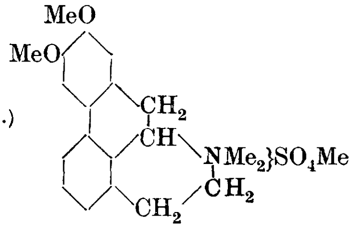
CCLXVI.—*Synthetical Experiments in the Phenanthrene Group of the Alkaloids. Part I.*

By Robert Robinson and Junzo Shinoda.

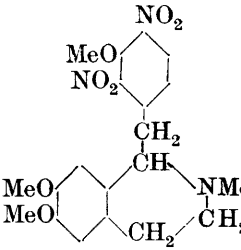
The observations of Hope and Robinson (1911) showing that pseudo-bases of the cotarnine type can be condensed with *o*-nitrotoluene or its derivatives with formation of variously substituted 1-*o*-nitrobenzyltetrahydro*iso*quinolines cleared the way for many possible new applications of Pschorr's reaction to the synthesis of naturally occurring bases of the phenanthrene group. The condensation product from *iso*quinoline methohydroxide and 6-nitrohomoveratrole (Robinson and Robinson, J., 1914, **105**, 1456) was converted into an *iso-apo*morphine dimethyl ether, but, as already intimated (*loc. cit.*), the specimens were destroyed by fire. Not long ago, however, a quantity of the methosulphate (I) of the final product was found in a clearly labelled tube and a description of the compound is included in this communication. The investigation is now in course of detailed repetition and it is being extended to the synthesis of *apo*morphine dimethyl ether by a similar method from 2-nitrohomoveratrole.

As is natural after the lapse of 15 years, this field has engaged the attention of other investigators, and Gadamer, Oberlin, and Schoeler (*Arch. Pharm.*, 1925, **263**, 81) have employed the condensation product of *iso*quinoline methohydroxide and *o*-nitrotoluene in order to obtain the parent base (aporphine) of the phenanthrene–*iso*quinoline group.

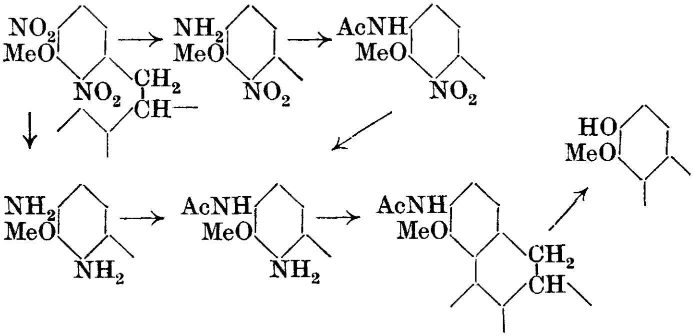
(I.)



(II.)



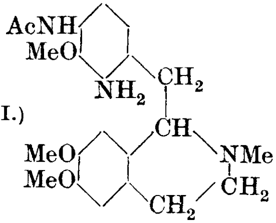
Assuming that 2-nitrohomoveratrole can be employed, as seems probable, for the synthesis of *apo*morphine, it does not necessarily follow that it would be equally serviceable in connexion with the bulbocapnine and corydine series, because hydrastinine has not yet been successfully condensed with a mononitrotoluene derivative. We have tried to overcome the difficulty by the use of 2 : 4-dinitro-3-methoxytoluene, which condenses very readily with pseudo-bases and is constitutionally related to 2-nitrohomoveratrole. The following scheme illustrates two of the possibilities which we had in view :



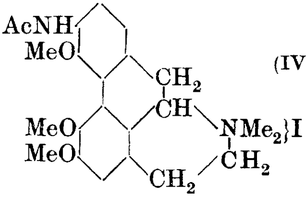
The starting-point chosen was 1-hydroxy-6 : 7-dimethoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (Pyman, J., 1909, **95**, 1266), which it is proposed * to call "laudaline" with reference to its analogy with hydrastinine and cotarnine and to the fact that it is an oxidation product of laudanosine. *Anhydrolaudaline*-2 : 4-*dinitro*-3-*methoxytoluene* (II) was obtained in good yield and reduced to a *diamine* which was analysed as the *dihydrochloride*, but monoacetylation could not be effected and we therefore concentrated our attention on the longer process outlined above. Partial reduction with ammonium sulphide or stannous chloride gave one and the same nitroamine, and in order to determine the constitution of this we made parallel experiments with anhydrocotarnine-2 : 4-dinitro-3-methoxytoluene (II in the preceding paper). The acetyl derivative of the nitroamine from this base furnished, on oxidation with potassium permanganate in acetone solution, an acid which was identical with one prepared by the oxidation of the acetylated reduction product of 2 : 4-dinitro-3-methoxytoluene itself. Therefore the nitro-group which is reduced in the anhydrocotarnine derivative is similarly situated to that which is reduced in the dinitromethoxytoluene. Deamination of the nitroaminomethoxytoluene gave 2-nitro-*m*-tolyl methyl ether (Haworth and Lapworth, J., 1923, **123**, 2993), so that in all cases the nitro-group in position 4 is preferentially attacked. That this is true also of the anhydrolaudaline compound follows from the ultimate production of a phenanthrene derivative.

Some difficulties (see p. 1991) were encountered in the preparation of *anhydrolaudaline*-2-*nitro*-4-*acetylamino*-3-*methoxytoluene*, which was reduced to *anhydrolaudaline*-2-*amino*-4-*acetylamino*-3-*methoxytoluene* (III) by means of iron powder and acetic acid or better by hydrogen in presence of palladium.

(III.)



(IV.)



The diazonium sulphate obtained from (III), on treatment with copper powder, gave a small yield of a phenanthrene derivative, which was isolated and analysed in the form of its *methiodide* (IV). At this interesting stage our supply of the somewhat inaccessible starting material had become so small that further progress was not possible. Replacement of the acetylamino-group by hydroxyl

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* After consultation with Professor Pyman.

would give a substance having one of the constitutional formulæ which may be assigned to *iso*corydine.

EXPERIMENTAL.

Anhydrolaudaline-2 : 4-dinitro-3-methoxytoluene (II).—A hot solution of "lodal" * (containing 82·4% of laudalinium chloride) (7·5 g.) and 2 : 4-dinitro-3-methoxytoluene (6 g.) in methyl alcohol (60 c.c.) was cooled and stirred during the addition of sodium methoxide (1·6 g. of sodium) dissolved in methyl alcohol (60 c.c.). The crystals which separated were collected after 48 hours and washed free from sodium chloride by water. A little unchanged dinitromethoxytoluene and a small quantity of the base could be recovered from the mother-liquor (total yield, 9·4 g.; 88·1%). The substance crystallised from methyl alcohol in large, squat, orange-yellow prisms, m. p. 111—112° (Found: C, 57·6; H, 5·6; N, 10·3. $C_{20}H_{23}O_7N_3$ requires C, 57·5; H, 5·5; N, 10·0%). The colourless *hydrochloride* crystallised from alcohol in glistening plates.

Anhydrolaudaline-2 : 4-diamino-3-methoxytoluene (II with $2NH_2$ in place of $2NO_2$).—The powdered dinitro-compound (5 g.) was added to a stirred and ice-cooled mixture of crystallised stannous chloride (5 g.), dissolved in concentrated hydrochloric acid (20 c.c.), acetic acid (20 c.c.), and granulated tin (10 g.). After 2 hours the stirring was discontinued and on the following day the solution was diluted and, after addition of an excess of potassium hydroxide, extracted with benzene. The base in the dried extract could not be induced to crystallise and therefore the *dihydrochloride* was precipitated by means of dry hydrogen chloride (yield almost quantitative). This salt crystallised from alcohol in colourless needles, m. p. 236—237° (Found: C, 55·7; H, 7·1; N, 9·4; Cl, 16·0. $C_{20}H_{27}O_3N_3,2HCl$ requires C, 55·8; H, 6·7; N, 9·7; Cl, 16·0%).

Numerous unsuccessful attempts were made to prepare the monoacetyl and monobenzoyl derivatives of the base and to condense it with oxalic acid (1 mol.). The benzoylation appeared to break the *iso*quinoline ring, since the product was devoid of basic properties.

Anhydrolaudaline-2-nitro-4-amino-3-methoxytoluene.—(A) A hot solution of anhydrolaudaline-2 : 4-dinitro-3-methoxytoluene (5 g.) in alcohol (30 c.c.) was cooled, quickly mixed with aqueous ammonia (1·6 g.; *d* 0·880), and a current of hydrogen sulphide passed, with cooling, until 1·2 g. had been absorbed. The mixture was heated on the steam-bath under reflux for ½ hour, acidified with dilute acetic acid, filtered, and the *base* isolated by means of benzene

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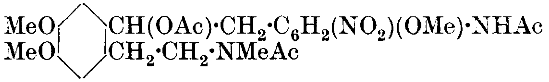
* The registered name of a product manufactured by Messrs. Burroughs Wellcome and Co.

after the addition of ammonia to the filtrate (yield 50%). The substance crystallised from benzene, in which it was readily soluble, in yellow plates or prisms, m. p. 145° (Found: C, 64·6; H, 6·9; N, 9·9. $C_{20}H_{25}O_5N_3,0{\cdot}5C_6H_6$ requires C, 64·7; H, 6·6; N, 9·8%). After drying at 110° in a high vacuum for 3 hours, it changed in colour, becoming yellowish-brown, and slightly decomposed (Found: C, 62·2, 62·3; H, 5·5, 5·3; N, 10·3. $C_{20}H_{25}O_5N_3$ requires C, 62·1; H, 6·4; N, 10·8%). The diazonium salt obtained from the base couples with β-naphthol, giving a crimson azo-compound.

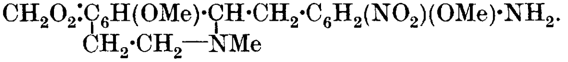
(B) The dinitro-base (5 g.), dissolved in alcohol (40 c.c.), was reduced by the addition of crystallised stannous chloride (8 g.) in alcohol (25 c.c., saturated with hydrogen chloride) during 3 hours, the mixture being stirred and cooled in ice and salt meanwhile. On the following day the base was isolated and crystallised from benzene and then from methyl alcohol; the yellow prisms obtained melted at 144°, alone or mixed with the specimen prepared by the method (A).

A solution of the nitroamine (6 g.) in acetic anhydride (20 c.c.) containing 2 or 3 drops of sulphuric acid was, after 1 hour, mixed with water; the *acetyl* derivative set free by ammonia, after being dried (4·5 g.), crystallised from dry ether in pale yellow needles, m.p. 151° (Found: C, 61·4; H, 6·2; N, 10·3. $C_{22}H_{27}O_6N_3$ requires C, 61·5; H, 6·3; N, 9·8%), which became brownish-purple on exposure to light. When anhydrolaudaline-2-nitro-4-amino-3-methoxytoluene (1 g.) was heated for 1 hour on the steam-bath with acetic anhydride (3 g.), and the product decomposed with water, a crystalline *substance* was obtained which separated from alcohol in very short, microscopic, prismatic needles, m. p. 194° (Found: C, 58·8, 58·4, 58·6; H, 6·5, 6·4, 6·1; N, 7·8. $C_{26}H_{33}O_9N_3$ requires C, 58·8; H, 6·1; N, 7·9%). The substance is devoid of basic properties and, as the indicated composition is that of the acetyl derivative (1 mol.) plus acetic anhydride (1 mol.), it is highly probable that its constitution is expressed by the formula



The facility with which the ring is broken in the production of this compound is noteworthy.

Anhydrocotarnine-2-*nitro*-4-*amino*-3-*methoxytoluene*,



$$\begin{array}{l}\mathrm{CH_2O_2{:}C_6H(OMe){\cdot}CH{\cdot}CH_2{\cdot}C_6H_2(NO_2)(OMe){\cdot}NH_2.}\\ \qquad\quad\mathrm{CH_2{\cdot}CH_2{-}NMe}\end{array}$$

—Anhydrocotarnine-2 : 4-dinitro-3-methoxytoluene (see preceding paper) was reduced exactly as in the case of the laudaline compound by means of alcoholic stannous chloride. The nitroamine crystallised from benzene in minute, yellow prisms, m. p. 184° (Found : C, 60·7, 60·6, 60·6; H, 5·7, 5·6, 5·4; N, 10·5. $C_{20}H_{23}O_6N_3,0{\cdot}25C_6H_6$ requires C, 60·4; H, 5·7; N, 10·0%).* The *acetyl* derivative, obtained by the action of cold acetic anhydride in the presence of a little sulphuric acid, crystallised from ether in pale yellow prisms, m. p. 134° (Found in air-dried material : C, 57·2; H, 5·6; H_2O, 4·4. $C_{22}H_{25}O_7N_3,H_2O$ requires C, 57·2; H, 5·8; H_2O, 3·9%).

*Aceto-2-nitro-3-methoxy-*p*-toluidide*, $CH_3{\cdot}C_6H_2(OMe)(NO_2){\cdot}NHAc$. —The semi-reduction of 2 : 4-dinitro-3-methoxytoluene by ammonium sulphide or alcoholic stannous chloride gave only one nitroamine. (2 : 4-Dinitrostilbene gives 2-nitro-4-aminostilbene or 4-nitro-2-aminostilbene according as the reducing agent is ammonium sulphide or stannous chloride; Thiele and Escales, *Ber.*, 1901, **34**, 2846.)

Hydrogen sulphide was led into a cooled solution of dinitromethoxytoluene (15 g.) in alcohol (45 c.c.) to which aqueous ammonia (10 g.; *d* 0·880) had been added. When the gain in weight was 8 g., the whole was boiled under reflux for 1 hour, the alcohol distilled off, acetic acid added to the residue, and the base extracted from the filtered solution with benzene. The *hydrochloride* precipitated by passing hydrogen chloride into the dried extract was recrystallised from alcohol and then had m. p. 205° (yield 15 g.). The oily base obtained from this was at once treated with acetic anhydride and a trace of sulphuric acid; the *acetyl* derivative crystallised from methyl alcohol and from water in almost colourless, flat needles or pale yellow prisms, m. p. 108—109° (Found : C, 53·9; H, 5·3. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·3%). The acetyl derivative of the product of reduction with alcoholic stannous chloride melted at 108—109°, alone or mixed with the preceding compound.

2-*Nitro*-4-*acetylamino*-3-*methoxybenzoic Acid*,
$NHAc{\cdot}C_6H_2(OMe)(NO_2){\cdot}CO_2H$.—
(A) Potassium permanganate (8 g.) was gradually added to a well-agitated suspension of aceto-2-nitro-3-methoxy-*p*-toluidide (4·8 g.) in a solution of magnesium sulphate (8·4 g.) in water (450 c.c.) at 75—80°. Heating was continued for a short time, and the excess of permanganate was then destroyed by the addition of acetic acid and a few drops of aqueous hydrogen peroxide. The filtered solution was evaporated to a small bulk and acidified with sulphuric acid, and the crystalline precipitate thus produced was removed and dissolved in aqueous sodium carbonate and, the impurities having been extracted by ether, reprecipitated; after crystallisation from methyl alcohol and finally from water, the

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* Liebermann and Lindenbaum (*Ber.*, 1902, **35**, 2917) found that acetylcochenillic acid crystallised with $\frac{1}{4}C_6H_6$.

acid was obtained in colourless needles, m. p. 228—229° (Found : C, 47·3 ; H, 4·1. $C_{10}H_{10}O_6N_2$ requires C, 47·2 ; H, 3·9%).

(B) Anhydrocotarnine-2-nitro-4-acetylamino-3-methoxytoluene was oxidised (*a*) in cold dilute acetone solution by potassium permanganate in about 24 hours, and (*b*) under conditions closely resembling those used in the case of the acetonitromethoxytoluidide. The acids isolated had m. p. 225° and 225—226°, respectively, which were not depressed on admixture with the acid, just described, of m. p. 228—229°. The properties of all the specimens were identical.

Deamination of 2-*Nitro*-3-*methoxy*-p-*toluidine*.—The crystallised hydrochloride (5 g.) of the base, prepared as described above, was dissolved in alcohol (150 c.c.), and a concentrated aqueous solution of sodium nitrite (1·8 g.) added. After 3 hours, pink crystals had separated, and the mixture was heated, at first slowly to 40—50° and after 2 hours for ½ hour on the steam-bath. A yellow oil isolated by steam distillation solidified on cooling in a freezing mixture and then crystallised from light petroleum in almost colourless prisms ; these melted at 50°, alone or mixed with a specimen of 2-nitro-*m*-tolyl methyl ether, m. p. 49°, for which we are indebted to Prof. A. Lapworth and Dr. R. D. Haworth. When mixed with 4-nitro-*m*-tolyl methyl ether, m. p. 62° (Staedel and Kalb, *Annalen*, 1890, **259**, 210), the substance liquefied.

Anhydrolaudaline-2-*amino*-4-*acetylamino*-3-*methoxytoluene* (III).—(A) Iron powder (6 g.) was slowly added to a stirred solution of anhydrolaudalinenitroacetylaminomethoxytoluene (5 g.) in acetic acid (40 c.c.), which was cooled in a mixture of ice and salt. After about 6 hours, the solution was diluted, filtered, and the base extracted with benzene. The *picrate* precipitated from the dried concentrated extract by the addition of picric acid and ether crystallised from ethyl acetate in bright yellow prisms, m. p. 168—169° (Found : C, 52·4 ; H, 5·0 ; N, 12·9 ; H_2O, 2·6. $C_{22}H_{29}O_4N_3,C_6H_3O_7N_3,H_2O$ requires C, 52·0 ; H, 5·2 ; N, 13·0 ; H_2O, 2·8%).

(B) The following method is preferable to that described under (A). A solution of the nitro-base (2 g.) in acetic acid (50 c.c.) containing also an acetic acid solution of palladous chloride (10 c.c. of 2%) was agitated with hydrogen for 3 hours. The filtered liquid was basified with sodium hydroxide, and then ether extracted a *base* which crystallised from ethyl acetate in colourless needles, m. p. 110° after sintering at 105° (Found : C, 63·5 ; H, 7·4 ; N, 10·3 ; H_2O, 4·4. $C_{22}H_{29}O_4N_3,H_2O$ requires C, 63·3 ; H, 7·4 ; N, 10·3 ; H_2O, 4·8%). The yield from 3 operations was 4·0 g. The base is readily soluble in most organic solvents, crystallises from water in clusters of microscopic needles, and yields the picrate, m. p. 168—169°, described above.

Dehydro-anhydrolaudaline-4-acetylamino-3-methoxytoluene Methiodide (IV).—The amino-base (8 g.) just described was dissolved in 2·5*N*-sulphuric acid (80 c.c.) and diazotised below 0° (24 c.c. of *N*-sodium nitrite). Addition of copper powder (3 g.) after a few minutes caused the evolution of nitrogen, and after 3 hours the base in the filtered solution was isolated by means of ammonia and ether. Crystallisation could not be induced and therefore the *methiodide* was prepared. This crystallised from acetone in colourless needles (0·25 g.) which sintered at 205° and had m. p. 210° (decomp.) (Found: C, 49·9; H, 6·0; I, 22·6; H_2O, 4·7. $C_{23}H_{29}O_4N_2I,1{\cdot}5H_2O$ requires C, 50·0; H, 5·8; I, 23·0; H_2O, 4·9%). The substance dissolves in sulphuric acid to a violet solution which becomes pink on heating.

iso-apo*Morphine Dimethyl Ether Methosulphate* (I).—1-(6-Nitrohomoveratryl)-2-methyl-1 : 2-dihydro*iso*quinoline (Robinson and Robinson, *loc. cit.*, p. 1459), when reduced by stannous chloride in acetic acid solution, furnished the corresponding amino-compound, which crystallised from ether. This base or the original substance, when heated with tin and concentrated hydrochloric acid in an atmosphere of hydrogen, yielded 1-(6-aminohomoveratryl)-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline as an oil. Ferric chloride developed in a dilute solution of this amine an intense blue coloration. A solution in dilute sulphuric acid was diazotised and treated with copper powder; the crude *iso-apo*morphine dimethyl ether isolated from the solution was purified through the picrate and so obtained in a crystalline condition. The crude base combined rapidly with pure methyl sulphate; the crystalline product, after several recrystallisations from water, was obtained in short, microscopic needles containing solvent of crystallisation. These dissolved when treated with alcohol, but at once separated again. The compound was crystallised from alcohol and dried at 100° (Found: C, 59·7; H, 6·5; S, 7·6. $C_{21}H_{27}O_6NS$ requires C, 59·9; H, 6·2; S, 7·6%). This salt, m. p. 246°, gives a rich royal-blue coloration with Fröhde's reagent.

6 : 7-*Dimethoxy*-1-(β-*dimethylaminoethyl*)*phenanthrene*, $C_{14}H_7(OMe)_2{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$.—Addition of sodium hydroxide to an aqueous solution of the preceding methosulphate produced no precipitate, but an oil separated on boiling. The substance was crystallised from methyl alcohol and recrystallised from aqueous methyl alcohol and then from light petroleum, being thus obtained in large, glistening leaflets, m. p. 111° (Found: C, 77·4; H, 7·7; N, 4·5. $C_{20}H_{23}O_3N$ requires C, 77·7; H, 7·4; N, 4·5%). This base is readily soluble in most organic solvents, but is sparingly soluble in light petroleum. Its *hydro-*

chloride is sparingly soluble in dilute hydrochloric acid and crystallises in colourless needles. The base develops with Fröhde's reagent an intense green coloration, and dissolves in sulphuric acid with a bright pink colour which rapidly disappears; addition of a drop of Mandelin's reagent then produces an ivy-green coloration.

Almost at once, when the base and methyl iodide were mixed in alcoholic solution, the *methiodide* crystallised in colourless needles. Sodium hydroxide was added to the clear solution obtained on dilution with water and, on boiling, a milkiness appeared which soon gave place to a crystalline substance and at the same time trimethylamine was evolved. A crystalline, non-nitrogenous, neutral substance was isolated by means of ether.

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