92. *Cinnolines. Part V. The Reaction between Pyridine, Acetic Anhydride, and 4-Hydroxycinnoline-3-carboxylic Acid.*

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

Treatment of 4-hydroxycinnoline-3-carboxylic acid (I) with a mixture of pyridine and acetic anhydride under appropriate conditions, produces a *substance*, $C_{16}H_{11}O_3N_3$, believed to be a resonance hybrid of the species (II, *a*—*c*) with the carbonium form (II*a*) making a major contribution. In its formulation, the production of " Reissert " compounds from quinoline, acid chlorides, and potassium cyanide has been used as a model, and ample experimental evidence is put forward in support for this analogy. Various reactions are described in which this substance, and its addition products (III, IV) with aniline and alcohols, are involved. Stepwise degradation of it has led to the isolation of derivatives of a new ring-system, provisionally represented as 3 : 9 : 10-*triazaphenanthrene* (as XIII), and also to the production of 4-(2′-*pyridyl*)*cinnoline* (X).

Comparative experiments have shown that the reaction with pyridine and acetic anhydride is highly specific to 4-hydroxycinnoline-3-carboxylic acids, as the 6-methoxy-acid undergoes a precisely similar reaction, but no comparable reaction occurs with the analogous quinolinecarboxylic acid or with 2-hydroxy-3-naphthoic acid.

In a previous paper (Schofield and Simpson, *J.*, 1945, 512) we stated that a complex reaction occurs when the three substances named in the title are heated together. Further study showed that the presence of both reagents is necessary—4-hydroxycinnoline-3-carboxylic acid (I) gives 4-acetoxycinnoline when boiled with acetic anhydride alone (Schofield and Simpson, *loc. cit.*), and the acid crystallises unchanged from pyridine —and that the reaction is specific to the particular grouping represented by the heterocyclic ring of (I). Thus 4-hydroxycinnoline gives 4-acetoxycinnoline when heated with acetic anhydride either alone or in pyridine solution (*loc. cit.*), and ethyl 4-hydroxycinnoline-3-carboxylate (unpublished) behaves similarly; we have also found that the mixed reagents convert 2-hydroxy-3-naphthoic acid into the normal acetoxy-acid, and are without action on 4-hydroxyquinoline-3-carboxylic acid. On the other hand, similar treatment of 4-hydroxy-6-methoxycinnoline-3-carboxylic acid brings about a complex reaction which is apparently exactly analogous to that which occurs with the Richter acid (I). In view of the highly specific nature of the reaction which these comparative experiments establish, and also because of the great reactivity of the product derived from (I), we now record an account of partly completed experiments in this field, which we hope to extend in various directions as opportunity allows.

When the Richter acid, pyridine, and acetic anhydride were heated at 60° and at 95° in the proportions of 2 : 9 : 13 approximately, a *substance*, m. p. 217°, gradually separated. This showed clearly defined amphoteric properties in the cold, but was decomposed by hot acid and alkali, and also by boiling solvents such as pyridine and the lower alcohols. This extreme reactivity, coupled with solubility characteristics, made it somewhat uncertain whether complete reliance could be placed on analytical data, but the mean value of analyses on three samples indicated that the most probable formula was $C_{16}H_{11}O_3N_3$ or $C_{21}H_{16}O_4N_4$.

The substance dissolved slowly in boiling methanol, ethanol, and *iso*propanol to form strongly fluorescent solutions, and on concentration of these solutions a series of *substances* resulted which, like their common precursor, were ampholytes and unstable to hot acid and alkali. Analyses showed that they were homologues derived from the parent substance by addition of the alcohols in question.

A study of the analytical data for the four substances showed that they could be represented by either of two series of formulæ, *A* and *B* (see table below).

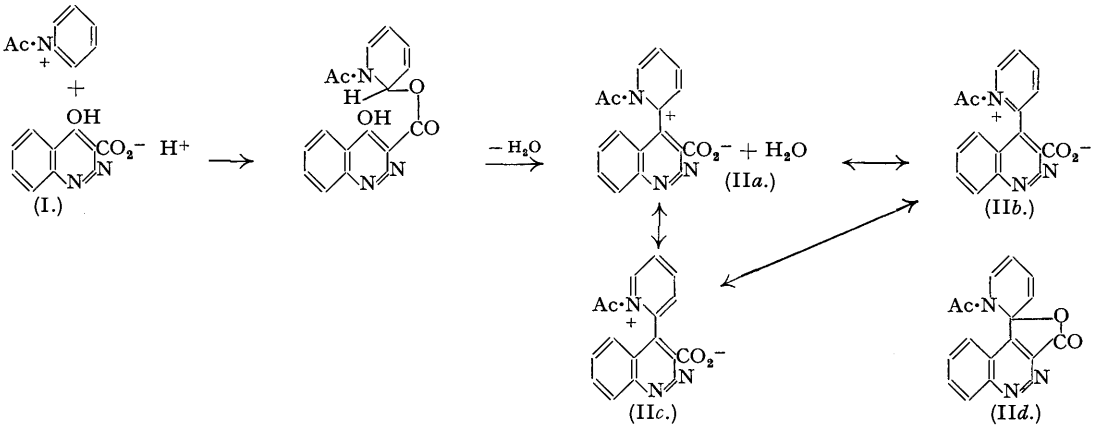
	Series A.	Series B.
Primary reaction product, m. p. 217°	$C_{16}H_{11}O_3N_3$	$C_{21}H_{16}O_4N_4$
Product from methanol	$C_{17}H_{15}O_4N_3$	$C_{22}H_{20}O_5N_4$
Product from ethanol	$C_{18}H_{17}O_4N_3$	$C_{23}H_{22}O_5N_4$
Product from *iso*propanol	$C_{19}H_{19}O_4N_3$	$C_{24}H_{24}O_5N_4$

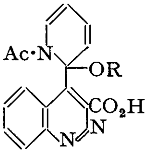
On the basis of nitrogen content, Series *A* would imply that the substance, m. p. 217°, is formed by condensation of a cinnolyl and a pyridyl residue; if, on the other hand, the sequence of products were correctly represented by Series *B*, then the primary reaction would involve condensation between a cinnolyl and two pyridyl groups, or, alternatively, a fusion of two cinnoline molecules, which would thus be stoicheiometrically independent of the basic solvent (*i.e.*, pyridine). In order to decide between these possibilities, the pyridine was replaced by quinoline; reaction again occurred, and although the primary product was not purified, reaction with ethanol furnished a *substance*, m. p. 170°, which differed from the corresponding compound, m. p. 128°, obtained from the pyridine reaction, and, as the analysis of the quinoline derivative was in much better agreement with Series *A* than with Series *B*, it followed that the original (pyridine) reaction could be represented as :

$$C_9H_6O_3N_2 + C_5H_5N + (CH_3\cdot CO)_2O \longrightarrow C_{16}H_{11}O_3N_3 + CH_3\cdot CO_2H + H_2O.$$

Further variations were then tried. The substitution of quinaldine for quinoline led to recovery of the Richter acid in high yield and caused no development of colour or fluorescence; α-picoline showed evidence (colour-development) of reaction, possibly due to impurity, as the only isolable product was unchanged Richter acid; and propionic anhydride with pyridine gave an obvious reaction, but the product was an oil. The quinoline ethanolysis product referred to above was obtained on only one occasion, several attempted repetitions giving only uncrystallisable oils, but the analyses of the numerous derivatives described later leave no doubt that Series *A*, and not Series *B*, is the correct one.

In seeking a possible explanation of these facts, our attention became focused on two alternative lines of approach to known analogies, namely the tendency of the quinolinium kation to assume covalency with a weak anion (*i.e.*, the formation of *N*-substituted 1 : 2-dihydroquinolines), and the ease with which fission of the pyridine ring may occur in certain circumstances, producing derivatives of glutacondialdehyde. In illustration of the first reaction, many examples of the formation of (covalent) pseudo-bases from quinolinium and pyridinium hydroxides have been observed (*e.g.*, Decker, *Ber.*, 1892, **25**, 443; Hantzsch and Kalb, *ibid.*, 1899, **32**, 3119), and Reissert (*ibid.*, 1905, **38**, 1603) has shown that quinoline, benzoyl chloride, and alkali cyanide yield *N*-benzoyl-2-cyano-1 : 2-dihydroquinoline, which in presence of acid furnishes quinaldinic acid, *via* the nitrile, by loss of benzaldehyde (see also Woodward, *J. Amer. Chem. Soc.*, 1940, **62**, 162; Grosheintz and Fischer, *ibid.*, 1941, **63**, 2021; Buchanan, Cook, and Loudon, *J.*, 1944, 325). If, then, in the condensation between the Richter acid (I), pyridine, and acetic anhydride, the first were to function as a weak anion, the reaction could take the course [(I) ⟶ (II, *a*—*c*)].





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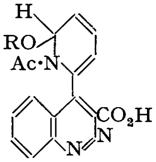
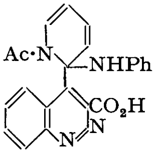


(IIIa.)



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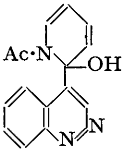

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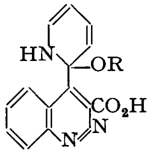

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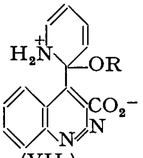

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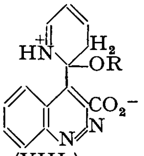

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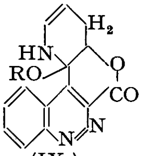

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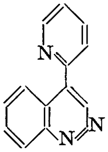
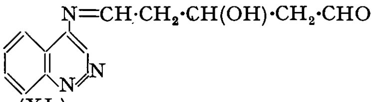


(X.)



(XI.)

Formal representation of the substance $C_{16}H_{11}O_3N_3$, m. p. 217°, by any of the three unperturbed structures (II, *a*—*c*) is to be preferred to the lactone form (II*d*) for the following reasons. First, its physical properties suggest a polar structure. Secondly, it is readily soluble in cold aqueous sodium carbonate. Thirdly, the facile additions of alcohols to give (III; R = Me, Et, and Pr^β) are more readily understood on the basis of ionic attack on a zwitterion than by the assumption that lower alcohols at their boiling points could bring about hydrolysis of the structure (II*d*). Such ionic attack could take place in either of two ways—by electromeric shift in the resonance hybrid towards the extreme form (II*b*), leading, *via* the usual quaternary salt–pseudo-base mechanism, to entry of the OR anion and formation of the pseudo-base ether, or, more simply and probably, by direct attack of OR on the carbonium ion (II*a*). Statistically, therefore, this homologous series of ether-acids is more likely to have the constitution (III) than (III*a*), which could only emerge from the species (II*c*). In complete agreement with the production of these ether-acids is the observation that the substance $C_{16}H_{11}O_3N_3$ adds on a molecular proportion of aniline in boiling benzene solution, yielding an *acid* (IV).

The fourth reason for preferring the dipolar structure (II, *a*—*c*) to the lactone form (II*d*) is that the compound $C_{16}H_{11}O_3N_3$ undergoes extremely facile hydration-decarboxylation, under certain conditions, to a colourless *base*, $C_{15}H_{13}O_2N_3$. This base was produced in comparatively high yield (a) when the zwitterion compound was refluxed in ordinary " purified " pyridine, and (b) * when a mixture of 4-hydroxycinnoline-3-

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* This was the method selected for routine preparation of the base, $C_{15}H_{13}O_2N_3$. Under these conditions, a small yield (2—3%) of a second crystalline *substance* of formula $C_8H_{6(7)}O_5N$ was produced. This substance was unchanged by short boiling with aqueous sodium hydroxide—a fact which differentiates it sharply from the substances under discussion—and has not been further investigated.

carboxylic acid, pyridine, and acetic anhydride, in the proportions of 1 : 3 : 1, was refluxed for 30 minutes, none of the intermediate zwitterion being isolated under these conditions. In sharp contrast to this, no crystalline product was produced either when (c) a mixture of the Richter acid, pyridine, and acetic anhydride was refluxed in those proportions (2 : 9 : 13) which furnish the C_{16} zwitterion at reaction temperatures of 60° or 95°, or when (d) the C_{16} zwitterion was substituted for the Richter acid in experiment (c). Further observations were (e) that the base, $C_{15}H_{13}O_2N_3$, was unaffected by acetic anhydride at 95°, and (f) that the zwitterion gave a moderate yield of the above-mentioned base when its aqueous suspension was refluxed for several hours.

These facts cannot be satisfactorily interpreted on the basis of the lactone structure (II*d*), and our explanation, on present evidence, is that the C_{15} base has the constitution (V) and is derived from an intermediate hydroxy-acid (III; R = H) which cannot be isolated under the conditions used in our experiments. We consider that the initial step in the formation of (III; R = H) is a rapid attack of hydroxyl ion on (II*a*); this particular canonical state would be expected to show the greatest kationic activity of the three forms (II, *a*—*c*), and may well contribute significantly to the resonance hybrid. In the presence of acetic anhydride, however, the C_{16} zwitterion would be forced to compete for any available hydroxyl ions, and this competition explains satisfactorily the high yield of (V) obtained both in experiment (a) [having regard to the fact that the pyridine used was not anhydrous and was present in considerable excess (15 : 1)] and in experiment (b) (where the proportion of acetic anhydride was low and a molecular proportion of water was eliminated during the first stage of the reaction). Again, the failure to isolate the base (V) from experiments (c) and (d) is in accord with the concept of competition, as in both these experiments the acetic anhydride was present in considerably greater quantity. The relatively poor yield of base from experiment (f) may be explained by the fact that the reaction was carried out on a suspension of the zwitterion in a neutral medium—conditions which would scarcely be expected to favour the postulated mechanism.

Our formulation of the series (II—V) as α-pyridinium (or α-dihydropyridyl) derivatives is based partly on the inhibition of reaction caused by substitution of quinaldine for pyridine or quinoline, and partly on analogy with the " Reissert compounds " (see above). This analogy, if well founded, should be susceptible of further substantiation by reactions involving the loss of the *N*-acetyl group of (III—V) (as acetic acid or its esters or anilide), and the following observations show that this adumbration is, indeed, largely borne out by experiment.

Treatment of (III; R = Me) with methanol–sulphuric acid yielded a bright yellow *substance*, which was also produced when ethanol was used instead of methanol. The reaction, therefore, cannot be one of esterification, and analytical data suggested that the most probable formula for the product is $C_{15}H_{13}O_3N_3$. Similar treatment of (III; R = Et) with both alcohols furnished identical specimens of a second *substance*, $C_{16}H_{15}O_3N_3$. The simplest explanation of these formulæ would be to regard the substances as secondary amines (VI; R = Me or Et) derived from (III; R = Me or Et) by deacetylation, the acetyl group concerned undergoing an amide–ester conversion. The two homologues, however, although showing the anticipated basic properties, were insoluble in cold aqueous sodium hydroxide. While it is true that insolubility in aqueous alkali is not invariably a criterion of the absence of a carboxyl group—for example, diphenyl-4-acrylic acid is almost insoluble in these reagents (Hey, *J.*, 1931, 2478)—there are obvious alternatives to (VI) which may be considered provisionally until further data are available. Thus * hydrogen bonding between the carboxyl and the >NH group of the dihydropyridine ring, or the transfer of a proton to the latter group, giving the dipolar structure (VII), might explain the properties of the two homologues. Other possibilities are (i) that the polarisability of the dihydropyridine ring (hetero-dienoid system) might be called into play, and the fully polarised form stabilised by a proton shift, giving (VIII), and (ii) that lactonisation between a double bond of the dihydropyridine ring and the carboxyl group could occur, producing (IX).

The action of hot aqueous sodium hydroxide on (VI; R = Me) led to further degradation with production of a *substance*, m. p. 153°, which showed basic, but no acidic, properties. This base is probably the end-product of mild acid or alkaline degradation of all members of the series (II—V); the decomposition of each member of the series has not yet been studied in detail, but, in addition to its formation from (VI; R = Me), the base has also been isolated by treatment of (V) with hot dilute hydrochloric acid or sodium hydroxide, by treatment of (III; R = Me) with either reagent, by the action of acid, followed by alkali, on (IV), and from the zwitterion (II) by means of hot acid. The compound (VI; R = Et), on the other hand, appeared to be stable under the roughly standard small-scale experimental conditions used; no attempt was made to recover it from the experiment, but no evidence could be observed of the production of the base, m. p. 153°, which in the other cases is formed in a highly characteristic manner involving, initially, the production of an intense permanganate-pink solution, the colour of which fades as the reaction proceeds.

On the basis of the constitutions which have been discussed, the only possible representation of the base, m. p. 153°, is the expression (X), and analytical data did, in fact, indicate a formula $C_{13}H_9N_3,2H_2O$. That the oxygen was present as water of crystallisation was eventually proved by analysis of the *picrate*, which

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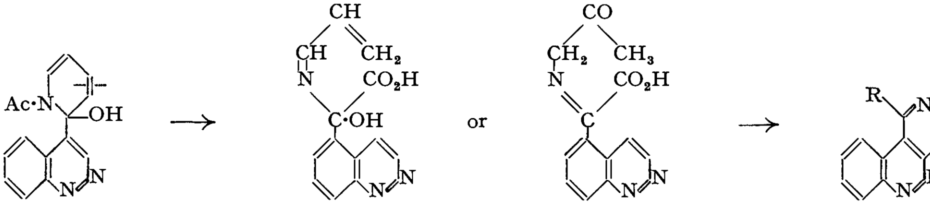
* For steric reasons, hydrogen bonding is not, as a rule, marked where the phenomenon would give rise to a seven-membered ring (cf. Remick, " Electronic Interpretations of Organic Chemistry," p. 42, Chapman & Hall, 1943), but one might anticipate a modified rôle for steric factors where the hydrogen and donor atoms are attached to different rings, as in (VI). A rough analogy is the production, so well known in bile acid chemistry, of anhydrides instead of ketones from substituted adipic acids in which one carboxyl group is attached to ring A and the other to ring C (or to B and D respectively) of the steroid nucleus.

was solvent-free; the ***styphnate*** was monohydrated, and the ***hydrochloride*** was a dihydrate. The base is rapidly oxidised by potassium permanganate at room temperature to an amphoteric compound, m. p. 146°, the structure of which is discussed below. In our view it was surprising that a substance of structure (X) should be so sensitive towards oxidation, and we should like to record that, at an early stage in our investigation, it was suggested to us by the research staff of Imperial Chemical Industries, Ltd., that the C_{13} base might be represented by some expression such as (XI), in order to account for the sensitivity which it displays towards permanganate. This hypothesis is based on analogies involving ring-opening of pyridine derivatives *via* intermediate quaternary salts (see, *e.g.*, Zincke *et al.*, *Annalen*, 1904, **330**, 361; **333**, 296; *J. pr. Chem.*, 1910, **82**, 1; Koenigs and Greiner, *Ber.*, 1931, **64**, 1049; Baumgarten, *ibid.*, 1926, **59**, 1166; 1933, **66**, 1633; 1936, **69**, 1938), and, although it was finally found to be untenable, it was of considerable value to us in furthering the progress of our work.

Of the various routes to the base (X) enumerated above, that involving the alkaline degradation of (V) was selected as being the most convenient for preparative purposes. The average yield from a number of experiments was only 60%, and an examination of the alkaline mother-liquors showed that the conversion of (V) to (X) is accompanied by side-reactions. Concentration of the alkaline filtrate readily yielded the sodium salt of a *substance*, m. p. 187°, of which the structure is discussed below. Acidification of the filtrate from this sodium salt furnished an *acid*, m. p. 170°, of formula $C_{13}H_9O_2N_3$, which also showed very slight basic properties. The acid underwent rapid and quantitative decarboxylation at the melting point, the product being a highly crystalline *substance*, m. p. 114°, of formula $C_{12}H_9N_3$, which showed definite, but rather weak, basic properties. On the basis of hydrogen content, this compound must contain a tricyclic skeleton in which all three nitrogen atoms participate. Now the production of the acid, $C_{13}H_9O_2N_3$, from the dihydropyridine base (V) must involve oxidative degradation in alkaline solution, and intermediate reactions, such as hydration of the dihydropyridine ring, and disproportionation (probably *via* Cannizzaro reactions), must be reckoned with. The base $C_{12}H_9N_3$ could then be formulated as 1-*methyl*-3 : 9 : 10-*triazaphenanthrene* (XIII; R = H), and the acid $C_{13}H_9O_2N_3$ as the related 4-carboxylic acid (XIII; R = CO_2H), produced from (V) by cyclodehydration of the hypothetical intermediate (XII) or (XII*a*). The position of the carboxyl group in the acid is clearly one from which, by simple analogy, ready elimination would be anticipated.



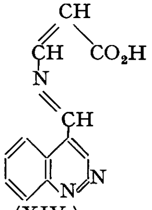
(V.) (XII.) (XII*a*.) (XIII.)

The substance, m. p. 187°, obtained from the sodium salt already mentioned, showed the behaviour of a weak ampholyte. Analytical data indicated the formula $C_{12}H_9ON_3$ or $C_{12}H_{10}ON_3$, and if the former be taken as correct the substance can be represented as (XIII; R = OH), an α-hydroxypyridine structure which is in accord with its weakly basic and weakly acidic properties.

The conversion of (V) into (XIII; R = CO_2H or OH) represents a type of degradation that one would scarcely predict as characteristic of such a substance—in particular, ring-closure into a heterocyclic nucleus is not usually a facile process—and to that extent the structures (XIII; R = CO_2H, OH, and H) must be regarded as provisional, even though no open-chain constitutions appear to be possible. The structures advanced are obviously capable of some degree of confirmation by analytical study, and a possible synthetic proof, which it is hoped to test, would consist in the preparation of the appropriate heteronuclear dinitrophenylpyridine, followed by reduction, a method which is of general application in the preparation of 3 : 4-benzocinnolines (cf., *e.g.*, Ullmann and Dieterle, *Ber.*, 1904, **37**, 23).

Acetic acid was identified in the filtrate from the acid (XIII; R = CO_2H), and, from the results of alkali titration, it was clear that the whole of the base (V) must have suffered loss of acetic acid during the polydirectional alkaline degradation; this is in conformity with the structures (X) and (XIII), and provides the final step in the analogy sought between the behaviour of (V) and the Reissert compounds.

The oxidation product, m. p. 146°, is produced from the base (X) in comparatively high yield and is apparently unaccompanied by side-products. It is amphoteric, and, in contrast to the yellow base from which it is derived, is reddish-orange in colour. Qualitatively, the colours of its solutions in acid or alkali are also similar. Elementary analysis indicated the formula $C_{12}H_9O_2N_3$, confirmed by analysis of its crimson *picrate*. The solubility of the substance in aqueous bicarbonate suggests that it contains a carboxyl group rather than a phenolic or readily enolisable carbonyl group; if, therefore, as we believe, the base (X) is correctly formulated, the expression (XIV) appears to be the only representation of the oxidation product which accounts adequately for the solubility relationships and analytical data. The nitrogen-free analogue of (XIV), δ-(1-naphthyl)-pentadienoic acid, does not appear to have been prepared, but there is little doubt that the colour of such a substance would be very much lighter than that of (XIV)—for example, cinnamylideneacetic acid is colourless (Sudborough and Gittins, *J.*, 1909, **95**, 320), as also, apparently, is its *o*-nitro-derivative (although the alkali-metal salts of this compound are bright yellow) (Diehl and Einhorn, *Ber.*, 1885, **18**, 2331), and α-phenyl-δ-(2-nitrophenyl)pentadienoic acid is yellow (Bachman and Hoaglin, *J. Org. Chem.*, 1943, **8**, 310). The deep colour of (XIV) must therefore be ascribed to the operation of pronounced bathochromic factors relative to its carbocyclic analogues, and these factors must clearly be bound up with the accumulation of nitrogen atoms in the extended conjugated system.* The bathochromic effect of a suitably located accumulation of nitrogen atoms has been clearly demonstrated for the quinoxaline cyanines in comparison with other cyanine types (Cook, Garner, and Perry, *J.*, 1942, 710; Cook and Perry, *ibid.*, 1943, 394; Anker and Cook, *ibid.*, 1944, 489), and we believe that the structure (XIV) accounts satisfactorily for the colour of the compound.



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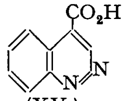

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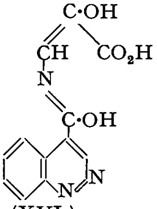
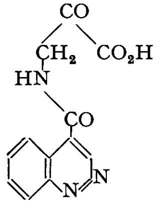
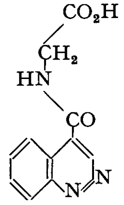


(XVI.)



(XVI*a*.)



(XVII.)

The high resonance energy which, from the depth of colour, one would attribute to the substance, m. p. 146°, is in accord with what is known of its stability. Small-scale tests showed that it is stable towards cold or warm permanganate, although it seemed to be attacked to some extent by the reagent in boiling solution. [In contrast to this stability, cinnamylideneacetic acid, with, presumably, less resonance energy, is oxidised by cold permanganate to benzaldehyde and tartaric acid (Doebner, *Ber.*, 1890, **23**, 2372).] It was also found that the substance was not affected by boiling 10% aqueous sodium hydroxide (1½ hours), and 40% was recovered, as the sole crystalline product, after mild treatment with hydrochloric acid. Under more drastic conditions, however, it was converted by hydrochloric acid into a mixture of two products, neither of which was the anticipated unknown cinnoline-4-carboxylic acid (XV). One was a *substance*, m. p. 195°, whose properties closely resembled those of its precursor. It crystallised in orange-pink needles, was amphoteric, and appeared to be stable towards hot aqueous permanganate. The analytical data were in moderate agreement with the formulæ $C_{12}H_9O_4N_3$ and $C_8H_5O_3N_2$, and as the properties of the substance indicated that it is a near derivative of the compound formulated as (XIV), preference must be given to the C_{12} formula. On the basis of (XIV), the substance could then be represented as (XVI); the existence of the substance pre dominantly in the enolic, rather than in the ketonic, form (XVI*a*) must be assumed in order to account for the colour, and could well be due to the extra stability conferred on the enolic structure by reason of the extended conjugation.

The other component of the mixture formed by the action of hydrochloric acid on the acid (XIV) was a colourless *substance*, m. p. 254°. This, like the compound discussed above, showed amphoteric properties, but appeared to have much less avidity for both acids and bases. Analysis suggested the formula $C_{11}H_7O_3N_3$, but the agreement with theory was not close, and if, as seems probable, the compound was not obtained analytically pure, alternative formulæ $C_{12}H_9O_3N_3$ and $C_8H_6O_2N_2$ must also be reckoned with. Until further data are available, any formulation of the compound, m. p. 254°, must be based largely on speculation. However, it is clear that in its formation the conjugation characteristic of its concomitant, m. p. 195°, has been destroyed (significantly, the substance reduced aqueous permanganate), and it is suggestive that the molecular formula $C_{11}H_7O_3N_3$, with which the analytical data are in best agreement, is that of the expression (XVII), a simple analogue of (XVI*a*) in which ring–side-chain conjugation is no longer possible. [Enolisation of this, as compared with that of (XVI*a*), would probably be reduced, as it would not be stabilised by conjugation.]

The substance, m. p. 195°, is not, apparently, an intermediate in the formation of the compound, m. p. 254°; the former was to some extent attacked by hydrochloric acid under conditions which produced the mixture of the two substances from (XIV), but, on the scale employed, the only crystalline substance isolated was unchanged material in much diminished yield, and it was established that no appreciable quantity of the compound, m. p. 254°, was formed during the reaction.

The work described in this paper has had to be temporarily interrupted. It is hoped to resume it when an opportunity occurs, but until the substances, m. p. 195° and 254°, can be adequately characterised the structures discussed in relation to these compounds are regarded as purely tentative.

That the oxidation of (X) to (XIV) should occur so readily is unexpected, but, here again, we know of no comparable data on which analogies could be based. The closest analogues of (X) which appear in the literature are the 2- and 4-lutidylquinolines of Cook, Heilbron, and Steger (*J.*, 1943, 413), but no data on the oxidation of these substances are available. In any event, the present experiments amply demonstrate the lack of analogy in chemical behaviour between certain cinnoline derivatives and their quinoline analogues, and it is not difficult to imagine that the adjacent nitrogen atoms in the cinnoline nucleus of (X) may be

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* On the other hand, Schwarzenbach, Lutz, and Felder (*Helv. Chim. Acta*, 1944, **27**, 584) state that the effect of the nitrogen atom in the anion of the substance $OHC\cdot[CH{:}CH]_2\cdot N{:}CH\cdot CH{:}CH\cdot CH_2\cdot CHO$ is hypsochromic. It is, however, to be noted that the absorption maximum of the nitrogen-free analogue, $OHC\cdot[CH{:}CH]_4\cdot CH_2\cdot CHO$, required for comparison was obtained by extrapolation and not by experimental observation.

responsible for the setting up of considerable initial polarisation, resulting in a concentration of the attack of the oxidising agent solely on the pyridine ring.

EXPERIMENTAL.

(Melting points are uncorrected.)

Preparation of C_{16} *Zwitterion.*—A mixture of crude Richter acid (15 g.), pyridine (70 c.c.), and acetic anhydride (100 c.c.) was heated on the steam-bath for 1 hour; a deep green solution was formed, from which a brownish-yellow, highly crystalline solid separated. The mixture was set aside overnight, and the solid then collected (13—14 g.); m. p. 215° (decomp.) after oven-drying. For analysis a sample was recrystallised from acetic acid–ligroin, from which the *substance* separated in small yellow polyhedra, m. p. 217° (decomp.). Other analytical samples were prepared directly from the pure reactants, and were rust-brown crystalline solids, m. p. 215—216° (decomp.) (Found : C, 64·85, 65·0, 65·9; H, 4·4, 3·55, 4·0; N, 14·5, 14·4. $C_{16}H_{11}O_3N_3$ requires C, 65·5; H, 3·8; N, 14·3. $C_{21}H_{16}O_4N_4$ requires C, 64·95; H, 4·1; N, 14·4%).

The substance was not appreciably soluble in cold water, but dissolved easily in aqueous sodium carbonate and in moderately concentrated hydrochloric acid. A suspension of the solid in aqueous dioxan gave an intensely bluish-purple solution, from which an amorphous blue solid was gradually precipitated after addition of a drop of concentrated ammonium hydroxide.

Reaction of C_{16} *Zwitterion with Alcohols.*—The substance was refluxed with the appropriate alcohol (methyl, 100 : 1, ethyl, 60 : 1; *iso*propyl, 120 : 1) for 1—1½ hours. In each case the original suspension gradually changed to a dark green, fluorescent solution, which was concentrated until crystallisation occurred. The *methyl* derivative separated from methyl alcohol in colourless polygonal plates, m. p. 143—144° (Found : C, 62·95, 62·25; H, 4·65, 4·8; N, 12·8, 13·0; OMe, 9·3, 9·45. $C_{17}H_{15}O_4N_3$ requires C, 62·75; H, 4·65; N, 12·9; OMe, 9·5. $C_{22}H_{20}O_5N_4$ requires C, 62·9; H, 4·8; N, 13·3; OMe, 7·4%). The *ethyl* derivative, from ethyl alcohol, formed very pale green, lustrous, irregular hexagons, m. p. 128—128·5° (Found : C, 64·05; H, 5·25; N, 12·35. $C_{18}H_{17}O_4N_3$ requires C, 63·7; H, 5·0; N, 12·4. $C_{23}H_{22}O_5N_4$ requires C, 63·6; H, 5·1; N, 12·9%). The iso*propyl* derivative crystallised from methyl alcohol in aggregates of faintly green, dull prisms, m. p. 130—131° (Found : C, 64·9; H, 5·45; N, 12·1. $C_{19}H_{19}O_4N_3$ requires C, 64·6; H, 5·4; N, 11·9. $C_{24}H_{24}O_5N_4$ requires C, 64·3; H, 5·4; N, 12·5%). These substances were insoluble in water, but soluble both in dilute sodium carbonate solution and in dilute hydrochloric acid. The ease of solution in alkali appeared to decrease somewhat in passing from the methyl to the *iso*propyl derivative.

Deacetylation of the Ether-acids (III).—(a) The methyl ether (III; R = Me) (1 g.) was refluxed with methyl alcohol (10 g.) and concentrated sulphuric acid (0·5 g.) for 4 hours; the solution gradually turned brown as the reaction proceeded. The product was neutralised with solid sodium bicarbonate, solvent removed in an exhausted desiccator, and water added to the residue, which was then extracted with ether. The dried and concentrated ethereal solution yielded 0·33 g. of lustrous yellow prismatic needles, m. p. 104—108°, which after several crystallisations from ether containing a little alcohol had m. p. 106—107° (Found : C, 63·1; H, 4·1; N, 15·05; OMe, 11·2. $C_{15}H_{13}O_3N_3$ requires C, 63·6; H, 4·6; N, 14·8; OMe, 10·95%). A sample prepared from an experiment in which ethyl alcohol was used in place of methyl alcohol was identical (m. p. and mixed m. p.) (Found : C, 63·05; H, 4·0; N, 14·85%). The substance was almost insoluble in cold water, but appreciably soluble in hot; it dissolved readily in moderately concentrated hydrochloric acid, and was insoluble in cold alkali carbonate and hydroxide; on warming with the latter, decomposition occurred (q.v.).

(b) The ethyl derivative (III; R= Et) was refluxed for 3—4 hours (0·75 g.) with concentrated sulphuric acid (0·37 g.) and either methyl or ethyl alcohol (7·5 g.) and the products worked up as in (a). In each case there was obtained *ca.* 0·4 g. of crude product, m. p. 135—139°, which after crystallisation from ether–alcohol formed large yellow lozenges, m. p. 140—141·5° [Found : (Methyl alcohol) C, 64·85; H, 4·7; N, 14·35; OMe, 15·3. (Ethyl alcohol) C, 65·15; H, 4·6; N, 14·6. $C_{16}H_{15}O_3N_3$ requires C, 64·6; H, 5·1; N, 14·1; OMe, 15·15%]. This compound, like that described in (a), showed basic properties towards hydrochloric acid, but was insoluble in cold sodium hydroxide; on warming the suspension a clear yellow solution was formed which gave no precipitate on cooling or acidification.

Reaction of C_{16} *Zwitterion with Aniline.*—A suspension of the powdered solid (1 g.) in benzene (13·5 c.c.) and aniline (1·5 c.c.) was heated under reflux; after 1 hour much suspended material remained, but this had almost completely dissolved after a further 1¾ hours of refluxing. The solution was diluted with ether and extracted thrice with aqueous sodium carbonate. The alkaline extract, after re-extraction with ether and clarification with charcoal, was made just acid to Congo red with dilute hydrochloric acid. The crude *acid* so obtained was washed, dried, and crystallised from ethyl acetate–ligroin (charcoal), giving 0·9 g. of almost pure material. An analytical sample formed soft, colourless needles, m. p. 161—162° after oven-drying (air-dried samples melted at 122—124° owing to solvation) (Found : C, 68·4; H, 4·6; N, 14·6. $C_{22}H_{18}O_3N_4$ requires C, 68·4; H, 4·7; N, 14·5%). The substance was very easily soluble in alcohol; it was only slightly soluble in cold 2N-hydrochloric acid, and the suspension decomposed when warmed (q.v.).

Preparation of Base, $C_{15}H_{13}O_2N_3$ (V), *and Substance,* $C_8H_{6(7)}O_5N$.—(a) The C_{16} zwitterion (0·3 g.) was refluxed in pyridine solution (5 c.c.) for 1 hour. The reaction proceeded, and the product was isolated, as described in (b) below, and the base (0·13 g.) identified by m. p. and mixed m. p.

(b) Crude Richter acid (5 g.) was refluxed for ½ hour with pyridine (15 c.c.) and acetic anhydride (5 c.c.). Vigorous gas evolution occurred during the first part of the reaction, and the usual green fluorescence, which is characteristic of experiments for the preparation of the zwitterion (II), gradually disappeared. The solvents were carefully distilled off at 15 mm., and the residual oil left over sulphuric acid in an exhausted desiccator; crystallisation occurred during 2 days. The crude solid was crystallised from alcohol (charcoal), 2·79 g. of the *base*, m. p. 158—161°, being obtained. An analytical sample separated from ethyl alcohol in colourless, shining leaflets, m. p. 161·5—162·5° (Found : C, 66·95; H, 4·6; N, 16·3. $C_{15}H_{13}O_2N_3$ requires C, 67·4; H, 4·9; N, 15·7%). The yield of base from a 2 g. run (reagents *pro rata*) was 1·2 g. The substance was insoluble in cold water and aqueous sodium hydroxide, and dissolved readily in 2N-hydrochloric acid.

On a larger scale, two 10 g. runs were carried out and worked up together; 14·6 g. (52%) of pure base were obtained after the mother-liquors had been worked up. The subsidiary crops of base were contaminated with a second *substance* which was comparatively sparingly soluble in hot alcohol : after several crystallisations from this solvent, it separated in long, straw-coloured, brittle needles, m. p. 259—261° (Found : C, 48·25; H, 3·15; N, 6·95. $C_8H_6O_5N$ requires C, 49·0; H, 3·1; N, 7·1. $C_8H_7O_5N$ requires C, 48·7; H, 3·55; N, 7·1%); yield, 0·5 g. of almost pure product from 20 g. of Richter acid. The substance was insoluble in 4N-ammonium hydroxide, slightly soluble in concentrated ammonium hydroxide, and soluble in warm 10% aqueous sodium hydroxide. A sodium salt separated from this solution, and dissolved on addition of water. The compound was unchanged (m. p. and mixed m. p.) after short boiling with 10% aqueous sodium hydroxide and subsequent acidification. It was slightly but appreciably soluble in boiling water, and crystallised well from the hot solution. Hot aqueous sodium carbonate was without chemical action. There was evidence of hydrochloride formation in concentrated hydrochloric acid, but not with dilute acid, and the substance crystallised from its solution in concentrated acid on dilution with water.

(c) The crude zwitterion (2 g.) was refluxed for 1 hour with water (70 c.c.). A deep red solution was formed, but much material remained in suspension. The solution was filtered, and the filtrate and solid extracted separately with ether (boiling solvent was used for the solid). The extracts were bulked, dried, and evaporated, and the crude residue recrystallised from ether, from which the base separated in white prismatic needles, m. p. and mixed m. p. 160—161°.

Preparation of Base, $C_{13}H_9N_3$ (X).—(a) For preparative purposes, attention has been concentrated on the production of this substance by alkaline decomposition of the base, $C_{15}H_{13}O_2N_3$, described above. The following conditions gave an average yield (10 runs) of 60%, but the yield is slightly variable, and optimum conditions may not yet have been found. A suspension of the C_{15} base (1 g.) in 10% aqueous sodium hydroxide (20 c.c.) was heated for 10 minutes at 75°; a further 20 c.c. of alkali were then added, and the mixture maintained at 90° for 10 minutes, with frequent shaking from the beginning of the experiment. During this time an intensely pink colour developed, caused by the action of the aqueous alkali on a black oil (A) which tended to settle out. At the end of the 20 minutes' heating, no solid material could be seen, and the supernatant liquid was then decanted from the oil and heated almost to boiling; this caused the pink colour to fade, usually rapidly, and, when the colour had changed to a somewhat dirty brown, crystals of the new base separated on cooling. The black oil (A) was heated just to boiling with more sodium hydroxide solution (10 c.c.) for a few minutes, and water (20 c.c.) was added; the intense pink which appeared on adding the alkali soon faded, and the hot liquid was decanted from the remaining black oil, which was again treated with fresh alkali and water (10 c.c. and 20 c.c.) as before. After this third treatment, almost all oil had disappeared when the pink colour had faded. The three solutions were then combined, boiled for a few minutes (the total reaction time was about ¾ hour), and filtered cold. The crude base from 10 runs was crystallised from hot water, from which 4·65 g. of almost pure material (m. p. 151—152°) separated. The pure *base* crystallised from hot water in long, silky yellow needles, m. p. 152·5—153·5° after oven-drying, which caused the crystals to fall to a dull yellow powder. Air-dried (solvated) material melted at about 125—130° (Found for material dried in high vacuum at 50°: C, 63·75; H, 4·6; N, 17·25. $C_{13}H_9N_3,2H_2O$ requires C, 64·2; H, 5·35; N, 17·3%). The base was recovered unchanged after treatment with acetic anhydride (short boiling), and after attempts to prepare a semicarbazone, an anil, and an alkylidenemalonic acid under ordinary conditions. It dissolved readily in hot hydrochloric acid, and, on cooling, the *hydrochloride* separated; this was readily hydrolysed to the free base when it was washed with water. For analysis, the salt was recrystallised from equal volumes of concentrated acid and water and dried at 75°/0·4 mm.; it formed long, brittle, orange-brown needles, m. p. 219—221° (efferv.) after previous shrinking (Found: C, 57·3; H, 4·15; N, 15·55; Cl, 12·0. $C_{13}H_9N_3,HCl,2H_2O$ requires C, 55·8; H, 5·0; N, 15·0; Cl, 12·7%). The *picrate*, prepared from 70 mg. of the base and 80 mg. of picric acid, was very sparingly soluble in alcohol; it separated from acetic acid in fine soft yellow needles on rapid cooling (leaflets on slow cooling), m. p. 207—208° (Found: C, 51·75; H, 2·75; N, 18·85. $C_{13}H_9N_3,C_6H_3O_7N_3$ requires C, 52·3; H, 2·8; N, 19·3. $C_{13}H_9N_3,C_6H_3O_7N_3,2H_2O$ requires C, 48·3; H, 3·4; N, 17·8%). The *styphnate*, similarly prepared, was also very sparingly soluble in alcohol, and formed clusters of soft, lustrous, yellow needles, m. p. 203—204°, from slightly aqueous acetic acid (Found: C, 48·3; H, 2·45; N, 18·1. $C_{13}H_9N_3,C_6H_3O_8N_3,H_2O$ requires C, 48·5; H, 3·0; N, 17·9%).

In addition to the foregoing method of preparation, the same base was also isolated from the following experiments, identification being made in each case by m. p. and mixed m. p.

(b) The C_{15} base (150 mg.) was refluxed with 2N-hydrochloric acid (8 c.c.) for 1 hour, and the product isolated by basification with ammonia. (c) The methyl derivative (III; R = Me) was treated as in (b). (d) The methyl derivative (III; R = Me) (150 mg.) was heated with 5% sodium hydroxide (12 c.c.), first at 65°, then at 85°, and finally at 100°. A further 1 c.c. of alkali was added, and the C_{13} base isolated by cooling the solution after the deep pink coloration had faded. (e) The C_{16} zwitterion (100 mg.) was refluxed with 2N-hydrochloric acid (6 c.c.) for 5 hours, and the base obtained from the filtered solution by addition of ammonia. (f) When a few milligrams of the yellow base (VI; R = Me) were warmed with 2N-sodium hydroxide, the substance dissolved to a yellow solution which rapidly acquired the deep pink colour characteristic of the production of the C_{13} base, and this compound, as usual, separated from the cooled solution when the colour had faded. (g) The anilino-derivative (IV) (100 mg.) gave a red suspension when warmed with 2 c.c. of 2N-hydrochloric acid, and the liquid became oily on cooling. After 10 minutes' refluxing, a clear wine-red solution was produced, which remained clear when cooled. Addition of ammonia precipitated a dirty-blue solid, which on boiling with sodium hydroxide solution gave the usual transient deep pink coloration, and finally yielded the typical silky needles of the C_{13} base.

Isolation of Ampholyte, $C_{12}H_9ON_3$ (XIII; R = OH), *and Acid*, $C_{13}H_9O_2N_3$ (XIII; R = CO_2H).—The combined filtrates from the preparation of the base (X) [from 10 g. of (V)] were concentrated on the steam-bath to about 250 c.c.; a sodium salt separated, the solubilities of which in cold and in hot water were not greatly different. Careful acidification (Congo red) of an aqueous solution of this salt furnished the *substance* (XIII; R = OH), which formed straw-coloured prismatic needles, m. p. 186·5—187·5°, from alcohol (Found: C, 68·1; H, 4·6; N, 19·9. $C_{12}H_9ON_3$ requires C, 68·2; H, 4·3; N, 19·9. $C_{12}H_{10}ON_3$ requires C, 67·9; H, 4·8; N, 19·8%). The yield of nearly pure substance was 0·78 g.; it was insoluble in cold sodium bicarbonate solution and somewhat soluble in the hot, but dissolved when aqueous ammonia was added to the bicarbonate solution. It dissolved readily in warm 2N-hydrochloric acid; the hydrochloride, which separated rapidly on cooling, formed prisms or flat needles, m. p. 222—223° (decomp.). The salt was insoluble in water, apparently owing to hydrolysis to the original base.

The filtrate from the foregoing sodium salt was made just acid to Congo red with dilute hydrochloric acid (considerable buffering was observed), and the crude *acid* (XIII; R = CO_2H) which separated was collected (0·45 g.). A small amount of a relatively strong base [probably (XIII; R = OH)] was removed by extracting the solid with hot 2N-hydrochloric acid; the insoluble fraction, and the material which crystallised from the acid solution on cooling, were combined, dissolved in dilute aqueous ammonia, and precipitated by acidification of the filtered (charcoal) solution. Recrystallisation of the solid product from a little alcohol yielded the acid in soft, fine, straw-coloured needles, m. p. 169—170° (decomp.) (Found: C, 65·15; H, 3·7; N, 17·3. $C_{13}H_9O_2N_3$ requires C, 65·3; H, 3·8; N, 17·6%). The acid was insoluble in water, and readily soluble in cold aqueous sodium bicarbonate. It separated unchanged from hot 2N-hydrochloric acid, in which it was very sparingly soluble, although more readily than in water alone.

Identification of Acetic Acid as a Degradation Product of Base (V).—The filtrate from the above acid [(XIII; R = CO_2H)] (800—900 c.c.), was distilled until crystallisation occurred while hot; more water was then added and the distillation continued, about 1500 c.c. of distillate being collected. Of this, the first 1000 c.c. required 198·6 c.c. of 0·1953N-KOH, and the final 500 c.c., 15·6 c.c.; removal of volatile acid was therefore regarded as virtually complete, and was equivalent to 41·83 c.c. N-alkali [10 g. of base (V) require 37·45 c.c.]. The resultant sodium salt was treated with 8·5 g. of *S*-benzylthiuronium chloride in slightly aqueous alcoholic solution; only 4·85 g. of *S*-benzylthiuronium acetate could be isolated [m. p. and mixed m. p. 143—144° (from methyl ethyl ketone; Bergel *et al.*, *J.*, 1944, 418, give m. p. 143—144°; Donleavy, *J. Amer. Chem. Soc.*, 1936, **58**, 1004, gives m. p. 134°)], but considerable hydrolysis to benzylthiol occurred during examination of the material, and there was no evidence of the presence of appreciable amounts of any other organic acid.

Preparation of Base, $C_{12}H_9N_3$ (XIII; R = H).—The acid (XIII; R = CO_2H) (75 mg.) was decarboxylated by heating it in an open tube at 180—185° (bath temp.) for a few minutes. The cooled melt was crystallised from ammoniacal alcohol, from which the *base* separated in long, soft, colourless needles, m. p. 113—114°, sparingly soluble in cold alcohol and in hot and cold 2N-hydrochloric acid, almost insoluble in hot water, and fairly easily soluble in warm 6N-hydrochloric acid (Found: C, 73·85; H, 4·7; N, 21·05. $C_{12}H_9N_3$ requires C, 73·9; H, 4·6; N, 21·5%).

Reaction between Richter Acid, Quinoline, and Acetic Anhydride.—The pure acid (0·5 g.) was heated on the steam bath for 2½ hours with quinoline (8 c.c.) and acetic anhydride (6 c.c.), and set aside overnight. The brown solid which separated was collected, and refluxed with alcohol (100 c.c.) for 2 hours; the resultant green fluorescent solution was concentrated, and the *ethyl* derivative crystallised from alcohol, from which it formed colourless fern-like blades, m. p. 170—171° (Found: C, 67·8; H, 5·1; N, 11·1. $C_{22}H_{19}O_4N_3$ requires C, 67·85; H, 4·9; N, 10·8. $C_{31}H_{26}O_5N_4$ requires C, 69·6; H, 4·9; N, 10·5%).

Oxidation of Base, $C_{13}H_9N_3$.—A 2% solution of potassium permanganate (225 c.c.) was added during 1 hour to a suspension of the base (1·5 g.) in water (100 c.c.). Oxidation was rapid, but to ensure its completion the mixture was warmed to 45° for 10 minutes, after which alcohol was added to remove excess permanganate. The suspension was filtered, and the filtrate made barely acid to Congo red with hydrochloric acid and extracted with ether; no material could be extracted at a higher pH. When the extraction appeared to be complete, the aqueous solution was made distinctly acid to Congo red if its colour was deeper than pale yellow; in such cases re-extraction gave a further yield of ether-soluble material. Concentration of the dried, orange-yellow ethereal extract gave a crystalline residue; this was combined with the product from a duplicate experiment, and, after one crystallisation from ethyl acetate, yielded heavy orange-red prisms (1·8 g.), m. p. 146—147°. The *substance* (XIV) separated characteristically from water, in which it is sparingly soluble in the cold, as a mixture of voluminous white and denser red needles (the latter tended to predominate on standing) of unchanged m. p. (Found: C, 63·9, 63·6; H, 3·85, 3·9; N, 18·8, 18·8. $C_{12}H_9O_2N_3$ requires C, 63·45; H, 4·0; N, 18·5%). Oxidations on a smaller scale gave similar results. A suspension of the substance in cold water dissolved on addition of aqueous sodium bicarbonate or dilute hydrochloric acid; the solutions in acid and alkali were orange in colour. The *picrate* (90 mg.), prepared from a hot solution of 50 mg. of the substance in 14 c.c. of water and 6 c.c. of saturated aqueous picric acid, formed long, lustrous red needles, m. p. 172—174°, unchanged by several crystallisations from water. The colour lightened to orange after drying (Found: C, 47·9; H, 2·7; N, 18·45. $C_{12}H_9O_2N_3,C_6H_3O_7N_3$ requires C, 47·4; H, 2·65; N, 18·4%).

Action of Hydrochloric Acid on (XIV).—The compound (1·5 g.) was refluxed for 3 hours with a mixture of equal volumes of water and concentrated hydrochloric acid (12·5 c.c.). The dark brown solution crystallised on cooling, and the solid (1·05 g.) was dissolved by treatment with hot 2N-sodium hydroxide followed by repeated digestion of the insoluble portion with hot water. The alkaline and aqueous solutions were combined, filtered (charcoal) from a trace of insoluble matter, and made just acid to Congo red with dilute hydrochloric acid. The precipitated solid (0·75 g.) was collected and washed (evaporation of the filtrate gave some tarry material which was discarded), and digested with boiling alcohol (15 c.c.). After a second digestion, the high-melting component of the mixture was obtained almost pure (0·33 g., m. p. 250—251°); the pure *substance* crystallised rapidly from acetic acid in small, slightly discoloured prisms, m. p. 253—254° (Found: C, 58·05; H, 3·25; N, 17·6. $C_{11}H_7O_3N_3$ requires C, 57·65; H, 3·1; N, 18·3. $C_{12}H_9O_3N_3$ and $C_8H_6O_2N_2$ require C, 59·3; H, 3·7; N, 17·3%). The substance was almost insoluble in boiling water, sparingly soluble in hot 2N-, and fairly easily soluble in hot 6N-hydrochloric acid. The yellow sodium salt was only formed to a slight extent in presence of warm aqueous bicarbonate, but more easily with warm sodium carbonate and sodium hydroxide solutions; this salt was sparingly soluble in water, and less so in alkali solutions.

The alcoholic filtrates from the above compound were combined and concentrated, and the crude acid, m. p. 175—185° (0·27 g.), crystallised repeatedly from alcohol (charcoal), after removal of a small quantity of insoluble material. The *acid* formed long, soft, orange-pink needles, m. p. 194—195°, very sparingly soluble in hot water, easily soluble in aqueous sodium bicarbonate and other alkalis and in hydrochloric acid giving orange solutions (that in dilute hydrochloric acid crystallised on cooling) (Found: C, 54·95; H, 3·0; N, 16·05. $C_{12}H_9O_4N_3$ requires C, 55·6; H, 3·5; N, 16·2. $C_8H_5O_3N_2$ requires C, 54·2; H, 2·8; N, 15·8%). A solution of the acid (110 mg.) in concentrated hydrochloric acid (1 c.c.) and water (1 c.c.) was refluxed for 3½ hours; no material separated on cooling. Solvent was removed in an evacuated desiccator, and, on treatment of the residue with aqueous sodium hydroxide, all but a trace dissolved. Acidification (to Congo red) of the filtered solution followed by crystallisation of the solid from alcohol (charcoal) gave 30 mg of unchanged material (m. p. 185—187°, mixed m. p. intermediate) as the least soluble fraction. The filtrate was evaporated to dryness, and the residue was found to be freely soluble in aqueous bicarbonate except for a trace of insoluble matter, thus indicating the absence of significant quantities of the substance, m. p. 254°, described above.

Derivatives of Product from Reaction between 4-*Hydroxy*-6-*methoxycinnoline*-3-*carboxylic Acid, Pyridine, and Acetic Anhydride.*—The crude cinnolinecarboxylic acid (5 g.) was heated at 95° for 1½ hours with pyridine (35 c.c.) and acetic anhydride (40 c.c.). After standing overnight at 0°, the solution had deposited 3·65 g. of a lustrous, brown crystalline solid, m. p. 214—216° (decomp.). No attempt was made to purify this substance, portions of which were treated as follows:

(a) 0·5 G. was refluxed with methyl alcohol (100 c.c.) for 2 hours. The *methyl* derivative (0·44 g.), obtained by concentration of the green fluorescent solution, separated from methyl alcohol in clusters of glistening, colourless, prismatic needles, m. p. 179—180° to a dark green liquid (Found: C, 60·8; H, 5·1; N, 12·1; OMe, 16·7. $C_{18}H_{17}O_5N_3$ requires C, 60·8; H, 4·8; N, 11·8; OMe, 17·45%).

(b) A similar experiment to (a) using ethyl instead of methyl alcohol gave 0·3 g. of a dirty white solid, m. p. 65—75°. This m. p. is unexpectedly low, and the substance has not yet been purified.

(c) 1 G. was refluxed for 1 hour with pyridine (16 c.c.), solvent removed at 15 mm., and the residual oil left to crystallise in an exhausted desiccator. The product, after several crystallisations from alcohol, formed clusters of pale yellow prismatic needles, m. p. 131·5—132·5° (Found: C, 64·5; H, 4·7; N, 14·4; OMe, 10·4. $C_{16}H_{15}O_3N_3$ requires C, 64·6; H, 5·1; N, 14·1; OMe, 10·4%).

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