132. *Cinnolines. Part IV. The Preparation of 4-Hydroxycinnolines, and the Mechanism of Cinnoline Syntheses.*

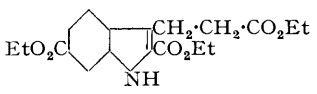
By K. Schofield and J. C. E. Simpson.

A simple method for the preparation of Ar-substituted 4-hydroxycinnolines consists in the diazotisation of appropriate *o*-aminoacetophenones. The limitations of this reaction are discussed, and a mechanism is advanced which correlates this reaction with two other methods of cinnoline synthesis previously studied (Widman–Stoermer and Richter reactions).

In the preceding paper we referred to the conversion of 5-nitro-2-aminoacetophenone into 6-nitro-4-hydroxycinnoline (IV; R = NO_2) (Borsche and Herbert, *Annalen*, 1941, **546**, 293) and to that of the indole (I) *via* the amine (II) into the cinnoline (III) (Koelsch, *J. Org. Chem.*, 1943, **8**, 295). These observations, apparently more or less fortuitous, suggested that the diazotisation of *o*-amino-ketones of the general formula *o*-$NH_2 \cdot C_6H_4 \cdot CO \cdot CH_2R$ might offer a simple and general route to 4-hydroxycinnolines. Within limits, this has proved to be the case. A convenient starting point is acetophenone, from which 6- and 8-*chloro*- (IV and V; R = Cl), 6- and 8-*bromo*- (IV and V; R = Br), 6-*cyano*- (IV; R = CN), and 6-nitro-4-hydroxycinnoline (IV; R = NO_2) have been prepared by way of the appropriate *o*-aminoacetophenones (in the press). The diazotisation of 5-bromo-2-aminoacetophenone was carried out by Gibson and Levin (J., 1931, 2388), who, in preparing the derived arsonic acid by the Bart reaction, isolated as a by-product an arsenic-free substance, m. p. 278°, which, on the basis of elementary analysis, they formulated as 5-bromo-2-nitrosoaminoacetophenone or 5-bromo-2-amino-oximinoacetophenone. In our experience, cyclisation of the diazotised amine to the cinnoline proceeds so smoothly on heating that there can be little doubt that Gibson and Levin's substance is actually 6-bromo-4-hydroxycinnoline (m. p. 277°), in spite of the discrepancy in analytical data.

We have also begun experiments to extend the reaction to the preparation of 3-substituted 4-hydroxycinnolines, and have found that β-(6-aminoveratroyl)propionic acid readily yields 4-*hydroxy*-6 : 7-*dimethoxycinnoline*-3-*acetic acid* (VI; R = H), which is also obtained, together with a small yield of the *ethyl* ester (VI; R = Et) by diazotisation of ethyl β-(6-aminoveratroyl)propionate. In connexion with this aspect of our work, it is of interest that de Diesbach and Klement (*Helv. Chim. Acta*, 1941, **24**, 158) have stated that diazotisation of ω-anilino-*o*-aminoacetophenone, followed by treatment with alkali, produces a substance, m. p. 283°, of

unknown structure, of which the analysis indicates the formula $C_{14}H_{11}ON_3$. We believe that de Diesbach and Klement's compound is 4-hydroxy-3-anilinocinnoline, and we are now investigating this reaction and also the diazotisation of other terminally-substituted *o*-aminoacetophenones.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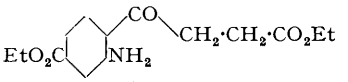
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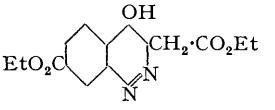
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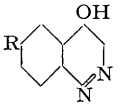
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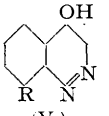
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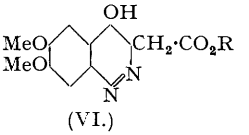
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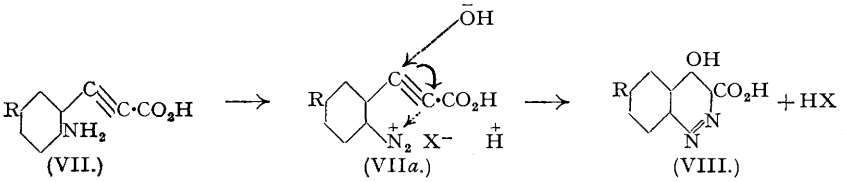
The yields of the cinnolines (IV, V, and VI) are in general high (70—90%), and the method is undoubtedly the best yet available for the preparation of 4-hydroxycinnolines. Negative results, however, were obtained with *o* : ω- (Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067) and 2 : 3-diaminoacetophenone, with 2-amino-3-methoxyacetophenone (in the press), and with 6-aminoacetoveratrone,* the products, after heating, being non-crystalline and partly phenolic. *o*-Aminoacetophenone proved to be a borderline case, giving much phenolic oil and about 10% of 4-hydroxycinnoline.

We have not yet sufficient evidence to state with certainty what are the conditions governing the success or otherwise of this reaction, but we believe that the weakness of the ketonic base may be one factor which influences it favourably. The 3- and 5-substituted aminoacetophenones which undergo the reaction should, on theoretical grounds, be weaker bases than those which were found to give negative results [*e.g.*, *p*-chloroaniline has K_b (at 25°) $28{\cdot}8 \times 10^{-12}$, as compared with the value for aniline of 126×10^{-12} (Bennett, Brooks, and Glasstone, J., 1935, 1821], and, of the bases in the latter category, 2-amino-3-methoxyacetophenone and 6-aminoacetoveratrone are much more soluble (qualitatively) in dilute hydrochloric acid than the halogeno-aminoacetophenones, and 5-nitro-2-aminoacetophenone, as might be expected, separates largely, if not entirely, as the free base on dilution of a strongly acid solution. It is therefore evident that, *ceteris paribus*, the more reactive is the diazonium kation, the more readily does cinnoline formation occur.

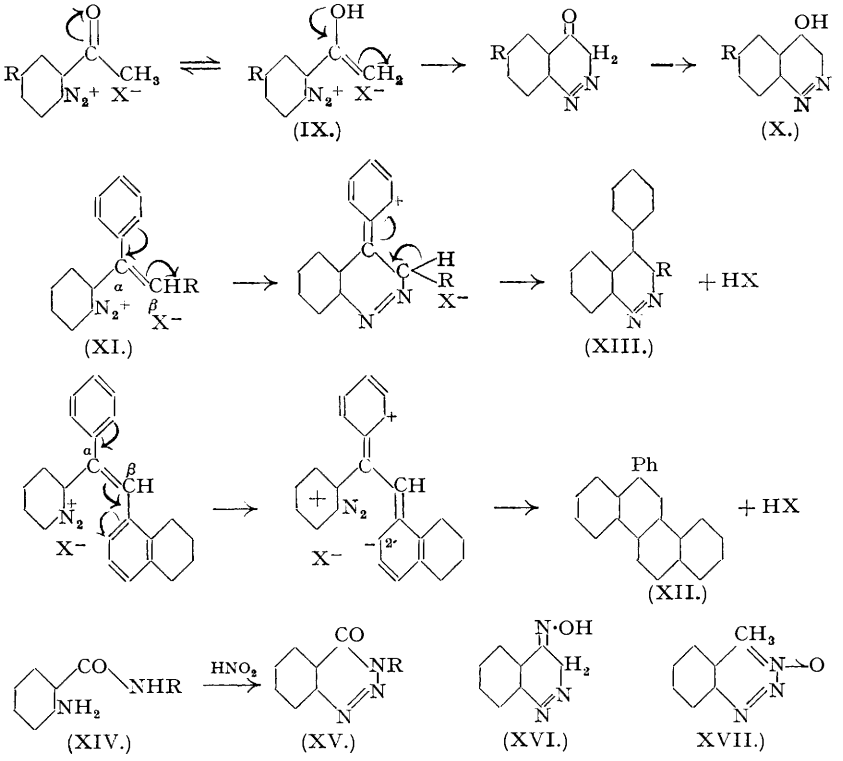
A second controlling factor in the reaction is probably the ease with which enolisation of the ketonic side chain takes place. In the cases under consideration (3- and 5-substituted 2-aminoacetophenones) it is unlikely that the variability of this factor is of primary importance, because the substituents are not suitably placed for the operation of a " *T* " effect. We are investigating the influence of 4-substituents in this connexion.

The question of whether enolisation of the ketonic side chain is a necessary prelude to cyclisation is of considerable theoretical interest; the speculation that such a step is involved is an attractive one, as it would enable both the present reaction and the Richter synthesis (preceding paper) to be correlated with the Widman–Stoermer reaction (Simpson, J., 1943, 447, and references there given). We have suggested (*loc. cit.*) that the formation of 4-hydroxycinnoline-3-carboxylic acid (VIII; R = H) by diazotisation of *o*-aminophenylpropiolic acid (VII; R = H) in dilute hydrochloric acid may involve intermediate formation of the 4-chloro-acid, because 4-chlorocinnoline contains a highly reactive halogen atom (Busch and Klett, *Ber.*, 1892, **25**, 2847, and unpublished work by us). The other obvious mechanism, involving hydration of the acetylenic linkage, is improbable, because, apart from other reasons discussed below, such hydrations usually require catalytic stimulus and a strongly acid medium (compare, *e.g.*, Johnson, Jacobs, and Schwarz, *J. Amer. Chem. Soc.*, 1938, **60**, 1885); but a process involving intramolecular co-ordination of the diazonium kation with the anionoid carbon atom, followed by addition of hydroxyl ion, as shown in (VII*a*; R = H), could well take place in dilute acid solution. [The argument that the polarisation of the acetylenic bond in (VII*a*) is in the direction shown has already been outlined by us (*loc. cit.*).] We have obtained support for this mechanism by the observation that diazotisation of (VII; R = H) in dilute sulphuric acid gives (VIII; R = H) in the same yield as when dilute hydrochloric acid is used. Furthermore, this mechanism seems to be the only feasible explanation of the production of the 6-methoxy-acid (VIII; R = OMe) by the Richter synthesis, because, although the corresponding 4-chloro-acid has not been prepared, the chlorine atom of 4-chloro-6-methoxycinnoline is comparatively highly resistant (unpublished), thus rendering the intermediate formation of the 4-chloro-acid and its subsequent hydrolysis an unlikely contingency.


(VII.) (VII*a*.) (VIII.)

* This constitution has been ascribed to two different substances (Lawson, Perkin, and Robinson, J., 1924, **125**, 626; Mannich and Berger, *Arch. Pharm.*, 1939, **277**, 117). The matter has been clarified in our laboratory and also at Oxford (private communication from Sir Robert Robinson), and the relevant evidence will be published shortly.

If, as we believe, the Richter synthesis, the Widman–Stoermer reaction, and the production of cinnolines from diazotised *o*-aminoacetophenones are essentially manifestations of the same fundamental process, then our experimental results with the Richter reaction can be explained in terms of the mechanism illustrated above, but not by a process involving an intermediate, but completed, hydration of the acetylenic linkage (*i.e.*, co-ordination of a proton with the anionoid carbon followed by eventual loss of HX). The reasons against such a mechanism are twofold. First, the mechanism would require that hydration of the acetylenic linkage should be much more rapid than diazotisation; if this were not so, and the two reactions were to occur at comparable rates, then the electromer (VII*a*) would be present at some stage, and the mechanism would become identical with that discussed above. Therefore, *ex hypothesi*, *o*-aminobenzoylacetic acid would of necessity be an intermediate in the " completed hydration " mechanism, and since all attempts to prepare this substance, or even its ethyl ester, have given rise to 2 : 4-dihydroxyquinoline (see, *e.g.*, Erdmann, *Ber.*, 1899, **32**, 3570; Gabriel and Gerhard, *loc. cit.*; Ashley, Perkin, and Robinson, J., 1930, 382), this quinoline derivative would be expected as a reaction product, which is contrary to our experience. Secondly, the " completed hydration " mechanism fails to account for the production in good yield of 4-hydroxycinnolines from *o*-amino- and from 2-amino-5-methoxy-phenylacetylene (Schofield and Simpson, *loc. cit.*), because the corresponding aminoacetophenones would perforce figure as intermediates. We have not prepared 2-amino-5-methoxyacetophenone, but the 3-methoxy-compound, which is a near analogy, fails, as already mentioned, to give a cinnoline, and we have also referred to the poor yield obtained from *o*-aminoacetophenone. For the production of cinnolines from *o*-aminoacetophenones in general, we may suppose that the anionoid character of the terminal carbon atom of the polarised enol form (IX) is insufficient to bring about co-ordination with the diazonium group when R is hydrogen, but that cyclisation occurs, leading to (X), when the kationic activity of the N_2 residue is enhanced by the presence of electron-attractive *p*-substituents (R = CN, NO_2, halogen).



The Widman–Stoermer reaction may be regarded as preceded by a similar polarisation, as shown in (XI), and the experimental data so far available (Simpson, *loc. cit.*) are in accord with this conception. Thus it is known that the reaction is stimulated when the α-substituent is aryl (electron donor), and inhibited when it is hydrogen. Furthermore, the Widman–Stoermer reaction is, in the case of 3 : 4-diphenylcinnoline, independent of the steric configuration of the related *o*-aminoarylethylene, both geometrical forms undergoing cyclisation with, qualitatively, equal ease. This point has been substantiated during further work (unpublished) on the preparation of 3-substituted 4-arylcinnolines, and this independence of steric relations is what would be expected on the basis of the ionic mechanism under consideration. The mechanism also accounts for the observed formation of 2-phenylchrysene (XII) as a concomitant of 4-phenyl-3-(α-naphthyl)cinnoline (XIII; R = α-$C_{10}H_7$), as the hydrocarbon would result from absorption of the anionic charge on C_β into the α-naphthyl nucleus, followed by interaction between the activated 2′-position and the (resonating) diazonium

kation. In view of the greater capacity of the naphthalene system than of a single aromatic ring to absorb electrons, substitution of C_β by phenyl instead of naphthyl should be less effective in relieving this atom of its charge, and should thus reduce the extent of hydrocarbon formation; this point also is borne out by experiment, (XI; R = Ph) giving (XIII; R = Ph) as the sole crystalline product (Simpson, *loc. cit.*). The behaviour of the naphthylethylene thus constitutes an interesting example of the dualistic function of aryl nuclei, according to environment, in electronic displacements. It is to be noted that in the Widman–Stoermer reaction the proton which is eliminated as HX comes from C_β; in the synthesis of cinnolines from aminoacetophenones the source of the proton is, almost certainly, the enolic hydroxyl group rather than C_β; and in the Richter reaction the proton source is the solvent.

Finally, the synthesis of benzotriazoles by diazotisation of substituted amides of anthranilic acid (XIV ⟶ XV) (*e.g.*, Weddige, *J. pr. Chem.*, 1893, **48**, 92 and earlier papers; Kratz, *ibid.*, 1896, **53**, 213; Mehner, *ibid.*, 1901, **63**, 285; Thode, *ibid.*, 1904, **69**, 105; Niementowski, *Ber.*, 1888, **21**, 1538; Königs and Reissert, *ibid.*, 1899, **32**, 782; Meyer, *Annalen*, 1907, **351**, 278), which would offer a formal analogy for a mechanism of cinnoline formation without the intervention of enolisation, is not in fact a truly comparable reaction, because the amide nitrogen, with its lone electron pair, would naturally tend to link up with the positive diazonium centre without preliminary electromeric shifts. In this connexion it is probably significant that the oxime of *o*-aminoacetophenone gives on diazotisation, not the unknown oximino-dihydrocinnolone (XVI), but methylanthranil by loss of nitrogen from the intermediately-formed benzotriazine oxide (XVII) (Auwers, *Ber.*, 1924, **57**, 461; Meisenheimer, Senn, and Zimmermann, *ibid.*, 1927, **60**, 1736).

Experimental.

(Melting points are uncorrected.)

4-Hydroxy-6-cyanocinnoline.—2-Amino-5-cyanoacetophenone (1 g.) was suspended in 2N-hydrochloric acid (15 c.c.) and treated with 5% aqueous sodium nitrite (8 c.c.) with ice-cooling. The diazotised solution was then heated on the steam-bath until it showed a negative coupling reaction (½—¾ hour). The cooled solution was filtered, and the solid dissolved in warm sodium carbonate solution, filtered (charcoal), and acidified with acetic acid. The *4-hydroxy-6-cyanocinnoline* so obtained crystallised from alcohol, in which it is moderately soluble, in small, soft, faintly yellow needles, m. p. 284—285°. It is appreciably soluble in hot water, from which it crystallises well, and easily soluble in hot aqueous acetic acid. The solutions show a characteristic green fluorescence (Found: C, 62·5; H, 3·1; N, 24·5. $C_9H_5ON_3$ requires C, 63·15; H, 2·9; N, 24·6%). Addition of sodium acetate to the reaction mixture immediately after diazotisation caused the precipitation of a dark red amorphous product.

6-Chloro-4-hydroxycinnoline.—A warm solution of 5-chloro-2-aminoacetophenone (25 g.) in 2N-hydrochloric acid (250 c.c.) gave a colourless suspension of the hydrochloride when cooled in ice. The almost clear solution obtained by the addition of 10% aqueous sodium nitrite (120 c.c.) was heated on the steam-bath. Separation of the cinnoline set in after 15—20 minutes, and the reaction was most rapidly completed by filtering off the first crop and re-heating the slightly diluted filtrate (if this was not done, the suspension still gave a positive coupling reaction after several hours' heating). The crude base (50·9 g. from 51·4 g. of the amino-ketone) was digested with boiling rectified spirit (500 c.c.) and filtered cold, yielding 41·9 g. of almost pure *6-chloro-4-hydroxycinnoline*, m. p. 291—293°. The pure substance (Found: C, 53·2; H, 2·85; N, 15·45. $C_8H_5ON_2Cl$ requires C, 53·2; H, 2·8; N, 15·5%), m. p. 294—295°, crystallised from alcohol, in which it is sparingly soluble, in fine, almost colourless needles, which gave a positive Beilstein reaction. It was almost insoluble in hot 4N-aqueous ammonia, but dissolved readily in aqueous sodium hydroxide; an experiment in which the crude reaction product was dissolved in alkali showed that the cinnoline base, and not a hydrochloride, separates from the diazotised amino-ketone solution.

8-Chloro-4-hydroxycinnoline.—The solution formed by diazotising (with 10% aqueous sodium nitrite) a suspension of 3-chloro-2-aminoacetophenone hydrochloride (from 1·2 g. of base, 1·2 c.c. of water, and 6 c.c. of concentrated hydrochloric acid) was heated on the steam-bath for 1 hour, cooled, and filtered. The solid was dissolved in hot dilute aqueous ammonia, clarified (charcoal), and acidified with acetic acid, yielding 0·95 g. of *8-chloro-4-hydroxycinnoline*, m. p. 195—197°. After crystallisation from alcohol, in which it is much more soluble than the isomeric 6-chloro-compound, the substance formed silky, fawn-coloured needles, m. p. 198—199° (Found: C, 53·3; H, 2·5; N, 16·0; Cl, 20·0. $C_8H_5ON_2Cl$ requires C, 53·2; H, 2·8; N, 15·5; Cl, 19·7%). On a larger scale, 7·5 g. of the amino-ketone gave 5·5 g. of the cinnoline, m. p. 194—196°.

6-Bromo-4-hydroxycinnoline.—Prepared similarly to the 6-chloro-derivative, the *6-bromo*-compound (0·8 g. from 1 g. of 5-bromo-2-aminoacetophenone and 15 c.c. of 2N-hydrochloric acid; the hydrochloride of the amino-ketone separated in beautiful colourless needles) formed small, pale yellow, dull prismatic needles, m. p. 276—277°, sparingly soluble in alcohol, and, with some difficulty, in warm aqueous ammonia, and readily soluble in aqueous sodium hydroxide (Found: C, 42·8; H, 2·2; N, 12·55. $C_8H_5ON_2Br$ requires C, 42·7; H, 2·2; N, 12·45%). The substance is slightly, but perceptibly, soluble in hot water and in moderately concentrated hydrochloric acid; both solutions readily crystallised on cooling.

8-Bromo-4-hydroxycinnoline.—A solution of 3-bromo-2-aminoacetophenone (0·5 g.) in concentrated hydrochloric acid (5 c.c.) was diazotised with 10% aqueous sodium nitrite. After 3 days at room temperature, the solution still gave a strong coupling reaction, but this became negligible after it had been heated for 1 hour on the steam-bath. The *cinnoline* which separated on cooling (and did not redissolve on warming) formed long, dull, tan needles, m. p. 193—194°, from aqueous alcohol; yield, 0·3 g. (Found: C, 42·3; H, 2·95; N, 13·0%). Qualitatively, the differences in solubility between this substance and the 6-bromo-isomer correspond to those between the two chloro-compounds, 8-bromo-4-hydroxycinnoline being readily soluble in alcohol and in warm aqueous ammonia. The solubility in hot 6N-hydrochloric acid seemed to be no greater than in hot water (very slight in each case).

6-Nitro-4-hydroxycinnoline.—The best conditions for the large-scale preparation of this substance were the following. A mixture of 5-nitro-2-aminoacetophenone (5 g.), acetic acid (90 c.c.), concentrated sulphuric acid (15 c.c.), and water (2·5 c.c.), maintained at 0—5°, was treated with 2·17 g. of solid sodium nitrite, added during 20 minutes. The mixture was left overnight at 0°, then heated for 1 hour at 85—90°, and finally diluted with water (35—40 c.c.). The products from 11 such runs were collected; yield, 45·5 g.; m. p. 328—329°. Larger individual batches gave somewhat lower yields.

4-Hydroxycinnoline from o-Aminoacetophenone.—A solution of the amine (1·35 g.) in acetic acid (5 c.c.) was treated with a mixture of concentrated sulphuric acid (3 c.c.) and water (1 c.c.); powdered sodium nitrite (0·7 g.) was then added

with ice-cooling. After 2 days at 10°, the mixture, which still gave a strong coupling reaction, was heated on the steam-bath; much effervescence occurred. The product was diluted with water, treated with sodium acetate to neutralise most of the sulphuric acid, and extracted with ether (this extract yielded only a phenolic oil). The aqueous solution was then concentrated to crystallisation point, after which the inorganic matter was dissolved in a little warm water, and the residue of 4-hydroxycinnoline collected; yield, 0·11 g.; m. p. 227—229° after previous sintering (identified by mixed m. p.). No hydroxycinnoline could be obtained when the reaction was carried out in dilute hydrochloric acid.

4-Hydroxy-6 : 7-dimethoxycinnoline-3-acetic Acid.—β-Veratroylpropionic acid has been prepared by various workers in somewhat discordant yields (Haworth and Mavin, J., 1932, 1485; Haq, Kapur, and Ray, J., 1933, 1087; Miki and Robinson, J., 1933, 1467; Ghosh and Robinson, J., 1944, 506; Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1936, **58**, 2314; Adams, Geissman, Baker, and Teeter, *ibid.*, 1941, **63**, 528). Using the quantities given by Haworth and Mavin, we consistently obtained the yields reported by them; batches of five runs were worked up together, and the acid, after precipitation from a clarified sodium carbonate solution, had m. p. 158—160° (contrast Fieser and Hershberg, *loc. cit.*). Nitration of the acid was carried out by the method of Miki and Robinson, in 50 g. batches, and the crude product was purified by digestion with alcohol; the acid so obtained had m. p. 210—212°, the extreme yields in six experiments being 41·1 and 43·6 g. The use of stronger nitrating acid (*d* 1·48) diminished the yield owing to fission of the side chain, much 4 : 5-dinitroveratrole being isolated. Reduction of the nitro-acid was carried out in 40-g. lots; each batch was dissolved in 4N-aqueous ammonia (200 c.c.) and added to the suspension prepared from ferrous sulphate (280 g.), water (560 c.c.), and ammonia (120 c.c., *d* 0·880), after which the mixture was heated for 1½ hours on the water-bath with frequent shaking. (In one case where a deficiency of ammonia was used, the amount of iron sludge was noticeably less, and a salt of the amino-acid, only moderately soluble in cold water, separated from the hot filtrate; the yield and quality of the acid were unaffected.) Acidification of the filtered solution with acetic acid gave small brown needles, m. p. 143—144°, of β-(6-aminoveratroyl)propionic acid (extreme yields in six reductions, 32·5 and 33·0 g.).

The foregoing acid (25 g.) was warmed slightly with 2N-hydrochloric acid (250 c.c.); it dissolved only partly; and the suspension was diazotised with 10% aqueous sodium nitrite (*ca.* 70 c.c., ice-cooling). On warming the resultant dark solution, which still contained some suspended matter, complete solution occurred, soon followed by separation of prismatic needles of the free cinnoline; complete disappearance of the coupling reaction was best effected as described for 6-chloro-4-hydroxycinnoline. From seven batches, 137 g. of crude *4-hydroxy-6 : 7-dimethoxycinnoline-3-acetic acid* were obtained; the substance dissolved readily in aqueous sodium carbonate, but was too insoluble to be recrystallised from the following solvents: water, alcohol, acetic acid, nitrobenzene, pyridine, and dioxan; it decomposed at 325—330° after previous darkening and shrinking. Dissolution of the substance (137 g.) was effected by a boiling mixture of concentrated hydrochloric acid (300 c.c.) and acetic acid (700 c.c.), from which it rapidly separated in almost colourless needles (129 g.), m. p. 327—330° (decomp; blackening at 300°) (Found: N, 10·9; Cl, nil. $C_{12}H_{12}O_5N_2$ requires N, 10·6%).

Ethyl 4-Hydroxy-6 : 7-dimethoxycinnoline-3-acetate.—A solution of β-(6-aminoveratroyl)propionic acid (20 g.) in absolute alcohol (200 c.c.) and concentrated sulphuric acid (10 c.c.) was refluxed for 4 hours, diluted with water (300 c.c.), and neutralised with solid sodium bicarbonate. The suspension was then warmed on the steam-bath and set aside overnight. The *ethyl β-(6-aminoveratroyl)propionate* was filtered off and washed with a little cold water; it (17·7 g.) separated from very dilute alcohol in silky, straw-coloured needles, m. p. 103—104·5° (Found: C, 59·8; H, 6·8; N, 5·4. $C_{14}H_{19}O_5N$ requires C, 59·75; H, 6·8; N, 5·0%).

A solution of the foregoing ester (5 g.) in 2N-hydrochloric acid (50 c.c.) was diazotised in the usual way and divided into two equal parts. One part was heated on the steam-bath for ¾ hour, and the solid which separated from the cooled solution [0·85 g. (A)] was washed with water and digested with warm sodium carbonate solution. The insoluble fraction (0·35 g.), after recrystallisation from slightly aqueous acetic acid, furnished the cinnoline *ethyl* ester as almost colourless, soft, pearly leaflets, m. p. 293—294° (decomp.) (Found: C, 57·25; H, 5·55. $C_{14}H_{16}O_5N_2$ requires C, 57·5; H, 5·5%). Further heating of the diluted filtrate from (A) gave an additional 1·2 g. of solid, which was completely soluble in aqueous sodium carbonate. The remainder of the diazotised solution was left for 4 days at room temperature and then filtered; the product (0·45 g.) yielded 0·2 g. of material insoluble in aqueous sodium carbonate, and the solid obtained by further heating of the diazotised solution was almost completely soluble in this reagent.

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