very high. The crude products were obtained in quantitative yields and the yields of recrystallized products were usually 80–95%.

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[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Cinnolines. VIII. The Reaction of 3-Aminocinnolines and 3-Aminoisoquinoline with Nitrous Acid[1,2]

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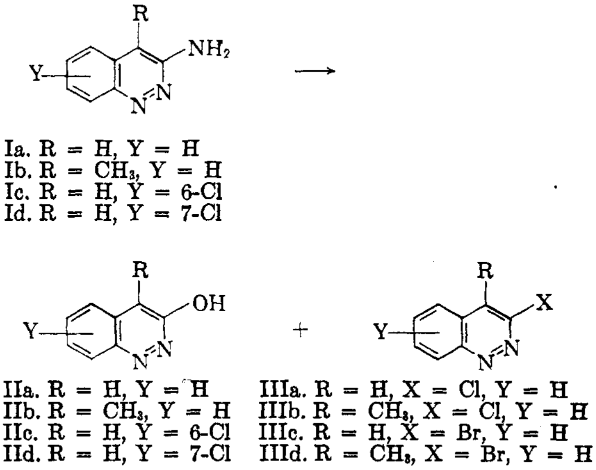
The reactions of 3-aminocinnoline and 3-aminoisoquinoline with nitrous acid in dilute mineral acid solution yielded 3-cinnolinol and 3-isoquinolinol. In concentrated hydrochloric or hydrobromic acids, 3-chloro- or 3-bromocinnoline were formed along with the 3-cinnolinol. Other 3-aminocinnolines behaved in an analogous fashion. Ionization constants for the amino and hydroxy compounds prepared are reported as are the infrared spectra of eight 3-cinnolinols and a number of related compounds.

Alford and Schofield[3c] have reported that, although 3-aminoquinoline is readily diazotized and thd diazonium salt forms a deep red azo compound with α-naphthol,[4] 3-aminocinnoline (Ia) in a similar test gave only a reddish-brown solution, and they concluded tentatively that Ia does not readily form a diazonium salt, if it does so at all. This communication reports the results of a study of the reactions of Ia and other 3-aminocinnolines as well as 3-aminoisoquinoline (IV) with nitrous acid in the presence of various mineral acids. After the preparative work in this study had been completed, a paper by Boyer and Wolford[5] appeared describing their experiments on the reaction of IV with nitrous acid, the results of which differed from ours in several minor respects. We have repeated both their and our own work and offer here a rationalization of the differences.

When solutions of Ia in dilute sulfuric or hydrochloric acids were treated with aqueous sodium nitrite in the cold, nitrogen was immediately evolved and 3-cinnolinol (3-hydroxycinnoline, IIa) was formed. When Ia was treated with nitrous acid in concentrated hydrochloric acid or in 48% hydrobromic acid solution, IIa was again formed but in lower yield accompanied by 3-chloro- (IIIa) or 3-bromocinnoline (IIIc), respectively. As indicated in Table I several other 3-aminocinnolines (Ib–d) showed similar behavior. In the case of 3-amino-4-methylcinnoline (Ib), none of the products analogous to those obtained by Ockenden and Schofield[6] from the reaction of nitrous acid and 3-aminolepidine were formed.

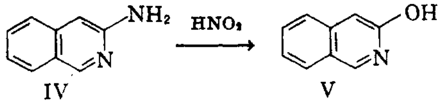


Ia. R = H, Y = H
Ib. R = CH_3, Y = H
Ic. R = H, Y = 6-Cl
Id. R = H, Y = 7-Cl

IIa. R = H, Y = H
IIb. R = CH_3, Y = H
IIc. R = H, Y = 6-Cl
IId. R = H, Y = 7-Cl

IIIa. R = H, X = Cl, Y = H
IIIb. R = CH_3, X = Cl, Y = H
IIIc. R = H, X = Br, Y = H
IIId. R = CH_3, X = Br, Y = H

In the reaction of IV with nitrous acid Boyer and Wolford[5] reported only an 18% yield of 3-isoquinolinol (3-hydroxyisoquinoline, V). This low yield we attribute to their use of three equivalents of sodium nitrite in the reaction, for in the present work, using one equivalent of the nitrite, yields of 53–65% were readily obtained. We observed (as did Boyer and Wolford[5]) that V reacted further with nitrous acid to give a substance of unknown



IV V

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[1] Paper VII. *J. Am. Chem. Soc.*, **82**, 4634 (1960).

[2] This work was initiated with the support of grant G-1090 of the National Science Foundation and completed with the support of grant CY-3090 of the U. S. Public Health Service.

[3] E. J. Alford and K. Schofield, (a) *J. Chem. Soc.*, 2102 (1952); (b) *J. Chem. Soc.*, 609 (1953); (c) *J. Chem. Soc.*, 1811 (1953).

[4] W. H. Mills and W. H. Watson, *J. Chem. Soc.*, **97**, 741 (1910).

[5] J. H. Boyer and L. T. Wolford, *J. Org. Chem.*, **21**, 1207 (1956).

[6] D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 1915 (1953).

TABLE I

REACTION OF 3-AMINOCINNOLINES AND 3-AMINOISOQUINOLINE WITH NITROUS ACID

Amine	Acid	Product	Yield, %	M.P.	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
Ia	Dil. HCl	IIa	44	203.5–204.5[a,b]							
Ia	Dil. H_2SO_4	IIa	40–66	203.5–204.5[a,b]							
Ia	Concd. HCl	IIa	30	203.5–204.5[a,b]							
		IIIa	18–27	91–92[c,d,e]							
Ia	Concd. HBr	IIa	30–40	203.5–204.5[a,b]							
		IIIc	21–29	92–93[c,d,f]							
Ib	Dil. HCl	IIb	53–83	232–234[a,g,h]	$C_9H_8N_2O$	67.48	67.63	5.03	5.06	17.48	17.76
Ib	Dil. H_2SO_4	IIb	67	232–234[a g,h]							
Ib	Concd. HCl	IIb	29	232–234[a,g,h]							
		IIIb	22–53	145–146[c,i,j]	$C_9H_7N_2Cl$	60.51	60.52	3.95	4.30	15.69	15.68
Ib	Concd. HBr	IIb	29–38	232–234[a,g,h]							
		IIId	23–28	158.5–159[c,k,l]	$C_9H_7N_2Br$	48.45	48.75	3.16	3.42	12.59	12.28
Ic	Dil. H_2SO_4	IIc	61–69	304–305[g,m,n]	$C_8H_5ClN_2O$	53.21	53.23	2.79	3.10	15.51	15.69
Id	Dil. H_2SO_4	IId	53–86	263–264.5[a,g,o]	$C_8H_5ClN_2O$	53.21	53.27	2.79	2.97	15.51	15.90
IV	Dil. H_2SO_4	V	53–65	195–196[a,p,q]	C_9H_7NO	74.46	74.80	4.86	4.71	9.65	9.95

[a] From benzene. [b] Lit.[3a] m.p. 201–203°. [c] From Skellysolve C,[22] then sublimed at 80° (0.2 mm.). [d] Kofler hot stage. [e] Lit.[3b] m.p. 90–91°. [f] Lit.[3b] m.p. 92–93°. [g] Dec. [h] M.p. of crude, air-dried product or product recrystallized from alcohol-water was 204–205° dec. One or more recrystallizations from benzene were required to raise m.p. to value listed. [i] From Skellysolve C,[22] then sublimed at 120° (0.2 mm.). [j] Calcd.: Cl, 19.85. Found: Cl, 20.19. [k] From Skellysolve C,[22] (m.p. 154–156°) then sublimed at 150° (0.2 mm.). [l] If the temperature was raised 5° per min., crystals melted completely at 145°. Crystals change form slowly above 100°. M.p. cited obtained by raising temperature 10° per min. from 130–145°, holding at 145° for 15 min., then raising *ca.* 0.5° per min. until sample melted. [m] From 95% ethanol (1 ml.l/mg.). [n] Lit.[3a] m.p. 262–265°. [o] In one run a small amount of material, m.p. 221–220° (from alcohol-water) was isolated from the benzene mother liquors. It was not examined further. [p] For discussion of phenomena at m.p. see Experimental. [q] Product obtained from the hydrolysis of 3-acetoxyisoquinoline[5] had m.p. 198–199°. (Lit.[5] m.p. 198–199°).

structure; however, we have been unable as yet to confirm their elementary analysis for this substance.

Although treatment of IV with an alkyl nitrite in acetic acid solution yielded 3-acetoxyisoquinoline,[5] similar treatment of Ia either gave none of the 3-acetoxycinnoline or the latter is quite unstable, for the only product isolated was IIa. Alford and Schofield[3] have reported that they were unable to prepare an acetate from IIa. Although IIa is converted by methyl sulfate and a deficiency of sodium hydroxide into 2-methyl-3-cinnolinone,[3] we were unable to isolate an analogous product from the tar formed from the treatment of V with methyl sulfate and a deficiency of alkali.

Attempts to deaminate Ia and Ib with hypophosphorous acid according to the procedure of Henry and Finnegan[7] were unsuccessful, IIa and IIb being the only products.

A number of attempts were made to prepare a diazonium salt from Ia in dilute hydrochloric or sulfuric acid solution which would couple with either α-naphthol or β-naphthol. Even under a variety of experimental conditions no coupling product was obtained. Similar behavior was observed with IV. If a diazonium salt forms under these conditions, it must decompose rapidly, probably to the products obtained in the experiments described above. The results support the conclusion that Ia and its derivatives do not readily form *stable* diazonium salts.[8] Thus, the behavior of the 3-aminocinnolines is qualitatively similar to that observed with many heterocyclic amines in which the amino group is *alpha* or *gamma* to a ring nitrogen and which react with nitrous acid to form the corresponding hydroxy compounds (or a tautomer thereof).[9]

The structure of 3-cinnolinol as a function of the tautomeric system, VI⇌VII (Y = N) (Fig. 1), has been discussed by Schofield and co-workers,[3,10] who concluded that the amide:enol ratio for 3-cinnolinol is smaller than that in 4- cinnolinol although the amide (lactam) form still predomi-

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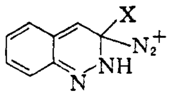
[7] R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, 76, 290 (1954).

[8] This conclusion is in agreement with that reached by Alford and Schofield[3a] provided that their statement that Ia does not form a diazonium salt is interpreted to mean that it does not form a *stable* diazonium salt.

[9] One rationalization of this behavior has been offered by S. J. Angyal and C. L. Angyal [*J. Chem. Soc.*, 1461 (1952)] who have suggested in essence an S_N1-type decomposition involving a heteroaryl carbonium ion. There is no evidence to support this suggestion other than that rather incomplete evidence pertaining to simple diazonium compounds (*cf.* J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 365). In the heterocyclic series an S_N2-type displacement involving a transition state having in acid solution contributing froms such as



or an S_Ni-type displacement involving the heteroaryl diazoic acid (*cf.* E. S. Lewis and M. D. Johnson, Abstracts of Papers of the American Chemical Society Meeting, Cleveland, Ohio, April 5–14, 1960, p. 490) appear to be more plausible.

[10] A. R. Osborn and K. Schofield, *J. Chem. Soc.*, 4207 (1956).

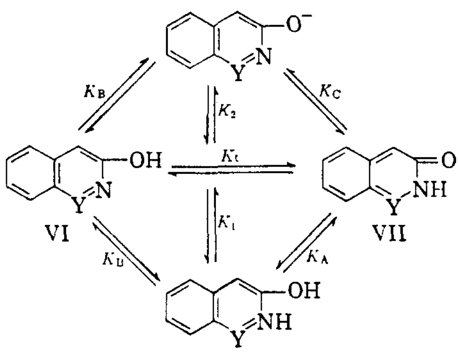


Fig. 1. Tautomeric equilibria. $K_1 = K_A + K_B$. $1/K_2 = 1/K_C + 1/K_D$. $K_t = K_A/K_B = K_D/K_C$

nates. It appears that no systematic study of 3-isoquinolinol as a tautomeric system of the type, VI⇌VII (Y = CH), has been reported. However, in view of the increasing evidence that similar hydroxyl derivatives of hetero-aromatic compounds exist predominantly in the amide form,[11,12] one would expect that the equilibrium would favor VII (Y = CH).[13] In the present study infrared spectra, ultraviolet spectra, and ionization constants were examined in an effort to support this expectation.

In Table II are given a number of ionization constants measured in the present work. In view of the recent excellent discussion given by Osborn, Schofield, and Short[14] on the basic strengths and ultraviolet spectra of some aminoisoquinolines and -cinnolines, further elaboration here is not necessary beyond noting that the new data fit rather well into their discussion. The chloro derivatives, Ic and Id, were found to be much weaker bases than Ia as would be expected because of the electron-withdrawing inductive effect of the chlorine atom. However, the small difference between the basic strengths of Ic and Id permits no rationalization of the difference due to position isomerism.

TABLE II

IONIZATION CONSTANTS OF AMINO AND HYDROXY CINNOLINES AND ISOQUINOLINES

Compound	Basic pK_a	Acidic pK_a
3-Aminocinnoline	3.70 ± 0.02	
3-Aminoisoquinoline	4.92 ± 0.02	
3-Amino-6-chlorocinnoline	3.24 ± 0.03	
3-Amino-7-chlorocinnoline	3.28 ± 0.01	
3-Cinnolinol	0.21[a]	8.62 ± 0.02 (9.08 ± 0.03)[b]
3-Isoquinolinol	2.18 ± 0.05 (*ca.* 1.9)[b]	9.62 ± 0.02 (10.21 ± 0.12)[b]
6-Chloro-3-cinnolinol		(8.41 ± 0.01)[b]
7-Chloro-3-cinnolinol		(8.48 ± 0.02)[b]

[a] Ref. 3c. [b] Determined for 50% ethanol.

In the study of IIc and IId the compounds were too insoluble to permit determination of their pK_a values in water. Therefore, the pK_a (pK_2 in Fig. 1) values for these compounds were determined in 50% ethanol and for comparison purposes pK_2 for IIa was also determined in the same solvent. The pK_2 values for IIc and IId show the expected increase in acid strength due to the inductive effect of the chloro substituent over that of IIa. Here again the pK_2 values for IIc and IId were too close for significant conclusions to be drawn as to the effects of position isomerism.

Based on the assumption that those ionizations involving the formation and separation of two charged particles from an initially uncharged molecular species will be dependent on the dielectric constant of the solvent, a decrease in the dielectric constant being unfavorable for the forward direction of the equilibrium, while those ionizations not involving a change in the number of ions will be less sensitive to the dielectric constant, several workers[15] have observed that on changing the solvent from water to 50% ethanol, phenols and carboxylic acids show a decrease in acid strength (increase in pK_a), whereas conjugate acids derived from amines show little change or a slight increase (decrease in pK_a). In general the ionization of lactams, imides, sulfonamides, and related species should show the same dependence on the dielectric properties of the solvent as that shown by carboxylic acids and phenols. Thus, Guerillot[16] has reported that the pK_a of phthalimide varies inversely with the dielectric constant. Interpolation of his data indicates an increase of approximately 0.40 pK_a units on changing the medium from water to 50% ethanol. From Fig. 1 it is apparent that on this basis on increase in the acidic pK_a (pK_2) of IIa would be expected for a similar solvent change. In the present work the pK_a of IIa was 0.46 units higher in 50% ethanol than in water.

3-Isoquinolinol (V) was a weaker acid than both 3-cinnolinol (IIa) and 3-hydroxyqinoline and

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[11] Presumably 3-cinnolinol will exist in equilibrium with a zwitterion form in which the proton is attached to N(1) rather than N(2) as shown; however, the contribution of the former should be relatively minor and is ignored in the present discussion.

[12] For a leading reference see: S. F. Mason, (a) *J. Chem. Soc.*, 4874 (1956); (b) *J. Chem. Soc.*, 5010 (1957); (c) *J. Chem. Soc.*, 674 (1958).

[13] Because 3-isoquinolinols are readily soluble in alkali and because they have a small number of resonance forms, W. J. Gensler (R. C. Elderfield's *Heterocyclic Compounds*, Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1950, p. 441) has suggested that the enolic (lactim) form is to be preferred. Boyer and Wolford[6] have reported that a band at 2.93 μ in the infrared spectrum of the compound determined in a potassium bromide wafer and a positive ferric chloride test are suggestive of the presence of a phenolic hydroxyl group. We found no band in the vicinity of 2.93 μ except that due to moisture commonly appearing in spectra run with potassium bromide wafers.

[14] A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 4191 (1956).

[15] H. C. Brown, D. H. McDaniel, and O. Hafliger in E. A. Braude and E. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press, Inc., New York, N. Y., 1955, p. 617.

[16] C. R. Guerillot, *Compt. rend.*, 240, 1107 (1955).

TABLE III

INFRARED SPECTRA[a]

Compound	Frequency, Cm.$^{-1}$			
	ν(N—H) Region		ν(C=O) Region	
	Solid[b]	Solution[c]	Solid[b]	Solution[c]
3-Isoquinolinol	2540bb	3370	1651	1649, 1637sh
3-Cinnolinol	3280, 3210, 2800bb[d]	3380	1672[e,f]	1657
2-Methyl-3-cinnolone			1648[g]	1655sh, 1647
5,6,7,8-Tetrahydro-3-cinnolinol	3290, 3240	3408	1655	1666
4-Methyl-3-cinnolinol	3260, 3200, 2795bb[d]	3365	1634, 1624[g]	1635
4-Benzyl-3-cinnolinol	2770bb	3382	1640	1636
4-Phenyl-3-cinnolinol	3280w, 2730bb	3365	1629	1638
6-Chloro-3-cinnolinol	2650bb	3355	1698	1660sh, 1655
7-Chloro-3-cinnolinol	2700bb	3380	1685, 1650sh	1665, 1657sh
1,5-Naphthyridin-2-ol		3400	1702, 1645[g]	1662
2-Methyl-1,5-naphthyridin-4-ol	3260w, 2930–2780bb[h]	3408	1653	1664
1,7-Naphthyridin-2-ol	3280w, 3140w, 2900–2780bb[h]		1659	
2-Methyl-5,6,7,8-tetrahydro-4-quinazolinol	3250w, 2920–2770bb[h]	3400	1651	1651

[a] Run using Perkin-Elmer model 21 spectrophotometer. [b] Run using sodium chloride prism and potassium bromide pellets. [c] Run using alcohol-free chloroform[1] and lithium fluoride prism for ν(N—H) region and sodium chloride prism for ν(C=O) region. [d] Hexachlorobutadiene mull and lithium fluoride prism. [e] In the hexachlorobutadiene mull using a lithium fluoride prism, this band was resolved into two bands, 1682sh and 1673 cm.$^{-1}$ [f] This value is the mean of six determinations using compound prepared by three different synthetic routes. Mason[12] reports for this compound, 1660 cm.$^{-1}$ [g] Nujol mull. [h] A series of three to four weak bands were superimposed on the broad band.

only slightly stronger than phenol. The basic strength of V was approximately equal to that of 4-quinolinol. Although from the available acidic and basic pK_a values (pK_2 and pK_1) no amide:enol ratio can be calculated, comparison of these values with those of compounds of known structure indicates a probable appreciable amide contribution. Based on the quantum mechanical considerations proposed by Mason,[12c] to a first approximation, log K_t for VII can be estimated to be of the same order of magnitude as that for 6-isoquinolinol (log $K_t = 0.3$).[17]

The acid pK_a (pK_2) for V was increased by about 0.6 pK_a unit on changing the solvent from water to 50% ethanol. Inasmuch as there is no change in the number of charged species in the ionization of the conjugate acid of VII, little change in the basic pK_a (pK_1) for a change from water to 50% ethanol would be expected. The approximate value of 1.9 obtained in 50% ethanol confirms this expectation.

In Table III are given the ν(N—H) and ν(C=O) frequencies determined in the solid and solution states for a number of *N*-heteroaromatic compounds of the general type VI$\leftrightarrows$VII,[18] as well as for some other compounds prepared in this work. It is clear from the values in Table II and from the earlier discussions of Mason[12c] that the 3-cinnolinols and 3-isoquinolinol as well as the other miscellaneous hydroxy compounds listed in Table III possess principally amide structures (type VII) in chloroform solution. All of the compounds studied are quasi-*o*-quinoid amides[12a] and absorb in the ν(N—H) region between 3355 and 3408 cm.$^{-1}$, which is fairly well within the range, 3360–3420 cm.$^{-1}$, suggested by Mason[12a] for such compounds. Inasmuch as the ν(C=O) frequencies for 4-benzyl-, 4-methyl-, and 4-phenyl-3-cinnolinol are well below that for 3-cinnolinol, it appears that the 4-substituents in the compounds must stabilize the polar form of VII (Y = N) through electron release thereby increasing the single bond character of the C—O bond.[19] It is interesting to note that the halogen atoms in IIc and IId have little effect on the ν(C=O) frequency. Possibly this is due to an approximate cancellation of opposing effects as in the *p*-haloacetophenones.[20]

In Table IV are given data on the ultraviolet spectra of a number of 3-cinnolinols and 3-isoquinolinols and 3-isoquinolinol (and some other compounds). These spectra are very similar in general

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(17) The amide contribution to the hybrid is a *para-para*-quinoid form in the case of 6-isoquinolinol and an *ortho-ortho*-quinoid form in the case of 3-isoquinolinol. In general, the isomer with *para*-quinoid resonance structures would be expected to have a higher value of K_t than the isomer with *ortho*-quinoid resonance structures provided that the oxygen and nitrogen atoms are not linked to the same carbon atom, but when they are so linked that amide tautomer appears to gain stability due to resonance involving the amide group.[12c] Thus, the factors determining the relative stabilities of 3-isoquinolinol and 6-isoquinolinol appear to counterbalance each other and to lend support to the approximation.

(18) Inasmuch as the determination of these spectra was spread over a number of years, the media used for the solid-state spectra vary from sample to sample, but, where material was available, all of the solution spectra were run on the same instrument with the same solvent within a fairly short time period.

(19) Although each of the values in Table III for these derivatives is the mean of several determinations, the differences among the three are too small to permit reliable detailed comparison.

(20) R. N. Jones, W. F. Forbes, and W. A. Mueller, *Can. J. Chem.*, 35, 504 (1957).

TABLE IV

ULTRAVIOLET SPECTRA[a]

Compound	λ_{max}, mμ	log ϵ_{max}
3-Amino-6-chlorocinnoline	220; 244; 388	4.31; 4.61; 3.48
3-Amino-7-chlorocinnoline	220sh; 243; 276sh; 395	3.89; 4.69; 3.72; 3.48
3-Aminoisoquinoline	234; 272; 282; 293; 366	4.67; 3.75; 3.87; 3.72; 3.46
3-Cinnolinol	230; 282sh; 312sh; 400	4.66; 3.41; 3.20; 3.52
4-Methyl-3-cinnolinol	235; 280sh; 393	4.65; 3.40; 3.72
4-Benzyl-3-cinnolinol	234; 288sh; 298	4.67; 3.41; 3.73
4-Phenyl-3-cinnolinol	233; 322sh; 413	4.62; 3.35; 3.81
6-Chloro-3-cinnolinol	237; 299; 310; 323; 390	4.67; 3.26; 3.24; 3.28; 3.45
7-Chloro-3-cinnolinol	236; 282; 390	4.70; 3.21; 3.44
3-Isoquinolinol	225; 234sh; 262; 274; 288; 302; 345; 400	4.54; 4.45; 3.49; 3.41; 3.32; 3.04; 3.26; 3.33

[a] Determined using a Cary model 11 recording spectrometer and 10^{-4} to 10^{-5} *M* solutions in 95% ethanol.

appearance to those reported previously for variety of *N*-heteroaromatic compounds of the general type VI$\rightleftharpoons$VII, showing in 95% ethanol solution two well defined bands, the first being a very intense maximum near 230 mμ and the second, a weaker band in the vicinity of 400 mμ.

EXPERIMENTAL[21]

Reaction of 3-aminocinnoline with nitrous acid. (*a*) *In dilute acids.* To a solution of 0.73 g. (0.005 mole) of 3-aminocinnoline, 5 ml. of concentrated sulfuric acid, and 20 ml. of water, cooled to 0° in an ice-salt bath, was added dropwise with stirring an ice cold solution of 0.35 g. (0.005 mole) of sodium nitrite in 5 ml. of water. During the addition of the sodium nitrite the solution evolved a colorless gas and changed from yellow to nearly colorless. The reaction mixture was allowed to stand for 1 hr. at room temperature, then was heated to 50° on the steam bath and cooled. Concentrated ammonium hydroxide (15 ml.) was added slowly with stirring until the mixture was faintly alkaline. After the mixture had been cooled in ice for 1 hr., it was filtered and the crude, bright yellow precipitate was dissolved (without drying) in an excess of 10% sodium hydroxide solution. The solution was filtered and acidified to *p*H 5–6 with acetic acid, chilled thoroughly, and refiltered. The dried precipitate was recrystallized from benzene to give 0.39 g. (53%) of 3-cinnolinol, m.p. 203.5–204.5°. Although crude yields were often nearly quantitative, there was considerable variation in the range of pure yields, 40–66%. Yields in the upper range were possible only when the various aqueous mother liquors were evaporated to dryness, the crude 3-cinnolinol in the residue was extracted with chloroform and added to the crude material for recrystallization from benzene, and the benzene mother liquors were worked up systematically for maximum recovery.

Substitution of dilute hydrochloric acid for the sulfuric acid gave substantially the same result; however, the product did contain small amounts of 3-chlorocinnoline, which was readily removed by the purification procedure described above.

(*b*) *In concentrated hydrochloric acid.* To a solution of 1.0 g. (0.0069 mole) of 3-aminocinnoline in 50 ml. of concentrated hydrochloric acid, chilled to 5° in ice, was added dropwise with stirring a solution of 1.0 g. (0.014 mole) of sodium nitrite in the minimum amount of water. A vigorous evolution of a colorless gas accompanied the addition. After the solution had stood for 10 min. in the ice bath, it was made strongly alkaline (*p*H > 11) with 33% potassium hydroxide solution and filtered. The tan precipitate was dried *in vacuo* and recrystallized from Skellysolve C,[22] giving colorless needles, 0.31 g. (27%), m.p. 91–92°, of 3-chlorocinnoline. Sublimation at 80° (0.2 mm.) did not change the melting point.

The aqueous filtrate was evaporated to dryness and the residue was extracted with chloroform. After evaporation of the chloroform, the brown-yellow residue was recrystallized from benzene, giving 0.30 g. (30%) of 3-cinnolinol, m.p. 202–204°.

(*c*) *In concentrated hydrobromic acid.* The procedure was identical with that described in (b) above except that 50 ml. of 48% hydrobromic acid was substituted for the hydrochloric acid. The crude gray to light purple precipitate was recrystallized from Skellysolve C,[22] giving colorless needles, 0.42 g. (29%), m.p. 93–94°, of 3-bromocinnoline. Material sublimed at 80° (0.2 mm.) melted at 92–93° (hot stage).

The 3-cinnolinol could be recovered in 30–40% yield from the aqueous filtrate as described above in (b).

Reactions of other 3-aminocinnolines with nitrous acid. The procedures used for the reactions of the other 3-aminocinnolines (Table I) were essentially the same as those described above for the reactions of 3-aminocinnoline. However, in most of the other experiments using concentrated acids no more than a 10% excess over the theoretical amount of sodium nitrite was used; the theoretical amount was used in all experiments with the dilute acids. In the reactions of the chloro-3-aminocinnolines the quantity of concentrated sulfuric acid used was 3 ml. per 0.001 mole rather than 1 ml. per 0.001 mole as in (a) above. The chloro-3-cinnolinols were sufficiently insoluble in water so that the working up of the aqueous mother liquors was usually unnecessary. It should be noted that (as pointed out by Alford and Schofield[3a]) some of the 3-cinnolinols (especially 4-methyl-3-cinnolinol in the present work) seem to retain water rather strongly (as indicated by analysis and lowering of the melting point well below that reported in Table I but with little effect on the infrared spectrum). Several recrystallizations from benzene, during which the trace of water may be removed by azeotropic distillation, usually bring the melting point up.

Reaction of 3-aminoisoquinoline with nitrous acid. A mixture of 1.44 g. (0.01 mole) of 3-aminoisoquinoline,[23-25] 10 ml. of concentrated sulfuric acid and 40 ml. of water was warmed gently until the amine dissolved. To the solution cooled to 0° in an ice-salt bath was added dropwise with stirring a cold solution of 0.70 g. (0.01 mole) of sodium nitrite in 10 ml. of water. During the addition of the sodium nitrite a colorless gas was evolved and a yellow precipitate (the acid sulfate of 3-isoquinolinol[5]) was formed. The resulting mixture was allowed to stand overnight, then was made strongly

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[21] Melting points are corrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.

[22] A hydrocarbon solvent, b.p. 88–98°.

[23] C. E. Teague, Jr., and A. Roe, *J. Am. Chem. Soc.*, **73**, 688 (1951).

[24] F. H. Case, *J. Org. Chem.*, **17**, 1297 (1952).

[25] H. E. Baumgarten and J. E. Dirks, *J. Org. Chem.*, **23**, 900 (1958).

basic with 33% potassium hydroxide[26] solution and filtered. The filtrate was neutralized by addition of acetic acid and the resulting yellow precipitate was collected by filtration, dried in air overnight and extracted with two 100-ml. portions of absolute ethanol. Removal of the alcohol on the steam bath gave 0.97–1.20 g. (65–83%) of crude 3-isoquinolinol. The crude product was recrystallized from benzene (or, if colored strongly, first from 95% ethanol (with charcoal) then benzene), giving 0.79–0.97 g. (53–65%) of 3-isoquinolinol as light yellow needles, which melted at 195–196°, then resolidified (in a preheated bath). On continued heating the solid gradually darkened, finally melting (dec.) at 257°. When the compound was inserted in the bath at any temperature below 194° and the temperature was raised slowly, it did not melt at 195–196° but slowly darkened and melted at 257°.

Potentiometric titrations. The procedure used for the determination of the pK_a values were patterned after that outlined by Linstead, Elvidge, and Whalley.[27] A Leeds and Northrup pH meter, in conjunction with a glass and calomel electrode, was used. The meter checked to within 0.02 pH units against standard buffers throughout the measurements. The measurements were made at 20 ± 0.05° under purified nitrogen. Each reported value is the mean of fourteen to twenty-one determinations.

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[26] Use of sodium hydroxide complicates the purification because of the insolubility of the sodium salt of 3-isoquinolinol.

[27] R. P. Linstead, J. A. Elvidge, and M. Whalley, *A Course in Modern Techniques of Organic Chemistry*, Academic Press, Inc., New York, N. Y., 1955, p. 153.

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORIES, UNIVERSITY OF NORTH CAROLINA]

Electrolytic Oxidation of Some Substituted Quinolines to Quinolinic Acids and Acylations with Substituted Quinolinic Anhydrides

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A series of quinolines bearing substituents on the pyridine ring have been oxidized electrolytically in sulfuric acid. The corresponding quinolinic acids were obtained from 3-fluoro-, 3-chloro-, 3-bromoquinoline and from quinoline itself. 3-Iodoquinoline gave an acidic material that did not contain iodine. Electrolysis of 2- and 4-chloroquinoline caused loss of halogen and yielded polymeric materials. No products were isolated from 2-phenylquinoline and from 3-aminoquinoline. Anhydrides were prepared from 5-fluoro-, 5-chloro-, 5-bromo-, 4-methyl-, and unsubstituted quinolinic acid, and Friedel-Crafts reaction of these anhydrides with benzene yielded in each case a single isomer, the corresponding 3-benzoylpyridine-2-carboxylic acid.

A variety of methods are available for the oxidation of quinoline and substituted quinolines to quinolinic acids, employing oxidizing agents such as potassium permanganate, manganese dioxide and fuming nitric acid.[2–5] One method of particular interest for its simplicity and convenience is the electrolytic procedure described in the thorough study by Kulka[6] of the anodic oxidation of quinoline in concentrated sulfuric acid solutions at different temperatures, employing both platinum and lead dioxide anodes. The application of electrolytic oxidations to heterocyclic derivatives has been but scantily investigated. Yokayama[7] has converted methylpyridines to pyridine carboxylic acids by electrolysis; Fichter and Kern[8] have applied electrolytic procedures to oxidations in the purine series, and Fischer and Chur[9] have oxidized quaternary pyridine salts to pyridines. In the present investigation, the procedure of Kulka[6] has been applied to quinolines substituted in the heterocyclic ring.

The general procedure involved the use of the apparatus described in the Experimental section, where the quinoline was dissolved in 75–80% sulfuric acid and was subjected to electrolysis at temperatures varying from 55° to 90°, employing a platinum gauze or lead dioxide anode. The oxidations of approximately 0.1 mole of the substituted quinolines required approximately eighty hours for completion at 3 to 4 v. and a current of 1 to 1.5 amp. The reaction was conveniently followed by color changes. Initially the electrolysis mixtures turned dark brown to black; at the end of the reaction the reaction mixtures changed from this dark color to a light amber over a period of less than one hour. The substituted quinolinic acids so obtained were conveniently isolated by formation of insoluble copper complexes that were readily de-

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[6] M. Kulka, *J. Am. Chem. Soc.*, 68, 2472 (1946).

[7] M. Yokayama, *Bull. Chem. Soc., Japan*, 7, 69 (1932); *Chem. Abstr.*, 26, 3250 (1932).

[8] F. Fichter and W. Kern, *Helv. Chim. Acta*, 9, 429 (1926).

[9] O. Fischer and M. Chur, *J. prakt. Chem.*, 93, 363 (1916).