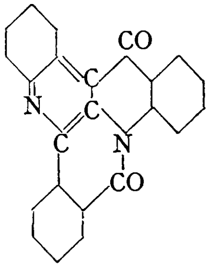
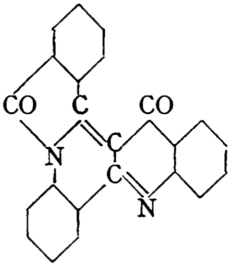
319. *The Complex Benzoylation Products of Indigotin. Höchst Yellow U.*

By E. Hope and J. S. Anderson.

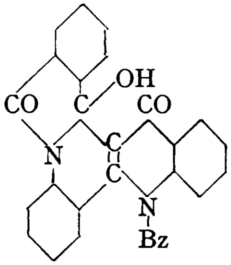
Recently the formula (I) has been proposed for the dye Höchst Yellow U (de Diesbach, de Bie, and Rubli, *Helv. Chim. Acta*, 1934, **17**, 113). The present authors disagree with this view on the ground of results obtained by them in this field during the last seven years, and propose the structure (II) instead. The main reason for disagreement is that (I) cannot be logically related to what we believe to be the true formula of Höchst Yellow R (III) (Hope, Kersey, and Richter, J., 1933, 1000). Our principal reason for advocating the structure (III) for Höchst Yellow R is that, up to the present, it is the only one which can give a reasonable account of the results of boiling the substance with dilute alkalis at the ordinary pressure.



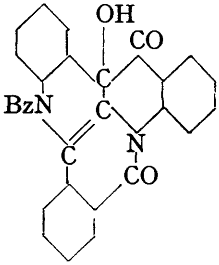
(I.)



(II.)



(III.)

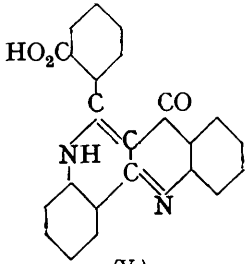


(IV.)

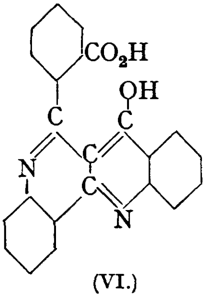
A satisfactory formula for Höchst Yellow R must explain the quantitative production of equivalent amounts of benzoic acid, anthranilic acid, and a lactam, $C_{16}H_9O_2N$, when alkali is applied to it under the conditions mentioned. It can be seen that (III) represents a substance which, after hydrolysis of the benzoyl group, contains a quinolone structure; this is the source of the anthranilic acid, which can arise without disturbance of the lactam linkage. Formula (IV) (proposed by de Diesbach *et al.*, *loc. cit.*), on the other hand, represents a substance which, after hydrolysis of the benzoyl group, would require severance of the lactam linkage to provide a route to anthranilic acid.

Höchst Yellow U is derived from Höchst Yellow R (III) by stirring in 80% sulphuric acid at 140°. It is likely that the sulphuric acid catalyses the separation of hydroxyl, and the complex radical (ion) remaining can gain stability by losing the benzoyl group, thus leaving Höchst Yellow U (II). It is known that, when Höchst Yellow U is digested with excess of ethyl-alcoholic sodium ethoxide, a deep blue-green solution is produced (Posner, Zimmermann, and Kautz, *Ber.*, 1929, **62**, 2150). This solution contains what these authors term " the monohydrate of Höchst Yellow U," to which they assigned a formula which can be no longer accepted.

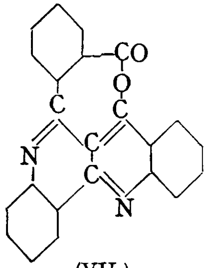
The present work deals in more detail with the nature of this " monohydrate," which is brick-red. It is clear from our results that the " monohydrate " is formed by the severance of the lactam ring in (II), thereby giving the amino-acid (V). This red amino-acid gives, on methylation with methyl sulphate and aqueous caustic soda, a red ***monomethyl*** and a scarlet ***dimethyl*** derivative, the first still having acid character and melting at 238—240°, the second being insoluble in alkali and melting at 168°. The latter compound is evidently the substance described by Posner *et al.* as the "monomethyl produkt des monohydrats von Höchster Gelb U." The dimethyl derivative loses one methyl group by the action of boiling hydriodic acid (Zeisel estimation). The monomethyl derivative is not affected by hydriodic acid at 140° and hence must have its methyl group on a nitrogen atom.



(V.)



(VI.)



(VII.)

Posner and his collaborators observed that the parent acid (V) reverts with great ease, by loss of water, to Höchst Yellow U, resembling the corresponding acid from Ciba Yellow 3G in this behaviour (Hope and Richter, J., 1932, 2786). This re-formation of the neutral lactam occurs when a solution of (V) in dilute alkali is warmed; also, in attempts to take the melting point of the acid (V), dehydration to Höchst Yellow U takes place (above 100°) long before melting. On the other hand, the red monomethyl derivative of (V) is a stable acid, remaining unaffected when warmed in dilute alkaline solution. The presence of the methyl group on the nitrogen atom precludes lactam formation.

The present investigation deals also with the effect of aqueous alkalis at high temperature on Höchst Yellow U. The dye is very resistant to such agents below 160° or thereabouts. Good results were obtained with the finely divided dye and 15% aqueous caustic soda at 210—215° in a steel autoclave, the main product being a colourless *amino-acid* produced by isomeric change of the amino-acid (V), and we assign to it the formula (VI). In accordance with this structure, it gives, on methylation with methyl sulphate and alkali, a *mono-* and a *di-methyl* derivative. The former is an ether-acid; the latter an ether-ester, from which hydriodic acid in a Zeisel estimation removes two methyl groups.

The acid (VI) holds on to co-ordinated water with remarkable tenacity. It is still attached after crystallisation of the substance from methyl alcohol, ethyl acetate, or glacial acetic acid, and does not come off in a melting point tube until about 180°. The acid (VI) forms a rather sparingly soluble *ammonium* salt. The methyl ether of (VI) yields a very sparingly soluble sodium salt. (VI) is a fairly strong base, dissolving readily in 4% hydrochloric acid. It was shown to give phthalic acid among the products of oxidation by potassium permanganate.

When specimens of the amino-acid which have been crystallised from ethyl acetate or methyl alcohol are thrown into boiling diphenyl ether, vigorous effervescence occurs and ceases after a few minutes. After a further period of boiling for 10 minutes, and subsequent cooling, a white insoluble product is obtained by adding excess of light petroleum, which dissolves the diphenyl ether. This decomposition *product* of (VI) differs from (VI) in being soluble in boiling benzene, from which it can be recrystallised. The purified product is insoluble in cold 5% caustic soda solution. It appears that lactone formation has occurred providing the lactone (VII).

The formula (I) proposed by de Diesbach *et al.* (*loc. cit.*) will explain most of the reactions of Höchst Yellow U described in this work, but cannot explain the above lactone formation.

Among the products of interaction of Höchst Yellow U with 15% caustic soda solution there is invariably an acidic *substance* which will not dissolve in the excess of hydrochloric acid used in dissolving the main product, *viz.*, the amino-acid. This substance, which is exceedingly troublesome to purify, appears to be isomeric with the amino-acid. We are inclined to the view that it has the formula (VI), with, however, the hydroxyquinoline structure in the isomeric quinolone form. This view would accord with the results of methylation, but it is somewhat difficult to understand the lack of basic character in an acid of that formula. It has not yet been possible to examine this substance in sufficient detail to characterise it completely.

EXPERIMENTAL.

The Höchst Yellow U was made by heating Höchst Yellow R with 80% sulphuric acid at 150° in an open vessel with vigorous stirring (G.P. 270943). When the reaction was over (about 3 hours), benzoic acid ceased to sublime out of the liquid. The product was recrystallised from xylene until its m. p. was 285—287°. The pure product was obtained in a finely divided state by solution in cold concentrated sulphuric acid and reprecipitation by water. The damp material was thoroughly air-dried for the experiments in which alcoholic sodium ethoxide was used.

Substance produced by the Action of Sodium Ethoxide on Höchst Yellow U.—The procedure described by Posner, Zimmermann, and Kautz (*loc. cit.*) was followed in obtaining the substance which these authors call " the monohydrate of Höchst Yellow U." This substance, the red amino-acid (V), dissolves in 3% aqueous caustic soda, giving a deep brown-red solution with a green fluorescence. This, on boiling for a few minutes, precipitates Höchst Yellow U. The cold dilute alkaline solution of (V) gives back the red acid when acidified with acetic acid, but concentrated hydrochloric acid in some excess gives a brownish-mauve precipitate, which is a hydrochloride. The red acid is also slightly soluble in 8% aqueous sodium carbonate, giving a red solution which precipitates Höchst Yellow U after some days. Solutions of the acid in caustic soda of more than 3% strength tend to precipitate a sparingly soluble sodium salt.

Methylation of the Red Amino-acid (V).—The acid, isolated as above (2 g.), was dissolved in a considerable excess of 4% caustic soda solution (a 7% solution did not give a clear liquid), methyl sulphate (6 c.c.) added in portions during some 10 minutes, with vigorous shaking, and alkalinity maintained by further additions of caustic soda. The insoluble product was collected, washed with dilute caustic solution and then water, dried, and crystallised from alcohol, giving the dimethyl derivative in well-formed scarlet crystals, m. p. 167—168°, with no sign of further change on heating to 280° (Found : C, 76·6; H, 3·9; N, 7·7; OMe, 7·0; *M*, 380. Calc. for $C_{25}H_{18}O_3N_2$: C, 76·1 ; H, 4·6; N, 7·1; 1OMe, 7·8% ; *M*, 394).

The filtered alkaline liquors from this methylation, on acidification with acetic acid, yielded a brownish-red precipitate of the *monomethyl* derivative. It gave a red solution in dilute aqueous caustic soda or sodium carbonate. At appropriate concentrations of alkali crystals of a sparingly soluble sodium salt separated. This compound crystallised well from alcohol (this fact distinguishes it at once from the parent red amino-acid, which yields Höchst Yellow U when boiled in that solvent. Further, the parent acid would be converted into Höchst Yellow U on heating in a melting point tube) and had m. p. 238—240° (efferv.) (Found : C, 74·9; H, 3·6; N, 6·6; OMe, nil. $C_{24}H_{16}O_3N_2$ requires C, 75·8; H, 4·2; N, 7·4%).

Both methylation products are fairly strong bases and dissolve in dilute hydrochloric acid, giving indigo-blue solutions.

Action of Aqueous Caustic Soda on Höchst Yellow U.—Pure Höchst Yellow U (25 g.) was finely divided as described (above) and, after thorough washing and pressing on a filter and drying in the open air for 12 hours on porous plates, was ground with 180 c.c. of 15% aqueous caustic soda with added solid alkali to correspond to the water in the damp paste. The reaction vessel (either a narrow cylindrical steel tube with a screw-on top and a lead washer, or a steel autoclave) was heated in an oil-bath at 215° for 7 hours. After cooling, the clear reddish-brown liquid was diluted with 200 c.c. of water and run into a large excess of 10% hydrochloric acid (preliminary experiments had shown that, if hydrochloric acid is added gradually to the alkaline liquid, the first-formed precipitate partly redissolves). The substance insoluble in the excess of hydrochloric acid was filtered off, stirred with dilute hydrochloric acid, collected, washed with water, and air-dried (yield, 7 g.). The two acid filtrates were united and partly neutralised with caustic soda, with cooling, and crystalline sodium acetate added. This precipitated a cream-coloured *amino-acid* (yield after filtration, washing, and drying, 11·4 g.).

This amino-acid (VI) was dissolved in cold 5% hydrochloric acid, reprecipitated by sodium acetate, washed with water, and air-dried; after remaining for 3 days over phosphoric oxide in a desiccator, it retained $2H_2O$; m. p. 182° (efferv.) after slight shrinking at 176°. It crystallised well from ethyl acetate; m. p. 232° (efferv.) (Found : C, 67·8; H, 5·15; N, 6·6. $C_{23}H_{14}O_3N_2,2H_2O$ requires C, 68·6; H, 4·5; N, 6·6%). It also crystallised well from methyl alcohol containing about 10% of water; m. p. (after drying in air) 198—199° (efferv.). The amino-acid formed sparingly soluble salts with sodium hydroxide and ammonium hydroxide. Excess of the cation in each case caused some precipitation. The *ammonium* salt was dried for 4 days over phosphoric oxide (Found : N, 10·4. $C_{23}H_{17}O_3N_3$ requires N, 10·0%).

Action of Heat on the Amino-acid (VI).—It is essential to use amino-acid which has been recrystallised from ethyl acetate or methyl alcohol. The acid (3 g.) was added in small amounts to boiling diphenyl ether (b. p. 257°) (15 c.c.); unless a high-boiling solvent is used, an intractable product is obtained. Each portion caused violent effervescence. Finally, the whole was boiled for 10 minutes. Addition of light petroleum (b. p. 40—60°) dissolved the diphenyl ether and left the *product* (VII) as a white precipitate, m. p. 207—212°. After crystallisation from benzene and from highly purified ethyl acetate, it melted at 230—231° (Found : C, 78·6; H, 4·0; N, 8·3. $C_{23}H_{12}O_2N_2$ requires C, 79·3; H, 3·4; N, 8·0%).

Derivatives of the Amino-acid (VI).—*Benzoylation.* The acid (4 g.) was dissolved in 10% caustic soda solution (40 c.c.), and benzoyl chloride (7 g.) added in small portions. The product was precipitated by neutralisation with hydrochloric acid, collected, extracted with boiling light petroleum (b. p. 60—80°), which removed the benzoic acid, crystallised from glacial acetic acid, and dried for 3 hours at 110°; the *benzoyl* derivative then melted at 265—267° (efferv.) (Found : C, 74·6; H, 4·5; N, 5·7. $C_{30}H_{18}O_4N_2,H_2O$ requires C, 73·7; H, 4·0; N, 5·7%). The effervescence was due to elimination of firmly attached water of hydration. The product so formed was identical with that produced by warming the original benzoyl derivative with acetic anhydride. After crystallisation from toluene–ligroin it melted at 212—213° [Found : N, 6·1; *M* (Rast), 441. $C_{30}H_{18}O_4N_2$ requires N, 5·95%; *M*, 470]. This dehydration product is a *carboxylic acid* like the benzoyl derivative from which it is derived. It dissolves, like that substance, in dilute sodium carbonate solution and is reprecipitated by acids.

Acetylation. The air-dried substance was boiled for a short time with a mixture of equal parts of acetic acid and acetic anhydride. The product crystallised on cooling; after recrystallisation from glacial acetic acid it melted at 272° with no sign of decomposition (Found : C, 73·9; H, 4·3; N, 6·6. $C_{25}H_{16}O_4N_2$ requires C, 73·5; H, 3·9; N, 6·9%). This *acetyl* derivative is a carboxylic acid, dissolving easily in dilute sodium carbonate solution.

Methylation. The substance (7 g.) was dissolved in 10% caustic soda solution (40 c.c.) and shaken with methyl sulphate (8 c.c.), added in 2 c.c. portions during 10 minutes. About 10 c.c. of 10% caustic soda solution were now added, and a further 3 c.c. of methyl sulphate, the temperature being allowed to reach 25°. The greyish crystalline *dimethyl* derivative was filtered off, ground with dilute caustic soda solution, and washed. It crystallised well from methyl alcohol. The pure product melted at 238—239° and showed no further change on being heated to 280°. It differs markedly from the parent amino-acid in having no affinity for solvent molecules (Found : C, 75·5; H, 5·5; N, 7·7; OMe, 16·8; *M*, 375. $C_{25}H_{18}O_3N_2$ requires C, 76·1; H, 4·8; N, 7·1; 2OMe, 15·7%; *M*, 394). It dissolves easily in 3% hydrochloric acid and is insoluble in alkalis. That it is an ester, is shown by boiling it for a short time with 8% hydrochloric acid. From the acid solution, sodium acetate precipitates an *acid* which differs from the parent amino-acid in many respects. It resists acetylation. It melts with decomposition at 308—310°. Heating with hydriodic acid shows that it retains one methoxy-group (Found : N, 7·1; OMe, 7·6. $C_{24}H_{16}O_3N_2,2H_2O$ requires N, 7·0; 1OMe, 8·2%). These results are in consonance with the view that the parent acid has the formula (VI) and that the substance, m. p. 308°, is an ether-acid.

Oxidation of the Amino-acid.—The acid (2 g.) was dissolved in 100 c.c. of 8% sulphuric acid. At 40—50°, a concentrated solution of potassium permanganate (total, 8 g.) was gradually run in. The liquid was filtered, made alkaline (smell of ammonia), again filtered, and evaporated to small bulk. Potassium sulphate was filtered off, and the filtrate extracted with ether. On evaporation of this, phthalic acid remained, which was converted into its anhydride, m. p. 130°.

The Second Acidic Product of the Action of Aqueous Alkali on Höchst Yellow U.—This *product* having no basic character, was left undissolved in the excess of 10% hydrochloric acid used to dissolve the amino-acid. It was redissolved in dilute sodium carbonate solution, boiled with charcoal, and reprecipitated by dilute hydrochloric acid. After washing and drying in the air, it had m. p. 222—227° (efferv.). The effervescence is not due to loss of carbon dioxide and must be due to water. The crude acid was dissolved in 10% caustic soda solution at 50°; a sparingly soluble sodium salt slowly separated in the cold. The acid separated from nitrobenzene in greyish crystals, which were washed with toluene and heated in an air-oven at 120° for 2 hours; m. p. 206—208° and effervescence at 212° (Found: C, 71·7, 71·9; H, 4·4, 4·8; N, 7·2. $C_{23}H_{14}O_3N_2,H_2O$ requires C, 71·8; H, 4·2; N, 7·3%).

Methylation. By treatment with methyl sulphate and caustic soda, this acid yielded a methylation *product*, which gradually separated from the alkaline liquor. Crystallisation from benzene–light petroleum gave yellowish crystals, m. p. 247—249° [Found: C, 76·4; H, 4·4; N, 6·75; OMe, 7·0; *M* (Rast), 336, 342. $C_{25}H_{18}O_3N_2$ requires C, 76·1; H, 4·6; N, 7·1; 1OMe, 7·8%; *M*, 394]. It seems that two methyl groups have been introduced in this methylation, and one only is removable by hydriodic acid. It is likely that the unaffected one is on a nitrogen atom, as suggested in the introduction.

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