## 49. *Steric Hindrance in Analytical Chemistry. Part V.* A New 2-Substituted 8-Hydroxyquinoline (Oxine).*

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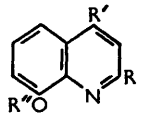
2-(1-Ethylpropyl)-8-hydroxyquinoline has been prepared from 2-(1-ethylpropyl)-8-methoxyquinoline, and the sensitivity of its precipitation reactions towards copper, zinc, aluminium, and indium compared with those of oxine (8-hydroxyquinoline), 2-methyloxine, and 2-phenyloxine.

Although the analytical reactions of 2-methyloxine (I; R = Me, R′ = R″ = H) are distinguished from those of oxine itself by its failure to give an insoluble tris-complex with aluminium, its reactions towards other ions are in no way exceptional.[1] A 2-methyl substituent decreases the stability of all metal complexes of 8-hydroxyquinolines so far studied,[2] owing to steric hindrance to co-ordination around the central ion. It was clearly of interest to see whether the small increase in selectivity effected by a 2-methyl group—and exhibited only in connection with the very small $Al^{3+}$ ion—would be extended to ions of larger ionic radius by increasing the spatial requirements of the substituent adjoining the chelating group.

2-(1-Ethylpropyl)-8-hydroxyquinoline (I; R = $CHEt_2$, R′ = R″ = H) was obtained as a low-melting solid by the decarboxylation of 2-(1-ethylpropyl)-8-hydroxyquinoline-4-carboxylic acid [3] (I; R = $CHEt_2$, R′ = $CO_2H$, R″ = H). Better overall yields were obtained by the successive demethylation and decarboxylation of 2-(1-ethylpropyl)-8-methoxyquinoline-4-carboxylic acid (I; R = $CHEt_2$, R′ = $CO_2H$, R″ = Me) which was prepared in 30% yield by the condensation of *o*-anisidine with pyruvic acid and α-ethylbutyraldehyde.



(I)

No precipitate was formed when an acidic solution of the new reagent and aluminium nitrate was gradually basified, provided tartrate was present to hold up hydroxide or other basic salts. By potentiometric titration of a solution in 0·1N-nitric acid in the presence, and in the absence, of aluminium ions it was established that the formation of any metal complex was too slight to be detectable. As in the analogous titration of a mixture of aluminium and 2-methyloxine, the white precipitate formed at pH ~4·2 was essentially of aluminium hydroxide.

The sensitivity of the reactions of 2-(1-ethylpropyl)-8-hydroxyquinoline towards a few typical cations was determined in three buffer solutions A, B, and C of pH 5·14, 8·4, and 12·4 respectively. The procedures previously described were adopted [1,4] apart from an increase in the amount of alcohol present which was found necessary to compensate for the lower solubility of the reagent in water: on this account the sensitivities quoted may be somewhat lower than if they had been determined under the conditions to which the bulk of the data in the Table refers.

2-(1-Ethylpropyl)-8-hydroxyquinoline gives brown and yellowish-green complexes respectively with $Cu^{2+}$ and $Zn^{2+}$, and the sensitivity of its reactions with these cations is similar to that of 2-methyl- and 2-phenyl-oxine. However, like all 2-substituted oxines so far studied, it fails to give an insoluble complex with $Al^{3+}$. With the appreciably larger ion, $In^{3+}$, a yellow complex is readily formed and the sensitivity of this reaction in buffer B is comparable with that for oxine and 5-methyloxine and distinctly greater than for 2-methyloxine. In buffer A the effect is equally marked and the new reagent is exceptional in giving a precipitate in the very alkaline buffer C. This could well be due to the effect

* Part IV, *J.*, 1958, 3540.

[1] Irving, Butler, and Ring, *J.*, 1949, 1489.
[2] Irving and Rossotti, *J.*, 1954, 2910; (Miss) Massey-Beresford, B.Sc. Thesis, Oxford 1955.
[3] Hollingshead, personal communication.
[4] Irving and Rossotti, *Analyst*, 1955, **80**, 245.

of the higher basicity conferred by the 2-alkyl substituent, reinforced by the " weighting effect " of the large alkyl group: together these two factors appear to dominate the

*Sensitivities of reactions between metals and homologues of 8-hydroxyquinoline (oxine).*

| | Copper | | | Zinc | | |
|---|---|---|---|---|---|---|
| Reagent | A | B | C | A | B | C |
| Oxine | 1·1—0·4 | 1·1—0·4 | 1·1—0·4 | 1·1—0·4 | 1·1—0·4 | 10·6—4·2 |
| 2-Methyloxine | 2·0—0·4 | 1·0—0·4 | 20·5—10·3 | 21·0—10·6 | 1·0—0·4 | 10·6—2·1 |
| 2-(1-Ethylpropyl)oxine | 2·0—1·0 | 2·0—1·0 | 2·1—1·0 | 20·4—10·3 | 2·1—1·0 | 2·0—1·0 |
| 2-Phenyloxine | 1·0—0·4 | 1·0—0·4 | 2·0—1·0 | 10·6—4·2 | 2·1—1·1 | 2·1—2·1 |
| 5-Methyloxine | 1·0—0·4 | 1·0—0·4 | 1·0—0·4 | 10·6—4·2 | — | N.P. |

| | Aluminium | | | Indium | | |
|---|---|---|---|---|---|---|
| Reagent | A | B | C | A | B | C |
| Oxine | 4·3—1·7 | 4·3—1·7 | N.P. | 5·26—3·6 | 5·2—3·6 | N.P. |
| 2-Methyloxine | N.P. | N.P. | N.P. | 18·5—7·4 | 18·5—7·4 | N.P. |
| 2-(1-Ethylpropyl)oxine | N.P. | N.P. | N.P. | 6·96—5·2 | 5·2—3·6 | 16·0—7·0 |
| 2-Phenyloxine | N.P. | N.P. | N.P. | — | — | — |
| 5-Methyloxine | 0·9—0·4 | — | N.P. | 1·85—0·95 | 5·3—3·6 | N.P. |

N.P. No precipitate was observed. Data for 2-methyl- and 2-phenyl-oxine from ref. 1. The figures are the smallest concentration of metal (in μg./ml.) which gave a perceptible precipitate under the standard condition [1,4] and the largest concentration which just failed to do so.

steric factors which are caused by substitution in the 2-position which operate to prevent chelation [1,2] and decrease the sensitivity of the reaction. The effect of steric factors in reducing sensitivity is clearly shown in the data for the two position-isomers, 2- and 5-methyloxine. That 2-(1-ethylpropyl)oxine reacts with the indium ion almost as readily as oxine itself and appreciably more readily than 2-methyloxine, despite the steric hindrance to co-ordination demonstrated by its failure to form a tris-complex with the smaller aluminium ion, must largely be due to a weighting effect. However it should not be overlooked that the sensitivity of such reactions depends both on the stability of the chelated complex and on its intrinsic solubility,[4] and a full interpretation requires an assessment of these effects separately.

It is to be expected that a 2-alkyl substituent in a substituted oxine would, on chelation, adopt that conformation which minimises steric hindrance to co-ordination. In the group $CHEt_2$ rotation of the ethyl groups can produce a 2-substituent with a much smaller interference volume than would appear at first sight. With a tertiary carbon atom in this position, steric effects should be more pronounced. Experiments with 2-(*tert.*-butyl)-8-hydroxyquinoline (I; R = $Bu^t$, R′ = R″ = H) to test this hypothesis will be reported later.

## Experimental

2-(1-*Ethylpropyl*)-8-*methoxyquinoline*-4-*carboxylic Acid.*—A mixture of α-ethylbutyraldehyde (44 g.) and pyruvic acid (24 g.) in ethanol (100 ml.) was added to a solution of redistilled *o*-anisidine (45·2 g.) in ethanol (400 ml.), and the whole heated under reflux for 17 hr. When cold the solution was seeded. Yellow crystals (30·4 g.) slowly separated. On recrystallisation from boiling ethanol (charcoal), 2-(1-*ethylpropyl*)-8-*methoxyquinoline*-4-*carboxylic acid* separated as yellow needles, m. p. 230° (Found: C, 70·3; H, 7·1; N, 5·3. $C_{16}H_{19}O_3N$ requires C, 70·3; H, 7·0; N, 5·1%).

2-(1-*Ethylpropyl*)-8-*hydroxyquinoline*-4-*carboxylic Acid.*—The methoxy-compound (3·5 g.) was heated under reflux for 4 hr. with fuming hydrobromic acid (20 ml.). The resulting clear solution was cooled, exactly neutralised with 2N-sodium hydroxide, and kept overnight in a freezing mixture. A greenish-yellow solid separated (18 g.). After recrystallisation, once from ethanol and twice from glacial acetic acid, 2-(1-ethylpropyl)-8-hydroxyquinoline-4-carboxylic acid was obtained as yellow crystals, m. p. 204°, which did not depress the m. p. of a specimen prepared from *o*-aminophenol, pyruvic acid, and α-ethylbutyraldehyde [3] (Found: C, 68·8; H, 7·4. Calc. for $C_{15}H_{17}O_3N$: C, 68·7; H, 7·4%).

2-(1-*Ethylpropyl*-8-*hydroxyquinoline.*—(a) *By decarboxylation of* 2-(1-*ethylpropyl*)-8-*hydroxyquinoline*-4-*carboxylic acid.* The acid (5·6 g.) was distilled *in vacuo* over a free flame.

The dark brown oily distillate solidified to a yellow mass, m. p. 130° (2·3 g.), which was extracted with hot dilute hydrochloric acid. Upon neutralisation with sodium carbonate the acid extract deposited a brown solid (1 g.), m. p. 44°. Recrystallisation from methanol and steam distillation gave white 2-(1-*ethylpropyl*)-8-*hydroxyquinoline*, m. p. 49° (Found: C, 78·0; H, 8·0; N, 6·6. $C_{14}H_{17}ON$ requires C, 78·1; H, 8·0; N, 6·5%).

(b) *From* 2-(1-*ethylpropyl*)-8-*methoxyquinoline*-4-*carboxylic acid*. It proved impossible to decarboxylate the methoxy-acid (I; R = $CHEt_2$, R′ = $CO_2H$, R″ = Me) by heating it in boiling diphenyl or quinoline, or with Adkins, Burgoyne, and Scheider's decarboxylation catalyst,[5] and it sublimed unchanged when heated in an oil-bath under a high vacuum. The acid (3·5 g.) was therefore heated at atmospheric pressure in a Wood's-metal bath to a temperature well above its m. p. Carbon dioxide was evolved and a pale yellow oil distilled (2·7 g.). Since the distillate did not crystallise it was demethylated without purification by being heated under reflux for 4 hr. with constant-boiling hydrobromic acid (20 ml.). After being cooled the clear solution was nearly neutralised with 2N-sodium hydroxide, and the oil which separated was removed and distilled in steam. Crude 2-(1-ethylpropyl)-8-hydroxyquinoline which separated in the aqueous distillate was collected, taken up in dilute aqueous sodium hydroxide, and reprecipitated with acetic acid. After recrystallisation from methanol it gave a colourless product, m. p. 46°, which did not depress the m. p. of the previous specimen.

When this preparation was repeated on a larger scale, the final product (10 g.; b. p. 172—174°/9 mm.) showed great reluctance to recrystallise. The demethylation stage was therefore repeated, 1·5 g. of the desired product being readily obtained. The remaining oil (7·3 g.) was then treated with picric acid (8·2 g.) in the minimum volume of hot ethanol. After repeated crystallisation from boiling ethanol the *picrate* of 2-(1-ethylpropyl)-8-hydroxyquinoline was obtained as yellow needles (5·3 g.), m. p. 187° (Found: N, 24·2. $C_{14}H_{17}ON,C_6H_3O_7N_3$ requires N, 24·0).

*Sensitivity Tests*.—The procedure already described [1,4] was adopted, but in measurements with 2-(1-ethylpropyl)oxine it was necessary to use 50% v/v aqueous ethanol in place of water when making up the test solution to the constant volume of 6·2 ml.

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[5] Adkins, Burgoyne, and Schneider, *J. Amer. Chem. Soc.*, 1932, **54**, 1138.