COMPETITIVE METHYLATION OF SOME PHENOLIC COMPOUNDS

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UDC 547.813.814:542.953:543.422.6

The competitive methylation of a mixture of 6-hydroxy-4-methylcoumarin and of 7-hydroxy-4-methylcoumarin and also of other compounds of phenolic nature has been studied. It had ben shown that in the presence of 1 mole of alkali, methylation of the more acidic hydroxyl takes place at the oxygen atom, and with 2 moles of alkali, the stronger conjugated base reacts.

In a preceding communication we reported a study of the selective alkylation of dihydroxycoumarins in which the conversion of one – the more acidic – hydroxy group into the conjugate base exerts a considerable influence on the acidity of the other hydroxyl. In the chemistry of phenolic compounds, including the flavonoids, the necessity not only for the selective alkylation of hydroxy groups interacting strongly or feebly with one another, but also for the performance of selective intermolecular alkylation frequently arises.

We have performed the methylation with dimethyl sulfate of a mixture of 6-hydroxy-4-methylcoumarin (Ia) and 7-hydroxy-4-methylcoumarin (IIa) in the presence of 1 and 2 moles of NaOH. As can be seen from Table 1, in the second case the 6-ether (Ib), and in the first case the 7-ether (IIb), is formed predominantly, i.e., in general the same situation is observed as in the alkylation of 6,7-dihydroxycoumarins. However, the selective competitive alkylation of monohydroxy derivatives is less well defined. This can be explained by the smaller difference in acidities [1] between the two OH groups in compounds (Ia) and (IIa). In fact, pK_a (Ia) – pK_a (IIa) = 10.56 – 9.35 = 1.21, and pK_a [6-OH in 6,7-dihydroxy-4-methylcoumarin (IIIa)] – pK_a [7-OH in (IIIa)] = 12 – 8.76 = 3.24, the latter difference actually being even greater, since the second ionization constant of (IIIa) corresponds to $pK_a \geq 12$. In the case of phenol (IVa) and p-nitrophenol (Va) [their methyl ethers being (IVb) and (Vb), respectively], for which $\Delta pK_a = 2.83$, the selectivity of methylation in the presence of NaOH proved to be higher (see Table 1). The replacement of NaOH did not lead to qualitatively different results.

It is generally considered [2, 3] that compounds of the type of 2-acylphenols, such as 2-hydroxybenzaldehyde or 2-hydroxyacetophenone (VIa), are considerably more difficult to alkylate than the corresponding para isomers (VIIa), since in ortho-substituted compounds the hydroxyl takes part in the formation of a strong intramolecular hydrogen bond. This bond is not broken even under the influence of such solvents as water and alcohols, as follows immediately from the values of the ionization constants of these acylphenols,which were determined in aqueous solutions [for example, according to handbook literature the pK_a values for (VIa) and (VIIa) are 11.86 and 8.05, respectively].* Such ideas have also been extended to the case of the 1-acyl-2,4-dihydroxybenzenes, including compounds of the type of the 5,7-dihydroxychromones: it is generally assumed that a para hydroxyl alkylates more easily than an ortho hydroxyl. However, no sufficiently clear delimitation has been made between the reactions of alkylation in alkaline

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*We may note that the chemical shift (12.3 ppm) of the proton of the hydroxy group in (VIa) scarcely changes with a variation in the concentration of the solutions in methanol from 4.0 to 0.4 M.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1185-1188, September, 1974. Original article submitted November 27, 1973.

TABLE 1. Results of the Competitive Methylation of Mixtures of Monohydroxy derivatives

Mixture of substances	Base	1 g-ion of HO^-		2 g-ions of HO^-	
		yield of ethers, %			
		total*	relative†	total*	relative†
Ia+IIa	NaOH	90	18,5 Ib; 81,5 IIb	98	70 Ib; 30 IIb
IVa+Va	NaOH	76	0 IVb; 100 Vb	67	88,2 IVb; 11,8 Vb
IVa+Va	LiOH	77	26 IVb; 74 Vb	97	85 IVb; 15 Vb
VIa+VIIa	NaOH	74	9 VIb; 91 VIIb	95	51 VIb; 49 VIIb
VIa+VIIa	$(CH_3)_4NOH$	82	16 VIb; 84 VIIb	90	58 VIb; 42 VIIb

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* In all cases, the total yields are given on the mixtures of crude ethers, calculated to 1 mole of phenol.

† The relative yields were determined by means of GLC.

media and methylation with diazomethane. There is no doubt that an ortho hydroxyl participating in a chelate hydrogen bond should react with diazomethane more slowly than a para hydroxy group. When, however, the reaction was performed with acetyl-2,4-dihydroxybenzenes in an alkaline medium, only alkylation in the presence of a weak base or of 1 mole of alkali was considered. Thus, recently a method has been proposed for the selective methyaltion of the 4-OH group in 2,4-dihydroxybenzophenone based on the performance of alkylation in a weakly alkaline medium (pH 7.4-7.8) [4].

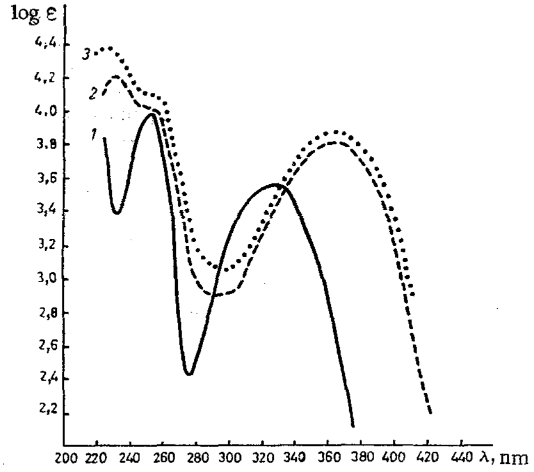

Fig. 1. UV spectra (c $1 \cdot 10^{-4}$-$1 \cdot 10^{-5}$ m): 1) (VIa) (in ethanol), λ_{max} 252, 326 nm (log ε 3.98, 3.55); 2) (VIa) in (59% ethanol + 100 moles of NaOH), λ_{max} 230-232, 360-365 nm (log ε 4.22, 3.81); 3) (VIa) [in 59% ethanol + 100 moles of $(CH_3)_4NOH$], λ_{max} 224-228, 360-365 nm (log ε 4.38, 3.88).

However, the question is justified as to what the relative reactivities of the o- and p-acylhydroxybenzenes will be when they are present completely in the form of the conjugate bases. It is natural to assume that the difference in their ionization constants in itself should not affect the relative rates of alkylation, since as a result of the transformation of these phenols into phenoxides the intramolecular hydrogen bond in the ortho isomers ceases to exist. Consequently, the reactivity of the o- and p-phenoxide ions with respect to an alkylating agent should depend on the corresponding nucleophilicity of these anions. It is true that, according to a widespread opinion [5], the Na salts of 2-acetylhydroxybenzenes have the chelate type of structure through the coordination of the metal with the carbonyl oxygen. But, according to our results, the UV spectra of the sodium and tetramethylammonium salts of (VIa) in 59% ethanol are identical (see Fig. 1, which, for comparison, also gives the spectrum of o-hydroxyacetophenone in a neutral medium), which is evidence against the specific role of sodium in the phenoxide of o-hydroxyacetophenone. Since the phenoxides of the alkali metals (Li, Na, K, Cs) in ethanolic solutions are present in the ionized state in the form of separated ion pairs [6],* it must be considered that the sodium and ammonium phenoxides of (VIa) in aqueous ethanol also exist as separated ion pairs.

By the competitive methylation of the sodium and tetramethylammonium phenoxides of (VIa) and (VIIa) it was shown that the nucleophilicities of these two anions are approximately the same (see Table 1). If, however, 1 mole of alkali was used for a mixture of the two phenols in an amount of 1 mole each, the phenoxide formed from the more acidic p-isomer is alkylated predominantly. The same conclusions can obviously be used in estimating the direction of the alkylation of the compounds of the type of the acyl-2,4-dihydroxybenzenes, including chromones with hydroxy groups in positions 3, 5, and 7.

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*The UV spectra for phenoxides in ethanol and DMFA are different: in the first case there are separated ion pairs, and the phenoxide ion is associated with solvent molecules, and in the second case, unseparated ions pairs predominate [6].

EXPERIMENTAL

GLC was performed on a Khrom-2 instrument. Chromosorbs G, 60/80 mesh, and W, 80/60 mesh, were used as supports, and the stationary phases were poly(tetramethylene succinate) and silicone polymer. The retention times of the second substances with respect to the first were: (Ib, IIb) (1.08; 200°C); (IVb, Vb) (2.16; 165°C); (VIb, VIIb) (1.36; 185°C). The error in the determination amounted to ±0.5-2%.

Methylation of a Mixture of 6-Hydroxy- and 7-Hydroxy-4-methylcoumarins (Ia and IIa). a) With stirring, a solution containing 0.44 g (2.5 mmole) each of (Ia) and (IIa) in 6 ml of DMSO was added to a solution of 0.1 g (2.5 mmole) of NaOH in 1.5 ml of water, and the mixture was cooled to 0°C, and then with stirring 0.33 g (2.6 mmole) of dimethyl sulfate was added dropwise, and the resulting mixture was stirred at 0°C for 6 h and was left at 0°C for ~16 h. After this, 10% NaOH was added, and the product was extracted with dichloroethane, giving 0.43 g of a mixture of (Ib) and (IIb) (see Table 1).

b) A mixture of 2.5 mmole each of (Ia) and (IIa) was methylated with 2.6 mmole of dimethyl sulfate in the presence of 5 mmole of NaOH as described above. This gave 0.47 g of a mixture of (Ib) and (IIb).

Methylation of a Mixture of Phenol (IVa) and p-Nitrophenol (Va). a) With stirring, a solution of 0.94 g (0.01 mole) of (IVa) and 1.38 g (0.01 mole) of (Va) in 12 ml of DMSO and then (at 20°C) 1.39 g (0.011 mole) of dimethyl sulfate were added to a solution of 0.4 g (0.01 mole) of NaOH in 3 ml of water, and the mixture was stirred for 6 h. After the addition of 10% NaOH, it was extracted with petroleum ether (bp ≤ 50°C) or diethyl ether. The organic layer was washed with water and dried, and the solvent was distilled off in a rotating flask without the application of vacuum, giving 1.16 g of (Vb).

b) A mixture of 0.01 mole each of (IVa) and (Va) was methylated with 0.011 mole of dimethyl sulfate in the presence of 0.02 mole of NaOH as described above. This gave 0.75 g of a mixture of (IVb) and (Vb),

c) With stirring, a solution of 0.94 g (0.01 mole) of (IVa) and 1.38 g (0.01 mole) of (Va) in 24 ml of DMSO and then (at 20°C) 1.39 g (0.011 mole) of dimethyl sulfate were added to a solution of LiOH formed by the addition of 0.07 g (0.01 g-atom) of lithium to 6 ml of water. After 75 h (20°C), 2 N KOH was added, and extraction with ether yielded 1.07 g of a mixture of IVb and Vb.

d) A mixture of 0.01 mole of IVa and Va was methylated with 0.011 mole of dimethyl sulfate in the presence of 0.02 mole of LiOH as described above, yielding 1.1 g of a mixture of IVa and Va.

Methylation of a Mixture of o- and p-Hydroxyacetophenones (VIa) and (VIIa). a) With stirring, a solution of 0.34 g (2.5 mmole) each of (VIa) and (VIIa) in 10 ml of DMSO, followed by 0.34 g (2.7 mmole) of dimethyl sulfate, was added to a solution of 0.1 g (2.5 mmole) of NaOH in 10 ml of water, and the mixture was stirred for 1 h and was left for ~16 h (20°C), after which NaOH was added and the products were extracted with ether, giving 0.28 g of a mixture of (VIb) and (VIIb).

b) A mixture of 2.5 mmole each of (VIa) and (VIIa) was methylated with 2.7 mmole of dimethyl sulfate in the presence of 5 mmole of NaOH as described above, giving 0.36 g of a mixture of (VIb) and (VIIb).

c) To 2.5 ml of aqueous solution of tetramethylammonium hydroxide (2.5 mmole) were added 7.5 ml of water and a solution of 0.34 g (2.5 mmole) each of (VIa) and (VIIa) in 10 ml of DMSO and 0.34 g (2.7 mmole) of dimethyl sulfate, and the reaction mixture was stirred for 1 h and left for ~16 h (20°C), after which 0.31 g of a mixture of (VIb) and (VIIb) was isolated as in the preceding experiment.

d) A mixture of 2.5 mmole each of (VIa) and (VIIa) was methylated with 2.7 mmole of dimethyl sulfate in the presence of 5 ml of the same base (5 mmole) with the addition of 5 ml of water as described above. This gave 0.34 g of a mixture of (VIb) and (VIIb).

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