

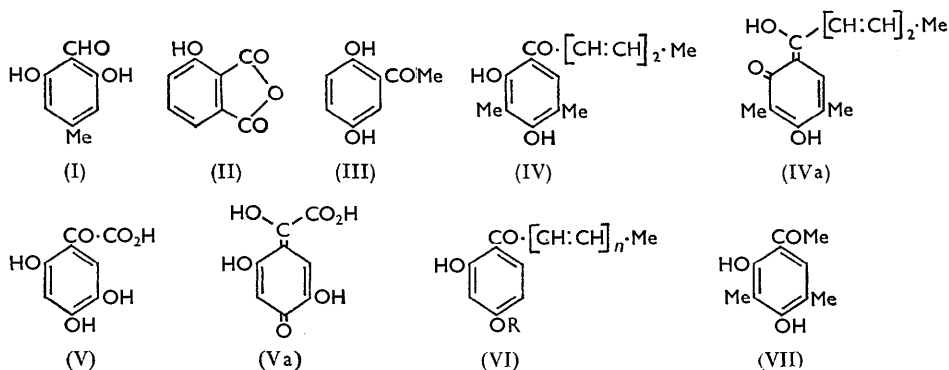
65. The Structure of Sorbicillin: Hydrogen Bonding in *o*-Hydroxyaryl Alkenyl Ketones.

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Examination of the absorption spectra of sorbicillin and related compounds leads to the conclusion that it has a benzenoid, and not a quinonoid, structure.

The solid-state infrared spectra of 2-hydroxy-4-methoxycrotonophenone, 2-hydroxy-4-methoxysorbophenone, and 2'-hydroxy-4'-methoxychalkone show sharply defined hydroxyl absorption at $2650 \pm 30 \text{ cm.}^{-1}$.

MANY aromatic *o*- and *p*-hydroxy-carbonyl compounds are coloured: *e.g.*, atranol (I), 3-hydroxyphthalic anhydride (II), and 2,5-dihydroxyacetophenone (III) are yellow; more striking are the mould metabolites sorbicillin¹ (IV), which is orange-yellow, and the bright red phenylglyoxylic acid² (V). The colour of these compounds has been associated with their tautomeric quinonoid structures (*e.g.*, IVa³ and Va^{2,4}), but no supporting evidence has been put forward and many analogous substances are devoid of colour, *e.g.*, 4-hydroxyphthalic anhydride and 2,4-dihydroxyacetophenone. We have attempted to define the structure of sorbicillin by spectroscopic comparison with related compounds.



Synthetic sorbicillin was obtained in low yield by condensing sorbic acid with 2,4-dimethylresorcinol in polyphosphoric acid.* 2,4-Dihydroxysorbophenone (VI; R = H,

* Since this work was carried out a more satisfactory condensation in boron trifluoride-ether has been reported.⁵ We are indebted to Dr. J. F. W. McOmie for information in advance of publication.

¹ Cram and Tishler, *J. Amer. Chem. Soc.*, 1948, **70**, 4238; Cram, *ibid.*, 1948, **70**, 4240.

² Ralph and Robertson, *J.*, 1950, 3380.

³ Fieser and Fieser, "Introduction to Organic Chemistry," Heath, Boston, 1957, p. 550.

⁴ Hargreaves, McGookin, and Robertson, *J. Appl. Chem.*, 1958, **8**, 273.

⁵ McOmie and Tute, *J.*, 1958, 3226.

$n = 2$) was prepared in the same way, and its structure was established by reduction to 2,4-dihydroxyhexanophenone. Methylation with methyl sulphate in alkaline solution gave the 4-monomethyl ether (VI; $R = \text{Me}$, $n = 2$) obtained previously by Kuhn and Staab.⁶ Friedel-Crafts condensation of resorcinol dimethyl ether with crotonyl chloride afforded the simpler crotonophenone (VI; $R = \text{Me}$, $n = 1$); this cyclised smoothly in alkaline solution to 7-methoxy-2-methylchroman-4-one in accordance with its structure.

As sorbicillin and the sorbophenones (VI; $R = \text{H}$ and Me) have the same structure, *i.e.*, are all benzenoid or all quinonoid, it was convenient, for infrared spectroscopy, to concentrate on 2-hydroxy-4-methoxysorbophenone. This compound was compared with 2-hydroxy-4-methoxy-crotonophenone and -acetophenone. The hydroxyl group of these compounds forms an intramolecular hydrogen bond, so their spectra in the solid state differed little from their spectra in carbon tetrachloride solution. Most of the strongest absorption bands of the solids (see Table) are common to all three compounds, strongly suggesting a common structure. Two absorption bands between 800 and 900 cm^{-1} are those to be expected from C-H out-of-plane vibrations of a benzene ring with 1,2,4-

Principal absorption bands (cm^{-1}) in the spectra of solid 2-hydroxy-4-methoxyacetophenone (A), 2-hydroxy-4-methoxycrotonophenone (C), and 2-hydroxy-4-methoxysorbophenone (S).

A	C	S	A	C	S	A	C	S
1628	{ 1647 1617	{ 1642 1623	1208 1139	1211 1141	1215 1135	978 951	972 962	— 963
1579	1575	{ 1575 1567	1609 1020	— 1023	— 1019	860 815	864 829	877 833
1368	1366	1362	—	—	1007	—	793	794
1255	{ 1279 1231	1258						

substitution,⁷ and a band of medium intensity at 1504 cm^{-1} in all three spectra also indicates a benzene ring.* This implies that all the sorbophenones have a benzenoid structure.

An unusual feature of the spectra of the solid crotono- and sorbo-phenones, and of the related 2'-hydroxy-4'-methoxychalkone (VI; $R = \text{Me}$, $n = 1$, Ph in place of Me) (Fig. 1) was their sharply defined hydroxyl absorption, with maxima between 2620 and 2680 cm^{-1} . For 2-hydroxy-4-methoxyacetophenone, the band overlies the C-H absorption at 2950 cm^{-1} , indicating weaker hydrogen-bonding. The assignment of the band was confirmed for the chalkone by substitution of deuterium for hydrogen, the band then being displaced to 2050 cm^{-1} . In solution, these compounds gave the more diffuse absorption usual for strongly chelated hydroxyl groups¹⁰ (Fig. 1). Few solid state spectra showing the absorption of strongly chelated hydroxyl groups have been published, but earlier work in this laboratory¹¹ showed that none of a number of solid tetralones, flavanones, and benzocycloheptenones containing *peri*-hydroxy-carbonyl structures gave distinct hydroxyl absorption near 2650 cm^{-1} . This feature of the spectra of 2'-hydroxy-4'-methoxychalkone and its analogues cannot be correlated solely with the unsaturated side chain, as solid 2'-hydroxychalkone gave only diffuse absorption in this region.

The suggestion³ that sorbicillin might have a quinonoid structure was based on the observation¹ that its ultraviolet and visible absorption was much broader and more intense than that of the simpler compound clavatul (VII), although apparently cross-conjugated. This enhanced absorption is particularly marked in its deep orange, alkaline

* 2-Substituted 1,4-benzoquinones⁸ and 4-substituted 1,2-benzoquinones⁹ also absorb light at 800–900 cm^{-1} but show no band near 1500 cm^{-1} .

⁶ Kuhn and Staab, *Chem. Ber.*, 1954, **87**, 266.

⁷ Randle and Whiffen, "Molecular Spectroscopy," Institute of Petroleum, London, 1955, p. 111.

⁸ Yates, Ardao, and Fieser, *J. Amer. Chem. Soc.*, 1956, **78**, 650.

⁹ Otting and Staiger, *Chem. Ber.*, 1955, **88**, 828.

¹⁰ Flett, *Spectrochim. Acta*, 1957, **10**, 21.

¹¹ Farmer, Hayes, and Thomson, *J.*, 1956, 3600.

solution, where, of course, quinonoid structures, *e.g.*, (VIII), contribute to the light absorption of the mesomeric anion. However, by Dewar's definition,¹² sorbicillin and similar molecules are not cross-conjugated, and it is evident that structures such as (IX) and (X), in which ring and side chain are in conjugation, make an important contribution to the light absorption. As can be seen from Fig. 2, extending the classical cross-conjugation, in fact, extends the light absorption. Also, the sorbophenone curves are very similar to that of 2'-hydroxy-4'-methoxychalkone (VI; R = Me, $n = 1$, Ph in place of Me) but the general absorption pattern differs from that of *o*-¹³ and *p*-benzoquinones.¹⁴

FIG. 1. C-H and O-H absorption of 2'-hydroxy-4'-methoxychalkone, (A) solid, and (B) in 0.1M-CCl₄ solution in a 0.5 mm. cell.

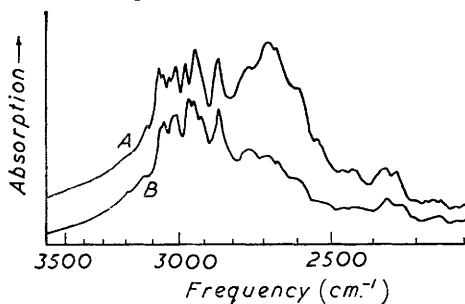
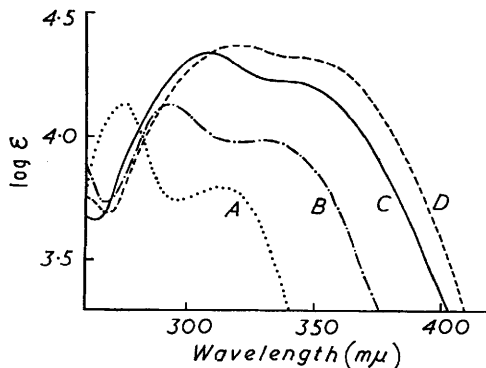
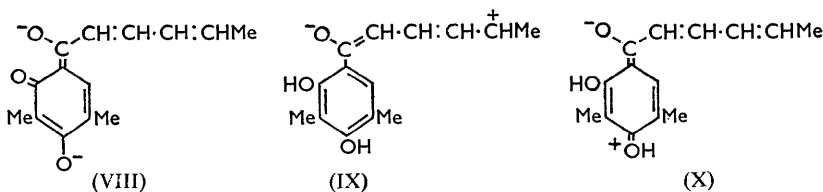


FIG. 2. (A) 2-Hydroxy-4-methoxyacetophenone, (B) 2-hydroxy-4-methoxycrotonophenone, (C) 2-hydroxy-4-methoxysorbophenone, (D) 2'-hydroxy-4'-methoxychalkone, in ethanol.



If sorbicillin is a quinone it should possess a very acidic hydroxyl group (vinylogous carboxyl group). However, sorbicillin is not soluble in aqueous sodium hydrogen carbonate (see also ref. 1). Moreover the colour of sorbicillin in alkaline solution is not



affected by treatment with sodium dithionite. Thus on both chemical and spectroscopic grounds we see little to support the view that sorbicillin is a quinone. This is likely to be the case also with most hydroxy-carbonyl compounds of the types illustrated on p. 346.

EXPERIMENTAL

2-Hydroxy-4-methoxycrotonophenone.—Anhydrous aluminium chloride (20 g.) was added in portions to a swirling mixture of resorcinol dimethyl ether (20.7 g.) and crotonyl chloride (15.7 g.) in carbon disulphide (80 ml.). After 10 min. more aluminium chloride (20 g.) was added, all at once, and the mixture was refluxed on a water-bath until evolution of hydrochloric acid ceased (*ca.* 3 hr.). The solvent was then decanted, the residual complex decomposed with ice and hydrochloric acid, and the product taken into ether and dried (MgSO₄). Distillation at 160—170° (bath)/0.05 mm. gave a yellow oil which partly crystallised. After being stirred in ice with an equal volume of methanol, the *ketone* was collected. It formed yellow plates, m. p. 89°, from methanol (Found: C, 68.6; H, 6.5. C₁₁H₁₂O₃ requires C, 68.7; H, 6.3%),

¹² Dewar, *J.*, 1952, 3544.

¹³ Teuber and Staiger, *Chem. Ber.*, 1955, 88, 802.

¹⁴ Flaig, Salfeld, and Baume, *Annalen*, 1958, 618, 117.

The yield was poor and variable. The ketone gave a red ferric colour, and formed a yellow solution in aqueous sodium hydroxide which quickly faded and became turbid. 2-Methyl-7-methoxychroman-4-one was obtained by adding 2% aqueous sodium hydroxide (4 ml.) to a solution of the ketone (0.25 g.) in warm alcohol (4 ml.). The mixture became turbid and deposited the oily chromanone (IV) which crystallised, separated from aqueous alcohol in plates, m. p. 77° (lit.,¹⁵ 77°) (Found: C, 68.5; H, 6.4. Calc. for $C_{11}H_{12}O_3$: C, 68.7; H, 6.3%), and gave a negative ferric chloride test.

2,4-Dihydroxysorbophenone.—A mixture of sorbic acid (5 g.) and resorcinol (5 g.) was added to polyphosphoric acid (90 g.) at 55°. After being stirred for 30 min. at this temperature the orange-red mass was poured on ice. The sticky red solid was separated, stirred with aqueous sodium hydrogen carbonate, set aside until it changed to a light orange precipitate, and crystallised from aqueous methanol in yellow needles, m. p. 133° (1.47 g.) (Found: C, 70.4; H, 5.9. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%). The ketone formed a yellow solution in aqueous sodium hydroxide and gave a dark brown colour with methanolic ferric chloride. When warmed for a few minutes with acetic anhydride containing anhydrous sodium acetate it yielded a *monoacetate*, crystallising from light petroleum (b. p. 100—120°) as yellow needles, m. p. 130° (Found: C, 68.2; H, 5.5. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%). The *diacetate*, formed when the acetylation mixture was boiled, crystallised in needles, m. p. 90°, from light petroleum (b. p. 60—80°) (Found: C, 66.2; H, 5.7; Ac, 31.0. $C_{16}H_{16}O_5$ requires C, 66.7; H, 5.6; Ac, 29.9%) and gave a negative ferric reaction.

2-Hydroxy-4-methoxysorbophenone.—To a stirred solution of 2,4-dihydroxysorbophenone (250 mg.) in methanol (12 ml.) containing dimethyl sulphate (2 ml.), *n*-sodium hydroxide was added in 35—45 min., so as to keep the mixture at pH ~9. The pH was then allowed to fall to ca. 4—5, a flocculent precipitate appearing. It formed yellow crystals (46 mg.), m. p. 110—111° (lit.,⁶ 111—112°) from methanol (Found: C, 71.2; H, 6.4. Calc. for $C_{13}H_{14}O_3$, C, 71.5; H, 6.5%). More product could be obtained by ether-extraction of the reaction mixture but was difficult to purify. It gave a yellow solution in aqueous sodium hydroxide and a brown ferric reaction.

2,4-Dihydroxyhexanophenone 2,4-Dinitrophenylhydrazone.—(a) Resorcinol (3 g.) was condensed with hexanoic acid (3 g.) in polyphosphoric acid (60 g.) at 90° for 30 min. Working up gave a yellow oil which distilled at 200—210°/10 mm. The ketone, which partly solidified, formed a *2,4-dinitrophenylhydrazone* crystallising in deep red plates, m. p. 232—235°, from acetic acid (Found: C, 56.0; H, 5.6; N, 14.3. $C_{18}H_{20}O_6N_4$ requires C, 55.7; H, 5.2; N, 14.4%).

(b) 2,4-Dihydroxysorbophenone (640 mg.) in alcohol (8 ml.) was hydrogenated over Adams's catalyst. When two mols. of hydrogen had been absorbed, the catalyst was removed and the solution was treated with 2,4-dinitrophenylhydrazine in alcohol. The product, crystallised from acetic acid, had m. p. and mixed m. p. 232—235°.

Sorbicillin.—2,4-Dimethylresorcinol (1.5 g.) was condensed with sorbic acid (1.2 g.) in polyphosphoric acid (30 g.) at 55° for 30 min. Treatment with ice and aqueous sodium hydrogen carbonate gave a precipitate which crystallised from aqueous methanol in yellow or orange plates. More sorbicillin was obtained by ether-extraction of the neutralised reaction liquor (total yield, 0.3 g.). The ultraviolet and infrared spectra of the synthetic material were identical with those of a sample of the natural product kindly supplied by Dr. D. J. Cram. Both samples softened at ca. 111° (without melting) and melted at ca. 125—130° (cf. refs. 1, 5, 6) (Found: C, 72.2; H, 7.1. Calc. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.9%). The monoacetate had m. p. 103—104° (lit.,¹ 103—104°) (yellow needles from aqueous methanol) (Calc. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found: C, 69.9; H, 6.7%).

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¹⁵ Richards, Robertson, and Ward, *J.*, 1948, 1610.