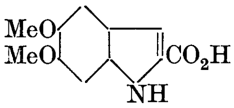
XLVI.—3 : 4- *and* 2 : 5-*Dimethoxyphenylhydrazine.*

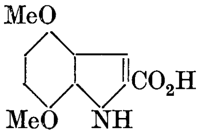
By WILLIAM HENRY PERKIN, jun., and LEON RUBENSTEIN.

IN a paper published a short time since (Blaikie and Perkin, J., 1924, **125**, 296; compare Kermack, Perkin, and Robinson, J., 1922, **121**, 1872), the synthesis was described of several derivatives of indole containing one methoxyl group in the benzene nucleus.

The present investigation was planned as a continuation of that research and it was hoped that it might be found possible to synthesise dimethoxy-derivatives of indole and to convert these into carbolines and indolediazines related to harmine and harmaline. We also desired to prepare and study more particularly such dimethoxy-derivatives of indole and tetrahydrocarbazole as



(I.)



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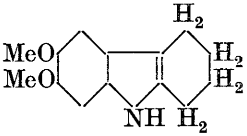


(III.)

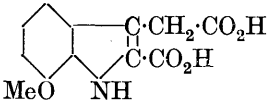
and to compare their reactions with those of brucine with the object of obtaining further evidence bearing on the question of the positions of the methoxy-groups in that alkaloid (compare Lions, Perkin, and Robinson, J., 1925, **127**, 1159). Unfortunately, the preparation of phenylhydrazines of the type $(MeO)_2C_6H_3 \cdot NH \cdot NH_2$ required for these experiments, from the corresponding anilines, proved to be a matter of unusual difficulty, and it is probably for this reason, and because they are so unstable when they have been obtained, that there is no mention of these important substances in the literature. These hydrazines, and especially the 2 : 5-dimethoxy-derivative, do not yield satisfactory condensation products with ketones such as *cyclo*hexanone or α-ketoglutaric acid and moreover the conversion of these hydrazones into the corresponding derivatives of indole or tetrahydrocarbazole by means of the usual acid reagents, alcoholic hydrochloric or sulphuric acid, glacial acetic acid, etc., is accompanied by the formation of so much tar that the preparation of these derivatives in any quantity was found to be impossible. Other methods must therefore be sought for the synthesis of these substances, and the present communication is confined to a brief description of the dimethoxyphenylhydrazines which have been prepared and of some indole and tetrahydrocarbazole derivatives which we have succeeded in obtaining in small quantities.

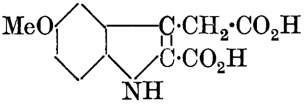
When 3 : 4-dimethoxyaniline hydrochloride (Fargher, J., 1920, **117**, 869) dissolved in acetic acid is treated with methyl nitrite, it yields brown needles of 3 : 4-*dimethoxybenzenediazonium chloride*, and this is converted by ammonium sulphite and ammonia into red crystals of *ammonium* 3 : 4-*dimethoxydiazobenzenesulphonate*. This salt is readily reduced by zinc dust to *ammonium* 3 : 4-*dimethoxyphenylhydrazinosulphonate*, the nearly colourless needles of which rapidly decompose on exposure and yield 3 : 4-*dimethoxyphenylhydrazine* (m. p. 81°) on treatment with sodium acetate. This very unstable substance combines with *cyclo*hexanone, and the syrupy hydrazone gives with alcoholic hydrochloric acid a small yield of 6 : 7-*dimethoxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (III; m. p. 98°).

In a second series of experiments, 3 : 4-dimethoxyphenylhydrazine was condensed with ethyl pyruvate, and the syrupy hydrazone gave, with alcoholic hydrochloric acid, so small a yield of 5 : 6-*dimethoxyindole*-2-*carboxylic ester* (m. p. 172°; compare I) that the substance could not be further investigated. We next prepared 2 : 5-*dimethoxyphenylhydrazine hydrochloride* from 2 : 5-dimethoxyaniline hydrochloride (Mühlhausen, *Annalen*, 1881, **207**, 254) by a process similar to that just described in the case of the 3 : 4-derivative, and, on treatment with sodium acetate, this yielded 2 : 5-*dimethoxyphenylhydrazine* (m. p. 85°). Both the hydrochloride and the free base are, however, so unstable and condense with ketones with such difficulty that the investigation could not be continued.

Included in this communication is a brief account of 2-*carboxy*-7-*methoxyindole*-3-*acetic acid* (IV) and 2-*carboxy*-5-*methoxyindole*-3-*acetic acid* (V) obtained respectively by condensing *o*-methoxyphenylhydrazine and *p*-methoxyphenylhydrazine with α-ketoglutaric acid and treating the products with alcoholic hydrochloric or sulphuric acid.

(IV.)





(V.)

On testing the various methoxy-derivatives described in this communication for the brucine reaction—the orange to red coloration produced on adding a drop of nitric acid to the solution of a trace of brucine in glacial acetic acid—it was found that the monomethoxyindole derivatives give only a yellow coloration. On the other hand, 6 : 7-dimethoxytetrahydrocarbazole (III) gives an immediate pink coloration which becomes deep red on warming and, in the case of 5 : 6-dimethoxyindole-2-carboxylic ester, the yellow colour produced at first becomes wine-red on warming. The behaviour of these substances seems to support the view of Lions, Perkin, and Robinson (*loc. cit.*, p. 1161) that brucine contains the two methoxyl groups in the *o*-position to each other.

EXPERIMENTAL.

3 : 4-*Dimethoxyphenylhydrazine*, $(MeO)_2C_6H_3\cdot NH\cdot NH_2$.—Finely powdered 3 : 4-dimethoxyaniline hydrochloride (20 g.; compare Fargher, *loc. cit.*) is added to glacial acetic acid (90 c.c.), and dried methyl nitrite passed into the well-stirred mixture, the temperature being maintained between 10° and 15°. The deep brown solution is poured into dry ether (500 c.c.), and the 3 : 4-dimethoxybenzenediazonium chloride thus precipitated in brown needles is immediately dissolved in ice-water and the solution added drop by drop and at 0° to a well-stirred, saturated ammonium sulphite solution (60 c.c.) containing ammonia (45 c.c.; *d* 0·880). The deep red product is kept for a few hours, and the red crystals (14 g.) of *ammonium* 3 : 4-*dimethoxydiazobenzenesulphonate* are collected (Found: N, 15·7; S, 12·0. $C_8H_{13}O_3N_3S$ requires N, 16·0; S, 12·1%). This substance is mixed with glacial acetic acid (10 c.c.), and zinc dust (3·7 g.) gradually added, the temperature being kept between 45° and 50°. The pale brown mixture is diluted with water, the zinc precipitated as sulphide and removed by filtration in an atmosphere of hydrogen sulphide to prevent oxidation. The yellow solution is concentrated by distillation under reduced pressure; *ammonium* 3 : 4-*dimethoxyphenylhydrazinosulphonate* (9·5 g.) then separates in greyish-white crystals with a metallic lustre (Found: N, 15·7; S, 12·0. $C_8H_{15}O_5N_3S$ requires N, 15·6; S, 12·1%).

This salt (12 g.) is boiled under reflux with alcoholic hydrochloric acid (30 c.c. of 15%) for ½ hour. The mixture of 3 : 4-dimethoxyphenylhydrazine hydrochloride and ammonium chloride which separates from the deep red solution is collected, extracted with boiling alcohol, and filtered off; the filtrate deposits the hydrazine hydrochloride (4·5 g.) in grey prisms which, after recrystallisation from alcohol, melt at 162° (decomp.) (Found : N, 13·7. $C_8H_{13}O_2N_2Cl$ requires N, 13·7%). 3 : 4-*Dimethoxyphenylhydrazine hydrochloride* has a strong odour of the phenylhydrazine and must be rapidly dried on porous porcelain over sulphuric acid, since it readily decomposes in contact with air, becoming a dark mass. It gradually loses hydrogen chloride under reduced pressure and the crystals dissolve in water or alcohol to solutions which rapidly become red.

3 : 4-*Dimethoxyphenylhydrazine* separates, on the addition of sodium acetate to the aqueous solution of the hydrochloride, in colourless needles, m. p. 81°, which rapidly decompose in contact with air.

6 : 7-*Dimethoxytetrahydrocarbazole* (III).—3 : 4-Dimethoxyphenylhydrazine hydrochloride (2·5 g.) is added to alcohol (15 c.c.) containing *cyclo*hexanone (1·2 g.) and sodium acetate (1·4 g.). The mixture is boiled under reflux during 2 hours and poured into water; the hydrazone then separates as a syrup which does not solidify on standing or cooling. This syrup is washed with water, boiled with alcoholic hydrochloric acid (12 c.c. of 20%) for a few minutes, and the dark solution poured into water; the 6 : 7-*dimethoxytetrahydrocarbazole* that separates crystallises from dilute alcohol in pale yellow prisms, m. p. 98° (Found : C, 72·5; H, 7·6; N, 6·3. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4; N, 6·1%).

Ethyl 5 : 6-*Dimethoxyindole-2-carboxylate* (compare I).—3 : 4-Dimethoxyphenylhydrazine hydrochloride (2·5 g.) was added to a solution of ethyl pyruvate (1·2 g.) and finely powdered sodium acetate (1·3 g.) in alcohol (25 c.c.). After boiling for 2 hours, the red solution was diluted with water; the oily hydrazone that separated did not solidify on cooling. It was washed with water and boiled for a few minutes with alcoholic hydrochloric acid (10 c.c. of 20%); on adding water, *ethyl* 5 : 6-*dimethoxyindole-2-carboxylate* separated in a very crude condition. This was ultimately obtained pure, crystallising from alcohol in yellow prisms, m. p. 172° (Found : C, 62·5; H, 6·0; N, 5·7. $C_{13}H_{15}O_4N$ requires C, 62·7; H, 6·0; N, 5·7%), but the amount available did not allow of the preparation of the acid in a pure state.

2 : 5-*Dimethoxyphenylhydrazine*.—The diazotisation of 2 : 5-dimethoxyaniline in dilute aqueous hydrochloric acid was not feasible owing to the effervescence which accompanies the reaction even at low temperatures. Finely divided 2 : 5-dimethoxyaniline hydro-

chloride (20 g.; compare Mülhausen, *loc. cit.*) is added to glacial acetic acid, and dry methyl nitrite passed into the well-stirred mixture at 10°. The deep brown solution is gradually poured into dry alcohol-free ether with stirring; 2 : 5-dimethoxybenzenediazonium chloride is then precipitated in small, yellow needles and is very unstable. The ether is decanted, the crystals are rapidly washed with ether and dissolved in ice-cold water (60 c.c.), and the solution is added drop by drop to a well-cooled saturated solution of ammonium sulphite (60 c.c.) containing ammonia (40 c.c.; *d* 0·880). After remaining for a few hours, the deep red mixture is filtered, when *ammonium* 2 : 5-*dimethoxydiazobenzenesulphonate* remains as brick-red crystals. This substance may be crystallised from a little water, in which it is rather readily soluble (Found: N, 15·7; S, 12·1. $C_8H_{13}O_5N_3S$ requires N, 16·0; S, 12·1%). This sulphonate (26 g.) was mixed with glacial acetic acid (23 c.c.) and water (7 c.c.), and zinc dust (7·5 g.) added at 40—50°, a little at a time. The solution, which gradually became lighter in colour, was kept at 50° for an hour, diluted with water, the zinc removed as sulphide in an atmosphere of hydrogen sulphide, and the filtrate concentrated under reduced pressure; the *ammonium* 2 : 5-*dimethoxyphenylhydrazinosulphonate* (19 g.) that separated as a grey, crystalline solid was recrystallised from hot alcohol (Found: N, 15·6; S, 12·1. $C_8H_{15}O_5N_3S$ requires N, 15·6; S, 12·1%).

When this sulphonate (25 g.) was boiled under reflux with alcoholic hydrochloric acid (60 c.c. of 15%), a precipitate consisting of 2 : 5-*dimethoxyphenylhydrazine hydrochloride* and ammonium chloride separated from the deep purple solution. After a few minutes, the hydrolysis was complete, more alcohol was then added and some animal charcoal, the boiling liquid filtered and concentrated; the hydrazine hydrochloride was then obtained in colourless crystals (9·5 g.) which darken above 250° (Found: C, 48·2; H, 6·0; N, 13·8. $C_8H_{13}O_2N_2Cl$ requires C, 48·0; H, 5·9; N, 13·7%). This hydrochloride is very soluble in water and moderately soluble in alcohol and rapidly decomposes on exposure to air. 2 : 5-*Dimethoxyphenylhydrazine* separated in needles on the addition of sodium acetate to the aqueous solution of the hydrochloride; after drying on porous porcelain over sulphuric acid, it melted at 84°.

2-*Carboxy*-7-*methoxyindole*-3-*acetic Acid* (IV).—α-Ketoglutaric acid (25 g.; compare Blaise and Gault, *Compt. rend.*, 1908, **147**, 199) was dissolved in water (200 c.c.) containing sodium acetate (12 g.) and glacial acetic acid (10 c.c.), and *o*-methoxyphenylhydrazine hydrochloride (25 g.; Blaikie and Perkin, J., 1924, **125**, 315) in water (100 c.c.) then added. After the turbid solution had been kept for a few hours, the yellow methoxyphenylhydrazone of α-ketoglutaric acid (35 g.) was collected. It separated from benzene in yellow prisms, m. p. 168° (decomp.).

This hydrazone (15 g.) was boiled under reflux with alcoholic hydrochloric acid (25 c.c. of 15%) for ½ hour. The hot, very dark coloured solution was filtered from the ammonium chloride, and the filtrate kept for several hours, crystallisation being assisted by occasional scratching. The crystals were collected, washed with small quantities of alcohol, and recrystallised three times from alcohol, from which *ethyl* 2-*carbethoxy*-7-*methoxyindole*-3-*acetate* separated in grey needles, m. p. 106°, b. p. 245—255°/11 mm. with slight decomposition (Found: C, 63·1; H, 6·0; N, 4·8. $C_{16}H_{19}O_5N$ requires C, 62·9; H, 6·2; N, 4·6%). This ester was boiled with 10% aqueous sodium hydroxide for 2 hours and the filtered solution acidified; the 2-*carboxy*-7-*methoxyindole*-3-*acetic acid* that separated crystallised from alcohol in brown needles, m. p. 253° (decomp.) (Found by titration: equiv., 251. Calc. for a dibasic acid $C_{12}H_{11}O_5N$: equiv., 249).

2-*Carboxy*-5-*methoxyindole*-3-*acetic Acid* (V).—*p*-Methoxyphenylhydrazine (Blaikie and Perkin, *loc. cit.*; 9·6 g.), dissolved in water (20 c.c.) containing potassium acetate (6 g.), was boiled under reflux for 2 hours with a solution of α-ketoglutaric acid (8 g.) in a mixture of alcohol (30 c.c.) and water (5 c.c.). The product was filtered off and the alcohol evaporated; the p-*methoxyphenylhydrazone* of *α-ketoglutaric acid* then remained as an oil which did not solidify on cooling and rubbing. The oil was boiled under reflux with alcoholic sulphuric acid (25 c.c. of 20%), mixed with water and ether, the tar which had separated removed by filtration, and the ethereal solution washed with water, dried, and evaporated. Since the syrupy ester did not crystallise, it was boiled under reflux with sodium hydroxide (10%) for an hour, cooled, and acidified; a gum then separated which gradually hardened and after repeated recrystallisation from alcohol, 2-*carboxy*-5-*methoxyindole*-3-*acetic acid* was obtained in pale yellow needles, m. p. 265° (Found: N, 5·9; equiv. by titration, 250. $C_{12}H_{11}O_5N$ requires N, 5·7%; equiv., 249).

THE DYSON PERRINS LABORATORY,
OXFORD.

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