Schofield and Swain: Cinnolines. Part XXV.

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# 85. Cinnolines. Part XXV. Experiments with 3-Halogeno-4hydroxycinnolines. 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  $\longrightarrow$  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.



Bülow and Schmachtenberg (Ber., 1908, 41, 2607) found that the decomposition of benzenediazonium perbromide in the presence of acetophenone gave  $\omega$ -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  $95^{\circ}$  converted 6-bromo-4-hydroxycinnoline into 4-chloro-6-bromocinnoline, a mixture of phosphorus oxychloride and pentachloride at  $135^{\circ}$  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-4hydroxycinnoline. 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-dibromoquinoline. 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	haloge <b>n</b>	exchange	reactions.

M. p.ª and exchange, %, of products from substituted 4-hydroxy-

•	-		
		cinn	nlin
		0444	.01111

	Cond	litions.		6-B1	omo	3-Br	omo	6-Cl 3-br	nloro- omo	3 : 6-D	ibromo
Re- agent.	Time (hrs.).	Temp.	Reflux or open. <sup>c</sup>	М.р.	Ex- change, %.	М. р.	Ex- change, %.	М. р.	Ex- change, %.	М.р.	Ex- change, %. <sup>d</sup>
M	2	95° 95	0	$113^{\circ}$ 126		147° •	34	142·5°	100	146°	47
M	$2^{4}$	95	Ř	120 	100 \$	143.5 *	37	$143.5^{f}$	83 51	147	47
M M	2	$135 \\ 135$	R		100 *	149.5 153	6	149.5	14	161	10
M M	$\begin{array}{c} 24\\ 24\end{array}$	$\begin{array}{c} 95 \\ 135 \end{array}$	R R	_		1 <b>3</b> 0 1 <b>43</b>		148	_	152	
0	$\frac{2}{2}$	95 135	R R	$118 \\ 113$		142 151-5		$\frac{145}{152}$		$148 \\ 159$	
P	ĩ,	95	R	126		127		140		141	
r	2	130	n			100		100		131	

(a) M. p.s of possible products: 3:4-dichlorocinnoline, m. p.  $126-127^{\circ}$ ; 4:6-dichlorocinnoline, m. p.  $112-113^{\circ}$ ; 3:4:6-trichlorocinnoline, m. p.  $141-142^{\circ}$ . (b) M = mixed phosphorus chloride; 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)  $\frac{1}{4}$  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  $C_{(3)}$ , and is more rapid at 95° than at 135°. (iv) Replacement of bromine, whether at  $C_{(3)}$  or  $C_{(5)}$ , 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  $-5^{\circ}$  to 0°. The suspension of brown granular solid produced was left overnight and then warmed at  $80^{\circ}$  for  $\frac{3}{4}$  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. 273–274°).  $275-276^{\circ}$ )

(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 preterview (0.21 g.) is mater (5.24 g.) and method up are in (ii) fielding 2000 of the

(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 (1.24 g.) and worked up as in (i) yielding 12.5% of 3-bromobromine (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  $95^{\circ}$  for 4 hours with sulphuryl chloride (0.51 g.), the mixture refluxed for 5 minutes and then cooled, sodium hydroxide (0.24 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.  $262-263^\circ$ ) from acetic acid gave 3-chloro-4-hydroxycinnoline (0.14 g., 22%), m. p.  $278-279^\circ$ , alone and mixed with an authentic specimen (m. p.  $278-279^\circ$ ). Acetylation with boiling acetic anhydride gave a derivative, m. p.  $124-125^\circ$ , which did not depress the m. p.  $(124-125^\circ)$  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.  $301-303^{\circ}$ , and its acetyl derivative, m. p.  $148-149^{\circ}$ , 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  $95^{\circ}$  for  $2\frac{1}{2}$  hours, crystals appearing after  $\frac{1}{4}$  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.  $235-237^{\circ}$ . 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.  $272-273^{\circ}$  showing no depression on admixture with a pure specimen, m. p.  $275-276^{\circ}$ . 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  $(25 \cdot 2 \text{ g.})$  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*  $\beta$ -(p-bromoanilino)-a-carbethoxyacrylate, m. p. 100—101° (Found : C, 48.4; H, 4.75. C<sub>14</sub>H<sub>16</sub>O<sub>4</sub>NBr 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  $\frac{1}{2}$  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<sub>12</sub>H<sub>10</sub>O<sub>3</sub>NBr 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<sub>10</sub>H<sub>6</sub>O<sub>3</sub>NBr 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<sub>9</sub>H<sub>6</sub>ONBr,<sup>1</sup><sub>2</sub>H<sub>2</sub>O requires C, 46.4; H, 3.0%). A similar result was obtained by heating the acid at 285° for <sup>1</sup>/<sub>4</sub> 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  $45^{\circ}$  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.  $>300^{\circ}$ ) crystallised from alcohol, giving white lustreless microcrystals of a *compound*, m. p.  $>320^{\circ}$  (Found : C, 42.1; H, 2.2. C<sub>9</sub>H<sub>4</sub>ONCl<sub>3</sub> 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  $45^{\circ}$ . There was an immediate reaction and the temperature rose to >100°. The mixture was kept at 60—65° for  $\frac{1}{2}$  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 vellow microcrystals of 3 : 6-dichloro-4-hydroxyquinoline, m. p. >320° (Found : C, 50.6; H, 2.5. C<sub>9</sub>H<sub>5</sub>ONCl<sub>2</sub> 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  $100^{\circ}$  for  $\frac{1}{2}$  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<sub>9</sub>H<sub>2</sub>ONClBr 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 10° 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.  $>320^{\circ}$  (Found : C, 42·4; H, 2·2. C<sub>9</sub>H<sub>5</sub>ONClBr 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 micro-crystals of 3:6-dibrome-4-hydroxyquinoline, m. p.  $>320^{\circ}$  (Found : C, 35.9; H, 1.7. C<sub>9</sub>H<sub>5</sub>ONBr<sub>2</sub> 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 etherligroin (b. p. 60-80°) (Found : N, 14-8; Cl, 36-2. C<sub>8</sub>H<sub>4</sub>N<sub>2</sub>Cl<sub>2</sub> 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<sub>8</sub>H<sub>3</sub>N<sub>2</sub>Cl<sub>3</sub> 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 (Konsferd and Simpson Les git) into 2 chloro 4 chameurscing (1/24 g.) which formed which pool

(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-4hydroxycinnoline 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  $95^{\circ}$  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  $135-140^{\circ}$  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.

[1950]

Product.	Possible product.						
Analysis, %.		Analys	is, %.				
Conditions. M. p. <sup>b</sup> C. H. Compound	. М.р.	C.	H.				
$(\mathbf{A})$							
(i) • $146.5 - 147^{\circ} + 42.1 + 1.9$							
(ii) • 143—143.5 42.3 2.0 >3 : 4-Dichlorocinnolir	ne 126—127°	<b>4</b> 8·3	$2 \cdot 0$				
(iii) <sup>•</sup> 148·5—149·5 39·95 1·75∫							
(iv) a, c $152.5 - 153 39.9 1.8$							
(v) $a$ 130—131 — — $4$ -Chloro-3-bromocini	ioline ?	39.5	1.7				
$(vi) \circ 143 - 144 J$							
(B)							
(i) • $112-113 14$ · 6 Dichlorogianaliz	119 114 d						
$(iv)^{a}$ 112-113 - $\int^{4} \cdot 0^{-D1} cmotochinom}$	113						
(i) For $\frac{1}{4}$ hour 126-127 $\frac{1}{24}$ - $\frac{1}{26}$	oline 196 -1974						
(iv) For $\frac{1}{4}$ hour " 112—113 — _ J = Chloro-bromoenn	120-121						
(C)							
(i) For 1 hour $142 - 142 \cdot 5 + 41 \cdot 7 + 1 \cdot 85$							
(ii) For 1 hour 4, c 143-143.5 39.9 1.4 3:4:6-Trichlorocinr	oline 141-142	<b>41</b> ·1	1.3				
(iii) • 149149·5 37·6 1·7 }							
$(iv)^{a,c}$ 154-154.5 35.4 1.4 $(4+6)$ Dichloro 2 brow	ocinnoline ?	24.6	1.1				
(vi) $a$ 147—148 — $\int 4 \cdot 0^{-1} D \cdot 0^{-1}$		94.0	1.1				
(D)							
(i) $\bullet, \circ$ 145.5-146 34.2 1.4 3 : 4 : 6-Trichlorocinr	oline 141-142	41.4	1.3				
(ii) $a$ 146.5—147 34.2 1.4 ) $a$ D i i i a							
(iii) $a$ 156-156.5 32.6 1.7 } 4 : 6-Dichloro-3-brom	ocinnoline ?	34.6	1.1				
(iv) a, c 160.5-161 30.5 1.4 3:4-Dichloro-6-brom	ocinnoline ?	34.6	1.1				
(vi) <sup>a</sup> 151-152 - 4-Chloro-3: 6-dibrom	ocinnoline ?	$29 \cdot 8$	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<sub>2</sub>SO<sub>4</sub>) 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  $95^{\circ}$  or  $\frac{1}{2}$  hour at 140—150°, and worked up as before. The results are given in Table V.

Preparation of 4-Chlorocinnolines with Phosphorus  $\bar{O}xychloride$ .—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.				
<i></i>		·	Analys	is, %.	~	Analys	is, %.		
Table II.	Compound.ª	М.р.	C.	H.	Compound.	C.	H.		
A (iv)	4-Chloro-3-bromocin- noline	143—144°	56.15	3.02	3-Bromo-4-phenoxycin- noline	55.8	<b>3</b> ∙0		
C (ii)	3:4:6-Trichlorocin- noline	107—108	56.7	2.95	3 : 6-Dichloro-4-phen- oxycinnoline	57.8	$2 \cdot 8$		
C (iv)	4 : 6-Dichloro-3-bromo- cinnoline	113—114	$53 \cdot 2$	$2 \cdot 6$	6-Chloro-3-bromo-4- phenoxycinnoline	50.1	$2 \cdot 4$		
D (i)	3: 4-Dichloro-6-bromo- cinnoline	128—129	50.1	$2 \cdot 5$	3-Chloro-6-bromo-4- phenoxycinnoline	50.1	$2 \cdot 4$		
D (iv)	4-Chloro-3 : 6-dibromo- cinnoline	135—136	<b>46</b> ·7	$2 \cdot 5$	3 : 6-Dibromo-4-phen- oxycinnoline	44.1	2.1		

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

TABLE IV.

		Crude product.		Recrystalli	sed product.
Compound.	Temp.	Yield (g.).	М.р.	Yield (g.).	М. р.
3-Bromo-4-hydroxycinnoline	$\begin{array}{r} 95^{\circ} \\ 135 \end{array}$	0·08 0·10	136—138° 151—152	0·05 0·08	141—142° 151—151·5
6-Bromo-4-hydroxycinnoline	$\begin{array}{c} 95\\ 135 \end{array}$	0·09 0·08	$116-117 \\ 105-107$	0·0 <b>4</b> 0·02	117 <b>—118</b> 112 <b>—113</b>
6-Chloro-3-bromo-4-hydroxycinnoline	$\begin{array}{c} 95 \\ 135 \end{array}$	0·09 0·10	$143 - 145 \\ 151 - 152$	0·05 0·07	144
3 : 6-Dibromo-4-hydroxycinnoline •	$\begin{array}{c} 95\\135\end{array}$	0·05 0·05	$141 - 143 \\ 155 - 156$	0·04 0·04	147—148 158—159

(a) 0.05 G. of hydroxy-compound used.

## TABLE V.

		Crude product.		Crystallise	ed product.
Compound.	Temp.	Yield (g.).	М.р.	Yield (g.).	М. р.
3-Bromo-4-hydroxycinnoline	95°	0.10	$121 - 123^{\circ}$	0.03	126—127°
	140	0.02	125 - 130		
6-Bromo-4-hydroxycinnoline	<b>95</b>	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	131133	0.01	140141

# TABLE VI.

	POCI,	Time,	mins.	Pr	oduct.	tallised.
Wt., g.	c.c.	140°.	95°.	G.	М. р.	m. p.
0.2	0.6	1/2	9 <u>‡</u>	0.17	73—74°	76—77°
0.1	0.6	$2^{-}$	8	0.1	127 - 128	127 - 128
0.2	0.6	$\frac{1}{2}$	$9\frac{1}{2}$	$0 \cdot 2$	111 - 112	111 - 112
0.1	0.6	$2^{-}$	8	0.1	144	149 - 150
0.2	0.6	$\frac{1}{2}$	$9\frac{1}{2}$	0.2	117118	126 - 127
0.1	0.9	4 <del>1</del>	$5\frac{1}{2}$	0.1	151 - 152	153 - 154
0.1	0.9	$5^{-}$	$5^{-}$	0.1	154 - 155	159 - 160
	Wt., g. 0·2 0·1 0·2 0·1 0·2 0·1 0·2 0·1 0·1	$\begin{array}{c} POCl_3,\\ Wt.,\ g. \ c.c.\\ 0.2 \ 0.6\\ 0.1 \ 0.6\\ 0.2 \ 0.6\\ 0.1 \ 0.6\\ 0.2 \ 0.6\\ 0.1 \ 0.9\\ 0.1 \ 0.9\\ 0.1 \ 0.9\\ \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

## TABLE VII.

Droduct

Compound. <sup>4</sup>	М. р.	Temp.	M. p.	Recrystallised, m. p.
4-Chloro-3-bromocinnoline	151—152°	$\begin{array}{c} 95^{\circ} \\ 135 \end{array}$	135—137° 138—139	137138° 143144
4:6-Dichloro-3-bromocinnoline	153 - 154	95	140-143	144 - 145
4-Chloro-3: 6-dibromocinnoline	160	95	144 - 145	146147

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

## TABLE VIII.

	W+	Time, mins.		Product.			
Compound.	g.	135°.	95°.	Wt., g.	<u>М. р.</u>	Recryst., m. p.	
6-Chloro-4-hydroxyquinoline	0.5	10		0.43	100-101°	103—104° °	
6-Bromo-4-hydroxyquinoline	$0 \cdot 2$	10		0.2	108-109	109-110 *	
3-Bromo-4-hydroxyquinoline	0.5	10		0.49	68 - 69	b	
3: 6-Dichloro-4-hydroxyquinoline	0.2	3	7	0.50	103-104	108-109 °	
3-Chloro-6-bromo-4-hydroxyquinoline	0.2	3	7	0.21	127 - 128	130.5-131 4	
6-Chloro-3-bromo-4-hydroxyquinoline	0.2	<b>2</b>	8	0.21	121 - 122	$124 - 124 \cdot 5 \bullet$	
3:6-Dibromo-4-hydroxyquinoline	0.2	4	6	0.2	130131	130.5-131.5 #	
3:3:6-Trichloro-3:4-dihydro-4-quinolone(?)	0.1	3	7	0.12	9193	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,  $46\cdot8$ ; H, 2·0. C<sub>9</sub>H<sub>4</sub>NCl<sub>3</sub> requires C,  $46\cdot5$ ; H, 1·7%). (d) 3:4-Dichloro-6-bromoquinoline formed white needles (Found : C,  $39\cdot3$ ; H, 1·6. C<sub>9</sub>H<sub>4</sub>NCl<sub>4</sub>Br requires C,  $39\cdot1$ ; H, 1·5%). (e) 4:6-Dichloro-3-bromoquinoline gave white needles (Found : C,  $39\cdot5$ ; 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,  $47\cdot0$ ; 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  $95^{\circ}$ , 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  $95^{\circ}$ , or 135— $140^{\circ}$ , for various times, and worked up as with the cinnoline analogues. The results are recorded in Table IX.

## TABLE IX.

				1 IOduci	•
Compound.	Wt., g.	Conditions.	Wt., g.	М. р.	Recryst., m. p.
3-Bromo-4-hydroxyquinoline	$0.5 \\ 0.5 \\ 0.5 \\ 0.5$	95°; 2 hours 135—140°; 2 hours 4 135—140°; 8 hours 4	$0.47 \\ 0.51 \\ 0.38$	$\begin{array}{c} 6566^{\circ}\ 6465\ 6768\end{array}$	67—68° 68—69 69—70 °
6-Bromo-4-hydroxyquinoline	$0.5 \\ 0.5$	95°; 2 hours 135—140°; 2 hours	0·49 0·49	$109-110 \\ 106-108$	109-110 ° 111-112
6-Chloro-3-bromo-4-hydroxyquinoline	$0.2 \\ 0.2 \\ 0.2 \\ 0.2 \\ 0.2$	95°; 2 hours 135—140°; 2 hours a 135—140°; 6 hours a 135—140°; 6 hours a	0·19 0·19 0·19 0·16	121—122 119—120 120—121 120—121	$\begin{array}{c} 122 - 122 \cdot 5 \\ 122 - 123 \ a \\ 122 - 123 \\ 123 - 124 \end{array}$
3:6-Dibromo-4-hydroxyquinoline	0·5 0·5 0·5 0·5	95°; 2 hours 135—140°; 2 hours 135—140°; 8 hours 135—140°; 8 hours 135—140°; 24 hours	0·39 0·41 0·39 0·10	$131 - 132 \\ 130 - 131 \\ 128 - 129 \\ 119 - 120$	131—132 130—131 130—131 131—132

(a) Bromine visible in reaction vessel. (b) This, when pure, formed spiky white needles, m. p.  $69-69\cdot5^{\circ}$  (Found : C,  $45\cdot2$ ; H,  $2\cdot15$ .  $C_{9}H_{5}NClBr$  requires C,  $44\cdot6$ ; H,  $2\cdot1\%$ ). (c) When pure, this gave large white needles, m. p.  $110-110\cdot5^{\circ}$  (Found : C,  $44\cdot6$ ; H,  $2\cdot2\%$ ). (d) As (c), m. p.  $122-122\cdot5^{\circ}$  (Found : C,  $40\cdot6$ ; H,  $1\cdot5$ .  $C_{9}H_{4}NCl_{2}Br$  requires C,  $39\cdot1$ ; H,  $1\cdot5\%$ ). (e) As (c), m. p.  $130\cdot5-131^{\circ}$  (Found : C,  $34\cdot6$ ; H,  $1\cdot3$ .  $C_{9}H_{4}NClBr_{2}$  requires C,  $33\cdot6$ ; H,  $1\cdot25\%$ ).

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