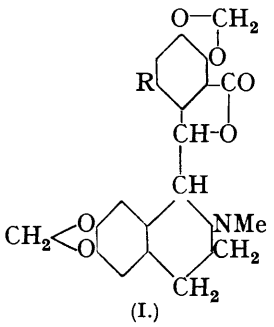
43. *Synthesis of Bicuculline. Part I.*

By P. W. G. Groenewoud and Robert Robinson.

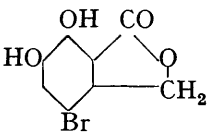
Development in the phthalide section of the *iso*quinoline group of the alkaloids appeared in recent years to have been arrested until the appearance of papers by R. H. F. Manske announcing the discovery of new members of the group in certain *Fumariaceae*.

Bicuculline (I, R = H) was first encountered as a constituent of *Dicentra cucullaria* (Manske, *Canadian J. Research*, 1932, **7**, 265) and subsequently found in *Corydalis sempervirens*, *Adlumia fungosa*, and *Corydalis aurea* (Manske, *ibid.*, 1933, **8**, 210, 407; **9**, 436). The constitution of the base was deduced from its character as a lactone and from the formation of hydrastinine and 2-carboxy-3 : 4-methylenedioxybenzaldehyde on oxidation.

The present memoir describes the synthesis of inactive bicuculline, and Part II, in collaboration with Dr. Manske, will deal with its stereochemical relations. We may anticipate Part II to the extent of stating that the inactive synthetic material has been resolved and the *d*-base proved identical with bicuculline.



(I.)



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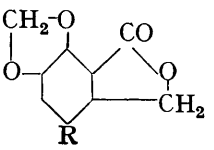

(III.)

The methylenedioxyphthalide (III, R = H) required for the synthesis according to the

methods of Hope and Robinson (J., 1911, **99**, 1153) and Hope, Pyman, Remfry, and Robinson (J., 1931, 236) was prepared by Perkin and Trikojus (J., 1926, 2925) from *o*-veratraldehyde by a series of processes, but we preferred a new method based on the observation of Robinson and Streight that bromomeconin can be demethylated (J., 1934, 1130).

Bromonormeconin (II) was found to be difficult to methylenate, but this was eventually effected in 45% yield by the use of methylene sulphate (cf. Baker, J., 1931, 1765); the product (III, R = Br) was debrominated by means of hydrazine and palladised strontium carbonate (Busch, *Z. angew. Chem.*, 1925, **38**, 519) or equally conveniently by means of zinc dust and boiling aqueous sodium hydroxide.

3 : 4-Methylenedioxyphthalide is readily converted into its 6-*nitro*-derivative (III, R = NO_2) and the facile condensation of the latter substance with cotarnine follows the usual course.

Coupling with lodal (Pyman, J., 1909, **95**, 1266) [carbinolamine related to 4 : 5-dimethoxy-2-(β-methylaminoethyl)benzaldehyde] furnished *nitro*-x-*adlumine*,* which it is hoped may be transformed into adlumine (Manske, *Canadian J. Research*, 1933, **8**, 210). The laudanosine necessary for the preparation of lodal was obtained in 90% yield by catalytic reduction of papaverine methochloride.

6-Nitro-3 : 4-methylenedioxyphthalide and hydrastinine afforded *nitro*-x-*bicuculline* (I, R = NO_2) in favourable yield and the usual methods were applied for the conversion of this base into *amino*-x-*bicuculline* and then into *iodo*-x-*bicuculline* and x-*bicuculline*. This route was selected in preference to the alternative through the hydrazino-derivative.

Experimental.

6-*Bromo*-3 : 4-*methylenedioxyphthalide* (III, R = Br).—Many unsuccessful or partly successful trials were made with methylene bromide or methylene iodide under various conditions for the methylenation of bromonormeconin. The following directions should be followed closely. A solution of sodium hydroxide (3·3 g.) in water (100 c.c.) was added to one of bromonormeconin (10·0 g.) in acetone (100 c.c.) (oxygen-free nitrogen atmosphere), and the mixture gently refluxed. Methylene sulphate (32·0 g.) and sodium hydroxide (19·6 g. in 75 c.c. of water) were then added alternately and in small portions with continued heating and vigorous stirring during 1 hour. Stirring was continued for 15 minutes; hydrochloric acid was then added in excess, and the acetone removed by distillation under diminished pressure. The acid solution was boiled and cooled, and the sticky solid collected. It was lixiviated with alcohol and the grey powder which remained was collected and dried (4·65 g. or 44%); bromonormeconin was recovered from the alcoholic solution. 6-*Bromo*-3 : 4-*methylenedioxyphthalide* crystallises from ethyl alcohol or acetic acid in white flakes, m. p. 196° (Found: C, 42·2; H, 2·1. $C_9H_5O_4Br$ requires C, 42·0; H, 2·0%); it is very sparingly soluble in cold alcohol or ether and it exhibits the behaviour of a lactone.

3 : 4-*Methylenedioxyphthalide*.—(A) Reduction of the bromo-derivative by means of aluminium amalgam in boiling alcoholic solution gave methylenedioxyphthalide in 73% yield. Perkin and Trikojus (*loc. cit.*) gave m. p. 227°, which was confirmed by Späth and Holter (*Ber.*, 1927, **60**, 1891). Manske (*Canadian J. Research*, 1933, **8**, 142) attributed the m. p. 234° to the substance, and in agreement we find m. p. 233—234° (Found: C, 60·7; H, 3·5. Calc. for $C_9H_6O_4$: C, 60·7; H, 3·5%).

The method was unsatisfactory when the scale of the operation was enlarged or when the bromo-derivative was not quite pure. The methods (B) and (C) are equally efficacious.

(B) A mixture of bromomethylenedioxyphthalide (4·0 g.), aqueous sodium hydroxide (150 c.c. of 10%), and zinc dust (10·0 g.) was refluxed for 8 hours; after cooling to 65°, filtration, and acidification, pure methylenedioxyphthalide (2·45 g. or 90%) separated.

(C) Bromomethylenedioxyphthalide (2·0 g.) was dissolved in the minimum of hot alcohol, and palladised strontium carbonate (4·0 g. of 2%), alcoholic potassium hydroxide (20 c.c. of 10%), and hydrazine hydrate (2·5 c.c.) added. The mixture was refluxed for 1 hour, filtered, concentrated, and acidified (yield, 1·2 g. or 86%).

6-*Nitro*-3 : 4-*methylenedioxyphthalide*.—Methylenedioxyphthalide (1·0 g.) was added portionwise to nitric acid (16 c.c., *d* 1·42), cooled in ice but allowed such a rise of temperature as to

* The *x* signifies that the allocation to the stereoisomeric series α and β has not yet been carried out.

ensure complete solution before crystallisation of the product began. The mixture was kept for 15 minutes at 0° and for 1 hour at room temperature, and after addition of water the yellow flocculent precipitate was collected (1·15 g. or 92%). The very sparingly soluble *substance* crystallised from much alcohol and from acetic acid in pale yellow tablets, m. p. 222—223° (Found: C, 48·2; H, 2·1; N, 6·5. $C_9H_5O_6N$ requires C, 48·4; H, 2·2; N, 6·3%). It is soluble in boiling aqueous alkali to a bright red solution and is recovered very slowly on acidification and heating. On exposure to light the substance becomes dark yellow.

Anhydrocotarnine-6-nitro-3 : 4-methylenedioxyphthalide.—Cotarnine (2·2 g.) was added to a boiling solution and suspension of nitromethylenedioxyphthalide (2·0 g.) in alcohol (150 c.c.); a clear orange solution was quickly formed. The product crystallised in less than a minute and after boiling for 20 minutes the mixture was cooled and the solid collected (3·1 g. or 78%). The *base* is readily soluble in chloroform and crystallises from chloroform–methyl alcohol as small yellow leaflets, m. p. 177—178° (Found: C, 56·8; H, 4·1; N, 6·5. $C_{21}H_{18}O_9N_2$ requires C, 57·0; H, 4·1; N, 6·3%). The base is readily soluble in hydrochloric acid to a bright yellow solution; it is decomposed into its generators on boiling with acetic acid.

Anhydrocotarnine-6-amino-3 : 4-methylenedioxyphthalide.—A solution of crystallised stannous chloride (6·0 g.) in concentrated hydrochloric acid (7 c.c.) was added to an ice-cold mixture of anhydrocotarninenitromethylenedioxyphthalide (1·0 g.), acetic acid (6 c.c.), and granulated tin (1·0 g.). The temperature was allowed to rise to 15—18° and crystallisation of the double tin salt commenced after 20 minutes. After 5 hours, enough water to dissolve the salts was added and the base, liberated by means of a large excess of potassium hydroxide, was extracted with chloroform. The dried chloroformic solution was evaporated nearly to dryness, methyl alcohol added to the residue, and the liquid again distilled in order to remove chloroform. This process was twice repeated and the very pale yellow crystals were then collected (0·71 g. or 70%). The *base* crystallised from chloroform–methyl alcohol as tiny rods, m. p. 204—205° (decomp.) (Found: C, 60·2; H, 5·3; N, 6·9. $C_{21}H_{20}O_7N_2$,0·5MeOH requires C, 60·3; H, 5·1; N, 6·5%). It resembles closely amino-β-gnoscopine in its behaviour with solvents and in its diazotisability.

Laudanosine.—Platinum oxide (from 1·0 g. of chloroplatinic acid; "Organic Syntheses," VIII, 92) was added to a solution of papaverine methochloride (18·0 g.) in 70% aqueous alcohol (75 c.c.), which was then shaken with hydrogen (2000 c.c. absorbed at approximately 900 c.c. per hour). The solution was filtered through charcoal, concentrated, and mixed with water (350 c.c.), and sodium carbonate (2·0 g.) added. The crude precipitated base had m. p. 111° (pure, m. p. 115°) and after crystallisation from 50% aqueous alcohol was obtained as feathery needles (14·8 g. or 92%).

Anhydrolodal-6-nitro-3 : 4-methylenedioxyphthalide (*Nitro*-x-*adlumine*).—Lodal was prepared by the method of Pyman (*loc. cit.*) and also by synthesis using prescriptions of Kindler and Peschke (*Arch. Pharm.*, 1932, **270**, 350). Under the usual conditions, lodal (3·0 g.) and nitromethylenedioxyphthalide (2·0 g.) in alcohol (200 c.c.) afforded pale orange crystals (3·4 g. or 85%) of *nitro*-x-*adlumine*. This resembles other substances of its class and crystallises from chloroform–methyl alcohol in orange rectangular plates, m. p. 180—181° (decomp.) (Found: C, 59·0; H, 4·9; N, 6·1. $C_{21}H_{20}O_8N_2$ requires C, 58·9; H, 4·7; N, 6·5%). The base is more than usually phototropic, becoming dark red when exposed to light and air for 2 hours. The reduction of the base was carried out as described above in the case of anhydrocotarninenitromethylenedioxyphthalide; the *amino*-derivative crystallised very slowly from chloroform–methyl alcohol as bundles of small needles, m. p. 218—219° (Found: C, 63·0; H, 5·6; N, 6·8. $C_{21}H_{22}O_6N_2$ requires C, 63·3; H, 5·5; N, 7·0%).

Nitro-x-*bicuculline* (I, R = NO_2).—Hydrastinine (10·5 g.) was added to a boiling solution and suspension of nitromethylenedioxyphthalide (11·5 g.) in ethyl alcohol (300 c.c.). The solution immediately assumed an orange-red colour and the nitro-compound had almost disappeared when the orange-red crystals of the condensation product made their appearance in the solution. The mixture was refluxed for 30 minutes, then cooled, and the product collected after a few hours (15·5 g. or 73%). Some nitromethylenedioxyphthalide was recovered from the mother-liquor. The *nitrobicuculline* is sparingly soluble in methyl and ethyl alcohols, but dissolves freely in acetone or chloroform. It can be conveniently crystallised from chloroform–methyl alcohol, separating in minute yellow needles, which sinter at 176° and blacken at 179° without exhibiting a definite m. p. (Found: C, 58·1; H, 4·2. $C_{20}H_{16}O_8N_2$ requires C, 58·3; H, 3·9%). The base can be recovered by the addition of ammonia to its yellow solution in dilute hydrochloric acid, but it is rapidly decomposed into its generators on heating with acetic acid.

Amino-x-bicuculline (I, R = NH_2).—Under the usual conditions of reaction and isolation, nitro-*x*-bicuculline (3·0 g.), acetic acid (18 c.c.), granulated tin (2·0 g.), hydrated stannous chloride (17·0 g.), and concentrated hydrochloric acid (19 c.c.) afforded a pale yellow, crystalline product, separating eventually from methyl alcohol (yield, 1·8 g. or 65%). This *amino-x-bicuculline* crystallises from mixtures of chloroform and methyl alcohol in flat, pale yellow prisms, m. p. 203—204° to a brown liquid (Found : C, 62·8; H, 5·0; N, 7·5. $C_{20}H_{18}O_6N_2$ requires C, 62·8; H, 4·7; N, 7·3%). The substance can be readily diazotised and coupled with β-naphthol to a crimson azo-compound.

Iodo-x-bicuculline (I, R = I).—Aqueous sodium nitrite was carefully added to a solution of amino-*x*-bicuculline (1 g.) in concentrated hydrochloric acid (12 c.c.) at 0° until a drop of the liquid after dilution was found to contain free nitrous acid. The solution became bright orange and a crystalline substance, presumably the diazonium chloride, separated. The mixture was diluted with water (30 c.c.) and gradually added to a solution of potassium iodide (8·0 g.) in water (150 c.c.) with vigorous stirring. After 10 minutes the iodine liberated was reduced by sulphurous acid and the *base* was collected (1·2 g. or 93%) after it had been liberated by means of ammonia. The colourless base is sparingly soluble in the simple alcohols and ether and crystallises from ethyl acetate or from chloroform–methyl alcohol as stout transparent prisms, m. p. 208—209° (Found : C, 48·5; H, 3·5; N, 3·1. $C_{20}H_{16}O_6NI$ requires C, 48·7; H, 3·3; N, 2·8%).

x-*Bicuculline* (*Anhydrohydrastinine*-3 : 4-*methylenedioxyphthalide*) (I, R = H).—A solution of iodo-*x*-bicuculline (0·6 g.) in ethyl alcohol (38 c.c.) and benzene (12 c.c.) was refluxed with an excess of amalgamated aluminium foil for 3 hours. The solvents were removed from the filtrate under diminished pressure, and the residue crystallised from chloroform–methyl alcohol (charcoal) (yield, 0·3 g. or 66% of halogen-free material). The *base* was obtained as colourless elongated plates, m. p. 215° (Found : C, 65·4; H, 4·6; N, 4·0. $C_{20}H_{17}O_6N$ requires C, 65·4; H, 4·6; N, 3·8%), sparingly soluble in the simple alcohols and ether, moderately readily soluble in benzene and ethyl acetate, readily soluble in chloroform.

The addition of ammonia or sodium hydroxide to a cold solution in dilute hydrochloric acid precipitates the base, but when the acid solution is added to hot aqueous sodium hydroxide, no precipitate is obtained owing to fission of the lactone ring. On acidification of the solution and heating, followed by cooling and addition of cold aqueous sodium hydroxide, the base is precipitated. The greenish-yellow solution in concentrated sulphuric acid becomes red and then dull purple on heating.

Derivatives of the base will be described in Part II.

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