Tetrahedron. Vol. 26, pp. 281 to 289. Pergamon Press 1970. Printed in Great Britain

THE SYNTHESES OF BRAZILIN AND HAEMATOXYLIN

F. MORSINGH* and R. ROBINSON†

Dyson Perrins Laboratory, S. Parks Road, Oxford (1955)

(*Received in the UK* 21 *August* 1969; *Accepted for publication* 23 *September* 1969)

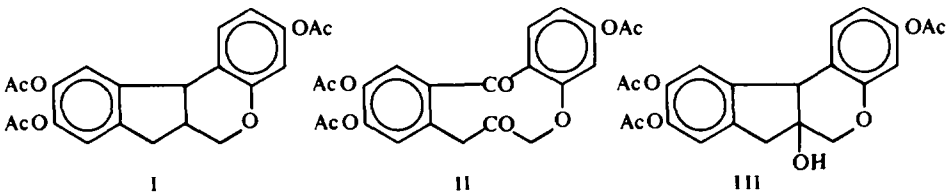
Abstract[1]—The synthesis of *dl*-brazilin and *dl*-haematoxylin have been achieved starting with O-trimethyldeoxybrazilone (or its analogue in the haematoxylin series). The chief obstacle was overcome by taking advantage of the formation of brazilein from a phenolic pinacol obtained in stages from O-trimethylbrazilane, which has already been synthesized. *dl*-Brazilin was resolved by formation and crystallization of its *l*-menthoxyacetate. The *d*-brazilin so obtained is identical with the naturally occurring product and has been shown[2,*a] to have *cis*-fusion of the chromane and indane rings. *d*-Haematoxylin was synthesized in an entirely analogous manner.

Nomenclature

Names containing "brazil" or "haematoxyl" imply the occurrence of substituents in the aromatic rings, as in brazilin and haematoxylin, respectively. Modifications of these substituents are stated. For example, the substance named isobrazilein sulphate by A. G. Perkin and Hummel, is simply brazylium hydrogen sulphate, and not trihydroxybrazylium hydrogen sulphate. The manner in which this principle is applied will be gathered from the text. Structural formulae are now written in accord with the rules of the Ring Index.

THE synthesis[3,*b] of O-trimethylanhydrobrazilin[4] (deoxy-O-trimethylbrazilone) has been carried through to *d*-brazilin (the naturally occurring form) as follows:

Catalytic reduction affords O-trimethylbrazilane which can be demethylated and acetylated to give O-triacetylbrazilone (I). Oxidation of this with chromic anhydride affords O-triacetylbrazilone (II). This is a stage in the synthesis, but II is more conveniently obtained by oxidation of O-triacetylbrazilin (III).



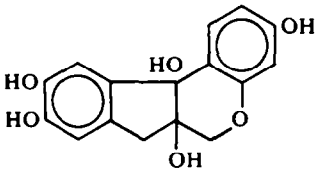
Present address: * University of Malaya, Penang, Malaysia.

† Shell Centre, London, S.E.1.

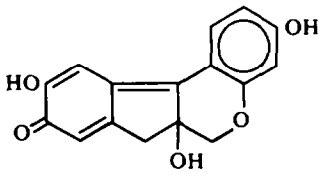
*a Prof. W. D. Ollis (private communication) respecting case of formation of certain anhydro-brazilin derivatives, giving, so far as we are aware, the first indication of the *cis*-fusion of chromane and indane rings. Also, the Ph.D. thesis of G. G. Clarke, one of Prof. Ollis' collaborators. Further reference to the work disclosed in this interesting thesis will be given in a later communication.

*b There followed alternating memoirs from the laboratories of the Universities of Bonn and Oxford, implementing an obvious intention. Completion of the synthesis involved reduction to a dihydro derivative, ring-closure of this to O-trimethylanhydrobrazilin, reduction of the double linkage and finally oxidation to O-trimethylbrazilone. Analogous syntheses were effected in the haematoxylin series. However, in this case the Oxford group (W. H. Perkin, A. Pollard and R. Robinson, *J. Chem. Soc.* 49 (1937)) made O-diethylenehaematoxylone, whereas Pfeiffer (*loc. cit. infra*) synthesized O-tetramethylhaematoxylone. In the present work we found it convenient to use tetramethylhaematoxylone as the starting point on account of the readier hydrolysis at a later stage.

Reduction of II by means of zinc and acetic acid affords an intramolecular pinacol which was not isolated since it occurs in admixture with other substances and the next transformation is unique for the desired products. On hydrolysis by alkali and acidification the phenolic pinacol (IV) is produced and this is quickly dehydrated in presence of acid to form *dl*-brazilein[6,*c] (V).



IV



V

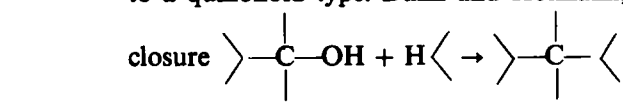
At this stage an anticipated difficulty was that involved in the reduction of brazilein to brazilin. We found however, that borohydride effects this process in good yield and stereo-selectivity so that the changes *d*-brazilin → *d*-brazilein → *d*-brazilin occur without change of configuration. In brazilein (structure V applies) there is one asymmetric C-atom and apparently no possibility for geometric isomerism. On reduction to brazilin, however, a second asymmetric C-atom appears and the ring system can occur in *cis* and *trans* fusion. It seems that an atom is added to the indane ring on the same side as the OH of the t-alcoholic function. The synthetic *dl*-brazilein gave, in this way, *dl*-brazilin (now known to be *dl-cis*-brazilin[7]). The optical resolution of *dl*-brazilin was fruitlessly tried by several methods, but was effected with surprising ease by following a suggestion made to us by the late Dr. L. J. Goldsworthy. This was to prepare and fractionally crystallize the tetra-l-menthyloxy-acetyl derivatives. The desired isomeride, the O-tetra-l-menthyloxy-acetyl-*d*-brazilin proved to be the more sparingly soluble and after crystallization to the constant properties, it was found to be identical with the authentic specimen prepared from pure *d*-brazilin of natural origin. Hydrolysis of this derivative afforded *d*-brazilin. The other isomer, O-tetra-l-menthyloxyacetyl-l-brazilin was collected from several experiments and it was intended to obtain *l*-brazilin from it, but the joint work was brought to an end before this could be accomplished.

The synthesis of *d*-haematoxylin; starting from O-tetra-methylhaematoxylone[8] followed that of *d*-brazilin in every particular, except that, as usual, the various substances isolated in the pyrogallol (haematoxylin) series crystallized far less readily than the corresponding resorcinol derivatives.

In a later communication (describing, however, earlier studies) jointly with J. N. Chatterjea and M. L. Tomlinson, we hope to discuss, *inter alia*, a method which facilitated the preparation of O-triacetylbrazilone.

Relatively recently Dann and Hofmann have described novel and elegant syntheses[8] of *dl*-brazilin (1963) and *dl*-haematoxylin (1965). The fundamental problem in all synthetic schemes in this series is only soluble by finding a reaction which will leave the t-OH in the 3-position of the chromane ring untouched. As seen above,

[*c] Mićović and Robinson established[6b] the position of the quinonoid group in O-trimethylbrazilein. It may plausibly be assumed that brazilein is analogously constituted, but this assignment has not yet been directly confirmed.

we managed this by using the very facile dehydration of a *p*-hydroxydiphenylcarbinol to a quinonoid type. Dann and Hofmann, to serve the same end, employ a ring-closure  based on the analogy of a reaction of veratrylalcohol, described by G. M. Robinson.[9,*d] This occurs so easily that the ring-closure competes successfully with the possible formation of a 4-chromanone.

EXPERIMENTAL

O-Trimethylbrazilane. O-Trimethylbrazilane was prepared from brazilin by the following series of reactions.

O-trimethylbrazilin was obtained in 80% yield by the methylation of brazilin, according to the method used by Perkin[10] and had m.p. 138–139°, reported m.p. 138–139°.

Oxidation of O-trimethylbrazilin (20 g) with chromic anhydride (12 g) in AcOH soln afforded trimethylbrazilone (12 g) m.p. 184–187°, reported[11,*e] m.p. 184–187°.

Reduction of O-trimethylbrazilone to deoxy-O-trimethylbrazilone was accomplished in the following manner:

O-trimethylbrazilone (10 g) was dissolved in warm AcOH (90 ml) and phenylhydrazine (20 ml) was added in one portion with swirling. There was a sharp rise in temp as reaction proceeded, and the soln darkened. After 1 hr at room temp, the crystalline solid which had separated was collected and recrystallized from acetone–ethanol, from which it separated as pale yellow, silky needles (6·1 g), m.p. 169–170° raised to 173° after a further recrystallization, reported m.p. 173°.

Hydrogenation of deoxytrimethylbrazilone in acetone soln under the usual conditions with Pd–$SrCO_3$ as catalyst afforded trimethylbrazilane in about 90% yield, m.p. 109° reported m.p. 109°.

O-Triacetylbrazilane. Hydrobromic acid (3·5 ml, of 47%) was added to a soln of O-trimethylbrazilane (1·5 g) in AcOH (40 ml), and the mixture was refluxed under N_2 at 115–120° for 3½ hr. The cooled soln was poured into water, and the clear red homogeneous soln that resulted was saturated with salt and extracted with EtOAc. The extract was washed successively with a dilute $NaHCO_3$ aq and water, dried over $MgSO_4$ and concentrated to afford a dark viscous oil which did not crystallize.

A mixture of the oil, Ac_2O (15 ml)and NaOAc (0·5 g) was heated on a steam-bath for 45 min. The cooled soln was poured into water, and the amorphous solid which separated was collected, dried *in vacuo* and crystallized from benzene–light petroleum (b.p. 60–80°). From the solvent O-*triacetylbrazilane* separated slowly as colourless prisms, m.p. 166–167° (0·6 g) after three recrystallizations. (Found: C, 66·9; H, 5·2 $C_{22}H_{20}O_7$ requires; C, 66·7; H, 5·05%).

A mixed m.p. with a specimen prepared from brazilein showed no depression.

O-Triacetylbrazilone. A soln of CrO_3 (1·5 g) dissolved in water (1 ml) and AcOH (10 ml) was added dropwise to a soln of O-triacetylbrazilane (1·7 g) in AcOH and the mixture kept at 50–55°. After the addition (15 min), heating and stirring were continued for 30 min longer. The soln was cooled and diluted with water (30 ml). The next day the very small amount of crystalline solid that had separated was collected and found to consist of starting material, m.p. 166–167°.

The aqueous mother liquor was diluted with much water and the amorphous solid which separated was collected and dissolved in acetone–ethanol. O-triacetylbrazilone crystallized slowly as colourless prisms, m.p. 183–186°, raised to 186–187° after three further recrystallizations. (Found: C, 61·7; H, 4·4. Calc for $C_{22}H_{18}O_9$: C, 62·0; H, 4·25%), reported m.p. (187°).

A mixed m.p. with an authentic specimen prepared by oxidation of triacetylbrazilin[13] showed no depression. The IR spectra of the two specimens were identical.

[*d] My late wife was misled by Mol. Wt. determinations made by a colleague which gave two thirds of the correct values. For precisely the same reason, a product from piperonylacetonitrile was thought to be a dimer, whereas it is actually tripiperonyl-*sym*-triazine, a trimer of the nitrile.

[*e] In Ref 11, the project successfully accomplished by the present synthesis was foreshadowed. As a preliminary step O-triacetylbrazilone was made from O-triacetylbrazilin.

In agreement with the earlier observation,[13] it was found that the addition of a little KOH to an alcoholic soln of the substance produced a yellow colouration, changing to green and then brown.

The pinacol from O-*triacetylbrazilone.* Finely powdered O-triacetylbrazilone (6 g) was refluxed in EtOH (700 ml) when much of the substance passed into soln. Zn dust (80 g) was then added to the cooled soln which was maintained at 30–35° with stirring under N_2. AcOH (5 ml) was added at half-hourly intervals until 60 ml had been introduced; stirring was then continued for 36 hr.

The filtered alcoholic soln was concentrated and poured into water. The amorphous solid which separated was collected after 4 hr and crystallized from EtOH. The crystals of the *pinacol* were in the form of colourless prisms, m.p. 180–182°, raised to 184–186° after three further crystallizations from the same solvent. (Found: C, 61·7; H, 4·8. $C_{22}H_{20}O_9$ requires: C, 61·7; H, 4·7%).

The Zn dust residue was extracted with acetone, and the concentrated soln poured into water. The ppt that was formed was taken up in EtOAc, and the soln was washed with water and concentrated to afford the *dimer pinacone* as colourless irregular prisms, m.p. 280° (0·2 g) after three recrystallizations from benzene. (Found: C, 60·3; H, 4·7. $C_{44}H_{37}O_{18}$, H_2O requires: C, 60·5; H, 4·6%).

dl-*Brazilein.* The pinacol from O-triacetylbrazilone (2·8 g) was dissolved in EtOH (40 ml), and alcoholic KOH aq (4 g in 6 ml water diluted with 25 ml EtOH) was added to the cooled soln (ice-bath) under N_2. The ice-bath was removed, and the purplish-red soln was kept at room temp (15°) for 2 hr, with occasional swirling.

The soln was then cooled and acidified with dil AcOH (10 ml in 40 ml water). Most of the EtOH was removed under reduced press, and the soln on standing overnight, deposited dark lustrous crystals of dl-*brazilein* (1·1 g) similar in appearance to brazilein from brazilin.

A sample was washed several times by decantation with hot water and dried *in vacuo* at 160°. (Found: C, 67·6; H, 4·4. $C_{16}H_{12}O_5$ requires: C, 67·6; H, 4·3%).

The IR spectrum was similar to that of *d*-brazilein.

UV spectra	Max	E_{molar}
Product	2750	5280
	4600	12,600
d-Brazilein	2750	5300
	4600	13,800

Iso-brazilein hydrogen sulphate (Brazylium hydrogen sulphate). Treatment of *dl*-brazilein in the manner described by Hummel and Perkin[14] afforded the iso-brazilein acid sulphate as a yellowish orange amorphous powder. It was washed a few times with glacial AcOH and dried at 80° *in vacuo.* (Found: C, 52·4; H, 3·4; S, 8·85. Calc for for $C_{16}H_{16}O_4HSO_4$: C, 52·7; H, 3·3; S, 8·8%).

dl-*Brazilin.* Potassium borohydride (1 g) was added in small portions during 45 min to a gently refluxing suspension of *dl*-brazilein (2 g) in warm MeOH (60 ml), kept under N_2. As reduction proceeded, the brazilein dissolved, and the colour of the soln became less intense. Refluxing was continued for 15 min after the last addition. The soln was acidified with dilute AcOH (3 ml in 30 ml water) and the alcohol removed by distillation. The cooled aqueous soln was then saturated with salt and repeatedly extracted with EtOAc. The extract was washed once with saline soln, dried over $MgSO_4$ and concentrated to afford dl-*brazilin* as reddish needles. The product was recrystallized once from aqueous-alcohol, m.p. 150–155° (1.1 g). A sample for analysis was dried *in vacuo* at 140°. (Found: C, 67·4; H, 4·9. $C_{16}H_{14}O_5$ requires: C, 67·1; H, 4·9%).

UV spectra	Max	E_{molar}
Product	2900	8900
Brazilin	2900	9200

The IR spectrum was nearly identical with that of natural brazilin. The very small variations are doubtless caused by contamination of either specimen compared, possibly with *trans*-brazilin.

dl-O-*Triacetylbrazilin. dl*-Brazilin (0·4 g) was heated with AcO and NaOAc on a boiling water-bath for 5 min. The cooled soln was poured into water and after 4 hr the semi-solid material that had separated was collected and recrystallized three times from alcohol, to give dl-O-*triacetylbrazilin* as colourless needles (0·2 g) m.p. 101–102°. (Found: C, 62·85; H, 5.9. $C_{22}H_{20}O_8$, C_2H_6O requires: C, 62·9; H, 5·7%). The IR spectrum of the substance was identical with that of dl-O-*triacetylbrazilin.*

O-*Tetra*-l-*menthoxyacetyl*-d-*brazilin*. *l*-Menthoxyacetic acid was prepared according to the method given in Organic Syntheses (Vol. *23*, 52).

l-Menthoxyacetyl chloride was prepared by heating the acid (5 g) and $SOCl_2$ (8 ml) at 50–60° for 3 hr. The excess $SOCl_2$ was then removed by distillation under reduced press.

The acid chloride was added dropwise at room temp to brazilin (1 g) dissolved in dry pyridine (8 ml) and kept under N_2. There was a slight rise in temp, and after the addition the soln was kept at room temp overnight.

The brownish-red soln was poured into ice and dil HCl and the precipitated gummy solid was taken up in ether. The ethereal soln was washed successively with dil HCl, $NaHCO_3$ and water, and finally dried over $MgSO_4$. Removal of the solvent left a viscous oil which crystallized slowly in contact with EtOH, affording *tetra*-l-*menthoxyacetyl*-d-*brazilin* as fine colourless needles, m.p. 95° (2·5 g), raised to 105–108° with softening at 100° after four recrystallizations from the same solvent. (Found: C, 70·7; H, 9·0. $C_{64}H_{95}O_{13}$, C_2H_6O requires: C, 71·0; H, 9·0%), 5·760 mg in 0·50 ml, $CHCl_3$ gave $-\alpha_D^{17°}$, −0·356 whence $[\alpha]_D^{17°}$, −61·9°.

Resolution of dl-*brazilin*. *dl*-Brazilin (0·4 g) dissolved in dry pyridine (6 ml) was treated with l-menthoxyacetyl chloride (2 g) under the same conditions as in the previous experiment. The product, isolated in the usual manner, gave a crystalline solid (Fraction A), m.p. 92–105° (0·25 g), on standing overnight in EtOH soln. The mother-liquor on keeping afforded the other diastereoisomer (Fraction B), m.p. 118–124° (0·15 g).

Fraction A crystallized in fine colourless needles and after recrystallizations from EtOH had m.p. 115–116° with softening at 105°. (Found: C, 71·3; H, 9·0. $C_{64}H_{94}O_{13}$, C_2H_6O requires: C, 71·0; H, 9·0%).

A mixed m.p. with authentic tetra-l-menthoxyacetyl *d*-brazilin showed no depression. The IR spectra of the two substances were identical. The optical rotations measured after successive recrystallizations are tabulated below:

No. of recrystallizations	Concentration (mg in 0·5 ml $CHCl_3$)	$\alpha_D^{17°}$	$[\alpha]_D^{17°}$
2	4·960	−0·380	−76·6°
4	5·310	−0·386	−72·6°
8	5·330	−0·376	−70·5°
8	5·580	−0·334	−59·8°

Fraction B crystallized in clusters of colourless needles, m.p. 127–128°. A mixed m.p. with Fraction A showed a depression. (Found: C, 71·1: H, 8·9. $C_{64}H_{94}O_{13}$, C_2H_6O requires: C, 71·0; H, 9·0%).

No. of recrystallizations	Concentration	$\alpha_D^{17°}$	$[\alpha]_D^{17°}$
4	5·600 mg in 0·5 ml $CHCl_3$	−0·500	−90°
6	2·650 mg in 0·3 ml $CHCl_3$	−0·404	−91·5°

Hydrolysis of tetra-l-*menthoxyacetyl* d-*brazilin*. A soln of KOH (1 g) in EtOH (20 ml) was added to an ice-cold suspension of tetra-l-menthoxyacetyl *d*-brazilin (2·5 g) in EtOH (40 ml) kept in an atm N_2. After 1 hr the soln was acidified with dil AcOH and most of the EtOH was removed by distillation. The aqueous soln was then saturated with salt and repeatedly extracted with ether.

The ethereal extract was evaporated and the residual viscous oil diluted with warm water. The aqueous soln was then extracted with light petroleum (60–80°) to remove the menthoxyacetic acid present. On standing the aqueous soln deposited crystals of brazilin (0·4 g). A sample for analysis was recrystallized twice from water and dried at 160° *in vacuo*, m.p. 249–250° (dec). (Found: C, 66·9; H, 5·0. Calc. for $C_{16}H_{14}O_5$: C, 67·1; H, 4·9%). The sample had the specific rotation—$[\alpha]_D^{17°} = +118°$.
Reported for brazilin $[\alpha]_D^{21·5°} = +121·5°$.

Reduction of d-*brazilein to* d-*brazilin*. *d*-Brazilein (2·6 g) was partially dissolved in warm MeOH (80 ml) and KBH_4 (1 g) was then added gradually to the refluxing soln, kept under N_2, until the red colour of the soln was discharged (30 min). Refluxing was continued for 15 min after which the light brown soln was acidified with AcOH (5 ml) diluted with water (40 ml). The alcohol was removed by distillation under reduced press and the aqueous soln was then saturated with salt and extracted with ether in a continuous extraction apparatus. After 48 hr the ethereal soln was concentrated to give a dark red liquid which crystallized slowly on keeping after the addition of a little water. The crystals were collected and re-

crystallized from water (1·4 g) m.p. 247–248°. (Found in material dried at 140° *in vacuo* C, 66·9; H, 4·9. Calc. for $C_{16}H_{14}O_5$: C, 67·1; H, 4·9%), lit., m.p. 250°.

A mixture with an authentic specimen of *d*-brazilin showed no depression of m.p. The IR spectra of the product and of *d*-brazilin were identical.

UV spectra	Max	E_{molar}
Product	2900	8700
Brazilin	2900	9200

Rotatory power: Product $[\alpha]_D^{21·5°}$ + 123·4° (6·060 mg in 0·5 ml MeOH)
Brazilin $[\alpha]_D^{21·5°}$ + 121·5° (6·340 mg in 0·5 ml MeOH)

O-Tetramethylhaematoxylane. O-Tetramethylhaematoxylane was prepared from haematoxylin by the following series of reactions.

O-Tetramethylhaematoxylin was prepared in 85% yield according to the method used by Perkin[15] m.p. 66–68°, reported m.p. 65–68°.[1c]

Oxidation of O-tetramethylhaematoxylin (20 g) with CrO_3 (12 g) in AcOH soln afforded O-tetramethylhaematoxylone (14 g), m.p. 194–195°, lit. m.p. 195°.[1c]

Treatment of O-tetramethylhaematoxylone (10 g) with phenylhydrazine (20 ml) in glacial AcOH soln (100 ml) gave deoxy-O-tetramethylhaematoxylone (6·2 g), m.p. 170–175°, lit. m.p. 170–175°.[16]

Catalytic hydrogenation of deoxy-O-tetramethylhaematoxylone in acetone soln under the usual conditions with Pd–$SrCO_3$ as catalyst afforded O-tetramethylhaematoxylane in about 90% yield, m.p. 149–150°, lit. m.p. 148–148·5°.[17]

Conversion of O-*tetramethylhaematoxylane to* O-*tetra-acetylhaematoxylane.* A mixture of the tetramethyl compound (1·7 g), HBr (3·5 ml) and AcOH (40 ml) was heated under reflux at 115–120° in an atmosphere of N_2 for 3½ hr. The cooled soln was added to water and the clear red soln was saturated with salt and extracted with EtOAc. The extract was washed successively with a dil $NaHCO_3$ aq and water, dried over $MgSO_4$ and concentrated to afford a dark viscous oil which did not crystallize.

The oil was acetylated by heating with Ac_2O (12 ml) and NaOAc (0·5 g) over a water-bath for 45 min. The cooled soln was poured into water and the solid which separated was collected. It crystallized slowly from acetone–ethanol as colourless irregular prisms, m.p. 156–160° (1·1 g), raised to 166–167° after three further recrystallizations. (Found: C, 63·6; H, 5·1. Calc. for $C_{24}H_{22}O_9$: C, 63·4; H, 4·9%).

A mixed m.p. with an authentic specimen showed no depression.

Oxidation of O-*tetra-acetylhaematoxylane to* O-*tetra-acetylhaematoxylone.* A soln of CrO_3 (2 g) dissolved in water (1 ml) and AcOH (10 ml) was added dropwise to a soln of O-tetramethylhaematoxylane (2 g) dissolved in AcOH and kept at 70°. After the addition (15 min), heating and stirring were continued for 30 min. The cooled soln was diluted with water (20 ml).

The next day no crystalline solid had separated. The soln was diluted with another 50 ml water and the amorphous solid which separated was collected and crystallized slowly from EtOH, m.p. 235°. This was the higher melting isomer.

The aqueous mother-liquor on keeping afforded a small quantity of an amorphous solid (0·1 g). It was collected and recrystallized twice from aqueous alcohol from which it separated as colourless needles, m.p. 150–151°. (Found: C, 57·1; H, 4·6. Calc. for $C_{24}H_{20}O_{11}$, H_2O: C, 57·4; H, 4·4%).

A mixed m.p. with an authentic specimen showed no depression.

The IR spectrum was identical with that of O-tetra-acetylhaematoxylone prepared from haematoxylin, as below.

Preparation of tetra-acetylhaematoxylone from haematoxylin. A mixture of haematoxylin (10 g) NaOAc (1 g) and Ac_2O (50 ml) was heated on a steam-bath for 45 min. The cooled soln was poured into water and the gummy solid collected. It could not be crystallized and was oxidized in AcOH soln in the usual way by dropwise addition of chromic acid, (6 g in 6 ml water), the temp being maintained at 10–15° by ice cooling. After keeping for 4 hr at room temp (17°), the dark green soln was poured into water and the amorphous solid collected. It crystallized from aqueous alcohol as colourless needles, m.p. 145–148° (4·2 g), raised to 150–151° after three further recrystallizations from the same solvent. (Found: C, 57·0; H, 4·5. Calc. for $C_{24}H_{20}O_{11}$, H_2O: C, 57·4: H, 4·4%; Found in material dried *in vacuo* at 160°: C, 59·8; H, 4·3. Calc. for $C_{24}H_{20}O_{11}$: C, 59·5; H, 4·2%).

dl-*Haematein.* Zn dust (90 g) was added to a soln of O-tetra-acetylhaematoxylone (9 g) in EtOH (550 ml) with stirring under a stream of N_2. The temp was maintained at 30–35°, and AcOH (5 ml) was added at half-hourly intervals until 60 ml had been introduced. Stirring was continued for 24 hr.

The filtered alcoholic soln was concentrated and poured into water. The aqueous soln was then extracted with ether, and the ethereal soln washed with water, dried over $MgSO_4$ and concentrated, yielding a yellow viscous oil (8 g) which could not be crystallized. The crude pinacol was next hydrolysed in the following manner.

The oil was dissolved in EtOH (50 ml) and an aqueous-alcholic soln of KOH (6 g in 8 ml water diluted with 30 ml EtOH) was added to the cooled soln (ice-bath) under N_2. The ice-bath was removed, and the purplish soln was kept at room temp (15°) for 2 hr with occasional swirling.

The soln was then cooled again, and acidified with dil AcOH (12 ml in 40 ml water). The dark red soln on standing deposited a reddish ppt of dl-*haematein* which was collected (2·9 g). Most of the alcohol was then distilled from the aqueous-alcoholic mother-liquor, and the soln on standing deposited more crystals of dl-*haematein*, similar in lustre to haematein from natural haematoxylin.

A sample was washed several times by decantation with hot water and dried *in vacuo* at 140°. (Found: C, 63·8; H, 3·9. $C_{16}H_{12}O_6$ requires: C, 64·0; H, 3·9. $C_{16}H_{12}O_6$ requires: C, 64·0; H, 4·0%).

UV absorption	Max	E_{molar}
Product	2800	5950
	4500	22,400
Haematein	2800	4640
	4500	23,900

Haematoxylium hydrogen sulphate. Following the procedure described by Hummel and Perkin [1,c] for the preparation of iso-brazilein acid sulphate from brazilein, *dl*-haematein was dissolved in cold conc H_2SO_4, followed by the addition of hot glacial AcOH. The *salt* which was thus obtained as a yellowish orange ppt, was washed several times with glacial AcOH and dried at 80° *in vacuo*. (Found: C, 50·2; H, 3·3; S, 8·2. $C_{16}H_{11}O_5$, HSO_4 requires: C, 50·5; H, 3·2; S, 8·4%).

dl-*Haematoxylin.* KBH_4 (1·2 g) was gradually added during 45 min to a gently refluxing suspension of *dl*-haematein (3 g) in warm MeOH (60 ml) kept under N_2. As reduction proceeded, the haematein dissolved and the colour of the soln became less intense. Refluxing was continued for 15 min after the last addition. The soln was acidified with dil AcOH (3 ml in 30 ml water) and the alcohol removed by distillation under diminished press. The cooled aqueous soln was then saturated with salt and extracted with ether in a continuous extraction apparatus. This took about 48 hr for almost complete extraction. The reddish dl-*haematoxylin* which had crystallized on the sides of the flask was collected and recrystallized from water containing a little AcOH, m.p. 210–212° (dec) (2·2 g). (Found in material dried at 160° *in vacuo*: C, 63·5; H, 4·7. $C_{16}H_{14}O_6$ requires: C, 63·6; H, 4·6%).

The IR absorption spectrum of the substance was identical with that of natural haematoxylin.

UV absorption	Max	E_{molar}
Product	2930	4360
Haematoxylin	2930	6790

O-*Penta*-l-*menthoxyacetyl*-d-*haematoxylin.* l-Menthoxyacetyl-chloride (10·8 g) was added dropwise at room temp to haematoxylin (2 g) dissolved in dry pyridine (32 ml) and kept under N_2. There was a slight rise in temp, and after the addition, the soln was kept at room temp for 12 hr.

The brownish-red soln was poured on ice and HCl and the precipitated gummy solid was taken up in ether. The ethereal soln was washed successively with dil HCl, $NaHCO_3$ aq and water, and finally dried over $MgSO_4$. Removal of the solvent left a viscous oil which crystallized from EtOH, affording penta-menthoxyacetyl-*d*-haematoxylin as fine colourless needles, m.p. 95–100°, raised to 100–102° after four recrystallizations from the same solvent. (Found: C, 70·3; H, 8·8. $C_{76}H_{114}O_{16}$, H_6O requires: C, 70·5; H, 9·0%); 6·380 mg in 0·5 ml $CHCl_3$ $\alpha_D^{18°}$, −0·528 $[\alpha]_D^{18°}$ −82·8°.

Resolution of dl-*haematoxylin. dl*-Haematoxylin (0·5 g) dissolved in dry pyridine (8 ml) was treated with l-menthoxyacetyl-chloride (2·7 g) under the same conditions as in the previous experiment. The product, isolated in the usual manner, afforded a crystalline solid, m.p. 90–95° (0·05 g), on seeding and standing in EtOH soln. It was recrystallized four times from EtOH from which it separated as fine colourless needles, m.p. 101–103°. (Found: C, 70·9; H, 8·8. $C_{76}H_{114}O_{16}$, C_2H_6O requires: C, 70·5; H, 9·0%).

A mixed m.p. with authentic pentamenthoxyacetyl-*d*-haematoxylin showed no depression. The IR

spectra of the two substances were identical. The optical rotatory power measured after successive recrystallizations are tabulated below:

No. of recrystallizations	Concentration (mg in 0·5 ml $CHCl_3$)	$\alpha_D^{18\cdot5°}$	$[\alpha]_D^{18\cdot5°}$
4	5·510	−0·496°	−90·0°
6	6·530	−0·566°	−86·6°
8	5·250	−0·456°	−86·8°

The mother-liquor on keeping deposited more crystalline solid which on four crystallizations from the same solvent had m.p. 118–120°. A mixed m.p. with an authentic specimen of pentamenthoxyacetyl-*d*-haematoxylin showed no depression. (Found: C, 70·5; H, 9·1. Calc. for $C_{76}H_{114}O_{16}$, C_2H_6O: C, 70·5; H, 9·0%); 5.340 mg in 0·5 ml $CHCl_3$ $\alpha_D^{18°}$, −0·456 $[\alpha]_D^{18°}$, −85·4°.

Hydrolysis of O-*penta*-l-*menthoxyacetyl*-d-*haematoxylin.* A soln of NaOH (1·2 g) in EtOH (20 ml) was added to an ice-cold suspension of O-penta-*l*-menthoxyacetyl-*d*-haematoxylin (2·5 g) in EtOH (80 ml) kept under N_2. After 1 hr the soln was acidified with dil AcOH and most of the EtOH was removed by distillation. The aqueous soln was then saturated with salt and repeatedly extracted with ether. The ethereal extract was evaporated and the residual viscous oil diluted with warm water. The aqueous soln was then extracted with benzene to remove the menthoxyacetic acid present. On standing, crystals of haematoxylin were deposited. A sample for analysis was recrystallized twice from water and dried at 160° *in vacuo*. (Found: C, 63·6; H, 5·0. Calc. for $C_{16}H_{14}O_6$: C, 63·6; H, 4·7%). The sample had $[\alpha]_D^{18°}$, +102·4°, lit., $[\alpha]_D^{21°}$, +101·5°.

Advantage has been taken in the course of the work described in this communication, of the accessibility of certain anhydrobrazilin and anhydrohaematoxylin derivatives obtained by acetylating reduction of brazilein or haematein, e.g. J. Herzig and J. Pollak, *Monatsh* **23**, 165 (1902). This aspect is the subject of a paper in preparation.

REFERENCES

[1] An account of the present work was presented to the XIVth Int. Congress of Pure & Applied Chemistry, Zurich, 1953, cf. F.M. and R.R., *Angew. Chem.* **67**, 761 (1955). Later reference to the work was made in a contribution to a tribute to K. Venkataraman on the occasion of his 60th Birthday. Also, in *Bull. de la Soc. Chim. de France* Centenary issue **1**, 125 (1958).

[2] J. C. Craig, A. R. Naik, R. Pratt and E. Johnson, *J. Org. Chem.* **30**, 1573 (1965).

[3] The method of synthesis was first clearly indicated by the description of 3-veratrylidene-7-methoxychromanone. (W. H. Perkin, Jnr., and R. Robinson), *Proc. Chem. Soc.* **28**, 7 (1912; cf. W. H. P., J. N. Ray and R.R., *J. Chem. Soc.* 941 (1926), *idem., Ibid.* 2094 (1927); 1504 (1928).

[4] W. H. Perkin, *J. Chem. Soc.* **81**, 221, 1008 (1902); W.H.P. and R.R., *Ibid.* **93**, 1115 (1908).

[5] W. H. Perkin, Jnr., J. N. Ray and R. Robinson, *Ibid.* 1504 (1928); P. Pfeiffer, O. Angern, E. Haack and J. Williams, *Ber. Dtsch. Chem. Ges.* **61**, 739 (1928).

[6] Preparation, structure, and transformations of O-trimethylbrazilein:
[a] P. Engels, W. H. Perkin, Jnr. and R. Robinson, *J. Chem. Soc.* **93**, 1115 (1908);
[b] V. Mićović and R. Robinson, *Ibid.* 43 (1937).

[7] Refs 2 and 8.

[8] O. Dann and H. Hofmann, *Liebigs Ann.* **667**, 116 (1963).

[9] G. M. Robinson, *J. Chem. Soc.* **107**, 267 (1915). The analogy with the method of Ref 8 holds, but the product of the condensation is triveratrylene. A. Oliverio and N. Bourris, *Gazzetta* **81**, 583 (1951); A. Oliverio and C. Casinovi, *Annali di Chimica* **42**, 168 (1952); F. Bertinotti, V. Carelli, A. M. Liquori and A. M. Nardi, Extract from *Struttaristica chimica*, Supplement to *La Ricarca Scientifica*, 22nd year (1952).

[10] A. W. Gilbody, W. H. Perkin, Jnr. and J. Yates, *J. Chem. Soc.*, **79**, 1397 (1901).

[11] A. W. Gilbody and W. H. Perkin, *Proc. Chem. Soc.* **15**, 27 (1899), and later papers; W. H. Perkin and R. Robinson, *J. Chem. Soc.* **95**, 381 (1909); *idem.* and J. N. Ray, *Ibid.* 1504 (1928).

[12] A. W. Gilbody and W. H. Perkin, *Ibid.* **81**, 1046 (1902).

[13] Perkin, Ray and Robinson, *loc. cit.*

[14] J. J. Hummel and A. G. Perkin, *J. Chem. Soc.* **41**, 367 (1882). Cf. W.H.P., R.R. and M. R. Turner, *Ibid.* **93**, 1085 (1908).
[15] W. H. Perkin, Jnr. and J. Yates, *Ibid.* **81**, 225 (1902).
[16] W. H. Perkin, Jnr., *Ibid*, **81**, 1057 (1902).
[17] Ref 16 and P. Pfeiffer, *Ber. Dtsch. Chem. Ges*, **618**, 294 (1928).