

329. Cinnolines. Part XV. The Alkaline Decomposition of Some Quaternary Salts of 4-Substituted Cinnolines.

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The reaction which occurs when 4-substituted alkylcinnolinium salts are treated with alkali depends markedly on the nature of the 4-substituent. 4-*p*-Hydroxyphenylcinnoline ethiodide gives, as major products, acetaldehyde and the parent base, and the reaction shows significant qualitative similarities to that previously studied (McIlwain, *J.*, 1937, 1704) with alkylphenazonium salts. On the other hand, retention of the *N*-alkyl group is observed with 6-chloro-4-aminocinnoline methiodide, which yields mainly ammonia and 6-chloro-1-methyl-4-cinnolone.

THE experiments described in this paper were undertaken with the object of locating the basic centre of 4-substituted cinnolines, the scheme envisaged being the preparation of quaternary salts of such compounds and study of their decomposition reactions in the hope that the point of quaternary salt formation, and hence the basic centre, might thus be disclosed. Combination of 4-phenyl-3-methyl-, 4-*p*-hydroxyphenyl-, and 3-phenyl-4-*p*-hydroxyphenylcinnoline with ethyl iodide proceeded readily, giving the corresponding ethiodides in reasonably high yields. Preliminary experiments showed that 4-*p*-hydroxyphenylcinnoline ethiodide (I; R = H) was very readily decomposed under mild alkaline conditions; an intense crimson coloration was first produced, and the parent cinnoline was isolated from the reaction mixture. Although this result was disappointing from the point of view of the objective mentioned, the reaction seemed of sufficient interest to merit further study. It was then found that the decomposition was not alkali-catalysed, that it could be effected by cold or hot aqueous sodium hydroxide or carbonate and by hot ammonium hydroxide, and that acetaldehyde was a major product of the reaction.

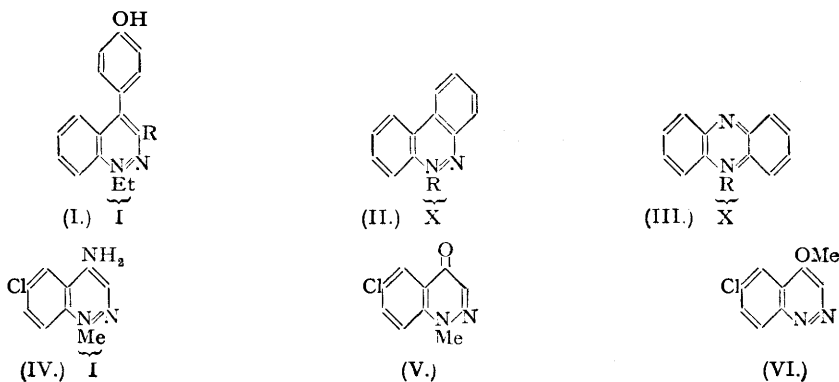
The decomposition of 3-phenyl-4-*p*-hydroxyphenylcinnoline ethiodide (I; R = Ph) was not examined in detail, but probably proceeds analogously, as the parent base was readily isolated, and the smell of acetaldehyde was noticeable during the reaction. It is possible that quaternary salts of 3 : 4-benzocinnoline (II) decompose in the same way, as Ullmann and Dieterle (*Ber.*, 1904, 37, 23) noted that the parent base was regenerated by treatment of such salts with alkali, but did not investigate the reaction further. This type of reaction is strongly reminiscent of that shown by phenazonium salts (III) in alkaline solution; the regeneration of the parent base from such salts has been observed by various workers, and a more recent study of this reaction by McIlwain (*J.*, 1937, 1704) has shown that it takes the course $2 \text{ BMe}\cdot\text{OH} \longrightarrow \text{B} + \text{BHMe} + \text{CH}_2\text{O} + \text{H}_2\text{O}$.

There is thus a striking parallel between the decomposition of alkylphenazonium salts and that of certain alkylcinnolinium halides. However, further examination of the decomposition of (I; R = H) disclosed that the yield both of 4-arylcinnoline and of acetaldehyde was 70–75 mols. % (based on quaternary salt) and thus indicated that the relationship between the reactions is merely qualitative. The extent to which the 25% of unrecovered cinnoline functions as hydrogen acceptor is unknown; identification of hydrogen as a product of reaction was not attempted, and the non-volatile residue, after removal of 4-*p*-hydroxyphenylcinnoline, was an oil. The properties of the latter suggested instability—for example, the oil was soluble in acetone giving a brilliant blue solution, the colour of which faded completely after some hours' exposure to the air; this behaviour, also, is reminiscent of that shown by alkylphenazonium salts, which give rise to free radicals (McIlwain, *loc. cit.*). Qualitative similarity between the reactions of the two series of salts was further suggested by the observation that, under suitable conditions, the decomposition of the cinnolinium salt is accompanied by nuclear iodination with formation of *x*-iodo-4-*p*-hydroxyphenylcinnoline; this is almost certainly a case of anionoid substitution, which is a characteristic feature of the decomposition of phenazonium salts (McIlwain, *loc. cit.*).

The resemblance between the decompositions of cinnolinium and of phenazonium salts is not unexpected in view of the vinylogous relationship existing between the location of the nitrogen atoms in the two heterocyclic systems. The reaction may not, however, be characteristic of all 4-arylcinnolinium compounds; for example, 4-phenyl-3-methylcinnoline ethiodide did not show this behaviour, and the following observations clearly indicate that the nature of the 4-substituent profoundly influences the reaction.

From 6-chloro-4-aminocinnoline (Part XVII, in the press) was obtained an excellent yield of the methiodide (IV), which on treatment with a large excess of alkali hydroxide at room

temperature was converted into the methohydroxide (or pseudo-base). This substance was stable at room temperature, but in hot alkaline solution decomposed into ammonia and 6-chloro-1-



methyl-4-cinnolone (V). The structure of (V) (the major product of the reaction) follows from its identity with the product of the action of methyl sulphate on 6-chloro-4-hydroxycinnoline, whereas treatment of 4:6-dichlorocinnoline with sodium methoxide furnished the isomeric 6-chloro-4-methoxycinnoline (VI). The position of quaternary salt formation in 6-chloro-4-aminocinnoline is thus established as N₁; this is, therefore, the basic centre of this substance, and probably of other Bz-substituted 4-aminocinnolines (Part XVII) also.

This evidence, taken in conjunction with the properties of 4-methylcinnolines described in Part XII (*J.*, 1947, 808), lends strong support to the suggestion (*loc. cit.*) that the basic nitrogen of all 4-substituted cinnolines is N₁; the alternative thesis, namely that the centre of basicity could be shifted from N₁ to N₂ by the introduction of suitable 4-substituents, now becomes a more remote contingency. It should be noted, however, that formal proof of this point is still lacking for 4-hydroxycinnolines; the fact that in these substances alkylation occurs at N₁ is irrelevant, because *N*-alkylation of any hydroxylated nitrogenous heterocyclic ring involves triad or pentad prototropy, irrespective of basicity. It happens that in 4-hydroxycinnolines N₁ functions in both capacities, but this need not always be so, and our experience with certain quinazoline derivatives (Morley and Simpson, in the press) has in fact demonstrated that in these compounds the positions of quaternary salt formation and *N*-alkylation are probably not identical.

The decomposition of (IV) also gave rise to small amounts of two other substances of unknown structure. One of these was a neutral compound (*substance X*), isomeric with (V) and (VI), which could not be hydrolysed under mild conditions; the formation of this compound was apparently independent of the pH of the medium provided alkalinity was maintained. The other compound was an *iodide*, m. p. 238°, isolated from faintly acid solution.

EXPERIMENTAL.

(Melting points are uncorrected.)

4-Phenyl-3-methylcinnoline Ethiodide.—A solution of the cinnoline (3 g.) in alcohol (15 c.c.) and ethyl iodide (7.5 c.c.) was refluxed for 4 hours. Concentration and cautious addition of ether precipitated the crude *ethiodide*, which separated from alcohol in soft, light-red needles, m. p. 206—207° [Found: C, 53.85; H, 4.8; I (mean of several inconsistent values), 35.3. C₁₇H₁₇N₂I requires C, 54.25; H, 4.55; I, 33.75%]. On the small scale, decomposition of the salt with aqueous sodium hydroxide at room temperature gave an amorphous basic solid from which no 4-phenyl-3-methylcinnoline could be isolated, and which did not give a crystalline picrate.

3-Phenyl-4-*p*-hydroxyphenylcinnoline Ethiodides.—A suspension of the cinnoline (2.5 g.) in alcohol (30 c.c.) and ethyl iodide (10 c.c.) was refluxed for 7 hours, a clear dark-coloured solution being gradually formed. On concentration, a mixture (2.35 g.) separated, from which substantially pure *monoethiodide* (0.9 g.) was obtained by recrystallisation from alcohol; the pure compound formed clusters of small orange leaflets, m. p. 227—228° (decomp.) (Found: C, 58.15; H, 4.45; I, 26.35. C₂₂H₁₉ON₂I requires C, 58.15; H, 4.2; I, 28.0%). It (400 mg.) was decomposed by hot *N*-sodium hydroxide (10 c.c.) (an intensely purple-crimson solution was produced) with regeneration of the original cinnoline (130 mg., m. p. 283—285°, mixed m. p. 284—286°); no search for other products was made, but the odour of acetaldehyde was observed during the decomposition [cf. the decomposition of 4-*p*-hydroxyphenylcinnoline ethiodide (*q.v.*)]. The salt gave an intense crimson solution in concentrated sulphuric acid; on dilution the colour faded and a precipitate was formed.

The filtrate from the crude monoethiodide (from another experiment) was concentrated further; the resultant solid, after several crystallisations from alcohol, formed deep ruby-red blades, m. p. 216—217°

(190—195° when mixed with the monoethiodide), and from analysis appeared to consist principally of a diethiodide (Found: C, 44.7; H, 3.25; I, 37.5. $C_{22}H_{24}ON_2I_2$ requires C, 47.2; H, 4.0; I, 41.6%).

Addition of a drop of piperidine to an alcoholic solution of the mixed ethiodides gave an intense green colour, becoming deep blue-green on dilution. Addition of acid to this solution destroyed the colour, which was restored (purple) by ammonia or sodium carbonate with precipitation at an intermediate stage of an amphoteric solid.

Preparation and Alkaline Decomposition of 4-*p*-Hydroxyphenylcinnoline Ethiodide.—The cinnoline (10 g.), alcohol (200 c.c.), and ethyl iodide (60 c.c.) were refluxed for 4 hours. The ethiodide, obtained by concentration, crystallised from alcohol in scarlet prisms, m. p. 237—239° (Found: C, 51.15; H, 4.15. $C_{16}H_{15}ON_2I$ requires C, 50.8; H, 4.0%; satisfactory iodine figures could not be obtained); yield of nearly pure compound, 13 g. The salt gave a deep crimson solution in concentrated sulphuric acid, becoming yellow on dilution. Addition of piperidine to an alcoholic solution produced a very intense purple colour, discharged by acid and restored by ammonia or sodium carbonate solution.

The following alkaline decompositions of the salt were carried out.

(a) A solution of the salt (1 g.) in warm water (80 c.c.) was treated with 2*N*-sodium carbonate (20 c.c.) and heated at 90—95°; nitrogen was bubbled through the liquid, and the issuing gases were passed into a solution of 2:4-dinitrophenylhydrazine (0.6 g.) in 10% sulphuric acid (66 c.c., v/v). After 1 hour the precipitated hydrazone was collected (0.43 g., m. p. 143—144°) and recrystallised from alcohol, yielding flat yellow needles, m. p. 166.5—167.5° alone and mixed with authentic acetaldehyde 2:4-dinitrophenylhydrazone. The alkaline solution in the reaction flask was acidified with acetic acid, giving almost pure 4-*p*-hydroxyphenylcinnoline (0.45 g.), m. p. 229—231°, and 232—233° (alone and in admixture with authentic material) after crystallisation from alcohol.

(b) An experiment carried out as in (a) except that the sodium carbonate was replaced by 2*N*-sodium hydroxide (20 c.c.) gave 4-*p*-hydroxyphenylcinnoline in identical yield and purity, but only 0.15 g. of crude aldehyde dinitrophenylhydrazone (m. p. 129—135°). From this, a small amount of acetaldehyde 2:4-dinitrophenylhydrazone, m. p. 161—163°, was obtained by repeated crystallisation from alcohol. Apparently other aldehydes had been present (probably formed by self-condensation of the acetaldehyde), but these were not identified. The identity of the cinnoline obtained in this and the preceding experiment was confirmed by acetylating the combined crops; 4-*p*-acetoxyphenylcinnoline (preceding paper), m. p. and mixed m. p. 127.5—128.5°, was thus obtained.

(c) A solution of the salt (2 g.) in water (240 c.c.) and 2*N*-sodium carbonate (40 c.c.) was left for 4 months in an uncorked flask at laboratory temperature. The solid which had separated was collected and washed with water until the washings were colourless; 0.95 g., m. p. 237—241°. As it could not be purified by crystallisation, the whole was acetylated (boiling acetic anhydride) and freed from solvent in an evacuated desiccator. The residue was repeatedly crystallised from benzene-ligroin (b. p. 60—80°), yielding *α*-*iodo*-4-*p*-acetoxyphenylcinnoline as stout, pale yellow polyhedra, m. p. 158—160° (Found: C, 50.2; H, 2.9; N, 7.9; I, 33.55. $C_{16}H_{11}O_2N_2I$ requires C, 49.2; H, 2.85; N, 7.2; I, 32.6%). From a small-scale experiment in which the alkaline solution had stood for only 10 weeks a mixture was isolated which could not be purified by direct crystallisation but which (m. p. 243—244°) contained iodocinnoline (Found: I, 18.35. Calc. for $C_{14}H_9ON_2I$: I, 36.5%). pure 4-*p*-acetoxyphenylcinnoline was readily isolated by acetylation of the more soluble material.

(d) In other experiments in which sodium and ammonium hydroxide were used, the reaction mixtures were extracted with ether before acidification; small amounts of a brown oil were thus obtained, which was easily soluble in acetone giving a brilliant and very intense purple solution, the colour of which faded perceptibly during 2 hours' exposure to the air, and completely on standing overnight.

(e) A solution of the salt (0.5 g.) in water (45 c.c.) and 4*N*-ammonia (5 c.c.) was left at laboratory temperature for 10 weeks in an open flask. A sticky solid separated during this time, from which unchanged quaternary salt was isolated (by extraction with hot water) as the only identifiable product.

6-Chloro-4-methoxycinnoline.—A solution of 4:6-dichlorocinnoline (2 g.; this vol., p. 917) and sodium methoxide (0.8 g.) in methyl alcohol (50 c.c.) was refluxed for 20 minutes, cooled, acidified with acetic acid, and diluted with water. The precipitate was filtered off, washed, and recrystallised from methyl alcohol, from which 6-chloro-4-methoxycinnoline (1.5 g.) separated in colourless narrow blades, m. p. 169.5—170° (Found: C, 55.6; H, 3.9; N, 13.9. $C_9H_7ON_2Cl$ requires C, 55.5; H, 3.6; N, 14.4%).

6-Chloro-1-methyl-4-cinnolone.—Methyl sulphate (2 c.c.) was added to a slightly warm solution of 6-chloro-4-hydroxycinnoline (2 g.; *J.*, 1945, 520) in aqueous potassium hydroxide (20%, 40 c.c.). The mixture was heated on the steam-bath, separation of the product (2 g., m. p. 188—200°) occurring almost immediately. After several crystallisations from water containing a little 2*N*-hydrochloric acid, and finally from alcohol, 6-chloro-1-methyl-4-cinnolone separated in stout, pale yellow, brittle needles, m. p. 221—222° after previous shrinking (Found: C, 55.85; H, 4.0; N, 14.2. $C_9H_7ON_2Cl$ requires C, 55.5; H, 3.6; N, 14.4%). Although the free base separates from dilute hydrochloric acid, it is distinctly more soluble therein than in water alone (from which it forms long, silky needles).

Preparation and Alkaline Decomposition of 6-Chloro-4-aminocinnoline Methiodide.—Prepared from 6-chloro-4-aminocinnoline (Part XVII, in the press) (8 g.), alcohol (100 c.c.), and methyl iodide (20 c.c.) (3½ hours under reflux), 6-chloro-4-aminocinnoline methiodide (crude yield, 12.1 g.) crystallised from hot water in long, saffron-coloured needles, m. p. 225—226° (decomp.) (Found: C, 32.35; H, 3.2; N, 12.5. $C_9H_8N_2ClI \cdot 0.5H_2O$ requires C, 32.7; H, 3.05; N, 12.7%). Halogen determinations were unsatisfactory. The following procedure was the outcome of several preliminary experiments.

A solution of the salt (4 g.) in water (160 c.c.) was treated with 2*N*-sodium hydroxide (100 c.c.) and left at laboratory temperature. The dark oil which soon separated from the green solution changed overnight to a mass of soft, almost colourless needles, which (1.5 g.) were filtered off (filtrate *A*) and, without purification (the substance was unstable and could not be recrystallised), dissolved in 50% aqueous acetic acid (10 c.c.) (solution *B*). One half of this solution was brought to pH 9 with sodium hydroxide and boiled gently for ¼ hour; a little ammonia was evolved. The solution was diluted

somewhat with water and filtered hot (charcoal); a solid separated on cooling, which on recrystallisation from water yielded *substance X* in long, colourless needles, m. p. 162—163°, which gave a positive Beilstein halogen test (Found : C, 55·9; H, 3·7; N, 14·4, 14·7. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%). This substance was less soluble in water than 6-chloro-1-methyl-4-cinnolone, and crystallised well from benzene. It gave a marked depression in melting point when mixed with 6-chloro-4-methoxycinnoline. It showed no basic or acidic properties, and was unaffected by short boiling with dilute hydrochloric acid or sodium hydroxide. The first filtrate from *substance X* was made alkaline to thymolphthalein (sodium hydroxide) and boiled; ammonia was again evolved, and recrystallisation (water; charcoal) of the solid which separated from the hot solution yielded 6-chloro-1-methyl-4-cinnolone, m. p. and mixed m. p. 220—221°. The other half of solution *B* was made strongly alkaline with sodium hydroxide and boiled; *substance X* and 6-chloro-1-methyl-4-cinnolone were separated (by the use of dilute hydrochloric acid) and identified (m. p. and mixed m. p.).

Filtrate *A* was divided into 2 parts. One was decomposed at pH 11 by boiling, and yielded ammonia, 6-chloro-1-methyl-4-cinnolone, and *substance X*. The other part was brought to pH 6 with acetic acid, boiled for 20 minutes, and concentrated on the steam-bath to 2/3 volume. The mixture which separated gave 6-chloro-1-methyl-4-cinnolone as the least soluble component, and the early filtrates from this compound contained an iodide; this *salt*, after several crystallisations from alcohol, formed yellow rosettes of small needles, m. p. 237—238° (Found : C, 43·05; H, 3·95; N, 12·6%).

Similar results to the above were obtained when the original treatment of the quaternary salt with sodium hydroxide was performed under nitrogen.

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