CXCVIII.—*Experiments on the Synthesis of Brazilin and Hæmatoxylin and their Derivatives.   Part III.**

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THE synthesis of deoxytrimethylbrazilone (I) (anhydrotrimethyl-brazilin) was described in Part II of this investigation (J., 1927, 2094) and it was not anticipated that the conversion of this substance into O-trimethylbrazilin (II) would offer any considerable difficulty.
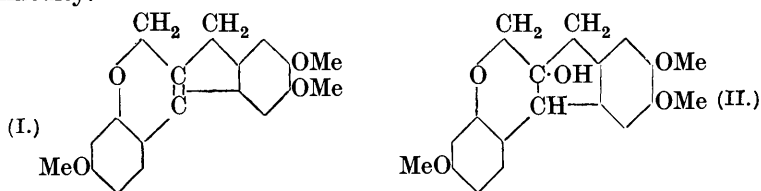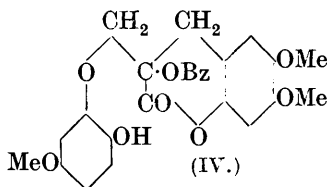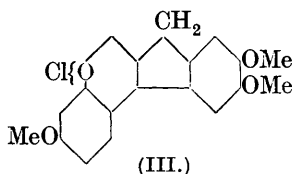
* This communication was written up for publication before the appearance of a paper by Pfeiffer, Angern, Haack, and Willems (*Ber.*, 1928, **61**, 839) dealing in part with a similar subject matter.

In view of this repeated duplication of research, we have thought it well to indicate clearly our projected lines of investigation. In the hæmatoxylin series, we prefer to publish our experiments in a more complete form; they have already reached the stage now disclosed in connexion with brazilin. We have, however, employed throughout protection of the hydroxyl groups by ethylene radicals in the place of methyl groups. Hence the substances we have made are different from those described by Pfeiffer and his collaborators and therefore there does not appear to be any necessity to hurry publication, no novel theoretical point being involved in the passage from the brazilin to the hæmatoxylin series.

Actually the problem has proved to be a very puzzling one, chiefly on account of the remarkable properties of deoxytrimethyl-brazilone (I). This substance is prone to undergo oxidation; when merely shaken with pyridine and aqueous sodium hydroxide a considerable proportion of the material becomes alkali-soluble in a short time, and in the presence of acids there is a strong tendency to form the *iso*brazilein salt.

When, for example, a stream of dry hydrogen chloride was led through a solution of deoxytrimethylbrazilone in cold chloroform, with ordinary precautions to exclude air, an orange crystalline substance was gradually deposited consisting of *iso*brazilein hydrochloride trimethyl ether (III).

$$CH_2 \quad\quad Cl\{O \quad OMe \quad OMe \quad MeO \quad (III.)$$

$$CH_2 \quad CH_2 \quad O \quad C\cdot OBz \quad OMe \quad CO \quad OMe \quad MeO \quad OH \quad O \quad (IV.)$$

Many other attempts to add the elements of water or of an acid, HX, to deoxytrimethylbrazilone were unsuccessful.
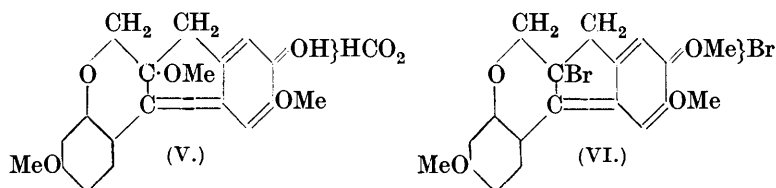
Oxidation of deoxytrimethylbrazilone with perbenzoic acid in chloroform solution gave various products under different conditions. The procedure described in the experimental section leads to the production of a *substance* to which we ascribe the formula (IV) largely by analogy with the products derived from brazilein derivatives by oxidation with hydrogen peroxide (Engels, Perkin, and Robinson, J., 1907, **91**, 1175).

In other experiments along these lines we obtained evidence that an oxygen atom may be inserted between the central carbon atom of the diphenylmethane structure and the pyrocatechol nucleus, because a crystalline oxidation product of deoxytrimethylbrazilone (1 mol.) with perbenzoic acid (1·5 mols.) was found to be converted, by gentle warming with sulphuric acid, into a pyrylium salt exhibiting the characteristic pink colour in acid solution and the phenomenal greenish-yellow fluorescence of methoxychromeno-dimethoxybenzopyrylium salts (Part I, J., 1926, 950). This oxidation product was quite homogeneous and had m. p. 123°, but unfortunately we have not succeeded in reproducing the conditions for its preparation. In none of these experiments, however, was there any indication that deoxytrimethylbrazilone could be transformed into an oxide of the ethylene oxide type.

The deep crimson dibromide of deoxytrimethylbrazilone closely resembles the compounds of trimethylbrazilein and tetramethyl-

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dihydrobrazileinol with acids and unquestionably all these substances are analogous to the salts derived from *o*- and *p*-methoxytriphenyl-carbinols and to the rosaniline salts. The characteristic trimethyl-brazilein formate, therefore, may be formulated as (V). Here the representation of one nucleus in the full quinonoid condition is adopted for purposes of convenience only; doubtless the kationic charge will be distributed in part to the oxygen atoms of the resorcinol nucleus, and even in part to the central carbon atom, and both nuclei will be partly quinonoid.

The corresponding formula for deoxytrimethylbrazilone di-bromide is (VI).

The action of zinc dust on (VI) in acetic acid suspension and solution leads to the formation of deoxytrimethylbrazilone and thus it is clear that the double bond of this substance is closely conjugated with the aromatic nuclei. All attempts to reduce the unsaturated quinonoid centres, leaving the centrally-situated bromine atom intact, were fruitless.

The analogy existing between (V) and (VI) is well brought out by the observation that the reduction of trimethylbrazilein by means of zinc dust in the presence of hot acetic and hydrochloric acids yielded a phenolic product and on methylation with methyl sulphate and sodium hydroxide this was transformed into deoxytrimethyl-brazilone. Furthermore the reduction of tetramethyldihydro-brazileinol (VII) under similar conditions gave deoxytrimethyl-brazilone. It is clear that the anhydro-hydrochloride of tetra-methyldihydrobrazileinol (VIII) behaves as if it were the additive
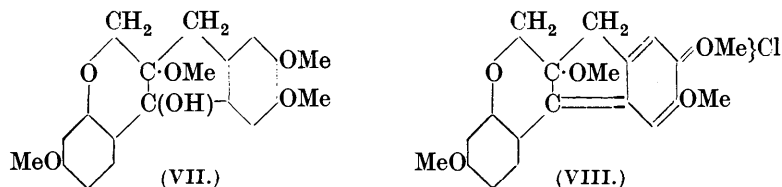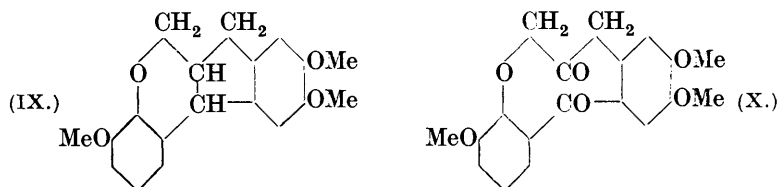

product, deoxytrimethylbrazilone–methyl hypochlorite. When the dibromide (VI) is treated in cold acetic acid suspension with potass-ium acetate a colourless, amorphous bromo-acetate is obtained. The acetoxy-group is doubtless attached to position 4 in the pyran
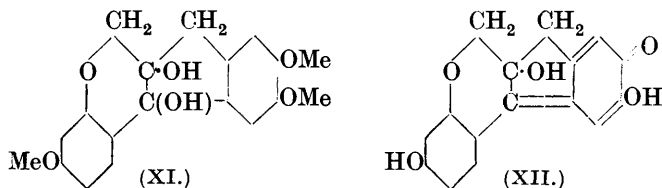
ring, but it was not found possible to replace the bromine atom by methoxyl and so achieve a synthesis of tetramethyldihydro-brazileinol (VII).

Preliminary experiments indicated that the bromo-acetate could be oxidised by chromic acid with formation of trimethylbrazilone. Another noteworthy property of deoxytrimethylbrazilone dibromide is the ease with which it loses hydrogen bromide with formation of *iso*brazilein hydrobromide trimethyl ether; this change occurs on keeping and very quickly in the presence of acetone.

On reduction with hydrogen and a palladium catalyst deoxytri-methylbrazilone furnishes a *dihydro*-derivative (IX) and this yields trimethylbrazilone (X) when it is oxidised by chromic acid in acetic acid solution. Thus trimethylbrazilone and its numerous derivatives have now been synthetically prepared and may be employed instead of deoxytrimethylbrazilone as starting points in attempted syntheses of *O*-trimethylbrazilin.

$$(IX.) \qquad \begin{array}{c} CH_2 \;\; CH_2 \\ O \quad CH \quad\quad OMe \\ \quad\;\; CH{-}\!\!\!-\!\!\!-OMe \\ MeO \end{array} \qquad\qquad \begin{array}{c} CH_2 \;\; CH_2 \\ O \quad CO \quad\quad OMe \\ \quad\;\; CO{-}\!\!\!-\!\!\!-OMe \\ MeO \end{array} (X.)$$

From this point of view the reduction of trimethylbrazilone to the *pinacol* (XI) is of much interest and this change was accomplished by means of zinc dust in alcoholic acetic acid solution. The product exhibited the reactions expected of a trimethyldihydro-brazileinol, giving crystalline, crimson salts of the type (V) with acids and *iso*brazilein hydrogen sulphate trimethyl ether on gentle warming with sulphuric acid. Reduction of (XI) in strongly acid solution afforded deoxytrimethylbrazilone, and experiments on the reduction products obtained in neutral or alkaline media are still in progress.

$$\begin{array}{c} CH_2 \;\; CH_2 \\ O \quad C{\cdot}OH \quad\quad OMe \\ \quad\;\; C(OH){-}\!\!\!-OMe \\ MeO \quad (XI.) \end{array} \qquad\qquad \begin{array}{c} CH_2 \;\; CH_2 \quad O \\ O \quad C{\cdot}OH \\ \quad\;\; C{=\!=}\quad OH \\ HO \quad (XII.) \end{array}$$

It would be surprising if it does not prove feasible to pass from the pinacol (XI) to *O*-trimethylbrazilin. Nevertheless brazilin itself is the real ultimate object of these synthetical experiments and one of the methods we contemplate is the following :

(A) Demethylation of (IX), followed by acetylation or benzoylation of the trihydric phenol and oxidation to triacetylbrazilone or tribenzoylbrazilone.

(B) Preparation of triacetylbrazilone or tribenzoylbrazilone from acetylated or benzoylated brazilin (see p. 1513).

(C) Reduction of triacetylbrazilone or tribenzoylbrazilone to a pinacol.

(D) Hydrolysis of the pinacol and formation of *dl*-brazilein (XII).

(E) Reduction of brazilein to brazilin and resolution of *dl*-brazilein or *dl*-brazilin into the enantiomorphous forms.

The details require further elaboration and we wish to reserve for a short time the investigation of the processes involved in the above scheme and naturally in the analogous syntheses of tetra-acyl hæmatoxylone, hæmatein, and hæmatoxylin.

EXPERIMENTAL.

Preparation of Deoxytrimethylbrazilone.—The methylation of brazilin by means of methyl sulphate does not appear to have been described.

Potassium hydroxide (30 g.), dissolved in water (40 c.c.) and methyl alcohol (20 c.c.), was added to a solution of brazilin (40 g.) in hot methyl alcohol (100 c.c.), air being excluded by means of coal-gas. Methyl sulphate (50 g.) was then introduced gradually, the temperature not being allowed to rise above 50°. Further quantities of potassium hydroxide and of methyl sulphate equal to those already used were then introduced and finally the reaction was completed by heating the mixture at 65° for 15 minutes. The product was precipitated by water (800 c.c.), washed, and dried (yield, 42—45 g.). It may be employed without crystallisation for the preparation of trimethylbrazilone.

The reduction of trimethylbrazilone by means of phenylhydrazine (Gilbody and Perkin, J., 1902, **81**, 1046) does not proceed satisfactorily in ethyl-alcoholic solution, but the following method works well and we are inclined to suspect that it is the method originally used and that " alcohol " is a manuscript error (*loc. cit.*, p. 1047, line 3). Trimethylbrazilone (8 g.) was gradually added to a mixture of acetic acid (40 c.c.) and phenylhydrazine (25 c.c.) at 40° so that the temperature remained between 60° and 70°. The mixture was then heated at 80° for $\frac{1}{2}$ hour, and the product began to crystallise. After cooling, the solid was collected and washed with small quantities of acetic acid and then with alcohol (yield, 4—4·5 g.).

On keeping, the mother-liquor deposited a by-product, which crystallised from acetic acid in bright yellow needles, m. p. 245° (Found : C, 71·8; H, 5·5; N, 6·8. Calc. for $C_{25}H_{24}O_4N_2$: C, 71·7 ;

H, 5·7; N, 6·7%. Calc. for $C_{25}H_{22}O_4N_2$: C, 72·4; H, 5·3; N, 6·8%). The substance is evidently identical with a compound, $C_{25}H_{22}O_4N_2$, m. p. 239—242°, described by Herzig and Pollak (*Ber.*, 1905, **38**, 2166) as the main product of the action of phenyl-hydrazine on trimethylbrazilone in acetic acid solution. This substance may be a pyrazoline derivative as already suggested (Perkin and Robinson, J., 1908, **93**, 489), but one of the annexed formulæ is also possible.
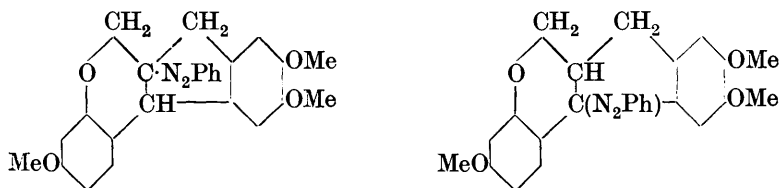
There is evidence that a nitrogen atom is attached to the diphenyl-methane carbon atom in that the substance is readily reduced by stannous chloride and hydrochloric acid, giving an eosin-red solution. This suggests the production of a diphenylcarbinol derivative in the reduction. The colourless reduction product, precipitated on the addition of water, is under examination. It dissolves in sulphuric acid to a deep green dichroic solution.

Attempts have been made to prepare deoxytrimethylbrazilone more directly from trimethylbrazilin by dehydration or equivalent processes. The action of phosphorus pentachloride on trimethyl-brazilin in cold chloroform solution was energetic and on the addition of light petroleum a quantity of *iso*brazilein hydrochloride trimethyl ether was thrown down. The filtrate contained a gum that could not be crystallised; the substance was doubtless the chloride corresponding to trimethylbrazilin, but when it was heated with dimethylaniline there was no evidence of the formation of deoxytri-methylbrazilone.

Action of Perbenzoic Acid on Deoxytrimethylbrazilone.—An ice-cold solution of perbenzoic acid (1·38 g.) in chloroform (30 c.c.) was added to one of deoxytrimethylbrazilone (3·1 g.) in chloroform (30 c.c.), and the mixture kept at 0° for 4 hours. The solution was then washed with cold aqueous sodium carbonate (0·5 g. in 30 c.c.), dried, and evaporated in a vacuum. The residue dissolved in alcohol (10 c.c.) and on keeping in the ice-chest a voluminous crystalline mass separated. The *substance* (IV) crystallised from alcohol in transparent, rectangular plates, m. p. 152° (Found : C, 64·5; H, 5·2. $C_{26}H_{24}O_9$ requires C, 65·0; H, 5·0%). The substance is sparingly soluble in alcohol and although it is not attacked by aqueous sodium carbonate, it dissolves in aqueous sodium hydroxide.

Decomposition occurs on heating and benzoic acid can be isolated after acidification of the solution. The yellow solution in sulphuric acid becomes successively green, blue, purple and brownish-red on heating. The reaction is similar to that shown by the oxidation product of tetramethyldihydrobrazileinol with hydrogen peroxide (Engels, Perkin, and Robinson, *loc. cit.*).

Deoxytrimethylbrazilone Dibromide (VI).—This substance is precipitated, when its components are mixed in acetic acid solution, in glistening, dark crimson needles and it may also be obtained by the addition of a solution of bromine in light petroleum to deoxytrimethylbrazilone dissolved in chloroform. Accurate analytical figures could not be obtained on account of two properties. When kept in a desiccator, the substance loses bromine with the formation of the *iso*brazilein salt (Found : Br, 22·0. Calc. : Br, 20·7%. Found in a specimen kept only 20 minutes : Br, 25·8%). Secondly, with an excess of bromine a *perbromide* is precipitated (Found : Br, 61·5. $C_{19}H_{18}O_4Br_6$ requires Br, 60·9%). The substance gives carmine solutions and its other properties are mentioned in the introductory section.

Dihydrodeoxytrimethylbrazilone (IX).—This substance, which might also be conveniently named O-*trimethylbrazilane*, was obtained by shaking a solution of deoxytrimethylbrazilone (2·5 g.) in ethyl acetate (200 c.c.), containing norite (1 g.) and 1% palladous chloride (10 c.c.), with hydrogen. Absorption of the gas was rapid at first and when it slackened the temperature of the mixture was raised to 40°. The *dihydro*-derivative separated from the concentrated, filtered solution and after twice crystallising from methyl alcohol was obtained in colourless, transparent, rod-like needles, m. p. 109° (Found : C, 72·7 ; H, 6·5. $C_{19}H_{20}O_4$ requires C, 73·1 ; H, 6·4%). This substance does not exhibit such characteristic colour-reactions as does deoxytrimethylbrazilone. On warming its pale yellow solution in concentrated sulphuric acid, a deeper yellow solution exhibiting a faint green fluorescence is obtained. The brownish-red solution in cold concentrated nitric acid on dilution with water also exhibits a weak green fluorescence.

Synthesis of Trimethylbrazilone (X).—A solution of chromic acid (0·8 g.) in water (3 c.c.) was gradually added to one of dihydrodeoxytrimethylbrazilone (1·0 g.) in acetic acid (6 c.c.) with good shaking ; the temperature was kept below 20°. After an hour the crystals that had separated were collected and quickly recrystallised from acetic acid (yield, 0·4 g.), forming almost colourless prisms, m. p. 185° when rapidly heated (Found : C, 66·6 ; H, 5·7. Calc. for $C_{19}H_{18}O_6$: C, 66·7 ; H, 5·2%). The melting point of a quickly heated, intimate mixture with an authentic specimen of trimethylbrazilone was also

185°. The identity was further confirmed by the formation of α-anhydrotrimethylbrazilone by the action of aqueous sodium hydroxide and of acetyl-α-anhydrotrimethylbrazilone by the action of acetic anhydride. The blue-green colour reaction with alcoholic potassium hydroxide and chloroform and the highly characteristic behaviour with concentrated nitric acid and of the product (nitrohydroxydihydrotrimethylbrazilone) with alcoholic potassium hydroxide were also observed.

Reduction of Trimethylbrazilone by Means of Amalgamated Aluminium.—Aluminium foil (1 g.) was amalgamated and added to a solution of trimethylbrazilone (2 g.) in ethyl acetate (200 c.c.) and after some time the temperature was raised to 50—60°. After 8 hours the filtered solution was concentrated in a vacuum; the residue crystallised from hot aqueous alcohol in colourless rods, m. p. 129° with evolution of gas (Found : C, 64·2; H, 6·0. $C_{19}H_{20}O_6,0·5H_2O$ requires C, 64·6; H, 6·0%). This view of the composition of the substance is put forward provisionally. The analyses fitted the formula $C_{23}H_{26}O_8$ ($C_{19}H_{18}O_6,CH_3·CO_2Et$) and the reduction was therefore carried out in moist benzene instead of ethyl acetate solution, with the result that the same substance was isolated.

This reduction product dissolves in sulphuric acid to a deep violet solution and on gentle warming this becomes brown and develops an intense green fluorescence. The colour of the fluorescence is, however, much duller than that due to the *iso*brazilein salts and it becomes very weak on dilution of the sulphuric acid with water. The reaction is reminiscent of the behaviour of certain substances in the α-anhydrotrimethylbrazilone series and suggests that the new compound is similarly constituted. The action of acetic anhydride on this substance leads to the formation of a crystalline *derivative*, m. p. 116°, which greatly depresses the m. p. of acetyl-α-anhydrotrimethylbrazilone. When heated at 80° for 3 hours in a vacuum, the substance lost 4·7%, but it is highly probable that this figure is not significant owing to the decomposition that accompanied dehydration.

We suggest tentatively that this substance is the secondary alcohol related to the aldol-type tautomeride of trimethylbrazilone and that the action of acetic anhydride dehydrates it to deoxy-α-anhydrotrimethylbrazilone. This matter will be further investigated.

Trimethyldihydrobrazilone (*Hydroxy-*O-*trimethylbrazilin, Dihydroxy-*O-*trimethylbrazilane,* iso*Trimethyldihydrobrazileinol*) (XI).—This intramolecular pinacol of trimethylbrazilone was obtained in the following manner : Acetic acid (20 c.c.) was added in small portions

to a solution of trimethylbrazilone (2·0 g.) in alcohol (300 c.c.) mixed with a large excess of zinc dust, the temperature being maintained at about 45° and the flask well shaken from time to time. After remaining over-night at room temperature, the product was isolated from the filtered solution by evaporation in a good vacuum, treatment of the residue with water and ethyl acetate and of the residue from the ethyl acetate layer with alcohol. The crystalline paste was drained and the substance recrystallised from not too much alcohol, forming stout, colourless prisms, m. p. 167—168° (Found in material dried in a vacuum desiccator : C, 65·5 ; H, 5·6. Found in material dried at 110° in a vacuum : C, 65·8 ; H, 5·8. $C_{19}H_{20}O_6$ requires C, 66·2 ; H, 5·8%). This *pinacol* adheres tenaciously to some water, but apparently not in any simple molecular ratio ; the anhydrous material acquired a salmon-pink colour but its m. p. was unchanged. It dissolves in concentrated hydrochloric acid to a crimson-scarlet solution, and in sulphuric acid to a carmine solution that rapidly becomes brownish-yellow and acquires very intense yellowish-green fluorescence, persistent on dilution with water ; unless the solution is very dilute, on addition of water to the sulphuric acid an orange, crystalline precipitate is obtained, and this was identified as *iso*brazilein trimethyl ether hydrogen sulphate by conversion into the corresponding ferrichloride and careful comparison with an authentic specimen. This behaviour with sulphuric acid recalls that of trimethylbrazilein and tetramethyldihydrobrazileinol, but in the present case the *iso*brazilein derivative is more rapidly produced. This is natural, since the reaction requires the elimination of water in the case of the pinacol and of methyl alcohol in the case of the trimethylbrazilein derivatives.

The pinacol dissolves in formic acid to a crimson-scarlet solution and a *formate* slowly crystallises from this in prisms. The most characteristic salt is, however, the *anhydro-sulphate*, which crystallises in deep red needles when sulphuric acid is added to an alcoholic solution of the pinacol. It is very sparingly soluble in alcohol. The *anhydro-hydrochloride* can be similarly isolated in crimson needles, but it is more readily soluble in alcohol than the sulphate. When the salts are decomposed by water the original substance is regenerated, but the carbinol has moderately strong basic properties and in the presence of dilute mineral acid a certain amount of the quinonoid salt is always present. Our investigation of this substance is incomplete and we have good reasons for the supposition that it will be possible to modify the diphenylcarbinol grouping and to reduce it to a diphenylmethane group. It is unlikely, however, that this will be accomplished by vigorous direct reduction in strongly acid solution. A small quantity of the pinacol was dissolved

in acetic acid and a volume of concentrated hydrochloric acid half that of the solution was added. Excess of zinc dust was then introduced, and the liquid boiled for a few minutes. The neutral product, after crystallisation from alcohol, had m. p. 173° with previous softening and was identified as deoxytrimethylbrazilone by its characteristic reactions and other properties.

O-*Triacetylbrazilone* (X with OAc in place of OMe).—This account of the substance is of a preliminary character. O-Triacetylbrazilin (10 g.), dissolved in acetic acid (40 c.c.), was oxidised at 15° by chromic acid (6 g. in 8 c.c. of water) which was gradually introduced. The prismatic needles that were deposited were isolated after 4 hours and crystallised from alcohol; m. p. 187° (decomp.) (Found : C, 61·1 ; H, 4·4. $C_{22}H_{18}O_9,0\cdot5H_2O$ requires C, 60·7 ; H, 4·4%. Found in material dried at 110° in a vacuum : C, 61·9 ; H, 4·2. $C_{22}H_{18}O_9$ requires C, 62·0 ; H, 4·2%). The solution in sulphuric acid is deep orange-yellow. When a little potassium hydroxide is added to an alcoholic solution of the substance a yellow coloration, changing to green and then brown, is produced.

O-*Tribenzoylbrazilone* was similarly obtained by the oxidation of O-tribenzoylbrazilin with chromic acid ; it crystallised from alcohol in colourless prisms, m. p. 205° (decomp.) (Found : C, 72·6 ; H, 4·0. $C_{37}H_{24}O_9$ requires C, 72·5 ; H, 3·9%).

This investigation is being continued.

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