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SOLVATION EFFECTS IN THE METHYLATION OF BARBITURIC ACID AND ITS DERIVATIVES BY DIAZOMETHANE

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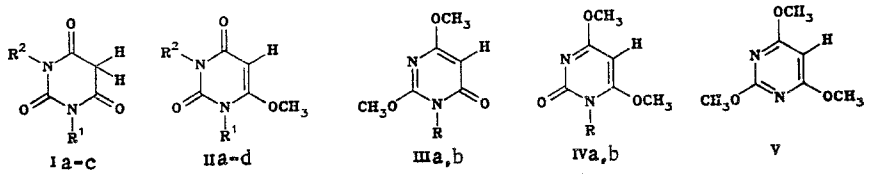
Methylation of barbituric acid and its N-methylderivatives by diazomethane in ethers and methanol occurs only at the oxygen atom of the β-dicarbonyl fragment. The resulting 6-methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine and its derivatives are methylated at both the oxygen and nitrogen atoms; relative to ethers, methanol facilitates a greater degree of methylation at the nitrogen atom.

The mechanism of methylation of acids by diazomethane involves the formation of acid anions [1]. Ionization of barbituric acid (Ia) and its derivatives results in the formation of ambident anions, in which the negative charge is delocalized among the oxygen, nitrogen, and carbon atoms. In ambident anions derived from oxopyrimidines, the oxygen atoms are the "hardest" sites, and the $C_{(5)}$ carbon atom is the "softest" site. Proton donating solvents tend to deactivate to a large extent the hard sites in ambident anions [2, 3], due to hydrogen bonding; thus, methylation of oxopyrimidines in methanol would be expected to lead to an increase in the fraction of alkylation occurring at the soft sites, relative to the corresponding reactions of these compounds in ethers (diethyl ether and 1,2-dimethoxyethane).

In order to determine the qualitative composition of the mixtures formed during the methylation of barbituric acid and its derivatives by diazomethane, we synthesized the following series of model compounds, using known methods:



Ia-c IIa-d IIIa,b IVa,b V

I, II a $R^1=R^2=H$; b $R^1=CH_3$, $R^2=H$; c $R^1=R^2=CH_3$; II d $R^1=H$, $R^2=CH_3$; III, IV a $R=H$, b $R=CH_3$

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TABLE 1. Thin Layer Chromatography and PMR Spectral Data for Hydroxypyrimidines

Compound	R_f*	δ, ppm (DMSO-D_6)**			
		NCH_3	OCH_3	$C_{(5)}H$	NH
Ia	0,35	—	—	3,41 (2H)	11,04 (2H)
Ib	0,48	3,04	—	3,56 (2H)	11,04
Ic	0,76	3,06 (6H)	—	3,65 (2H)	—
IIa	0,11	—	3,74	4,91	10,71
IIb	0,13	3,11	2,82	4,96	11,01
IIc	0,37	3,07; 3,16	3,83	5,17	—
IId	0,22	3,01	3,78	5,00	10,83
IIIa	0,12	—	3,68; 3,76	5,17	—***
IIIb	0,52	3,17	3,68; 3,86	5,24	—
IVa	0,15	—	3,76 (6H)	5,42	11,84
IVb	0,25	3,14	3,75; 3,89	5,54	
V	0,85	—	3,78 (6H); 3,82 (3H)	5,76	—

*In system A, see Experimental.
**All signals are singlets.
***The signal could not be observed, due to exchange.

PMR spectral analysis of the compounds (Table 1) revealed that the $C_{(5)}$ proton signals do not overlap one another for these compounds, which makes it possible to use PMR, along with TLC, to establish both qualitatively and quantitatively the composition of the product mixtures formed in these reactions.

It is possible to introduce no more than three methyl groups into a molecule of barbituric acid by methylation with diazomethane [4]. In complete methylation of acids Ia-c upon reaction in ether solvent resulted from treatment of 1 mole of acid with approximately 1 mole of diazomethane; in methanol solution a 2-3-fold excess of diazomethane was employed, due to its interaction with solvent. Complete methylation was achieved by prolonged treatment of these compounds with a large excess (more than 5 moles) of diazomethane.

It is clear from the results obtained in the incomplete methylation of barbituric acid and its N-methyl derivatives Ib, c (Table 2) that initially reaction takes place at the oxygen atoms of the β-dicarbonyl fragment $O_{(4)}$–$C_{(4)}$–$C_{(5)}$–$C_{(6)}$–$O_{(6)}$. This is consistent with the data obtained for the structures of barbituric acid monoanions [5]. These reactions result in the formation of 6-methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (IIa) or its derivatives IIb-d. Methylation of the $C_{(5)}$ carbon atom is not observed. This can be explained in terms of the large difference in the hardness of the $C_{(5)}$ and oxygen atoms in the β-dicarbonyl fragment. In the methylation of N-methylbarbituric acid (Ib) with diazomethane in ether solvents, isomer IIb is formed in a twofold greater amount than IId (Table 2). In methanol solution, the yields of these two isomers are almost equal, due to specific solvation of the anion of acid Ib.

Since the reaction of barbituric acid with diazomethane resulted only in the formation of 6-methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine, we examined the methylation of this substance, as well as of its possible monomethylation products, namely, IIb, d, IIIa, IVa. Incomplete methylation of 6-methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine in ether solvents gave a product mixture consisting of only one dimethyl derivative IIb, as well as the products of complete methylation, IIIb and V, whereas incomplete methylation in methanol gave compounds IIb, c, IIIb, and IVb (Table 2). Methylation of 1-methyl-6-methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (IIb) with diazomethane gave a mixture of compounds IIc and IVb. Compound IId is methylated to give a mixture of products IIc and IIIb. Methylation of hydroxypyrimidines IIIa and IV leads to a mixture of products IIIb and V, and IVb, and V, respectively. In all cases the yields of methylation products at the nitrogen atoms was significantly greater when the reactions were carried out in methanol than when they were done in ether solvents; this was especially true in the case of pyrimidone IVa (Table 2).

Using the results obtained in the methylation of compounds IIa, b, d, IIa, and IVa, we were able to determine the composition of the product mixture formed in the monomethylation of 6-methoxy-2,4,dioxo-1,2,3,4-tetrahydropyrimidine. Thus, in ether solvents compound IIb

TABLE 2. Methylation of Barbituric Acids and Hydroxypyrimidines by Diazomethane

Starting material	Solvent*	Methylation**	1,2-Dimethoxyethane
Ia	1,2-Dimethoxy	A	IIa (90), Ia (10)
	Ether	B	IIc (34), V (32), IIIb (23), IVb (11)
	Methanol	A	IIa (80), Ia (20)
	Methanol	B	IIc (78), IIIb (16,5), IVb (5), V (0,5)
Ib	Ether	A	IId (62), IIb (28), Ib (10)
	Ether	B	IIc (75), IIIb (19), IVb (6)
	Methanol	A	IIb (43), IId (37), Ib (16), IIc (2)
	Methanol	B	IIc (80), IIIb (15), IVb (5)
Ic	Ether	B	IIc (100)
	Methanol	B	IIc (100)
IIa	Ether	A	IIa (50), IIb (28), V (12), IIIb (10)
	Ether	B	IIc (36), V (30), IIIb (22), IVb (12)
	Methanol	A	IIb (50), IIa (30), IIc (13), IIIb (5), IVb (2)
	Methanol	B	IIc (79), IIIc (16), IVb (4,5), V (0,5)
IIb	Ether	B	IIc (80), IIIb (20)
	Methanol	B	IIc (90), IIIb (10)
IIc	Ether	B	IIc (72), IIIb (28)
	Methanol	B	IIc (85), IIIb (15)
IIIa	Ether	B	IIIb (59), V (41)
	Methanol	B	IIIb (75), V (25)
IVa	Ether	B	V (80), IVb (20)
	Methanol	B	IVb (71), V (29)

*In the case of "ether," the average results obtained in diethyl ether and 1,2-dimethoxyethane are reported; these deviated from one another by less than 3%.
**A, incomplete; B, complete methylation.

is formed in 44% yield, IIIa, 40%, and IVa in 16% yield; in methanol, the products are IIb, 85%, and IIIa, 15%. The yield of compound IIb was based directly on its concentration in the reaction mixture, while the yields of compounds IIIa and IVa were based on the concentration of compounds IIIb and IVb in the mixtures obtained by complete methylation of compound IIa by diazomethane in ether or methanol solvents. Thus, methylation of compound IIa in ether occurs at the $N_{(1)}$, $O_{(2)}$, and $O_{(4)}$ atoms, and does not occur at the $N_{(3)}$ atom; this is completely consistent with the structural data for the monoanion of this compound [6]. Reaction of compound IIa with diazomethane in methanol occurs at the $N_{(1)}$ and $O_{(2)}$ atoms, and the yield of the $O_{(2)}$ methylation product is substantially lower than when the reaction is carried out in ether solvents; methylation at the $O_{(4)}$ atom is not observed under these conditions.

The ratio of methylation products at $N_{(1)}$ and $O_{(2)}$ obtained upon methylation of compound IId with diazomethane in methanol is the same as that produced upon methylation of IIa. This is apparently due to the similarity in the structures of the monoanions of these two compounds [6]. Compound IIb, whose anion has a different structure than that of the anion of IIa, undergoes methylation at the $N_{(3)}$ and $O_{(4)}$ atoms (Table 2).

Complete methylation of barbituric acid or compound IIa with excess diazomethane (greater than 5 mole excess) leads to identical results (Table 2). When the reactions are carried out in ether solvents the total amount of methylation products at oxygen is 66%, the amount of nitrogen methylation products being equal to 34%; in contrast, in methanol the amount of oxygen methylation is 40%, the amount of nitrogen methylation 60%.

Treatment of acid Ia or acids Ib, c with diazomethane results in reaction at only the $O_{(4)}$ or $O_{(6)}$ oxygen atoms. The pyrimidine derivatives IIa, b, d, which are formed in this manner can then undergo further methylation at either oxygen or nitrogen atoms; when the reactions are carried out in methanol, solvation of the oxygen atoms facilitates a higher degree of methylation at the nitrogen atoms of the pyrimidine ring. The composition of the resulting products is in excellent agreement with the structures of the monoanions of the methylated compounds.

EXPERIMENTAL

PMR spectra were obtained on an RYa-2309 (90 MHz) spectrometer using solutions in dimethylsulfoxide-D6 versus HMDS as internal standard. Thin layer chromatography was carried

out on Silufol UV-254 plates in acetone–hexane, 1:1 (A), or ethyl acetate (B) solvent systems.

N-Methylbarbituric (Ib) and N,N-dimethylbarbituric (Ic) acids were prepared from the corresponding substituted ureas according to [4]. 6-Methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (IIa), 3-methyl-6-methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (IId), and 1,3-dimethyl-6-methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (IIc) were prepared from 6-fluoro-2,4-dioxo-1,2,3,4-tetrahydropyrimidine [6], 3-methyl-6-chloro-2,4-dioxo-1,2,3,4-tetrahydropyrimidine [6], and 1,3-dimethyl-6-chloro-2,4-dioxo-1,2,3,4-tetrahydropyrimidine [7], respectively, via treatment with sodium methoxide according to [5]. 1-Methyl-6-methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (IIc) was isolated from the mixture obtained by methylation of barbituric acid with diazomethane in ether according to [8]. 4,6-Dimethoxy-2-oxo-1,2-dihydropyrimidine (IVa) was obtained from the potassium salt of 4,6-difluoro-2-oxodihydropyrimidine [6] by treatment with sodium methoxide [9]; 1-methyl-4,6-dimethoxy-2-oxo-1,2-dihydropyrimidine (IVb) was synthesized by reaction of compound (IVa) with diazomethane in methanol [9]. 1-Methyl-2,4-dimethoxy-6-oxo-1,6-dihydropyrimidine (IIIb) was prepared by isomerization of 2,4,6-trimethoxypyrimidine (V) upon treatment with methyl iodide [8]. 2,4-Dimethoxy-6-oxo-1,6-dihydropyrimidine was obtained from 2,4-dimethoxy-6-fluoropyrimidine [5] by treatment with aqueous base.

Diazomethane was synthesized from chloroform, hydrazine hydrate, and potassium hydroxide in alcohol [10]. The gas which was evolved was bubbled directly into the mixture to be methylated. Diazomethane was added in dosed amounts corresponding to the amount of chloroform used, taking into account that the yield of diazomethane by this method is around 10%, based on iodometric titration data.

Incomplete Methylation of Compounds Ia, b, IIa. A. To a solution or suspension of 0.01 mole compound Ia, b or IIa in 50 ml ether (diethyl ether or 1,2-dimethoxyethane) over 3-5 min was added approximately 0.01 mole diazomethane with stirring at 20°C. After the yellow color of the solution had dissipated the solvent was evaporated under vacuum and the residue was analyzed by TLC and PMR. In diethyl ether the reaction requires 1-2 h, in 1,2-dimethoxyethane, several minutes only, due to the greater solubility of the pyrimidine derivatives in the latter solvent.

A'. Methylation in methanol was carried out with a 2-3-fold excess of diazomethane, due to its reaction with methanol. To a solution containing 0.01 mole compound Ia, IIb, or IIa in 40-50 ml methanol was added over 5-7 min 0.02-0.003 mole diazomethane. The reaction proceeds practically instantaneously. The reaction mixture was worked up as described above.

Complete Methylation of Compounds Ia-c, IIa-c, IIIa, and IV. B. A solution or suspension of 0.01 mole of the appropriate compound in 50 ml ether was saturated with diazomethane and allowed to stand for one day at 20°C. In the case of compounds Ia, b, IIa, c, methylation required 10 days, and the solutions were freshly saturated each day. Further treatment was analogous to that written above.

B'. To a solution or suspension of 0.01 mole compound in 30-40 ml methanol was added diazomethane at 20°C; the mixture was then cooled with water until no more nitrogen evolved and the solution had a stable yellow color. After the reaction was complete the solvent was evaporated under vacuum and the residue was analyzed by TLC and PMR (Tables 1 and 2).

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