SYNTHESIS, STRUCTURE, AND CARBAMOYLATION OF 5-ALKYL-$N_{(1)}$-(β-HYDROXYETHYL)-4,5-DIHYDRO-1,2,4-TRIAZIN-6-ONES

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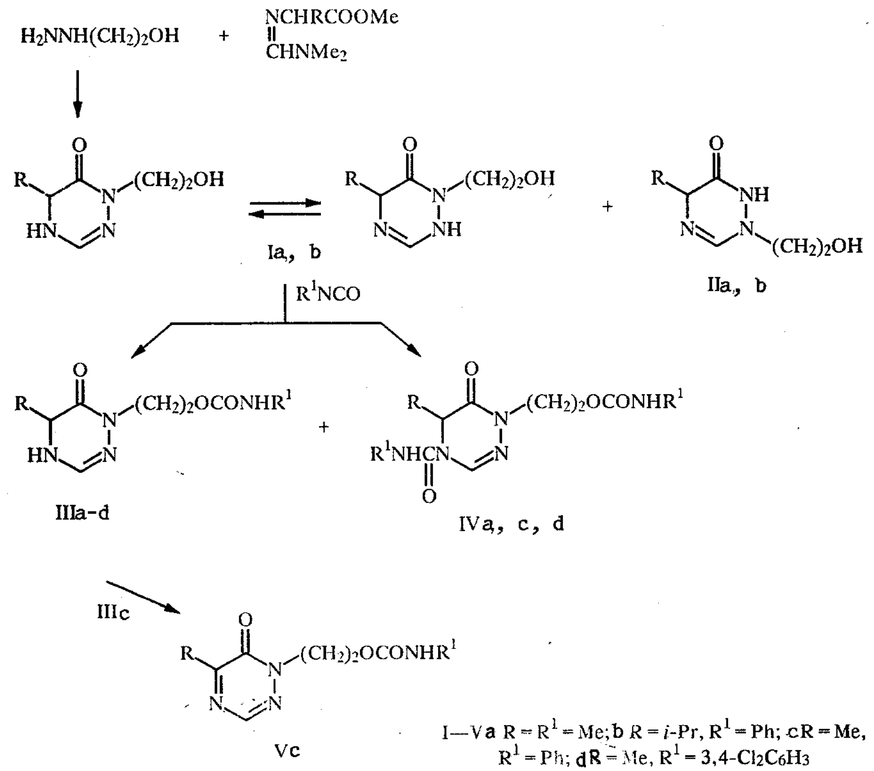
The condensation of methyl α-(dimethylaminomethyleneamino)alkanoates with β-hydroxyethylhydrazine gave the isomeric $N_{(1)}$*- and* $N_{(2)}$*-(β-hydroxyethyl)-5-alkyl-4,5-dihydro-1,2,4-triazin-6-ones. It was shown by IR spectroscopy that the products exist in the form of betaines both in solution and in the crystalline state. The reaction of the* $N_{(1)}$ *isomers with alkyl and aryl isocyanates leads to the formation of mono- or dicarbamoyl-substituted triazines. The preferred reaction path involves carbamoylation of the β-hydroxyethyl group.*

Earlier we reported on the synthesis of some 5-alkyl-4,5-dihydro-1,2,4-triazin-6-ones and their reactions with electrophilic reagents (alkyl halides, ethoxymethyldiethylamine, alkyl and aryl isocyanates) [1]. In a continuation of these researches in the present work we synthesized functionally substituted $N_{(1)}$-(β-hydroxyethyl)-4,5-dihydro-1,2,4-triazin-6-ones (Ia, b) and studied their behavior in carbamoylation.

The triazines (I, II) were obtained by the condensation of methyl α-(dimethylaminomethyleneamino)alkanoates with β-hydroxyethylhydrazine by the method in [2].



I—Va $R = R^1 = Me$; b $R = i\text{-}Pr$, $R^1 = Ph$; c $R = Me$, $R^1 = Ph$; d $R = Me$, $R^1 = 3,4\text{-}Cl_2C_6H_3$

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TABLE 1. Characteristics and IR Spectra of the Triazines (I-V)

Compound	Molecular formula	mp, °C or n_D^{20}	IR spectrum, ν, cm^{-1}*			R_f (1:1 hexane–acetone)	Yield, %
			CO	C=N	NH (CCl_4)		
Ia	$C_6H_{11}N_3O_2$	1,5321	1655	1600	3449	**	74
Ib	$C_8H_{15}N_3O_2$	108...110	1655	1598	3450	**	73
IIa	$C_6H_{11}N_3O_2$	174...178	—	—	—	**	2
IIb	$C_8H_{15}N_3O_2$	188...191	—	—	—	**	4
IIIa	$C_8H_{14}N_4O_3$	104...107	1715, 1665	1625	3440, 3470	0,08	59
IIIb	$C_{15}H_{20}N_4O_3$	115...117	1730, 1665	1630	3450	0,33	57
IIIc	$C_{13}H_{16}N_4O_3$	Oil	1730, 1665	1635	3440	0,38	30
IIId	$C_{13}H_{14}Cl_2N_4O_3$	134...136	1725, 1660	1625	3440	0,27	67
IVa	$C_{10}H_{17}N_5O_4$	1,5020	1730...1680 bs	1640	3460, 3360 bs	0,17	94
IVc	$C_{20}H_{21}N_5O_4$	Oil	1730 bs 1665	1630	3440, 3320 bs	0,70	13
IVd	$C_{20}H_{17}Cl_4N_5O_4$	158...160	1725, 1700, 1655	1630	3440, 3370 bs	0,52	21
Vc	$C_{13}H_{14}N_4O_3$	100...102	1730, 1655	1630	3440	0,70	—

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*The spectra of compounds (Ia, b, IIIa, d, IVa, d, Vc) were recorded in tablets with potassium bromide, and those of compounds (IIIb, c, IVc) were recorded in chloroform.

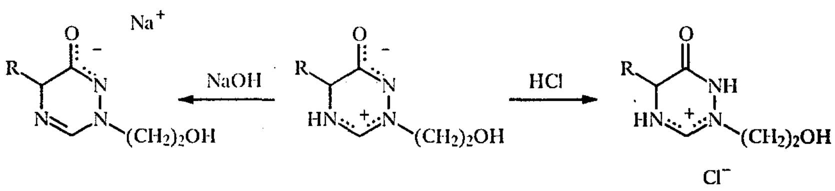
**The reference spots.

The reaction leads to the preferential formation of the triazines (I). The isomeric triazines (II) were isolated as impurities. Thus, when the initial components were boiled in acetonitrile, 5-alkyl-$N_{(2)}$-(β-hydroxyethyl)-2,5-dihydro-1,2,4-triazin-6-ones (II) were isolated in the analytically pure form with yields of about 4%. When the solvent was evaporated, the isomers (I) were isolated with yields of about 75%. The triazines (II) are characterized by higher melting points than the isomers (I) and by the absence of solubility in polar aprotic solvents.

Significant differences were observed in the IR spectra of the isomeric diazines. The IR spectrum of the triazine (Ia) (in tablets with potassium bromide) contained strong bands at 1655 cm^{-1} (C=O) and 1600 cm^{-1} (C=N). The last band was stronger in the Raman spectrum, and this confirms its assignment to the stretching vibrations of the C=N bond. Analysis of the IR spectra of the triazine (Ia) in the region of 1500-1800 cm^{-1} showed that the $\nu_{C=N}$ frequency depended more on the nature of the solvent and the state of aggregation of the substance than the $\nu_{C=O}$ frequencies. Whereas the $\nu_{C=N}$ value changed from 1605 cm^{-1} in D_2O solution to 1640 cm^{-1} in dioxane, the $\Delta\nu_{C=O}$ value in these solvents amounted to 8 cm^{-1}. In the IR spectra of the triazine (Ia) in solutions in THF and diglyme there were two bands for the C=N stretching vibrations at 1640 and 1625 cm^{-1}, and this may be explained by the existence of the compound as mixture of two tautomeric forms. In other solvents (chloroform, dioxane, DMSO, methanol, D_2O) only one of the forms is present.

In the region of the NH and OH stretching vibrations (in tablets with potassium bromide) there is a group of strong bands at 3290, 3230, and 3065 cm^{-1}, corresponding to the vibrations of these groups involved in the formation of hydrogen bonds. After dilution in carbon tetrachloride solution a narrow NH band is observed at 3449 cm^{-1}, and there is a broad band centered at ~3470 cm^{-1} and belonging to the stretching vibrations of the hydroxy group involved in the formation of an intramolecular hydrogen bond apparently with the $N_{(2)}$ nitrogen atom. In dioxane solution there are two bands in this region at 3340 and 3466 cm^{-1}. Since dioxane is a solvent capable of forming a hydrogen bond, the ν_{NH} frequency in this solvent should not be higher than the frequency of the free NH group in dilute solution in the inert solvent carbon tetrachloride. Consequently the more low-frequency band of the two bands observed in dioxane solution belongs to the NH stretching vibrations. The ν_{OH} band in dioxane solution has the same frequency as in carbon tetrachloride solution.

Analysis of the IR spectra of the isomeric triazines (II) makes it possible to suppose that they exist in the form of betaines both in the crystalline state and in solution (D_2O, methanol). The IR spectra of these compounds (in tablets with potassium bromide) contain strong absorption in the region of 2880-2200 cm^{-1}, indicating a salt-like structure containing the $^{+}$NH group [3].



The strong absorption at 1685 cm^{-1} can be assigned to the stretching vibrations of the C═NH double bond. The symmetric and asymmetric vibration of the O═C═N anion correspond to strong bands at 1520 and 1430 cm^{-1}, while the hydroxy group connected by a hydrogen bond corresponds to a band at 3200 cm^{-1}. In D_2O solution there are characteristic bands at 1680, 1535, and 1450 cm^{-1}, which make it possible to conclude that the triazines (II) exist in one form both in the crystalline state and in solution. Acidification of the solution leads to the appearance of bands at 1660 cm^{-1} (C═O) and 1704 cm^{-1} ($C{=}N^+H$). Similar absorption was assigned to the vibrations of the $C{=}N^+H$ bond in the hydrochlorides of amidoximes [4]. In an alkaline medium the triazine (II) undergoes deprotonation, the band at 1704 cm^{-1} ($C{=}N^+H$) disappears, and a band appears at 1605 cm^{-1}, coinciding with the C═N absorption in the triazines (I). Bands in the regions of 1535 and 1439 cm^{-1} characterize the O═C═N anion. The betaine form is probably characteristic of all the $N_{(2)}$-alkyl-substituted 2,5-dihydro-1,2,4-triazin-6-ones. In [5] it was concluded that $N_{(2)}$-methyl-5-alkyl-3-benzyl-2,5-dihydro-1,2,4-triazin-6-ones have a betaine structure.

The physicochemical constants and the IR and PMR spectra of the triazines (I, II) are given in Tables 1, 2.

The mass spectra of the triazines (I) contain $M^{+\cdot}$ peaks with intensities of 6% for (Ia) and 50% for (Ib). Their dissociation mostly takes place with the ejection of the β-hydroxyethyl substituent in compound (Ia) (m/z 44, 100%) or the isopropyl group in compound (Ib) ($M - C_3H_7$, m/z 142, 100%). The fragmentation of the triazine ring takes place in two main directions. First, the C—C bond of the β-hydroxyethyl substituent is cleaved, and the obtained $[M - CH_2OH]^{+\cdot}$ ion undergoes stepwise dissociation (Φ_1) → $[\Phi_1 - CO]^+$ (Φ_2) → $[\Phi_2 - CH_2{=}N{-}N{=}CH]^+$ (Φ_3). The second direction involves dissociation of the heterocyclic $[M - CH_2{=}CHOH]^{+\cdot}$ ion for (Ia) or the $[M - R{-}CH_2{=}CHOH]^+$ ion for (Ib) at the $C_{(6)}N_{(1)}$ and $C_{(3)}N_{(4)}$ bonds.

The acylation of the triazines (I) by alkyl and aryl isocyanates was also studied. In the initial triazines there are two reaction centers capable of entering into nucleophilic addition with isocyanates, i.e., the oxygen atom of the hydroxy group and the $N_{(4)}$ nitrogen atom. It was, therefore, necessary to expect the formation of O- and N-carbamoylation products.

The reaction was conducted in acetonitrile at 40-50°C in the presence of triethylamine. It was observed that the reaction time depended on the nature of the isocyanate, the substituent R in the initial triazine, and the reagent ratio.

Only the carbamate (IIIa) was formed during the reaction of the triazine (Ia) with methyl isocyanate in a ratio of 1:1. The disubstitution product (IVa) was obtained with a high yield when a larger excess of methyl isocyanate was used. In reactions with phenyl and 3,4-dichlorophenyl isocyanates (1:1) the triazine (Ia) formed a mixture of monocarbamoylation (IIIc, d) and dicarbamoylation (IVc, d) products. With an excess of the triazine (Ia) the reaction with 3,4-dichlorophenyl isocyanate led to the formation of only the O-carbamoylated compound (IIId). With phenyl isocyanate (1:1) the triazine (Ib) only formed the carbamate (IIIb). In this case reaction at the $N_{(4)}$ nitrogen atom is probably prevented by the presence of the bulky isopropyl group at the $C_{(5)}$ carbon atom.

It is known that polyfunctional compounds (ethanolamine, hydroxylamine) react with isocyanates primarily at the nucleophilic hydrogen atom of the amino group [6,7]. The preferential formation of the O-carbamoylation products in our case may indicate reduced nucleophilic character for the $N_{(4)}$ nitrogen atom in the cyclic system of 5-alkyl-4,5-dihydro-1,2,4-triazin-6-one.

The carbamoylated triazine (IIIc) is an unstable compound, and during purification on silica gel or on standing in solution at room temperature it is oxidized to the aromatic triazine (Vc). Immediately after chromatographic separation of the reaction mixture on silica gel the carbamate (IIIc) was characterized by the PMR spectrum, which confirmed its structure (Table 2). The carbamate (IIIc) is a thick oil; during an attempt to crystallize it by dissolving it in ether, followed by cooling, a small amount of the crystalline triazine (Vc), the PMR spectrum of which differed significantly from the spectrum of the triazine (IIIc) (Table 2), was isolated from the solution. The PMR spectrum of the dicarbamoylation product (IVc), recorded immediately after separation on silica gel also contained signals for compound (Vc), amounting to about 20%. It was not possible to separate the compounds on account of the identical R_f values. These processes probably explain the fact that it was impossible to isolate compounds (IIIc, IVc) in the analytically pure form.

TABLE 2. PMR Spectra of the Triazines (I-V)

Compound	Chemical shifts δ, ppm (J, Hz)*							
	3-H	5-H	R	NCH_2	OCH_2	$N_{(4)}H$, bs	R^1NH, bs	R^1
Ia	7,00 s	4,21 m	1,28 (3H, d, J=7,1, CH_3)	3,56 m	3,68 m	—	—	—
Ib	6,92 d (J=4,1)	3,77 qd (J=2,0 J=3,4)	0,91 (3H, d, J=7,3, CH_3); 0,95 (3H, d, J=7,3, CH_3); 2,16 (1H, qd, J=3,4, J=7,3, CH)	3,14 m	3,67 m	6,51	—	—
IIa	7,04 s	4,14 q	1,33 (3H, d, J=7,0, CH_3)	3,75 (4H, m, NCH_2CH_2O)		—	—	—
IIb	7,96 s	3,75 q	0,92 (3H, d, CH_3); 0,95 (3H, d CH_3); 2,16 (1H, qd, CH)	3,55 m	3,80 m	—	9,16	—
IIIa	6,74 d	3,97 q	1,32 (3H, d, CH_3)	3,82 q	4,12 q	5,72	6,21	2,66 (3H, d, CH_3)
IIIb	6,92 d	3,96 q	0,88 (3H, d, CH_3); 0,92 (3H, d, CH_3); 2,15 (1H, m, CH)	3,82 m	4,28 m	6,57	8,68	7,26...7,60 (5H, m, C_6H_5)
IIIc	6,91 d	4,06 q	1,28 (3H, d, CH_3)	3,78 m	4,25 m	6,41	8,65	7,25...7,60 (5H, m, C_6H_5)
IIId	6,77 s	4,05 m	1,29 (3H, d, CH_3)	3,82 m	4,23 m	6,25	8,78	7,27...7,72 (3H, m, $C_6H_3Cl_2$)
IVa	7,57 s	4,58 m	1,24 (3H, d, CH_3)	3,85 m	4,19 m	—	6,13 (1H); 6,86 (1H)	2,65 (3H, d, CH_3); 2,79 (3H, d, CH_3)
IVc	7,76 s	4,74 m	1,32 (3H, d, CH_3)	3,98 m	4,40 m	—	8,78 (1H); 8,81 (1H)	7,01...7,56 (10H, m, C_6H_5)
IVd	7,72 s	4,65 m	1,30 (3H, d, CH_3)	3,95 m	4,48 m	—	7,97 (1H); 7,99 (1H)	7,26...7,72 (6H, m, $C_6H_3Cl_2$)
Vc	8,07 s	—	2,36 (3H, s, CH_3)	3,75 m	4,45 m	—	8,60	7,21...7,50 (5H, m, C_6H_5)

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*The spectra of compounds (Ib, IIIa-Vc) were recorded in acetone-d_6, the spectra of compounds (Ia, IIa) were recorded in D_2O, and the spectrum of (IIb) was recorded in methanol-d_4.

The structure of the carbamoylated triazines was proved by means of the IR and PMR spectra (Tables 1 and 2). In the IR spectra of the triazines (III) a high-frequency band for the CO stretching vibrations appears at 1715-1730 cm^{-1}, characteristic of urethanes. In the PMR spectra of these compounds the broad singlet of the $N_{(4)}H$ proton and the doublet character of the $C_{(3)}H$ proton with a chemical shift close to or coinciding in value with $\delta C_{(3)}H$ for the initial triazines are retained. The signals for the NH protons of the carbamate and urea fragments lie in the downfield region compared with the $N_{(4)}H$ signal.

The mass spectra of the carbamates (III) contain $M^{+\cdot}$ peaks with intensities of 23-51%. The common initial process in the dissociation of $M^{+\cdot}$ under electron impact is cleavage of the ester bond and the formation of ions corresponding to $[R'NCO]^{+\cdot}$ and $N_{(1)}$-vinyltriazines. The low intensity of the $M^{+\cdot}$ peak in the spectrum of the triazine (IIIc) (2%) confirms its low stability. The intensity of the $[M - 2]^{+\cdot}$ ion, which correspond to the aromatic triazine (Vc), amounts to 37% (100% at 15 eV). The dicarbamoylated triazines (IV) do not form $M^{+\cdot}$ ions. The initial process in their dissociation probably involves elimination of the carbamoyl group from the $N_{(4)}$ nitrogen atom and subsequently coincides with the fragmentation of the monocarbamoylated compounds (III).

EXPERIMENTAL

The absorption spectra were obtained on a Bruker IFS-45 Fourier spectrometer and on a Perkin-Elmer 457 instrument. The Raman spectra were recorded on a Coderg T-800 instrument. The PMR spectra were obtained on WM-250 (250 MHz) and XL-400 (400 MHz) spectrometers with TMS as internal standard. The mass spectra were obtained on an LKB-20-91 instrument with direct injection at 15 and 70 eV. Compounds (III-V) were isolated by preparative TLC on plates with Silpearl 245 in a 1:1 mixture of hexane and acetone. The purity of the compounds was monitored by TLC on Silufol UV-254 plates in 3:2 or 1:1 mixtures of hexane and acetone.

The elemental analyses corresponded to the calculated data. The characteristics and the IR and PMR spectra of compounds (I-V) are given in Tables 1 and 2.

1(2)-N-(β-Hydroxyethyl)-5-alkyl-4,5(2,5)-dihydro-1,2,4-triazin-6-ones (Ia, b, IIa, b). A mixture of 0.025 mole of the methyl dimethylaminoethyleneaminoalkanoate and 0.025 mole of freshly distilled β-hydroxyethylhydrazine in 30 ml of dry acetonitrile was heated at 80°C in a stream of nitrogen for 8 h. The reaction mass was cooled, the crystals of the triazines (IIa, b) were separated, the filtrate was evaporated, and the residue was treated with boiling ether (3 × 20 ml) and dissolved in acetone without heat. After evaporation of the acetone the triazines (Ia, b) were isolated (Table 1).

1-[β-(N-Methylcarbamoyl)hydroxyethyl]-5-methyl-4,5-dihydro-1,2,4-triazin-6-one (IIIa). A mixture of 0.4 g (3.0 mmole) of the triazine (Ia), 0.17 g (3.0 mmole) of methyl isocyanate, and a catalytic amount of triethylamine in 25 ml of acetonitrile was stirred at room temperature for 1 h and was then kept at 40°C for 7 h. The solvent was evaporated, and the residue was crystallized from ether with the addition of chloroform.

1-[β-(N-Methylcarbamoyl)hydroxyethyl]-4-methylcarbamoyl-5-methyl-4,5-dihydro-1,2,4-triazin-6-one (IVa). A mixture of 0.4 g (3.0 mmole) of the triazine (Ia), 0.86 g (1.5 mmole of methyl isocyanate, and two drops of triethylamine in 25 ml of acetonitrile was kept at room temperature for 7 days and at 40°C for 7 h. The solvent was evaporated, the residue was extracted with chloroform, and the triazine (IVa) was isolated.

1-[β-(N-Phenylcarbamoyl)hydroxyethyl]-5-isopropyl-4,5-dihydro-1,2,4-triazin-6-one (IIIb). A mixture of 0.8 g (4.0 mmole) of triazine (Ib), 0.5 g (4.0 mmole) of phenyl isocyanate, and two drops of triethylamine in 30 ml of acetonitrile was heated at 50°C for 12 h. The reaction mass was cooled, the diphenylurea (0.05 g) was separated, and the filtrated was evaporated. The residue was submitted to chromatographic separation, and 0.44 g of the carbamate (IIIb), 0.08 g of diphenylurea, and 0.33 g of the initial triazine (Ib) were obtained.

1-[β-(N-Arylcarbamoyl)hydroxyethyl]-5-methyl-4,5-dihydro-1,2,4-triazin-6-ones (IIIc, d) and 1-[β-(N-Arylcarbamoyl)hydroxyethyl]-4-(N-arylcarbamoyl)-5-methyl-4,5-dihydro-1,2,4-triazin-6-ones (IVc, d). A mixture of 9.5 mmole of the triazine (Ia), 9.5 mmole of the aryl isocyanate, and 2 drops of triethylamine in 25 ml of acetonitrile was heated at 45-50°C for 8-10 h. The solvent was evaporated, the residue was chromatographed on silica gel, and the triazines (IIIc, d, IVc, d) were isolated (Tables 1 and 2).

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