85. *Cinnolines. Part XXV. Experiments with 3-Halogeno-4-hydroxycinnolines. Some Halogen Exchange Reactions.*

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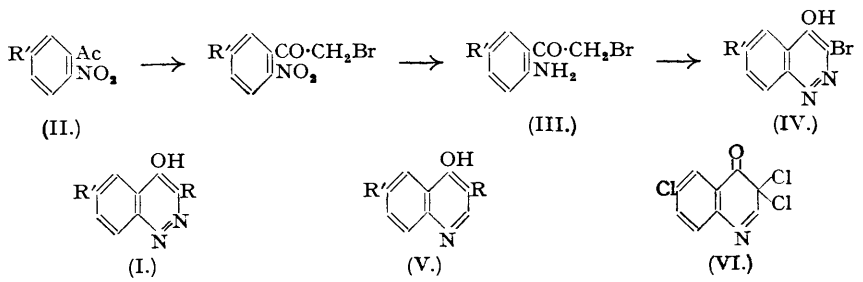
The bromination of diazotised *o*-aminoacetophenone, and the bromination and chlorination of 4-hydroxycinnoline, have given mediocre yields of 3-halogeno-4-hydroxycinnolines. The substitution of bromine by chlorine which occurs when bromo-4-hydroxycinnolines react with phosphorus chlorides appears to proceed by different mechanisms, depending on the presence of the bromine at $C_{(3)}$ or $C_{(6)}$. Qualitative comparison with related 4-hydroxyquinolines shows that these undergo chlorination and bromination more rapidly and more efficiently at $C_{(3)}$ than do analogous cinnolines, but halogen exchange reactions occur much more slowly, if at all.

The synthesis of some 3-halogeno-4-hydroxycinnolines (I; R = Cl or Br, R′ = H, Cl or Br) was recently reported (Schofield and Simpson, *J.*, 1948, 1170). Some experiments with these compounds and a qualitative comparison with analogous quinoline derivatives are now described.

The original synthesis of 3-bromo-4-hydroxycinnolines (II ⟶ IV) suffers from the disadvantages, especially in the case of (II; R′ = H), that pure nitroacetophenones are essential, and that compounds (III) are unstable. Thus, before beginning a study of 3-bromo-

4-hydroxycinnolines, some experiments were made in search of a simplified route to these compounds. The results are of interest, but it cannot be claimed that the desired products have been rendered any easier of access.



(II.) (III.) (IV.)

(I.) (V.) (VI.)

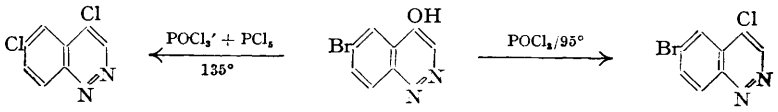
Bülow and Schmachtenberg (*Ber.*, 1908, **41**, 2607) found that the decomposition of benzenediazonium perbromide in the presence of acetophenone gave ω-bromoacetophenone, and Hopf and Le Fèvre (*J.*, 1939, 1067) also observed the brominating action of a compound of this type. It seemed possible, therefore, that decomposition of the perbromide from diazotised *o*-aminoacetophenone might provide 3-bromo-4-hydroxycinnoline, obviating the need for pure *o*-nitroacetophenone, *o*-aminoacetophenone being available from the crude nitro-compound arising from the nitration of acetophenone (Schofield and Swain, *J.*, 1948, 384). Under a variety of conditions 3-bromo-4-hydroxycinnoline was obtained by this method. In no case was the yield greater than 34%, but the experiments were not exhaustive and the reaction might repay further study.

Direct halogenation of the readily available 4-hydroxycinnolines promised to be an attractive route to 3-halogeno-4-hydroxycinnolines. Examples of analogous brominations of quinoline derivatives are mentioned in the early literature (Chick and Wilsmore, *J.*, 1910, **97**, 1990; Knorr, *Annalen*, 1886, **236**, 91; Meyer and Heinmann, *Compt. rend.*, 1936, **203**, 264), and recently Riegel and his co-workers (*J. Amer. Chem. Soc.*, 1946, **68**, 1229, 1532) prepared 3-bromo-4-hydroxyquinolines by this method, whilst Surrey and Cutler (*ibid.*, p. 2570) made a comprehensive study of the direct halogenation of ethyl 4-hydroxyquinaldates with sulphuryl chloride, bromine, and iodine monochloride, in acetic acid, obtaining the corresponding 3-halogeno-derivatives. Consequently, we treated 4-hydroxy-, 6-chloro-4-hydroxy-, and 6-bromo-4-hydroxy-cinnoline with both sulphuryl chloride and bromine in acetic acid. In no case was halogenation so rapid or so efficient as with the related quinoline derivatives under the same conditions. The products appeared to be mixtures, from which mediocre yields (*ca.* 20%) of 3-halogeno-4-hydroxycinnolines (I; R = Cl or Br; R′ = H, Cl or Br) were isolated.

For comparative purposes, and because the products were required for the work described later in this paper, the quinoline analogues (V; R = Cl or Br, R′ = H, Cl or Br) of the above cinnolines were prepared. 4-Hydroxy- and 6-chloro-4-hydroxy-quinoline are readily prepared by the ethoxymethylenemalonic ester reaction (see, among others, Price and Roberts, *ibid.*, p. 1204) and we have now prepared *6-bromo-4-hydroxyquinoline* by this method (see Experimental). By the action of sulphuryl chloride on 4-hydroxyquinoline we isolated a low yield of a trichloro-derivative (cf. Riegel *et al.*, *ibid.*, p. 1229). Surprisingly, this compound appeared to be converted by mixed phosphorus chlorides into a trichloroquinoline which did not depress the m. p. of 3 : 4 : 6-trichloroquinoline (see below). Although mixed m. p.s are not reliable with compounds of this type, the sequence of reactions suggests some such structure as (VI) for the initial product. With 6-chloro- and 6-bromo-4-hydroxyquinoline (in contrast to the cinnoline derivatives), sulphuryl chloride effected rapid and efficient monochlorination, giving what we regard as 3 : 6-*dichloro-* and 3-*chloro*-6-*bromo*-4-*hydroxyquinoline*. Bromination of the hydroxy-compounds under the conditions of Surrey and Cutler (*loc. cit.*) (Riegel *et al.*, *loc. cit.*, used a longer reaction time) proceeded rapidly enough at 95° to give good yields of 3-*bromo-*, 6-*chloro*-3-*bromo-*, and 3 : 6-*dibromo*-4-*hydroxyquinoline* in ten minutes.

One of our objects in preparing the above halogeno-4-hydroxycinnolines was to examine further the problem of halogen exchange. In previous cinnoline studies (Schofield and Simpson, *loc. cit.*; Atkinson and Simpson, *J.*, 1947, 232; Keneford, Morley, and Simpson, *J.*, 1948, 1702) cases of the replacement of a bromine atom by a chlorine atom in the diazonium salt stage of the Borsche synthesis have been observed. But another type of replacement involving a

bromine atom in a cinnoline nucleus was observed by Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 419), who noticed that, although phosphorus oxychloride at 95° converted 6-bromo-4-hydroxycinnoline into 4-chloro-6-bromocinnoline, a mixture of phosphorus oxychloride and pentachloride at 135° produced a compound which they suggested was 4 : 6-dichlorocinnoline. This suggestion was readily proved correct. Morley, Keneford, and Simpson (*loc. cit.*)



observed what is probably a similar replacement of the nitro-group in 7-chloro-6-nitro-4-hydroxycinnoline. Our own interest in reactions of this sort was prompted by the observation that mixed phosphorus chlorides converted 3-bromo-4-hydroxycinnoline into a product intermediate in composition between 4-chloro-3-bromo- and 3 : 4-dichloro-cinnoline. We have examined the action of phosphorus oxychloride and pentachloride, alone and mixed, at 95° and 135°, on 3-bromo-, 6-bromo-, 6-chloro-3-bromo-, and 3 : 6-dibromo-4-hydroxycinnoline.

Three criteria were used to detect and roughly estimate the occurrence of bromine replacement by chlorine. Most important was elementary analysis of the products, and of the derived 4-phenoxy-compounds. Secondly, although with these compounds mixed m. p.s are of little value since depressions are not in general observed, yet m. p.s of the products provided a useful criterion since it was found that they rose as the degree of exchange decreased. In this connection 4 : 6-dichloro- and 4-chloro-6-bromo-cinnoline, required as standard substances, were already known (Keneford and Simpson, *J.*, 1947, 917; Leonard and Boyd, *loc. cit.*), and by usual methods we prepared 3 : 4-*dichloro-* and 3 : 4 : 6-*trichloro-cinnoline*, and also 3-*chloro*-4-*phenoxycinnoline*. Thirdly, if replacement was occurring, bromine appeared in the reaction vessel.

The essential results, obtained under the standard conditions used in these experiments, are summarised in Table I, from which the degree of exchange in any example can be judged roughly by the m. p. of the product, and also by the approximate calculation of percentage exchange based on the carbon content of the compounds.

It was important to decide if the 4-hydroxy-group was involved in the exchange reaction, or if its replacement by chlorine was completed before substitution of bromine by chlorine occurred. The latter possibility seemed the more likely since Leonard and Boyd (*loc. cit.*) reported that the hydroxyl group of 4-hydroxycinnoline was replaced in five minutes under the action of phosphorus oxychloride, and Surrey and Cutler (*loc. cit.*) have shown that in ten minutes the same reagent can convert many 4-hydroxyquinolines into the 4-chloro-compounds. We find that 4-chloro-, 4 : 6-dichloro-, and 3 : 4-dichloro-cinnoline are formed quantitatively in this short reaction time, and by this means it was possible to convert bromine-containing 4-hydroxycinnolines into the 4-chloro-compounds with a minimum of halogen exchange, although the products were not quite pure. Complete proof that the 4-hydroxy-group is not essential to the exchange reaction was provided by showing that further treatment of these fairly pure 4-chloro-bromocinnolines with phosphorus chlorides caused exchange of chlorine for bromine in the same way as when the 4-hydroxy-compounds were used in the reaction.

The quinoline derivatives described above provided an interesting comparison with their cinnoline analogues, when treated under the conditions which caused halogen exchange in the latter. 4 : 6-Dichloro- and 4-chloro-3-bromo-quinoline have been described by Riegel *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1264, 1229), and we have now prepared 4-*chloro*-6-*bromo-*, 3 : 4 : 6-*trichloro-*, 3 : 4-*dichloro*-6-*bromo-*, 4 : 6-*dichloro*-3-*bromo-*, and 4-*chloro*-3 : 6-*dibromo-quinoline*. Treatment of the bromine-containing compounds with phosphorus chlorides, under conditions which replace, partly or completely, the bromine in the cinnoline analogues, did cause some halogen exchange (as evinced by bromine vapour appearing in the reaction vessels) but analysis showed it to have occurred to a very small extent. This was expected in view of earlier reports of the preparation of 4-chloro-compounds from bromine-substituted 4-hydroxyquinolines. Thus, Kermack and Weatherhead (*J.*, 1939, 563) boiled 6-bromo-4-hydroxyquinaldine for four hours with phosphorus oxychloride without apparently replacing the bromine atom. Steck and his co-workers (*J. Amer. Chem. Soc.*, 1946, **68**, 129, 380) satisfactorily prepared 4-chloro-5-, -6-, and -7-bromo-3-methylquinoline by a similar method, and Riegel *et al.* (*loc. cit.*) likewise obtained 4-chloro-3-bromoquinoline.

The conclusions to be drawn from Table I and from the above discussion can be stated briefly: (i) Replacement of the 4-hydroxy-group precedes halogen exchange and is indeed a very

TABLE I.

Summary of results obtained in halogen exchange reactions.

Conditions.				M. p.[a] and exchange, %, of products from substituted 4-hydroxycinnoline.							
				6-Bromo-.		3-Bromo-.		6-Chloro-3-bromo-.		3 : 6-Dibromo-.	
Reagent.[b]	Time (hrs.).	Temp.	Reflux or open.[c]	M. p.	Exchange, %.	M. p.	Exchange, %.	M. p.	Exchange, %.	M. p.	Exchange, %.[d]
M	2	95°	O	113°	—	147°[e]	34	142·5°	100	146°	47
M	¼	95	O	126	—	—	—	—	—	—	—
M	2	95	R	—	—	143·5[e]	37	143·5[f]	83	147	47
M	2	135	O	113[g]	100[h]	149·5	7·5	149·5	51	156·5	31
M	2	135	R	—	—	153	6	154·5	14	161	10
M	24	95	R	—	—	130	—	—	—	—	—
M	24	135	R	—	—	143	—	148	—	152	—
O	2	95	R	118	—	142	—	145	—	148	—
O	2	135	R	113	—	151·5	—	152	—	159	—
P	1	95	R	126	—	127	—	140	—	—	—
P	½	135	R	—	—	130	—	135	—	141	—

(*a*) M. p.s of possible products: 3 : 4-dichlorocinnoline, m. p. 126—127°; 4 : 6-dichlorocinnoline, m. p. 112—113°; 3 : 4 : 6-trichlorocinnoline, m. p. 141—142°. (*b*) M = mixed phosphorus chlorides; P = phosphorus pentachloride; O = phosphorus oxychloride. (*c*) R = reflux; O = open vessel. (*d*) Based on total bromine (2 atoms). (*e*) This is the only case where reaction under reflux caused more exchange, but the difference is small. (*f*) 1 hour's heating. (*g*) ¼ hour or 2 hours. (*h*) From Leonard and Boyd's figures (*loc. cit.*).

rapid reaction. (ii) A mixture of phosphorus oxychloride and pentachloride being used, replacement of the bromine at $C_{(6)}$ is relatively rapid, and occurs more readily at the higher of the two temperatures used. (iii) By comparison, replacement of a bromine atom at $C_{(3)}$ is relatively slow, appears to be encouraged by the presence of a halogen atom at $C_{(6)}$, and is more rapid at 95° than at 135°. (iv) Replacement of bromine, whether at $C_{(3)}$ or $C_{(6)}$, by using phosphorus pentachloride, proceeds more rapidly at the higher temperature. (v) Phosphorus oxychloride, in contrast, produces similar results to those obtained with the mixed chlorides. (vi) Generally, use of an open vessel, whence bromine can easily escape, facilitates exchange, and the reverse is true for reactions carried out under reflux. (vii) Halogen exchange in the quinoline series proceeds very much more slowly, if at all appreciably, than in the cinnoline series.

Useful discussion of these results is rendered difficult, first by the absence of true analogies, and secondly by ignorance of the mechanism of reactions between phosphorus chlorides and compounds of the present type. Several examples of the replacement of bromine atoms by chlorine, through the agency of phosphorus pentachloride, in both the benzene and the naphthalene series have been reported (Schmidt and Wagner, *Annalen*, 1912, **387**, 164; Cone and Robinson, *Ber.*, 1907, **40**, 2160; Sindall, *Chem. News*, 1890, **60**, 58), but the conditions have usually been comparatively severe. In any case, different mechanisms may be involved in these examples. At first it seemed possible that the 4-hydroxy-group might be intimately connected with exchange of the 3-bromo-atom, somewhat in the manner in which a hydroxyl group adjacent to a halogen atom in a naphthalene compound controls the subsequent mode of halogenation (Fries and Schimmelschmidt, *Annalen*, 1930, **484**, 245), but the facts presented make it clear that the hydroxyl group is in no way involved in the reaction.

The different form of temperature dependence of the substitution at $C_{(6)}$ as against $C_{(3)}$ seems to suggest that different mechanisms of replacement are operative at each position. Possibly replacement of the 6-bromo-atom is an ordinary nucleophilic substitution, and from the point of view of comparative heterocyclic chemistry it is interesting that the cinnoline compounds are more susceptible to nucleophilic replacement than are the members of the quinoline series.

The qualitative results of bromination and chlorination of 4-hydroxycinnolines and 4-hydroxyquinolines suggest, on the other hand, that in the quinoline compounds $C_{(3)}$ is more readily attacked by electrophilic reagents than $C_{(3)}$ in 4-hydroxycinnolines. This is also true of our observation that 4-hydroxycinnoline fails to partake in a Mannich reaction under conditions which produce substitution of this kind in 4-hydroxyquinoline derivatives (Price and Jackson, *J. Amer. Chem. Soc.*, 1946, **68**, 1282). It should be noted that our results do not allow us to decide if $C_{(3)}$ in 4-hydroxyquinolines is absolutely more susceptible to electrophilic substitution than $C_{(3)}$ in 4-hydroxycinnolines, or only relatively so, as compared with other positions in the

two nuclei. Only a knowledge of the fate of material not accounted for as 3-halogeno-4-hydroxycinnoline, *i.e.*, whether it remained unsubstituted or whether substitution occurred at positions other than $C_{(3)}$, could decide this question.

It would clearly be of interest to examine the ease of halogen exchange in cinnolines unsubstituted at $C_{(4)}$ and this we hope to do.

Experimental.

(M. p.s are uncorrected.)

Bromination of Diazotised o-*Aminoacetophenone.*—(i) The amine (1 g.) in sulphuric acid (10 c.c.; 60% v/v) was diazotised at 0° with aqueous sodium nitrite (10%), and a solution of potassium bromide (1·47 g.) and potassium bromate (0·41 g.) in water (10 c.c.) added slowly at −5° to 0°. The suspension of brown granular solid produced was left overnight and then warmed at 80° for ¾ hour, and the tarry resin formed crystallised twice from alcohol. 3-Bromo-4-hydroxycinnoline (0·25 g., 15%) was thus isolated as pale brown needles, m. p. 273—274°, alone and mixed with an authentic specimen (m. p. 275—276°).

(ii) *o*-Aminoacetophenone (0·5 g.) was treated as in (i) but the suspension was left for 1 week at room temperature before being worked up as before. There resulted 0·28 g. (34%) of 3-bromo-4-hydroxycinnoline, m. p. 271—272°.

(iii) The ketone (0·59 g.) was diazotised as before, treated with a solution of potassium bromide (1·18 g.) and potassium bromate (0·21 g.) in water (5 c.c.), and worked up as in (ii), yielding 20% of the desired product.

(iv) The amine (1 g.) was diazotised and treated with a solution of potassium bromide (1·24 g.) and bromine (2·04 g.) in water (10 c.c.), left overnight, and worked up as in (i), yielding 12·5% of 3-bromo-4-hydroxycinnoline.

Direct Halogenation of 4-Hydroxycinnolines.

Chlorination of 4-Hydroxycinnoline.—The cinnoline (0·5 g.) in acetic acid (20 c.c.) and acetic anhydride (1 c.c.) was warmed at 95° for 4 hours with sulphuryl chloride (0·51 g.), the mixture refluxed for 5 minutes and then cooled, sodium hydroxide (0·2 g.) in water (10 c.c.) added, and the solution left at 0° for 3 hours. Recrystallisation of the precipitate (0·24 g.; m. p. 262—263°) from acetic acid gave 3-chloro-4-hydroxycinnoline (0·14 g., 22%), m. p. 278—279°, alone and mixed with an authentic specimen (m. p. 278—279°). Acetylation with boiling acetic anhydride gave a derivative, m. p. 124—125°, which did not depress the m. p. (124—125°) of genuine 3-chloro-4-acetoxycinnoline.

Chlorination in boiling acetic acid for 4 hours gave the same result, but one experiment at 95° using only 2 drops of acetic anhydride gave none of the chlorocinnoline.

Chlorination of 6-Chloro-4-hydroxycinnoline.—The cinnoline (0·5 g.), acetic acid (20 c.c.), acetic anhydride (1 c.c.), and sulphuryl chloride (0·42 g.) were refluxed together for 4 hours and worked up as above. The product (0·19 g., 32%), m. p. 301—303°, and its acetyl derivative, m. p. 148—149°, were identical with 3 : 6-dichloro-4-hydroxycinnoline (m. p. 302—303°) and 3 : 6-dichloro-4-acetoxycinnoline (m. p. 149—150°), respectively.

Chlorination of 6-Bromo-4-hydroxycinnoline.—By the same method 6-bromo-4-hydroxycinnoline (0·5 g.) gave 22% of 3-chloro-6-bromo-4-hydroxycinnoline, m. p. 306—307°, giving no depression on admixture with a pure specimen, m. p. 309—310°.

Bromination of 4-Hydroxycinnoline.—4-Hydroxycinnoline (1 g.), acetic acid (20 c.c.), and bromine (1·15 g.) were warmed at 95° for 2½ hours, crystals appearing after ¼ hour. After removal of the solvent under reduced pressure the residue (hydrobromides) was triturated with dilute ammonia solution, leaving a white solid (1·17 g.), m. p. 235—237°. Neutralisation of the ammoniacal washings with acetic acid gave some impure starting material (0·04 g.). Three crystallisations of the product from ethanol gave substantially pure 3-bromo-4-hydroxycinnoline (0·31 g., 20%), m. p. 272—273° showing no depression on admixture with a pure specimen, m. p. 275—276°. The acetyl derivative, m. p. 139—140°, was also identical with 3-bromo-4-acetoxycinnoline, m. p. 139—140°.

Bromination in boiling acetic acid during 1 hour gave 15% of 3-bromo-4-hydroxycinnoline.

Bromination of 6-Chloro-4-hydroxycinnoline.—The cinnoline (1 g.), treated as above, provided after trituration with ammonia a white solid (1·18 g., m. p. 275—276°). Four crystallisations from alcohol gave white needles (0·28 g., 19·5%), m. p. 308—309°, alone and mixed with genuine 6-chloro-3-bromo-4-hydroxycinnoline, m. p. 310—311°. The acetyl derivative, m. p. 165—166°, was identical with 6-chloro-3-bromo-4-acetoxycinnoline, m. p. 166—167°.

Bromination of 6-Bromo-4-hydroxycinnoline.—A white solid (1·02 g.; m. p. 275—277°) was obtained by brominating 6-bromo-4-hydroxycinnoline in the same way as above and triturating the product with ammonia. Four crystallisations from alcohol gave white needles (0·30 g., 22%), m. p. 313—314° (acetyl derivative, m. p. 178—179°), identical with 3 : 6-dibromo-4-hydroxycinnoline, m. p. 315—316° (acetyl derivative, m. p. 179—180°).

Halogenated 4-Hydroxyquinolines.

6-Bromo-4-hydroxyquinoline.—(*a*) *p*-Bromoaniline (25·2 g.) and ethyl ethoxymethylenemalonate (32 g.) (Fuson, Parham, and Reed, *J. Org. Chem.*, 1946, **11**, 194) were heated at 95° for 2 hours, and the alcohol formed was removed under reduced pressure. One crystallisation from methanol gave pale yellow crystals of a product suitable for further use (46 g.; m. p. 98—99°), and further crystallisation gave stout white needles of *ethyl β-(p-bromoanilino)-α-carbethoxyacrylate*, m. p. 100—101° (Found: C, 48·4; H, 4·75. $C_{14}H_{16}O_4NBr$ requires C, 49·1; H, 4·7%).

(*b*) The above compound (40 g.), finely powdered, was added during 10 minutes to boiling diphenyl ether (400 g.), and the mixture refluxed for ½ hour. After the mixture had cooled, ligroin was added (400 c.c.), and the product collected, washed with more ligroin and some ether, and dried, yielding pure

ethyl 6-bromo-4-hydroxyquinoline-3-carboxylate (34 g., 99%). It formed lustreless white microcrystals (from alcohol), m. p. 286—287° (Found: C, 48·8; H, 3·5. $C_{12}H_{10}O_3NBr$ requires C, 48·7; H, 3·4%).

(*c*) The ester (30 g.) was refluxed with potassium hydroxide solution (250 c.c.; 10%) for 2 hours, and the solution filtered (charcoal) and acidified with concentrated hydrochloric acid. The precipitate (22·7 g., 84%) of almost pure *4-hydroxyquinoline-3-carboxylic acid* separated from alcohol in white microcrystals, m. p. 271° (decomp.) (Found: C, 45·5; H, 2·3. $C_{10}H_6O_3NBr$ requires C, 44·8; H, 2·5%).

(*d*) The acid (5 g.) was added to boiling diphenyl ether (25 g.) during 5 minutes, the mixture was boiled under reflux for 25 minutes, cooled, and diluted with ligroin (25 c.c.), and the precipitate collected and washed with ligroin and ether. The substantially pure product (4·02 g.) formed stout pale yellow needles of *6-bromo-4-hydroxyquinoline*, m. p. 282—283°, from alcohol (Found: C, 46·3; H, 3·0. $C_9H_6ONBr,\frac{1}{2}H_2O$ requires C, 46·4; H, 3·0%).

A similar result was obtained by heating the acid at 285° for ¼ hour, but the initial product was not so pure as that obtained by the first method.

Chlorination of 4-Hydroxyquinoline.—4-Hydroxyquinoline (1 g.) in acetic acid (3·2 c.c.) and acetic anhydride (0·8 c.c.) at 45° was added to sulphuryl chloride (1·05 g.). The mixture was kept at the same temperature for 25 minutes, boiled for 5 minutes, and diluted with water (6 c.c.). The white solid (0·57 g.; m. p. 270—280°) was digested with alcohol (40 c.c.), and the residue (0·24 g.; m. p. >300°) crystallised from alcohol, giving white lustreless microcrystals of a *compound*, m. p. >320° (Found: C, 42·1; H, 2·2. $C_9H_4ONCl_3$ requires C, 43·5; H, 1·6%).

3 : 6-Dichloro-4-hydroxyquinoline.—6-Chloro-4-hydroxyquinoline (1·64 g.) in acetic acid (9 c.c.) and acetic anhydride (1 c.c.) was added to sulphuryl chloride (1·37 g.) at 45°. There was an immediate reaction and the temperature rose to >100°. The mixture was kept at 60—65° for ½ hour, boiled for 5 minutes, and then cooled, and sodium hydroxide (0·4 g.) in water (6 c.c.) added. Recrystallisation of the almost pure product (1·38 g.) from acetic acid gave lustreless yellow microcrystals of *3 : 6-dichloro-4-hydroxyquinoline*, m. p. >320° (Found: C, 50·6; H, 2·5. $C_9H_5ONCl_2$ requires C, 50·5; H, 2·4%).

3-Chloro-6-bromo-4-hydroxyquinoline.—6-Bromo-4-hydroxyquinoline (1·3 g.) was chlorinated as above, but after addition to sulphuryl chloride (0·87 g.) the mixture was kept at 100° for ½ hour. The product (1·14 g.) formed white microcrystals of *3-chloro-6-bromo-4-hydroxyquinoline*, m. p. >320°, from acetic acid (Found: C, 41·8; H, 2·3. $C_9H_5ONClBr$ requires C, 41·8; H, 1·95%).

3-Bromo-4-hydroxyquinoline.—Addition of bromine (0·72 c.c.) to 4-hydroxyquinoline (2 g.) in acetic acid (6 c.c.) at 70° caused an immediate reaction, the temperature rising to >100°. After 10 minutes at 70° the solution was cooled, and sodium hydroxide (0·55 g.) in water (10 c.c.) added, yielding a white solid (3·03 g.; m. p. 272—274°). Crystallisation from alcohol gave white microcrystals of 3-bromo-4-hydroxyquinoline (2·43 g., 79%), m. p. 281—282° (Riegel *et al.*, *loc. cit.*, give m. p. 288—289°, yield 89%).

6-Chloro-3-bromo-4-hydroxyquinoline.—The quinoline (2 g.), acetic acid (6 c.c.), and bromine (0·6 c.c.) were heated at 95° for 10 minutes, much solid being quickly deposited. Worked up as above, the mixture gave a white solid (2·4 g.) which separated from acetic acid as dull buff microcrystals of *6-chloro-3-bromo-4-hydroxyquinoline*, m. p. >320° (Found: C, 42·4; H, 2·2. $C_9H_5ONClBr$ requires C, 41·8; H, 1·95%).

3 : 6-Dibromo-4-hydroxyquinoline.—6-Bromo-4-hydroxyquinoline (2 g.), treated as above (0·5 c.c. of bromine), gave a pale yellow solid (2·51 g.) which separated from acetic acid as pale yellow microcrystals of *3 : 6-dibromo-4-hydroxyquinoline*, m. p. >320° (Found: C, 35·9; H, 1·7. $C_9H_5ONBr_2$ requires C, 35·7; H, 1·7%).

Halogen Exchange Reactions and Related Experiments with Cinnoline Derivatives.

3 : 4-Dichloro- and 3 : 4 : 6-Trichloro-cinnoline.—By the usual method (Keneford and Simpson, *loc. cit.*), 3-chloro- (1 g.) and 3 : 6-dichloro-4-hydroxycinnoline (0·4 g.) gave the desired products (0·7 g. and 0·3 g., respectively). *3 : 4-Dichlorocinnoline* formed white needles, m. p. 126—127°, from ether–ligroin (b. p. 60—80°) (Found: N, 14·8; Cl, 36·2. $C_8H_4N_2Cl_2$ requires N, 14·1; Cl, 35·6%), and *3 : 4 : 6-trichlorocinnoline* gave pale yellow needles, m. p. 141—142°, from the same solvent (Found: C, 41·2; H, 1·2; Cl, 45·9. $C_8H_3N_2Cl_3$ requires C, 41·15; H, 1·3; Cl, 45·6%).

3-Chloro-4-phenoxycinnoline.—3 : 4-Dichlorocinnoline (1·5 g.) was converted by standard means (Keneford and Simpson, *loc. cit.*) into *3-chloro-4-phenoxycinnoline* (1·74 g.), which formed white needles, m. p. 120—121°, from ether–ligroin (b. p. 60—80°) (Found: C, 64·7; H, 3·9; N, 10·9. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9%).

Action of Mixed Phosphorus Chlorides on Bromo-4-hydroxycinnolines.—The experiments with 3-bromo-4-hydroxycinnoline are described in some detail and serve as a model for those with other compounds, indicating the sort of yield obtained in these reactions. The products from 3-bromo-4-hydroxycinnoline are described in Table II (A), and those obtained under similar conditions from 6-bromo-, 6-chloro-3-bromo-, and 3 : 6-dibromo-4-hydroxycinnoline, in Table II (B), (C), and (D), respectively. All the products were purified by crystallisation from ether–ligroin (b. p. 60—80°).

(i) 3-Bromo-4-hydroxycinnoline (0·5 g.), phosphorus pentachloride (1 g.), and phosphorus oxychloride (5 c.c.) were heated at 95° for 2 hours in a short-necked flask fitted with a calcium chloride tube, and the mixture was decomposed with ice, basified (20% sodium hydroxide), and extracted with ether. The dried (Na_2SO_4) extract yielded a white solid (0·46 g.).

(ii) The cinnoline (0·4 g.) was treated in the same way, except that the flask was fitted with a water condenser. Yield: 0·38 g.

(iii) The cinnoline (0·4 g.) was treated as in (i), but at 135—140° for 2 hours, the flask being fitted with a short condenser so arranged that the refluxing vapours could just escape, the loss being made up by addition of phosphorus oxychloride from a tap funnel. Yield: 0·39 g.

(iv) The cinnoline (0·4 g.) was treated as in (iii), but under complete reflux. Yield: 0·38 g.

(v) 3-Bromo-4-hydroxycinnoline (0·2 g.) was treated as in (i), but for 24 hours. Yield: 0·19 g.

(vi) The hydroxycinnoline (0·2 g.) was treated as in (iv), but for 24 hours. Yield: 0·18 g.

TABLE II.

Product.				Possible product.			
		Analysis, %.				Analysis, %.	
Conditions.	M. p.[b]	C.	H.	Compound.	M. p.	C.	H.
				(A)			
(i) [a]	146·5—147°	42·1	1·9	3 : 4-Dichlorocinnoline	126—127°	48·3	2·0
(ii) [a]	143—143·5	42·3	2·0				
(iii) [a]	148·5—149·5	39·95	1·75				
(iv) [a, c]	152·5—153	39·9	1·8	4-Chloro-3-bromocinnoline	?	39·5	1·7
(v) [a]	130—131	—	—				
(vi) [a]	143—144	—	—				
				(B)			
(i) [a]	112—113	—	—	4 : 6-Dichlorocinnoline	113—114 [d]	—	—
(iv) [a]	112—113	—	—				
(i) For ½ hour	126—127	—	—	4-Chloro-6-bromocinnoline	126—127 [d]	—	—
(iv) For ½ hour [a]	112—113	—	—				
				(C)			
(i) For 1 hour	142—142·5	41·7	1·85	3 : 4 : 6-Trichlorocinnoline	141—142	41·1	1·3
(ii) For 1 hour [a, c]	143—143·5	39·9	1·4				
(iii) [a]	149—149·5	37·6	1·7				
(iv) [a, c]	154—154·5	35·4	1·4	4 : 6-Dichloro-3-bromocinnoline	?	34·6	1·1
(vi) [a]	147—148	—	—				
				(D)			
(i) [a, c]	145·5—146	34·2	1·4	3 : 4 : 6-Trichlorocinnoline	141—142	41·4	1·3
(ii) [a]	146·5—147	34·2	1·4	4 : 6-Dichloro-3-bromocinnoline	?	34·6	1·1
(iii) [a]	156—156·5	32·6	1·7				
(iv) [a, c]	160·5—161	30·5	1·4	3 : 4-Dichloro-6-bromocinnoline	?	34·6	1·1
(vi) [a]	151—152	—	—	4-Chloro-3 : 6-dibromocinnoline	?	29·8	0·9

(*a*) Bromine was visible in the reaction vessel. (*b*) M. p.s are uncorrected. They were determined with an ordinary thermometer in a small oil-bath, the temperature being raised 1° per minute. Usually 3 specimens were examined at once. Mixtures of the products did not show depressions, but melted at an intermediate temperature. (*c*) These products were phenoxylated. See Table III. (*d*) Leonard and Boyd (*loc. cit.*) give m. p. 113—114° and 126—127°, respectively.

Phenoxylation of Products from Exchange Reactions.—The product (1 part) was heated with phenol (10 parts) at 180° for 2 hours, and the mixture cooled somewhat and poured into excess 5N-sodium hydroxide solution. Ether removed the derivative, which was isolated from the dried (Na_2SO_4) extract in an almost pure state (90—95% yield), and recrystallised from ether–ligroin (b. p. 60—80°), forming white or cream-coloured needles.

Action of Phosphorus Oxychloride on Bromo-4-hydroxycinnolines.—In each case the cinnoline (0·1 g.) and phosphorus oxychloride (2 c.c.) were heated at 95°, or at 135° under reflux, for 2 hours, and the products isolated and crystallised in the usual way. In conjunction with the above results the m. p.s of the products (see Table IV) serve to indicate the extent of halogen exchange.

Action of Phosphorus Pentachloride on Bromo-4-hydroxycinnolines.—An intimate mixture of the cinnoline (0·1 g.) and phosphorus pentachloride (1 g.) was heated, for either 1 hour at 95° or ½ hour at 140—150°, and worked up as before. The results are given in Table V.

Preparation of 4-Chlorocinnolines with Phosphorus Oxychloride.—The hydroxy-compound was refluxed with the oxychloride at 135—140° until a clear solution was obtained, and heating was then continued at 95° to a total of 10 minutes. The products (see Table VI) were isolated as before and crystallised once.

TABLE III.

Supposed 4-chloro-compound.		Product.			Possible product.		
			Analysis, %.			Analysis, %.	
Table II.	Compound.[a]	M. p.	C.	H.	Compound.	C.	H.
A (iv)	4-Chloro-3-bromocinnoline	143—144°	56·15	3·05	3-Bromo-4-phenoxycinnoline	55·8	3·0
C (ii)	3 : 4 : 6-Trichlorocinnoline	107—108	56·7	2·95	3 : 6-Dichloro-4-phenoxycinnoline	57·8	2·8
C (iv)	4 : 6-Dichloro-3-bromocinnoline	113—114	53·2	2·6	6-Chloro-3-bromo-4-phenoxycinnoline	50·1	2·4
D (i)	3 : 4-Dichloro-6-bromocinnoline	128—129	50·1	2·5	3-Chloro-6-bromo-4-phenoxycinnoline	50·1	2·4
D (iv)	4-Chloro-3 : 6-dibromocinnoline	135—136	46·7	2·5	3 : 6-Dibromo-4-phenoxycinnoline	44·1	2·1

(*a*) *I.e.*, the substance to which the analysis in Table II approximates most closely.

TABLE IV.

Compound.	Temp.	Crude product. Yield (g.).	M. p.	Recrystallised product. Yield (g.).	M. p.
3-Bromo-4-hydroxycinnoline	95°	0·08	136—138°	0·05	141—142°
	135	0·10	151—152	0·08	151—151·5
6-Bromo-4-hydroxycinnoline	95	0·09	116—117	0·04	117—118
	135	0·08	105—107	0·02	112—113
6-Chloro-3-bromo-4-hydroxycinnoline	95	0·09	143—145	0·05	144—145
	135	0·10	151—152	0·07	152—153
3 : 6-Dibromo-4-hydroxycinnoline [a]	95	0·05	141—143	0·04	147—148
	135	0·05	155—156	0·04	158—159

(*a*) 0·05 G. of hydroxy-compound used.

TABLE V.

Compound.	Temp.	Crude product. Yield (g.).	M. p.	Crystallised product. Yield (g.).	M. p.
3-Bromo-4-hydroxycinnoline	95°	0·10	121—123°	0·03	126—127°
	140	0·02	125—130	—	—
6-Bromo-4-hydroxycinnoline	95	0·05	123—125	0·02	125—126
6-Chloro-3-bromo-4-hydroxycinnoline	95	0·10	137—139	0·05	140—141
	140	0·02	132—135	—	—
3 : 6-Dibromo-4-hydroxycinnoline	140	0·04	131—133	0·01	140—141

TABLE VI.

Compound.	Wt., g.	$POCl_3$, c.c.	Time, mins. 140°.	95°.	Product. G.	M. p.	Recrystallised, m. p.
4-Hydroxycinnoline	0·2	0·6	½	9½	0·17	73—74°	76—77°
3-Chloro-4-hydroxycinnoline	0·1	0·6	2	8	0·1	127—128	127—128
6-Chloro-4-hydroxycinnoline	0·2	0·6	½	9½	0·2	111—112	111—112
3-Bromo-4-hydroxycinnoline	0·1	0·6	2	8	0·1	144—145	149—150
6-Bromo-4-hydroxycinnoline	0·2	0·6	½	9½	0·2	117—118	126—127
6-Chloro-3-bromo-4-hydroxycinnoline	0·1	0·9	4½	5½	0·1	151—152	153—154
3 : 6-Dibromo-5-hydroxycinnoline	0·1	0·9	5	5	0·1	154—155	159—160

TABLE VII.

Compound. [a]	M. p.	Temp.	Product. M. p.	Recrystallised, m. p.
4-Chloro-3-bromocinnoline	151—152°	95°	135—137°	137—138°
		135	138—139	143—144
4 : 6-Dichloro-3-bromocinnoline	153—154	95	140—143	144—145
4-Chloro-3 : 6-dibromocinnoline	160—161	95	144—145	146—147

(*a*) Named according to probable major component, as revealed in above work.

TABLE VIII.

Compound.	Wt., g.	Time, mins. 135°.	95°.	Product. Wt., g.	M. p.	Recryst., m. p.
6-Chloro-4-hydroxyquinoline	0·5	10	—	0·43	100—101°	103—104° [a]
6-Bromo-4-hydroxyquinoline	0·2	10	—	0·2	108—109	109—110 [b]
3-Bromo-4-hydroxyquinoline	0·5	10	—	0·49	68—69	— [b]
3 : 6-Dichloro-4-hydroxyquinoline	0·2	3	7	0·20	103—104	108—109 [c]
3-Chloro-6-bromo-4-hydroxyquinoline	0·2	3	7	0·21	127—128	130·5—131 [d]
6-Chloro-3-bromo-4-hydroxyquinoline	0·2	2	8	0·21	121—122	124—124·5 [e]
3 : 6-Dibromo-4-hydroxyquinoline	0·2	4	6	0·2	130—131	130·5—131·5 [e]
3 : 3 : 6-Trichloro-3 : 4-dihydro-4-quinolone (?)	0·1	3	7	0·12	91—93	104—105 [f]

(*a*) Riegel *et al.* (*loc. cit.*) give m. p. 105°. (*b*) Riegel *et al.* (*loc. cit.*) give m. p. 67—69°. (*c*) 3 : 4 : 6-*Trichloroquinoline*, m. p. 109·5—110° (Found : C, 46·8; H, 2·0. $C_9H_4NCl_3$ requires C, 46·5; H, 1·7%). (*d*) 3 : 4-*Dichloro*-6-*bromoquinoline* formed white needles (Found : C, 39·3; H, 1·6. $C_9H_4NCl_2Br$ requires C, 39·1; H, 1·5%). (*e*) 4 : 6-*Dichloro*-3-*bromoquinoline* gave white needles (Found : C, 39·5; H, 1·55%). (*f*) The product on recrystallisation gave only 13% yields of a specimen which did not depress the m. p. of 3 : 4 : 6-trichlorocinnoline. When pure it gave white needles, m. p. 105—105·5° (Found : C, 47·0; H, 1·9%). (*g*) See following table for analyses.

Action of Mixed Phosphorus Chlorides on Bromo-4-chlorocinnolines.—The 4-chlorocinnolines (1 part), prepared as in the foregoing table, phosphorus pentachloride (2 parts), and phosphorus oxychloride (10 volumes) were heated at 95°, or 135—140° under reflux, and worked up as in previous cases. The results are given in Table VII.

Halogen Exchange Reactions and Related Experiments in the Quinoline Series. Preparation of 4-Chloroquinolines.—The 4-hydroxyquinoline (1 part) and phosphorus oxychloride (3 volumes) were boiled under reflux until a clear solution resulted, and then heated at 95° to make a total heating time of 10 minutes. The products were worked up as described for the cinnoline analogues. The results are given in Table VIII.

Action of Mixed Phosphorus Chlorides on Bromo-4-hydroxyquinolines.—The hydroxy-compound (1 part), phosphorus pentachloride (2 parts), and phosphorus oxychloride (10 volumes) were heated at 95°, or 135—140°, for various times, and worked up as with the cinnoline analogues. The results are recorded in Table IX.

TABLE IX.

Compound.	Wt., g.	Conditions.	Product. Wt., g.	M. p.	Recryst., m. p.
3-Bromo-4-hydroxyquinoline	0·5	95°; 2 hours	0·47	65—66°	67—68°
	0·5	135—140°; 2 hours [a]	0·51	64—65	68—69
	0·5	135—140°; 8 hours [a]	0·38	67—68	69—70 [b]
6-Bromo-4-hydroxyquinoline	0·5	95°; 2 hours	0·49	109—110	109—110 [c]
	0·5	135—140°; 2 hours	0·49	106—108	111—112
6-Chloro-3-bromo-4-hydroxyquinoline	0·2	95°; 2 hours	0·19	121—122	122—122·5
	0·2	135—140°; 2 hours [a]	0·19	119—120	122—123 [d]
	0·2	135—140°; 6 hours [a]	0·19	120—121	122—123
	0·2	135—140°; 24 hours [a]	0·16	120—121	123—124
3 : 6-Dibromo-4-hydroxyquinoline ...	0·5	95°; 2 hours [a]	0·39	131—132	131—132
	0·5	135—140°; 2 hours [a]	0·41	130—131	130—131
	0·5	135—140°; 8 hours [a]	0·39	128—129	130—131 [e]
	0·5	135—140°; 24 hours [a]	0·10	119—120	131—132

(*a*) Bromine visible in reaction vessel. (*b*) This, when pure, formed spiky white needles, m. p. 69—69·5° (Found: C, 45·2; H, 2·15. C_9H_5NClBr requires C, 44·6; H, 2·1%). (*c*) When pure, this gave large white needles, m. p. 110—110·5° (Found: C, 44·6; H, 2·2%). (*d*) As (*c*), m. p. 122—122·5° (Found: C, 40·6; H, 1·5. $C_9H_4NCl_2Br$ requires C, 39·1; H, 1·5%). (*e*) As (*c*), m. p. 130·5—131° (Found: C, 34·6; H, 1·3. $C_9H_4NClBr_2$ requires C, 33·6; H, 1·25%).

The authors are indebted to the Chemical Society for a grant from the Research Fund, and to the Council of University College, Exeter, and Messrs. Imperial Chemical Industries Ltd. for financial aid.

WASHINGTON SINGER LABORATORIES,
UNIVERSITY COLLEGE OF THE SOUTH WEST, EXETER. [*Received, September 28th*, 1949.]