227. *The Chemistry of Simple Heterocyclic Systems. Part V. A Comparative Study of Some 4-Substituted Cinnolines, Quinazolines, and Quinolines.*

By J. R. KENEFORD, J. S. MORLEY, J. C. E. SIMPSON, and P. H. WRIGHT.

An account is given of the reactions undergone by derivatives of cinnoline, quinazoline, and quinoline containing a series of identical substituents attached to $C_{(4)}$. Differences in reactivity between compounds of each heterocyclic type are considered in relation to their strengths as acids or bases. It is shown that there is substantial qualitative agreement between the observed order of reactivity of comparable compounds of each heterocyclic type and the predicted order as deduced from the electron-density calculations of Longuet-Higgins and Coulson (*J.*, 1949, 971).

THE possibility of providing a theoretical background to the chemistry of a group of related heterocyclic ring-systems by a comparative study of their reactions has hitherto largely escaped attention. In the present communication some aspects of this subject are considered for the related ring-systems named in the title. We considered that an initial survey should be as broadly based as possible and have therefore examined, semi-quantitatively, the behaviour of a wide range of 4-substituted derivatives of each of these heterocyclic types, so as to ascertain either the approximate conditions required to produce a given result or the fate of the compounds under roughly identical conditions. These studies have been supplemented by determinations of dissociation constants (Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356) and of the ultra-violet absorption spectra of appropriate compounds; the spectra were determined by Professor R. A. Morton, whose co-operation it is a pleasure to acknowledge, and his results will be published later.

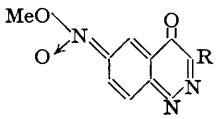
Another reason for our study was that recently there has been increasing recognition of the importance of basic (or acidic) strength, hydrogen bonding, and tautomeric and resonance phenomena in general as factors which may influence the activity of drugs in various fields of chemotherapy [cf., *e.g.*, Albert and his collaborators, *Brit. J. Exp. Path.*, 1942, **23**, 69; 1945, **26**, 160; Bell and Roblin, *J. Amer. Chem. Soc.*, 1942, **64**, 2905; Kumler and Daniels, *ibid.*, 1943, **65**, 2190 (antibacterial agents); Curd, Rose, *et al.*, *J.*, 1946, 343 and later papers (antimalarials); Walls, *J. Soc. Chem. Ind.*, 1947, **66**, 182 and earlier papers (bovine trypanosomiasis); Welch *et al.*, *Science*, 1947, **105**, 486 (filariasis)]. Simple 4-substituted derivatives of the three ring-systems were chosen because the importance of substitution at position 4 (amongst others) for the development of chemotherapeutic activity in the quinoline molecule is already well established (Iensch, *Angew. Chem.*, 1937, **50**, 891; Wiselogle, "Survey of Antimalarial Drugs," 1941—1945), and chemotherapeutic activity has also been demonstrated for certain 4-substituted derivatives of cinnoline (Keneford and Simpson, *J.*, 1947, 917; Keneford, Lourie, Morley, Simpson, Williamson, and Wright, *Nature*, 1948, **161**, 603) and of quinazoline (Chapman, Gibson, and Mann, *J.*, 1947, 890).

We have been able to reach definite conclusions on the relative reactivity of comparable compounds in each heterocyclic series. It is of interest that these conclusions agree qualitatively with those immediately deducible from the electron-density calculations for quinoline,

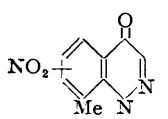
quinazoline, and cinnoline recently published by Longuet-Higgins and Coulson (*J.*, 1949, 971). These matters are discussed after the following description of the reactions which we have examined.

Reactions of 4-*Hydroxy-compounds.*—(a) *Acetylation.* 4-Hydroxycinnolines are usually readily acetylated by boiling acetic anhydride (*J.*, 1945, 512; 1946, 1035; 1947, 232; 1948, 354, 1170, 1702; this paper). 4-Hydroxycinnoline-3-carboxylic acid thus gives 4-acetoxycinnoline (*J.*, 1945, 512), but with added pyridine undergoes a complex reaction (*J.*, 1946, 472). 8-Nitro-4-hydroxy- and 4-hydroxy-8-methyl-cinnolines are not acetylated by acetic anhydride (*J.*, 1947, 237; 1948, 354, 1702). 4-Hydroxyquinazoline and its 6- and 7-nitro- (*J.*, 1948, 360) and 2-methyl derivatives (Bogert and Gotthelf, *J. Amer. Chem. Soc.*, 1900, **22**, 522) do not react with boiling acetic anhydride, and 4 : 7-dihydroxy-2-methylquinazoline gives only a monoacetyl derivative (Bogert, Amend, and Chambers, *ibid.*, 1910, **32**, 1297). Some 4-hydroxyquinolines do not react under these conditions [ethyl 4-hydroxyquinoline-3-carboxylate (*J.*, 1946, 1035), its 2-phenyl derivative (Niementowski, *Ber.*, 1905, **38**, 2044), and 4-hydroxy- and 6-nitro-4-hydroxy-quinoline (this paper)]. 2 : 4-Dihydroxyquinoline and its nitration products give only monoacetyl derivatives (Ashley, Perkin, and Robinson, *J.*, 1930, 382). On the other hand, 4-hydroxy-2-phenylquinoline (John and Wünsche, *J. prakt. Chem.*, 1928, **119**, 43), 8-nitro-4-hydroxyquinoline (this paper), and ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate (*J.*, 1946, 1035) are acetylated but slowly.

(b) *Methylation.* From 4-hydroxyquinazoline (Knape, *J. prakt. Chem.*, 1891, **43**, 209) and its 6- and 7-nitro-derivatives (Morley and Simpson, *J.*, 1948, 360) methyl sulphate or iodide in alkali furnishes the corresponding 3-methyl-4-quinazolines as the sole isolable products. In the 4-hydroxyquinoline series *N*-methylation also occurs under these conditions,* as shown by the results obtained for the parent compound and for 6-nitro-4-hydroxyquinoline (Simpson and Wright, *J.*, 1948, 1707). 4-Hydroxy- and 6-chloro-4-hydroxy-cinnoline react similarly (*J.*, 1945, 512; 1947, 1653), but 6-nitro-4-hydroxy- and 6-nitro-4-hydroxy-3-methyl-cinnoline give mixtures of the corresponding 1-methylcinnolones and the methyl nitronates (I; R = H and Me) (*J.*, 1945, 512; this paper). 5(or 7)-Nitro-4-hydroxy-8-methylcinnoline, conversion of which into a methyl nitronate is not formally possible, gives only a single product, presumably 5(or 7)-*nitro*-1 : 8-*dimethyl*-4-*cinnolone* (as II), with methyl sulphate and alkali.



(I.)



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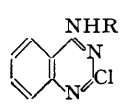


(III.)

Reactions of 4-*Amino-compounds.*—(a) *Acetylation.* 4-Amino-cinnolines, -quinazolines, and -quinolines are readily converted into 4-acetamido-derivatives in boiling acetic anhydride (*J.*, 1948, 358, 360, 1707; 1949, 1354; this paper).

(b) *Hydrolysis.* The results of treating a number of 4-amino- and 4-dialkylaminoalkylamino-cinnolines, -quinolines, and -quinazolines with boiling aqueous hydrochloric acid are summarised in Table I. The cinnoline derivatives are recovered unchanged (4-acetamidocinnoline yields 4-aminocinnoline). The same is true of the three quinoline derivatives tested, and this result is in accord with the statement (Baker, Dobson, and Riegel, *J. Amer. Chem. Soc.*, 1947, **69**, 704) that concentrated sulphuric acid at 200° converts 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)quinoline into 7-chloro-4-aminoquinoline, and with the observation (Ramsay, Baldwin, and Tipson, *ibid.*, p. 67) that 4-*p*-dialkylaminobenzylideneaminoquinolines yield the corresponding aldehydes and 4-aminoquinolines by treatment with 10% hydrochloric acid at 100°. The quinazoline compounds, on the other hand, are hydrolysed more or less readily with formation of the corresponding 4-hydroxyquinazolines, and Tomisek and Christensen (*ibid.*, 1945, **67**, 2112) have obtained similar results, although Curd, Landquist, and Rose (*J.*, 1947, 776) found that 2-chloro-4-alkylaminoalkylaminoquinazolines (III; R = alkylaminoalkyl) are " unexpectedly stable to hydrolysis by acid or alkali " under conditions which were not specified.

Reactions of 4-*Chloro-compounds.*—(a) *Hydrolysis.* From the results, given in Table II, of the hydrolysis of a few 4-chloro-derivatives of each heterocyclic type, in initially neutral or

* Under different conditions, *viz.*, treatment of the quaternary salts with alkali, 7-chloro-4-hydroxyquinoline and 4-hydroxy- and 6-acetamido-4-hydroxy-quinoline give *O*-methyl derivatives (Pratt and Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 4065; Maurin, *Ann. Chim.*, 1935, **4**, 301).

in acid aqueous solution, it is clear that 4-chloro-cinnolines and -quinazolines have very labile chlorine atoms and that 4-chloroquinolines are decidedly less reactive.

TABLE I.

Hydrolysis of 4-amino-quinolines, -cinnolines, and -quinazolines.

Substituents.	Conditions of refluxing.	Result : initial material.	Result : hydroxy-compound.
Quinolines :			
6-NO_2-4-NH_2-	5N-HCl/3 hrs.	+	—
8-NO_2-4-NH_2-	5N-HCl/3 hrs.	+	—
4-NH_2-	5N-HCl/3 hrs.	+	—
Cinnolines :			
7-Cl-4-NH_2-	5N-HCl/3 hrs.	+	—
7-Cl-4-NH·$[CH_2]_3$·NBu^n_2	N-HCl/2 hrs.	+	—
7-Cl-4-NH·$[CH_2]_2$·NMe_2	5N-HCl/2 hrs.	+	—
7-Cl-4-NH·$[CH_2]_2$·NEt_2	5N-HCl/2 hrs.	+	—
4-NHAc-	5N-HCl/½ hr.	4-NH_2	—
Quinazolines :			
6-NO_2-4-NH_2-	2N-HCl/1 hr.	—	+
6-NO_2-4-NHAc-	2N-HCl/1 hr.	—	+
7-NO_2-4-NH_2-	2N-HCl/1 hr.	—	+
7-NO_2-4-NHAc-	2N-HCl/1 hr.	—	+
7-Cl-4-NH·$[CH_2]_2$·NEt_2	N-HCl/2 hrs.	+	—
,,	5N-HCl/2 hrs.	—	+
7-NO_2-4-NH·$[CH_2]_2$·NEt_2	N-HCl/2 hrs.	+	—
,,	5N-HCl/½ hr.	+ (30%)	+ (70%)
7-Cl-4-NH·CHMe·$[CH_2]_3$·NEt_2	N-HCl/½ hr.	+	—
,,	5N-HCl/2 hrs.	? +	+ (70%)
4-NH·$[CH_2]_2$·NEt_2	N-HCl/½ hr.	+ (25%)	+ (75%)

TABLE II.

Hydrolysis of 4-chloro-quinolines, -cinnolines, and -quinazolines.

Substituents.	Conditions of refluxing.	Result : initial material.	Result : hydroxy-compound.
Quinolines :			
4-Cl-	5N-HCl/4 hrs.	+ (80%)	— *
,,	18N-H_2SO_4/1½ hrs.	+ (80%)	— *
4-Cl-6-NO_2-	Water/7 hrs.	+	—
,,	0·02N-HCl/½ hr.	+ (50%)	+ (50%)
,,	0·02N-HCl/1 hr.	—	+
4-Cl-8-NO_2-	0·02N-HCl/1 hr.	+ (10%)	+ (90%)
,,	0·2N-HCl/¾ hr.	—	+
Cinnolines :			
4-Cl-	Water/¼ hr.	—	+
4 : 7-Di-Cl-	Water/1 hr.	+	+
,,	0·02N-HCl/1 hr.	—	+
4-Cl-6-NO_2-	Water/20 mins.	—	+
4-Cl-8-NO_2-7-Me-	N-HCl/½ hr.	+	trace ?
,,	5N-HCl/2 hrs.	—	+
4-Cl-5(or 7)-NO_2-8-Me-	Water/1 hr.	+ (50%)	+ (50%)
,,	Water/3 hrs.	—	+
,,	0·02N-HCl/1 hr.	—	+
Quinazolines :			
4-Cl-	Water/¼ hr.	—	+
4-Cl-6-NO_2-	Water/½ hr.	—	+
4-Cl-7-NO_2-	Water/½ hr.	—	+

* None isolated; this compound however is much more soluble than other hydroxy-compounds studied, and small amounts would probably escape detection.

(b) *Formation of 4-anilino-derivatives.* By condensing 4-chloro-derivatives with aniline in weakly acid aqueous acetone, 4-anilino-compounds of each heterocyclic type may be prepared rapidly and in good yield (*J.*, 1948, 354, 360, 1702, 1707; 1949, 1014; this paper).

(c) *Formation of 4-phenoxy-derivatives.* Compounds of the cinnoline series are prepared by interaction of 4-chlorocinnolines at 95° with phenol containing either 1—2 equivalents of potassium hydroxide or (for Bz-nitro-compounds) an excess of powdered ammonium carbonate (*J.*, 1947, 227, 917; 1948, 354, 358, 1702). 4-Chloro-6-methoxycinnoline and some 8-substituted 4-chlorocinnolines are comparatively resistant, but these react readily with phenol and potassium hydroxide at 150°. Of 4-phenoxyquinazolines, only the parent compound and its 6- and 7-nitro-analogues have been prepared; these are readily obtained by either of the methods mentioned above, but considerable amounts of the 4-amino-compounds are also produced when ammonium carbonate is used (*J.*, 1948, 360; 1949, 1354). 4-Phenoxyquinolines are likewise obtained from the 4-chloro-compounds and phenol in presence of potassium hydroxide (*J.*, 1948, 1707; this paper).

(d) *Formation of 4-methoxy-derivatives.* 4-Chloro-quinolines, -cinnolines, and -quinazolines yield the corresponding 4-methoxy-derivatives when treated with methanolic sodium methoxide under appropriate conditions (*J.*, 1945, 512; 1947, 1653; 1948, 360, 1707; this paper).

Reactions of 4-Phenoxy-compounds.—(a) *Hydrolysis.* The results of a number of hydrolyses of 4-phenoxy-cinnolines, -quinazolines, and -quinolines are set out in Table III.

TABLE III.

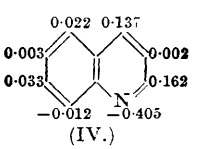
Hydrolysis of 4-phenoxy-quinolines, -cinnolines, and -quinazolines.

Substituents.	Conditions of refluxing.	Result: initial material.	Result: hydroxy-compound.
Quinolines:			
4-OPh-	5N-HCl/3 hrs.	+	—
,,	18N-H_2SO_4/3 hrs.	+	—
6-NO_2-4-OPh-	2N-HCl/1 hr.	+ (10%)	+
8-NO_2-4-OPh-	2N-HCl/20 mins.	+ (10%)	+
,,	2N-HCl/1 hr.	—	+
Cinnolines:			
4-OPh-	Water/2 hrs.	—	—
,,	0·02N-HCl/½ hr.	—	+
7-Cl-4-OPh-	0·1N-HCl/½ hr.	—	+
6-NO_2-4-OPh-	Water/1 hr.	—	—
,,	0·02N-HCl/1 hr.	—	+
8-NO_2-4-OPh-	0·02N-HCl/1 hr.	trace	+
Quinazolines:			
4-OPh	Water/2 hrs.	—	—
,,	0·02N-HCl/1 hr.	—	+
6-NO_2-4-OPh	Water/1 hr.	+	—
,,	0·02N-HCl/1 hr.	—	+
7-NO_2-4-OPh	Water/4 hrs.	—	—
,,	0·02N-HCl/1 hr.	—	+

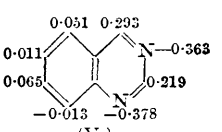
(b) *Formation of 4-amino-compounds.* The conversion of 4-phenoxy- into 4-amino-derivatives by fusion with ammonium acetate is applicable to all three heterocyclic types, and in general gives good yields (*J.*, 1948, 358, 360, 1702, 1707; 1949, 1354).

DISCUSSION.

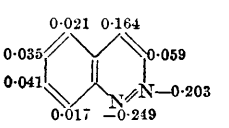
In the following sections are given the conclusions reached on the basis of the results outlined above and in other papers. Where it has been possible to do so, comparisons are made between our experimental findings and predictions arising from the electron-densities calculated by Longuet-Higgins and Coulson (*J.*, 1949, 971) for quinoline, quinazoline, and cinnoline, the figures for which are reproduced in formulæ (IV), (V), and (VI).



(IV.)



(V.)



(VI.)

(i) *Basic centres of cinnoline and quinazoline derivatives.* As shown in (VI), the basic centre of cinnoline is probably $N_{(1)}$. Experimental proof of this is lacking (*J.*, 1949, 1354), but it has

been shown that $N_{(1)}$ is the basic centre in 4-methyl- and 4-amino-cinnolines (*J.*, 1947, 808, 1653). Similarly, the expression (V) suggests that $N_{(1)}$ may be the basic centre of quinazoline, but that the similarity of charge between $N_{(1)}$ and $N_{(3)}$ would make the balance delicate and liable to disturbance by substituents. Experiment shows that quaternary salt formation involves $N_{(3)}$ in quinazoline (*Ber.*, 1904, **37**, 3643), and $N_{(1)}$ in certain 4-phenoxy- and 4-acetamido-quinazolines (*J.*, 1948, 360; 1949, 1354).

(ii) *Basic strengths of cinnolines, quinazolines, and quinolines.* Inspection of (IV), (V), and (VI) shows that the predicted order of basic strength is quinoline > quinazoline > cinnoline. This is likewise the observed order of basic strength,* both for the unsubstituted bases and also for 4-hydroxy-, 4-chloro-, 4-phenoxy-, and 4-methoxy-derivatives of the three ring-systems (*J.*, 1949, 1356). Correspondingly, the observed order of strengths as acids for the three 4-hydroxy-compounds is cinnoline > quinazoline > quinoline.

(iii) *Mobility of hydrogen in 4-hydroxy-compounds.* It has been stated above (*a*) that 4-hydroxycinnolines, but not 4-hydroxyquinolines or 4-hydroxyquinazolines, are in general readily acetylated; (*b*) that, among 6-nitro-4-hydroxy-compounds of each type, only the cinnolines yield methyl nitronates on alkylation (although such compounds are equally derivable, formally speaking, from 6-nitro-4-hydroxy-quinolines and -quinazolines); and (*c*) that 4-hydroxycinnoline is a stronger acid than the quinazoline or the quinoline analogue. These observations are mutually consistent and indicate that, of the three heterocyclic types, the 4-hydroxycinnolines have the most mobile replaceable hydrogen atom.

(iv) *Anomalous behaviour of 8-substituted cinnolines and quinolines.* The properties of 4-hydroxy-, 4-chloro-, and 4-amino-cinnolines carrying an additional substituent at $C_{(8)}$ are seen to be anomalous in light of the general reaction outlined above. Thus, 8-substituted 4-hydroxy-compounds resist acetylation, and the yields of 4-chloro-8-nitro-7-methyl- and 4-chloro-5(or 7)-nitro-8-methyl-cinnoline from the hydroxy-compounds are greatly reduced if reaction is prolonged for more than a few minutes (*J.*, 1948, 1702). When treated with phenol and ammonium carbonate, 4-chloro-8-nitrocinnoline gives† mainly the amino-compound, 4-chloro-8-methylcinnoline is only partly phenoxylated (under these conditions 4-chloro-cinnoline gives 85% of 4-phenoxycinnoline), and 4-chloro-5(or 7)-nitro-8-methylcinnoline is largely unchanged (*J.*, 1948, 1702). The last-named compound does not yield a 4-methoxy-derivative under standard conditions, being either unchanged or converted into the hydroxy-cinnoline. 4-Chloro-8-nitro-7-methylcinnoline is unexpectedly stable towards acid hydrolysis (Table II), and reacts incompletely with aniline and with phenol under standard conditions (*J.*, 1948, 1702). These anomalies are, in general, the failure or incompleteness of a reaction which proceeds readily in the absence of an 8-substituent (NO_2 or Me).‡

A comparison of the acetylation of 4-hydroxy-, 6-nitro-, and 8-nitro-4-hydroxy-cinnoline with that of the corresponding quinoline derivatives shows that an 8-nitro-group exerts opposite effects in the two ring-systems, the reaction being inhibited and facilitated, respectively, by the substituent. Similarly, data in Tables II and III suggest that an 8-nitro-group facilitates the acid hydrolysis of 4-chloro- and 4-phenoxy-quinolines, and Gouley *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 303) state that "apparently the relative rate of (acid) hydrolysis of 4-chloro-8-nitro-quinoline is at least twice that of the 4-chloro-5-nitro-isomer." Again, the yields of phenoxy-compounds obtained at 95° from 4-chloro-6-nitro- and 4-chloro-8-nitro-quinoline are 58 and 86% (*J.*, 1948, 1707).

The explanation of these differences is at present obscure, but it is interesting that, according to Longuet-Higgins and Coulson's calculations, $C_{(8)}$ carries charges of opposite character in cinnoline and quinoline.

(v) *Abnormal behaviour of quinazoline derivatives.* (*a*) In Part IV of this series (*J.*, 1949, 1356) we pointed out that the normal order of basic strengths of 4-substituted compounds,

* The values on which this statement is based were determined in 50% alcohol, but pK_a values in water for the parent bases have been published by Albert, Goldacre, and Phillips (*J.*, 1948, 2240). These authors also give data for phthalazine and quinoxaline, the observed order for the five bases being quinoline > quinazoline > phthalazine > cinnoline > quinoxaline. Quinoxaline is thus a much weaker base than would be expected from the calculations of Longuet-Higgins and Coulson, the predicted order being quinoline > quinoxaline > quinazoline > phthalazine > cinnoline.

† The conditions which produce this result are evidently critical (cf. Schofield and Theobald, *J.*, 1949, 2404).

‡ To explain the non-acetylation of 8-nitro-4-hydroxycinnoline it was previously suggested (*J.*, 1947, 237) that hydrogen-bonding existed between the NO_2-group and the hydrogen atom attached to $N_{(1)}$ (the hetero-ring being assumed to be in the cinnolone form). This explanation may or may not be correct, but clearly cannot apply to the 8-methyl analogue, which is also resistant (*J.*, 1948, 1702).

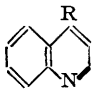
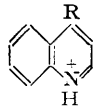
namely quinoline > quinazoline > cinnoline, no longer holds for 4-amino- and 4-anilino-compounds, the observed order for which is quinoline > cinnoline > quinazoline.

(*b*) 4-Aminoquinazolines differ from their cinnoline and quinoline counterparts in being readily hydrolysed to 4-hydroxyquinazolines in acid solution (data in Table I).

(*c*) If *N*-alkylated derivatives of 4-hydroxy-compounds of each group are treated with hot aqueous sodium hydroxide, the quinolones and cinnolones are stable, whereas 1-methyl- and 3-methyl-4-quinazolones undergo fission of the heterocyclic ring (*J.*, 1948, 360; 1949, 1354).

No comprehensive explanation of these three sets of observations is yet possible, but they are without doubt closely related and may be due to the amidine-like character of some quinazoline compounds (*J.*, 1948, 360; Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405).

(vi) *Acid-catalysed reactions of 4-substituted derivatives.* The reactions to be considered under this heading are the hydrolysis of 4-chloro- and 4-phenoxy- to 4-hydroxy-compounds, and the conversion of 4-chloro- into 4-anilino-derivatives. The data in Tables II and III indicate that a given quinoline derivative is less readily hydrolysed than its cinnoline or quinazoline analogue, and that a given 4-phenoxy-compound is less readily hydrolysed than the corresponding 4-chloro-compound. Within these limits it follows (cf. *J.*, 1949, 1356) that a given compound is less readily hydrolysed than one of lower basicity. This result accords with the view that these reactions are acid-catalysed; for, *ex hypothesi*, hydrolysis involves the conversion of (VII) into (VIII); this entails a greater measure of electron-release from R and

(VII.)   (VIII.)

$C_{(4)}$, with resultant development of cationoid reactivity at $C_{(4)}$, in the case of a weak base than it does for a stronger one; and the hydrolysis (entry of hydroxyl ion) is thus proportionately facilitated. In the conversion of 4-chloro- into 4-anilino-derivatives (a reaction which has previously been shown to be acid-catalysed; cf. *J.*, 1949, 1014), cinnolines, quinazolines, and quinolines behave in a seemingly identical manner, evidently because the catalytic stimulus of the experimental conditions is too great to enable differences in reactivity to be discerned.

(vii) *Cationoid reactivity of 4-substituted derivatives.* This heading refers to substitutions by anionoid reagents which are not catalysed by acids, namely the phenoxylation and methoxylation of 4-chloro-compounds, and the conversion of 4-phenoxy- into 4-amino-compounds. In these reactions the 4-substituted quinolines, cinnolines, and quinazolines (devoid of other substituents) exhibit increasing reactivity in the order named. This may be clearly seen from the behaviour of the 4-chloro-compounds on treatment with sodium methoxide in methanol and potassium hydroxide in phenol (see Experimental). The reaction between the phenoxy-compounds and ammonium acetate at 180—190° (preparation of 4-amino-compounds; data in Table V) is rapid, and under the conditions chosen the differences in reactivity are not very great; the sequence quinoline < cinnoline < quinazoline is however clearly discernible. Moreover, the facts that 4-aminoquinazolines may be prepared from 4-chloroquinazolines and aqueous ammonia at room temperature (*J.*, 1948, 360; 1949, 1354), whereas 4-chlorocinnoline is unchanged under these conditions, are additional evidence of greater cationoid reactivity of the quinazoline type.

There is substantial qualitative agreement between these results and the behaviour predictable from Longuet-Higgins and Coulson's calculations, which show an increased positive charge at $C_{(4)}$ in the order quinoline < cinnoline < quinazoline. However, the reactions discussed both in this and in the preceding section disclose a greater difference in reactivity between the quinoline and the cinnoline than between the cinnoline and the quinazoline types. This approximation of reactivity between cinnoline and quinazoline compounds, and the wide divergence between quinoline and cinnoline derivatives, are not predictable from Longuet-Higgins and Coulson's figures, which at first sight appear to predict the reverse situation; but it is possible that the cationoid activity of different heterocylic types falls off very rapidly as a certain minimum charge value is approached.

Experimental.

(M. p.s are uncorrected.)

4 : 6-*Diacetamidocinnoline.*—A solution of 6-nitro-4-aminocinnoline (*J.*, 1948, 358) (3·3 g.) in acetic acid (40 c.c.) was added to a stirred solution of stannous chloride (14·8 g.) in concentrated hydrochloric

acid (32 c.c.) and water (11 c.c.). Reduction was exothermic, and after 10 minutes the solution was heated at 85—90° for 20 minutes. Basification of the cold solution precipitated crude 4 : 6-diaminocinnoline, and more was obtained by evaporating the filtrate under reduced pressure (total yield, 80%); the base formed grey irregular plates, m. p. 260° (decomp.), which darkened on storage. The *hydrochloride* separated from dilute hydrochloric acid in orange prismatic needles, m. p. 315—316° (decomp.) (Found: C, 45·9; H, 5·65; N, 26·2. $C_8H_9N_4Cl,\frac{3}{4}H_2O$ requires C, 45·7; H, 5·05; N, 26·65%). When the base (1 part) was refluxed with acetic anhydride (9 parts), 4 : 6-*diacetamidocinnoline* (90%) rapidly separated; it crystallised from hot water as almost colourless fluffy needles, m. p. 272—273° (decomp.) (Found: C, 54·95; H, 5·35; N, 21·2. $C_{12}H_{12}O_2N_4,H_2O$ requires C, 54·95; H, 5·4; N, 21·35%).

6-*Chloro*-4-*acetoxycinnoline*.—The 4-hydroxy-compound (*J.*, 1945, 520) was refluxed for ¾ hour with acetic anhydride (4 parts). The product which separated on cooling was crystallised from alcohol, giving almost colourless needles (90—95%) of 6-*chloro*-4-*acetoxycinnoline*, m. p. 159—160° (Found: C, 53·75; H, 3·15; N, 12·8. $C_{10}H_7O_2N_2Cl$ requires C, 53·9; H, 3·15; N, 12·6%).

Methylation of 6-*Nitro*-4-*hydroxycinnoline*.—(*a*) The following conditions are preferred to those given by Schofield and Simpson (*J.*, 1945, 512); in particular, owing to an error in transcription, the quantity of alkali required is incorrectly stated in the earlier paper. A solution of the hydroxy-compound (10 g.) in the minimum quantity (175 c.c.) of 2% aqueous potassium hydroxide was treated with methyl sulphate (5 c.c.), added at 50° with mechanical stirring. After ½ hour the solid which had separated was collected (7·07 g.) and recrystallised from alcohol, yielding the almost pure methyl nitronate (5·9 g., 55%), m. p. 223—225° (decomp.), raised to 225—227° (decomp.) by further crystallisation. The compound is readily decomposed in hot sodium hydroxide solution, but is stable towards acid; after being refluxed for 1 hour with 2N-hydrochloric acid (100 parts), 90% of the material was recovered as orange-yellow needles, m. p. 231—232° (decomp.) (Schofield and Simpson give m. p. 228—229°).

The alcoholic mother-liquors were concentrated, and the material so obtained was digested with warm 0·5N-sodium hydroxide (the methyl nitronate being thus converted into alkali-soluble decomposition products) and finally recrystallised from water, from which 6-nitro-1-methyl-4-cinnolone separated in yellow needles (0·52 g., 4·8%), m. p. 190—191° (lit., 183—183·5°). After being refluxed for 2 hours in 2N-sodium hydroxide solution, this compound, its 3-methyl analogue (*vide infra*), and 6-nitro-1-methyl-4-quinolone (Simpson and Wright, *J.*, 1948, 1707) were recovered unchanged.

TABLE IV.

Phenoxylation of 4-*chloro-quinazoline, -cinnoline, and -quinoline.*

Temp.	Time from start of experiment.	4-Chloro-quinazoline.	4-Chloro-cinnoline.	4-Chloro-quinoline.
50°	5 minutes	Complete reaction	Unchanged	—
	17 ,,	—	Unchanged	—
	40 ,,	—	Mixture	—
	60 ,,	—	Mixture	—
	120 ,,	—	—	Unchanged
95°	150 ,,	—	—	Mixture
	210 ,,	—	—	Mixture
	330 ,,	—	—	Almost complete

TABLE V.

Amination of 4-*phenoxy-quinazoline, -cinnoline, and -quinoline.*

Temp.	Time from start of experiment.	4-Phenoxy-quinazoline.	4-Phenoxy-cinnoline.	4-Phenoxy-quinoline.
170°	0	—	—	—
184	4 minutes	Almost complete	Mixture	—
195	9 ,,	Complete reaction	Complete reaction	Mixture
195	15 ,,	—	—	Complete reaction

(*b*) 6-Nitro-4-hydroxycinnoline (2 g.) and methyl toluene-*p*-sulphonate (2·5 g.) were heated at 150° for 2 hours. The product was extracted with hot water (100 c.c.), and the solution filtered (charcoal) from insoluble material, yielding the crude methyl nitronate [1·05 g.; m. p. 215—217° (decomp.)], which after crystallisation from water had m. p. 225—226° (decomp.) alone and mixed with authentic material (yield 0·7 g.) (Found: C, 52·2; H, 3·5; N, 20·9. Calc. for $C_9H_7O_3N_3$: C, 52·7; H, 3·4; N, 20·5%).

Methylation of 6-*Nitro*-4-*hydroxy*-3-*methylcinnoline*.—A solution of the hydroxy-compound (1 g.; Keneford and Simpson, *J.*, 1948, 354) in the minimum quantity (21 c.c.) of 2% aqueous potassium hydroxide was treated as above with methyl sulphate (0·5 c.c.) at 45°. After 10 minutes the solid was collected (0·85 g.; m. p. 145—150°) and recrystallised from alcohol. Massive yellow prismatic needles (0·31 g.), m. p. 181—183°, of 6-*nitro*-1 : 3-*dimethyl*-4-*cinnolone* (Found: C, 55·1; H, 4·3; N, 18·8. $C_{10}H_9O_3N_3$ requires C, 54·8; H, 4·15; N, 19·2%) first separated, followed by orange flattened needles, which, recrystallised from aqueous alcohol, yielded the *methyl nitronate* (0·15 g.) as orange flakes, m. p. 161—162° (146—149° when mixed with the preceding compound) (Found: C, 54·9; H, 4·1; N, 18·6. $C_{10}H_9O_3N_3$ requires C, 54·8; H, 4·15; N, 19·2%). If the amount of alkali is slightly increased the yield of methyl nitronate is reduced, and from an experiment with 50 c.c. of alkali none of this compound could be isolated.

6-*Nitro*-4-*methoxy*-3-*methylcinnoline*.—A solution of sodium methoxide (0·6 g.) in methanol (5 c.c.) was added to a warm suspension of 4-chloro-6-nitro-3-methylcinnoline (Keneford and Simpson, *J.*, 1948, 354). The mixture was heated on the steam-bath for 2—3 minutes, cooled, and diluted with water (10 c.c.), yielding pure 6-*nitro*-4-*methoxy*-3-*methylcinnoline* (1·6 g.), which formed golden prismatic needles, m. p. 149—150°, from methanol, and was rapidly hydrolysed to the hydroxy-compound by dilute mineral acids (Found: C, 54·85; H, 4·1; N, 19·3. $C_{10}H_9O_3N_3$ requires C, 54·8; H, 4·15; N, 19·2%).

Methylation of 5(or 7)-*Nitro*-4-*hydroxy*-8-*methylcinnoline*.—Treatment of a solution of this compound (0·4 g.; Keneford, Morley, and Simpson, *J.*, 1948, 1702) in a slight excess (10 c.c.) of 2% aqueous potassium hydroxide with methyl sulphate (0·3 c.c.) at 50° gave as sole product (0·37 g.; m. p. 254—255°) a compound, presumably 5(or 7)-*nitro*-1 : 8-*dimethyl*-4-*cinnolone*, which formed beige-coloured prismatic needles, m. p. 257—258° (decomp.), from aqueous acetic acid (Found: C, 55·1; H, 4·2; N, 19·4. $C_{10}H_9O_3N_3$ requires C, 54·8; H, 4·15; N, 19·2%).

8-*Nitro*-4-*acetoxyquinoline*.—8-Nitro-4-hydroxyquinoline (200 mg.) was refluxed for 6 hours with acetic anhydride (1 c.c.). The solution was diluted with dry ether, and the solid which separated in the cold (120 mg.; m. p. 142—144°) was recrystallised from alcohol, yielding 8-*nitro*-4-*acetoxyquinoline* as almost colourless needles, m. p. 142—143° (Found: C, 56·8; H, 3·5; N, 12·4. $C_{11}H_8O_4N_2$ requires C, 56·9; H, 3·5; N, 12·1%). Evaporation of the acid anhydride filtrate over sulphuric acid in an evacuated desiccator gave unchanged 8-nitro-4-hydroxyquinoline (40 mg.), m. p. and mixed m. p. 196—197°.

After treatment as above, 4-hydroxy- and 6-nitro-4-hydroxy-quinoline were quantitatively recovered unchanged.

Rates of Phenoxylation of 4-*Chloro-compounds and Rates of Amination of* 4-*Phenoxy-compounds*.—The results given in Table IV were obtained from simultaneous experiments in which each chloro-compound (2 g.) was heated with phenol (10 g.) containing potassium hydroxide (0·76 g.). Samples from the well-stirred reaction mixtures were removed at the times stated and were worked up by basification and extraction with ether; the quinoline products were identified by conversion into the picrates. For comparative purposes, 4-phenoxyquinoline was obtained after reaction for 1 hour at 125—130°, in 95% yield, as a viscous oil, b. p. 157—159°/2—3 mm.; the picrate had m. p. 177—178° (Backeberg and Marais, *J.*, 1942, 381, give m. p. 179°). The phenoxylation of 4-chlorocinnoline is complete after 1 hour at 95° (*J.*, 1947, 917).

The results shown in Table V were likewise obtained by sampling simultaneous experiments in which each phenoxy-compound (2 g.) was heated with ammonium acetate (12 g.) which had been previously heated to 180° and allowed to cool to 170°. On the preparative scale, 4-aminoquinoline was obtained in almost quantitative yield, m. p. 153—154° alone and mixed with a sample prepared from cinchoninic acid [Renshaw and Friedman, *J. Amer. Chem. Soc.*, 1939, **61**, 3320, give m. p. 154—156° (corr.)].

In Tables IV and V the temperatures are those of the oil-bath. Each case of " complete reaction " was checked by examining a further sample withdrawn after a suitable interval.

Methoxylation of 4-*Chloro-quinazoline, -cinnoline, and -quinoline*.—(*a*) When solutions of 4-chloroquinazoline (0·2 g.) in methanol (3 c.c.) and of sodium methoxide (0·14 g.) in methanol (3 c.c.) were mixed, heat was evolved and sodium chloride rapidly separated. After 5 minutes, water was added and the product collected by extraction with ether. Evaporation of the washed and dried extract gave a crystalline residue (0·16 g.) of 4-methoxyquinazoline, m. p. 33—35°, which gave no depression on admixture with an authentic specimen (m. p. 37·5—38·5°; b. p. 65—66°/0·1 mm.; Bogert and May, *J. Amer. Chem. Soc.*, 1909, **31**, 507, give m. p. 35°).

(*b*) When 4-chlorocinnoline was substituted for 4-chloroquinazoline in the above experiment, no heat was evolved, and separation of sodium chloride occurred only slowly. After 1 hour, isolation of the product as above gave 4-methoxycinnoline (0·08 g.), m. p. and mixed m. p. 125—126°.

(*c*) After 4-chloroquinoline (1 g.) had been heated under reflux for 6 hours with a solution of sodium methoxide (0·4 g.) in methanol (10 c.c.), little sign of reaction was evident, and 90% of the material was recovered as impure 4-chloroquinoline picrate. 4-Methoxyquinoline (1·95 g.) was obtained by heating a solution of 4-chloroquinoline (2·2 g.) and sodium methoxide (0·8 g.) in methanol (35 c.c.) for 3 hours in a sealed tube at 140° ± 7°. The picrate had m. p. 203—204° (Backeberg, *J.*, 1933, 618, gives m. p. 203°), and the base regenerated from this had b. p. 91—93°/0·1 mm. and crystallised on cooling.

4-*Anilinoquinoline*.—4-Chloroquinoline (1·6 g.) was refluxed for ½ hour with aniline (1·24 g.) in acetone (5 c.c.) and water (10 c.c.) containing concentrated hydrochloric acid (3 drops). Removal of the acetone, addition of aqueous ammonia, and crystallisation of the precipitated solid from aqueous alcohol gave colourless needles (88%) of 4-anilinoquinoline, m. p. 198° (Ephraim, *Ber.*, 1893, **26**, 2227, gives m. p. 198°) (Found: C, 81·6; H, 5·6. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5%).

4-*Anilinoquinazoline and* 4-*Anilinocinnoline*.—Prepared under the above conditions, 4-anilinoquinazoline (0·61 g. from 0·5 g. of 4-chloroquinazoline) formed colourless prisms, m. p. 219·5—220°, from alcohol (Lange and Sheibley, *J. Amer. Chem. Soc.*, 1931, **53**, 3867, give m. p. 221—222°), and 4-anilinocinnoline (0·7 g. from 0·5 g. of chloro-compound) crystallised from alcohol in pale greenish-yellow needles, m. p. 236—237° (Keneford and Simpson, *J.*, 1947, 917, give m. p. 229·5—230·5°).

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