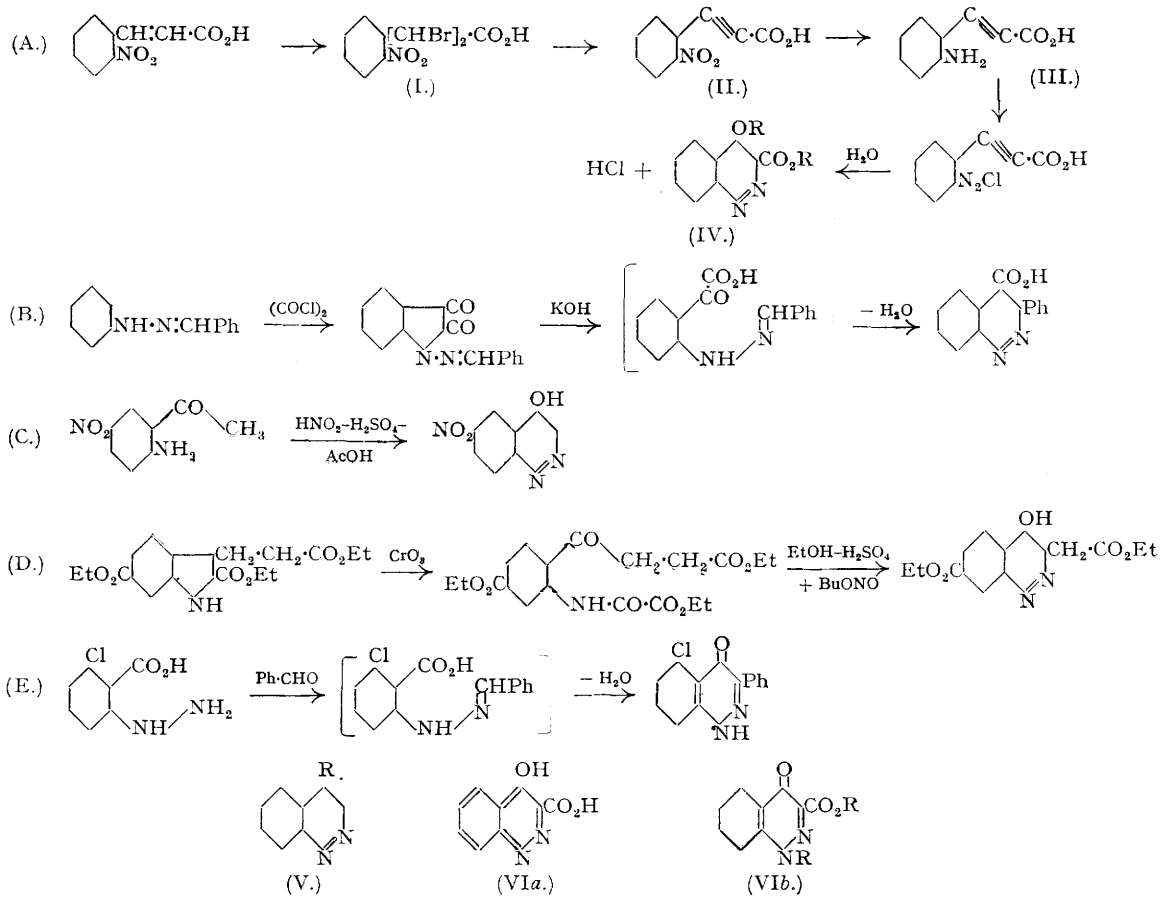
131. *Cinnolines. Part III. The Richter Reaction.*

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

The available routes to cinnolines are summarised [Widman–Stoermer reaction and reactions (A)—(E)]; one of these, the Richter reaction (A), has now been studied in some detail. The mechanism of this reaction is discussed with reference to the known electromeric behaviour of arylacetylenes, and it is shown that the success of the reaction is not dependent on the terminal carboxyl group of acids of type (III), hydroxycinnolines being obtained by reduction and diazotisation of *o*-nitrophenylacetylene and of 2-*nitro*-5-*methoxyphenylacetylene*. 2-Nitro-4 : 5-methylenedioxy- and -5-methoxy-cinnamic acid have been converted by successive bromination and dehydrobromination into the corresponding *propiolic acids*, and thence into the related *cinnolines* by reduction and diazotisation; bromination and dehydrobromination of 2-nitro-4 : 5-dimethoxycinnamic acid, on the other hand, give only the corresponding α(or β)-*bromoacrylic acid*, which could not be converted into a cinnoline. Nitration of 4-hydroxycinnoline gives mainly the 6-nitro-derivative, together with 5- and 8(or 7)-*nitro*-4-*hydroxycinnoline*. 4-*Methoxycinnoline* and the isomeric 1-*methyl*-4-*cinnolone* are described, and also three isomeric *methyl* ethers of 6-nitro-4-hydroxycinnoline.

Although the Widman–Stoermer reaction has been successfully applied in a number of cases to the synthesis of cinnolines (Widman, *Ber.*, 1884, **17**, 722; Stoermer and Fincke, *ibid.*, 1909, **42**, 3115; Stoermer and Gaus, *ibid.*, 1912, **45**, 3104; Simpson and Stephenson, J., 1942, 353; Simpson, J., 1943, 447), its usefulness as a means of studying cinnoline chemistry in general is limited by the fact that it gives rise (with one exception) to 4-arylcinnolines, a circumstance which necessarily restricts the investigation of 4-substituent reactivity. There are, however, a few scattered instances in the literature of syntheses of cinnolines in which C_4 does not carry a hydrocarbon residue. Of these, the first (A) is due to Richter (*Ber.*, 1883, **16**, 677). Method (B), leading to 3-phenylcinnoline-4-carboxylic acid, was encountered by Stollé and Becker (*ibid.*, 1924, **57**, 1123) in the course of an unsuccessful attempt to prepare *N*-aminoisatin. The third reaction (C) was recently discovered by Borsche and Herbert (*Annalen*, 1941, **546**, 293) during a study of the reactions of *o*-bromoacetophenone. Substantially the same reaction was subsequently observed by Koelsch (*J. Org. Chem.*, 1943, **8**, 295) following the synthesis of ethyl β-(2 : 6-dicarbethoxy-3-indolyl)propionate, which was converted into a cinnoline derivative by the reactions shown in (D). Lastly, Pfannstiel and Janecke (*Ber.*, 1942, **75**, 1096) have found that 5-chloro-4-hydroxy-3-phenylcinnoline (which they formulate as the isomeric cinnolone) is formed in small

yield (the main product being 4-chloroindazolone) when 6-chloro-2-hydrazinobenzoic acid is refluxed with benzaldehyde (reaction E), a synthesis which closely resembles the final stage of the Stollé–Becker reaction. It is noteworthy that, in each of the cases (B)—(E), the formation of the cinnoline was incidental to the main purpose of the investigation, and has merely been recorded without reference to any previous work.

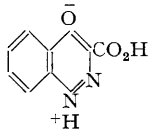
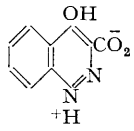


The cursory details given in the literature for the preparation of αβ-dibromo-β-(2-nitrophenyl)propionic acid (I) and *o*-nitrophenylpropiolic acid (II) were unsuitable for large-scale work, and conflicting statements have been made regarding the conversion of (III) into (IV; R = H). Thus Richter (*loc. cit.*) claimed a quantitative yield of (IV; R = H) from (III), whereas Busch and Klett (*Ber.*, 1892, **25**, 2847) found that Richter's diazotisation conditions produced large amounts of 4-chlorocarbostyril, and even under modified conditions their yield of 4-hydroxycinnoline (V; R = OH) [obtained by decarboxylation of (IV; R = H)] was only 13% of that theoretically derivable from (II). After some experience, we devised conditions which consistently gave (V; R = OH) in 39% of the theoretical amount, based on (II) [31% based on (I)]. The conditions finally adopted for the decarboxylation of (IV; R = H), after trial of several methods, consisted in heating the acid in benzophenone, this rather unorthodox procedure being the outcome of an application of the findings of Ashworth, Daffern, and Hammick (J., 1939, 809) in an attempt to determine the fine structure of Richter's acid. These authors consider that the unusually facile decarboxylation of picolinic, quinaldinic, and *iso*quinaldinic acids is conditioned by the grouping $-\overset{|}{N}:\overset{|}{C}\cdot CO_2H$ peculiar to these compounds, and involves chelation followed by formation of cyclic ions of the type $\left[\overset{\frown}{N{=}C}\right]^-$, the presence of such ions being demonstrated by their combination with aromatic aldehydes or ketones *in situ* to yield carbinols by an additive process analogous to cyanohydrin formation. In view of the extreme ease with which the acid (IV; R = H) loses carbon dioxide, it seemed possible that it, also, might have a structure (VI*a* or VI*b*; R = H) which would permit the formation of a cyclic cyanide ion. When, however, the acid was heated with benzophenone, there was no evidence of carbinol formation, the only isolable product being (V; R = OH) in yields more consistent than those obtainable by other means.

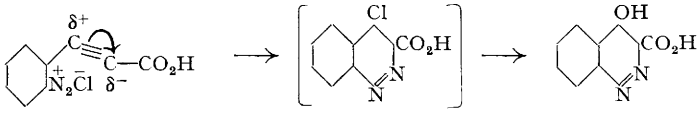
The acid (IV; R = H) cannot be esterified in alcoholic solution with either hydrogen chloride or concentrated sulphuric acid. Treatment with ethereal diazomethane gave a mixture, from which a small yield of an *ester–ether* (VI*b* or IV; R = Me), m. p. 110°, was isolated. Attempts to make the 4-acetoxy-acid were un-

successful; the acid was slowly attacked by boiling acetic anhydride to yield **4-*acetoxycinnoline*** (V; R = OAc), more conveniently obtained from 4-hydroxycinnoline and acetic anhydride either alone or in pyridine; treatment of the hydroxy-acid with acetic anhydride in pyridine, on the other hand, leads to a complex reaction, details of which will be published later. In agreement with the amphoteric nature of 4-hydroxycinnoline noted by Richter (*loc. cit.*), we find that 4-hydroxycinnoline-3-carboxylic acid reacts with more than one equivalent of sodium hydroxide, but a sharp end-point cannot be obtained with phenolphthalein as indicator. The high m. p. (268°) of the acid and its insolubility in hydrocarbon solvents are suggestive of a " zwitterion " structure [(VII*a*) or (VII*b*)]; the substance is probably best represented as a resonance hybrid involving hydrogen-bonding of the unperturbed structures (VII*a*) and (VII*b*). (The reasons for selecting N_1, rather than N_2, as the salt-forming centre will be discussed in a subsequent paper.)

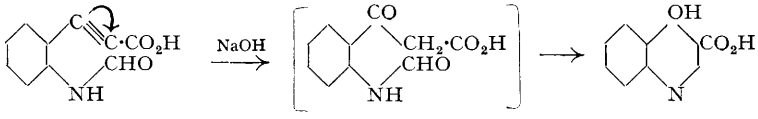
It has recently been shown (Simpson, *loc. cit.*) that the success of the Widman–Stoermer reaction depends markedly on the extent and nature of the substitution on the α- and β-carbon atoms of the relevant *o*-amino-

(VII*a*.)   (VII*b*.)

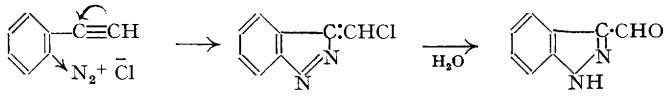
arylethylenes, and therefore it was obviously of interest to determine whether the terminal carboxyl group of the aminoacetylene is an analogous conditioning factor in the Richter synthesis. The cyclisation of the diazotised amine occurs gradually in hot acid solution, and may involve formation of the 4-chloro-acid, followed by hydrolysis (an alternative mechanism is discussed in Part IV), the initial polarisation therefore being



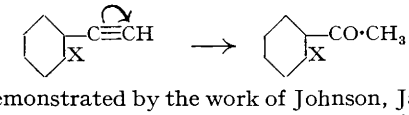
A similar polarisation of the acetylenic linkage is clearly involved in the cyclisation of *o*-formamidophenylpropiolic acid to 4-hydroxyquinoline-3-carboxylic acid (Camps, *Ber.*, 1901, **34**, 2703):



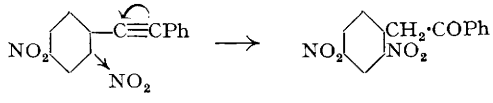
From these reactions it might be argued that the direction of the electromeric shift is determined by the electron-attractive power of the terminal carboxyl group, and that in diazotised *o*-aminophenylacetylene the direction would therefore be reversed, particularly in view of the positive charge residing on the diazonium grouping. Diazotisation of *o*-aminophenylacetylene might thus be expected to lead to indazole-3-aldehyde:



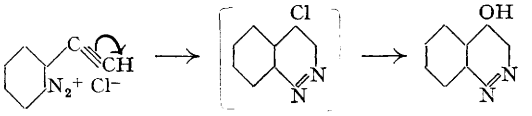
Against this view, however, is the fact that phenyl- and *o*-aminophenyl-acetylene both yield the corresponding acetophenone on hydration (Friedel and Balsohn, *Bull. Soc. chim.*, 1881, **35**, 54; Baeyer and Bloem, *Ber.*, 1884, **17**, 963), and in these reactions the aryl group clearly functions as an electron source:



This tendency is even more clearly demonstrated by the work of Johnson, Jacobs, and Schwartz (*J. Amer. Chem. Soc.*, 1938, **60**, 1885), who have shown that acetylenes of the type $CH_2{\cdot}Ar{\cdot}C{\equiv}CAr'$ on hydration yield exclusively benzylacetophenones, $CH_2Ar{\cdot}CH_2{\cdot}COAr'$, and none of the dibenzyl ketone $CH_2Ar{\cdot}CO{\cdot}CH_2Ar'$; *i.e.*, the proton mobility which might have been expected from analogy with arylacetonitriles, $Ar{\cdot}CH_2{\cdot}C{\equiv}N \longrightarrow Ar{\cdot}CH{:}C{:}NH$, has been suppressed by the reverse change $Ar{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}Ar'$. Only when the acetylenic linkage is *directly* attached to two competing aryl groups does the $\pm I$ (or *E*) effect of an *o*-substituent become the de-determining factor; *e.g.*, 2 : 4-dinitrotolan gives, as expected, 2 : 4-dinitrophenylacetophenone (*Chem. Rev.*, 1938, **23**, 247):

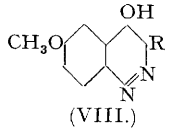


From these considerations we therefore anticipated that *o*-aminophenylacetylene should cyclise by the process:

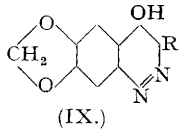


and this was in fact found to be the case, 4-hydroxycinnoline being readily isolated. It therefore seems likely that a variety of 3-substituted 4-hydroxycinnolines could be prepared from suitably substituted *o*-nitrophenylacetylenes.

It was also of interest to ascertain the extent to which substitution in the nucleus affects the Richter reaction. Of the numerous substituted *o*-nitrobenzaldehydes which have been described, the majority are not very easily available; we therefore restricted our experiments to 6-nitropiperonal (Parijs, *Rec. Trav. chim.*, 1930, **49**, 18), 2-nitro-5-methoxybenzaldehyde (Mason, J., 1925, **127**, 1196), and 6-nitroveratraldehyde (Cassaday and Bogert, *J. Amer. Chem. Soc.*, 1939, **61**, 2461). The cinnamic acids corresponding to these aldehydes have already been described (Perkin, J., 1891, **59**, 150; Chakravarti, Ganapati, and Aravamudhachari, J., 1938, 171; Kanevskaja, Schemjakin, and Bamdass-Schemjakina, *Arch. Pharm.*, 1934, **272**, 770), and it has now been found that bromination of these substances readily affords the corresponding *αβ-dibromo-β-arylpropionic acids*, the first two of which on dehydrobromination pass into the related nitroarylpropiolic acids. Similar treatment of the veratryl acid, on the other hand, gave *α*(or *β*)-*bromo*-*β*-(*2-nitro*-4 : *5-dimethoxyphenyl*)*acrylic acid*. Argument from analogy suggests the *α*-bromo-structure for this acid, since *α*-bromocinnamic acid is formed by dehydrobromination of cinnamic acid dibromide (Sudborough and Thompson, J., 1903, **83**, 666). Such a structure is also consistent with the failure of the acid to yield a cinnoline after reduction and diazotisation (Widman–Stoermer reaction). Representation of the acid as a *β*-bromo-*β*-arylacrylic acid, on the other hand, would give rise to an amino-acid which is formally capable of undergoing the Widman–Stoermer reaction, but the fact that this reaction does not occur cannot, *per se*, be used as evidence against this structure, as the limiting conditions of the reaction, so far as substitution on the *α*- and *β*-carbon atoms of the amino-ethylene is concerned, are not yet fully understood (Simpson, *loc. cit.*). From the two propiolic acids mentioned above, *4-hydroxy-6-methoxycinnoline-3-carboxylic acid* (VIII; R = CO_2H) and *4-hydroxy-6 : 7-methylenedioxycinnoline-3-carboxylic acid* (IX; R = CO_2H) were obtained in fair yield by reduction and diazotisation. *2-Nitro-5-methoxyphenylpropiolic acid* underwent decarboxylation in boiling aqueous solution to *2-nitro-5-methoxyphenylacetylene*, which, analogously to *o*-nitrophenylacetylene, gave the expected *4-hydroxy-6-methoxycinnoline* (VIII; R = H) after reduction and diazotisation. *2-Nitro-4 : 5-methylenedioxyphenylpropiolic acid* was also decomposed in boiling aqueous solution, but no crystalline product could be isolated. The two cinnoline acids (VIII and IX; R = CO_2H) were decarboxylated in benzophenone solution, yielding, respectively, 4-hydroxy-6-methoxycinnoline, identical with the specimen referred to above, and *4-hydroxy-6 : 7-methylenedioxycinnoline* (IX; R = H). When heated alone, however, the acid (VIII; R = CO_2H) gave an unexpected result, for whereas 4-hydroxycinnoline and 4-hydroxy-6 : 7-methylenedioxycinnoline are the sole isolable products from the decarboxylation of the parent acids by either method, the reaction with the methoxy-acid is more complex. The least soluble product (in alcohol) was a *substance*, m. p. 313° (decomp.), of probable formula $C_{18}H_{14}O_4N_4$ or $C_9H_8O_2N_2$. Next to this in solubility was 4-hydroxy-6-methoxycinnoline, the main product of the reaction, and the most soluble fractions formed a low-melting mixture, easily soluble in water, from which one component was isolated in small yield as a *picrate*, m. p. 197°, of probable formula $C_{15}H_{12}O_9N_4$. The reaction was accompanied by the development of an odour of indole type—a further point of contrast to the decarboxylation of the unsubstituted acid.



(VIII.)

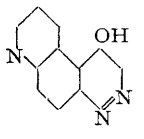


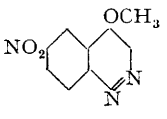
(IX.)

By the nitration of 4-hydroxycinnoline three isomeric mononitro-derivatives have been obtained, of which one, m. p. 331°, predominates; this was characterised as its *4-acetoxy*-derivative, m. p. 148°. The m. p. of this nitrohydroxycinnoline, and the colour of its solution in aqueous sodium hydroxide, suggested its identity with the 6-nitro-4-hydroxycinnoline described by Borsche and Herbert (*loc. cit.*), and a comparison of specimens prepared by each method, as well as of their acetoxy-derivatives, confirmed this. Of the remaining isomers, one, m. p. 185°, was unaffected by boiling acetic anhydride, and is therefore provisionally regarded as *5-nitro-4-hydroxycinnoline*; the other, m. p. 277°, is presumably the 8(or 7)-*analogue*. Representation of the substance, m. p. 185°, as 3-nitro-4-hydroxycinnoline, which superficially would appear to be an equally plausible alternative, seems to be excluded on grounds of analogy, Ashley, Perkin, and Robinson (J., 1930, 382) having found that 3-nitro-2 : 4-dihydroxyquinoline and its analogues are sterically unhindered and that they give, like 2 : 4-dihydroxyquinoline itself, monoacetyl derivatives [the failure of these dihydroxy-compounds to acetylate in both positions is undoubtedly bound up with the difference in acidity between 4-hydroxyquinolines and carbostyrils, of which the former give a characteristic blood-red ferric reaction which is not shown by the latter (Camps, *loc. cit.*)].

Of comparable nitrations in the heterocyclic field, that of kynurin, which would provide the closest analogy, does not appear to have been studied; carbostyril gives 6-nitrocarbostyril (Friedländer and Lazarus, *Annalen*, 1885, **229**, 233; Decker, *J. pr. Chem.*, 1901, **64**, 85), and the same position is attacked in the nitration of

2-methyl- and 2 : 3-dimethyl-4-quinazolone (Bogert and Cook, *J. Amer. Chem. Soc.*, 1906, **28**, 1449) and of " benzoylene-urea " (2 : 4-diketotetrahydroquinazoline; Bogert and Scatchard, *ibid.*, 1919, **41**, 2052). These reactions do not appear to have been studied with a view to isolating subsidiary products, and it is therefore premature to attempt to assess the theoretical significance of the side reactions encountered with 4-hydroxycinnoline. It is hoped to establish the structures of the isomers, m. p. 185° and 277°, by synthesis from appropriate aldehydes. Preliminary experiments in this direction had been started before the work of Borsche and Herbert came to our notice, the scheme then envisaged being to synthesise one and the same cinnoline analogue of phenanthroline both from the cinnoline and from the appropriate nitroquinoline aldehyde; *e.g.*,


(X.)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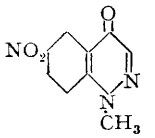
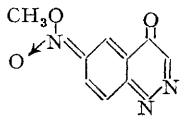

(XII.)


(XIII.)

the structure (X) could theoretically be reached from 6-nitro-4-hydroxycinnoline and 6-nitro-5-formylquinoline *via* Skraup and Richter reactions, respectively. [Substances of type (X) would also be of interest in other connexions.] This method was, however, abandoned in view of practical difficulties on the quinoline side. Thus, it has been shown in at least one case, that of 5-nitro-6-methylquinoline (Bogert and Fisher, *J. Amer. Chem. Soc.*, 1912, **34**, 1569), that the methyl group is highly resistant to oxidation, and it therefore seemed likely that the requisite nitroquinoline carboxylic acids would have to be made directly by the Skraup method. This reaction does not appear to have been tried with nitroaminobenzoic acids, and experiments with two suitably oriented acids (see Experimental) were not encouraging. Furthermore, Niemann and Hays have recently stated (*ibid.*, 1943, **65**, 482) that the Stevens–McFadyen aldehyde synthesis, which we had hoped to apply to the nitroquinoline acids, is inapplicable to *o*-nitro-acids, thus resembling the Sonn–Müller and the Stephen method.

Difficulties have also been encountered in the reduction of 6-nitro-4-hydroxycinnoline, and none of the methods so far tried has yielded an appreciable quantity of the corresponding amine. As this might be in part due to the difficulty of isolating an amphoteric substance, we examined the action of methyl sulphate on the nitro-compound. Under the usual alkaline conditions, this led, surprisingly, to extensive decomposition and formation of a tar, but by the action of excess of methyl sulphate on 6-nitro-4-hydroxycinnoline dissolved in the minimum of alkali an almost quantitative yield of crystalline methylated product was secured. This proved to be a mixture of isomeric pale yellow and orange *methyl ethers*, m. p. 183° and 229°, respectively, of which the latter predominated. The deep colour of this substance suggested *N*- rather than *O*-methylation, and we therefore regarded the yellow and the orange compound as 6-nitro-4-methoxycinnoline (XI) and 6-nitro-1-methyl-4-cinnolone (XII), respectively. Methylation of 4-hydroxycinnoline, however, gave a colourless *methyl ether*, m. p. 165°, as almost the sole product of reaction; this was isomeric with the 4-*methoxycinnoline* (V; R = OMe), m. p. 128°, which resulted from the action of sodium methoxide on 4-chlorocinnoline (cf. Busch and Klett, *loc. cit.*), and since *O*-methylation must unquestionably have occurred in the latter reaction, the isomer, m. p. 165°, must be 1-methyl-4-cinnolone (XII; H instead of NO_2). The complete lack of colour of this substance, together with the fact that in this case the reaction with methyl sulphate was effected under normal (*i.e.*, alkaline) conditions, suggested that the orange nitro-ether, m. p. 229°, might have the nitronate structure (XIII). Further evidence in support of this view was obtained by the preparation of a third isomeric nitro-ether, m. p. 194°, by treatment of 4-chloro-6-nitrocinnoline with sodium methoxide; this ether is undoubtedly 6-*nitro*-4-*methoxycinnoline* (XI), and the isomers, m. p. 183° and 229°, are accordingly formulated as 6-*nitro*-1-*methyl*-4-*cinnolone* (XII), and the *methyl nitronate* (XIII).

Experimental.

(Melting points are uncorrected.)

4-Hydroxycinnoline-3-carboxylic acid.—It was possible to nitrate cinnamic acid by the normal method (Beilstein, Vol. IX, p. 604) in 200-g. batches, but batches of 100 g. were found to be more convenient. Ethyl *o*-nitrocinnamate (50 g., m. p. within the range 35—42°) was hydrolysed by boiling it for 15 minutes with a mixture of equal volumes of water, acetic acid, and concentrated sulphuric acid (250 c.c.); the crude acid was digested with alcohol and then had m. p. 238°. The acid (50 g.) was refluxed very gently for ½ hour with a solution of bromine in acetic acid (200 c.c. of 30% by weight). Dilution with an equal volume of water gave 72 g. of crude *o*-nitrophenyldibromopropionic acid, m. p. 165—170°, which after one crystallisation from acetic acid (120 c.c.) formed dense, yellow needles, m. p. 184—186° (decomp.) (52 g., 57%). A sample, after two further crystallisations from acetic acid, had m. p. 185—186° (Baeyer, *Ber.*, 1880, **13**, 2257, gives m. p. 180°) (Found : C, 30·35; H, 2·2; Br, 44·75. Calc. for $C_9H_7O_4NBr_2$: C, 30·6; H, 2·0; Br, 45·3%). A solution of the dibromo-acid (50 g.) in 10% sodium hydroxide solution (300 c.c.) was left for 10 hours at room temperature and then poured into 2N-nitric acid (500 c.c.). The crude *o*-nitrophenylpropiolic acid, after thorough washing and drying in an exhausted desiccator, had m. p. 145—146° (decomp.), raised to 161—163° (decomp.) by digestion with three 100-c.c. portions of boiling chloroform (yield, 22 g. or 79%). For analysis a portion was crystallised from hot water, from which it separated in fine colourless needles, m. p. 166—167° (decomp.) (Baeyer, *loc. cit.*, gives m. p. 155—156°) (Found : C, 55·6; H, 2·95; N, 7·5. Calc. for $C_9H_5O_4N$: C, 56·5; H, 2·6; N, 7·3%). The acid (20 g.) in water (60 c.c.) and aqueous ammonia (9 c.c., *d* 0·880) was added with shaking during 15 minutes to a mixture prepared from ferrous sulphate crystals (220 g.), water (440 c.c.), and aqueous ammonia (110 c.c., *d* 0·880). After ¾ hour, with occasional shaking but no external cooling, the suspension was filtered, the residue washed, and the combined filtrates treated with ammonium acetate (60 g.) and made faintly acid with acetic acid. The solution was cooled to 0° by addition of crushed

ice, and then made acid to Congo-red with concentrated hydrochloric acid (70—80 c.c.); at this stage, separation of the amino-acid sometimes commenced. More hydrochloric acid (20 c.c., 2N) was immediately added, and the turbid solution diazotised with 20% aqueous sodium nitrite, after which it was kept at 70°. The cinnoline acid separated during ¾ hour as a dark brown, granular solid, m. p. 260—265° (yield about 12·5 g. from either crude nitrophenylpropiolic acid or material purified by chloroform digestion). After two crystallisations from acetic acid, the acid formed a mixture of almost colourless, fine silky needles and light brown, compact, prismatic needles, m. p. 268—268·5° (decomp.), as described by Richter (*loc. cit.*), who gives m. p. 260—265° (Found: C, 57·3; H, 3·15; N, 14·5. Calc. for $C_9H_6O_3N_2$: C, 56·8; H, 3·2; N, 14·7%).

A suspension of the foregoing acid (0·5 g.) in excess of ethereal diazomethane gave a play of colours (green → blue → red), changing to brown on standing over-night. The solution was filtered from amorphous material (A), the solvent removed, and the brown oily residue dissolved in benzene–ligroin (b. p. 40—60°). After two months the solution crystallised; the first crop (m. p. 115—128°) was removed, whereupon a second crop was quickly deposited; two crystallisations of this from benzene–ligroin gave yellow needles, m. p. 109—110° (40 mg.) of the *ester–ether* (Found: C, 61·15; H, 4·85; N, 13·1; OMe, 16·75. $C_{11}H_{10}O_3N_2$ requires C, 60·55; H, 4·6; N, 12·8; OMe, 14·2%). Extraction of (A) with benzene left a deep blue residue, m. p. 148—150°, which has not been investigated.

4-*Hydroxycinnoline.*—(*a*) A mixture of 4-hydroxycinnoline-3-carboxylic acid (10 g.) and benzophenone (50 g.) was heated at 205—210° (oil-bath) for 2½ hours. The cooled mass was then broken up, warmed with ether (150 c.c.), and the whole extracted with 5N-hydrochloric acid (4 × 50 c.c.). The filtered acid extracts were concentrated on the steam-bath to 20 c.c., whereupon 4-hydroxycinnoline hydrochloride separated, m. p. 205—207° after crystallisation from concentrated hydrochloric acid; the salt is very easily hydrolysed. For preparative purposes, the hydrochloride was not isolated, but hydrolysed by treatment of its warm solution in hydrochloric acid with sodium acetate solution; 4-hydroxycinnoline (about 5 g.) was thus obtained as a light fawn solid, which after crystallisation from glacial or aqueous acetic acid formed slightly discoloured leaflets or small needles, m. p. 233·5—234° (lit. 225°) (Found: C, 65·5; H, 4·1; N, 18·6. Calc. for $C_8H_6ON_2$: C, 65·75; H, 4·1; N, 19·2%). Variable yields of 4-hydroxycinnoline were obtained when the acid was heated alone. Heating the acid dispersed in medicinal paraffin gave unsatisfactory results. No crystalline product could be isolated when the acid was heated in quinoline.

(*b*) *o*-Nitrophenylpropiolic acid (1 part, purified by digestion with chloroform) was refluxed with water (160 parts) for 20 hours, giving *o*-nitrophenylacetylene in 66% yield (compare Kippenberg, *Ber.*, 1897, **30**, 1130). The compound is very volatile in steam, and was washed out periodically from the condenser by means of ether. It has a pronounced but not unpleasant smell, and crystallises very readily from aqueous alcohol in long, colourless needles, m. p. 81—82° (lit. 81—82[5]). It (1·5 g.) was reduced with zinc dust and ammonium hydroxide according to Baeyer and Bloem (*loc. cit.*), after which the reaction mixture was extracted with ether (40 c.c.). The ethereal solution was extracted with several portions (40 c.c. in all) of 2N-hydrochloric acid; the acid extract was then cooled to 2—3° and treated with aqueous sodium nitrite (6·3 c.c. of 5%). Half of the solution so obtained was heated at 70° for 1 hour (a pungent phenolic smell developed) and then extracted with ether. This extract gave 90 mg., and the aqueous solution, after concentration, a further 170 mg., of 4-hydroxycinnoline, m. p. 225—227°. Each crop was identified by mixed m. p. with authentic material, and by conversion into 4-acetoxycinnoline (*q.v.*), m. p. and mixed m. p. 128—130°. The remainder of the diazotised solution was left at room temperature for a week; it then gave a negative coupling reaction with β-naphthol, and yielded 4-hydroxycinnoline when worked up as described above.

4-*Acetoxycinnoline.*—This *substance* was prepared by refluxing 4-hydroxycinnoline (1 part) with acetic anhydride (3 parts); it separated from slightly aqueous alcohol in fawn needles, m. p. 127—128° (Found: C, 64·15; H, 4·65; N, 15·0. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3; N, 14·9%).

4-*Methoxycinnoline.*—A solution of 4-chlorocinnoline (0·5 g.; Busch and Klett, *loc. cit.*) in absolute methanol (5 c.c.) was added to one of sodium methoxide (0·25 g.) in methanol (15 c.c.), and the whole refluxed for 1 hour. After 2 hours at room temperature, water was added (15 c.c.), and most of the alcohol removed on the steam-bath. The resultant suspension of crystalline material was extracted with ether, the dried and evaporated extract yielding 4-*methoxycinnoline* (330 mg.), very sparingly soluble in water, slightly soluble in ligroin, and very easily soluble in alcohol. The substance formed colourless needles from ether–ligroin, m. p. 127—128° to a green melt which quickly turned red (Found: C, 67·2; H, 5·0. $C_9H_8ON_2$ requires C, 67·5; H, 5·0%).

4-*Ethoxycinnoline.*—This was prepared in a similar manner (0·5 g. of 4-chlorocinnoline in 5 c.c. of absolute alcohol added to a solution of 0·1 g. of sodium in 15 c.c. of alcohol); 0·44 g. of crude ether, m. p. 100—101°, was obtained. It crystallised from ligroin in long, silky, colourless needles, m. p. 101—102° to a colourless liquid (Busch and Klett, *loc. cit.*, give m. p. 106°) (Found: C, 68·75; H, 5·5. Calc. for $C_{10}H_{10}ON_2$: C, 69·0; H, 5·75%).

1-*Methyl*-4-*cinnolone.*—A solution of 4-hydroxycinnoline (0·5 g.) in 20% aqueous potassium hydroxide (12 c.c.) was treated at 50° with methyl sulphate (0·5 g.). The temperature was raised to 70°, and a further 0·5 c.c. of potassium hydroxide solution added. After 10 minutes, more alkali (1 c.c.) was added, and the cooled solution extracted with chloroform (50 c.c. in all). The extract was dried (sodium sulphate) and evaporated, and the residue (0·5 g.) repeatedly digested with ether (5 × 10 c.c.). The material so obtained (320 mg., m. p. 160—163°) was crystallised from chloroform–ether, yielding dull fawn needles of 1-*methyl*-4-*cinnolone*, m. p. 165—166·5° (Found: C, 63·9; H, 5·25. $C_9H_8ON_2,\frac{1}{2}H_2O$ requires C, 63·9; H, 5·3%).

6-*Nitro*-4-*hydroxycinnoline.*—(*a*) 4-Hydroxycinnoline (8 g.) was added during ¾ hour to a mixture of nitric acid (16 c.c., *d* 1·48) and concentrated sulphuric acid (13 c.c.) with stirring at 30°. After a further 4 hours, the solution was poured into water, and the precipitated solid crystallised from acetic acid (450 c.c.), giving 4·65 g. (44%) of dense red-brown prismatic needles, m. p. 327—329°. A further crystallisation gave the pure 6-nitro-compound, m. p. 330—331° alone and when mixed with a sample of the same m. p. prepared from 5-nitro-2-aminoacetophenone by the method of Borsche and Herbert (*loc. cit.*) (Found: C, 49·2; H, 2·95; N, 21·3. Calc. for $C_8H_5O_3N_3$: C, 50·3; H, 2·6; N, 22·0%). Acetylation of each sample (acetic anhydride under reflux) gave 6-*nitro*-4-*acetoxycinnoline*, which separated from alcohol in almost colourless plates (sometimes mixed with discoloured needles), m. p. 147—148° (Found: C, 51·55; H, 3·2; N, 18·2. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0; N, 18·0%).

(*b*) 4-Hydroxycinnoline (2 g.) was added in one portion to nitric acid (6 c.c., *d* 1·48); the temperature of the resultant solution rose to 50°, and was maintained at 50—53° for 3 hours. On pouring into water (20 c.c.), 1·65 g. of mixed nitro-compounds were precipitated. This material was dried, digested with boiling benzene–alcohol (1 : 1, 20 c.c.), and filtered after 24 hours at room temperature. The resultant solid (1·35 g., m. p. 288—293°) was extracted with boiling acetic acid (50 c.c.), and the insoluble fraction recrystallised from more of the same solvent, giving 0·55 g., m. p. 329—331° alone and when mixed with the sample prepared as in (*a*). The acetic acid extract was filtered cold (filtrate A), and the product (0·57 g.) digested with benzene–alcohol, yielding a further 0·27 g. of almost pure material, m. p. 326—329°. 6-Nitro-4-hydroxycinnoline forms hard brown needles, which powder to a light yellow solid; it is soluble in aqueous sodium carbonate and sodium hydroxide, moderately soluble in hot acetic acid, and practically insoluble in benzene, alcohol, acetone, and ether.

5-*Nitro*-4-*hydroxycinnoline.*—The acetic acid filtrate (750 c.c.) from the recrystallisation of crude 6-nitro-4-hydroxy-

cinnoline [prepared by method (*a*) above] was evaporated to dryness, and the resultant solid (2·3 g., m. p. 165—250°) digested with boiling acetone (100 c.c.); 0·33 g. of 6-nitro-4-hydroxycinnoline remained undissolved, and the filtrate on standing deposited dense brown prisms (B), m. p. 178—200° (0·77 g.), and, on concentration, a second crop (C), m. p. 165—177° (1·05 g.). A solution of (B) in acetone (50 c.c.) yielded, first, a mixture (0·25 g., m. p. 178—200°), followed by light yellow needles (0·3 g., m. p. 178—180°), which on repeated crystallisation from alcohol gave *5-nitro-4-hydroxycinnoline*, m. p. 184—186°. This substance is soluble in sodium carbonate and sodium hydroxide solutions, and moderately soluble in hot acetone and alcohol; it separated from the latter as a mixture of yellow needles and tablets (Found: N, 21·9%). A solution of (C) in acetone (40 c.c.) gave a further 0·5 g. of the 5-nitro-compound as the least soluble fraction, and, after concentration, a small fraction (90 mg.) which after crystallisation melted at 275—280° (after considerable previous softening) alone and when mixed with 8(or 7)-nitro-4-hydroxycinnoline (*q.v.*). 5-Nitro-4-hydroxycinnoline was quantitatively recovered after it had been refluxed with acetic anhydride, thus affording additional evidence of homogeneity.

8(or 7)-*Nitro*-4-*hydroxycinnoline*.—The benzene–alcohol mother-liquors from 6-nitro-4-hydroxycinnoline [experiment (*b*)] were combined with the acetic acid filtrate (A), the solvent removed, and the residual solid digested with acetone (30 c.c.) and filtered from a little crude 6-nitro-compound. The acetone filtrate was concentrated until it crystallised in the hot, yielding 0·23 g. of a solid, m. p. 269—272°, which, after several crystallisations from alcohol, gave 8(or 7)-*nitro*-4-*hydroxycinnoline* as soft, light brown needles, m. p. 276·5—277·5° easily soluble in hot alcohol (Found: C, 49·75; H, 2·95; N, 21·05%).

4-*Chloro*-6-*nitrocinnoline*.—6-Nitro-4-hydroxycinnoline (2 g.) was added to a mixture of phosphorus pentachloride (4 g.) and oxychloride (6 g.), and the whole heated at 95° for 1 hour. The product was poured on ice, just basified with sodium hydroxide solution, and extracted with ether. Concentration of the dried (sodium sulphate) extract gave 1·72 g. of lustrous, ginger-coloured plates, m. p. 135—137°. As this highly reactive substance decomposed rapidly on keeping for a few hours, it was not analysed, but was characterised by conversion into the 6-*nitro*-4-*anilino*-derivative; the chloro-compound (0·2 g.) was heated at 95° for ¾ hour with aniline (2 c.c.), and the resultant solid collected and combined with a further crop obtained by dilution of the filtrate with ether. After crystallisation from weakly ammoniacal alcohol and then from aqueous alcohol, the substance formed silky, deep orange needles, m. p. 228·5—229·5°, which showed a characteristic lag in crystallising (Found: C, 63·15; H, 3·8; N, 21·35. $C_{14}H_{10}O_2N_4$ requires C, 63·2; H, 3·8; N, 21·05%).

6-*Nitro*-4-*methoxycinnoline*.—A solution of 6-nitro-4-chlorocinnoline (1·3 g.) in benzene (25 c.c.) was added to one of sodium methoxide (0·69 g.) in dry methanol (10 c.c.). Solid quickly separated from the deep red solution, and after standing for 2 days with occasional shaking, the whole was diluted with water, acidified with acetic acid, and extracted with ether. The extract was washed with sodium carbonate solution (60 c.c., 2N) and a little water, and the washings added to the aqueous layer, which contained much suspended solid. This suspension was made strongly alkaline with sodium hydroxide solution, and the remaining solid collected (0·21 g., m. p. 191—193°). Acidification of the filtrate with acetic acid precipitated 0·6 g. of 6-nitro-4-hydroxycinnoline, m. p. 319—323° alone and mixed with an authentic specimen. The concentrated ethereal extract gave 0·23 g. of yellow prismatic needles, which after one crystallisation from alcohol had m. p. 186—188° and gave no depression with the alkali-insoluble material, m. p. 191—193°. Both crops were combined and crystallised thrice from alcohol, yielding dull yellow needles of 6-*nitro*-4-*methoxycinnoline*, m. p. 194—194·5° (Found: C, 52·1; H, 3·7. $C_9H_7O_3N_3$ requires C, 52·7; H, 3·4%).

Methylation. This nitro-compound (1 g.) was dissolved in the minimum (3·04 c.c.) of 2% aqueous potassium hydroxide and warmed to 50°; methyl sulphate (0·5 c.c.) was added, and the mixture stirred briskly. A yellow solid separated, which was filtered cold after a few minutes. This product (0·87 g., m. p. 171—176°) was crystallised from alcohol (25 c.c.), and after two further crystallisations the *substance* (XIII) separated in orange flakes, m. p. 228—229°, unchanged by digestion with ether and further crystallisation from alcohol (Found: C, 52·65; H, 3·65. $C_9H_7O_3N_3$ requires C, 52·7; H, 3·4%). Concentration of the original alcoholic filtrate gave 0·21 g. of a light yellow solid, from which, after four further crystallisations, 6-*nitro*-1-*methyl*-4-*cinnolone* was obtained as silky, mustard-yellow needles, m. p. 183—183·5° (168—169° when mixed with 6-nitro-4-methoxycinnoline) (Found: C, 52·8; H, 3·5%). Methylation on a larger scale gave, in addition to these two ethers, material not identical with either but which has not yet been obtained pure.

Reduction of 6-*Nitro*-4-*hydroxycinnoline*.—(*a*) Iron powder (0·5 g.) was added in four portions at 5-minute intervals to a refluxing suspension of the nitro-cinnoline (0·5 g.) in a mixture of methylated spirit and concentrated hydrochloric acid (25 : 1, 5·5 c.c.). After being refluxed for 2 hours, the filtered solution was concentrated, yielding 80 mg. of a crystalline solid, which after repeated crystallisation from hot water gave yellow needles of, apparently, somewhat impure 6-*amino*-4-*hydroxycinnoline*, m. p. 269—270° (Found: C, 58·55; H, 4·55; N, 26·1. $C_8H_7ON_3$ requires C, 59·6; H, 4·4; N, 26·1%). No further organic material could be isolated.

(*b*) A solution of the nitro-compound (1·5 g.) in glacial acetic acid (200 c.c.) was treated at 90—95° with iron powder (2·3 g., added during 1 hour with frequent shaking); additions of water (10, 20, 20 c.c.) were made at intervals of 20, 60, and 90 minutes from the start of the reaction. After 2½ hours the mixture was largely diluted with water and extracted with ether (extract A). This extract was filtered, washed with sodium carbonate solution, dried, and evaporated, giving 0·39 g. of a mixture from which, as sole isolable product, a water-soluble substance (70 mg., m. p. 288—291°) was obtained, apparently different from the amine obtained in (*a*); it was not investigated further. Re-extraction with ether of the combined aqueous solution and sodium carbonate washings from extract (A), after basification with ammonia, gave only 50 mg. of solid, m. p. 288—303°. The aqueous ammoniacal solution was then evaporated to dryness, and the thoroughly dry residue refluxed with acetic anhydride (5 c.c.) for ½ hour. Water was then added, and the insoluble fraction (0·27 g.) crystallised twice from acetic acid, yielding a *substance* which formed rosettes of white prisms, m. p. 328—329° [Found: C, 57·55; H, 5·05. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·5% (monoacetyl derivative). $C_{12}H_{11}O_3N_3$ requires C, 58·75; H, 4·5% (diacetyl derivative)].

4-*Hydroxy*-6-*methoxycinnoline*-3-*carboxylic Acid*.—2-Nitro-5-methoxycinnamic acid (25 g.), m. p. 227° (lit., 227°), was heated at 95° for ¼ hour with a solution of bromine in glacial acetic acid (75 c.c. of 30% by weight). After addition of water (60 c.c.), the crude solid was collected, dried, and purified by extraction with benzene (8 × 100 c.c.); the filtered extracts were concentrated to 400 c.c., giving 22 g. (51%) of brown prismatic needles of *β*-(2-*nitro*-5-*methoxyphenyl*)-*αβ*-*dibromopropionic acid*, m. p. 150—155° (decomp.), sufficiently pure for the next stage. In the preparation of an analytical specimen, alcohol was used at one stage of the purification, and, after further crystallisations from benzene, light yellow, solvated prisms were obtained, m. p. 156—157° (decomp.) (Found: C, 32·95; H, 3·15. $C_{10}H_9O_5NBr_2,\frac{1}{2}C_2H_5OH$ requires C, 32·5; H, 3·0%).

A solution of the foregoing acid (20 g.) in aqueous sodium hydroxide (400 c.c. of 10% and 300 c.c. of water) was left at 5° for 14 hours and then poured into 2N-nitric acid (500 c.c.). The crude 2-*nitro*-5-*methoxyphenylpropiolic acid* so obtained (8—9 g.) had m. p. 144° (decomp.), and after several crystallisations from benzene, in which it is somewhat sparingly soluble, formed small colourless needles, m. p. 155·5° (decomp.) [Found (mean of two analyses): C, 53·3; H, 3·5. $C_{10}H_7O_5N$ requires C, 54·3; H, 3·2%]. The acid is easily soluble in alcohol.

The propiolic acid (10 g.) was dissolved in concentrated aqueous ammonia (15 c.c.) and water (70 c.c.), and the solution was added during ¼ hour with continuous shaking to ferrous hydroxide (from ferrous sulphate, 100 g.; water, 200 c.c.;

concentrated ammonia, 50 c.c.). After ¾ hour the solution was filtered, cooled to 0°, treated with 2N-hydrochloric acid (160 c.c.), and diazotised with the theoretical amount of 5% aqueous sodium nitrite. The resultant clear brown solution was quickly warmed to 75°, and the solid which separated in a few minutes was collected after ¾ hour (6·8 g., m. p. 256—258°). Two crystallisations from aqueous acetic acid gave glistening, slightly coloured leaflets of *4-hydroxy-6-methoxycinnoline-3-carboxylic acid*, m. p. 268° (decomp.) (Found: C, 53·35; H, 3·95; N, 12·3. $C_{10}H_8O_4N_2$ requires C, 54·55; H, 3·6; N, 12·7%). The acid is fairly soluble in glacial and aqueous acetic acid, and the solutions show marked blue fluorescence; it is slightly soluble in alcohol, dioxan, and methyl ethyl ketone, and virtually insoluble in benzene, ethyl acetate, and water.

4-Hydroxy-6-methoxycinnoline.—(*a*) After the foregoing acid (10 g., crude) had been heated for 2 hours at 210° with benzophenone (50 g.), the product from two batches was extracted with boiling ether, and the insoluble residue (14·6 g., m. p. 225—230°) repeatedly extracted with boiling water (5 l. in all; charcoal). The filtered solution on concentration gave *4-hydroxy-6-methoxycinnoline* (10 g., 62·5%), m. p. 253—255°. An analytical specimen, obtained by recrystallising this material from water, formed fine white needles, m. p. 255—256° (Found: N, 16·0. $C_9H_8O_2N_2$ requires N, 15·9%). The substance crystallises well from hot water, in which it gives a blue fluorescent solution.

(*b*) Pure 2-nitro-5-methoxyphenylpropiolic acid (0·52 g.) was refluxed with water (70 c.c.) for 5 hours. The solid in the condenser was collected with ether and combined with the ethereal extract of the aqueous solution which had been made alkaline with sodium carbonate. The residue from the dried and evaporated ethereal solution was crystallised from aqueous alcohol, giving colourless needles of *2-nitro-5-methoxyphenylacetylene*, m. p. 96—97° (0·2 g.) (Found: C, 60·85; H, 3·75. $C_9H_7O_3N$ requires C, 61·0; H, 4·0%). The substance is considerably less volatile, and has a less pronounced odour, than *o*-nitrophenylacetylene. The acetylene (140 mg.) was reduced with water (1·75 c.c.), concentrated aqueous ammonia (1 c.c.), and zinc dust (0·45 g.) at 40° during 10 minutes. After a further 20 minutes at room temperature, the product was extracted with ether, and the base taken into 2N-hydrochloric acid (7 c.c.). The acid solution was diazotised with aqueous sodium nitrite (0·9 c.c. of 5%), kept at 75° for ¾ hour, and then evaporated to 3 c.c. The deposited solid (60 mg.) was collected and crystallised from water, yielding fine, hair-like needles, m. p. 252—253°, undepressed by admixture with the specimen described in (*a*). The neutral ethereal solution contained 40 mg. of impure nitro-acetylene.

Action of Heat on 4-Hydroxy-6-methoxycinnoline-3-carboxylic Acid.—The crude acid (2 g.) was heated under an air-condenser for 2 hours at 265—275° (bath temp.). Light-brown needles sublimed, a hard black solid cake was formed in the flask, and a powerful and repulsive odour developed. The whole product was extracted with alcohol (6 × 25 c.c.), leaving 0·47 g. of black intractable granular material which did not melt at 330°. The brown, fluorescent, alcoholic solution was concentrated to half volume, giving 130 mg. of a solid (A), m. p. 313—323°. The filtrate was again taken to half volume, yielding a solid (B), m. p. 225—230° (130 mg.). The filtrate from this fraction was evaporated to dryness, leaving 0·48 g. of solid, m. p. 105—120°, soluble in hot water and very soluble in the alcohols. By crystallising a portion from hot water, traces of impure 4-hydroxy-6-methoxycinnoline could be isolated. When the solid (0·24 g.) was dissolved in alcohol (3 c.c.), and the same weight of picric acid added, 70 mg. of a yellow *picrate* were obtained. This was very sparingly soluble in alcohol, and after two crystallisations formed soft, bright yellow needles, m. p. 195—197° (Found: C, 45·85; H, 3·3. $C_9H_9O_2N,C_6H_3O_7N_3$ requires C, 45·9; H, 3·1%).

Solid (B) was impure 4-hydroxy-6-methoxycinnoline (m. p. 247—253° after crystallisation; identified by mixed m. p.). Solid (A) was crystallised from alcohol, in which it was sparingly soluble; the *substance* so obtained formed pale yellow, prismatic needles, m. p. 313° (decomp.) (Found: C, 61·1; H, 4·5; N, 15·65. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·5; N, 15·9%. $C_{18}H_{14}O_4N_4$ requires C, 61·7; H, 4·0; N, 16·0%).

4-Hydroxy-6 : 7-methylenedioxycinnoline-3-carboxylic Acid.—2-Nitro-4 : 5-methylenedioxycinnamic acid was prepared by heating 6-nitropiperonal (60 g.), malonic acid (68·6 g.), pyridine (100 c.c.), and piperidine (3 c.c.) at 100° for 1½ hours, and finally boiling for 10 minutes. The crude acid, isolated by means of hydrochloric acid, had m. p. 271—273° (70 g., 96%), unchanged by digestion with boiling alcohol, from which it separated in pale yellow needles [Perkin, *loc. cit.*, gives m. p. 240° (decomp.)] (Found: C, 51·1; H, 3·35; N, 6·4. Calc. for $C_{10}H_7O_6N$: C, 50·6; H, 2·95; N, 5·9%). The acid (10 g.) was refluxed for ½ hour with bromine in glacial acetic acid (30 c.c. of 30% by weight) and then diluted with water (2 vols.). The crude solid, easily soluble in alcohol, acetic acid, and ether, was crystallised from ether–ligroin (b. p. 40—60°), giving almost pure *αβ-dibromo-β-(2-nitro-4 : 5-methylenedioxyphenyl)propionic acid*, m. p. 174—175° (9 g.); a sample purified for analysis had m. p. 180—181° and formed light yellow cubes (Found: C, 30·35; H, 2·1; N, 4·25. $C_{10}H_7O_6NBr_2$ requires C, 30·25; H, 1·8; N, 3·5%). This acid (20 g.) was dissolved in water (230 c.c.) containing sodium hydroxide (17·5 g.) and left at 5° for 12 hours. The sodium salt which had separated was filtered off, dissolved in water, and added to dilute nitric acid, giving 9 g. (76%) of crude *2-nitro-4 : 5-methylenedioxyphenylpropiolic acid*, m. p. 140—144° (decomp.). The acid was somewhat difficult to purify, but the crude product was suitable for reduction. Crystallisation from aqueous dioxan raised the m. p. to 148°, but involved considerable loss of material. For analysis the crude acid was crystallised thrice from aqueous alcohol, from which it separated in fawn prismatic needles, decomposing at 155° (Found: C, 51·2; H, 2·55. $C_{10}H_5O_6N$ requires C, 51·1; H, 2·1%).

A solution of the propiolic acid (4 g.) in water (52 c.c.) and ammonia (36 c.c., *d* 0·880) was reduced in the usual way with ferrous sulphate (36 g.), water (72 c.c.), and ammonia (18 c.c.). The ice-cold filtered solution was treated with 2N-hydrochloric acid (120 c.c.) and immediately diazotised with aqueous sodium nitrite (16 c.c. of 5%). The solution was filtered from some amorphous material which did not melt at 330° (possibly the related carbostyril) and heated rapidly to 75° for ½ hour. The precipitated *4-hydroxy-6 : 7-methylenedioxycinnoline-3-carboxylic acid* was collected (1·46 g.) and crystallised from slightly aqueous acetic acid, from which it separated in small almost colourless prismatic needles, m. p. 276—278° (decomp.) (Found: C, 50·7; H, 2·65. $C_{10}H_6O_5N_2$ requires C, 51·3; H, 2·6%). The acid is virtually insoluble in alcohol and acetone, difficultly so in glacial acetic acid, and more readily in aqueous acetic acid and in nitrobenzene.

4-Hydroxy-6 : 7-methylenedioxycinnoline.—Decarboxylation of the crude acid was effected in benzophenone in the usual way, and the product worked up with ether and hydrochloric acid in the manner already described. *4-Hydroxy-6 : 7-methylenedioxycinnoline* (yield, 23%) was sparingly soluble in water, alcohol, and acetone, and easily so in glacial and aqueous acetic acid, from which it separated in long, glistening, light brown needles, which decomposed at 316—318° without melting (Found: C, 57·4; H, 3·1. $C_9H_6O_3N_2$ requires C, 56·8; H, 3·2%). Decarboxylation of the cinnoline acid by heating it alone at 280—290° gave much intractable amorphous material, from which a 10% yield of the hydroxycinnoline, m. p. and mixed m. p. 316—318°, was obtained by extraction with alcohol.

Derivatives of 2-Nitro-4 : 5-dimethoxycinnamic Acid.—This acid, prepared from 6-nitroveratric aldehyde (Cassaday and Bogert, *loc. cit.*), by the same method as that described for 2-nitro-4 : 5-methylenedioxycinnamic acid, had m. p. 292° after crystallisation from acetic acid (lit. m. p. 281—282°) (Found: C, 51·65; H, 4·7; N, 5·9. Calc. for $C_{11}H_{11}O_6N$: C, 52·2; H, 4·4; N, 5·5%).

The acid (2 g.) was heated at 95° for 1 hour with a solution of bromine in acetic acid (6 c.c. of 30% by weight). The solution was cooled, treated with water (9 c.c.), and the precipitated acid collected and washed (2·84 g., m. p. 109—110°, unchanged after being dried for 2 days at 50°). The product was digested with boiling benzene (4 × 25 c.c.), the extract

yielding prismatic needles (0·93 g.) of the *dibromo-acid*, which had m. p. 135—138°, followed by solidification and remelting at 160—163° (decomp.). After further crystallisation from benzene the substance formed lustrous, light yellow prisms, m. p. 172—173° (decomp.) after being dried for 7 hours at 65° and 0·03 mm. (Found: C, 32·05; H, 2·55. $C_{11}H_{11}O_6NBr_2$ requires C, 32·0; H, 2·7%). The residue from the above benzene extraction was crystallised from 50% aqueous alcohol; light brown prismatic needles separated, m. p. 112—114° followed by solidification and remelting at 160—163° (decomp.) (0·94 g.). Two further crystallisations from aqueous alcohol gave light yellow needles, m. p. 154—156° (decomp.) after being dried for 10 hours at 65° and 0·05 mm. (Found: C, 32·0; H, 2·75%). Neither this sample nor that obtained from benzene gave a satisfactory bromine determination (Found: Br, 34·0 and 35·75, respectively. $C_{11}H_{11}O_6NBr_2$ requires Br, 38·7%).

Preliminary experiments showed that each form of the above dibromo-acid gave the same substance on dehydrobromination. The crude acid (5·5 g.) was accordingly dissolved in sodium hydroxide solution (83 c.c. of 10%) and water (108 c.c.). After 12 hours at room temperature the solution was worked up as described for previous cases. The crude product (3·75 g.) was crystallised repeatedly from alcohol, from which *α*(or *β*)-*bromo*-*β*-(2-*nitro*-4 : 5-*dimethoxyphenyl*)-*acrylic acid* crystallised in fern-like clusters of mustard-yellow needles, m. p. 215—217° (Found: C, 39·6; H, 3·3; Br, 24·0. $C_{11}H_{10}O_6NBr$ requires C, 39·8; H, 3·0; Br, 24·1%).

Skraup Reactions with Nitro-aminobenzoic Acids.—(*a*) 2-Nitro-3-aminobenzoic acid was prepared by nitration of *m*-acetamidobenzoic acid according to Kaiser (*Ber.*, 1885, **18**, 2942; see also English, *et al.*, *J. Amer. Chem. Soc.*, 1945, **67**, 300), 90 g. giving 95 g. of mixed nitro-acids containing 2-nitro-3-acetamidobenzoic acid as major product; this was obtained fairly pure by way of the barium salt as described by Kaiser, and final purification of the acid (53 g.) was most easily effected by successive extractions with portions of boiling water, the pure acid [26 g., m. p. 240—242° (decomp.) (lit., 240—241°)] separating from each extract except the first. Hydrolysis with 10% aqueous baryta (20 vols.) gave the amino-acid, which formed long, hard, orange-yellow needles, m. p. 154—156° (lit., 156—157°). The Skraup reaction (2·5 g. of acid, 2 g. of arsenic acid, 0·2 g. of ferrous sulphate, 4·2 g. of glycerol, and 4 g. of concentrated sulphuric acid) set in at 145—150°. The product obtained after 2½ hours at 150° was a black intractable amphoteric mass, from which no crystalline material could be obtained.

(*b*) The oxidation of 2-nitro-4-acetotoluidide to 2-nitro-4-acetamidobenzoic acid is mentioned by Bogert and Kropff (*J. Amer. Chem. Soc.*, 1909, **31**, 841) without experimental detail. The following procedure gave satisfactory results. To a boiling suspension of the toluidide (50 g.) in water (2·5 l.), together with magnesium sulphate (40 g.), was added (during 1½ hrs.) a mixture of potassium permanganate (120 g.) and magnesium sulphate (40 g.). After filtration and thorough washing of the sludge, unoxidised material (6 g.) was recovered from the filtrate; the crude acid obtained on acidification was purified by digestion with alcohol, giving 28 g. of 2-nitro-4-acetamidobenzoic acid, m. p. 217—220° (efferv.) [lit., 219° (corr.)]. Hydrolysis with 10% aqueous potassium hydroxide (20 vols.) gave brown, prismatic needles, m. p. 244—245° (decomp.) [lit., 239·5° (corr.)], of the amino-acid after crystallisation from aqueous alcohol. In the Skraup reaction (quantities as above), considerable gassing occurred (140°) before the reaction proper set in at 155—160°. The product was a basic oil devoid of acid properties, which gave a solid mixture of, presumably, 5- and 7-nitroquinoline; from this mixture two apparently pure picrates, m. p. 244—245° and 201—203°, were obtained but not investigated.

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