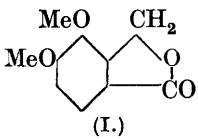
179. *β-Pseudognoscopine.*

By MORRISON GREENWOOD and ROBERT ROBINSON.

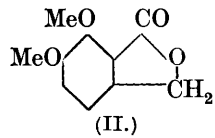
THE alkaloid gnoscopine was isolated from mother-liquors obtained in the preparation of narcotine from opium (M. Smith, *Pharm. J.*, 1878, **9**, 82; T. and H. Smith, *ibid.*, 1893, **52**, 794) and was synthesised and resolved into *d*- and *l*-narcotine in 1911 (Perkin and Robinson, J., 1911, **99**, 777). Subsequently Hope and Robinson (J., 1914, **105**, 2085) obtained a stereoisomeride of gnoscopine by the condensation of cotarnine with nitromeconine and elimination of the nitro-group from the resulting anhydro-cotarninenitromeconine. They therefore proposed to denote the naturally occurring bases as α-gnoscopine and α-narcotine and the synthetic stereoisomerides as β-gnoscopine and β-narcotine.

The present investigation was initiated with the object of extending the series by the preparation of bases related to pseudomeconine (I) in the same way that narcotine is related to meconine (II). Preliminary experiments were made by one of us and Dr. E. Hope (P., 1910, **26**, 228).

Nitropseudomeconine (III) condensed readily with cotarnine in alcoholic solution with formation of an apparently homogeneous nitropseudognoscopine (IV, R = NO_2), but, on reduction, two isomeric aminopseudognoscopines were obtained. By analogy with the similar substances isolated by Hope, Pyman, Remfry, and Robinson (J., 1931, 236) by the reduction of nitro-*dl*-hydrastine, the aminopseudognoscopine, m. p. 236°, has been termed amino-α-pseudognoscopine, and that of m. p. 193° amino-β-pseudognoscopine (IV, R = NH_2).



(I.)



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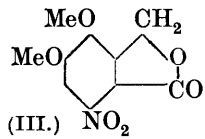
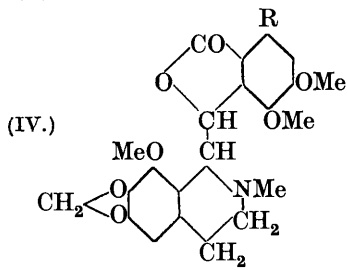


(III.) NO_2



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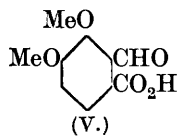


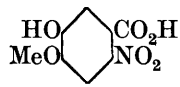
(V.)

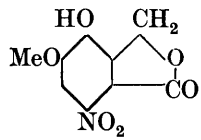
Amino-β-pseudognoscopine has been successively transformed into

iodo-β-pseudognoscopine and β-pseudognoscopine (IV, R = H) by applications of methods of Hope and Robinson (*loc. cit.*); the work on α-pseudognoscopine is, however, not yet complete. On oxidation with nitric acid, β-pseudognoscopine yields cotarninium nitrate and pseudopianic acid (V) : this appears to be the first synthesis of the acid independent of its formation in the degradation of berberine (Perkin, J., 1890, **57**, 1065).

The nitropseudomeconine required for this investigation was prepared, partly by a modification of the method of Salomon (*Ber.*, 1887, **20**, 883), which depends on the nitration of pseudomeconine, and also by a new synthesis.

It is known that the action of boiling aqueous sodium hydroxide on 4-nitroveratrole effects the hydrolysis of the methoxyl in the *p*-position to the nitro-group exclusively (Cardwell and Robinson, J., 1915, **107**, 258). The same process, applied to 6-nitroveratric acid, has now been found to give 6-*nitro*isovanillic *acid* (VI). The

(VI.) 



(VII.)

acid condensed readily with formaldehyde in the presence of hot concentrated hydrochloric acid with the formation of 6-*nitro*-3-*hydroxy*-4-*methoxyphthalide* (VII) (compare Edwards, Perkin, and Stoyle, J., 1925, **127**, 195).

This readily accessible substance is difficult to methylate and success was only achieved by the use of Purdie's method. The nitropseudomeconine so obtained was identical with the product of nitration of pseudomeconine.

Experimental.

6-*Nitro*isovanillic *Acid* (VI).—Methyl veratrate, m. p. 58°, was obtained in 86% yield when hydrogen chloride was led into a mixture of veratric acid (65 g.) and methyl alcohol (350 c.c.) for 4 hours.

The ester (20 g.) was nitrated at 0—5° by dissolution in nitric acid (100 c.c., *d* 1·4). After 1 hour, the product was precipitated by water and crystallised from aqueous alcohol (yield, 19 g.; m. p. 143°).

A mixture of methyl 6-nitroveratrate (10 g.) and aqueous sodium hydroxide (150 c.c. of 10%) was refluxed for 24 hours with occasional removal of the condenser to allow the escape of methyl alcohol. The cooled filtered liquid was acidified with hydrochloric acid; the precipitate crystallised from boiling water in yellow rectangular prisms, m. p. 181° (decomp.) after shrinking and becoming

almost colourless at 108° (Found: loss at 120° in 24 hours, 14·7. $C_8H_7O_6N,2H_2O$ requires $2H_2O$, 14·5%. Found in anhydrous material: C, 45·1; H, 3·3. $C_8H_7O_6N$ requires C, 45·1; H, 3·3%). The solvent of crystallisation is lost slowly at room temperature in a vacuum over sulphuric acid.

6-*Nitroisovanillic acid* is readily soluble in the simple alcohols, ether, or acetone, moderately readily soluble in acetic acid or boiling water, and sparingly soluble in benzene or chloroform. It gives a greenish-brown coloration with alcoholic ferric chloride, and its alkaline solutions are orange-yellow. The acid is not identical with the nitro*iso*vanillic acid, m. p. 172—173°, prepared by Matsmoto (*Ber.*, 1878, **11**, 133) by nitration and subsequent hydrolysis of *O*-acetyl*iso*vanillic acid.

The *acetyl* derivative, obtained by boiling with acetic anhydride for 2 hours, crystallised from aqueous alcohol in thin colourless plates, m. p. 214° (decomp.) (Found: C, 46·8; H, 4·0. $C_{10}H_9O_7N$ requires C, 47·0; H, 3·5%).

Nitration of 6-nitro*iso*vanillic acid (2 g.) at 0° by means of nitric acid (15 c.c., *d* 1·5) during an hour furnished 2:6-dinitro*iso*vanillic acid, m. p. 211°, identical with the substance prepared by the method of Wegscheider and Klemenc (*Monatsh.*, 1910, **31**, 719). These authors record the m. p. 206°, but a repetition of their experiments afforded the acid, m. p. 211°.

6-*Nitro*-3-*hydroxy*-4-*methoxyphthalide* (VII).—A mixture of 6-nitro-*iso*vanillic acid (20 g.), 40% aqueous formaldehyde (26 c.c.), and hydrochloric acid (160 c.c., *d* 1·16) was heated over a gauze until a clear solution was obtained and then transferred to the steam-bath. After a few hours, the whole mass became solid. The crystals were collected after 18 hours, washed with water, and converted, by treatment with cold aqueous sodium carbonate (the yield was increased by the addition of sodium chloride and by cooling in ice; any unchanged nitro*iso*vanillic acid remained in the solution), into the blood-red sodium salt, which was collected and washed; the free *hydroxy-lactone*, regenerated by acidification, crystallised from boiling water in long yellow needles, m. p. 221° (Found: C, 48·2; H, 3·4. $C_9H_7O_6N$ requires C, 48·0; H, 3·1%).

The *acetyl* derivative, obtained by boiling with acetic anhydride and a few drops of pyridine for 2 hours, crystallised from glacial acetic acid in colourless prismatic needles, m. p. 188° (Found: C, 49·3; H, 3·4. $C_{11}H_9O_7N$ requires C, 49·4; H, 3·4%).

This substance is at first insoluble in cold aqueous sodium hydroxide, but it gradually dissolves to an orange-yellow solution; acidification then throws down a mixture of hydroxy- and acetoxy-nitromethoxyphthalides. It follows that, at least in part, the

phthalide ring is opened before hydrolysis of the acetoxy-group occurs.

Benzoylation of the nitrohydroxymethoxyphthalide could not be effected by the Schotten–Baumann method. The above acetyl derivative does not condense readily with cotarnine.

6-*Nitropseudomeconine* (III).—(A) Silver oxide (from 15 g. of silver nitrate) was gradually added to a boiling solution of nitrohydroxymethoxyphthalide (5 g.) in methyl alcohol (60 c.c.) and methyl iodide (12 c.c.), and the mixture was refluxed for 2 hours. The filtered solution was concentrated and the needles that separated were collected and washed with cold dilute aqueous sodium hydroxide in order to remove unchanged phenolic lactone. The substance crystallised from methyl alcohol in needles, m. p. 164—165°, unchanged in admixture with a specimen prepared by the following modification of Salomon's method (*loc. cit.*). (B) The unmodified method gives chiefly nitrohemipinic acid. Pseudomeconine (20 g.) was gradually added to nitric acid (110 c.c., *d* 1·4) with stirring and cooling in ice-water. After 1 hour the product was isolated (crude, m. p. 165°); it crystallised from aqueous alcohol in almost colourless needles, m. p. 166° (yield, 22 g. or 95%).

The nitration of methyl 6-nitroveratrate has been investigated in a preliminary manner. The statement of Wegscheider and Klemenc (*Monatsh.*, 1910, **31**, 718) that methyl 2 : 6-dinitroveratrate is produced was confirmed and evidence of the formation of methyl 5 : 6-dinitroveratrate also was obtained. Neither 6-bromo- nor 6-nitro-veratric acid could be condensed with formaldehyde to a phthalide derivative.

Nitropseudognoscopine (IV, R = NO_2).—Dry cotarnine (20 g.) was added at once to a boiling solution and suspension of nitropseudomeconine (20 g.) in ethyl alcohol (400 c.c.); complete solution rapidly occurred and crystallisation of the product began in 10 minutes. The mixture was refluxed for an hour and the lemon-yellow crystals were then collected, washed with alcohol, and dried at 100° (yield, 28 g. or 70%; m. p. 184°). The substance is readily soluble in chloroform and sparingly so in most other neutral organic solvents; it crystallises from chloroform–alcohol in canary-yellow needles, m. p. 186° (Found: C, 57·5; H, 4·8. $C_{22}H_{22}O_9N_2$ requires C, 57·6; H, 4·8%). Fractional crystallisation failed to reveal the presence of stereoisomerides in this material, m. p. 186°, and we are of the opinion that it is homogeneous. This case supports the suggestion of Hope, Pyman, Remfry, and Robinson (*loc. cit.*) that the conditions of reduction of nitro-*dl*-hydrastine appeared to affect the proportion of the resulting α- and β-amino-*dl*-hydrastines.

The *hydrochloride* crystallised in colourless needles when a solution

of the base in concentrated hydrochloric acid was diluted with five volumes of water (Found : Cl, 6·9. $C_{22}H_{22}O_9N_2$,HCl requires Cl, 7·1%).

The picrate, prepared by mixing acetone solutions of the components, crystallised in yellow rhombohedra, m. p. 173° (decomp.). A solution of the base in glacial acetic acid deposited colourless needles of the acetate, but, when such a solution was boiled, decomposition ensued with formation of nitropseudomeconine (m. p. 163°) and cotarnine (picrate, m. p. 139°). The decomposition is not so facile as in the case of nitrognoscopine ; under comparable conditions (1 g. in 10 c.c.) the latter is completely hydrolysed in 1—2 minutes and nitropseudognoscopine requires at least 5 minutes.

Amino-α-pseudognoscopine (IV, R = NH_2).—A well-cooled solution of crystallised stannous chloride (25 g.) in concentrated hydrochloric acid (30 c.c.) was added to a mixture of nitropseudognoscopine (10 g.) and glacial acetic acid (75 c.c.) with some granulated tin, cooled in ice ; the temperature was not allowed to rise above 12°. After 6 hours the liquid was diluted, and rendered strongly alkaline by means of carbonate-free sodium hydroxide, the precipitate was collected, and both it and the filtrate were extracted with chloroform. The combined chloroform solutions were dried over potassium carbonate and concentrated ; when the bulk of the solvent had been removed, a large volume of methyl alcohol was added and the distillation continued until chloroform was no longer present in the distillate. The *amino-α-pseudognoscopine* separated during this process in brilliant prisms and the mixture was filtered hot (filtrate, Y). The crude material (2·8 g.) had m. p. 231—233° and the base crystallised from chloroform in many-sided squat prisms, m. p. 235°. This specimen gave consistently low values (0·6%) for the carbon content, but a specimen crystallised from much ethyl acetate also had m. p. 235° and gave a satisfactory analysis (Found in material dried at 110° in a high vacuum over phosphoric oxide : C, 61·7 ; H, 5·7. $C_{22}H_{24}O_7N_2$ requires C, 61·6 ; H, 5·7%). The substance is very sparingly soluble in most organic solvents, but dissolves freely in hot chloroform or pyridine.

The related diazonium salt couples with β-naphthol in alkaline solution with formation of a crimson azo-compound, the solution of which in concentrated sulphuric acid is deep blue.

The *acetyl* derivative (IV, R = NHAc) was isolated from a solution of the base (1 g.) in acetic acid and acetic anhydride (5 c.c.) that had been kept for 1 hour. It crystallised from alcohol in white rectangular plates, m. p. 227° (Found : C, 61·1 ; H, 5·6. $C_{24}H_{26}O_8N_2$ requires C, 61·3 ; H, 5·5%), and was not diazotisable.

Amino-β-pseudognoscopine (IV, R = NH_2).—On cooling, the

methyl-alcoholic filtrate (Y) deposited large prisms, m. p. 189°, and more of the same substance could be obtained by concentration of the mother-liquor. Two recrystallisations gave colourless rhombic prisms of constant m. p. 193° (Found : C, 61·5; H, 5·4. $C_{22}H_{24}O_7N_2$ requires C, 61·6; H, 5·6%). This *base* resembles the α-isomeride and other substances of the class (such as aminognoscopine and amino-*dl*-hydrastine); it yields a characteristic hydrochloride, much more sparingly soluble than that derived from the α-base.

The *acetyl* derivative is readily soluble in alcohol and crystallises from concentrated solutions in irregular colourless plates, m. p. 163° (Found : C, 61·3; H, 5·5. $C_{24}H_{26}O_8N_2$ requires C, 61·3; H, 5·5%).

Iodo-β-pseudognoscopine (IV, R = I).—Amino-β-pseudognoscopine (3 g.), suspended in concentrated hydrochloric acid (30 c.c.), was diazotised at 0° with a saturated solution of sodium nitrite. The solution was added to water (100 c.c.) and mixed with potassium iodide (20 g. in 150 c.c. of water), after 10 minutes free iodine was removed by means of sulphur dioxide, and the pale yellow precipitate was collected and triturated with ammonia; it crystallised from ethyl acetate in colourless, not quite rectangular tablets and prisms, m. p. 222° (decomp.) (Found : C, 48·8; H, 4·0; I, 23·5. $C_{22}H_{22}O_7NI$ requires C, 49·0; H, 4·1; I, 23·6%). This *base* is very sparingly soluble in most neutral organic solvents. It crystallises from much alcohol in very well-shaped rhombic prisms. The picrate crystallises from acetone in yellow prisms, m. p. 187°.

β-Pseudognoscopine (IV, R = H).—Freshly prepared aluminium amalgam (from 5 g. of thin aluminium foil) was added to a boiling solution of iodo-β-pseudognoscopine in methyl alcohol (70 c.c.), the mixture refluxed for 30 minutes and filtered, and the filtrate and washings concentrated to a small volume. Large rectangular prisms separated and the substance was recrystallised several times from methyl alcohol (charcoal), forming well-shaped, elongated, rhombic prisms, m. p. 80—82°, resolidifying and then melting at 136°; a pure specimen dried at the ordinary temperature in a vacuum over sulphuric acid had m. p. 137—138° (Found in rapidly air-dried material : loss at 110° after 12 hours and in a vacuum over sulphuric acid after 24 hours, 6·6. $C_{22}H_{23}O_7N,CH_4O$ requires CH_4O, 7·2%. Found in solvent-free material : C, 63·7; H, 5·4; N, 3·4. $C_{22}H_{23}O_7N$ requires C, 63·9; H, 5·5; N, 3·4%). The hydrochloride is sparingly soluble in dilute hydrochloric acid and crystallises in colourless rectangular prisms; the picrate crystallises from acetone in minute, canary-yellow, prismatic needles, m. p. 216°.

Oxidation of β-Pseudognoscopine.—β-Pseudognoscopine (3·1 g., dried at 110°) was dissolved in water (15 c.c.) at 60°, and nitric acid (7 c.c., *d* 1·42) gradually added. When almost the whole quantity

had been introduced, the oxidation commenced and the vessel was removed from the source of heat and wrapped in wool. The temperature gradually fell to 45° and it was then raised to, and maintained at, 50° for 2 hours. The solution was nearly neutralised but kept acid and extracted with much ether; the ethereal solutions were extracted with several small quantities of aqueous sodium carbonate and the alkaline solution was concentrated and acidified with hydrochloric acid. The colourless woolly needles that separated recrystallised in the same form from hot water and had m. p. 121—122° (Found in material dried at 100°: C, 57·0; H, 5·1. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). The acid had all the properties of pseudopianic acid obtained by Perkin (*loc. cit.*) by the hydrolysis of berberal. For confirmation of its identity it was reduced to pseudomeconine, m. p. 124°, and also converted into hemipinimide, m. p. 226°.

The acid solution from which pseudopianic acid had been extracted was concentrated under diminished pressure and mixed with concentrated aqueous potassium hydroxide; cotarnine then separated in a crystalline condition. The base was identified by conversion into anhydrocotarninenitromethane (Hope and Robinson, J., 1911, **99**, 2136), which crystallised from alcohol in colourless needles, m. p. 121—122° (Found: C, 57·3; H, 5·8. Calc. for $C_{12}H_{14}O_4N_2$: C, 57·6; H, 5·6%).

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