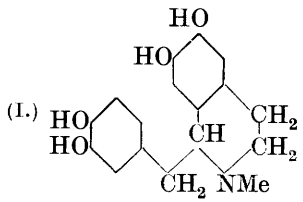
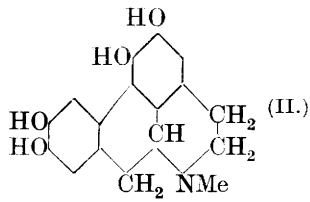
103. *Preliminary Synthetic Experiments in the Morphine Group. Part IV. A Dehydro-derivative of Laudanosoline Hydrochloride and its Constitution.*

By Robert Robinson and Shigehiko Sugasawa.

Our working hypothesis (compare Part I; J., 1931, 3163) of the biogenesis of alkaloids of the morphine group indicated the desirability of studying the oxidation of laudanosoline (I), because there is a possibility of effecting dehydrogenation with formation of *nor*glaucine (II).





The results described below make it appear improbable that this oxidative coupling of the aromatic nuclei can be brought about unless the basic function of the nitrogen atom is repressed by acylation or by quaternary salt formation, and as a sequel to the present investigation enquiries in these directions are in progress.

Laudanosoline is readily oxidisable, but no definite substances could be isolated from the products in numerous experiments until it was discovered that a relatively smooth oxidation was brought about by chloranil applied in alcoholic solution and in the presence of potassium acetate. The product was isolated as the acetate or chloride and analysis showed that the laudanosoline salt had suffered the loss of two hydrogen atoms.

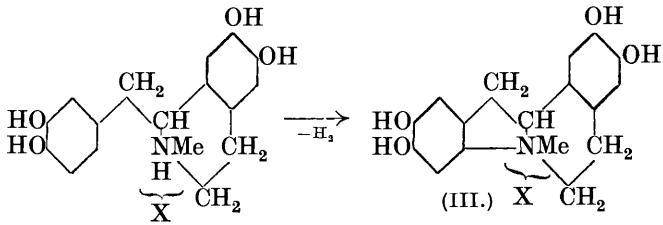
As this agreed with anticipations, we naturally first tested the idea that the substance was *nor*glaucine, but found that exhaustive methylation proceeded in an entirely different fashion from that characteristic of a member of the glaucine group. A nitrogen-free compound could not be obtained and with the aid of a specimen of boldine, kindly supplied by Dr. K. Warnat, to whom we are greatly indebted, we were able to control our technique and had no difficulty in isolating tetramethoxyvinylphenanthrene from quite small quantities of the alkaloid by exhaustive methylation.

It then occurred to us that the substance might be a *nor*pavine (compare Pyman, J., 1909, **95**, 1610; 1915, **107**, 176) or a laudanosoline derivative containing an ethylenic bond; these suggestions were, however, found to be untenable. The course of the exhaustive methylation excluded the former idea and the fact that the oxidation product could not be reduced, catalytically or otherwise, disposed of all formulæ containing unsaturated groups.

The possibility that the methyl attached to nitrogen might have taken part in the reaction leading to a base of tetrahydro*nor*berberine type was also considered, but rejected on account of the fact that the oxidation product was found to contain methyl attached to nitrogen. The result of comparisons of the methylated methiodide derived from the oxidation product with authentic specimens of tetrahydropalmatine and *nor*coralydine methiodides showed that it differed from these substances.

The solution of the problem was revealed when it was realised that the dehydrolaudanosoline hydrochloride is a *quaternary salt* and that the acetyl derivatives obtained from it (see below) are the outcome of more deep-seated changes than simple acetylation of the corresponding base.

Actually the oxidation occurs in accordance with the scheme :



This view is justified by a consideration of the properties of the oxidation product and of its derivatives, the main points being the following :—

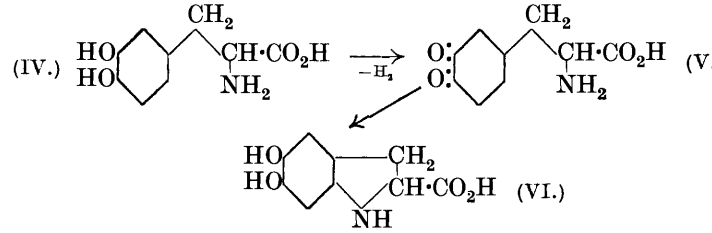
(1) The oxidation product contains NMe and yields an *O*-tetramethyl ether which is a quaternary salt; the original substance is therefore a quaternary salt.

(2) The course of the exhaustive methylation of the *O*-tetramethyl ether (Hofmann and also Emde methods) showed that the nitrogen atom is a member of two ring systems.

(3) The final product of the Emde degradations was identified with that from laudanosine itself; this proved that the carbon skeleton remained unchanged.

(4) Definite indole colour reactions of some of the derivatives were observed.

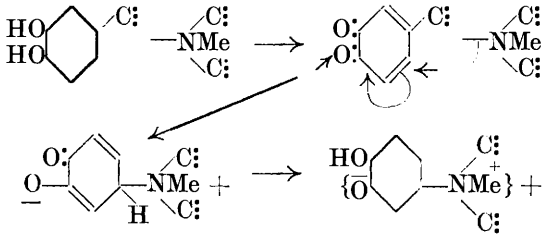
The oxidation of a tertiary base to a quaternary salt by indole-ring closure appears to be novel, but the work of Raper (*Biochem. J.*, 1927, 89) on the conversion of tyrosine into indole derivatives under the influence of tyrosinase provides a close analogy. The intermediate products are 3 : 4-dihydroxyphenylalanine (IV) and probably the related *o*-quinone (V); the dihydroindole (VI) then suffers further oxidation in two directions leading to true aromatic indole derivatives.



In considering the mechanism of the variation of the process which we have encountered, the idea that the kationic nitrogen of an ammonium salt group can attack a quinonoid or phenolic nucleus has no advantages and we are led to the view that the oxidation involves a separation of charges in the free base.

Probably the unshared electrons of the nitrogen atom are donated

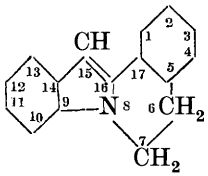
to the quinonoid nucleus and at the same time the latter is reduced and a covalency formed between the nucleus and the nitrogen atom. The result is a phenol-betaine, and a keto-enol tautomeric change must also occur at some stage.

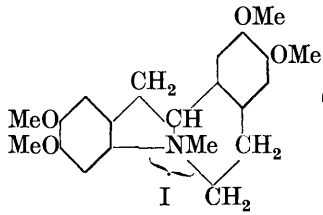


The fact that this process can take place with tertiary bases indicates that in all similar cases the fundamental mechanism is the reduction of a quinonoid nucleus by the unshared electrons of atoms such as nitrogen and oxygen.

The ring-system contained in (III) is derived from a dibenzodihydropyrrocoline (VII) and the methylated oxidation product (iodide) is therefore 2 : 3 : 11 : 12-tetramethoxy-8-methyldibenzotetrahydropyrrocolinium iodide (VIII).

(VII.)



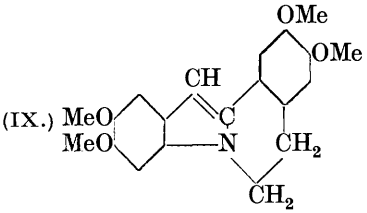


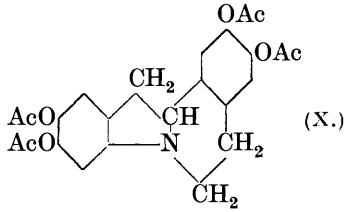
(VIII.)

When the chloride corresponding with (VIII) was cautiously heated, methyl chloride was evolved : the product is no doubt tetramethoxydibenzotetrahydropyrrocoline, but on crystallisation the melting point rises and tetramethoxydibenzodihydropyrrocoline (IX) is produced as the result of oxidation in the air ; the mother-liquors mixed with methyl iodide afford the iodide (VIII), thus proving that the tetrahydro-base is among the products.

A similar phenomenon was noticed in connexion with the products of acetylation of the original oxidation product (III) by means of boiling acetic anhydride and pyridine. The results were very difficult to understand until it was realised that the process involves *N*-demethylation. The products were a substance $C_{16}H_{11}N(OAc)_4$, m. p. 148°, and a second derivative $C_{16}H_9N(OAc)_4$, m. p. 215°. Neither could be reduced in the presence of platinum oxide, but the more fusible form was converted into the less fusible by this treatment. The latter gives an intense reaction with Ehrlich's reagent,

whereas the substance, m. p. 148°, gives a feeble reaction. It is clear that the lower-melting acetate is to be represented by the formula (X) and that the substance, m. p. 215°, is the related true aromatic indole derivative (like IX).





This theory was finally confirmed by a direct determination of methyl attached to nitrogen in the derivative, m. p. 215°, which gave a negative result.

The formation of these two acetyl derivatives was used to show that the oxidation of laudanosoline (acetate or carbonate) can be effected by prolonged exposure of aqueous solutions to light and air. The products of the oxidation by means of chloranil were isolated in the course of these experiments in yields which must be considered very satisfactory under the conditions.

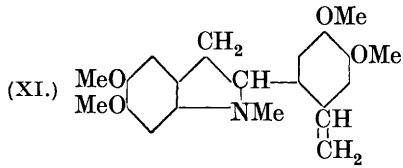
Thus, if laudanosoline salts occurred in a plant, they would probably be converted into the dehydro-derivatives as the result of aëration.

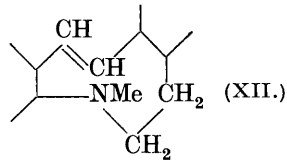
There remains for consideration the course of the exhaustive methylation of the oxidation product, in which series of processes we have employed not only Hofmann's method but also that introduced by Emde (*Arch. Pharm.*, 1912, **391**, 88) depending on the reduction of the quaternary salts in acid solution by means of sodium amalgam.

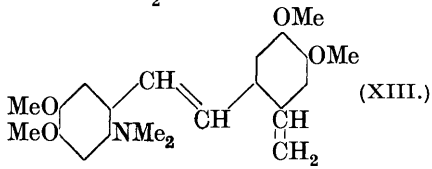
The methine derived by either method from (VIII) (methosulphate) must have the constitution (XI) rather than the alternative (XII), because the product of its dehydrogenation by means of palladium exhibits indole-type colour reactions and also because the methine in acid solution shows no tendency to revert to the quaternary salt. On the other hand, Pyman's large-ring methine-A from tetrahydroberberine methohydroxide reverts to the quaternary condition with facility (compare J., 1913, **103**, 828). A further argument tending in the same direction is noted below. Incidentally the methine (XI) is constituted in some respects analogously to brucidine and its characteristic reaction with ferric chloride is quite similar to that of brucidine.

The second Hofmann-stage gives the base (XIII), from which the nitrogen cannot be eliminated by further methylation. The related

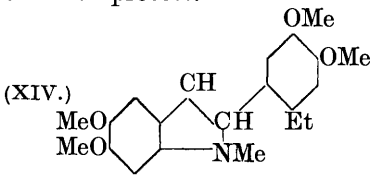
methohydroxide loses methyl alcohol when heated and the original base (XIII) is recovered.

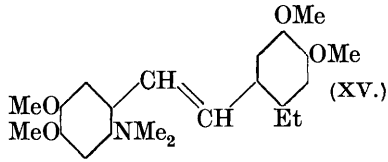






The catalytic reduction of (XI) affords the dihydro-derivative (XIV); the methine derived from this base is (XV), and like (XIII) it retains the nitrogen on further treatment of its metho-salts by the Hofmann or Emde process.

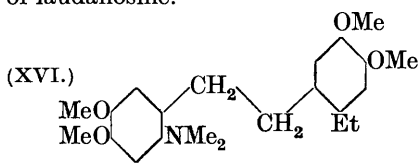


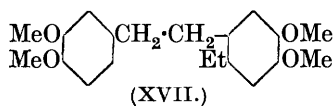


On the other hand, the application of Emde's method to the metho-derivative of (XIV) furnished reduced methine (XVI), the structural relation of which to (XV) was proved by its production from the latter substance (or from XIII) by catalytic reduction. Neither the Hofmann nor the Emde method succeeds with the base (XV), but the Emde-degradation of (XVI) gives about half the theoretical amount of the nitrogen-free product (XVII). The constitution of this substance was confirmed by its formation by catalytic hydrogenation of the tetramethoxyvinylstilbene,

$$(MeO)_2C_6H_3\cdot CH{:}CH\cdot C_6H_2(CH{:}CH_2)(OMe)_2$$

(XVIII), which is the final product of the exhaustive methylation of laudanosine.





The difference in behaviour exhibited by the quaternary metho-salts derived from (XV) and (XVI) is noteworthy and the stabilising influence of the unsaturated group in the *o*-position is probably the

result of the increased electron pressure which it effects at the aromatic carbon atom joined to nitrogen.

The degradation (as opposed to decomposition to tertiary base and methane) is doubtless initiated by electron-attack (from the sodium amalgam) at the nuclear carbon and this tendency is opposed by the electromeric process in the polyenoid system including the aromatic nucleus and the ethylene linkage of the stilbene group.

Incidentally the divergence in behaviour of the quaternary salts from (XV) and (XVI) would not be explicable if the original methine (XI) had the constitution (XII). It is clear that on such an assumption (XV) and (XVI) would necessarily have the constitutions $(MeO)_2C_6H_2(NMe_2)\cdot CH_2\cdot CH_2\cdot C_6H_2(CH{:}CH_2)(OMe)_2$ and $(MeO)_2C_6H_2(NMe_2)\cdot CH_2\cdot CH_2\cdot C_6H_2(CH_2\cdot CH_3)(OMe)_2$, respectively, and it will be agreed that the vinyl group would then be too remote from the point of attack of the reducing agent to produce the large effect actually observed.

All conjugative effects are interrupted in this case by two methylene groups and only a direct influence through the intervening space can be postulated.

EXPERIMENTAL.

Laudanosoline Hydrochloride.—A certain amount of the salt employed was prepared by the method described in the preceding communication, but the following modification of Oberlin's procedure (compare *Arch. Pharm.*, 1927, **265**, 256) was found to be more convenient.

A mixture of *dl*-laudanosine (10 g.), powdered aluminium chloride (60 g.), and dry xylene (15 c.c.) was heated in an oil-bath at 140—150° for 20 minutes, and the temperature finally raised to 180—190° for 5 minutes; the mixture was occasionally stirred during the progress of the reaction. The product was decomposed with ice and hydrochloric acid and distilled in steam, the residual liquid treated with charcoal, and the filtered solution concentrated until crystals were deposited. On cooling, a grey, sandy, crystalline powder (8·5—9 g.) was obtained, which was pure enough for most purposes. After crystallisation from dilute hydrochloric acid the salt had m. p. 240—242° and was identified with the product described in the preceding communication. In order to show that the process involves no structural change other than demethylation a specimen was treated with methyl sulphate and aqueous potassium hydroxide, and the product transformed into the iodide. It proved to be identical with *dl*-laudanosine methiodide.

2 : 3 : 11 : 12-*Tetrahydroxy*-8-*methyldibenzotetrahydropyrrocolinium Salts* (III).—(A) After a large number of preliminary experiments

the following method was adopted : A mixture of potassium acetate (1·5 g.), alcohol (50 c.c.), and laudanosoline hydrochloride (5 g.) was gently heated on the steam-bath until a clear solution was obtained. Chloranil (3·7 g.) was dissolved in hot alcohol (1000 c.c.), and the solution cooled with stirring so as to cause a fine crystallisation; it was then added to the cooled laudanosoline solution in a thin stream with shaking.

A reddish-brown coloration appeared on the addition of the oxidising agent, but this disappeared rapidly; it probably signified the formation of the intermediate *o*-quinone as in Raper's experiments (*loc. cit.*). Crystallisation of the oxidation product commenced when about half of the chloranil had been introduced and towards the end of the operation the initial coloration was more persistent and finally the solution had a permanent reddish-brown colour.

After 2—3 hours' keeping, the grey precipitate was collected and washed with water, alcohol and ether. Dilute hydrochloric acid was added to the filtrate, which was then evaporated to dryness in a vacuum, the residue triturated with alcohol, and the solid collected and washed with water. After conversion of the crystalline acetate into hydrochloride the total yield amounted to 3—3·5 g. Occasionally the acetate did not separate and in such cases the whole product was worked up as hydrochloride (yield, about 3 g.).

This *hydrochloride* is remarkably sparingly soluble, even in boiling water, and recrystallisation was effected by solution in hot aqueous potassium acetate (charcoal) and addition of an excess of dilute hydrochloric acid. Repetition of the process afforded faintly grey, microscopic prisms, m. p. 303—305° (Found : C, 58·0; H, 5·9; N, 4·0; Cl, 10·3; NMe, 8·6. $C_{17}H_{18}O_4NCl,H_2O$ requires C, 57·7; H, 5·7; N, 4·0; Cl, 10·0; NMe, 8·2%). The substance is soluble in aqueous sodium hydroxide, sodium carbonate or ammonia but not in aqueous sodium bicarbonate; the alkaline solutions become brown on exposure to air. Addition of ferric chloride to a very dilute alcoholic solution produces an intense green coloration, which becomes bluer on keeping and is changed to intense reddish-violet on the addition of sodium carbonate; later a deep maroon precipitate is deposited from a colourless solution.

(B) A solution of laudanosoline hydrochloride (1 g.) and sodium carbonate (5 g.) in water (100 c.c.) was placed in an open situation and kept for 2 months. The liquid was filtered, acidified with hydrochloric acid, and evaporated to dryness under diminished pressure. The residue crystallised from dilute hydrochloric acid as a grey sandy powder, m. p. 300—303° (yield, 0·3 g.).

(C) Potassium acetate (0·3 g.) was substituted for the sodium

carbonate used in (B). Otherwise the method was identical and 0·5 g. of the hydrochloride, m. p. 301—303°, was obtained.

The identity of the products obtained by the three methods (A), (B), and (C) was proved by direct comparisons but especially by the preparation of the acetyl derivatives, m. p. 148° and m. p. 215°, from each specimen. The acetyl derivatives from the different sources showed undepressed melting points when mixed.

2 : 3 : 11 : 12 - *Tetra - acetoxydibenzotetrahydropyrrocoline* (X). — A mixture of tetrahydroxymethyldibenzotetrahydropyrrocolinium chloride (0·5 g.), acetic anhydride (5 c.c.), and a few drops of pyridine was refluxed for an hour. The product was decomposed by crushed ice (2—3 hours), and the solid collected, triturated with aqueous sodium carbonate, washed with water, and dried (0·5 g.). The crude product consisted of two substances readily separable by means of ethyl acetate. The substance soluble in this solvent was precipitated therefrom by means of light petroleum (b. p. 40—60°) and then crystallised from ethyl alcohol (some sparingly soluble residue) in needles, m. p. 145—158°. Six recrystallisations effected complete removal of the less soluble acetate and furnished colourless feathery needles, m. p. 148° with sintering from 144° (Found : C, 63·8; H, 5·3; N, 3·1; *M*, by micro-Rast, 500, 485. $C_{24}H_{23}O_8N$ requires C, 63·6; H, 5·1; N, 3·1%; *M*, 453). This derivative is readily soluble in hot alcohol, sparingly so in the cold solvent and in ether. It is a weak base; a solution in glacial acetic acid gives a milky suspension when poured into water, but this is cleared by the addition of hydrochloric acid. With Ehrlich's reagent (*p*-dimethylaminobenzaldehyde in aqueous-alcoholic hydrochloric acid solution) this substance gives only a weak reaction, but, on heating, the violet colour gradually deepens, probably as the result of oxidation to an indole derivative. That the acetylation process does not break up the tetracyclic structure of the oxidation product of laudanosoline hydrochloride was proved by the conversion of the derivative, m. p. 148°, into the tetramethoxymethyldibenzotetrahydropyrrocolinium iodide mentioned below.

The acetyl compound (1 g.) was dissolved in alcohol (20 c.c.) on the steam-bath and in an atmosphere of hydrogen; alcoholic potassium hydroxide (3 c.c. of 10%) was added and after 5 minutes' heating 5% hydrochloric acid (10 c.c.) was introduced and the liquid evaporated under diminished pressure.

The crystalline hydrochloride sintered at 270° and decomposed at about 290°. It was methylated by means of potassium hydroxide and methyl sulphate as described below; the iodide derived from the product, crystallised from aqueous methyl alcohol, had m. p. 240—242° (decomp.) and exhibited the same behaviour when mixed

with authentic tetramethoxymethyldibenzotetrahydropyrrocolinium iodide.

2 : 3 : 11 : 12-*Tetra-acetoxydibenzodihydropyrrocoline* (IX; AcO instead of OMe).—The crude product (0·5 g.) of the acetylation described in the last section crystallised from ethyl acetate in light amber-coloured prisms (0·1 g.), m. p. 213°, and on recrystallisation, m. p. 215° (Found: C, 64·2; H, 4·8; N, 3·2; NMe, 0·0; *M*, by micro-Rast, 520, 519. $C_{24}H_{21}O_8N$ requires C, 63·9; H, 4·7; N, 3·1%; *M*, 451). When crystallised rapidly, the substance separated in leaflets. It is very sparingly soluble in ether and alcohol and rather sparingly soluble in ethyl acetate. It exhibits no basic properties and with Ehrlich's reagent it gives an intense bluish-violet coloration. The substance is also resistant to catalytic hydrogenation and indeed it can be prepared by attempting the catalytic reduction of the acetate, m. p. 148°. This dehydrogenation was, however, more conveniently carried out by boiling an alcoholic solution of the acetate, m. p. 148°, in which platinum-black, prepared from platinum oxide, was suspended. Leaflets began to separate after 5 minutes and after 30 minutes the liquid was cooled and the solids were collected and extracted with boiling ethyl acetate. The acetate, m. p. 214—215° (Found: C, 64·3; H, 4·7; N, 3·4%), was thus isolated in almost theoretical yield. Identity with the product of the acetylation was established by the undepressed melting point of the mixed specimens.

The benzoylation of the laudanosoline hydrochloride oxidation product by Einhorn's method and also the action of diazomethane on a methyl-alcoholic suspension of the substance did not afford crystalline derivatives.

2 : 3 : 11 : 12-*Tetramethoxy*-8-*methyldibenzotetrahydropyrrocolinium Salts* (VIII).—The hydrochloride (III) (0·5 g.) was suspended in water (*ca.* 3 c.c.) under hydrogen, aqueous potassium hydroxide (5 c.c. of 33%) added, and the mixture shaken until a clear solution resulted. Pure methyl sulphate (3 c.c.) was then introduced and vigorous agitation continued for about 10 minutes; a rather sudden reaction then occurred. Further quantities of aqueous potash and methyl sulphate equal to those already used were added and after 2—3 minutes the product began to separate. Finally, third portions of the reagents were added and when the reaction had subsided the product was precipitated by the addition of aqueous potash (15 c.c. of 33%). After several hours' keeping, the methosulphate was collected and dried in a desiccator (0·7 g., m. p. 222—226°) without having been washed. This salt and also the chloride show the behaviour of quaternary salts and do not give precipitates on the addition of ammonia to their aqueous solutions; moreover, no base,

soluble in organic solvents, is produced on the addition of caustic alkalis.

The related *iodide*, prepared by double decomposition with sodium iodide in aqueous solution, crystallised from aqueous methyl alcohol in colourless prisms which became yellow in the air without alteration of the m. p., 242—243° (decomp.) (Found : C, 51·1; H, 5·6; N, 2·5; I, 26·1; MeO, 25·9; NMe, 5·5. $C_{22}H_{28}O_4NI,3{\cdot}5H_2O$ requires C, 51·2; H, 5·5; N, 2·9; I, 25·8; 4MeO, 25·7; NMe, 6·0%).

2 : 3 : 11 : 12-*Tetramethoxydibenzodihydropyrrocoline* (IX).—The iodide described in the last section was converted into the chloride by means of silver chloride in aqueous methyl-alcoholic solution. On concentration of the filtered solution, the salt was obtained as a white crystalline powder, m. p. 225° (decomp.). The dry chloride (0·5 g.) was slowly heated by means of a bath of sulphuric acid and under diminished pressure; effervescence began at 215°. After heating at 220° for 10 minutes and at 225° for a further 2—3 minutes, the product was dissolved in hot methyl alcohol and, on cooling, light yellow crystals (0·2 g.), m. p. 100—115°, separated. On recrystallisation the substance became more sparingly soluble and after three crystallisations it was obtained in plates, m. p. 180—187°. This material was now too sparingly soluble in methyl alcohol for convenient recrystallisation, and it was crystallised twice from ethyl acetate, forming microscopic yellow plates, m. p. 201—203°, unchanged by further crystallisation (Found : C, 70·5; H, 6·3; N, 4·3. $C_{21}H_{21}O_4N$ requires C, 70·8; H, 6·2; N, 4·1%). The substance is not a base and it develops a very intense, pure royal-blue coloration when treated with Ehrlich's reagent in cold alcoholic solution.

From an experiment with the specimen, m. p. 180°, it was found that the substance does not react with methyl iodide, but the first methyl-alcoholic mother-liquors from the crystallisation of the original crude product were mixed with methyl iodide and, on keeping, a substance gradually separated in colourless prisms, m. p. 242—244° (decomp.). This was identified with tetramethoxymethyldibenzotetrahydropyrrocolinium iodide by direct comparison and by the m. p. 242—244° (decomp.) of a mixture with an authentic specimen.

It is evident that the decomposition of the methochloride proceeded normally with formation of tetramethoxydibenzotetrahydropyrrocoline, which is basic and can be transformed into its methiodide, but that this dihydroindole derivative is oxidised by air in the course of crystallisation. It is thus much less stable than the corresponding tetra-acetoxy-compound described above (m. p. 148°). Furthermore, both these tetracyclic substances are far more readily oxidised than the methines (see below), which also are dihydroindoles.

5 : 6-Dimethoxy - 2 - (3′ : 4′- dimethoxy -6′-vinylphenyl)-1 - methyldihydroindole (XI).—(A) The crude methylated methosulphate (0·5 g.) of the form (VIII) was dissolved in hot water (10 c.c.), and the solution filtered, mixed with aqueous potassium hydroxide (30 c.c. of 33%), and heated (oil-bath at 120—130°) for 1·5 hours; a brown oil then floated on the surface. After cooling, this was isolated by means of ether; the substance crystallised from methyl alcohol (yield, 0·3—0·35 g.; m. p. 124—125°), ultimately in colourless aggregates, m. p. 126—127° (Found : C, 71·0; H, 7·3; N, 4·1; MeO, 35·2. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0; N, 3·9; 4MeO, 34·9%). The methine is readily soluble in most organic solvents with the exception of light petroleum; it is a rather weak base, being precipitated from its solution in glacial acetic acid by the addition of water. It does not yield a methiodide in methyl-alcoholic solution.

When the base was dissolved in acetic acid and a little 0·5% hydrochloric acid, the solution diluted, and ferric chloride added, a deep olive-green coloration with a pink dichroism (not so clear as that due to brucidine under similar conditions) was produced. The action of excess of the reagent is to change the colour to brownish-yellow and then orange. These changes resemble very closely those obtained with brucidine, but apparently in the latter case the green colour is more stable. On keeping, or on warming, the ultimate results are practically identical.

A pure specimen gave an entirely negative result with Ehrlich's reagent in the cold and a faint dull violet on heating. However, when the base (0·02 g.) was heated with palladium-black (0·1 g.) at 195—200° for 30 minutes, the product gave a deep dull magenta coloration with Ehrlich's reagent in the cold and the colour became bluer and brighter on heating. The dehydrogenation of this dihydroindole derivative is by no means so easily accomplished as in the cases of the tetracyclic substances mentioned above. It occurs in the cold to some extent, however, because the crude product of catalytic hydrogenation under ordinary conditions exhibits the indole colour reaction.

(B) The Emde degradation of the methylated methosulphate (0·5 g.) was accomplished by solution in hot water (15 c.c.) and treatment with 5% sodium amalgam (5 g.) on the steam-bath for 2 hours. A further equal quantity of the amalgam was added and the heating continued for 3 hours. The product (0·3 g.), crystallised from methyl alcohol, melted at 125—127°, alone or mixed with the product of the Hofmann elimination.

5 : 6 - Dimethoxy - 2 - (3′ : 4′- dimethoxy -6′-ethylphenyl) - 1 - methyldihydroindole (XIV).—The methine (0·5 g.), dissolved in alcohol (20 c.c.), was hydrogenated in presence of platinum oxide–platinum

black: reduction ceased when 40 c.c. (theory, 32 c.c.) of hydrogen had been absorbed. The filtrate from the catalyst was evaporated; the residue crystallised from alcohol in colourless prisms (0·4 g.), m. p. 92—93° (Found: C, 70·6; H, 7·7; N, 4·0. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·5; N, 3·9%). This dihydro-derivative is a stronger base than the methine (XI) from which it was derived. It gives an intense magenta coloration with Ehrlich's reagent, but this is due to a trace of impurity and a recovered specimen of the substance gave a much weaker reaction.

6-*Dimethylamino*-3 : 4 : 3′ : 4′-*tetramethoxy*-6′-*vinylstilbene* (XIII).—Methyl sulphate (1 g.) was added to a solution of the methine (XI) (0·5 g., m. p. 127°) in dry benzene (15 c.c.), and the mixture heated on the steam-bath for 2 hours. The separation of the methosulphate in slender needles was completed, after cooling, by the addition of ether.* The salt was collected and dissolved in hot water (5 c.c.), and aqueous potassium hydroxide (20 c.c. of 40%) added; the whole was then heated on the steam-bath for 5 hours (no volatile base was evolved). The product, isolated by means of ether, crystallised from methyl alcohol in greenish-yellow rhombic plates (0·25 g.), m. p. 109—110° after slight previous softening (Found: C, 71·6; H, 7·6; N, 4·0. $C_{22}H_{27}O_4N$ requires C, 71·5; H, 7·3; N, 3·8%).

Examination of the ethereal solution (*) led to the recovery of unchanged methine, m. p. 127°. When the methosulphate of the new base m. p. 110°, was heated with potash, no trimethylamine was produced and the original base was recovered.

Reduction of the methosulphate of the methine (XI), m. p. 127°, by means of sodium amalgam furnished a base, m. p. 61—66°, which was not further investigated but was doubtless tetramethoxydimethylaminovinyldiphenylethane.

6-*Dimethylamino*-3 : 4 : 3′ : 4′-*tetramethoxy*-6′-*ethylstilbene* (XV).—A mixture of the dihydromethine (XIV) (0·7 g.), pure methyl sulphate (1·5 g.), and benzene (10 c.c.) was heated on the steam-bath for 2 hours, cooled, and dry ether (30 c.c.) added. The pasty methosulphate was separated, washed with fresh ether, and dissolved in water (5 c.c.). The solution was mixed with aqueous potassium hydroxide (20 c.c. of 40%) and heated for 4 hours in a boiling water-bath. The oil was taken up in ether, and the extract washed with dilute hydrochloric acid; the hydrochloride then separated in colourless crystals and was collected. The *base*, liberated from this salt and isolated by means of ether, crystallised from methyl alcohol in small colourless needles (0·5 g.), m. p. 123—124° (Found: C, 71·0; H, 7·8; N, 3·9; MeO, 33·1; NMe_2, 11·4. $C_{22}H_{29}O_4N$ requires C, 71·2; H, 7·8; N, 3·8; 4MeO, 33·4; NMe_2, 11·9%). The metho-

sulphate of this base was readily obtained, but when it was heated with aqueous potassium hydroxide, no trimethylamine was produced and the original substance, m. p. 123—124°, was recovered. The same result was obtained when the methosulphate was reduced by means of sodium amalgam : as pointed out in the Introduction, this behaviour is in striking contrast to that of the related diphenylethane derivative, which gives a non-nitrogenous product in Emde's reaction.

6-Dimethylamino-3 : 4 : 3′ : 4′-tetramethoxy-6′-ethyl-αβ-diphenylethane (XVI).—This substance has been obtained by applying the Emde method to the base (XIV) and by catalytic reduction of the bases (XIII) and (XV).

(A) The dihydromethine (XIV) (1 g.) was converted into its methosulphate in benzene solution as in other cases and the product, dissolved in water (25 c.c.), was reduced by means of 5% sodium amalgam (5 g.). After 2 hours' heating on the steam-bath, a further quantity (5 g.) of sodium amalgam was added, and the heating continued for 3 hours more with occasional shaking. The oil that separated was taken up in ether and removed from the extract by washing with dilute hydrochloric acid ; on keeping, the hydrochloride separated in colourless prisms, m. p. 130—131°, apparently homogeneous.

The base liberated from this salt and collected by means of ether crystallised from aqueous methyl alcohol in aggregates of colourless needles (0·4 g.), m. p. 63—64°, and on recrystallisation, m. p. 65° (Found : C, 71·0 ; H, 8·3 ; N, 4·2 ; MeO, 32·8. $C_{22}H_{31}O_4N$ requires C, 70·8 ; H, 8·3 ; N, 3·8 ; 4MeO, 33·2%).

(B) and (C). The catalytic reduction of the bases (XIII) and (XV) was accomplished in alcoholic solution with a platinum oxide–platinum-black catalyst under the usual conditions at room temperature. Hydrogen was absorbed very slowly and the reduction of (XIII) occupied not less than 20 hours. In both cases the base was isolated by evaporation of the alcoholic filtrate from the catalyst and crystallisation from aqueous methyl alcohol; the respective products had m. p. 63—64° and m. p. 64—65° and mixtures of these specimens with one obtained as under (A) melted at the same temperatures. In every respect the substances were found to be identical.

3 : 4 : 3′ : 4′-Tetramethoxy-6′-ethyl-αβ-diphenylethane (XVII).—The foregoing base (XVI) (1 g.) was converted into its methosulphate in the usual manner, and the reduction with sodium amalgam carried out under exactly the same conditions and with the same quantities as in the process described in the last section under (A). The formation of a volatile base was observed when the temperature reached 60°, and the amine was collected in dilute hydrochloric acid.

The oil was taken up in ether, and the solution washed well with dilute hydrochloric acid to remove any recovered base; the neutral compound, remaining in the ether, crystallised from aqueous methyl alcohol (yield, 0·3 g.) and then from aqueous acetic acid in elongated, thin, colourless plates, m. p. 78° (Found: C, 72·6; H, 7·9. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%). About half of the original substance (0·5 g., m. p. 62—63°) was recovered from the acid washings and after crystallisation it was identified with an authentic specimen. The volatile base was converted into the chloroaurate, which crystallised from dilute hydrochloric acid in yellow fern-like crystals, decomposing at 248—250° (Found: Au, 49·0. Calc. for $NMe_3,HAuCl_4$: Au, 49·4%).

In order to confirm the constitution of the neutral product we have prepared it from *dl*-laudanosine, which, by a two-stage Hofmann degradation, yields tetramethoxyvinylstilbene (XVIII). We found the substance had the melting point and other properties assigned to it by Decker and Galatty (*Ber.*, 1909, **42**, 1183).

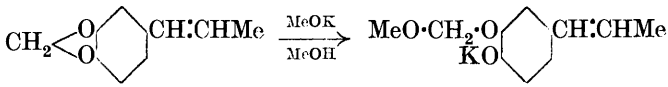
On hydrogenation by the Adams method it absorbed exactly the theoretical volume of hydrogen (2 mols.) without difficulty and afforded a substance crystallising from dilute acetic acid in thin plates, m. p. 78° alone or mixed with the specimen obtained as described above.

3 : 4-*Dihydropapaverine Methiodide.*—In the course of our work it was thought necessary to examine the behaviour of the dihydropapaverine derivatives.

According to Pictet and Finkelstein (*Ber.*, 1909, **42**, 1988) dihydropapaverine methiodide constitutes "eine rotgelbe firnissartige Masse." 3 : 4-Dihydropapaverine synthesised by the method of these authors was heated in methyl-alcoholic solution with an excess of methyl iodide for 4 hours on the steam-bath. The *methiodide* separated when the solution was kept in the ice-chest and crystallised from methyl alcohol in yellow rhombic plates, m. p. 191—193° with slight previous softening (Found: C, 51·8; H, 5·3; N, 2·8; I, 26·2. $C_{21}H_{26}O_4NI$ requires C, 52·2; H, 5·4; N, 2·9; I, 26·3%).

dl-*Tetrahydropalmatine Methiodide.*—This substance was also prepared for the purpose of making comparisons. The first method followed was that of Späth and Lang (*Ber.*, 1921, **54**, 2073) in which tetrahydroberberine is heated with methyl-alcoholic potassium hydroxide at 180° for 25 hours, and the product methylated. The methiodide which we obtained in this way crystallised from methyl alcohol in pale yellow crusts, m. p. 215°, whereas the melting point of the product obtained by Späth and Lang was 245° and Haworth, Koepfli, and Perkin obtained α- and β-forms of the methiodide, m. p.'s 230° and 266° respectively (J., 1927, 2261).

Applying the second method of Späth and Quietensky (*Ber.*, 1925, **58**, 2270) for the conversion of berberine into palmatine, we obtained the methiodide in small, yellow, rhombic pillars which decompose at 261—263°. Späth and Quietensky (*loc. cit.*) attribute the m. p. 245° to this product also. It appears to us that the second method furnishes the β-form of the expected methiodide, but the first, at least in our hands, has given something different. Actually the action of methyl-alcoholic potassium hydroxide on a methylenedioxy-group frequently gives rise to a methoxymethyl ether as in the case of *iso*safrole :



A further investigation of the anomaly is in progress.

Penta-acetyltetrahydropapaverine.—Späth (*Ber.*, 1929, **62**, 1027) obtained satisfactory results in the reduction of methylpapaverine by an electrolytic method, but we have been unable to apply the process of reduction at a lead cathode (90 cm.^{2}) by a current of 7—7·5 amps. in 25% sulphuric acid to papaverine itself with any satisfactory outcome. The yield of tetrahydropapaverine was only about 20—25%. The reduction by Pyman's method (J., 1909, **95**, 1610) was found to proceed exactly as described. The method of demethylation employed by Pyman is an excellent one, but in order to avoid the use of sealed tubes we adopted the following process, although the yield was somewhat inferior.

A mixture of tetrahydropapaverine (10 g.), dry xylene (25 c.c.), and powdered aluminium chloride (55 g.) was heated (oil-bath) : the reaction started when the temperature reached 120°. The mixture was maintained at 140—150° for 15 minutes and then at 170° for a few minutes and occasionally shaken. After cooling, the mass was decomposed by crushed ice, the xylene removed by steam-distillation, and the solution filtered (charcoal) and concentrated to crystallisation (yield, 7—8 g.). The salt crystallised from 10% hydrochloric acid in nearly colourless rhombic plates, m. p. 278—280° (Pyman, *loc. cit.*, gave m. p. 291—293° corr.) (Found : C, 58·8; H, 5·6; N, 4·2; Cl, 11·5. Calc. for $C_{16}H_{18}O_4NCl$: C, 59·3; H, 5·6; N, 4·3; Cl, 11·0%). A mixture of the hydrochloride (5 g.), acetic anhydride (20 c.c.), and pyridine (1 c.c.) was boiled for 1 hour; the product (6 g.), isolated in the usual manner, crystallised from aqueous acetic acid in aggregates of colourless needles, m. p. 109—110° with sintering a few degrees lower (Found : C, 62·6; H, 5·6; N, 3·0. $C_{26}H_{27}O_9N$ requires C, 62·8; H, 5·4; N, 2·8%). This derivative is readily soluble in most organic solvents but is sparingly soluble in ether and very sparingly soluble in light petroleum.

The penta-acetyltetrahydropapaverine was converted into a substance believed to be *N*-acetyltetrahydropapaverine by hydrolysis with aqueous-alcoholic potassium hydroxide in an atmosphere of hydrogen. The product had the anticipated properties but unfortunately could not be crystallised; it was devoid of basic properties. This substance was treated with chloranil in alcoholic solution, but it was not readily attacked by this oxidising agent. Very little change occurred in the cold and, on heating, a brown solution was obtained and no definite products could be isolated.

Other substances which are not readily or smoothly oxidised by chloranil are laudanosine, pseudolaudanine narcotine, and even tetrahydropapaveroline.

The investigation is being extended to other types of phenolic alkaloids of the *iso*quinoline group.

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