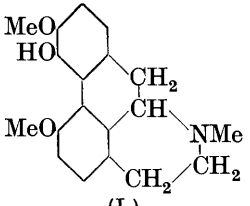
CLXXXV.—*Synthetical Experiments on the Aporphine Alkaloids. Part VI.* iso*Thebaine. Attempted Syntheses of* 3 : 4 : 5-*Trimethoxyaporphine.*

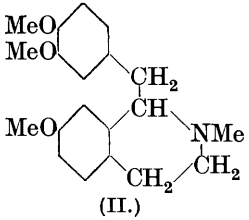
By Robert Kenneth Callow, John Masson Gulland, and Robert Downs Haworth.

In 1914, Klee (*Arch. Pharm.*, 1914, **252**, 211) assigned the constitution (I) to *iso*thebaine, the phenolic alkaloid which occurs in *Papaver orientale* after the period of blooming and the withering of the aerial parts. During the time of vigorous growth and flowering, thebaine is the chief alkaloidal constituent, and the amount of *iso*thebaine which can then be isolated is extremely small. The alternation of thebaine and *iso*thebaine as the chief alkaloid of *Papaver orientale* during the annual cycle renders the latter base one of the most interesting members of the aporphine series.

There can be little doubt that Klee was correct in classifying *iso*thebaine as an aporphine alkaloid; its general reactions show conclusively that it contains the ring system of *apo*morphine and morphothebaine. On the other hand, the location of the oxygen atoms in positions 3, 4, and 5 was based on more slender evidence : Klee converted *iso*thebaine methyl ether by exhaustive methylation, oxidation of the vinyl group thus produced, and elimination of carbon dioxide from the resulting carboxylic acid, into a trimethoxyphenanthrene picrate (m. p. 160°) which he considered was impure 3 : 4 : 5-trimethoxyphenanthrene picrate (m. p. 166°, Vongerichten and Dittmer, *Ber.*, 1906, **39**, 1718; m. p. 167°, Pschorr and Koch, *Annalen*, 1912, **391**, 40). This conclusion clearly requires confirmation.



(I.)



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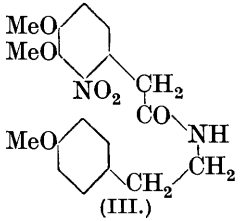


(III.)

No later publication on the subject has appeared, possibly on account of the difficulty of obtaining a supply of *iso*thebaine, and an attempt was therefore made to synthesise 3 : 4 : 5-trimethoxyaporphine (II) by the Bischler–Napieralski method in order to compare its properties with those of *iso*thebaine methyl ether. The observations of Pictet and Sprengler (*Ber.*, 1911, **44**, 2030) and of Fränkel and Zeimer (*Biochem. Z.*, 1920, **110**, 234) show that

it is possible to convert a β-4-hydroxyphenylethylamine into a derivative of tetrahydro*iso*quinoline, but there is no record of a similar transformation in the case of a β-4-methoxyphenylethylamine, and this research was initiated with some misgiving, since it seemed doubtful whether the activation of the nucleus of the requisite amide (III) would be sufficient to allow the formation of the *iso*quinoline ring to proceed in the usual manner.

2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-4-*methoxyphenylethylamide* (III), prepared from 2-nitro-3 : 4-dimethoxyphenylacetyl chloride and β-4-methoxyphenylethylamine (Barger and Walpole, J., 1909, **95**, 1720), could not be induced to form a benzyldihydro*iso*quinoline under any of the conditions which were investigated. No reaction took place with phosphorus pentachloride in cold chloroform solution, and the action of mixtures of phosphoric oxide with phosphorus pentachloride and phosphoryl chloride on the amide in boiling toluene or chloroform yielded a substance which was isomeric with the desired *iso*quinoline derivative but was devoid of basic properties. The conditions for obtaining this compound have been carefully investigated, and it was probably analogous to the non-basic compounds which Kay and Pictet (J., 1913, **103**, 947) and Gadamer, Oberlin, and Schoeler (*Arch. Pharm.*, 1925, **263**, 81) obtained from 2′-nitro-3′ : 4′-dimethoxyphenylaceto-β-phenylethylamide and 2′-nitrophenylaceto-β-phenylethylamide respectively as the products of similar reactions, and the consideration of its properties leads us to regard it as 2′-*nitro*-3′ : 4′-*dimethoxyphenyl*-(β-4-*methoxyphenylethylamino*)*acetylene* (IV). The prolonged action of a considerable excess of phosphoric oxide (compare Späth and Hromatka, *Ber.*, 1929, **62**, 325) failed to yield any crystalline material.

The conclusion was drawn that the facile closure of the *iso*quinoline ring is dependent on the presence of a strongly *p*-directive group in the *p*-position to that at which condensation is to take place. It was hoped, therefore, that the introduction of such a *p*-directive group into the 3-position of the nucleus of β-4-methoxyphenylethylamine would enhance the reactivity at the 6-position sufficiently to allow ring formation to be brought about. The acylamino-group was the most suitable for this purpose, since it was essential that the group selected should be capable of being removed at a later stage. Experiments were therefore instituted in order to determine the most convenient method of introducing an amino-group into position 3 of β-4-methoxyphenylethylamine by the nitration and reduction either of the amine itself, or of one of the intermediate compounds in its preparation.

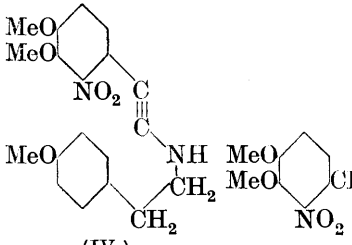
Nitration of β-4-methoxyphenylethylamine in fuming nitric acid

yielded chiefly β-3 : 5-*dinitro*-4-*methoxyphenylethylamine nitrate*, together with a smaller quantity of β-3 : 5-*dinitro*-4-*hydroxyphenylethylamine* (Waser and Sommer, *Helv. Chim. Acta*, 1923, **6**, 54). The first-mentioned substance exhibited some remarkable properties. Although itself pale yellow, it formed a red solution in warm water, and the examination of such a solution which had been boiled gently for one hour led us to the conclusion that the action of water on this nitrate was that of hydrolytic dissociation and demethylation. From the cooled solution a mixture of dark red nodules (probably impure β-3 : 5-dinitro-4-hydroxyphenylethylamine) and orange needles separated, and the analytical figures obtained for the latter product showed that it had suffered partial demethylation. β-3 : 5-Dinitro-4-methoxyphenylethylamine nitrate was decomposed by sodium hydroxide with the production both of neutral, sparingly soluble, complex products and of highly coloured, explosive sodium salts. These abnormal results may possibly be paralleled by the recent investigations of Elbs and Schaaf (*J. pr. Chem.*, 1928, **120**, 1). They found that the methyl ether of azopicric acid was hydrolysed by boiling water, and that it passed from a yellow into a red variety on recrystallisation. This alteration they ascribed to a conversion into the *aci*-form, and a similar change may account in part for the red colour which is developed when β-3 : 5-dinitro-4-methoxyphenylethylamine nitrate is treated with hot water. Further, Elbs and Schaaf observed that caustic alkalis converted azopicric acid into tarry products and that the action of potassium carbonate under various conditions yielded trinitrophloroglucinol and partly reduced derivatives, such as dinitrohydroxylaminophloroglucinol; similar complicated reactions would seem to interfere with the conversion of β-3 : 5-dinitro-4-methoxyphenylethylamine nitrate into the free base.

Unsuccessful attempts were then made to prepare a mononitro-derivative of β-4-methoxyphenylethylamine. Nitration did not take place in cold concentrated nitric acid in presence of urea nitrate. Neither the base nor its hydrochloride underwent substitution when dissolved in glacial acetic acid containing fuming nitric acid and urea nitrate at room temperature, but when the temperature of this mixture was raised to about 60° β-3 : 5-dinitro-4-hydroxyphenylethylamine was isolated from the product. The nitration of β-4-methoxyphenylethylamine sulphate in concentrated sulphuric acid afforded only β-3-*nitro*-4-*methoxyphenylethylamine*-5-*sulphonic acid*, and it was found impossible to remove the sulphonyl group by hydrolysis.

The nitration of β-4-methoxyphenylpropionic acid, on the other hand, readily took place in concentrated nitric acid and yielded

β-3-*nitro*-4-*methoxyphenylpropionic acid* as the main product, together with a small quantity of β-3 : 5-*dinitro*-4-*hydroxyphenylpropionic acid*.* The mono-nitrated acid yielded β-3-*nitro*-4-*methoxyphenylpropionamide* by the action of ammonia on the acid chloride, and this amide was converted by the Hofmann reaction into β-3-*nitro*-4-*methoxyphenylethylamine*, which was reduced to β-3-*amino*-4-*methoxyphenylethylamine* by means of stannous chloride in a mixture of hydrochloric and acetic acids. 2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3-(2″-*nitro*-3″ : 4″-*dimethoxyphenylacetamido*)-4-*methoxyphenylethylamide* (V) was obtained by the interaction of this diamine with 2-nitro-3 : 4-dimethoxyphenylacetyl chloride, and as it was found impossible to acylate the more basic, aliphatic amino-group independently of the aromatic one, this double amide (V) was the only available substance for the application of the *iso*quinoline synthesis.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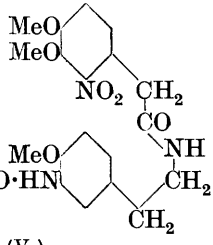
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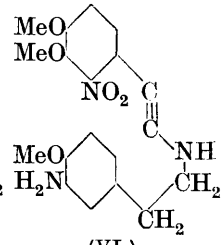
(VI.)

The action of phosphorus pentachloride in cold chloroform solution, or of phosphoric oxide in boiling toluene, on the diamide (V) failed to yield any basic material, and converted it into a very weakly basic, tarry product; this formed a picrate from which no pure substance could be liberated. Hydrolysis of the crude product by boiling concentrated hydrochloric acid yielded basic 2′-*nitro*-3′ : 4′-*dimethoxyphenyl*-(β-3-*amino*-4-*methoxyphenylethylamino*)*acetylene* (VI), which was purified by conversion into, and regeneration from, the *picrate*. This base was shown to contain a primary amino-group, and was isomeric with the desired 1-(2′-nitro-3′ : 4′-dimethoxybenzyl)-6-amino-7-methoxy-3 : 4-dihydro*iso*quinoline, but the insolubility in acids of the *benzoyl* derivative, and the feeble basicity of the 2-nitro-3 : 4-dimethoxyphenylacetyl derivative from which the base was originally derived by hydrolysis, indicated that the attempted ring closure had followed the same course as in the case of the amide (III), where no steps had been taken to increase the

* The occurrence of demethylated dinitrated by-products in this case and during the nitration of β-4-methoxyphenylethylamine may be compared with the results of Thoms and Drauzburg (*Ber.*, 1911, **44**, 2125), who obtained dinitropropylphenol on nitrating dihydroanethole.

reactivity of the phenylethylamine nucleus. This behaviour may largely be accounted for by the insufficient activating power of the 2-nitro-3 : 4-dimethoxyphenylacetamido-group, and partly, perhaps, by the complexity of the amide. A small amount of a non-basic *by-product* was isolated from the toluene mother-liquors of these experiments, but lack of material has prevented us from assigning a constitution to this substance.

Although the experiments here described have thrown no further light on the constitution of *iso*thebaine, we hope to solve the problem by other methods of attack.

EXPERIMENTAL.

β-4-*Methoxyphenylethylamine.*—The following chain of reactions was used by Barger and Walpole in the first synthesis of β-4-methoxyphenylethylamine, but the methods now employed have differed in detail.

4-Methoxycinnamic acid was obtained (yield, 92%) when anisaldehyde (120 g.), malonic acid (200 g.), and piperidine (7 c.c.) were heated in pyridine (320 c.c.) on the water-bath for 1½ hours and the solution was then boiled for 10 minutes, cooled, and poured into an excess of dilute hydrochloric acid.

β-4-Methoxyphenylpropionic acid was prepared (yield, 85—90%) by reducing the crude cinnamic acid in weakly alkaline, aqueous solution by the gradual addition of 12 parts of 4% sodium amalgam at a temperature just below the boiling point, and cooling, filtering, and acidifying the solution.

β-4-Methoxyphenylpropionamide was obtained (yield, 67%) when a solution of the acid (125 g.) and thionyl chloride (105 c.c.) in chloroform (400 c.c.) was kept for 24 hours at room temperature and then warmed gently for 1 hour, cooled, and poured slowly into a mixture of ammonia solution (*d* 0·880; 1750 c.c.) and sodium hydroxide (71 g.); the chloroform and excess of ammonia were removed by distillation, the solution was cooled, and the resulting amide crystallised from a mixture of water (1750 c.c.) and ethyl alcohol (250 c.c.).

β-4-Methoxyphenylethylamine was obtained by adding powdered β-4-methoxyphenylpropionamide (50 g.) to a solution of sodium hypochlorite prepared from 10% sodium hydroxide solution (550 c.c.) and the calculated amount of chlorine (from hydrochloric acid and potassium permanganate, 16·5 g.). When the amide had dissolved, the solution was heated at 70—80° for 30 minutes, mixed with potassium hydroxide (165 g.), heated for 3 hours at 80°, and cooled. The amine was extracted with benzene (400 c.c.), the solvent removed, and the amine (b. p. 127—130°/12 mm.; yield,

45%) purified by distillation under reduced pressure. The sulphate was obtained as colourless leaflets, m. p. above 280°, by dissolving the amine in the calculated amount of 20% sulphuric acid and cooling the solution.

2′-Nitro-3′ : 4′-dimethoxyphenylaceto-β-4-methoxyphenylethylamide (III).—2-Nitro-3 : 4-dimethoxyphenylacetyl chloride (from 12 g. of the acid), dissolved in dry benzene (30 c.c.), was added to a solution of β-4-methoxyphenylethylamine (8 g.) in dry benzene (30 c.c.). An excess of 10% sodium hydroxide solution was then added, and the solid amide collected. A further amount was obtained by separating and evaporating the benzene layer, and the total yield was 97%. Recrystallisation from 70% aqueous alcohol furnished *2′-nitro-3′ : 4′-dimethoxyphenylaceto-β-4-methoxyphenylethylamide* as colourless needles, m. p. 97·5—98·0° (Found : C, 61·2; H, 5·9. $C_{19}H_{22}O_4N_2$ requires C, 61·0; H, 5·9%). When crystallised from benzene, the amide formed needles, m. p. 76—88°, which contained one molecule of benzene of crystallisation (Found : loss at 97°, 16·8. Calc., 17·2%). The following reagents failed to convert the amide into basic material when allowed to react with cold chloroform solutions during periods varying from 4 days to 1 month : (*a*) phosphorus pentachloride; (*b*) phosphoric oxide; (*c*) a mixture of phosphoric oxide and phosphorus pentachloride; (*d*) anhydrous ferric chloride; (*e*) a mixture of ferric chloride and phosphorus pentachloride; (*f*) a mixture of aluminium chloride and phosphorus pentachloride. A 5% yield of tarry basic substance was obtained when phosphoric oxide (6 g.) was added gradually to a boiling toluene solution of the amide (1 g.), but all attempts to purify this or prepare derivatives were unsuccessful.

2′-Nitro-3′ : 4′-dimethoxyphenyl-(β-4-methoxyphenylethylamino)-acetylene (IV) was obtained from the amide (III) in very small yield by the action of phosphorus pentachloride on a cold chloroform solution, and in rather larger amount by heating a chloroform solution for 1 hour with a mixture of phosphoric oxide and phosphorus oxychloride. Better yields were obtained, however, when the amide (1 g.), phosphoric oxide (0·5 g.), and phosphorus pentachloride (0·5 g.) were heated in boiling benzene or toluene for 15—30 minutes. The solution, when decanted from the tarry layer, deposited the compound (IV), and further quantities were obtained by extracting the residue with hot benzene. After recrystallisation of the mixed fractions (0·5 g.) once from benzene and several times from ligroin, the *acetylene* derivative (IV) was obtained in pale yellow needles, m. p. 143·5—144°, which were devoid of basic properties (Found in different specimens : by

macroanalysis, C, 64·5; H, 5·9; N, 7·6: by microanalysis, C, 64·3; H, 5·8; N, 7·7. $C_{19}H_{20}O_5N_2$ requires C, 64·0; H, 5·6; N, 7·9%).

Nitration of β-4-*Methoxyphenylethylamine.*—(i) *In concentrated nitric acid.* The amine was recovered unchanged after treatment with cold concentrated or fuming nitric acid in presence of an excess of urea nitrate.

(ii) *In acetic acid.* The amine was not attacked by an acetic acid solution of fuming nitric acid and urea nitrate until the temperature of the mixture was raised to 50—75° for 40 minutes; then β-3 : 5-dinitro-4-hydroxyphenylethylamine was isolated and identified as the picrate, m. p. 209—209·5° (decomp.) (Waser and Sommer, *loc. cit.*). The nitration of the amine hydrochloride under similar conditions yielded very small amounts of solid black products.

(iii) *In concentrated sulphuric acid.* A mixture of nitric acid (*d* 1·4; 3·5 g.) and concentrated sulphuric acid (12·5 c.c.) was slowly added to a mechanically stirred solution of β-4-methoxyphenylethylamine sulphate (7·5 g.) in concentrated sulphuric acid (12·5 c.c.), which was cooled in a freezing mixture. The product was poured on ice; the resulting yellow precipitate (9·2 g.) crystallised from 60 parts of boiling water as a mixture of brown rectangular plates and a small amount of dark brown needles, which were separated mechanically. Either separately or mixed, they blackened at 293° and melted at 297° (efferv.). When recrystallised from dilute sulphuric acid, both varieties yielded β-3-*nitro*-4-*methoxyphenylethylamine*-5-*sulphonic acid* as a golden-brown mixture of plates and needles, which were separated mechanically. There can be no doubt that the plates and needles are dimorphous forms of the acid. Both were insoluble in the usual organic solvents, both lost one molecule of water of crystallisation at about 145° and became light yellow, and both on further heating darkened at about 290° but did not melt at 310° (Found in material dried at 135°: C, 39·1; H, 4·5; S, 11·7. $C_9H_{12}O_6N_2S$ requires C, 39·1; H, 4·4; S, 11·6. Found: loss at 145°; needles, 6·0; plates, 5·9. $C_9H_{12}O_6N_2S,H_2O$ requires loss, 6·1%). When the sulphonic acid was subjected to the action of superheated steam at 190—200°, it began to char and a small quantity of oil distilled.

(iv) *In fuming nitric acid.* The amine (6 g.) was added very gradually to vigorously stirred nitric acid (*d* 1·5; 30 c.c.) cooled in a freezing mixture. After 10 minutes' stirring, the mixture was poured on ice, and the yellowish-buff precipitate (6·0 g.) was collected and dried on porous tile (m. p. 148° decomp.). This product appeared to be decomposed by water, with which it developed a red

colour, but after three recrystallisations * from 2*N*-nitric acid β-3 : 5-*dinitro-4-methoxyphenylethylamine nitrate* was obtained in pale yellow microscopic plates, m. p. 161° (decomp.) [Found : C, 35·7; H, 4·1; N, 18·2; OMe, 8·7. $C_8H_8O_4N_3(OMe),HNO_3$ requires C, 35·5; H, 4·0; N, 18·4; OMe, 10·2%].

Several attempts were made to liberate the base from this nitrate by means of sodium hydroxide or ammonia. The action of warm dilute aqueous sodium hydroxide yielded a red solution (X) and a reddish-yellow tar, which soon solidified. This material was only partly soluble in dilute nitric acid, concentrated hydrochloric acid, or boiling dilute sodium hydroxide solution, and was insoluble in methyl or ethyl alcohol. The alkaline solution (X) slowly deposited small purple nodules which exploded on heating, and the mother-liquor yielded a red precipitate when mixed with alcohol. Both these substances were converted by dilute nitric acid into a green solid which exploded spontaneously when allowed to dry. The action of ammonia on a solution of the nitrate was somewhat similar to that just described.

When a solution of the nitrate (0·5 g.) in water (15 c.c.) was boiled under reflux for 1 hour and cooled over-night, a mixture of light yellow needles and a small quantity of dark red nodules separated, which were collected. The dark red nodules were picked out; they melted at 230—240° (decomp.) and were probably impure β-3 : 5-dinitro-4-hydroxyphenylethylamine. Evaporation of the filtrate yielded yellow plates, m. p. 166—167° (decomp.). The two yellow crystalline fractions were united and crystallised from water containing a trace of nitric acid. Pale yellow plates were obtained, m. p. 166—167°, which formed in water a red solution becoming yellow on the addition of a little dilute nitric acid [Found : N, 19·1; OMe, 6·1. Calc. for $C_8H_8O_4N_3(OMe),HNO_3$: N, 18·4; OMe, 10·2 : and for $C_8H_8O_4N_3(OH),HNO_3$: N, 19·3; OMe, 0%]. It is evident that hydrolytic dissociation and demethylation have occurred to some extent. A mixture of this product with β-3 : 5-dinitro-4-methoxyphenylethylamine nitrate melted at 163—164°.

* Ammonia precipitated from the mother-liquors a bright red, crystalline substance which darkened above 220° but did not melt at 300° (Found : C, 41·4; H, 4·1; N, 17·5. Calc. for $C_8H_9O_5N_3$: C, 42·3; H, 4·0; N, 18·5%). This appeared to be impure *β*-3 : 5-dinitro-4-hydroxyphenylethylamine (Waser and Sommer, *loc. cit.*). The picrate was prepared by boiling a solution in alcoholic picric acid, cooling, collecting the mixture of bright yellow needles and red powder, separating the needles mechanically, and crystallising them several times from water. They melted at 209—209·5° and appeared to be identical with *β*-3 : 5-dinitro-4-hydroxyphenylethylamine picrate (Found : N, 18·3. Calc. for $C_9H_9O_5N_3,C_6H_3O_7N_3$: N, 18·4%).

β-3-*Nitro*-4-*methoxyphenylpropionic Acid.*—Dried powdered β-4-methoxyphenylpropionic acid (66 g.) was added slowly to vigorously stirred nitric acid (*d* 1·42; 300 c.c.), the temperature being allowed to rise from 10° to 25°. Stirring was continued for 10 minutes after the acid had dissolved, and the mixture was then poured on ice (600 g.). The product (56·5 g.; m. p. 110—120°), which separated as an oil and quickly solidified, was collected and dried, and was then sufficiently pure for the preparation of the amide. (See below for the examination of the mother-liquor.) The acid was purified for analysis by crystallisation from aqueous methyl alcohol, precipitation from benzene by ligroin, crystallisation from water, and finally from carbon tetrachloride, which yielded β-3-*nitro*-4-*methoxyphenylpropionic acid* in pale yellow needles, m. p. 128—130·5° (Found: N, 6·0. $C_{10}H_{11}O_5N$ requires N, 6·0%). This acid was readily soluble in methyl and ethyl alcohols, chloroform, and benzene, moderately easily soluble in boiling, and sparingly soluble in cold, water, slightly soluble in boiling carbon tetrachloride, and insoluble in ligroin.

β-3 : 5-*Dinitro*-4-*hydroxyphenylpropionic Acid.*—The acid filtrate from the separation of the crude β-3-nitro-4-methoxyphenylpropionic acid slowly deposited a mixture (16 g.) of a reddish-yellow oil and crystals. After repeated crystallisation from dilute acetic acid and from 50% aqueous alcohol, fine, light yellow, glistening plates, m. p. 133—138°, were obtained. Since the melting point was not altered by further crystallisation, the substance was purified by conversion into the reddish-yellow barium salt, which was precipitated by the addition of barium chloride to a solution in dilute aqueous ammonia. This salt, when decomposed by dilute hydrochloric acid, yielded β-3 : 5-*dinitro*-4-*hydroxyphenylpropionic acid*, m. p. 136—139° after crystallising from water (Found: C, 42·5; H, 3·3; N, 11·3. $C_9H_8O_7N_2$ requires C, 42·2; H, 3·1; N, 10·9%). The solution in sodium hydroxide was red. In hot water the acid formed an orange solution which became yellow on the addition of a few drops of dilute sulphuric acid.

β-3-*Nitro*-4-*methoxyphenylpropionamide.*—β-3-Nitro-4-methoxyphenylpropionic acid (53 g.) and thionyl chloride (70 g.) in chloroform (300 c.c.) were allowed to react at room temperature overnight. Next day, the temperature was raised to 40° for 3 hours, and the solution was poured into concentrated ammonia (*d* 0·88; 900 c.c.) containing sodium hydroxide (25 g.). When the chloroform had been removed by distillation, β-3-*nitro*-4-*methoxyphenylpropionamide* (35·5 g.), m. p. 123—127°, crystallised from the hot solution, and was sufficiently pure for use in the next stage. A specimen purified for analysis by crystallisation first from benzene

and then from water formed pale yellow, hexagonal plates, m. p. 126·5—127° (Found: N, 12·2. $C_{10}H_{12}O_4N_2$ requires N, 12·5%). A small amount of the unchanged acid was recovered from the ammoniacal mother-liquor of the amide by acidification with dilute sulphuric acid.

β-3-*Nitro*-4-*methoxyphenylethylamine*.—β-3-Nitro-4-methoxyphenylpropionamide (37·5 g.) was dissolved in a solution of sodium hypochlorite, prepared from sodium hydroxide solution (400 c.c. of 2*N*) and chlorine (from the calculated quantity of potassium permanganate, 15 g.). After the solution had been maintained at 70—80° for 30 minutes, solid potassium hydroxide (100 g.) was added, and the heating continued for 2 hours at the same temperature. When cold, the mixture was extracted with benzene (1 l. in five portions), the benzene shaken with dilute hydrochloric acid (300 c.c. of 2*N*), and the acid solution of the amine thus obtained evaporated to a paste on the water-bath. The resulting β-3-*nitro*-4-*methoxyphenylethylamine hydrochloride* (16 g.) was crystallised from methyl alcohol (100 c.c.); a specimen for analysis, recrystallised from absolute methyl alcohol (2·5 parts), formed yellow needles, m. p. 231—232° (Found: N, 11·9. $C_{19}H_{12}O_3N_2$,HCl requires N, 12·0%). The base was obtained as an oil when sodium hydroxide was added to an aqueous solution of the hydrochloride, and treatment of this suspension with benzoyl chloride yielded the *benzoyl* derivative, which crystallised from alcohol or benzene in yellow needles, m. p. 129—130°, which became red when exposed to light (Found: C, 63·7; H, 5·1. $C_{16}H_{16}O_4N_2$ requires C, 64·0; H, 5·3%).

On one occasion in the preparation of the amine on which too little alkali had accidentally been employed, a solid product separated when the amide was warmed with sodium hypochlorite solution, and only a trace of the amine hydrochloride was ultimately isolated. This *substance* was crystallised from methyl and amyl alcohols and from acetic acid, and formed grey nodules, m. p. 197—198° (Found: C, 55·7; H, 5·5; N, 13·1. $C_{20}H_{22}O_7N_4$ requires C, 55·8; H, 5·1; N, 13·0%). It thus appeared to have been formed by the elimination of one molecule of water from two molecules of β-3-nitro-4-methoxyphenylpropionamide, but we have come to no conclusion as to its structure. It was unaffected by short boiling with concentrated sodium hydroxide solution or hydrochloric acid.

β-3-*Amino*-4-*methoxyphenylethylamine*.—Stannous chloride (30 g., 6 mols.) was added gradually to a boiling solution of β-3-nitro-4-methoxyphenylethylamine hydrochloride (15·7 g.) in glacial acetic acid (40 c.c.) and concentrated hydrochloric acid (40 c.c.). A bulky precipitate separated at first, but disappeared as the reduction

proceeded. The cooled solution was made alkaline with a large excess of sodium hydroxide (100 g.) in water (400 c.c.), and extracted with ether. Hydrogen chloride was passed into the dried ethereal extract to precipitate β-3-*amino*-4-*methoxyphenylethylamine dihydrochloride* (9·4 g.), m. p. 248—251°, which was purified for analysis by the addition of ether to an alcoholic solution until crystals separated. The dihydrochloride was thus obtained as colourless needles, m. p. 253—254° (decomp.) (Found, by titration, Cl, 29·8. $C_{19}H_{14}ON_2,2HCl$ requires Cl, 29·7%). An attempt to prepare a monoacylated derivative of this diamine by adding 2-nitro-3 : 4-dimethoxyphenylacetyl chloride (1 mol.) to the diamine (1 mol.) in benzene solution led to the formation of the diamide (V) and β-3-amino-4-methoxyphenylethylamine dihydrochloride.

2′-*Nitro*-3′ : 4′-*dimethoxyphenylaceto*-β-3-(2″-*nitro*-3″ : 4″-*dimethoxyphenylacetamido*)-4-*methoxyphenylethylamide* (V).—A benzene solution of β-3-amino-4-methoxyphenylethylamine (obtained from 2·4 g. of the dihydrochloride by decomposition with sodium hydroxide) was added to a cooled solution of 2-nitro-3 : 4-dimethoxyphenylacetyl chloride (prepared from 4·8 g. of the acid) in benzene (40 c.c.). After the addition of a slight excess of sodium hydroxide, the benzene layer was filtered from a small amount of tar and evaporated. The gummy residue crystallised when rubbed with a little methyl alcohol (yield, 5·7 g.), and when recrystallised from the same solvent, the *diamide* was obtained in colourless needles, m. p. 158—159° (Found: N, 9·0. $C_{29}H_{32}O_{11}N_4$ requires N, 9·1%). This substance was moderately easily soluble in benzene, from which it separated in ill-defined crystals.

2′-*Nitro*-3′ : 4′-*dimethoxyphenyl*-(3-*amino*-4-*methoxy*-β-*phenylethylamino*)*acetylene* (VI).—(i) A solution prepared by adding the diamide (V) to a solution of phosphorus pentachloride (3 g.) in chloroform (20 g.) which had been freshly distilled over phosphoric oxide was preserved in a closed flask for 6 days. It rapidly became reddish-brown, but no solid separated. The solution was washed exhaustively with water: the washings contained scarcely any basic material, since they merely became slightly cloudy when made alkaline with ammonia. The chloroform layer was evaporated under reduced pressure at room temperature, leaving a non-basic brittle red gum (A; see below) (3·6 g.; m. p. 87—100° decomp.), which could not be crystallised. The picrate was tarry when prepared in alcoholic solution, but after recrystallisation from alcohol, followed by fractional precipitation from benzene by light petroleum, it softened at 92°, melted at 105—115°, and decomposed at 120°. Attempts to obtain the base from the picrate were unsuccessful, and the crude product (A) was therefore hydrolysed by heating

with concentrated hydrochloric acid (10 parts) on the water-bath for 2 hours in order to remove the 2-nitro-3 : 4-dimethoxyphenylacetyl group. The dark solution was filtered from tarry material and made alkaline with ammonia. The yellow precipitate (m. p. 68—88° or 65—75° in different experiments) obtained in a yield of 10—20% by weight was very soluble in alcohol and sparingly soluble in benzene or ligroin, and attempts to crystallise it were unsuccessful. The *picrate*, however, formed yellowish-brown needles, m. p. 194—195° (decomp.) (Found : C, 49·7; H, 4·2. $C_{19}H_{21}O_5N_3,C_6H_3O_7N_3$ requires C, 50·0; H, 4·0%), when prepared in alcoholic solution, followed by the addition of water, and crystallisation from dilute alcohol. The *base* (VI) was obtained as a brown powder by decomposing the picrate with 2*N*-sodium hydroxide, and after repeated crystallisation from ligroin (b. p. 100—120°) it formed microscopic yellow needles, m. p. 169·5—170° (Found by microanalysis : C, 61·1; H, 5·6; N, 11·2. $C_{19}H_{21}O_5N_3$ requires C, 61·4; H, 5·7; N, 11·3%). It became gummy and slowly dissolved in dilute hydrochloric acid, and a deep cherry-red colour was developed when this solution was diazotised and added to an alkaline solution of β-naphthol. Treatment of the base with benzoyl chloride and sodium hydroxide yielded a benzoyl derivative, which crystallised from methyl alcohol in yellow nodules, m. p. 206—208°, and was insoluble in dilute hydrochloric acid.

(ii) Phosphoric oxide (6 g.) was gradually added to a boiling solution of the diamide (V) in dry toluene (100 c.c.). The oxide darkened and became lumped together, but the last few additions remained flocculent. The mixture was boiled for 30 minutes, cooled, and mixed with concentrated hydrochloric acid (10 c.c.), and the solid was freed from toluene by decantation, washed by stirring with ether, and heated with a further 30 c.c. of boiling concentrated hydrochloric acid for 20 minutes (charcoal). The filtrate thus obtained was made alkaline with ammonia, and the tarry precipitate dissolved as far as possible in warm dilute hydrochloric acid. This solution, when filtered and made alkaline with ammonia, yielded a yellow precipitate of the base (VI) (0·2 g.), which was worked up as described above and identified by m. p., mixed m. p., and by conversion into the benzoyl derivative. The same base (VI) was isolated from a similar experiment in which the initial boiling of the toluene solution lasted 1½ hours.

The toluene solution and ether washings from the first experiment deposited small white nodules mixed with gum when allowed to evaporate slowly. The nodules were scraped together, and when crystallised from dilute methyl and dilute ethyl alcohols, this *substance* formed soft aggregates of ill-defined crystals, m. p. 168·5—

170·5° (Found by microanalysis: C, 54·0, 53·4; H, 5·0, 4·6%). These figures do not correspond to those required for the 2-nitro-3 : 4-dimethoxyphenylacetyl derivative of the base (VI).

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