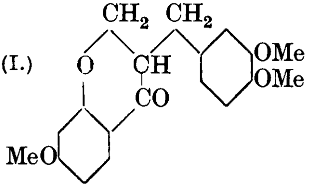
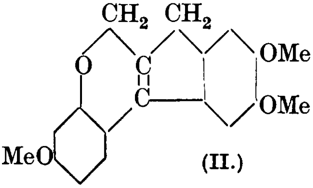
CCLXXVII.—*Experiments on the Synthesis of Brazilin and Hæmatoxylin and their Derivatives. Part II. A Synthesis of Deoxytrimethylbrazilone and of* iso*Brazilein Ferrichloride Trimethyl Ether.*

By WILLIAM HENRY PERKIN, jun., JNANENDRA NATH RÂY, and ROBERT ROBINSON.

IN Part I of this investigation (J., 1926, 941) it was explained that our object in attempting the preparation of 3-homoveratryl-7-methoxychromanone (I) was to examine its behaviour towards dehydrating agents, which should convert it into the indene derivative (II), a near relative of *O*-trimethylbrazilin.

(I.)

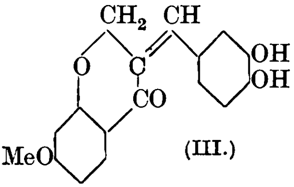




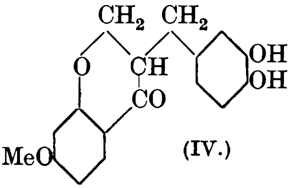
(II.)

Considerable progress in this direction has since been made and we had hoped to be able to defer publication until our experiments on the final stages of the synthesis of trimethylbrazilin were completed; an interim report has, however, become necessary as the result of a communication received on June 7th from Professor P. Pfeiffer and we therefore submit at once an account of the stage already reached in our work. Professor Pfeiffer's letter mentions results similar in many respects to those which we have obtained and in view of this duplication of research we wish to direct attention to the clear statement of our position which we thought it wise to make at the time of publication of Part I of this series (*loc. cit.*, p. 942) and which it is unnecessary to repeat. The reduction of veratrylidene-7-methoxychromanone by means of hydrogen in presence of palladium yielded (*loc. cit.*, p. 946) 3-homoveratryl-7-methoxychroman, m. p. 96°, instead of the expected ketone (I), which, however, Pfeiffer and Emmer (*Ber.*, 1920, **53**, 945) claimed to have obtained when they employed platinum as the catalyst. The ketone was stated to melt at 89° and in Part I we expressed some doubt in regard to the accuracy of the interpretation of their results. Since, however, we had not repeated these experiments, our remarks were guarded and summarised in the statement (p. 947): "We do not go so far as to assert that the products of hydrogenation of veratrylidenemethoxychromanone in presence of platinum and of palladium are identical, although we think it probable that this will prove to be the case." The suggestion so expressed was, however, not correct, as the experiments mentioned below indicate, and Professor Pfeiffer informs us that he has re-examined his substance and proved that it is a ketone by the preparation of its oxime. Although we were unable to accomplish satisfactorily the reduction of veratrylidenemethoxychromanone to a related saturated ketone, the formation of the saturated ketone (IV) from 3 : 4-dihydroxybenzylidene-7-methoxychromanone (III) proceeds smoothly under these conditions.

This substance (III) was obtained by the condensation of protocatechualdehyde with 7-methoxychromanone (a new and improved method for the preparation of which is described on p. 2097) in acetic acid solution by means of hydrogen chloride. On methylation in the usual manner, (IV) yields the ketone (I), which has m. p. 92°, and the whole of the substance which we have used in this investigation was prepared in this way. Subsequently the same compound was isolated in poor yield from the products of the partial hydrogenation of veratrylidenemethoxychromanone in presence of palladium.

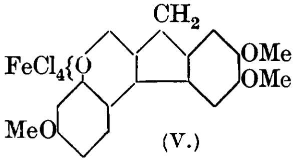


(III.)

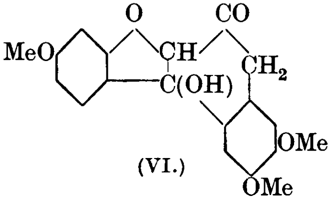


(IV.)

On treatment with phosphoric anhydride in boiling benzene the dehydration of (I) to (II) was effected, and the first indication of its structure and of the fact that it contains the brazilin skeleton was provided by the oxidation of the crude substance to *iso*brazilein ferrichloride trimethyl ether (V) (Engels, Perkin, and Robinson, J., 1908, **93**, 1121; Crabtree and Robinson, J., 1918, **113**, 859), a process effected by means of ferric chloride in acetic acid solution. The salt was identified by comparison with an authentic specimen prepared from brazilein. Later, the compound (II) was obtained from (I) in a pure condition by the dehydrating action of phosphoric anhydride and identified by direct comparison with deoxytrimethylbrazilone, $C_{19}H_{18}O_4$, a substance obtained by the reduction of trimethylbrazilone, $C_{19}H_{18}O_6$, with phenylhydrazine (Gilbody and Perkin, J., 1902, **81**, 1046). Deoxytrimethylbrazilone, prepared from brazilin, was also found to yield the *iso*brazilein derivative in the manner described above. Professor Pfeiffer's letter directs attention to the possibility that his dehydration product of the ketone (I) may be deoxytrimethylbrazilone and that the pyrylium salt which it yields on oxidation with ferric chloride may be *iso*brazilein ferrichloride trimethyl ether. The synthetical proof that deoxytrimethylbrazilone has the constitution (II) and contains the brazilin skeleton necessitates a view of the nature of trimethylbrazilone differing somewhat from that expressed in the formula (VI) (Perkin and Robinson, J., 1908, **93**, 948). It was then suggested that the oxidation of trimethylbrazilin with chromic acid leads to the disruption of the bond common to the chroman and hydrindene nuclei and to the production of a diketone (VII) which passes into (VI) by an intramolecular aldol condensation. In harmony with the conclusions drawn by Professor J. F. Thorpe and his collaborators from extensive researches on ring-chain and intra-annular tautomerism (VI) and (VII) might be regarded as tautomerides.

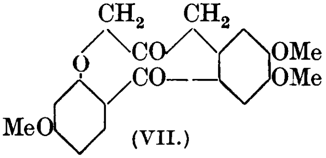


(V.)

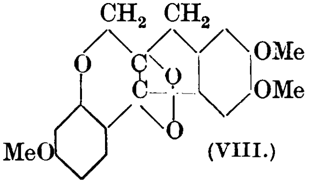


(VI.)

Bearing in mind the phenomena encountered by Willstätter in his study of the *o*-quinones and by Schönberg among the benzils (compare *Annual Reports*, 1922, 109), we might also postulate the peroxidic phase (VIII), the complete tautomeric system being (VI) $\rightleftharpoons$ (VII) $\rightleftharpoons$ (VIII). The phase (VI) must be, at least, an intermediate in the formation of the β-naphthol derivative, α-anhydrotrimethylbrazilone, under the influence of aqueous alkalis, whilst



(VII.)



(VIII.)

VIII) offers an explanation of the remarkable behaviour with phenylhydrazine. Nevertheless, (VI) and (VIII) can only be related through (VII) and the last seems to be the most satisfactory single expression of the whole character of trimethylbrazilone which it is possible to select. In this phase, some coherence of the carbonyl groups may be manifested as the result of the dipolar character of these groups.

Further evidence bearing on this aspect of the chemistry of brazilin will, it is hoped, be discussed in a future communication and it is proposed to extend the synthetical work indicated above to the analogous hæmatoxylin derivatives. Naturally we are also engaged in attempts to convert deoxytrimethylbrazilone into trimethylbrazilin.

EXPERIMENTAL.

7-*Methoxychromanone*.—The following method of preparation of this substance is much more convenient than any of those hitherto described. A solution of β-*m*-methoxyphenoxypropionic acid (14 g.) in 80% sulphuric acid (100 c.c.) was heated to 60° during an hour, then at 60—80° for an hour, and finally at 80—90° for a third hour. The ketone was isolated by means of ether in the usual manner from the diluted mixture and freed from acids. The crude product crystallised when dry and weighed 7—8 g. (yield, about 60%). Several new substances which have been prepared in the course of our work may be mentioned here. *Ethyl* β-m-*methoxyphenoxypropionate*, $MeO{\cdot}C_6H_4{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$, obtained by esterification of the acid with boiling ethyl-alcoholic sulphuric acid, crystallises from aqueous alcohol in plates, m. p. 45° (Found: C, 63·8; H, 7·3. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·1%). This ester could not be condensed with veratraldehyde. *Veratrylidene*-7-*methoxychromanone dibromide*, prepared in cold carbon tetrachloride solution, has m. p. 137—138° (Found: C, 46·2; H, 3·6. $C_{19}H_{18}O_5Br_2$ requires C, 46·8; H, 3·7%) and yields veratrylidenemethoxychromanone on treatment with zinc dust and acetic acid.

Veratrylidenemethoxychromanone yields an *oxamino-oxime* when treated with hydroxylamine hydrochloride (3 mols.) and sodium acetate in boiling alcoholic solution. The colourless substance crystallises from alcohol in prismatic needles (Found: C, 61·0; H, 5·8; N, 7·0. $C_{19}H_{22}O_6N_2$ requires C, 61·0; H, 5·9; N, 7·5%).

3-(3′ : 4′-*Dihydroxybenzylidene*)-7-*methoxychromanone* (III).—An ice-cold solution of 7-methoxychromanone (5 g.) and protocatechualdehyde (5 g.) in acetic acid (30 c.c.) was saturated with hydrogen chloride and set aside. Next day, the garnet crystals which had separated were collected and decomposed by trituration with water at 0°. The substance crystallised from aqueous alcohol (charcoal) in brownish-yellow, microscopic needles, m. p. 212° (Found: C, 68·5; H, 4·8. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%).

The alcoholic solution develops a green coloration on the addition of ferric chloride. Aqueous alkaline solutions are deep crimson to blood-red according to the concentration. Methylation by means of methyl sulphate and sodium hydroxide yields veratrylidenemethoxychromanone, m. p. 141°.

3-(3′ : 4′-*Dihydroxybenzyl*)-7-*methoxychromanone* (IV).—A solution of dihydroxybenzylidenemethoxychromanone (1·5 g.) in alcohol (100 c.c.) to which palladous chloride (15 c.c. of 0·5% aqueous solution) had been added was stirred with hydrogen; 60 c.c. of the gas were absorbed at 15° in 28 minutes. The nearly colourless liquid was filtered and concentrated; the reduction product, then precipitated on dilution with water, crystallised from aqueous alcohol (about 20%) in rectangular plates, m. p. 138° (Found: C, 68·0; H, 5·7. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%). Ferric chloride added to an alcoholic solution of this substance produces a green coloration changing to crimson on keeping. The cherry-red solution in sulphuric acid soon acquires a yellowish-green fluorescence and on addition of water a fluorescent orange solution is obtained. The action of hydrogen chloride on this ketone in glacial acetic acid solution yielded, together with other products, a crystalline *substance*, m. p. 139° (mixed, 118—124°), the investigation of which is not yet complete.

3-*Homoveratryl*-7-*methoxychromanone* (I).—(A) The dihydric phenol described in the last section was methylated in methyl-alcoholic solution by means of methyl sulphate and potassium hydroxide in the usual manner; the product crystallised from aqueous alcohol and then from aqueous acetone in glistening, rectangular plates, m. p. 92° (Found: C, 70·1; H, 6·3. Calc. for $C_{19}H_{20}O_5$: C, 69·6; H, 6·1%). The substance is insoluble in aqueous alkalis and gives no coloration with ferric chloride in alcoholic solution.

(B) When veratrylidenemethoxychromanone was reduced in acetic acid solution by means of the calculated volume of hydrogen in presence of palladium the greater part of the unsaturated ketone was recovered unchanged, whilst an unlimited reduction gave homoveratrylmethoxychroman, m. p. 96°, as previously described (*loc. cit.*). Under the following conditions, however, the dihydro-derivative could be isolated, although in poor yield. A solution of veratrylidenemethoxychromanone (1·4 g.) in pure acetic acid (100 c.c.) to which palladous chloride (20 c.c. of 0·5% solution) had been added was agitated with hydrogen at 18°; 50 c.c. were absorbed in 12 minutes, and a further 50 c.c. in 50 minutes, after which absorption of a third equal volume occurred at 40—45°. The filtered solution was concentrated under diminished pressure to 35 c.c., and water (10 c.c.) added, causing the precipitation of unchanged material, which was crystallised from alcohol (0·7 g., m. p. 141°). The acetic acid and alcoholic filtrates were diluted with water and the precipitated material was fractionally crystallised from aqueous alcohol and aqueous acetone. About 0·1 g. of a substance crystallising in glistening, rectangular plates, m. p. 92°, was isolated. The m. p. of a mixture with the ketone prepared as described under (A) was 92°, whilst a mixture with homoveratrylmethoxychroman, m. p. 96°, melted at 71—86°. A minute amount of the chroman derivative, m. p. 96°, was isolated from the mother-liquors.

Deoxytrimethylbrazilone (II).—There are indications that 3-homoveratrylmethoxychromanone may be dehydrated by means of a variety of condensing agents, *e.g.*, zinc chloride, stannic chloride, phosphoryl chloride, etc., in that the products are partly oxidised in acid solution to *iso*brazilein salts, the fluorescence of which is so characteristic. Phosphoric anhydride (30 g.) was added to a solution of the ketone (3·5 g.) in benzene (150 c.c.), and the solution gently boiled for 10 minutes. The dark mass was decomposed by the addition of ice, the mixture was heated and agitated, the benzene layer, separated from the strongly fluorescent aqueous solution, was washed with water and aqueous sodium hydroxide, dried with potassium carbonate (charcoal), and filtered, and the solvent was removed in a vacuum. The residue (R) was dissolved in alcohol, and the solution concentrated; the substance which separated on keeping crystallised from alcohol as a satiny mass of colourless sheaves of needles, m. p. 166—171°. This substance was found by direct comparison to be identical with deoxytrimethylbrazilone prepared by the method of Gilbody and Perkin (*loc. cit.*). This and also a mixture of the two specimens had m. p. 166—171°. The colour reactions and solubilities described by Gilbody and Perkin were identical in the cases of the synthetical specimen and that derived from brazilin. Some more details regarding the characteristic reactions of this substance may be given. The solution in an excess of nitric acid is intense eosin-red rather than purple (Gilbody and Perkin) and on dilution with water gives a clear red solution exhibiting very bright yellowish-green fluorescence. The more blue-toned red solution results, however, if the volume of nitric acid employed is greatly diminished, and dilution with water then gives the purple precipitate mentioned by Gilbody and Perkin. A benzene solution was treated with dilute nitric acid (1 vol., *d* 1·42, and 2 vols. of water); a crimson colour then appeared in both layers accompanied by intense yellowish-green fluorescence. On shaking, an orange substance separated from the benzene layer, the colour of which faded. An acetic acid solution treated with a trace of bromine becomes intense crimson and the usual fluorescence is almost absent; on boiling, the colour changes to orange and dark green fluorescence appears. This becomes brilliant on dilution with alcohol and is of the *iso*brazilein type. Iodine, in most solvents, gives a similar reaction. Bromine, in an acetone solution containing hydrobromic acid, however, immediately oxidises the chromene to the pyrylium bromide, which separates in orange needles. The substance was recognised by conversion into the ferrichloride, identical with the product obtained by the method given below.

iso*Brazilein Ferrichloride Trimethyl Ether* (V).—A characteristic property of deoxytrimethylbrazilone is the ease with which it is oxidised in acid solution with formation of the *iso*brazilein salts and a convenient method is provided by the use of ferric chloride in acetic acid solution. The deoxytrimethylbrazilone was dissolved in warm acetic acid, the solution cooled, and anhydrous ferric chloride introduced; the ferrichloride soon separated as a crimson mass of needles that appeared orange by transmitted light. In some cases, and especially if cooling was used, a deep crimson ferrichloride separated in slender needles and the solution remained red. This was an intermediate product and, on gently warming, the solution became orange and the brownish-orange *iso*brazilein ferrichloride trimethyl ether separated at once. In this form the substance was practically pure and after one crystallisation from acetic acid was identified by careful comparison with a specimen obtained from pure tetramethyldihydrobrazileinol (Engels, Perkin, and Robinson, *loc. cit.*). At a much earlier stage of the investigation, the residue (R) mentioned in the last section was submitted to similar treatment; the ferrichloride so obtained crystallised from glacial acetic acid in slender, orange needles and was directly compared with an exceptionally pure specimen of *iso*brazilein ferrichloride trimethyl ether, with the result that no differences could be detected. The comparison was made in almost the same manner as that instituted by Crabtree and Robinson (*loc. cit.*) with a similar purpose in view and in all cases the properties of the specimens were examined side by side. It is not considered necessary to reproduce the account of these properties, since important variations from the description were not observed.

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