Constituents of the Higher Fungi. Part VI.* Some Analogues of Hispidin

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The preparation of a number of hispidin analogues is described. Their infrared carbonyl absorption frequency is dependent on the position of the hydroxyl group in the phenyl ring.

DURING our study of the infrared spectra of hispidin [6-(3,4-dihydroxystyryl)-4-hydroxy-2-pyrone] and its derivatives,[1] we noted that the carbonyl absorption of those derivatives containing hydroxyl groups in the phenyl ring was inconsistent with a 2-pyrone structure. Because of the possible natural occurrence of other related hydroxylated compounds, and because several of their ethers were required for photochemical study, we have prepared a number of 6-styryl-2-pyrones and examined their infrared and ultraviolet spectra. The compounds prepared may be classified into three groups: (*a*) those in which the phenyl ring and the 4-position of the pyrone ring are methoxylated or methoxymethoxylated; (*b*) those in which the phenyl ring is hydroxylated and the pyrone ring is methoxylated or methoxymethoxylated; (*c*) those in which both the phenyl and the pyrone ring are hydroxylated.

These compounds were prepared by condensing

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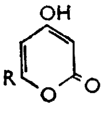
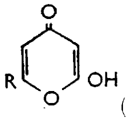
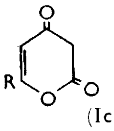
* Part V, R. L. Edwards and G. C. Elsworthy, preceding Paper.

[1] R. L. Edwards, D. G. Lewis, and D. V. Wilson, *J. Chem. Soc.*, 1961, 4995.

methoxy- and methoxymethoxy-aldehydes with 4-methoxy-6-methyl and 4-methoxymethoxy-6-methyl-2-pyrones in the presence of magnesium methoxide.[2] The free phenols were prepared by hydrolysis of the methoxymethoxy-compounds with dilute sulphuric acid. Compounds methoxylated or methoxymethoxylated on the pyrone ring must, from their method of preparation, possess the 2-pyrone structure; any change in the carbonyl absorption frequency caused by a change of substituents on the phenyl ring will be independent of tautomeric changes. On the other hand, compounds containing a hydroxylated pyrone ring can exist in one or more of the tautomeric forms (Ia), (Ib), (Ic), and the predominant enol may vary with the solvent, pH, or change of state. Other workers determined the infrared spectra of pyrones (Ia),[2-5] (Ib),[3,5] and (Ic),[3,6] either in solution (CCl_4 and $CHCl_3$) or in Nujol, and these investigations have established the following correlations: (i) 2-pyrones absorb near 1724 cm.$^{-1}$; (ii) the first carbonyl stretching band of 4-pyrones appears near 1667 cm.$^{-1}$; (iii) when both 2- and 4-isomers are available, the one with the longer wavelength main maximum in the ultraviolet is the 2-isomer. On the basis of these generalisations, Djerassi and his co-workers[3] regard the phenyl analogues of triacetic lactone as the 4-isomer (Ib; R = Ph) in the solid state and the 2-isomer (Ia; R = Ph) in solution. For this investigation all infrared spectra were determined in potassium bromide discs, and the carbonyl bands are summarised in the Table.


(Ia)


(Ib)


(Ic)

In the fully methoxylated compounds the absorption frequency varies between 1724—1700 cm.$^{-1}$. Yangonin [4-hydroxy-6-(4-methoxystyryl)-2-pyrone] and its 3-styryl analogue absorb near 1724 cm.$^{-1}$; the frequency falls to 1716 in the 2-, and to 1701 in the 3,4-di-methoxystyryl compound. This fall is closely followed by the fully methoxymethoxylated compounds, but in those compounds containing a methoxylated pyrone ring and a methoxymethoxylated phenyl ring the frequencies are between 1710 and 1705 cm.$^{-1}$. Large changes occur when the methoxymethoxyl group on the phenyl ring is replaced by hydroxyl. The presence of hydroxyl groups in the 2-, 4- and 3-positions of the styryl part results in falls to 1700, 1697, and 1662 cm.$^{-1}$, respectively; the last low value is to be compared with the similar absorption at 1667 in monomethylhispidin (3,4-dihydroxystyryl) and 1668 in the 2,5-dihydroxystyryl compound. By comparison, the 2,4-dihydroxystyryl compound absorbs at 1688 cm.$^{-1}$. Where both 2- and 4-pyrone structures are possible (OH on pyrone ring), the carbonyl absorption occurs between 1680 and 1690 cm.$^{-1}$ and is less dependent on the position of substitution in the phenyl ring. In no case does the frequency fall to the low value observed in 3-hydroxystyryl- and 3,4- and 2,5-dihydroxystyryl-4-methoxy-2-pyrone.

From these results, it is apparent that fixed rules for

Ultraviolet and infrared absorptions of hispidin analogues

Styryl substituents 2-	3-	4-	5-	Pyrone subst. 4-	M. p.*	$\lambda_{max.}$ (mμ)	ν(C=O) (mμ)	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
H	H	O·CH$_2$·OMe	H	OMe	151°	357	1705	67·05	5·5	66·7	5·55
,,	O·CH$_2$·OMe	H	,,	,,	116	347	1705	66·7	5·6	66·7	5·55
O·CH$_2$·OMe	H	,,	,,	,,	119	355	1710	67·0	5·8	66·7	5·55
,,	,,	,,	O·CH$_2$·OMe	,,	90	365	1726	62·0	5·7	62·1	5·7
,,	,,	O·CH$_2$·OMe	H	,,	109	370	1726	62·1	5·5	62·1	5·7
H	,,	OMe	,,	,,	158	367	1723	69·85	5·5	69·7	5·4
,,	OMe	H	,,	,,	137	350	1724	69·8	5·5	69·7	5·4
OMe	H	,,	,,	,,	164	370	1716	69·75	5·45	69·7	5·4
H	OMe	OMe	,,	,,	164	367	1701	66·6	5·4	66·7	5·6
,,	H	OH	,,	,,	277 (d.)	368	1697	68·8	5·3	68·85	4·9
,,	OH	H	,,	,,	212 (d.)	375	1662	68·8	5·05	68·85	4·9
OH	H	,,	,,	,,	224 (d.)	367	1700	64·15	5·1	64·1	5·3 †
H	OH	OH	,,	,,	257	378	1667	64·7	4·8	64·6	4·6
OH	H	,,	,,	,,	285 ‡	395	1688	64·8	4·7	64·6	4·6
,,	,,	,,	OH	,,	272 (d.)	394	1668	64·3	4·7	64·6	4·6
H	,,	O·CH$_2$·OMe	H	O·CH$_2$·OMe	119	364	1719	64·25	6·0	64·15	5·7
,,	O·CH$_2$·OMe	H	,,	,,	135	353	1724	64·8	6·2	64·15	5·7
O·CH$_2$·OMe	H	,,	,,	,,	127	360	1710	64·1	6·1	64·15	5·7
H	,,	OMe	,,	,,	136—140	367	1718	66·5	6·0	66·7	5·55
OMe	,,	H	,,	,,	145—150	367	1725	66·6	5·95	66·7	5·55
H	,,	OH	,,	OH	250—255 (d.)	375	1685	67·47	4·6	67·8	4·3
,,	OH	H	,,	,,	190—195 (d.)	363	1690	67·5	4·7	67·8	4·3
OH	H	,,	,,	,,	200 (d.)	379	1686	67·6	4·6	67·8	4·3
H	OH	OH	,,	,,	259 (d.)	373	1683	58·7	4·7	59·1	4·5 †

* d. = With decomposition. † Hydrated, 1 mol. H_2O. ‡ Decomposes without melting.

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[2] J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 1960, 502.

[3] D. Herbst, W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, 1959, **81**, 2471.

[4] W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, 1957, **79**, 4507.

[5] I. Chimelewska, J. Cieslak, K. Gorczynska, B. Kontnik, and K. Pitchowska, *Tetrahedron*, 1958, **4**, 36.

[6] R. H. Wiley and C. H. Jarboe, *J. Amer. Chem. Soc.*, 1956, **78**, 624.

defining structure, based on the frequency of the carbonyl absorption, must be used with caution, and that such rules cannot be applied to those compounds containing hydroxyl groups on the phenyl ring. This applies especially to those compounds containing a 3-hydroxyl on the styryl group.

EXPERIMENTAL

Infrared spectra were determined in potassium bromide discs on a SP 521 spectrophotometer, ultraviolet spectra in alcohol solutions on a 137 instrument, and melting points on a Kofler hot stage.

Methoxymethoxybenzaldehydes.—Chloromethyl ether (14 ml., 0·2 mole) was added during 15 min. to a stirred refluxing mixture of *p*-hydroxybenzaldehyde (10 g., 0·09 mole), dry acetone (200 ml.), and anhydrous potassium carbonate (30 g.). After stirring for an additional 15 min. the mixture was allowed to cool, filtered, and the residual potassium carbonate washed with acetone. After removal of the acetone, the residual oil was dissolved in ether (40 ml.), and the solution washed with 2N-sodium hydroxide and water, and dried. Evaporation, and distillation of the residual oil gave p-*methoxymethoxybenzaldehyde* as a colourless oil (11 g.), b. p. 118—120°/4 mm. (Found: C, 65·2; H, 5·9. $C_9H_{10}O_3$ requires C, 65·05; H, 6·0%). m-*Methoxymethoxybenzaldehyde* was similarly prepared from *m*-hydroxybenzaldehyde as a colourless oil, b. p. 98°/1 mm. (Found: C, 65·1; H, 6·0%). 2,4-*Di*(*methoxymethoxy*)*benzaldehyde*, b. p. 156°/2 mm., m. p. 48° (Found: C, 58·3; H, 6·2. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%), and 2,5-*di*(*methoxymethoxy*)*benzaldehyde*, b. p. 139—142°/0·8 mm. (Found: C, 58·4; H, 6·1%), were prepared from 2,4- and 2,5-dihydroxybenzaldehyde by the action of chloromethyl ether on the sodium salts in dry toluene.[7]

4-*Methoxy*-6-(4-*methoxymethoxystyryl*)-2-*pyrone*.—A mixture of *p*-methoxymethoxybenzaldehyde (4·2 g., 0·025 mole), 4-methoxy-6-methyl-2-pyrone (3·7 g., 0·025 mole), and magnesium methoxide [from magnesium (1·8 g.) and methanol (70 ml.)] was refluxed for 6 hr. The mixture was evaporated to dryness, and the residue washed in chloroform with dilute acetic acid (30 ml.). The chloroform layer was separated, washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and passed over magnesium oxide. Development with chloroform and evaporation of the eluate gave a viscous oil which slowly yielded crystals of the *product*, pale yellow needles (from methanol) (3·4 g.), m. p. 150—151° (Found: C, 67·05; H, 5·5. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·5%), $\nu_{max.}$ 1705 cm.$^{-1}$, $\lambda_{max.}$ 220 and 357 mμ.

6-(4-*Hydroxystyryl*)-4-*methoxy*-2-*pyrone*.— 4-Methoxy-6-(4-Methoxymethoxystyryl)-2-pyrone (0·28 g., 0·01 mole) was refluxed in a mixture of acetic acid (5 ml.), water (2 ml.), and sulphuric acid (2N; 3 drops) for 3 min. The solution was set aside at room temperature, and the *product* was filtered off, washed with water, and dried. Recrystallisation from ethanol or acetic acid gave yellow plates (0·19 g.), m. p. 277—280° (decomp.) (Found: C, 69·2; H, 5·05. $C_{14}H_{12}O_4$ requires C, 68·85; H, 4·9%), $\nu_{max.}$ 1697 cm.$^{-1}$, $\lambda_{max.}$ 219 and 368 mμ.

The authors thank the Governors of Bradford Institute of Technology for a Research Scholarship (to I. M.).

[6/784 *Received, June 23rd*, 1966]

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[7] R. L. Edwards and D. V. Wilson, *J. Chem. Soc.*, 1961, 5003.