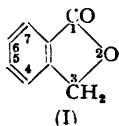


273. *Infra-red Spectroscopy and Structural Chemistry. Part V. Hydroxyphthalides.*

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4- and 7-Hydroxyphthalides may be distinguished by their infra-red spectra in dilute solution, wherein intramolecular hydrogen bonding in 7-hydroxyphthalides causes a characteristic lowering of the C=O stretching frequencies.

It is well established that $\alpha\beta$ -unsaturated γ -lactones, as in phthalide (I), have C=O stretching frequencies near 1750 cm^{-1} in the solid state (Grove and Willis, *J.*, 1951, 877). In addition, many examples are known of the behaviour of pure substances containing the *o*-hydroxyaroyl structure wherein strong intramolecular hydrogen bond formation causes both the hydroxyl and the carbonyl stretching frequencies to be markedly lower than those of the corresponding methyl ethers or non-hydroxylated compounds (Flett, *J.*, 1948, 1441; Hunsberger, *J. Amer. Chem. Soc.*, 1950, 72, 5626). These decreases persist in dilute solution in a non-polar solvent, and, since similar effects are not observed in the corresponding *m*- and *p*-hydroxy-compounds (Martin, *Nature*, 1950, 166, 474), have been used to detect chelation. However, Grove (*Biochem. J.*, 1952, 50, 648), in attempting to apply this to the orientation of hydroxyphthalides of unknown constitution, found little difference between the C=O frequencies of 7-methoxy- and 7-hydroxy-4:6-dimethylphthalide in the solid state, and Hochstein and Pasternack (*J. Amer. Chem. Soc.*, 1952, 74, 3905) commented on the similarity of the spectra of 7- and 4-hydroxy-3-methylphthalide although they report significant differences between the C=O frequencies of 7-methoxy- and 7-hydroxy-3-methylphthalide in chloroform solution. The present paper reports a systematic examination of the infra-red spectra of 7- and 4-hydroxyphthalides in the solid state and in solution, and shows how these compounds may be distinguished.



EXPERIMENTAL

Materials.—4-Hydroxyphthalide, m. p. 254–260° (decomp.), and 4-methoxyphthalide, m. p. 127°, were prepared by the method of Buehler, Powers, and Michels (*J. Amer. Chem. Soc.*, 1944, 66, 417) who established their structures by unambiguous syntheses.

7-Methoxyphthalide was prepared by reduction of 3-methoxyphthalic anhydride with zinc and acetic acid in concentrated hydrochloric acid. It was separated from the 4-methoxyphthalide, which is formed simultaneously, by recrystallisation from methanol and then from benzene—

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light petroleum, to give colourless prisms, m. p. 96° (Found : C, 65.85; H, 5.1; OMe, 18.9. C₉H₈O₃ requires C, 65.85; H, 4.9; OMe, 19.0%).

Demethylation with hydrobromic acid and crystallisation of the product from water gave 7-hydroxyphthalide, m. p. 132° (Found : C, 63.75; H, 4.0. Calc. for C₈H₆O₃ : C, 64.0; H, 4.0%), which gave an intense blue colour with ferric chloride in aqueous or ethanolic solution. Vène and Tirouflet (*Compt. rend.*, 1951, 232, 2329) give m. p. 128—129°.

7-Hydroxy-, m. p. 158°, and 7-methoxy-4 : 6-dimethylphthalide, m. p. 113° (Raistrick and Ross, *Biochem. J.*, 1952, 50, 635), were obtained by degradation of gladiolic acid (Grove, *loc. cit.*). Purified phthalide, m. p. 73°, methyl *m*-hydroxybenzoate, m. p. 70°, and methyl salicylate, n_D^{20} 1.537, were used.

Infra-red Spectra.—The spectra were measured with a Grubb Parsons S 3A spectrometer. The case of the instrument was sealed and dry air circulated through it. Solids were examined as "Nujol" mulls, and the solutions were all approx. 0.02M, except for 7-hydroxyphthalide which was 0.005M in carbon tetrachloride. Carbonyl frequencies in solution were measured with a rock-salt prism and path lengths of 0.25 mm.; a lithium fluoride prism and path lengths varying between 0.25 and 5 mm. were used for the measurement of -OH stretching frequencies. Accuracy : ± 3 cm.⁻¹.

Solvents.—"AnalaR" carbon tetrachloride was distilled over phosphoric oxide before use. Chloroform containing about 1% of ethanol as a stabiliser was dried and distilled before use, but the ethanol was not removed. Dioxan was purified according to Hess and Frahm's method (*Ber.*, 1938, 71, 2627).

RESULTS AND DISCUSSION

The annexed Table lists the carbonyl stretching frequencies of some hydroxyphthalides, as solids and in dilute solution in carbon tetrachloride, dioxan, and chloroform. The corresponding figures for phthalide itself are included.

Carbonyl stretching frequencies of some phthalides as solids and in solution.

Phthalide	Solid	Solution in			Phthalide	Solid	Solution in		
		CCl ₄	dioxan	CHCl ₃			CCl ₄	dioxan	CHCl ₃
7-Hydroxy-4 : 6-dimethyl-	1737	1747	1750	1734	7-Methoxy-4 : 6-dimethyl-	1749	1771	1768	1756
7-Hydroxy-	1726	1749	1754	1738	7-Methoxy-	1748	1782	1772	1754
4-Hydroxy-	1723	Insol.	1772	1760	4-Methoxy-	1765	1783	1774	1764
					Phthalide	1752	1778	1770	1761

In the solid state 4- and 7-hydroxyphthalide absorb at lower frequencies than do the corresponding methyl ethers, and the lactone C=O frequency cannot be correlated with the proximity of the hydroxyl and carbonyl groups in the molecule. However, the frequencies found for the dioxan solutions fall into two groups, namely, those near 1750 cm.⁻¹, characteristic of 7-hydroxyphthalides, and those near 1770 cm.⁻¹, given by the remainder.

These results are closely paralleled by those obtained from solutions in carbon tetrachloride and in chloroform. In carbon tetrachloride the 7-hydroxyphthalides again absorb near 1750 cm.⁻¹ while the remainder absorb at higher frequencies, in this case near 1780 cm.⁻¹. 4-Hydroxyphthalide is too insoluble for measurement even when using a 1 cm. thickness of a saturated solution, but from its carbonyl frequency in dioxan solution it is reasonable to predict that a dilute solution in carbon tetrachloride of a 4-hydroxyphthalide should show carbonyl absorption near 1780 cm.⁻¹. In chloroform the carbonyl frequencies are all lower than in the other two solvents, the 7-hydroxy-compounds absorbing near 1735 cm.⁻¹ and the others between 1755 and 1765 cm.⁻¹.

A further distinction can be found between 7-hydroxyphthalides and the remainder by comparing their respective carbonyl frequencies in two of the solvents used; the 7-hydroxy-compounds have a slightly lower frequency in carbon tetrachloride than in dioxan, while the remainder show a difference of 5—10 cm.⁻¹ in the opposite direction.

The hydroxyl stretching frequencies of three hydroxyphthalides are as follows :

7-Hydroxy-4 : 6-dimethyl-		7-Hydroxy-		4-Hydroxy-	
Solid	In CCl ₄	Solid	In CCl ₄	Solid	In CCl ₄
3405	3420	3490	3420	3190 broad	Insol.
3340 weak	—	3402	—	—	—

There are insufficient data to enable structural correlations to be made. It can be seen, however, that 4-hydroxyphthalide is strongly bonded in the solid state, the band with a peak at 3190 cm^{-1} being very broad and extending from 3100 to 3300 cm^{-1} approximately. It is probable that a dilute solution of a soluble 4-hydroxyphthalide in carbon tetrachloride would absorb near 3600 cm^{-1} , as does methyl *m*-hydroxybenzoate. The 7-hydroxyphthalides absorb at much lower frequencies than this.

The interpretation of the above results is straightforward. In the solid state both types of hydroxyphthalide studied form hydrogen bonds between their hydroxyl and carbonyl groups. In dilute solutions the intermolecular bonds dissociate and the 7-hydroxyphthalides contain weak intramolecular bonds. This behaviour is somewhat different from that observed with hydroxybenzoic esters wherein intramolecular hydrogen bonds are much stronger. The carbonyl and hydroxyl stretching frequencies of methyl salicylate and methyl *m*-hydroxybenzoate as pure substances and as 0.02M-solutions are as follows :

	<i>Methyl m-hydroxybenzoate</i>				<i>Methyl salicylate</i>		
	Pure substance	In CCl_4	In dioxan		Pure substance	In CCl_4	In dioxan
OH ...	3340	3580	—	OH...	3184 (broad)	3198 (broad)	—
	3361 (shoulder)	3437 (broad)	—	CO ...	1678	1681	1683
CO ...	1695	1728	~1722				
	—	1702	—				

When the hydroxy-group is *ortho* to the carbomethoxy-group, a strong intramolecular hydrogen bond is formed between them, both in the pure state and in solution.

The spectrum of *m*-hydroxybenzoic ester in solution has two carbonyl and two hydroxyl bands due to the presence of an equilibrium between non-bonded molecules and intermolecularly bonded ones. It is interesting that, like the hydroxyphthalides, the intramolecularly bonded *o*-hydroxybenzoate shows a slight increase and the non-associated *m*-hydroxybenzoate a decrease in carbonyl frequency on changing from carbon tetrachloride to dioxan as solvent.

The difference in behaviour of the *o*-hydroxyphthalides and benzoates must be connected with the strained 5-membered ring present in the former. Molecular models show that in 7-hydroxyphthalide, strain in the lactone ring bends the carbonyl group away from the hydroxyl group to an extent requiring a C-H-O distance approaching 3 Å. This is near the limit for hydrogen-bond formation (Pauling, "Nature of the Chemical Bond," Oxford Univ. Press, London, 2nd Edn., p. 289) and a bond of this length would be expected to be weak. It is apparent that intermolecular hydrogen bonding in solid 4-hydroxyphthalide is as strong as bonding in solid 7-hydroxyphthalide and therefore spectra of Nujol "mulls" should not be used for detecting chelation in hydroxyaroyl compounds of unknown orientation. The necessary information can, however, be obtained from the spectra of dilute solutions.