1273. *Gallotannins. Part X.*[1] *The Methanolysis of Pyrocatechol Monoesters*

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Infrared spectroscopic examination of pyrocatechol monoesters has shown that these exist predominantly as a mixture of two hydrogen-bonded conformers in carbon tetrachloride solution. In the presence of methanol a third species is formed in which it is suggested that a methanol molecule is bound to the *ortho*-hydroxy-ester by hydrogen bonding. The mechanism of the methanolysis [2] is considered in relation to these spectroscopic and kinetic data.

IN recent years experimental evidence has been obtained to show that a hydroxyl group in an appropriate structural environment may facilitate ester solvolysis by neighbouring-group participation.[3] An important reaction of this type is the methanolysis of pyrocatechol monoesters [2] in which methanol at neutral pH may be used to cleave specifically *ortho*-hydroxydepside linkages in gallotannin molecules. The mechanism of this reaction has been studied by using infrared spectroscopic and kinetic measurements and the results of these studies are reported here.

EXPERIMENTAL

Materials.—The following *o*-hydroxyphenyl esters were prepared by published methods except that crystallisation was carried out from benzene or methylene dichloride and light petroleum (b. p. 60—80°): 1-*O*-benzoylpyrocatechol,[2] methyl 3-*O*-benzoylprotocatechuate,[2] 1-*O*-*m*-nitrobenzoylpyrocatechol,[4] 1-*O*-*p*-nitrobenzoylpyrocatechol,[4] 2-*O*-benzoyl-4-nitropyrocatechol,[5] 1-*O*-benzoyl-3-nitropyrocatechol,[5] and 2-*O*-benzoyl-4-chloropyrocatechol.[6] The following compounds were prepared by substitution of the appropriate acid chloride for benzoyl chloride in the preparation of 1-*O*-benzoylpyrocatechol: [2] 1-O-m-*methoxybenzoylpyrocatechol*, m. p. 84° (Found: C, 68·6; H, 4·9. $C_{14}H_{12}O_4$ requires C, 68·9; H, 4·9%), 1-O-p-*chlorobenzoylpyrotecatechol*, m. p. 130° (Found: C, 62·8; H, 3·8. $C_{13}H_9ClO_3$ requires C, 62·7; H, 3·6%), 1-O-m-*chlorobenzoylpyrocatechol*, m. p. 109° (Found: C, 62·4; H, 3·8. $C_{13}H_9ClO_3$ requires C, 62·7; H, 3·6%).

1-O-p-*Methoxybenzoylpyrocatechol* was prepared by refluxing an equimolar mixture of *p*-methoxybenzoyl chloride and pyrocatechol in dry benzene for 3 hr. with a slow stream of nitrogen passing through the solution. The benzene solution was washed with dilute sodium hydrogen carbonate solution and then with water, and dried (Na_2SO_4). Removal of the solvent and crystallisation from methylene dichloride and light petroleum (b. p. 60—80°) gave the product as needles, m. p. 134° (Found: C, 68·4; H, 4·8. $C_{14}H_{12}O_4$ requires C, 68·9; H, 4·9%).

Spectroscopic Measurements.—Spectroscopic methods and notations were as outlined previously.[7]

Kinetic Measurements.—(*a*) *Colorimetric method*. The methanolyses were carried out in conical flasks (250 c.c.) immersed in a thermostat-controlled water-bath (temperature stable to ±0·05°). Methanol (90 c.c.) and M-acetate buffer solution (pH 5·56; 9·0 c.c.) were introduced by pipette into the flask and allowed to equilibrate for 15 min.; a solution of the pyrocatechol ester (*ca*. 0·001 mole) in dioxan (1·0 c.c.) was then added and the whole mixed by swirling. Aliquot portions (5·0 c.c.) were withdrawn at noted time intervals and added to a solution of ferrous tartrate [8,9] (25·0 c.c.) and M-sodium acetate solution (20·0 c.c.) and the whole diluted to 100 c.c. with water. The optical density was measured at 530 mμ against a blank

[1] Part IX, D. Cornthwaite and E. Haslam, *J.*, 1965, 3008.
[2] R. Armitage, E. Haslam, R. D. Haworth, S. D. Mills, H. J. Rogers, and T. Searle, *J.*, 1961, 1836.
[3] B. Capon, *Quart. Rev.*, 1964, **18**, 45.
[4] C. Seibenmann and R. J. Schnitzer, *J. Amer. Chem. Soc.*, 1943, **65**, 2126.
[5] D. H. R. Barton, W. H. Linell, and N. Senior, *Quart. J. Pharm.*, 1945, **18**, 41.
[6] H. Inoue, O. Simarnura, and K. Takamizawa, *Bull. Chem. Soc., Japan*, 1962, **35**, 1958.
[7] R. Biggins, T. Cairns, G. Eglinton, E. Haslam, and R. D. Haworth, *J.*, 1963, 1750.
[8] L. Mitchell, *Analyst*, 1923, **48**, 2.
[9] S. Glasstone, *Analyst*, 1925, **50**, 49.

solution of the reagents. The relation between optical density and pyrocatechol concentration was linear and the change in optical density was used directly as a measure of the extent of the reaction. This method was satisfactory except for 1-*O*-*m*-nitrobenzoylpyrocatechol and 1-*O*-*p*-nitrobenzoylpyrocatechol with which it was found necessary to carry out the colorimetric extimation at 10°.

The methanolysis of 1-*O*-benzoyl-3-nitropyrocatechol was followed by measurement of the change in optical density at 300 mμ using an Adkins cell holder [10] fitted with a thermostat. A similar procedure was adopted for 2-*O*-benzoyl-4-nitropyrocatechol using the absorption band at 400 mμ and a temperature-stabilised system similar to that of Hill.[10]

General base catalysis measurements were performed on 2-*O*-benzoyl-4-nitropyrocatechol at 25° using the following solutions of methanol, M-sodium acetate (pH 5·56), and M-sodium chloride (A: 90 c.c., 9·0 c.c., 0 c.c.; B: 90 c.c., 7·0 c.c., 2·0 c.c.; C: 90 c.c., 5 c.c., 4 c.c.; D: 90 c.c., 3 c.c., 6 c.c.: E: 90 c.c., 1·0 c.c., 8·0 c.c.).

The methanolysis of 2-*O*-benzoyl-4-nitropyrocatechol was studied over the pH range 4·0—12·77, three buffering systems, acetate,[11] diethylbarbiturate,[12] and glycine [13] being used and a constant ionic strength of 0·09 being maintained with sodium chloride. The rate constants were determined at pH 4·0 and 4·4 by measuring the decrease in intensity of the ester absorption band at 310 mμ and over the range pH 4·8—12·77 in the manner previously described.

(*b*) *Gas chromatographic method.* The gas chromatographic method was utilised to confirm the results obtained by the colorimetric method. Methyl benzoate formed in the methanolysis was estimated by comparison of its peak area with that of an internal standard ethyl benzoate. Methanolyses were carried out as described above in solutions containing ethyl benzoate (0·015 g.). Samples (0·2 c.c.) were withdrawn at noted times and the volatile components collected by microdistillation (2 mm., 20°) with the receiver cooled in liquid nitrogen and samples (10 μl) injected by syringe through a Suba-seal cap into the electrically heated gas-inlet tube of a vapour phase chromatogram (column 12 ft., 10% apiezon on Celite maintained at 118°, hydrogen carrier gas, flow rate 54 c.c./min.). The detector used was a hydrogen flame-ionisation type used in conjunction with an amplifier (I.E. 115, Gas chromatography Ltd.) and a Kent recorder. Peak areas were estimated from the product of the half-band width and the peak height. Pseudo-first-order rate constants were determined by the method of Guggenheim.[14] 1-*O*-Benzoylpyrocatechol was methanolysed in 90% methanol at pH 5·56 and 40°; estimation of the pseudo-first-order rate constant colorimetrically gave values of 2·32, 2·20, and 2·27 × 10^{-4} sec.$^{-1}$ and by the gas chromatographic method 2·38, 2·40, 2·35 × 10^{-4} sec.$^{-1}$. The gas chromatographic method was tedious and unsuitable for 1-*O*-benzoylpyrocatechol derivatives yielding non-volatile methyl esters on methanolysis.

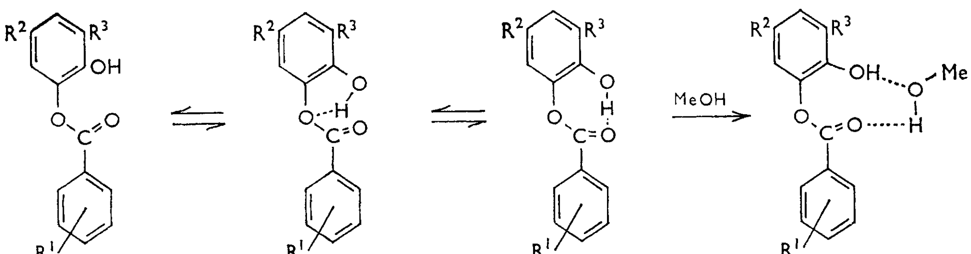
Order of Reaction.—The order of the methanolysis reaction with respect to methanol was determined by a series of methanolyses at 40°, pH 5·56, a constant initial concentration of 1-*O*-benzoylpyrocatechol (0·03 or 0·10 mole l.$^{-1}$) being used with various concentrations of methanol (20·0, 15·0, 5·0, 2·0, 1·75, 1·5, 1·25, 1·0, 0·75 moles l.$^{-1}$). The reaction was followed by the colorimetric or gas chromatographic methods and concentration (pyrocatechol or methyl benzoate, respectively) against time curves obtained. The initial rates were measured by constructing tangents to these plots at zero time using a plane mirror method. A plot of the logarithm of the initial rates against the logarithm of the methanol concentrations gave straight lines whose slopes, which measure the order of the reaction with respect to methanol, varied from 1·07 to 0·93 over the range of concentrations studied.

Results and Discussion

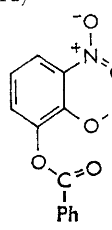
An interpretation of the infrared spectra of 1-*O*-benzoylpyrocatechol (Ia; $R^1 = R^2 = R^3 = H$) in dilute carbon tetrachloride solution has been made [7] on the basis of the molecule existing predominantly as an equilibrium mixture of the species (Ia, Ib, Ic; $R^1 = R^2 = R^3 = H$) and as in similar situations either of the species (Ib) or (Ic) may be postulated as facilitating the methanolysis of the ester linkage. Thus Henbest [15] and

[10] J. Price, " Unicam Spectrovision," 1961, **11**, 10, 11.
[11] G. S. Walpole, *J.*, 1914, 2521.
[12] L. Michaelis, *J. Biol. Chem.*, 1930, **87**, 33.
[13] A. I. Vogel, " Quantitative Inorganic Analysis," Longmans, 1951, 871.
[14] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.
[15] H. B. Henbest and B. J. Lovell, *J.*, 1957, 1965.

Kupchan [16] suggested that the ready solvolysis of steroidal 1,3-diaxial hydroxy-acetates was an instance of concerted general base—general acid catalysis involving species analogous to (Ib)—but from a study of the hydrolysis of monoacetates of various cyclopentanediols Bruice and Fife [17] made the alternative postulate that a species such as (Ic) participated in the reaction by a process of internal solvation of the transition state for the attack of hydroxide ion at the ester carbonyl group. In an extension of this work substituted 1-*O*-benzoylpyrocatechols were examined in order to study the effects of substituent groups on the equilibrium of the hydrogen-bonded conformations (Ib) and (Ic). The spectra showed no major differences from that of the parent compound with the exception of 1-*O*-benzoyl-3-nitropyrocatechol where competitive intramolecular hydrogen bonding with the nitro-group was evident (II). Electron-attracting groups in the benzoate ring caused a shift to higher frequency of both carbonyl bands and an apparent decrease in the proportion of the lower frequency band (Ic) presumably due to the withdrawal of electrons from the carbonyl group making it a less favourable site for hydrogen bonding. Opposite effects were observed for electron-donating groups (Table 1) and for all compounds these changes in the carbonyl absorption patterns were accompanied by the appropriate changes in the hydroxyl-stretching modes of the spectra. The apparent proportion (*R**) of each conformation (Ib) and (Ic) was estimated on the assumption that the ratio of the absolute extinction coefficients of the two carbonyl bands is approximately the same for each compound and hence that the ratios of the intensities of these bands is a measure of the proportion of the two conformers; a plot of *R** against the Hammett σ constants for substituents in the benzoyl group showed a linear relationship. Over a more limited number of samples the effects of electron-withdrawing groups in the catechol residue were clearly not so favourable towards the formation of (Ib).



(Ia) (Ib) high ν (CO) (Ic) low ν (CO) (Id)



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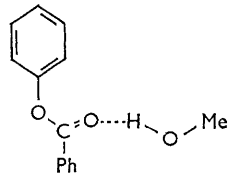


(III)

Bruice and Fife have suggested [17] that a neighbouring hydroxyl group may assist ester solvolysis by a change in the microscopic medium surrounding the ester group, as for example by a specific binding or orientation of water molecules in the critical transition state. To investigate this possibility in the methanolysis the effect of methanol on the spectra of compound (Ia; $R^1 = R^2 = R^3 = H$) in carbon tetrachloride was examined. At relatively low concentration (0·25M) methanol had little effect on the spectra of phenyl benzoate and guaiacol benzoate but the carbonyl band became asymmetric and decreased in intensity as the methanol concentration increased (1·25M) until a second carbonyl

[16] S. M. Kupchan, S. P. Eriksen, and M. Friedman, *J. Amer. Chem. Soc.*, 1962, **84**, 4159.
[17] T. C. Bruice and T. H. Fife, *J. Amer. Chem. Soc.*, 1962, **84**, 1977.

band ($\nu_{max.}$ 1728 cm.$^{-1}$) assigned to species such as (III) became apparent (5·0M). The spectrum of 1-*O*-benzoylpyrocatechol showed a greater susceptibility to methanol (Table 2) and at 0·05M concentration a third carbonyl absorption ($\nu_{max.}$ 1731 cm.$^{-1}$) was present. Increase in the methanol concentration enhanced the proportion of the species corresponding to the new band at the expense of the species (Ic), but had little effect on species (Ib). The solutions were spectroscopically stable and hence the new carbonyl absorption was not due to a product of ester methanolysis. In suggesting the structure (Id; $R^1 = R^2 = R^3 =$ H) for the new species account has been taken of its extremely ready formation at low methanol concentration apparently from structure (Ic; $R^1 = R^2 = R^3 =$ H) and it is suggested that this is probably due to the fact that this species is already suitably disposed sterically to form the complex (Id; $R^1 = R^2 = R^3 =$ H) whereas the free carbonyl group of structure (Ib; $R^1 = R^2 = R^3 =$ H) would only be expected to have a similar tendency to solvate as that of guaiacol benzoate. The presence of substituents in the parent molecule had analogous effects on the equilibrium (Ic) $\rightleftharpoons$ (Id) in methanolic solution as outlined for that in carbon tetrachloride, *i.e.*, electron-attracting groups in the benzoyl residue favoured the formation of species (Ib) and conversely electron-donating groups the new species (Id); the ratio of the apparent concentrations of the two species (Ib and Id; R^*_{MeOH}) again showed a linear correlation with the Hammett σ values for the substituents (Table 1).

TABLE 1

Carbonyl absorptions of some 1-*O*-benzoylpyrocatechol derivatives in carbon tetrachloride and carbon tetrachloride–methanol and their relative rates of methanolysis at 30°

Compound (Ia)	CCl_4				CCl_4–MeOH				
	ν(CO)	$\Delta\nu_{\frac{1}{2}}{}^{a}$	ε^{a}	R^*	ν(CO)	$\Delta\nu_{\frac{1}{2}}{}^{a}$	ε^{a}	R^*_{MeOH}	$K^{30}_{rel.}$
R^1; $R^2 = R^3 =$ H									
p-OMe	1747	14	315	1·09	1740	13	135	0·392	0·16
	1704	16	290		1724	20	345		
m-OMe	1750	17	260	1·30	1742	16	155	0·647	1·4
	1711	20	200		1728	14	240		
p-Cl	1752	12	395	1·46	1746	12	250	0·736	3·5
	1714	16	270		1733	15	340		
m-Cl	1754	15	330	1·57	1749	11	230	0·789	7·6
	1716	17	210		1735	19	292		
m-NO_2	1755 †	14	465	2·16	1752	11	263	1·22	47·9
	1719	17	215		1741	14	215		
p-NO_2	1754	13	390	2·17	1751	12	272	1·23	60·3
	1719	21	180		1740	13	220		
R^2; $R^1 = R^3 =$ H									
CO_2Me	1755 †	17	325	—	1749				8·2
	1726	15	800		1724				
	1712	(sh)	—		1706				
Cl	1753	13	365	1·40	1749	12	270	0·83	4·2
	1712	19	260		1732	15	327		
NO_2	1760 †	13	340	1·69	1752	12	392	1·43	32·5
	1714	18	195		1734	15	275		
R^3; $R^1 = R^2 =$ H									
NO_2	1751	14	415	—	1753				19·3
	1743	(sh)	—		1719				
	1694	13	915		1702				

Spectra in CCl_4, 1·5mM in 0·5 cm. cells, except † 0·3mM solutions in 2 cm. cells. Spectra in CCl_4–MeOH, 1·5mM solutions in 0·5 cm. cells, 1·0M in MeOH. $R^* = \varepsilon^a$ (high-frequency band)/ε^a (low-frequency band). $K^{30}_{rel.} = K^{30}_{obs.}/K$ where K is rate constant for the methanolysis of 1-*O*-benzoylpyrocatechol (Ia; $R^1 = R^2 = R^3 =$ H) at 30° (= $8{\cdot}24 \times 10^{-5}$ sec.$^{-1}$) and $K^{30}_{obs.}$ is rate constant for the methanolysis of substituted 1-*O*-benzoylpyrocatechol.

Although the species (Id; $R^1 = R^2 = R^3 =$ H) may well exist in methanolic solutions of 1-*O*-benzoylpyrocatechol this cannot be a kinetically important species in the solvolysis since the reaction was shown to be first-order with respect to methanol concentration over

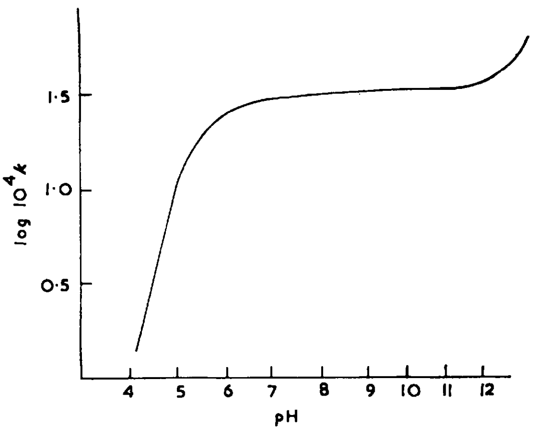
TABLE 2

Carbonyl absorption of 1-*O*-benzoylpyrocatechol (Ia; $R^1 = R^2 = R^3 = H$) in CCl_4 with varying concentrations of MeOH

[MeOH] (mole/l.)	ν(CO)	$\Delta\nu_{\frac{1}{2}}$ [a]	ε [a]	R^*_{MeOH}	[MeOH] (mole/l.)	ν(CO)	$\Delta\nu_{\frac{1}{2}}$ [a]	ε [a]	R^*_{MeOH}
— †	1753	13	310	1·35	0·25 †	1750	14	195	0·60
	1712	21	230			1731	17	325	
0·01 †	1753	13	330	1·44		1715	(sh)	—	
	1712	20	230		0·50 †	1749	12	175	0·515
0·05 †	1752	15	300	1·54		1731	16	340	
	1729	—	—		1·25 ‡	1748	11	190	0·567
	1712	20	195			1731	17	335	

† Solutions 1·5 mM. in 1·0 cm. cells. ‡ Solutions 3·0 mM in 0·5 cm. cells.

a wide range of methanol concentrations. The relative rates of methanolysis shown in Table 1 were obtained in 90% methanol wherein the reaction is pseudo-first-order and illustrate the effects of various substituents in the benzoyl group on the rate of reaction. A plot of log $[k_{obs}/k]$ against the Hammett σ values for the substituents in the benzoyl group gave a straight line with a reaction constant $\rho = 2{\cdot}35$, comparable with values obtained for the analogous reaction of the alkaline hydrolysis of alkyl benzoates [18] and indicating therefore that the influence of substituents in the benzoyl group is mainly one of increasing or decreasing the electrophilic nature of the carbonyl carbon atom. The methanolysis of 2-*O*-benzoyl-4-nitropyrocatechol (Ia; $R^1 = R^3 = H$; $R^2 = NO_2$) was shown not to be general base-catalysed by the observed invariance of the reaction rate in a series of acetate buffers of constant buffer ratio and ionic strength but varying concentration.[16] Hence mechanisms involving the general base-catalysed reaction of methanol with the ester species (Ib) or (Ic) are unlikely and it is evident that hydrogen bonding determined for the

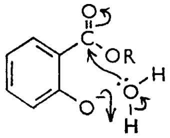


The pH dependence of the rate of methanolysis of 2-*O*-benzoyl-4-nitropyrocatechol (Ia; $R^1 = R^3 = H$, $R^2 = NO_2$) at 25°

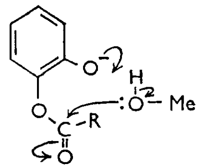
ground state of the ester (Ia) in aprotic media does not necessarily reveal kinetically important species in the methanolysis reaction. The pH dependence of the rate of methanolysis of structure (Ia; $R^1 = R^3 = H$, $R^2 = NO_2$) was of the form shown in the Figure with a region of pH independence (pH ~7—11) and a first-order dependence of rate on hydroxide-ion concentration in weakly acid solution. The pH profile is typical of a mechanism involving prior ionisation of a substrate molecule followed by a rate-determining reaction of the resultant anion and is closely analogous in the regions studied to that for the hydrolysis of salicylate esters investigated by several workers and most recently by Bender and his colleagues.[19] Bender concluded that, of the various possibilities, the pH-independent hydrolysis of salicylate esters in the alkaline region was a case of intramolecular

[18] C. K. Ingold and W. S. Nathan, *J.*, 1936, 222.
[19] M. L. Bender, F. J. Kezdy, and B. Zerner, *J. Amer. Chem. Soc.*, 1963, **85**, 3017.

basic catalysis in which water reacts with the ionised ester (IV) in the rate-determining stage and he suggested that whilst all examples of neighbouring hydroxyl-group assistance to ester solvolysis may not occur by the same mechanism all previous examples could be



(IV)



(V)

satisfactorily interpreted in terms of this particular one. Although the kinetic data presented here do not rule out possible mechanisms for the methanolysis in which the methoxide ion attacks the un-ionised ester (Ib) or (Ic), the reaction, by analogy with the salicylate ester case, is most readily rationalised in terms of the attack of a neutral methanol molecule on the ionised ester (V).

The authors thank Professor R. D. Haworth for his interest and encouragement, Dr. G. Eglinton (University of Glasgow) for helpful discussions, and Middlesbrough Education Committee for a maintenance grant (R. B.).

Chemistry Department, The University, Sheffield 10. [*Received, March 5th,* 1965.]