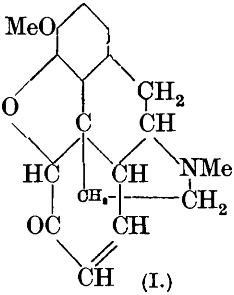
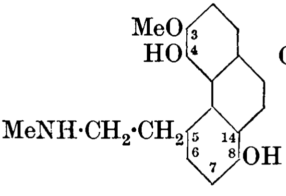
CXXII.—*The Constitution of Thebenine.*

By John Masson Gulland and Cyril Joseph Virden.

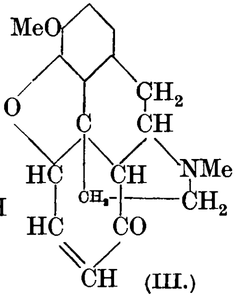
Of the surprising degradations which are found in the chemistry of the morphine alkaloids, perhaps the most remarkable is that in which thebenine (II) is formed (*a*) from thebaine, or (*b*) from codeinone (I), the first product of the hydrolysis of thebaine, or (*c*) from *pseudo*codeinone (III).



(I.)



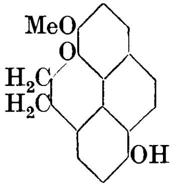
(II.)

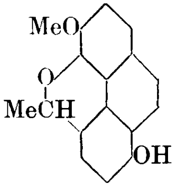


(III.)

In the cases (*a*) and (*b*) the conversion readily takes place on heating for a short time with dilute hydrochloric acid (Freund, *Ber.*, 1897, **30**, 1357; 1899, **32**, 168; Knorr, *ibid.*, 1903, **36**, 3074), whereas in (*c*) boiling acetic anhydride is necessary (Knorr and Hörlein, *ibid.*, 1907, **40**, 2037), and the product contains an aromatic phenanthrene nucleus in which the C–C–N group of the parent substance is present in the form of a side chain. The researches of Pschorr and his collaborators (*Ber.*, 1904, **37**, 2780; 1907, **40**, 2001; *Annalen*, 1910, **373**, 51, 75) have demonstrated conclusively the positions occupied by the methoxyl and hydroxyl groups of thebenine, but the allocation of the side chain to position 5 is based on less definite evidence. It depends on the fact that the product of the exhaustive methylation of thebenine is thebenol, in which the initial vinyl group has reacted further with one of the phenolic hydroxyls. Pschorr (*loc. cit.*) has shown that it is the hydroxyl in position 4, not that in position 8, which is involved in this ring formation, and he assigned to thebenol the formula (IV). In view of the ease of formation and stability of six-membered oxide rings, we prefer to adopt the formula (V) (compare Cahn, J., 1926, 2562). From stereochemical considerations, therefore, and from the fact that thebenol is converted into pyrene when distilled with zinc dust or reduced by hydriodic acid and phosphorus (Freund, *Ber.*, 1897, **30**, 1357; 1910, **43**, 2128), it seems probable that the side chain of thebenine is in position 5, and the experiments which are described in this paper have shown beyond doubt that this is actually the case.

(IV.)





(V.)

Before describing this work in detail, it is necessary to mention two experiments made in order to test the accuracy of a mechanism which has recently been suggested for the thebenine transformation. Schöpf and Borkowsky (*Annalen*, 1927, **458**, 148) explain the formation of thebenine from codeinone by 1 : 4-addition of water (VIa) to the conjugated system produced in an enolic form of codeinone (VI), followed by the codeine–*pseudo*codeine transformation (VIb). The stage (VIa) is the formula which must now be given to the hydroxycodeine * which is obtained by the reduction of 14-hydroxycodeinone (Freund and Speyer, *J. pr. Chem.*, 1916, **94**, 135; Speyer, Selig, and Heil, *Annalen*, 1922, **430**, 1; compare Gulland and Robinson, *Mem. Manchester Phil. Soc.*, 1925, **69**, No. 10), and it seemed interesting to test this theory by direct experiment. We have found that 14-hydroxycodeine is quite unaffected by boiling hydrochloric acid (*d* 1·07, the strength used in the preparation of thebenine), and that prolonged heating with acetic anhydride yields no triacetylthebenine, but a mixture of two *bases*, one crystalline, the other amorphous, which are still under

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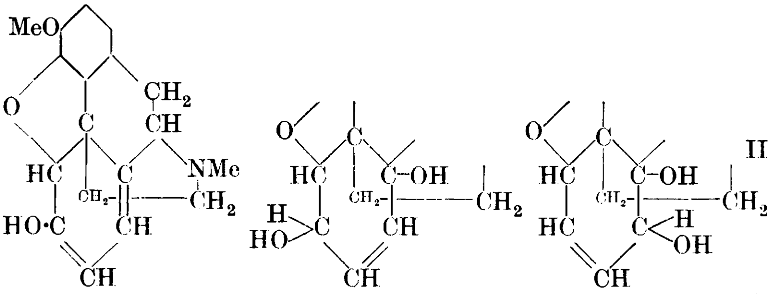
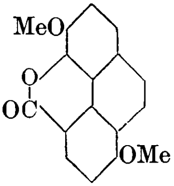
* Assuming that this substance is an unsaturated alcohol.

investigation. A consideration of these facts leads us to believe that Schöpf's theory is improbable.

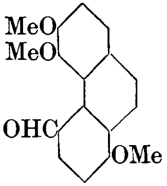


(VI.) (VIa.) (VIb.)

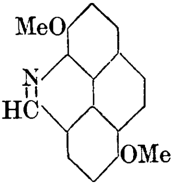
The comparative experiments described in this paper were based in the first instance on the analogous work which has been carried out with *apo*morphine and morphothebaine—the methylation of the phenolic hydroxyl groups, the elimination of the nitrogen atom by exhaustive methylation, the conversion of the resulting vinyl group into methoxyl through the stages of carboxylic acid, hydrazide, azide (Curtius, *Ber.*, 1894, **27**, 778), and the comparison of the methoxyphenanthrene thus obtained with a phenanthrene derivative synthesised by Pschorr's method (*Ber.*, 1896, **29**, 496). Pschorr and his collaborators have converted methebenine, the 8-methyl ether of thebenine, into 3 : 4 : 8-trimethoxy-5-vinylphenanthrene, and have oxidised this to 3 : 4 : 8-trimethoxyphenanthrene-5-carboxylic acid. We have experienced no difficulty in preparing these compounds by the same methods, and the *methyl* ester of the acid readily yielded the corresponding *hydrazide.* A solution of this substance in glacial acetic acid on the addition of sodium nitrite deposited the *azide* as an oil which soon crystallised. When the azide was warmed with ethyl alcohol, nitrogen was evolved, but instead of the expected urethane, a crystalline non-nitrogenous substance, $C_{17}H_{12}O_4$, separated in almost theoretical yield. The same compound was obtained when the azide was heated slowly to 65°, or when methyl or amyl nitrite acted on the hydrazide in alcoholic hydrogen chloride solution. Since this substance contains only two methoxyl groups, and dissolves in methyl-alcoholic potash, although scarcely soluble in methyl alcohol, we regard it as the *lactone* of 4-hydroxy-3 : 8-dimethoxyphenanthrene-5-carboxylic acid (VII), and some confirmation of this view is obtained from its formation in the acid hydrolysis of 3 : 4 : 8-trimethoxy-5-cyanophenanthrene (see below), and from the facility with which the same methoxyl is hydrolysed when methebenol is produced by the crystallisation from acetic acid of the trimethoxyvinylphenanthrene mentioned above.



(VII.)



(VIII.)



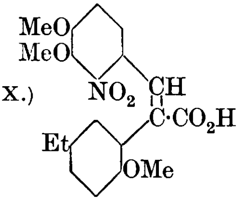
(IX.)

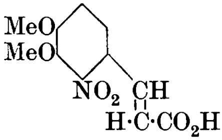
The chief product of the oxidation of 3 : 4 : 8-trimethoxyvinylphenanthrene is a non-acidic substance, $C_{18}H_{16}O_4$, which Pschorr termed " oxymethebenol," but which we have shown by the preparation of an *oxime* and a *semicarbazone* to be 5-*aldehydo*-3 : 4 : 8-*trimethoxyphenanthrene* (VIII). The poor yield (20—30%) of trimethoxyphenanthrenecarboxylic acid led us to try to prepare it from this aldehyde by oxidation, but in this we were unsuccessful in spite of a number of attempts. An indirect method of oxidation was therefore attempted; the oxime of (VIII) yielded 3 : 4 : 8-*trimethoxy*-5-*cyanophenanthrene* on dehydration by boiling with acetic anhydride and sodium acetate, but this compound appeared to be stable to boiling alcoholic potash, and was converted into (VII) either by boiling with a mixture of hydrochloric and acetic acids, or by hydrolysing the corresponding imino-ester hydrochloride. A by-product of the dehydration of the oxime was a base, $C_{17}H_{13}O_2N$, the properties of which were so reminiscent of those of thebenidine (Vongerichten, *Ber.*, 1901, **34**, 767) that we consider the substance to be 3 : 8-*dimethoxythebenidine* (IX), or the isomeride in which the CH and N are transposed. This transposition is analogous to the rearrangement which takes place when *iso*quinoline is produced by the dehydration of cinnamaldoxime (Bamberger and Goldschmidt, *Ber.*, 1894, **27**, 1954).

The experiments described above indicated that the conversion of methebenine into 3 : 4 : 5 : 8-tetramethoxyphenanthrene was impracticable, and we decided therefore to modify the original scheme. 3 : 4 : 8-Trimethoxy-5-vinylphenanthrene was reduced catalytically to 3 : 4 : 8-*trimethoxy*-5-*ethylphenanthrene*, which proved to be identical with a specimen prepared synthetically. The materials required for this synthesis were 2-nitroveratraldehyde (Pschorr and Sumuleanu, *Ber.*, 1899, **32**, 3405; Pisovschi, *ibid.*, 1910, **43**, 2137) and 6-methoxy-3-ethylphenylacetic acid, and the starting point for the preparation of this acid was *p*-ethylanisole, obtained by the reduction of *p*-methoxyacetophenone by Clemmensen's method (*Ber.*, 1914, **47**, 51). This was converted into

6-*methoxy*-3-*ethylbenzaldehyde* by the modification of Gattermann's aldehyde synthesis which has been introduced by Adams and Levine (*J. Amer. Chem. Soc.*, 1923, **45**, 2373; 1924, **46**, 1518), and the aldehyde yielded 6-*methoxy*-3-*ethylphenylacetic acid* in good yield through the intermediate stages of *azlactone* and 6-*methoxy*-3-*ethylphenylpyruvic acid.* The condensation of 2-nitroveratraldehyde with sodium 6-methoxy-3-ethylphenylacetate by heating at 100° with acetic anhydride results in a mixture of trans-α-(6′-*methoxy*-3′-*ethylphenyl*)-2-*nitro*-3 : 4-*dimethoxycinnamic acid* (X) and trans-2-*nitro*-3 : 4-*dimethoxycinnamic acid* (XI). Some derivatives of the second acid (XI) are described in the experimental part of this paper. On reduction with ferrous sulphate and ammonia, the acid (X) yielded trans-α-(6′-*methoxy*-3′-*ethylphenyl*)-2-*amino*-3 : 4-*dimethoxycinnamic acid,* and an aqueous methyl-alcoholic solution of the diazonium sulphate of this amino-acid deposited 3 : 4 : 8-*trimethoxy*-5-*ethylphenanthrene*-9-*carboxylic acid* (XII) on boiling or on addition of copper powder. This acid (XII) lost carbon dioxide when its solution in glacial acetic acid was heated at 230°, and the resulting 3 : 4 : 8-*trimethoxy*-5-*ethylphenanthrene* was identical with the preparation obtained from thebaine.

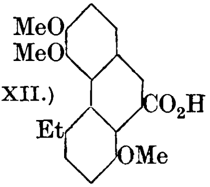
(X.)





(XI.)

(XII.)



EXPERIMENTAL.

The Action of Hydrochloric Acid and Acetic Anhydride on 14-*Hydroxycodeine.*—This base, prepared according to Speyer, Selig, and Heil (*loc. cit.*), was recovered unchanged when ammonia was added to a solution in hydrochloric acid (*d* 1·07) which had been boiled under reflux for 2 hours. It was therefore refluxed with ten times its weight of acetic anhydride for 8 hours; the addition of water to the solution obtained precipitated no non-basic material. Ammonia was added, the precipitate was taken up in chloroform, washed with water, and dried with sodium sulphate, and the solvent was evaporated. When the resinous residue was rubbed with hot alcohol, part dissolved (see below) and part separated in colourless needles, which were collected and recrystallised from ethyl alcohol; m. p. 304° (Found: C, 68·0; H, 5·9%). These figures are in agreement with a number of possibilities, and the substance is still under examination. It is readily soluble in dilute acetic or hydrochloric acid, and is very sparingly soluble in cold alcohol.

The alcoholic mother-liquor (see above) was evaporated to dryness, and the residue was dissolved in ether, dried, and freed from solvent by distillation. It was a pale yellow oil which dissolved in dilute acetic and hydrochloric acids, and was readily soluble in the usual solvents except ligroin; from this it separated as an oil when a hot solution was cooled. The picrate, hydrochloride, hydriodide, and perchlorate were amorphous.

3 : 4 : 8-*Trimethoxy-5-vinylphenanthrene.*—In preparing the stages intermediate between this substance and thebaine, we have followed closely the details given by Freund and Holthoff (*Ber.*, 1899, **32**, 168) and Pschorr and Massaciu (*Ber.*, 1904, **37**, 2780), but throughout the series of reactions we have been able to improve the yields. Pschorr's method of preparing trimethoxyvinylphenanthrene proved unsatisfactory, and the following process was found more suitable. Dimethylmethebenine methosulphate (m. p. 283—285°; Pschorr and Massaciu give m. p. 268—270°) (12 g.) and *sodium* hydroxide solution (200 c.c. of 20%) were boiled gently under reflux for 12 hours; during the reaction the vinylphenanthrene separated in small, colourless needles (yield, 76%), m. p. 121° (Pschorr gives 122·5° corr.).

3 : 4 : 8-Trimethoxyphenanthrene-5-carboxylic acid (m. p. 236—237°) was obtained as described by Pschorr, Loewen, and Rettberg (*Annalen*, 1910, **373**, 51; m. p. 224—226°) by the oxidation by permanganate of 3 : 4 : 8-trimethoxy-5-vinylphenanthrene in acetone solution. The *methyl* ester separated when a solution of the acid in methyl-alcoholic hydrogen chloride was boiled for 18 hours and allowed to cool. After recrystallisation from methyl alcohol, it melted at 149—151°.

The *hydrazide* was prepared by boiling under reflux for 18 hours a mixture of equal weights of the ester, hydrazine hydrate, and ethyl alcohol. It separated on cooling, and crystallised from ethyl alcohol in colourless needles, m. p. 177° (Found : N, 8·4. $C_{18}H_{18}O_4N_2$ requires N, 8·6%).

The *azide* was obtained by the gradual addition of sodium nitrite solution (1·5 c.c. of 5*N*) to a cooled solution of the hydrazide (0·5 g.) in glacial acetic acid (5 c.c.). It separated as an oil which crystallised rapidly, and was collected, washed, and dried on porous tile. The azide decomposed smoothly at 65° when heated slowly (see below), but exploded at 80° if suddenly immersed in a bath at that temperature.

5-*Aldehydo*-3 : 4 : 8-*trimethoxyphenanthrene* (VIII).—The acetone filtrate from the preparation of the trimethoxyphenanthrenecarboxylic acid was evaporated to dryness, and the residual oil, which crystallised on rubbing, was recrystallised first from ethyl alcohol and then from benzene–ligroin. The aldehyde formed colourless plates, m. p. 151°, which were readily soluble in benzene (Found : C, 72·9; H, 5·5. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

The *semicarbazone* separated in colourless needles when an aqueous-alcoholic solution of the aldehyde and an excess of semicarbazide hydrochloride and sodium acetate were heated on the water-bath for 2 hours. It was sparingly soluble in the usual solvents, but was recrystallised from nitrobenzene; m. p. 243—246° (decomp.) (Found : N, 11·8. $C_{19}H_{19}O_4N_3$ requires N, 11·6%).

The *oxime* was prepared by boiling under reflux for 2 hours a mixture of the aldehyde, a slight excess of hydroxylamine hydrochloride and potassium acetate, and aqueous alcohol; water precipitated the crude product as an oil which soon crystallised. After drying in a vacuum desiccator, the oxime was crystallised repeatedly from benzene, and dried in a vacuum desiccator, being obtained in dull yellow, lozenge-shaped leaflets, which softened at 110°, became pasty at 140—142°, and were molten at 153° (Found : loss at 100°, 11·5. $C_{18}H_{17}O_4N,\frac{1}{2}C_6H_6$ requires loss, 12·2%. Found in material dried at 100° : N, 4·9. $C_{18}H_{17}O_4N$ requires N, 5·0%). It dissolved readily in warm 2*N*-sodium hydroxide; on cooling, the *sodium* salt separated in cream-coloured leaflets, which redissolved on addition of water.

3 : 4 : 8-*Trimethoxy*-5-*cyanophenanthrene*.—The oxime described above (4 g.), anhydrous sodium acetate (4 g.), and acetic anhydride (20 c.c.) were boiled under reflux for 6½ hours. After the product had been cooled and mixed with water, the crystalline *nitrile* was collected, washed, pressed on tile (3·5 g.), and crystallised twice from methyl alcohol, forming pale brown needles, m. p. 145—146° (Found : C, 73·8; H, 5·4. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1%). The nitrile dissolved readily in benzene, forming a solution which exhibited a blue fluorescence, but was sparingly soluble in ether. It crystallised unchanged when a solution in aqueous methyl-alcoholic potash which had been boiled on the water-bath for 5 hours was cooled.

The orange-coloured acid mother-liquor from the preparation of the nitrile contained a small quantity of a base, probably 3 : 8-*dimethoxythebenidine* (IX), which was precipitated by ammonia as a yellow, flocculent mass. This substance was extracted by chloroform, and, after being dried by anhydrous sodium sulphate, it separated as orange-yellow leaflets during the concentration of the solvent. When recrystallised from methyl alcohol, it formed orange leaflets, m. p. 229—230° (Found in material dried at 100° : C, 77·1;

H, 5·1; N, 5·2. $C_{17}H_{13}O_2N$ requires C, 77·6; H, 4·9; N, 5·3%). The properties of this base closely resemble those of thebenidine (Vongerichten, *loc. cit.*). It formed an orange-yellow solution in dilute hydrochloric acid, from which it was precipitated unchanged by alkali, and the colour of the acid solution was almost completely discharged on reduction by tin. The base did not appear to react with nitrous acid. It exhibited pronounced fluorescence in different solvents: in very dilute hydrochloric acid, green; in concentrated sulphuric acid, an intense emerald-green; in chloroform, blue.

The *picrate* separated from a methyl-alcoholic solution of the base and picric acid in wart-like nodules; after recrystallisation from methyl alcohol (bright green fluorescence), it formed orange needles, m. p. 255° (decomp.).

Lactone of 4-*Hydroxy*-3 : 8-*dimethoxyphenanthrene*-5-*carboxylic Acid* (VII).—This substance was obtained from derivatives of 3 : 4 : 8-trimethoxyphenanthrene-5-carboxylic acid in the following ways: (i) A small quantity of the azide was heated gently to 65° and maintained at that temperature until the evolution of gas ceased.

(ii) Methyl nitrite was passed into an ice-cold solution of the hydrazide (2 g.) in alcoholic hydrogen chloride (70 c.c. of 0·3*N*), or alternatively amyl nitrite (0·2 c.c.) was added to an ice-cold solution of the hydrazide (0·1 g.) in alcoholic hydrogen chloride (5 c.c. of 0·5*N*). In either case, on standing overnight, the lactone separated in practically theoretical yield.

(iii) The nitrile (1 g.) was heated on a sand-bath for 6 hours with concentrated hydrochloric acid (15 c.c.) and glacial acetic acid (15 c.c.). The lactone, part of which separated during the reaction, was completely precipitated by the addition of water.

(iv) An ice-cold solution of the nitrile (1 g.) in dry benzene (100 c.c.) and methyl alcohol (2 c.c.) was saturated with dry hydrogen chloride. Next day the light brown needles of the imino-ester hydrochloride (1 g.) were collected, washed with benzene, and dissolved in 50 c.c. of water. When the solution was warmed on the water-bath, the lactone separated in crystalline condition.

The *lactone*, prepared by any of the methods just described, crystallised from glacial acetic acid, in which it was very sparingly soluble when cold, in faintly yellow needles, m. p. 246—247° (Found: C, 72·9; H, 4·3; *M* in camphor by Rast's method, 267. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%; *M*, 280). It was very sparingly soluble in boiling methyl alcohol and insoluble in boiling sodium hydroxide solution, but dissolved readily in hot methyl-alcoholic potash and did not separate on cooling. On addition of water, a clear solution was obtained which immediately began to deposit the unchanged lactone in an amorphous condition; presumably the potassium salt of the phenolic acid is hydrolysed in aqueous solution. In estimating methoxyl by Zeisel's method, it was necessary to prolong the reaction for a number of hours at 150—160° [Found: OMe, 20·9. $C_{15}H_6O_2(OMe)_2$ requires OMe, 22·1%]. The demethylated substance, presumably the *lactone* of 3 : 4 : 8-trihydroxyphenanthrene-5-carboxylic acid, crystallised from the hydriodic acid, and after being collected and washed with sodium thiosulphate solution, crystallised from ethyl alcohol in colourless needles; it decomposed from 305° onwards, and formed a yellow solution in sodium hydroxide, but was insoluble in bicarbonate solution.

p-*Ethylanisole*.—*p*-Methoxyacetophenone (25 g.) (Gattermann, *Ber.*, 1890, **23**, 1202) was heated on the water-bath for several hours with amalgamated zinc (100 g.) and concentrated hydrochloric acid (Clemmensen, *loc. cit.*), and after being decanted from the excess of zinc the mixture was steam-distilled. Ethylanisole passed over and was taken up in ether, dried with potassium carbonate, and distilled, being obtained as a colourless oil, b. p. 199—200° (Moschner, *Ber.*, 1901, **34**, 1257, gives b. p. 199—200°, and Klages, *ibid.*, 1903, **36**, 3584, b. p. 196—197°). The yield was 40% of that theoretically possible, and there remained a considerable non-volatile residue (compare Steinkopf and Wolfram, *Annalen*, 1923, **430**, 113). Attempts to improve the yield by modifying the conditions were unsuccessful, and the method of Gilman and Hoyle (*J. Amer. Chem. Soc.*, 1922, **44**, 2621) using magnesium, bromoanisole, and ethyl sulphate proved unsatisfactory.

6-*Methoxy*-3-*ethylbenzaldehyde*.—The aldehydo-group was introduced into *p*-ethylanisole by the method of Adams and Levine (*loc. cit.*). A mixture of *p*-ethylanisole (50 g.), zinc cyanide (95 g.), and dry benzene (350 c.c.) was stirred mechanically in a flask fitted with an inlet for dry hydrogen chloride, an efficient stirrer passing through a mercury seal, and an outlet tube connected through a reflux condenser with a Woulff's bottle containing sulphuric acid. The stirred mixture was saturated with hydrogen chloride (24 hours), aluminium chloride (80 g.) added, and the flask warmed at 50° for 12 hours while the mixture was again saturated with hydrogen chloride. The stirring was then stopped, and next day the upper of the two layers into which the mixture had separated was poured off, and the dark-coloured lower one was hydrolysed by boiling hydrochloric acid (150 c.c. of 3*N*) and submitted to steam distillation. The residual benzene distilled rapidly, and then 6-methoxy-3-ethylbenzaldehyde passed over slowly, and was taken up in ether. The crude oil left by distillation of the ether was converted into the bisulphite compound, which separated from the hot sodium bisulphite solution on cooling and was then hydrolysed by hot hydrochloric acid. The resulting oil was extracted with ether, washed with water, and dried, and the removal of the ether left the aldehyde (yield 55%), which was converted directly into the azlactone.

6-Methoxy-3-ethylbenzaldehyde is an oil, b. p. 261—262°, which was analysed in the form of its *semicarbazone*. The aldehyde (1 g.), semicarbazide hydrochloride (3 g.), and sodium acetate (4 g.) in aqueous alcohol were heated on the water-bath for 2 hours. The semicarbazone, which separated on cooling, crystallised from ethyl alcohol in colourless needles, m. p. 226—227° (Found: N, 19·2. $C_{11}H_{15}O_2N_3$ requires N, 19·0%).

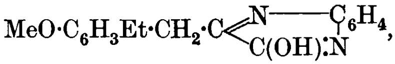
5-Keto-2-phenyl-4-(6′-methoxy-3′-ethylbenzylidene)-4 : 5-dihydro-oxazole,  $MeO{\cdot}C_6H_3Et{\cdot}CH{:}C\genfrac{}{}{0pt}{}{<N{:}CPh>}{<CO>}O$.—This azlactone was obtained by heating together on a water-bath for 30 minutes 6-methoxy-3-ethylbenzaldehyde (10 g.), hippuric acid (12 g.), fused sodium acetate (12 g.), and acetic anhydride (20 c.c.). The yellow solid produced was washed with cold alcohol and repeatedly with boiling water. Further treatment was unnecessary for the next stage, but the azlactone crystallised from acetic acid, ethyl acetate, or ethyl alcohol in bright yellow needles, m. p. 159° (Found: N, 4·5. $C_{19}H_{17}O_3N$ requires N, 4·6%).

6-Methoxy-3-ethylphenylpyruvic acid,

$$MeO{\cdot}C_6H_3Et{\cdot}CH_2{\cdot}CO{\cdot}CO_2H,$$

was prepared from the azlactone (10 g.) by boiling with sodium hydroxide solution (50 c.c. of 10%) for 12 hours. The *sodium* salt of the acid, which separated in colourless plates, m. p. 184°, when the dark liquid was allowed to remain for some hours, was recrystallised from water (Found: loss at 100° after drying in a vacuum desiccator, 3·4. $C_{12}H_{13}O_4Na,\frac{1}{2}H_2O$ requires loss, 3·6%. Found in dried material: Na, 9·2. $C_{12}H_{13}O_4Na$ requires Na, 9·4%). The *acid* was obtained as an oil, which slowly crystallised in needles, by acidifying an aqueous solution of the salt, and the alkaline liquor from which the salt had separated after the hydrolysis of the azlactone yielded a further quantity of the acid when acidified by sulphur dioxide (Haworth, Perkin, and Rankin, J., 1924, **125**, 1686). The total yield was 70% of that theoretically possible.

6-Methoxy-3-ethylphenylpyruvic acid dissolved readily in ethyl alcohol, ether, acetone, or acetic acid, but was somewhat less soluble in methyl alcohol, and crystallised from this solvent in yellow prisms, m. p. 185°, which liquefied on being kept for a short time. Satisfactory analyses of the acid could not be obtained, and it was therefore analysed in the form of 3-*hydroxy*-2-(6′-*methoxy*-3′-*ethylbenzyl)quinoxaline*,



$MeO{\cdot}C_6H_3Et{\cdot}CH_2{\cdot}C{<}\begin{matrix}N\text{———}C_6H_4\\ C(OH){:}N\end{matrix}$, which separated when a hot alcoholic solution of the acid and *o*-phenylenediamine was cooled. This substance crystallised from ethyl alcohol in very small, colourless needles, m. p. 184—185° (Found: N, 9·4. $C_{18}H_{18}O_2N_2$ requires N, 9·5%).

6-*Methoxy*-3-*ethylphenylacetic Acid*, $MeO{\cdot}C_6H_3Et{\cdot}CH_2{\cdot}CO_2H$.—An ice-cold solution of sodium 6-methoxy-3-ethylphenylpyruvate in 2*N*-sodium hydroxide was oxidised by a slight excess of 30% hydrogen peroxide diluted with four volumes of water. Next day the phenylacetic *acid* (85% yield) was precipitated in shining leaflets by dilute sulphuric acid, and was collected, dried, and recrystallised from light petroleum (b. p. 60—80°); it formed colourless leaflets, m. p. 68—69°, which readily dissolved in ethyl alcohol, ether, and benzene (Found in material dried at 100°: C, 67·9; H, 7·6. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). The *sodium* salt was prepared by evaporating to dryness a solution of the acid in the requisite amount of sodium carbonate solution. It was very readily soluble in water.

The Condensation of 2-*Nitroveratraldehyde with* 6-*Methoxy*-3-*ethylphenylacetic Acid.* trans-α-(6′-*Methoxy*-3′-*ethylphenyl*)-2-*nitro*-3 : 4-*dimethoxycinnamic Acid* (X) *and* trans-2-*Nitro*-3 : 4-*dimethoxycinnamic Acid* (XI).—A mixture of sodium 6-methoxy-3-ethylphenylacetate (7 g.), 2-nitroveratraldehyde (14 g.), and acetic anhydride (80 c.c.) was heated under reflux at 100° for 72 hours. Water was then added to destroy the acetic anhydride, and the residual oil was taken up in ether. The ether was repeatedly extracted with sodium carbonate solution, and when the mixed extracts were fractionally precipitated by hydrochloric acid the *acid* (X) separated first; it was recrystallised from ethyl alcohol.

trans-α(6′-*Methoxy*-3′-*ethylphenyl*)-2-*nitro*-3 : 4-*dimethoxycinnamic acid* formed pale lemon-yellow prisms, m. p. 193—194° (Found: C, 62·6; H, 5·5. $C_{20}H_{21}O_7N$ requires C, 62·0; H, 5·4%). The acid dissolved readily in hot dilute ammonia, but on cooling, the *ammonium* salt separated in pale yellow, silky needles.

Both this acid (X) and the acid (XI) (below) have the *trans*-configuration, since on reduction they yield the corresponding amino-acids, and not the carbostyril derivatives (compare Stoermer, *Annalen*, 1915, **409**, 13).

In the fractional precipitation by acid (see above), the partly neutralised solution was decanted from the first oily precipitate when crystals began to separate. The crystals are the acid (XI), and complete precipitation yielded this acid in a comparatively pure condition; on recrystallisation from ethyl alcohol, trans-2-*nitro-3 : 4-dimethoxycinnamic acid* formed colourless needles, which softened at 217° and melted at 229° (Found: C, 52·5; H, 4·4. $C_{11}H_{11}O_6N$ requires C, 52·2; H, 4·3%). This acid was identical in every way with a specimen prepared by the following method. 2-Nitroveratraldehyde (4 g.), malonic acid (6·3 g.), piperidine (0·5 c.c.), and pyridine (20 c.c.) were heated together on the water-bath for 1 hour, and the mixture was then poured into water and acidified by hydrochloric acid. The precipitated acid was collected, washed, purified by solution in sodium carbonate and reprecipitation, and crystallised from ethyl alcohol, from which it separated in pale yellow needles, m. p. 229° after softening at 217°.

2-*Amino*-3 : 4-*dimethoxycinnamic Acid* (as XI, but with NH_2 instead of NO_2).—A hot ammoniacal solution of the nitro-acid was added to a reducing mixture prepared from the theoretical quantity of ferrous sulphate ($7H_2O$)* and an excess of ammonia. After heating on the water-bath for 20 minutes, the solution was filtered, and the amino-acid precipitated by acetic acid (yield, 65%). This acid crystallised from ethyl alcohol in colourless needles, m. p. 173—178° (decomp.) (Found: N, 6·4. $C_{11}H_{13}O_4N$ requires N, 6·3%). The *hydrochloride* was sparingly soluble, and crystallised from water in colourless leaflets which charred on heating. The *acetyl* derivative was prepared by heating the acid with acetic anhydride on the water-bath for 15 minutes, precipitated with water, and crystallised from ethyl alcohol. It formed colourless needles, m. p. 253° (decomp.), which were soluble in sodium bicarbonate.

7 : 8-*Dimethoxycarbostyril*.—The amino-acid or its acetyl derivative (1 g.) was heated on the water-bath for 15 minutes with acetic anhydride (10 c.c.) and one drop of concentrated sulphuric acid. Water and an excess of sodium bicarbonate were then added; the *carbostyril*, which separated in plates, crystallised from ethyl alcohol in the same form, m. p. 166—168° (Found: N, 6·8. $C_{11}H_{11}O_3N$ requires N, 6·8%). It dissolved in dilute alkali and acid.

trans-α-(6′-*Methoxy*-3′-*ethylphenyl*)-2-*amino*-3 : 4-*dimethoxycinnamic Acid* (as X, but with NH_2 instead of NO_2).—An ammoniacal solution of the corresponding nitro-acid (X) (4·2 g.) was added to a hot reducing mixture prepared by adding ammonia (*d* 0·880; 50 c.c.) in water (35 c.c.) to ferrous sulphate (27·2 g.) in hot water (100 c.c.). After heating on the water-bath for 30 minutes, the

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* Experiments on a number of reductions of this type have shown that the use of the theoretical amount of ferrous sulphate is essential. An excess of ferrous hydroxide, if present, passes through the filter, and forms ultimately the insoluble basic acetate.

mixture was filtered and the amino-acid obtained in almost theoretical yield by acidifying the filtrate with acetic acid. It was purified further by solution in hydrochloric acid and precipitation by means of sodium acetate, and after being collected, washed, and dried, was crystallised from benzene; it formed lemon-yellow, flat prisms, m. p. 151—152° (Found: C, 67·2; H, 6·4. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·4%), which were very soluble in alcohol but insoluble in light petroleum.

3 : 4 : 8-*Trimethoxy*-5-*ethylphenanthrene*-9-*carboxylic Acid* (XII).—The calculated quantity of sodium nitrite solution (freshly standardised; approximately *N*) was added slowly to an ice-cold solution of α-(6′-methoxy-3′-ethylphenyl)-2-amino-3 : 4-dimethoxycinnamic acid (1 g.) in methyl alcohol (16 c.c.) and sulphuric acid (10 c.c. of 2*N*). The clear red solution, diluted with ice-water (30 c.c.), was divided into two parts. (i) On heating, nitrogen was evolved, and the acid (XII) separated as a gum, which crystallised from ethyl alcohol in colourless needles, m. p. 207°. (ii) Copper bronze powder was added to the second part; when the evolution of nitrogen ceased, the solution was made alkaline with sodium carbonate and filtered, and the acid (XII) precipitated by sulphuric acid. The yield in either case was about 35%, and the acid crystallised from benzene in needles, m. p. 207°, which were sparingly soluble in acetic acid (Found: C, 70·1; H, 5·8. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%).

3 : 4 : 8-*Trimethoxy*-5-*ethylphenanthrene* was obtained either by the reduction of 3 : 4 : 8-trimethoxy-5-vinylphenanthrene (from thebaine), or by the elimination of the carboxyl group of the acid (XII).

(i) A methyl-alcoholic solution of trimethoxyvinylphenanthrene (1 g.) absorbed a volume of hydrogen equivalent to one molecule when shaken in an atmosphere of the gas in presence of palladinised charcoal (6 g.), prepared as described by Oxford, Perkin, and Robinson (J., 1927, 2389). The filtered solution was evaporated to dryness; the residue crystallised from ethyl alcohol in colourless needles, m. p. 112—113° (Found: C, 77·0; H, 7·0. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·7%). A cold acetone solution of this substance resisted oxidation by potassium permanganate to a marked extent.

(ii) The acid (XII) (0·6 g.) in glacial acetic acid (30 c.c.) was heated in a sealed tube at 230° for 44 hours. The product was poured into an excess of dilute ammonia and extracted with ether. The extract, after being washed with water and dried with potassium carbonate, was distilled, yielding a dark-coloured oil which was extracted repeatedly with cold methyl alcohol in order to free the product from a black, insoluble residue. The methyl-alcoholic solution was concentrated (charcoal), and on cooling deposited yellow columns, m. p. 165—166° ; the examination of this substance is described below. The methyl-alcoholic mother-liquor was concentrated to a very small volume; 3 : 4 : 8-*trimethoxy*-5-*ethylphenanthrene* then separated, and after recrystallisation from ethyl alcohol (charcoal) melted at 112—113° (Found : C, 77·0; H, 7·1%). There was no depression of the melting point of a mixture of this substance with the preparation described in (i).

The substance, m. p. 165—166°, was recrystallised from ethyl alcohol, and the m. p. remained constant (Found : C, 73·9; H, 5·6%). The properties of this substance were those of a lactone; it dissolved immediately in hot dilute alcoholic sodium hydroxide, and the solution remained clear on dilution with water. Acidification with dilute sulphuric acid precipitated a yellow amorphous acid which became crystalline on standing. It was recrystallised from alcohol, from which it separated in minute prisms, m. p. 155—157° after softening at 140°. This substance dissolved in sodium carbonate, and the melting point of a mixture of it with the original compound, m. p. 165°, was depressed. The amount of material was insufficient for further examination, but it is suggested tentatively that the substance, m. p. 165°, is the *lactone* of 8-hydroxy-3 : 4-dimethoxy-5-ethylphenanthrene-9-carboxylic acid ($C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%).

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