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1,1,2-TRICARBAMOYL-2-CYANOETHANE IN CONDENSATION PROCESSES WITH ALDEHYDES

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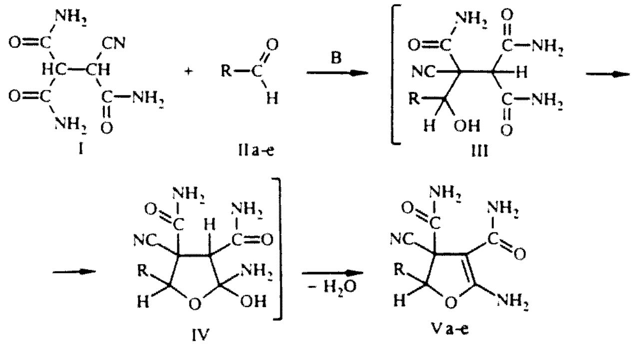
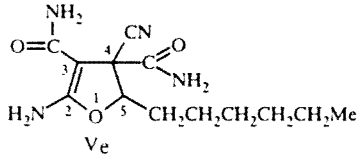
5-Alkyl-2-amino-3,4-dicarbamoyl-4-cyano-4,5-dihydrofurans were synthesized by the reaction of 1,1,2-tricarbamoyl-2-cyanoethane with carbonyl compounds in the presence of catalytic amounts of triethylamine in an aqueous medium. The structure of the dihydrofuran (Vb) was proved by x-ray crystallographic investigation of a single crystal.

Earlier the synthesis of 1,1,2-tricarbamoyl-2-cyanoethane (I) by the hydrolysis of symmetrical tetracyanoethane in the presence of pyruvic acid (III) was reported. Compound (I), which is a CH acid, has the broadest synthetic prospects connected with the possibility of intramolecular cyclization both at the amide fragments and at the cyano group.

As the simplest subjects for investigation of the transformations of the triamide (I) we chose carbonyl compounds and their nitrogen derivatives (azomethines). Being, probably, a fairly weak CH acid, and also as a result of poor solubility compound does not react with carbonyl compounds when they are mixed in a solvent. However, with a catalytic amount of a base it was possible to bring the triamidoethane into reaction with aldehydes (II). As a result of reaction in aqueous acetonitrile or aqueous isopropyl alcohol, which probably takes place through the intermediates (III) and (IV), the 5-alkyl-2-amino-3,4-dicarbamoyl-4-cyano-4,5-dihydrofurans (Va-e) were isolated. The structure of the dihydrofuran (Vb) was established by x-ray crystallographic investigation of a single crystal (Fig. 1 and Tables 3-5).



The data from the ^{13}C NMR spectrum of the dihydrofuran (Ve) agree with the proposed structure.



Ve

Ve δ, ppm: $C_{(2)}$ 169,83; $C_{(3)}$ 79,64; $C_{(4)}$ 58,96; $C_{(5)}$ 84,96; C(CN) 117,58; $C(CONH_2)$ 166,72; 166,84; $C(CH_2)$ 32,32; 31,22; 28,44; 84,80; 22,18; $C(CH_3)$ 14,12

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*Deceased.

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TABLE 1. Characteristics of 5-Alkyl-2-amino-3,4-dicarbamoyl-4-cyano-4,5-dihydrofurans (Va-e)

Compound	R	Molecular formula	mp, °C (solvent)	Yield, %
Va	CH_3	$C_8H_{10}N_4O_3$	195...200 (decomp.) (from CH_3CN-H_2O, 1 : 1)	58
Vb	*n*-C_3H_7	$C_{10}H_{14}N_4O_3$	188...190 (from H_2O)	26
Vc	*i*-C_3H_7	$C_{10}H_{14}N_4O_3$	168...170 (from H_2O)	22
Vd	*n*-C_4H_9	$C_{11}H_{16}N_4O_3$	156...158 (from H_2O)	22
Ve	*n*-C_6H_{13}	$C_{13}H_{20}N_4O_3$	171...173 (from CH_3CN-H_2O, 1 : 4)	12

TABLE 2. Parameters of the IR and Mass Spectra of Dihydrofurans (Va-e)

Compound	IR spectra, cm^{-1}					Mass spectra,* *m/z* (relative intensity, %)
	ν_{NH}	$\nu_{C\equiv N}$	$\nu_{C=O}$	δ_{NH}	$\nu_{C=C}$	
Va	3415, 3310, 3200	2254	1675, 1645	1630, 1625	1595	210 (2), 193 (9), 183 (11), 167 (19), 165 (96), 150 (11), 149 (23), 140 (11), 122 (48), 52 (52), 44 (100)
Vb	3430, 3310, 3200	2250	1675, 1645	1625, 1615	1575	238 (2), 236 (85), 219 (9), 193 (24), 166 (12), 165 (11), 135 (15), 121 (13), 79 (17), 55 (23), 44 (100)
Vc	3470, 3420, 3315, 3210	2255	1675, 1650	1615, 1600	1575	238 (0,5), 221 (4), 211 (3), 196 (4), 195 (10), 194 (55), 160 (27), 151 (23), 135 (21), 123 (13), 43 (100)
Vd	3440, 3330, 3270	2250	1675, 1645	1615, 1610	1585	252 (1), 225 (2), 209 (15), 208 (100), 191 (9), 174 (18), 165 (32), 148 (7), 106 (8), 79 (11), 55 (9)
Ve	3445, 3330, 3260, 3170	2250	1675, 1650	1625, 1610	1585	280 (0,5), 257 (6), 238 (15), 237 (20), 221 (33), 145 (77), 194 (100), 180 (31), 164 (73), 163 (61), 123 (81)

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*Molecular ion peak and the 10 strongest fragment peaks are given.

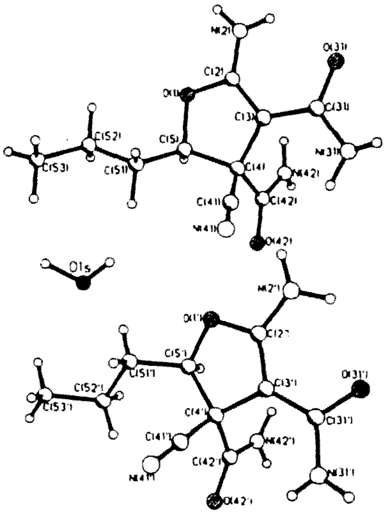

Fig. 1. Independent part of the crystal structure of compound (Vb).

The results of IR and mass spectrometry (Table 2) of compounds (Va,c,d) agree with the spectral data of compounds (Vb,d).

TABLE 3. Bond Lengths in the Molecule of (Vb)

Bond	d, Å	Bond	d, Å	Bond	d, Å
$O_{(1)}$—$C_{(2)}$	1,353(5)	$N_{(42')}$—$C_{(42')}$	1,319(5)	$C_{(1)}$—$C_{(52)}$	1,529(6)
$O_{(31)}$—$C_{(31)}$	1,255(5)	$C_{(3')}$—$C_{(4')}$	1,511(5)	$O_{(1')}$—$C_{(2')}$	1,354(5)
$N_{(2)}$—$C_{(2)}$	1,306(5)	$C_{(4')}$—$C_{(5')}$	1,571(5)	$O_{(31')}$—$C_{(31')}$	1,254(5)
$N_{(41)}$—$C_{(41)}$	1,142(5)	$C_{(4')}$—$C_{(42')}$	1,549(5)	$N_{(2')}$—$C_{(2')}$	1,328(5)
$C_{(2)}$—$C_{(3)}$	1,376(5)	$C_{(51')}$—$C_{(52')}$	1,523(6)	$N_{(41')}$—$C_{(41')}$	1,141(5)
$C_{(3)}$—$C_{(31)}$	1,438(5)	$O_{(1)}$—$C_{(5)}$	1,450(5)	$C_{(2')}$—$C_{(3')}$	1,363(6)
$C_{(4)}$—$C_{(41)}$	1,478(6)	$O_{(42)}$—$C_{(42)}$	1,236(5)	$C_{(3')}$—$C_{(31')}$	1,431(6)
$C_{(5)}$—$C_{(51)}$	1,493(6)	$N_{(31)}$—$C_{(31)}$	1,343(5)	$C_{(4')}$—$C_{(41')}$	1,484(5)
$C_{(52)}$—$C_{(53)}$	1,513(6)	$N_{(42)}$—$C_{(42)}$	1,301(5)	$C_{(5')}$—$C_{(51')}$	1,504(5)
$O_{(1')}$—$C_{(5')}$	1,453(5)	$C_{(3)}$—$C_{(4)}$	1,504(5)	$C_{(52')}$—$C_{(53')}$	1,509(7)
$O_{(42')}$—$C_{(42')}$	1,220(5)	$C_{(4)}$—$C_{(5)}$	1,587(5)		
$N_{(31')}$—$C_{(31')}$	1,336(5)	$C_{(4)}$—$C_{(42)}$	1,556(5)		

TABLE 4. Bond Angles in the Molecule of (Vb)

Angle	ω, deg	Angle	ω, deg
$C_{(2)}$—$O_{(1)}$—$C_{(5)}$	109,8(3)	$O_{(1)}$—$C_{(2)}$—$N_{(2)}$	116,8(3)
$O_{(1)}$—$C_{(2)}$—$C_{(3)}$	113,5(3)	$N_{(2)}$—$C_{(2)}$—$C_{(3)}$	129,7(3)
$C_{(2)}$—$C_{(3)}$—$C_{(4)}$	109,3(3)	$C_{(2)}$—$C_{(3)}$—$C_{(31)}$	122,0(3)
$C_{(4)}$—$C_{(3)}$—$C_{(31)}$	128,7(3)	$C_{(3)}$—$C_{(4)}$—$C_{(5)}$	101,6(3)
$C_{(3)}$—$C_{(4)}$—$C_{(41)}$	111,8(3)	$C_{(5)}$—$C_{(4)}$—$C_{(41)}$	111,1(3)
$C_{(3)}$—$C_{(4)}$—$C_{(42)}$	114,9(3)	$C_{(5)}$—$C_{(4)}$—$C_{(42)}$	107,4(3)
$C_{(41)}$—$C_{(4)}$—$C_{(42)}$	109,7(3)	$O_{(1)}$—$C_{(5)}$—$C_{(4)}$	105,6(3)
$O_{(1)}$—$C_{(5)}$—$C_{(51)}$	109,6(3)	$C_{(4)}$—$C_{(5)}$—$C_{(51)}$	116,0(3)
$O_{(31)}$—$C_{(31)}$—$N_{(31)}$	121,0(3)	$O_{(31)}$—$C_{(31)}$—$C_{(3)}$	119,9(3)
$N_{(31)}$—$C_{(31)}$—$C_{(3)}$	119,1(3)	$N_{(41)}$—$C_{(41)}$—$C_{(4)}$	176,2(4)
$O_{(42)}$—$C_{(42)}$—$N_{(42)}$	125,1(3)	$O_{(42)}$—$C_{(42)}$—$C_{(4)}$	119,5(3)
$N_{(42)}$—$C_{(42)}$—$C_{(4)}$	115,4(3)	$C_{(5)}$—$C_{(51)}$—$C_{(52)}$	113,8(3)
$C_{(51)}$—$C_{(52)}$—$C_{(53)}$	112,4(4)	$C_{(2')}$—$O_{(1')}$—$C_{(5')}$	108,6(3)
$O_{(1')}$—$C_{(2')}$—$N_{(2')}$	115,0(3)	$O_{(1')}$—$C_{(2')}$—$C_{(3')}$	113,7(3)
$N_{(2')}$—$C_{(2')}$—$C_{(3')}$	131,3(4)	$C_{(2')}$—$C_{(3')}$—$C_{(4')}$	109,0(3)
$C_{(2')}$—$C_{(3')}$—$C_{(31)}$	123,6(4)	$C_{(4')}$—$C_{(3')}$—$C_{(31')}$	127,3(3)
$C_{(3')}$—$C_{(4')}$—$C_{(5')}$	100,9(3)	$C_{(3')}$—$C_{(4')}$—$C_{(41')}$	109,9(3)
$C_{(5')}$—$C_{(4')}$—$C_{(41')}$	111,4(3)	$C_{(3')}$—$C_{(4')}$—$C_{(42')}$	114,8(3)
$C_{(5')}$—$C_{(4')}$—$C_{(42')}$	112,9(3)	$C_{(41')}$—$C_{(4')}$—$C_{(42')}$	106,9(3)
$C_{(1')}$—$C_{(5')}$—$C_{(4')}$	105,4(3)	$O_{(1')}$—$C_{(5')}$—$C_{(51')}$	108,6(3)
$C_{(4')}$—$C_{(5')}$—$C_{(51')}$	117,6(3)	$O_{(31')}$—$C_{(31')}$—$N_{(31')}$	119,7(4)
$O_{(31')}$—$C_{(31')}$—$C_{(3')}$	121,3(4)	$N_{(31')}$—$C_{(31')}$—$C_{(3')}$	119,0(3)
$N_{(41')}$—$C_{(41')}$—$C_{(4')}$	176,8(4)	$O_{(42')}$—$C_{(42')}$—$N_{(42')}$	112,0(4)
$O_{(42')}$—$C_{(42')}$—$C_{(4')}$	119,5(4)	$N_{(42')}$—$C_{(42')}$—$C_{(4')}$	116,3(3)
$C_{(5')}$—$C_{(51')}$—$C_{(52')}$	114,0(3)	$C_{(51')}$—$C_{(52')}$—$C_{(53')}$	112,0(4)

From the structure of compounds (Va-e) we suppose that the described reaction takes place through nucleophilic addition of the triamide (I) at the carbonyl group by the stronger CH acid center. The adduct (III) then undergoes intramolecular cyclization with the participation of one of the terminal carbamoyl groups and forms the tetrahydrofuran (IV). This process is similar to the hydrolysis of amides, but in this case stabilization by the elimination of water to the dihydrofuran (V) is probably preferred to the formation of the corresponding lactone.

As expected, aldehydes enter into this reaction more readily than ketones, with which it was not possible to isolate the desired compounds — most of the reactions with ketones lead to resinous masses, which cannot be identified.

The stage of the formation of the adduct (III) is fairly fast; the initial substances dissolve in several minutes and are not detected in the reaction mass. The cyclization and the elimination of water probably take place slowly. Compounds (Vb-e) crystallized out after 14-20 days with the formation of a large amount of resinous decomposition products. In our opinion these facts determine the low yields of the dihydrofurans (V).

TABLE 5. Atomic Coordinates in the Molecule of (Vb) ($\times 10^4$)

Atom	x	y	z	Atom	x	y	z
$O_{(1)}$	3664(2)	1432(3)	6468(1)	$O_{(1')}$	5877(2)	1477(3)	6033(1)
$O_{(31)}$	5695(2)	1734(3)	7307(1)	$O_{(31')}$	4949(2)	1689(3)	4958(1)
$O_{(42)}$	2042(2)	4404(3)	7159(1)	$O_{(42')}$	7569(2)	5058(3)	5444(1)
$N_{(2)}$	4966(2)	331(3)	6729(1)	$N_{(2')}$	4940(3)	308(3)	5629(1)
$N_{(31)}$	5021(3)	3772(3)	7452(1)	$N_{(31')}$	5800(3)	3647(3)	4917(1)
$N_{(41)}$	4106(3)	5842(4)	6729(1)	$N_{(41')}$	5362(3)	5615(4)	5805(1)
$N_{(42)}$	2485(3)	2291(3)	7331(1)	$N_{(42')}$	8062(2)	2875(3)	5430(1)
$C_{(2)}$	4367(3)	1381(4)	6731(1)	$C_{(2')}$	5519(3)	1382(4)	5692(1)
$C_{(3)}$	4333(3)	2470(4)	6964(1)	$C_{(3')}$	5808(3)	2427(4)	5473(1)
$C_{(4)}$	3468(3)	3374(4)	6863(1)	$C_{(4')}$	6431(3)	3416(4)	5690(1)
$C_{(5)}$	3065(3)	2654(4)	6508(1)	$C_{(5')}$	6599(3)	2582(4)	6047(1)
$C_{(31)}$	5054(3)	2642(4)	7249(1)	$C_{(31')}$	5498(3)	2563(4)	5105(1)
$C_{(41)}$	3798(3)	4781(4)	6787(1)	$C_{(41')}$	5848(3)	4674(4)	5760(1)
$C_{(42)}$	2592(3)	3394(4)	7141(1)	$C_{(42')}$	7425(3)	3858(4)	5509(1)
$C_{(51)}$	3119(3)	3476(4)	6170(1)	$C_{(51')}$	6475(3)	3322(4)	6400(1)
$C_{(52)}$	2724(3)	2733(4)	5836(1)	$C_{(52')}$	7306(3)	4338(4)	6480(1)
$C_{(53)}$	2824(4)	3575(5)	5496(1)	$C_{(53')}$	7147(4)	5056(5)	6836(1)
$O_{(1S)}$	4901(3)	-2001(3)	6245(1)				

TABLE 6. Data from Elemental Analysis of the Dihydrofurans (Va-e)

Compound	Found, %			Molecular formula	Calculated, %		
	C	H	N		C	H	N
Va	45,77	4,83	26,53	$C_8H_{10}N_4O_3$	45,71	4,79	26,66
Vb	50,37	5,82	23,55	$C_{10}H_{14}N_4O_3$	50,41	5,9	23,52
Vc	50,43	5,98	23,47	$C_{10}H_{14}N_4O_3$	50,41	5,92	23,52
Vd	52,45	6,46	22,15	$C_{11}H_{16}N_4O_3$	52,37	6,39	22,21
Ve	55,74	7,23	19,85	$C_{13}H_{20}N_4O_3$	55,70	7,19	19,99

The reaction of the ethane (I) with Schiff bases, having basic characteristics, takes place readily without the use of a catalyst (triethylamine). However, nitrogen-containing heterocycles were not obtained as a result, and the dihydrofurans (V) were isolated. Hydrolysis of the azomethine compounds probably occurs under the reaction conditions, and the released amine catalyzes the reaction of the triamide (I) with the aldehyde formed during hydrolysis. Mixed melting tests with these compounds and the dihydrofurans (V) obtained from the aldehydes did not give a melting point depression.

EXPERIMENTAL

The purity of the synthesized compounds and the course of the reactions were monitored by TLC on Silufol UV-254 plates with iodine vapor as developer. The IR spectra were recorded on a UR-20 instrument for suspensions in Vaseline oil. The mass spectra were obtained on an MX-1321A instrument at 70 eV.

The elemental analyses corresponded to the calculated values.

The x-ray crystallographic investigations were conducted on an automatic Syntex $P2_1$ four-circle diffractometer (−90°C, $\lambda MoK\alpha$, β filter, $\theta/2\theta$ scan, $\theta_{max} = 27°$).

2-Amino-3,4-dicarbamoyl-5-methyl-4-cyano-4,5-dihydrofuran (Va). To a solution of 2 g (4.5 mmole) of acetaldehyde in 7 ml of a 2:1 mixture of acetonitrile and water we added 0.5 g (2.7 mmole) of 1,1,2-tricarbamoyl-2-cyanoethane (I) and then 0.12 g (1 mmole) of triethylamine. The reaction mixture was stirred until the initial substances had completely dissolved. After 20 min a precipitate separated, and it was filtered off and recrystallized from a 1:1 mixture of acetonitrile and water. We obtained 0.33 g (58%) of compound (Va) (Table 1).

5-Alkyl-2-amino-3,4-dicarbamoyl-4-cyano-4,5-dihydrofurans (Vb-e). To a solution of 12 mmole of the respective carbonyl compound (IIb-e) in 25 ml of a 1:1 mixture of acetonitrile and water we added in a single portion 10 mmole of compound (I) and, while stirring, about 1.5 mmole of triethylamine. The mixture was stirred until compound (I) had completely dissolved. The reaction mixture was kept until the solvent had almost completely evaporated (15-20 days). The residue was washed with isopropyl alcohol, filtered off, and recrystallized from water. The yields and the melting points are given in Table 1.

Principal Crystallographic Data. $a = 13.340(7)$, $b = 9.832(4)$, $c = 37.04(2)$ Å, $V = 4858(4)$ Å^3, $d_{calc} = 1.352$ g/cm^3, $C_{10}H_{14}N_4O_3 \cdot 0.5H_2O$. Space group Pbca, Z = 16. The structure was interpreted by the direct method and refined by full-matrix least-squares treatment in anisotropic approximation for the nonhydrogen atoms. The solvation of the water molecule was revealed in a Fourier difference synthesis. The hydrogen atoms, localized objectively in the Fourier difference synthesis, were included in the refinement with fixed temperature parameters ($U_{iso} = 0.04$ Å^2). The final divergence factors were $R = 0.05$ and $R_w = 0.061$ in 1976 unique reflections with $i > 3_s(I)$. The molecule is shown in Fig. 1, the bond lengths and bond angles are given in Tables 3 and 4, and the atomic coordinates are given in Table 5. (The indicated values and the temperature factors have been deposited in the Cambridge databank of structural data.)

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