**249.** *The Polarographic Reduction of Hydroxy- and Methoxy-anthraquinones.*

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The behaviour at the dropping-mercury cathode of many hydroxyanthra-quinones and of their methyl ethers has been studied.

In strongly acid ethanol solution the methyl ethers are either reducible or non-reducible, and the division into these two well-marked classes is accounted for structurally. Under similar conditions hydroxyanthraquinones do not show such a clearly defined classification.

In alkaline solution all hydroxy- and methoxy-anthraquinones are re-ducible.

It is suggested that polarography can be used to give information on the configuration of some hydroxy- or methoxy-anthraquinones.

THE basic strength of methoxy-10-thioxanthones and methoxyxanthones was investigated by Smiles and his co-workers (Roberts and Smiles, *J.*, 1929, 863, 1322; Levi and Smiles, *J.*, 1931, 520; Roberts, Wiles, and Kent, *J.*, 1932, 1792), and was extended to methoxy-anthraquinones by Roberts (*J.*, 1932, 1982). The basic strength of the parent ketone is increased greatly when a methoxy-group is substituted *ortho* to a carbonyl group; for instance, 1-methoxy-4-methyl-10-thioxanthone (I) is readily soluble in cold, concentrated hydrochloric acid, and forms a trihydrochloride at room temperature, whereas the isomeric 1-methyl-4-methoxy-10-thioxanthone (II) is much less soluble in hydrochloric acid and does not give an addition compound with hydrogen chloride under the same conditions. Similarly



the formation of relatively stable salts by methoxyanthraquinones is confined to those compounds which have methoxyl in one or more of the $\alpha$(1, 4, 5, or 8)-positions.

The theory of resonance would explain the stability of the salts of these methyl ethers by postulating the existence of various resonance forms which would confer stability on the system (cf. Sidgwick, *Ann. Reports*, 1933, **30**, 112; 1934, **31**, 40). The polar carbonyl group can form a salt by combining a proton with the oxygen atom, $>C = O \longrightarrow >C = \overset{+}{O}H$,

but the stability of such a compound is very small. Anthraquinone is, for example, a weak monoacid base, $K_b = 7 \times 10^{-23}$. With o-methoxy-ketones, however, resonance structures such as (III)—(V) would enhance the stability of the salts.



(III)          (IV)          (V)
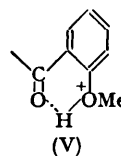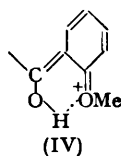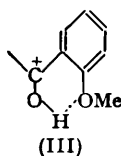
Doubt has recently been cast on the extent of the contribution made by resonance effects in stabilising hydrogen bonds, and the bond may be largely electrostatic in nature (" Symposium on the Hydrogen Bond," Royal Institute of Chemistry Lectures, Monographs and Reports, 1950, No. 1. p. 18). If salts of o-methoxy-ketones have these hydrogen bonds it seemed likely that the reduction of a carbonyl group involved in the link might be hampered. It was therefore decided to examine polarographically the reduction of methoxyanthraquinines in acid and in alkaline media. For comparison an investigation of the corresponding hydroxyanthraquinones was made, since in these compounds the hydrogen of α-hydroxyl groups has an intramolecular bond with the carbonyl group.

Some previous work has been done on the polarographic reduction of compounds in which a hydrogen bond is linked with the reducible group to form a chelate ring. Scaramelli (*e.g., Atti R. Accad. Italia,* 1940, **1**, 764), studying the polarographic reduction of hydroxy- and alkoxy-substituted benzaldehydes and similar compounds, found that molecules in which intramolecular hydrogen bonding was to be expected were *more difficult* to reduce (*i.e.,* their reduction potentials were more negative) than molecules where the hydrogen bond was not possible. The reduction of nitrophenols has been examined by Astle and McConnell (*J. Amer. Chem. Soc.,* 1943, **65**, 35) and by Pearson (*Trans. Faraday Soc.,* 1948, **44**, 692). Although differing in their interpretation of the results, these workers agree that in acid solution the intramolecular hydrogen bond in o-nitrophenol allows the reduction of the nitro-group to proceed *more readily* than with *m*- and *p*-nitrophenol. The hydrogen bond in o-nitrophenol interferes with the resonance of the nitro-group, the oxygen atoms are no longer equivalent, and the compound loses stability. Similar results have been found with nitro-amidines (Runner, Kilpatrick, and Wagner, *J. Amer. Chem. Soc.,* 1947, **69**, 1406; Rabinowitz and Wagner, *ibid.,* 1951, **73**, 3030). Furman and Stone (*ibid.,* 1948, **70**, 3055) have examined the reduction potentials of a few hydroxyanthraquinones chiefly in alkaline solution with different buffers, so this aspect of the work has not been repeated.

*Summary of Results.*—The reduction potentials given in the following table are half-wave potentials $(-E_{\frac{1}{2}})$ in volts relative to the saturated calomel electrode. The solutions

| Position of substituents in anthraquinone (none) | Half-wave reduction potentials : | | |
| --- | --- | --- | --- |
| | Acid solution (pH 1·25) 0·18 | | Alkaline solution (pH 11·2) 0·75 |
| | Hydroxyanthraquinone | Methoxyanthraquinone | |
| 1- | 0·21 | 0·12 | 0·73 |
| 2- | 0·22 | 0·20 | 0·78 |
| 1 : 2-Di- | 0·26 | 0·17 | 0·73 |
| 1 : 3-Di- | 0·25 | 0·14 | 0·73 |
| 2 : 3-Di- | 0·25 | 0·25 | 0·78 |
| 1 : 4-Di- | 0·27 | Not reducible | 0·76 |
| 1 : 5-Di- | Not reducible | Not reducible | 0·76 |
| 1 : 8-Di- | 0·23 | 0·12 | 0·74 |
| 1 : 2 : 3-Tri- | 0·27 | 0·14 | 0·73 |
| 1 : 2 : 4-Tri- | 0·31 | Not reducible | 0·79 |
| 1 : 2 : 7-Tri- | 0·27 | 0·17 | 0·73 |
| 1 : 2 : 5 : 8-Tetra- | 0·30 | Not reducible | 0·75 |
| 1 : 4 : 5 : 8-Tetra- | Not reducible | Not reducible | 0·79 |
| 2-Methyl-1 : 5 : 6 : 7-tetra- | — | Not reducible | 0·74 |
| 2-Methyl-1 : 5-dihydroxy-6 : 7-di- | — | Not reducible | — |

contained *ca.* 70% of ethanol, and the measured pH values are " apparent " values un-corrected for the non-aqueous solvent errors.

Methoxyanthraquinones which have methoxy-groups *ortho* to *both* carbonyl groups are not polarographically reducible in strongly acid solution. If one (or both) of the carbonyl groups has no *o*-methoxy-group then the compound is reducible. Hydroxyanthra-quinones which have one of the carbonyl groups free from intramolecular hydrogen bonding are reducible in acid (*e.g.*, −OH at 1-, 2-, 2 : 3-, 1 : 2 : 7-). If both carbonyl groups have hydrogen bonds the compound may be reducible (*e.g.*, −OH at 1 : 4-, 1 : 2 : 4-, 1 : 2 : 5 : 8-) or it may not (*e.g.*, −OH at 1 : 5-, 1 : 4 : 5 : 8-). Methoxyanthraquinones which have methoxyl *ortho* to only one carbonyl group are more readily reducible than the correspond-ing hydroxyanthraquinones. Hydroxyanthraquinones are reduced with greater difficulty than anthraquinone.

*Discussion of Results.*—(a) *Methoxyanthraquinones.* The results suggest that the hydrogen-bridge structure postulated for salts of *o*-methoxy-ketones is probably correct. When both carbonyl groups are linked with methoxyl through hydrogen the salt may be resonance-stabilised and the non-reducibility of the compounds is to be expected. Alter-natively, the absence of reduction may be attributed to the diminished proton-attracting power of the oxygen atom of the carbonyl groups owing to the attachment of the two bridge protons. If the resonance view is adopted then it seems that (IV) with its *o*-quinonoid form must play little part ; if it did contribute to any extent all *o*-methoxyanthra-quinones would be readily reducible. That the *o*-quinonoid resonance form is unlikely has also been inferred by Flett (*J.*, 1948, 1441) from the infra-red absorption spectrum of 1 : 4-dimethoxyanthraquinone.

Additional support for the hydrogen-bridge hypothesis is given by the work of Zahn and Koch (*Ber.*, 1938, **71**, 172), who showed that in the catalytic reduction of α-methoxy-anthraquinones by hydrogen under pressure, *i.e.*, in the absence of acid, it is the carbonly group in the *peri*-position to the methoxy-group which is reduced, *e.g.*, 1-methoxyanthra-quinone (VI) gives 1-methoxy-10-anthrone (VII).



(VI)          (VII)          (VIII)          (IX)
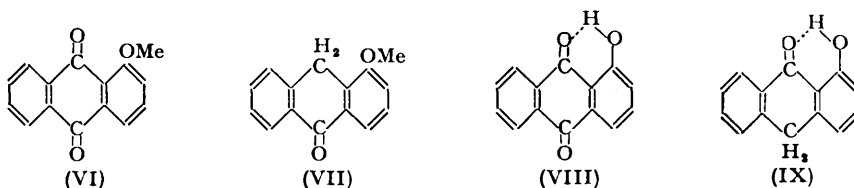
(b) *Hydroxyanthraquinones.* The reduction of α-hydroxyanthraquinones by chemical reagents frequently leaves unaffected the carbonyl group linked with the hydrogen bond; *e.g.*, reduction of 1-hydroxyanthraquinone (VIII) by zinc and acetic acid gives 1-hydroxy-anthrone (IX). Furman and Stone (*loc. cit.*) state that polarographic reduction of an



(X)          (XI)          (XII)
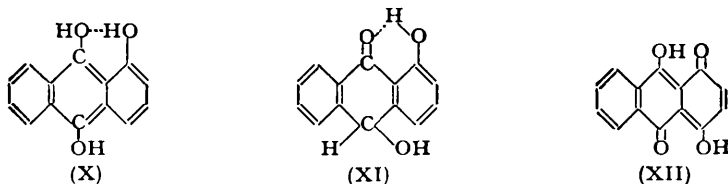
anthraquinone can produce the anthraquinol, so reduction of 1-hydroxyanthraquinone may occur as shown by (X). Alternatively, the reduction may leave the hydrogen bond intact and give an oxanthrone (XI). The results with hydroxyanthraquinones are not as simple as with methoxyanthraquinones and hydrogen bonding may be a complicating factor in the reduction of α-hydroxyanthraquinones.

1 : 4-Dihydroxyanthraquinone gives a well-defined reduction wave, but 1 : 5-dihydroxy-anthraquinone is not reducible in acid solution. This implies a difference in the strengths

of the hydrogen bonds in these two compounds. Evidence of variation in the strength of hydrogen bonds in hydroxyanthraquinones has been adduced by Flett (*loc. cit.*), and he concludes that the hydrogen bonds in 1 : 4-dihydroxy- and 1 : 2 : 4-trihydroxy-anthraquinone are rather stronger than in the 1 : 5-dihydroxy-compound. On this evidence one would have expected that 1 : 4-dihydroxy- and 1 : 2 : 4-trihydroxy-anthraquinone would have been more difficult to reduce than 1 : 5-dihydroxyanthraquinone, whereas the reverse is the case. It is noteworthy that Green (*J.*, 1926, 1428; 1927, 2384) found chemical evidence for the behaviour of 1 : 4-dihydroxyanthraquinone as 1 : 10-dihydroxy-4 : 9-anthraquinone (XII) so the polarographic reduction may not proceed at carbonyl groups in the 9- or the 10-position.

Heyrovsky and Ilkovic (*Coll. Czech. Chem. Comm.*, 1935, **7**, 198) have shown that for reversible oxidation–reduction reactions a graph of the applied voltage ($E$) against log $i/(i_d - i)$ (where, at any point on the polarographic wave, $i$ is the current produced by the applied voltage, and $i_d$ is the diffusion current) gives, at 25°, a straight line of slope $0.059/n$, where $n$ is the number of electrons involved in the reaction. Some hydroxy- and methoxy-anthraquinones were examined in this way in acid and in alkaline solution. In general, the graphs show that the reductions are not reversible processes. A possible exception is 1-methoxyanthraquinone in acid solution, for which a straight line of slope 0.033 corresponds approximately to a 2-electron reduction.

*Suggested Application of the Foregoing Results.*—The differences in the ease of reduction of methoxy- and hydroxy-anthraquinones may prove useful in confirming the structure of some anthraquinones. The hydroxy-compounds and their methyl ethers frequently occur in Nature, and their isolation is often difficult and in poor yield. The use of the polarograph is attractive as it requires extremely small amounts of pure material. The following illustrates a likely application of the method.

1 : 2 : 3 : 5- *and* 1 : 2 : 3 : 7-*Tetrahydroxyanthraquinone.* Condensation of gallic acid and *m*-hydroxybenzoic acid gives two isomeric tetrahydroxy-compounds, one insoluble and the other difficultly soluble in benzene. These were first isolated by Noah (*Ber.*, 1886, **19**, 2337) but he was not able to distinguish them. The assignment to them of definite configurations (*e.g.*, Thorpe, " Dictionary of Applied Chemistry," 4th edtn., **1**, 226; Heilbron, " Dictionary of Organic Compounds," 1st edn., Vol. III, p. 710) is not based on published evidence. Briggs (*J.*, 1948, 990) has tentatively advanced reasons for believing that the 1 : 2 : 3 : 5-isomer is the one more soluble in benzene, and it is likely that its tetramethyl ether will not be reducible polarographically in acid solution whereas the corresponding 1 : 2 : 3 : 7-tetramethyl ether should be. This matter is being investigated.

<div align="center">EXPERIMENTAL</div>

A Cambridge Instrument Co. polarograph giving photographic recording of the current–voltage curves was used. The instrument was operated so that the rate of change of voltage was the slowest available, *viz.*, 1·0 volt in 80 seconds. The form of the reduction waves was sometimes improved by using the expanded scale technique (Werthessen and Baker, *Endocrinology*, 1945, **36**, 351) in which the normal 6-volt input to the potentiometer was reduced to 2 volts. No correction of the half-wave potentials for the voltage drop in the circuit was necessary as the values were very small and did not exceed the accuracy with which the potentials could be read from the polarograms. The dropping-mercury electrode had the following characteristics : the drop time ($t$) on open circuit into 0·1M-potassium chloride solution was 3·35 seconds, the weight of mercury dropping per second ($m$) was 1·649 mg., and $m^{2/3} t^{1/6}$ was 1·71.

The acid solvent contained *ca.* 70% of ethanol. It was saturated with potassium chloride as the supporting electrolyte, and concentrated hydrochloric acid was added to give a strongly acid solution the pH of which was measured by a Marconi meter. The alkaline solvent also contained *ca.* 70% of ethanol. In order that it should be adequately buffered it was made 0·2M with both boric acid and sodium hydroxide, and it was also saturated with potassium chloride. The measured pH was 11·2 and that estimated by British Drug Houses " Narrow Range " Indicator papers was 8·5—8·8. Both acid and alkaline solvents were polarographed to ensure that they contained no reducible substances likely to cause interference with the reduction waves. Where possible the anthraquinone solutions were $10^{-3}$M, but solubility sometimes

limited the concentrations to smaller values, and a saturated solution of the anthraquinone was then used.

The cell containing the solution under examination, the dropping-mercury electrode, and the saturated calomel electrode were immersed in a water-bath regulated at $25° \pm 0.1°$. Before a photographic record was made the anthraquinone solutions were de-oxygenated by bubbling oxygen-free nitrogen through them for about 30 minutes.

The hydroxyanthraquinones were commercial samples and were purified by crystallization from ethanol or acetic acid, or by sublimation. The methoxyanthraquinones were prepared from the hydroxy-compounds by the use of methyl sulphate and alkali. The resistance of hydroxyl at the 1-, 4-, 5-, or 8-positions to methylation was frequently encountered and it was generally best to use the method outlined below.

The following two compounds are new.

*1 : 2 : 4-Trimethoxyanthraquinone.* Potassium hydroxide (3 mols.) was dissolved in methyl alcohol, 1 : 2 : 4-trihydroxyanthraquinone (1 mol.) was added, and the solvent evaporated. The dry potassium salt was intimately mixed with anhydrous potassium carbonate (10 mols.) and transferred to a large boiling-tube. Methyl sulphate (10 mols.), dissolved in an equal volume of acetone, was added so that the solid was well saturated with the liquid, and the acetone then evaporated. The mixture was heated at 180° for 7 hours under reflux. After extraction with 10% sodium hydroxide solution the *trimethoxy*-compound crystallized from ethanol in fine yellow needles, m. p. 168° (corr.) (Found : C, 68.5; H, 4.7; OMe, 30.0. $C_{17}H_{14}O_5$ requires C, 68.5; H, 4.7; OMe, 31.2%).

*1 : 2 : 5 : 8-Tetramethoxyanthraquinone.* This *compound*, prepared from the tetrahydroxy-compound by the above method, crystallized from ethanol in golden-yellow needles, m. p. 202° (corr.) (Found : C, 65.6; H, 5.0; OMe, 36.7. $C_{18}H_{16}O_6$ requires C, 65.9; H, 4.9; OMe, 37.8%).

The following anthraquinones had m. p.s (corr.) which differed from previously recorded values (lit. values in parentheses) : 1 : 2 : 3-trihydroxy-, 316° (310°, 312—313°, 313—314°); 1 : 4-dimethoxy-, 172° (143°, 170—171°).

M. p.s (corr.) for the following anthraquinones are also recorded, as literature values are inconsistent : 1-hydroxy-, 194—195° (190°, 191°, 193°, 190—193°, 200—201°); 2-hydroxy-, 312° (302°, 305°, 306°, 302—306°, 314°); 1 : 4-dihydroxy-, 194° (193°, 194°, 197—198°, 200—202°),* bronze plates from acetic acid; 1 : 2 : 4-trihydroxy-, 257° (253°, 253—254°, 255—257°, 259°); 1 : 3-dimethoxy-, 164° (151—153°, 155°, 164—165°); 1 : 5-dimethoxy-, 237° (234—236°, 236°, 238—240°, 241°).

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* According to Lindpainter (*Mikrochemie*, 1937, **27**, 27) this compound has two enantiotropic forms, one orange, m. p. 195°, and the other dark red, m. p. 201°.