The Analytical Properties of 8-Hydroxy-5-, -6-, and -7-trifluoromethylquinoline.

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The sensitivities of 8-hydroxy-5-, -6-, and -7-trifluoromethylquinoline towards selected metal ions have been determined. 8-Hydroxy-5- and -6-trifluoromethylquinoline reacted with the majority of those tested, but the 7-trifluoromethyl isomer did not give a precipitate with any. The relationships between the structures of these hydroxy-compounds and the observed reactions are discussed.

Syntheses have been reported for 8-hydroxy-5- (Pettit and Tatlow, *J.*, 1954, 3852), -6-, and -7-trifluoromethylquinoline (Belcher, Stacey, Sykes, and Tatlow, *J.*, 1954, 3846). We now describe and discuss the analytical properties of these compounds.

8-Hydroxyquinoline (" oxine ") has long been used as a reagent in analytical chemistry, but it is not very selective. Many attempts have been made to modify its analytical properties by the introduction of substituent groups into the molecule (see, *e.g.*, Welcher, " Organic Analytical Reagents," D. Van Nostrand Co. Inc., New York, 1947, Vol. 1, p. 323). Only one such derivative, however, 8-hydroxy-2-methylquinoline (Merritt and Walker, *Ind. Eng. Chem. Anal.*, 1944, **16**, 387) exhibits any profound difference from the parent compound: it does not precipitate aluminium. This greater selectivity has been attributed to its increased molecular size (*idem, loc. cit.*). Irving, Butler, and Ring (*J.*, **1949**, 1489) studied the analytical properties of 8-hydroxy-2-, -5-, -6-, and -7-methylquinoline, 8-hydroxy-2-phenylquinoline, and some related compounds, and advanced a stereochemical explanation to account for the failure of the 2-methyl derivative to precipitate aluminium. They also noted that 8-hydroxy-7-methylquinoline had an increased sensitivity as compared with oxine and with 8-hydroxy-5- and -6-methylquinoline. Irving and Rossotti (*J.*, 1954, 2910) have, however, shown that the complexes formed by 8-hydroxy-7-methylquinoline are actually less stable than those formed by oxine, again owing, possibly, to steric effects.

TABLE 1.*

Metal used :	Al^{3+}		Cr^{3+}		Fe^{3+}	
Test solution :	A	B	A	B	A	B
Quinoline						
8-OH	4·4—1·7	4·4—1·7	8·4—3·4	16·8—8·4	1·8—0·9	1·8—0·9
	(*a*)		(*a*)		(*a*)	
$8-OH-5-CF_3$	97·0—64·5	64·5—32·0	N.P.	N.P.	3·2—1·6	3·2—1·6
	(lemon-yellow)		(—)		(greenish-black)	
$8-OH-6-CF_3$	0·16—0·06	0·32—0·16	6·4—3·2	12·8—6·4	1·2—0·6	1·2—0·6
	(lemon-yellow)		(pale yellow)		(greenish-black)	

Metal used :	Cu^{2+}			Zn^{2+}		
Test solution :	A	B	C	A	B	C
Quinoline						
8-OH	1·0—0·4	1·0—0·4	1·0—0·4	1·1—0·4	1·0—0·4	10·6—4·2
		(*a*)			(*a*)	
$8-OH-5-CF_3$	1·6—0·65	1·6—0·65	32·2—16·1	1·6—0·65	1·6—0·65	N.P.
		(lime-green)		(white)		
$8-OH-6-CF_3$	0·65—0·32	0·65—0·32	3·2—1·6	1·6—0·65	3·2—1·6	N.P.
		(lime-green)		(yellow-green)		

Metal used :	Ga^{3+}		Mg^{2+}		Ca^{2+}	Th^{4+}	
Test solution :	A	B	B	C	C	A	B
Quinoline							
8-OH	2·3—1·1	2·3—1·1	N.P.	32·0—16·0	64·0—32·0	16·0—6·5	6·5—3·2
	(*a*)			(lemon)	(yellow)	(lemon)	
$8-OH-5-CF_3$	6·4—3·2	6·4—3·2	64·0—32·0	N.P.	N.P.	16·0—6·5	6·5—3·2
	(pale yellow)		(white)		(—)	(lemon-yellow)	
$8-OH-6-CF_3$	3·2—1·6	3·2—1·6	32·0—16·0	32·0—16·0	64·0—32·0	1·6—0·65	3·2—1·6
	(pale yellow)		(lemon)		(lemon)	(yellow-green)	

Metal used :	WO_4^{2-}	MoO_4^{2-}	VO_3^-		UO_2^{2+}	
Test solution :	A	A	A	B	A	B
Quinoline						
8-OH	64·0—32·0	6·5—3·2	64·0—32·0	N.P.	64·0—32·0	16·0—6·5
	(white)	(white)	(green-black)		(red-brown)	
$8-OH-5-CF_3$	128·0—64·0	64·0—32·0	N.P.	N.P.	6·5—3·2	6·5—3·2
	(white)	(yellow)	(—)		(red-brown)	
$8-OH-6-CF_3$	64·0—32·0	16·0—6·5	32·0—16·0	128·0—64·0	64·0—32·0	16·0—6·5
	(lemon)	(yellow)	(green-black)		(red-brown)	

For significance of A, B, and C see p. 380.

* N.P. signifies that there was no precipitate of complex. Where a column for test solution A, B, or C is omitted entirely, there was no precipitate with any of the three reagents. Sensitivity limits are given as µg./ml. The colour of the precipitate is given below the sensitivity limits. (*a*) Indicates that these figures are quoted directly from the literature (Irving, Butler, and Ring, *loc. cit.*).

The conditions used for the determination of the sensitivities of the trifluoromethyl-8-hydroxyquinolines followed exactly those of Irving, Butler, and Ring (*loc. cit.*), so a direct comparison could be made with their results. The figures recorded in Table 1 are, for each combination of reagent and test solution, the smallest concentration (in μg./ml.) of metal ion which gave a precipitate and the largest concentration which just failed to do so under the standardised test conditions. Table 2 lists a further selection of metallic ions which gave precipitates with the reagents.

TABLE 2.

Metal ion used (128·0 μg./ml.)	Colour of precipitate with: 8-hydroxy-5-trifluoromethylquinoline	8-hydroxy-6-trifluoromethylquinoline
Cadmium	White	Pale yellow
Cerium(IV)	Red-brown	Red-brown
Cobalt	White	Yellow
Lead(II)	Pale yellow	Yellow
Manganese	White	Pale yellow
Mercury(II)	Bright yellow	Bright yellow
Nickel	White	Yellow
Silver	Pale yellow	Yellow
Zirconium	Pale yellow	Pale yellow

The sensitivity of 8-hydroxy-6-trifluoromethylquinoline towards the selected metal ions was virtually the same as that of oxine itself. 8-Hydroxy-5-trifluoromethylquinoline, however, was somewhat less sensitive than either of these two compounds. Further, it gave a precipitate with only one metal, copper, in alkaline solution (C), and, even in this case, precipitation was slow and incomplete. Pettit and Tatlow (*loc. cit.*) have, however, shown that 8-hydroxy-5-trifluoromethylquinoline readily loses fluorine, as fluoride ion, in alkaline solution, and during measurements of the dissociation constant (see p. 380) it was found that this hydrolysis occurs in solutions of pH 8 or above. Under the conditions used in the tests, the presence of fluoride ions in the solution was demonstrated, but the expected carboxylic acid could not be isolated. It may be that the trifluoromethyl group was only partially hydrolysed, and that an ether-type polymer was formed by evolution of hydrogen fluoride from the trifluoromethyl and hydroxyl groups of adjacent molecules, or by interaction of trifluoromethyl and phenoxide functions (see Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2346, for a similar effect with *p*-hydroxybenzotrifluoride). Such a compound would not precipitate metal ions because the hydroxyl function is destroyed, and Berg (*Z. anorg. Chem.*, 1932, **204**, 208) has shown that 8-hydroxyquinoline-5-carboxylic acid will not precipitate metal ions in alkaline solution, so that, in either case, no insoluble metal complexes should be formed.

In contrast with the other isomers, 8-hydroxy-7-trifluoromethylquinoline did not give a precipitate with any of the metals listed in Tables 1 and 2, or with any of the following ions: ammonium, beryllium, bismuth, copper(I), gold(III), iridium, lanthanum, lithium, molybdenum(VI), osmium, palladium, potassium, rhodium, ruthenium, sodium, thallium(I), and tin(II). This failure is rather surprising: extraction of the free hydroxyquinoline from the test solutions in several cases showed that soluble complexes were not formed.

Calvin and Wilson (*J. Amer. Chem. Soc.*, 1945, **67**, 2003), Calvin and Bailes (*ibid.*, 1946, **68**, 949), and Duffield and Calvin (*ibid.*, p. 557) have shown that the basic or acidic strength of an organic compound can have a considerable effect on the stability of its metal complexes. A strong base and a weak acid both have a great tendency to share their electron pairs with metal ions, but the introduction of electron-attracting groups into the molecule will increase the acidic, or decrease the basic, strength, and hence should lower the stability of the complexes. The trifluoromethyl group exerts a strong electron-attracting effect and its introduction into the benzenoid part of an 8-hydroxyquinoline should lead to an increase in the acidity of the phenolic group, and, possibly, to a decrease in the basicity of the heterocyclic nitrogen. The effect on the former should be greatest when the trifluoromethyl group is placed *ortho* or *para*, and least when it is *meta*, to the hydroxyl group. Accordingly, attempts were made to relate the dissociation constants of 8-hydroxyquinoline and the three trifluoromethyl-substituted derivatives to their analytical properties.

Several procedures have been employed for determining the dissociation constants of 8-hydroxyquinolines, the potentiometric titration and the spectrophotometric method being now the most frequently used (see, *e.g.*, Näsänen, Lumme, and Mukula, *Acta Chem. Scand.*, 1951, **5**, 1199; Irving, Ewart, and Wilson, *J.*, 1949, 2672). Both are equally satisfactory (Vandenbelt, Henrich, and Vandenberg, *Anal. Chem.*, 1954, **26**, 726). Though there have been discrepancies in earlier work, a value of 9·85 ± 0·05 (at 25°) is now accepted for the thermodynamic dissociation constant, pK_A, of the phenolic group of 8-hydroxyquinoline (Näsänen *et al.*, *loc. cit.*; Irving *et al.*, *loc. cit.*). In the present work an orthodox potentiometric titration method was used. In aqueous solution at 25°, the following values for the (Brønsted) acid dissociation constants (pK_{OH}') were obtained: 8-hydroxyquinoline; 9·83 ± 0·11; 8-hydroxy-6-trifluoromethylquinoline, 10·01 ± 0·11; 8-hydroxy-7-trifluoromethylquinoline, 8·99 ± 0·10. Attempts to measure the value of pK_{OH}' for 8-hydroxy-5-trifluoromethylquinoline under these conditions were unsuccessful since the trifluoromethyl group is extremely sensitive to alkali (Pettit and Tatlow, *loc. cit.*). In solutions of pH 8 or above, fluoride ion was liberated and the solution became brown. The dissociation constants of the trifluoromethyloxines were measured also in 50% aqueous ethanol, since under these conditions the attack on the trifluoromethyl group of the 5-isomer was somewhat less rapid at pH 8—9, and an approximate value for the constant could then be obtained. The relative acidities of the other compounds were in the same order as in aqueous solution, and the 5-isomer consistently gave the lowest value for pK_{OH}', though the reproducibility of the results was not good, showing that some decomposition was probably proceeding. Thus, 8-hydroxy-6-trifluoromethylquinoline is very similar to oxine in its acid strength, but the other two isomers are more acidic; it is probable that the 5-trifluoromethyl isomer is the strongest acid of the three. Irving and Rossotti (*loc. cit.*) have shown that pK_{OH}' values in aqueous dioxan for 8-hydroxy-5-, -6-, and -7-methylquinoline and for oxine are, respectively, 11·11, 10·71, 11·31, and 10·80. Here the inductive effects are, of course, opposite to those in the fluoro-derivatives, and it is of interest that the 6-isomers in each case appear to be very slightly anomalous. The dissociation constants of the $\vdots NH^+$ groups of the 8-hydroxyquinolinium ions were also measured in aqueous solution at 25° and were: 5·0 ± 0·1 for 8-hydroxyquinoline, and 1·8 ± 0·2, 2·6 ± 0·3, and 2·4 ± 0·4 for the 5-, 6-, and 7-trifluoromethyl derivatives, respectively. The potentiometric method is probably less suitable for measurement of basic dissociation constants of this type than for acidic ones (cf. Vandenbelt *et al.*, *loc. cit.*) and no great accuracy is claimed for the values given above. However, it appears reasonably certain that the trifluoromethyl group has a surprisingly large effect on the basicities of the heterocyclic nitrogen functions. This would be in accord with the effect, on the acidities of certain benziminazoles, of trifluoromethyl groups carried on the benzenoid ring (Belcher, Sykes, and Tatlow, *J.*, 1954, 4159).

Thus the acidic dissociation constants of 8-hydroxy-5- and -6-trifluoromethylquinoline and of oxine itself are in general accord with the relative abilities of the compounds to give insoluble complexes. It seems, however, that the weakly basic characters of these two trifluoromethyl-oxines cannot have a great effect on their properties as precipitants. The 7-trifluoromethyl isomer is clearly abnormal in its analytical properties, and it is very unlikely that its comparatively low acidity is the reason for this. Also, though it is a weak base, its basicity is comparable with those of its isomers, so that this also does not appear to explain its behaviour. Another apparent abnormality of the compound lies in its m. p., which is some 150° higher than those of the isomers, though in similar *O*-derivatives of the three phenols the m. p.s are of the same general order. The abnormalities probably arise from *ortho*-effects such as steric factors, or intramolecular hydrogen bonding between the hydroxyl and trifluoromethyl groups. Jones (*loc. cit.*) postulated an effect similar to the latter to account for the unusually low b. p.s of *o*-hydroxy- and *o*-amino-benzotrifluoride. The trifluoromethyl group is larger than the methyl group, from which it has been postulated that steric effects may arise (Irving and Rossotti, *loc. cit.*) and this size might be sufficient to prevent the formation of insoluble complexes. However, other 7-substituted oxines with relatively large substituents, in particular bromo- and iodo-derivatives, do, in some cases, give precipitates with metal ions (Yoe and Sarver, " Organic Analytical Reagents," John Wiley and Sons, New York, 1941, p. 238; Welcher, *op. cit.*; Albert and Magrath, *Biochem. J.*, 1947, **41**, 534).

EXPERIMENTAL

Preparation of Reagents.—8-Hydroxy-5-, -6-, and -7-trifluoromethylquinoline were prepared as described by Pettit and Tatlow (*loc. cit.*) and Belcher, Stacey, Sykes, and Tatlow (*loc. cit.*).

Testing of Reagents.—(a) *Composition of test solutions.* Solutions A, B, and C were prepared as described by Irving, Butler, and Ring (*loc. cit.*). The solutions of metal ions were prepared from " AnalaR " and " Specpure " compounds. Each organic reagent was used as a 0·1M-solution in ethyl alcohol.

(b) *Procedure.* Portions (1·0, 0·5, 0·25, and 0·1 ml.) of metal solution (0·4 mg./ml.) were placed in four test-tubes together with solution A (2·0 ml.), ethyl alcohol (1·0 ml.), the reagent solution (0·2 ml.), and sufficient water to give a final volume of 6·2 ml. A fifth tube contained reagent, ethyl alcohol, and water so that the behaviour of the reagent alone could be observed, whilst a sixth tube contained metal solution, ethyl alcohol, and water, to indicate the behaviour of the metal ions alone. Each tube was heated at 80° for 15 min., and then cooled before being examined for precipitation. When a precipitate was formed in the solution containing 0·1 ml. of 0·4 mg./ml. metal-ion solution, the tests were repeated with more dilute metal-ion solutions (0·04 mg./ml., and then 0·004 mg./ml.). This sequence of testing was then repeated for each metal in each solution, and for each reagent. The sensitivities recorded by Irving, Butler, and Ring (*loc. cit.*) were unaffected by the replacement, in the test solution, of water (1·0 ml.) by ethyl alcohol (1·0 ml.). These results are given in Table 1.

Test solutions containing the 7-trifluoromethyl isomer and certain of the metal ions were extracted with chloroform, and in each case the quinolinol was recovered in good yield. The metals examined in this way were calcium (solutions A, B, and C), copper(II) (A, B, and C), iron(III) (A, B, and C), uranyl (B and C), and zinc (A and C).

Other Metals tested.—The metals listed in Table 2 were shown to give precipitates in solution A by the following procedure: The metal-ion solution (2·0 ml.), solution A (2·0 ml.), ethyl alcohol (1·0 ml.), water (1·0 ml.), and reagent solution (0·2 ml.) were placed in a test-tube and heated at 80° for 15 min. The tube was cooled and the formation and colour of the precipitate were observed. The procedure was repeated for each metal and each reagent.

This procedure was also applied to the tests carried out on 8-hydroxy-7-trifluoromethylquinoline, with these and other metals, in solutions A, B, and C.

Measurements of Dissociation Constants.—In the determinations of pK_{OH}', in aqueous solution, the compounds (about 0·1 g.) in approx. 0·05N-sodium hydroxide (20 c.c.) were titrated against approx. 0·1N-hydrochloric acid at 25° ± 0·1°. A blank determination, identical except that the compound was omitted, was done in each case. The pH was measured by using a glass electrode (Doran Type M 4999) and a saturated calomel electrode, with a saturated potassium chloride bridge, in conjunction with a pH meter [Marconi Type TF 717A, standardised against 0·05M-potassium hydrogen phthalate (pH 4·005) and 0·05M-sodium borate (pH 9·18)]. The titrations were done in a sealed Polythene vessel, and nitrogen was bubbled through the solutions. The dissociation constants were calculated from the volumes of alkali bound, *i.e.*, the differences between the sample titration and the blank titration, at various pH values near the half-neutralisation point. Each compound was tested in several independent runs, and the constants quoted are average ones with the limits defining the highest and lowest values obtained. No reliable figures for pK_{OH}' could be measured for the 5-trifluoromethyl isomer, since fluoride ion was liberated and a brown colour formed in solutions of pH greater than 8. The effect occurred also when alkali was added to a solution of the compound in acid.

Values for the acid dissociation constants were obtained also in 50% aqueous ethyl-alcoholic solutions by direct titration with alkali (approx. 0·1N). Basic dissociation constants were measured by titration of the compound (about 0·1 g.) in 0·05N-hydrochloric acid, with 0·1N-sodium hydroxide. In both of these series of measurements the " solvent correction " was applied.

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