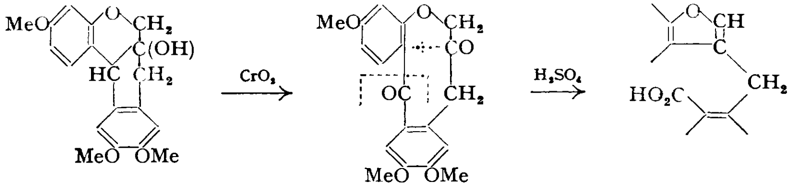
276. *A Synthesis of β-Anhydrotrimethylbrazilone.*

By K. W. Bentley and Sir Robert Robinson.

β-Anhydrotrimethylbrazilone is obtainable from *O*-trimethylbrazilin in three stages which involve a series of molecular rearrangements such that the product bears no obvious relation to the starting point. This α-naphthol derivative has been synthesised from an appropriately substituted *o*-hydroxydeoxybenzoin by conversion into a related phenoxyacetic acid and then ring-closure to a substituted coumaronecarboxylic acid bearing a metathetic relation to ψ-trimethylbrazilone. Conversion into the acid chloride and ring-closure by Kipping's method afforded β-anhydrotrimethylbrazilone.

The formation of trimethylbrazilone in the oxidation of trimethylbrazilin by chromic acid was discovered by Gilbody and Perkin in 1899 (*Proc. Chem. Soc.*, **15**, 27; cf. *idem*, *J.*, 1902, **81**, 1040). Among its remarkable transformations is the change to ψ-trimethylbrazilone (IV) brought about by dissolution in concentrated sulphuric acid. This was first observed by Herzig, Pollak, and Galitzenstein (*Ber.*, 1904, **37**, 631) and elucidated by Perkin and Robinson (*J.*, 1909, **95**, 381). The annexed scheme illustrates the course of the rearrangement.

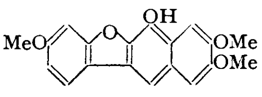


= (IV)

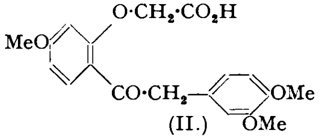
The conversion of ψ-trimethylbrazilone (IV) into β-anhydrotrimethylbrazilone (I) involves a swing-round of the lower part of the molecule and elimination of the elements of water between the carboxyl group and hydrogen in the furan ring.

In order to synthesise (I) we proposed to dehydrate the acid (III) which should be obtainable from (II). This scheme was eventually realised but the methods found to be necessary to effect these ring-closures were different from those which were contemplated at the outset.

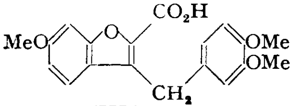
The intermediate for (II) is the ketone (V) which was obtained in only moderate overall yield. Hence the analogous series starting with (VI) was first investigated.



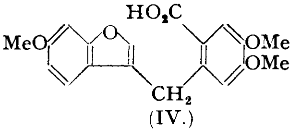
(I.)



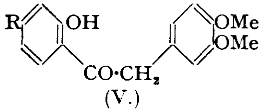
(II.)



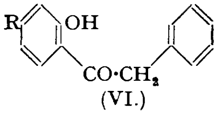
(III.)



(IV.)



(V.)



(VI.)

The preparation of 2-hydroxy-4-methoxyphenyl benzyl ketone (VI; R = OMe) by the Hoesch condensation of resorcinol and phenylacetonitrile to give 2 : 4-dihydroxyphenyl benzyl ketone (VI; R = OH) (Chapman and Stephen, *J.*, 1923, 406), followed by partial methylation of this product in alcoholic solution (Tambor, *Ber.*, 1910, **43**, 1884), gave very poor overall yields (7—10%), and much better results were obtained by the condensation of phenylacetyl chloride with 1 : 3-dimethoxybenzene in carbon disulphide solution in the presence of anhydrous aluminium chloride.

The condensation of (VI; R = OMe) with ethyl bromoacetate was very difficult to effect but was finally successfully carried out in boiling ethanol in the presence of sodium ethoxide. The resulting 5-methoxy-2-phenylacetylphenoxyacetic acid gave an intractable tar on being heated with sodium acetate and acetic anhydride under reflux for 3—4 hours, but 6-methoxy-3-benzylcoumarilic acid was produced on heating it with phosphoric anhydride in boiling benzene for an hour, a reaction which was never subsequently reproduced. Better yields were, however, consistently obtained when the ring-closure was effected by means of sodium ethoxide in boiling ethanol. Several attempts to convert this compound into 6-hydroxy-3-methoxy-β-brazan gave either polymerised compounds, which nevertheless gave the colour reactions expected for this compound from analogy (cf. Lustgarten, *Monatsh.*, 1882, **3**, 720; Perkin and Robinson, *loc. cit.*, p. 391), or gave no indication of reaction. Among the methods tried were heating with phosphoric anhydride in xylene, and heating with sodium acetate and acetic anhydride at 250° for 50 hours, followed by conversion into the acid chloride and treatment of this with aluminium chloride.

The synthesis of β-anhydrotrimethylbrazilone itself proceeded better than did the analogous reactions in the model series.

The hydroxy-ketone (V; R = OMe) was prepared in the two ways indicated for the preparation of (VI; R = OMe): first, by the partial methylation of 2 : 4-dihydroxyphenyl 3′ : 4′-dimethoxybenzyl ketone (V; R = OH), prepared by the condensation of 3 : 4-dimethoxyphenylacetonitrile and resorcinol, and, secondly, by the condensation of 3 : 4-dimethoxyphenylacetyl chloride with 1 : 3-dimethoxybenzene in boiling benzene solution in presence of anhydrous aluminium chloride. Again the second method gave the better yields.

Conversion of (V; R = OMe) into the phenoxyacetic acid derivative (II) by condensation with ethyl bromoacetate in the presence of sodium ethoxide followed the optimum conditions worked out for the preparation of 5-methoxy-2-phenylacetylphenoxyacetic acid. As with the latter, (II) was converted into an intractable tar by the action of sodium acetate and acetic anhydride at the boiling point, but was successfully changed into (III) by the action of sodium ethoxide in boiling ethanol. The related acid chloride gave β-anhydrotrimethylbrazilone (I) on treatment with an excess of powdered anhydrous aluminium chloride in cold benzene during 5 hours. The synthetic product was identified with an authentic specimen prepared from trimethylbrazilone by the method of Herzig, Pollak, and Galitzenstein (*loc. cit.*).

EXPERIMENTAL.

2-*Hydroxy*-4-*methoxyphenyl Benzyl Ketone* (VI; R = OMe).—Powdered anhydrous aluminium chloride (44 g.) was added to a mixture of 1 : 3-dimethoxybenzene (46 g.) and carbon disulphide (50 c.c.) slowly, with constant shaking and ice-cooling. Phenylacetyl chloride (51 g.) in carbon disulphide (50 c.c.) was then slowly added, and the mixture heated at the b. p. until evolution of hydrogen chloride ceased (about 1 hour). The excess of carbon disulphide was removed, and the hard purple aluminium complex decomposed by ice-water and hydrochloric acid. The product was isolated by means of ether, freed from acids, and crystallised from ethanol (40 g.; m. p. 90°). After one recrystallisation the m. p. was 92°, or 91° with a specimen m. p. 90° prepared by the method of Tambor (*Ber.*, 1910, **43**, 1884).

The 2 : 4-*dinitrophenylhydrazone* separated from chloroform–light petroleum in short, deep-red needles, m. p. 212° (Found: C, 59·4; H, 4·3; N, 13·5. $C_{21}H_{16}O_6N_4$ requires C, 59·7; H, 4·3; N, 13·3%).

5-*Methoxy*-2-*phenylacetylphenoxyacetic Acid*.—Sodium (4·38 g.) was dissolved in absolute ethanol (100 c.c.), and a solution of 2-hydroxy-4-methoxyphenyl benzyl ketone (9·2 g.) in ethanol (75 c.c.) added with vigorous stirring whilst the mixture was boiled under reflux. Ethyl bromoacetate (31·75 g.) was slowly added to the boiling suspension of the sodium salt, during approx. 15 minutes, and the mixture heated on the steam-bath for a further hour. Aqueous sodium hydroxide (50 c.c. of 25%) was then added, and the mixture heated for 2 hours, diluted with water (750 c.c.), acidified, and thrice extracted with 150-c.c. portions of ether. The combined extracts were shaken with five portions (25 c.c. each) of 2N-sodium carbonate, and the combined aqueous solutions cooled in ice and acidified with ice-cold hydrochloric acid. The 5-*methoxy*-2-*phenylacetylphenoxyacetic acid* separated as a semi-solid mass, which became crystalline when kept overnight with dilute acetic acid. The solid was collected at the pump, and crystallised from aqueous alcohol (yield, 5·2 g.), and obtained in the form of slender, colourless needles on recrystallisation from benzene; it had m. p. 130° (Found: C, 67·8; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). The acid is very sparingly soluble in cold water and in light petroleum, sparingly soluble in hot water, and readily soluble in ethanol, chloroform, or acetone. Its solution in concentrated sulphuric acid exhibited a dark green fluorescence.

6-*Methoxy*-3-*benzylcoumarilic Acid*.—(*a*) 5-Methoxy-2-phenylacetylphenoxyacetic acid (1 g.) was added to a suspension of phosphoric anhydride (5 g.) in boiling benzene (50 c.c.), and the mixture refluxed for an hour and then filtered hot, and the benzene removed by distillation. The residue was crystallised from benzene, 6-*methoxy*-3-*benzylcoumarilic acid* being obtained as long, slender, colourless needles, m. p. 190°, almost insoluble in water, light petroleum, or cold benzene, readily soluble in ethanol, acetone, or hot benzene. Its solution in cold, concentrated sulphuric acid exhibited an intense emerald-green fluorescence; when this solution was kept, the fluorescence became dark green and less intense, and dilution no longer precipitated the acid (Found : C, 72·0; H, 4·9. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%).

On evaporation of the mother-liquors from the recrystallisation of this compound a small quantity of a non-crystalline solid was obtained. This was soluble in alkali, and this solution when warmed to 60° with chloroform developed a green colour, indicating the presence of 6-hydroxy-3-methoxy-*β*-brazan.

(*b*) Sodium (1·9 g.) was dissolved in ethanol (80 c.c.), and 5-methoxy-2-phenylacetylphenoxyacetic acid (5 g.) added. The mixture was heated under reflux for an hour, diluted with cold water, and acidified with dilute hydrochloric acid. The bulky white mass which separated was dried and crystallised from benzene (yield, 4 g.); the acid had m. p. 190°, alone or mixed with the above product.

Attempted Preparations of 6-*Hydroxy*-3-*methoxy*-*β*-*brazan*.—(*a*) 6-Methoxy-3-benzylcoumarilic acid was treated with phosphoric anhydride in refluxing xylene. The product was a greenish-yellow semi-solid mass which could not be crystallised. On being warmed with chloroform and alkali, the mixture developed a green colour, and on treatment with alkali and benzenediazonium chloride a deep red colour developed. These reactions indicated the presence of the required compound.

(*b*) 6-Methoxy-3-benzylcoumarilic acid was converted into the acid chloride by warming it with pure thionyl chloride, and anhydrous aluminium chloride was added to a solution of the acid chloride in carbon disulphide. The mixture was heated until evolution of hydrogen chloride ceased, and the hard black aluminium complex was decomposed by ice-water and hydrochloric acid, yielding a dark brown amorphous solid, which could not be obtained crystalline and showed no signs of melting below 320°. The solid was soluble in alkali, and gave both the above-mentioned colour reactions.

(*c*) 6-Methoxy-3-benzylcoumarilic acid was recovered unchanged after being heated for 52 hours at 240° in a sealed tube with acetic anhydride and fused sodium acetate, and after being heated with phosphoric anhydride and syrupy phosphoric acid for 8 hours.

2 : 4-*Dihydroxyphenyl* 3′ : 4′-*Dimethoxybenzyl Ketone* (V; R = OH).—Hydrogen chloride was passed through a mixture of 3 : 4-dimethoxyphenylacetonitrile (10 g.), resorcinol (10 g.), and powdered anhydrous zinc chloride (8 g.) in dry ether (250 c.c.) for 2 hours. The ketimine hydrochloride crystallised overnight as a mass of small, pale pink needles; it was hydrolysed by boiling it with 2N-hydrochloric acid (200 c.c.) for 2 hours. The *ketone*, a bulky, pale pink solid, was collected and crystallised from ethanol, being obtained as short, stout, colourless prisms, m. p. 176·5°. It is readily soluble in ether, benzene, acetone, or hot ethanol. The ferric reaction in alcoholic solution was a deep reddish-violet coloration (Found : C, 66·4; H, 5·3. $C_{16}H_{16}O_5$ requires C, 66·6; H, 5·5%).

The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in bright red needles, which became chocolate-brown on drying; m. p. 229° (Found : C, 56·2; H, 4·5; N, 11·4. $C_{22}H_{20}O_8N_4$ requires C, 56·4; H, 4·3; N, 11·9%).

2-*Hydroxy*-4-*methoxyphenyl* 3′ : 4′-*Dimethoxybenzyl Ketone* (V; R = OMe).—(*a*) Methyl sulphate (5·95 c.c., 7·82 g.) was slowly added to a well-stirred solution of 2 : 4-dihydroxyphenyl 3′ : 4′-dimethoxybenzyl ketone (6·2 g., 1 mole) in alcoholic sodium hydroxide (24·8 c.c. of 10%) and the mixture then heated for an hour, cooled, and poured into water (150 c.c.). The solid was crystallised twice from ethanol (yield, 2 g.) and obtained as bunches of very long, slender, colourless needles, m. p. 119° (Found : C, 67·9; H, 6·1. $C_{17}H_{18}O_5$ requires C, 67·6; H, 5·9%).

2-*Hydroxy*-4-*methoxyphenyl* 3′ : 4′-*dimethoxybenzyl ketone* is sparingly soluble in water, light petroleum, or cold ethanol, readily soluble in benzene, acetone, or hot ethanol. The alcoholic solution developed a deep violet-red colour on addition of ferric chloride.

The 2 : 4-*dinitrophenylhydrazone* crystallised from benzene in long, slender, orange needles, m. p. 198° (Found : C, 57·1; H, 4·4; N, 11·5. $C_{23}H_{22}O_8N_4$ requires C, 57·2; H, 4·6; N, 11·6%).

(*b*) Phosphorus pentachloride (13·5 g.) was slowly added to a suspension of homoveratric acid (12·5 g.) in dry benzene (40 c.c.), with exclusion of moisture. The solution was heated for 5 minutes on a steam-bath and then slowly added to a mixture of 1 : 3-dimethoxybenzene (8·8 g.) and powdered anhydrous aluminium chloride (8·5 g.) in boiling benzene (40 c.c.). The mixture was refluxed until evolution of hydrogen chloride ceased (about 1 hour). After decomposition by ice and hydrochloric acid, the benzene layer was removed, washed with dilute sodium carbonate solution and with water, dried, and evaporated. The residue after removal of the solvent was crystallised from ethanol (yield, 10 g.); m. p. 119°, alone or mixed with the product obtained as in (*a*).

5-*Methoxy*-2-(3 : 4-*dimethoxyphenylacetyl*)*phenoxyacetic Acid* (II).—2-Hydroxy-4-methoxyphenyl 3′ : 4′-dimethoxybenzyl ketone (5 g.) in ethanol (75 c.c.) was added to a solution of sodium ethoxide (1·52 g. of sodium in 150 c.c. of ethanol) with constant stirring. Ethyl bromoacetate (11·0 g.) was added to the boiling mixture, during approx. 15 minutes, and the solution refluxed for a further hour. Aqueous sodium hydroxide (50 c.c. of 20%) was added and the mixture boiled for 2 hours, and then cooled, added to water (75 c.c.), acidified with hydrochloric acid, and thrice extracted with ether. The combined extracts were shaken with five portions (20 c.c. each) of 2N-sodium carbonate solution, and the combined aqueous solutions were acidified with ice-cold hydrochloric acid. The semi-solid mass became crystalline on trituration with dilute acetic acid. The solid *acid* was collected and crystallised from glacial acetic acid (yield, 2·5 g.), being obtained as bunches of short, colourless needles, m. p. 142°, sparingly soluble in water, light petroleum, or benzene, readily soluble in ethanol, ethyl acetate, or warm glacial acetic acid (Found : C, 63·2; H, 5·6. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·6%).

6-*Methoxy*-3-(3 : 4-*dimethoxybenzyl*)*coumarilic Acid* (III).—Sodium (0·5 g.) was dissolved in ethanol (20 c.c.), and 5-methoxy-2-(3 : 4-dimethoxyphenylacetyl)phenoxyacetic acid (2 g.) added. The mixture was refluxed for 15 minutes, kept overnight, then diluted with water (100 c.c.) and acidified with hydrochloric acid. The bulky white solid was collected, washed with water, and crystallised from glacial acetic acid. The *coumarilic acid* was obtained as short, slender, colourless needles, m. p. 196·5°, sparingly soluble in water, light petroleum, benzene, or cold ethanol (Found : C, 66·3; H, 5·7. $C_{19}H_{18}O_6$ requires C, 66·6; H, 5·3%).

β-*Anhydrotrimethylbrazilone* (I).—Phosphorus pentachloride (0·8 g.) was slowly added to a suspension of 6-methoxy-3-(3′ : 4′-dimethoxybenzyl)coumarilic acid (1·2 g.) in benzene (35 c.c.), and the mixture was heated to boiling for 10 minutes on a steam-bath. After the mixture had cooled, powdered anhydrous aluminium chloride (1 g.) was introduced and the whole kept in the cold for 5 hours. The bright red aluminium complex was decomposed by ice-water, and the solid collected and crystallised from a large volume of ethanol. The minute, very pale pink prisms so obtained had m. p. 220°, alone or mixed with an authentic specimen of β-anhydrotrimethylbrazilone. A comparison of the characteristic colour reactions of the two specimens confirmed their identity.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

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