the minor alkaloids of *S. Nux-vomica.*

The resinous mixture (1500 g.) was dissolved in water (5 l.) containing sufficient hydrochloric acid to make the final solution slightly acid, and the mixture diluted with water (15 l.). The solution was clarified by adding with stirring an aqueous solution of aluminium sulphate (25 g.), followed by sufficient ammonia to make the solution nearly neutral. The mixture was kept overnight, then filtered, and the mixed alkaloids were precipitated by the addition of dilute aqueous ammonia. The gummy precipitate was collected by decantation, washed with water and dissolved with heating, in water (approx. 3 l.) containing sufficient hydrochloric acid (20%) to neutralise the alkaloids. One-half of the equivalent volume of hydrochloric acid was added and the cooled solution extracted with chloroform (20 × 2500 ml.) to remove brucine and strychnine hydrochlorides. Small amounts of solid (novacine hydrochloride) separating from the chloroform phase towards the end of the extraction were collected. The dark aqueous solution was basified with ammonia solution (10—15%) and kept overnight. The dark-brown granular alkaloids (150 g.) were collected, washed with water, and dissolved in water (200 ml.) containing sufficient tartaric acid to make the solution acid to litmus. Ethanol (100 ml.) was added and the mixture kept overnight. The crystalline solid (45 g.) was collected and treated with ammonia solution, and the crystalline base collected and recrystallised from acetone, to give vomicine as prisms, m. p. 281° alone or mixed with an authentic specimen, $[\alpha]^{20}_{D}$ +84° (*c*, 0·55 in ethanol) (Found: C, 69·7; H, 6·7. Calc. for $C_{22}H_{24}O_4N_2$: C, 69·5; H, 6·4%).

The aqueous-alcoholic mother-liquor was concentrated, cooled, diluted to 200 ml. with water, and basified with ammonia solution (15%). After several days the brown granular alkaloid (70 g.) was collected, washed with water, and dissolved in water (100 ml.) containing sufficient hydrochloric acid (*d*, 1·18) to give a slightly acid solution. The solution was concentrated to a small volume and set aside for several days, and the partly crystalline mixture triturated with 90% ethanol. The crystalline solid, novacine hydrochloride (30·0 g.), was collected, washed with 90% ethanol, and dried.

Novacine.—An aqueous solution of the hydrochloride was treated with ammonia solution. The oil separating rapidly solidified. For analysis a specimen was converted into the hydrogen tartrate by crystallisation from a concentrated aqueous solution containing tartaric acid (1 mol.), and the salt was recrystallised six times from water and decomposed with aqueous ammonia; the free alkaloid was collected, dried, recrystallised twice from ethyl acetate, and dried for 3 hours at 120°/0·2 mm. Novacine was thereby obtained as prisms, m. p. 231—232°, $[\alpha]^{20}_{D}$ −17·7° (*c*, 5·0 in chloroform) (Found: C, 68·0, 68·2, 68·05; H, 6·8, 6·7, 6·8; N, 6·9, 6·9, 7·0. Calc. for $C_{24}H_{28}O_5N_2$: C, 68·0; H, 6·65; N, 6·6%). A specimen of *N*-methyl-*sec.*-*pseudo*brucine prepared by Leuchs and Boit's method (*Ber.*, 1940, **73**, 885) crystallised from ethyl acetate as prisms, m. p. 231—232° alone or mixed with a specimen of novacine, $[\alpha]^{20}_{D}$ −18·2° (*c*, 1·8 in chloroform) (Found: C, 68·3; H, 6·7%). A comparison of the infra-red absorption spectra of the two specimens, for which we are indebted to Professor E. R. H. Jones, F.R.S., confirmed their identity.

Novacine hydrochloride separates from ethanol as prismatic needles, m. p. 229—230° (Found, in a specimen dried for 3 hours at 100°/0·2 mm.: C, 59·8; H, 6·5; Cl, 7·4. $C_{24}H_{28}O_5N_2,HCl,H_2O$ requires C, 60·2; H, 6·5; Cl, 7·4%). *Novacine picrate* separates from ethanol as yellow prisms, m. p. 250° (decomp.) (Found: C, 55·2; H, 4·8; N, 10·7. $C_{24}H_{28}O_5N_2,C_6H_3O_7N_3$ requires C, 55·2; H, 4·8; N, 10·7%). *Novacine hydrogen tartrate* separates from water as prisms, m. p. 235° (decomp.) (Found: C, 58·0; H, 5·9; N, 5·1. $C_{24}H_{28}O_5N_2,C_4H_6O_6$ requires C, 58·6; H, 6·0; N, 4·9%). *Novacine hydrogen oxalate* crystallises from water as prisms, m. p. 246° (decomp.) (Found, in a specimen dried for 30 minutes at 140°/0·2 mm.: C, 58·5; H, 5·7; N, 5·7. $C_{24}H_{28}O_5N_2,C_2H_2O_4,H_2O$ requires C, 58·7; H, 6·1; N, 5·3%).

Dihydronovacine.—Hydrogenation of novacine by Leuchs and Tessmar's method (*loc. cit.*) and crystallisation of the product from ethyl acetate gave dihydronovacine as prisms, m. p. 237—238°, $[\alpha]^{20}_{D}$ +168° (*c*, 2·4 in chloroform) (Found: C, 67·7; H, 6·9; N, 6·7. Calc. for $C_{24}H_{30}O_5N_2$: C, 67·6; H, 7·1; N, 6·6%). A specimen of dihydro-*N*-methyl-*sec.*-*pseudo*brucine prepared similarly had m. p. 237—238° alone or mixed with a specimen of dihydronovacine, $[\alpha]^{20}_{D}$ +168° (*c*, 2·6 in chloroform).

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