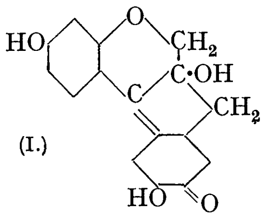
10. *The Constitution of Brazilein.*

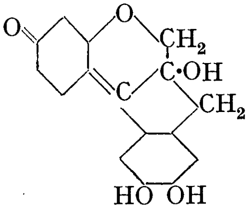
By V. M. Mićović and Robert Robinson.

The methylation of brazilein by means of methyl sulphate and potassium hydroxide affords trimethylbrazilein, tetramethyldihydrobrazileinol and a dimethylbrazilein which has phenolic properties (Engels, Perkin, and Robinson, J., 1908, **93**, 1115). The formation of the last substance in considerable relative amount was held to favour (I) rather than the alternative (II) as a representation of the structure of brazilein. This argument lacked precision and no confirmatory evidence was available. Indeed Pfeiffer (cf. Meyer and Jacobson, " Lehrbuch d. Org. Chem.," V, 1, 197) has put forward the suggestion that brazilein is (II), a view not supported by any new experimental data.

We have now been able to demonstrate that *O*-trimethylbrazilein, of known constitution in other respects, is a derivation of (I) rather than of (II), and hence brazilein should be (I). As in the case of other potentially tautomeric systems immobilised by substitution, we can determine the structure of the derivative alone with certainty. Nevertheless in the present example it will be agreed that brazilein very probably affords a true trimethyl ether and no isomeride of this derivative has been isolated.

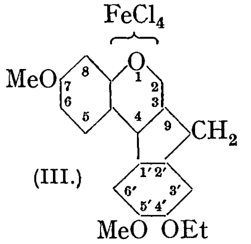


(I.)

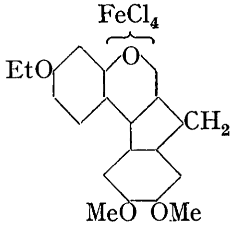


(II.)

The hydration of the quinonoid group of trimethylbrazilein probably gives rise to stereoisomerides, of which one is produced in predominating amount; this trimethyldihydrobrazileinol affords a crystalline *ethyl ether*. On gentle heating of the solution of this substance in concentrated sulphuric acid, the *dimethoxyethoxybrazylium* * *acid sulphate* is produced and this salt is precipitated on the addition of water. It was converted in the usual manner into a related *ferrichloride*, which might have structure (III) or (IV) according as trimethylbrazilein is based on (I) or (II) respectively. The salts (III) and (IV) have therefore been synthesised and, although they closely resembled one another, it was found possible to distinguish between them—a matter requiring special attention.



(III.)



(IV.)

The ferrichloride (III) was found to be identical with the salt obtained from brazilein as described above. The methods employed for the syntheses were adaptations of those already recorded in connection with trimethoxybrazylium salts. Thus (III) was derived from a *deoxydimethylethylbrazilone* prepared from *O-ethylisovanillylidene-7-methoxychroman-*

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* It seems desirable to abandon the use of the expressions *iso*brazilein and *iso*hæmatein, because these substances are really anhydrobrazilein and anhydrohæmatein. Their salts are pyrylium derivatives and, as a considerable number are known, it is suggested that 4 : 3-indenobenzopyrylium (1 : 4) of earlier memoirs [more correctly designated indeno(2′ : 3′ : 3 : 4)benzopyrylium] may be termed *brazylium*. The numbering is by analogy to that used for *flavylium*, despite the fact that substitution or addition at 3, 4, 1′ and 2′ is impossible. The so-called *iso*hæmatein salts now become derivatives of tetrahydroxybrazylium.

one following the stages of the method contemporaneously worked out by Pfeiffer and his collaborators (*Ber.*, 1917, **50**, 911; 1920, **53**, 945; 1925, **58**, 1947; 1928, **61**, 1923) and by Perkin, Rây, and Robinson (J., 1926, 941; 1928, 1504. Cf. *Proc. Chem. Soc.*, 1906, **22**, 160). The earlier synthesis of Crabtree and Robinson (J., 1918, **113**, 859) was suitably modified for the preparation of (IV).

Except as indicated below, this investigation was completed in 1931 but it was found impossible to reach a definite conclusion because the ferrichlorides from the three sources (from brazilein and the two syntheses) differed in appearance and habit of crystallisation. This has quite recently been found to be due to traces of foreign substances, especially iodine, in the product obtained from brazilein, and bromine in the synthetic salt (III).

Prevention proved better than cure, and the observance of some simple precautions enabled us to equate (III) (synthetic) in all respects with the salt from brazilein. Several analytically pure specimens of the salt (IV) have been examined and although these differed somewhat from one another in appearance in mass, the crystalline forms were identical and the melting points (decomp.) were the same and 8—10° higher than that of (III). Mixtures of (III) and (IV) (all specimens) showed a depressed melting point.

EXPERIMENTAL.

ω-*Homoveratrylresacetophenone.*—The following method of preparation of this substance is superior to that previously described (Baker and Robinson, J., 1925, **127**, 1433). A mixture of β-veratrylpropionitrile (19·1 g.), resorcinol (11 g.), zinc chloride (4 g.), and dry ether (100 c.c.) was saturated at 0° with dry hydrogen chloride during 1 hour and kept for 40 hours. The solid product was washed with ether and dissolved in ice-water, and the solution extracted with ether in order to remove unchanged substance and then decomposed by boiling for 15 minutes. After crystallisation from methyl alcohol the ketone had m. p. 146—147° (10·5 g. or 35%).

β-*Veratrylethyl* 2-*Hydroxy*-4-*ethoxyphenyl Ketone.*—Ethyl iodide (7 g.) was added to a solution of the sodium salt obtained from sodium (0·9 g.), alcohol (100 c.c.), and homoveratrylresacetophenone (11·5 g.), and the mixture was refluxed for 4 hours. Alcohol was removed and dilute aqueous sodium hydroxide was added to the residue, a solid being precipitated. This crystallised from methyl alcohol in prismatic needles, m. p. 97—98° (Found: C, 69·1; H, 6·8; MeO,* 18·7; EtO,* 13·6. $C_{19}H_{22}O_5$ requires C, 69·1; H, 6·7; 2MeO, 18·8; EtO, 13·6%). The same *substance* was obtained by condensation of β-veratrylpropionitrile and *m*-ethoxyphenol by means of hydrogen chloride in presence of zinc chloride, which shows that the condensation occurs in the *o*-position to the phenolic hydroxyl group.

4′ : 5′-*Dimethoxy*-7-*ethoxybrazylium Ferrichloride* (IV).—A mixture of homoveratrylresacetophenone ethyl ether (6·6 g.), fused zinc chloride (10 g.), and anhydrous formic acid (40 g.) was refluxed for 6 hours. After cooling, dilute hydrochloric acid and an excess of ferric chloride dissolved in 20% hydrochloric acid were added, whereby a dark mass was precipitated. After collection this crystallised from acetic acid in glistening, chocolate-coloured needles (Found: C, 46·6; H, 3·6; Cl, 26·2; Fe, 10·3; MeO, 11·8; EtO, 8·6. $C_{20}H_{19}O_4Cl_4Fe$ requires C, 46·1; H, 3·7; Cl, 27·2; Fe, 10·7; 2MeO, 11·5; EtO, 8·4%). The *substance* loses chlorine on further crystallisation from glacial acetic acid (Found: C, 46·9; H, 3·8; Cl, 26·1; Fe, 10·0%). It was, however, obtained in a pure condition by solution in the minimum of hot absolute formic acid and addition of 2 volumes of glacial acetic acid containing a trace of ferric chloride and of hydrogen chloride. In this way slender orange needles, m. p. 211—212° (decomp.), could be consistently obtained (Found: C, 46·2; H, 3·7; Cl, 27·1%). A description of the properties of this salt (specimen A) is given below.

7-*Methoxy*-3-(4′-*methoxy*-3′-*ethoxybenzylidene*)*chromanone.*—A solution of 7-methoxychromanone (3·6 g.) (Perkin, Rây, and Robinson, J., 1927, 2097) and *O*-ethyl*iso*vanillin (3·6 g.) in acetic acid (20 c.c.) was saturated with dry hydrogen chloride at 0°. Next day the product was decomposed with crushed ice and the solid collected and crystallised from methyl alcohol, from which it separated in pale yellow needles, m. p. 120° (5 g. or 73·5%) (Found: C, 70·7; H, 5·9. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%).

7-*Methoxy*-3-(4′-*methoxy*-3′-*ethoxybenzyl*)*chromanone.*—A solution of methoxyethoxybenzylidenechromanone (1·7 g.) in ethyl acetate (100 c.c.), to which norit (2 g.) and palladous chloride (15 c.c. of 0·5% aqueous solution) had been added, was shaken with hydrogen. 130 C.c. of the gas were absorbed at 23° in 12 minutes. The operation was stopped, the liquids were

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* Calc. on the assumption 2MeO : 1EtO.

filtered, and the separated ethyl acetate solution was evaporated under diminished pressure. The reduction *product* was crystallised from aqueous methyl alcohol and then from methyl alcohol; it formed colourless prisms, m. p. 83° (Found : C, 70·0; H, 6·4. $C_{20}H_{22}O_5$ requires C, 70·1; H, 6·5%).

When methoxyethoxybenzylidenechromanone (0·8 g.) was reduced under similar conditions for a longer period, 7-*methoxy*-3-(4'-*methoxy*-3'-*ethoxybenzyl*)*chromanone* was obtained. 160 C.c. of hydrogen were absorbed during 40 minutes and further absorption did not occur. The colourless product, crystallised from aqueous methyl alcohol, had m. p. 87—90° (Found : C, 73·0; H, 7·5. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%).

Deoxydimethylethylbrazilone.—Phosphoric oxide (5 g.) was added to a solution of the above ketone (1 g.) in benzene (10 c.c.); the mixture was well shaken and gently refluxed during 2 hours. More phosphoric oxide (*ca.* 1 g.) was then added, and the operation repeated after 2 hours. After 12 hours the mixture was decomposed with ice and extracted with ether with the addition of salt, the ethereal solution washed with water and aqueous sodium hydroxide, dried with potassium carbonate and filtered, and the solvent removed. The residue, crystallised from methyl alcohol, had m. p. 145—147° (yield, 14%) (Found : C, 74·0; H, 6·2. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%). This *substance* closely resembles deoxytrimethylbrazilone in all its characteristic properties.

7 : 5'-*Dimethoxy*-4'-*ethoxybrazylium Ferrichloride* (III).—The foregoing synthetic deoxydimethylethylbrazilone (0·85 g.) was dissolved in acetone (25 c.c.), and the solution shaken with bromine vapour mixed with a large relative volume of air. A crimson coloration was produced and this gradually faded and was replaced by an orange colour; a trace more bromine was then introduced in the same way and so on until the red colour was no longer observed. It is important to avoid excess of bromine at any stage and as the reaction proceeds the dimethoxyethoxybrazylium bromide separates in orange microscopic prismatic needles. After the addition of dry ether, the salt was collected (0·9 g.), dissolved in the minimum of alcoholic hydrogen chloride (10%), and mixed with a large excess of ferric chloride dissolved in concentrated hydrochloric acid. An orange-brown ferrichloride was precipitated and was crystallised from acetic acid containing a trace of hydrogen chloride and a trace of ferric chloride. The orange-brown prismatic needles were orange by transmitted light under the microscope (specimen B). When a concentrated solution in anhydrous formic acid was mixed with twice its volume of acetic acid, long, slender, microscopic needles and obliquely cut, prismatic needles separated. Less pure specimens crystallise in rosettes of slender needles. Recrystallisation is attended by some decomposition and the above specimen (B) was the purest obtained; its properties are described below (Found : C, 46·0; H, 3·6; Cl, 27·0; Fe, 10·5. $C_{20}H_{19}O_4Cl_4Fe$ requires C, 46·1; H, 3·7; Cl, 27·2; Fe, 10·7%).

O-*Trimethylethyldihydrobrazileinol.*—For the preparation of this substance it is necessary to employ pure crystallised trimethyldihydrobrazileinol, m. p. 182—185° (cf. Engels, Perkin, and Robinson, *loc. cit.*, p. 1137); otherwise the ethyl ether is obtained as an uncrystallisable gum.

A mixture of trimethyldihydrobrazileinol (5 g.), ethyl iodide (25 c.c.), acetone (50 c.c.), and powdered potassium carbonate (20 g.) was refluxed for 2 hours, then cooled, and mixed with ether and water and the ethereal solution was washed several times with dilute aqueous sodium hydroxide. The residue, after removal of ether from the dried solution, crystallised from benzene–light petroleum in slender colourless needles, which were recrystallised from methyl alcohol and then had m. p. 142° (Found : C, 67·7; H, 6·2. $C_{21}H_{24}O_6$ requires C, 67·8; H, 6·4%). This *substance* closely resembles tetramethyldihydrobrazileinol in its properties, but shows a much greater tendency to crystallise. In view of the fact that the highest m. p. recorded for the tetramethyl ether is 55—60°, it would appear that a homogeneous specimen has not yet been obtained. There is obviously a possibility of the formation of stereoisomerides when the quinonoid group of trimethylbrazilein is hydrated. Trimethylethyldihydrobrazileinol dissolved in anhydrous formic acid to an intense crimson solution exhibiting a weak green fluorescence; it was recovered unchanged on the addition of water.

Dimethoxyethoxybrazylium Ferrichloride (*from Brazilein*).—*O*-Trimethylethyldihydrobrazileinol (1·5 g.) was dissolved in sulphuric acid (40 c.c.), and the crimson solution heated to 40—50°; it then quickly became orange in colour and acquired a brilliant yellowish-green fluorescence. When the crimson colour had been discharged, the oxonium sulphate, precipitated on the addition of ice (200 g.), was collected and dissolved in alcoholic hydrogen chloride (7%), and the chloride precipitated by the addition of 5% hydrochloric acid; this process was repeated and the crude chloride was washed with a little alcoholic hydrogen chloride (10%). The salt was then converted into ferrichloride in the usual manner; this derivative crystallised from acetic acid containing traces of hydrogen chloride and ferric chloride in brownish-orange needles (specimen C) (Found : C, 46·0; H, 3·7; Cl, 26·9; Fe, 10·5. $C_{20}H_{19}O_4Cl_4Fe$ requires C, 46·1; H, 3·7; Cl, 27·2; Fe, 10·7%).

Comparison of the Specimens A, B and C.—The three specimens closely resembled the known trimethoxybrazylium ferrichloride in all general properties; the yellow aqueous solutions exhibited intense green fluorescences identical to visual observation. The behaviour with nitric acid (cf. Crabtree and Robinson, *loc. cit.*) was also the same in the three cases and the only superficial differences that could be noted were the following :—

On heating solutions of (A), (B) or (C) in sulphuric acid, they darkened, became brown and acquired a much deeper intense green fluorescence; at equivalent concentrations (A) underwent these changes more rapidly than (B) or (C), which behaved alike. The solubilities of (B) and (C) in formic acid were similar and crystallisation on the addition of acetic acid synchronised in the case of parallel experiments; on the other hand (A) was less soluble in formic acid than (B) or (C) and crystallisation on the addition of acetic acid was more rapid.

The crystal forms were variable and dependent on the purity of the specimens. Actually both (B) and (C) crystallised in characteristic prismatic needles, but other specimens of these salts occurred as rosettes of slender needles or as thicker pointed needles. Mixtures of the pure salts and less pure specimens recrystallised as the intermediate thicker needle form and it is interesting that this was found to be true of (B) mixed with less pure (C) and of (C) mixed with less pure (B). (A) always crystallised in slender needles and mixtures with (B) or (C) gave a splintered-needle form on recrystallisation. On heating, (A) began to shrink at 212° and melted with decomposition at 212—217°; after recrystallisation (A) had m. p. 210—211°, indicating slight deterioration. Both (B) and (C) had m. p. 202—204° (decomp.) after sintering at 198° and a mixture showed the same behaviour. A mixture of (A) and (B) had m. p. 187—189° (decomp.) and one of (A) and (C) had m. p. 188—190° (decomp.); the decomposition was only slight if the capillary tube was at once withdrawn from the bath.

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