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REACTION OF 2-CYANOETHANE-1,1,2-TRICARBOXAMIDE WITH α-ALKYLACROLEINS

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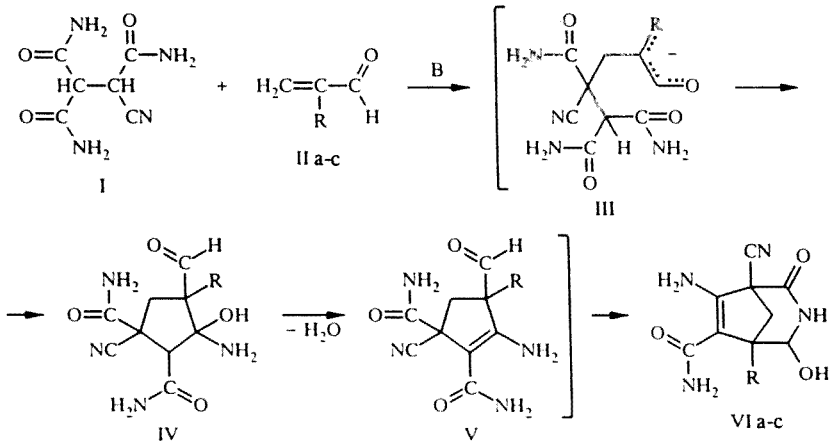
In the presence of catalytic amounts of triethylamine 2-cyanoethane-1,1,2-tricarboxamide forms Michael adducts with α-alkylacroleins. After two intramolecular cyclizations, the adducts are converted into 5-alkyl-6-amino-4-hydroxy-7-carbamoyl-2-oxo-1-cyano-3-azabicyclo[3.2.1]oct-6-enes.

The new polyfunctional CH acid 2-cyanoethane-1,1,2-tricarboxamide (I) that we obtained [1] is undoubtedly of considerable interest as a synthon with broad synthetic possibilities. In the adducts from addition intramolecular cyclization can take place not only at the carbonyl fragments but also at the cyano group. Having fairly weak acidity, the cyanide (I) reacts readily with aldehydes in the presence of a base [2]. Recently the reaction of compound (I) with crotonaldehyde was described [3]. While continuing research into the properties of 2-cyanoethane-1,1,2-tricarboxamide, we extended the range of α,β-unsaturated aldehydes used in the condensation. During the reaction with acrolein it was not possible to isolate any individual compound, since rapid polymerization and resinification occurred under the reaction conditions. α-Alkylacroleins proved more stable in these processes. By analogy with saturated aldehydes, the reactions with α-alkylacroleins were conducted in the presence of triethylamine, since addition does not take place without the base on account of the low acidity of (I) in the water—alcohol medium. As with crotonaldehyde, the reaction probably takes place according to the following scheme:



Michael addition probably takes place initially with the formation of the enolate anion (III), in which intramolecular cyclization occurs by nucleophilic attack at one of the terminal carbamoyl fragments. The intermediately formed compound (IV) is then converted into the cyclopentene (V) as a result of the elimination of a molecule of water. In (V) another intramolecular cyclization takes place through the addition of the amide fragment at the aldehyde group. The 5-alkyl-6-amino-4-

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TABLE 1. Characteristics of the Obtained Compounds

Compound	R	mp. °C	Found, % / Calculated, %			Molecular formula	Yield, %
			C	H	N		
VIa	C_2H_5	189...191 (dec.)	52,83 / 52,79	5,69 / 5,64	22,31 / 22,39	$C_{11}H_{14}N_4O_3$	32
VIb	C_3H_7	192...193 (dec.)	54,56 / 54,54	6,15 / 6,10	21,15 / 21,20	$C_{12}H_{16}N_4O_3$	35
VIc	C_4H_9	184...185	56,16 / 56,10	6,57 / 6,52	20,07 / 20,13	$C_{13}H_{18}N_4O_3$	33

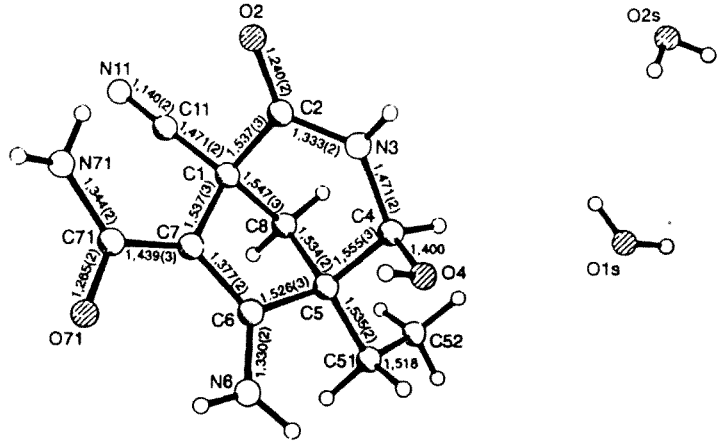

Fig. 1. Independent part of the crystal structure of compound (VIa). (The bond lengths, Å, are given.)

hydroxy-7-carbamoyl-2-oxo-1-cyano-3-azabicyclo[3.2.1]oct-6-enes (VIa-c) were isolated with yields of up to 35%. The idea of a repeated cyclization at the aldehyde group was confirmed by the data from x-ray crystallographic analysis of a single crystal of (VIa) (Fig. 1, Table 3).

From the IR spectra of compounds (VIa-c) (Table 2), in which an absorption band characteristic of the C≡N bond is observed in the region of 2255-2260 cm^{-1}, it can be supposed that all the intramolecular cyclizations take place without participation of the cyano group. In the IR spectrum there are bands which suggest the presence of a carbamoyl fragment. The ^{13}C NMR spectrum also agrees with the structure of (VI).

The mass spectra of compounds (VIa-c) are characterized by the presence of strong molecular ions (Tables 2 and 4); their dissociation gives rise to the Φ_1 and Φ_3 ions (Fig. 2), the formation of which is characteristic of amides [4]. The second amide fragment, which is in the heterocycle, is probably responsible for the Φ_2, Φ_4, Φ_5, and Φ_6 ions.

Thus, 2-cyanoethane-1,1,2-tricarboxamide (I) enters into the Michael reaction with α,β-unsaturated aldehydes in the presence of catalytic amounts of triethylamine, while the subsequent intramolecular cyclizations only take place at the amide fragments without affecting the cyano group.

EXPERIMENTAL

The reactions and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates with development by UV light and iodine vapor. The IR spectra were recorded on a UR-20 instrument in suspensions in Vaseline oil. The ^{13}C NMR spectrum was obtained on a Varian Gemini 300 spectrometer at 75 MHz with DMSO-d_6 as solvent and HMDS as internal standard. The mass spectrum was obtained on an MX-1321 instrument with direct injection into the

TABLE 2. IR and Mass Spectra of the Obtained Compounds

Compound	IR spectrum, cm^{-1}					Mass spectrum,* m/z (I, %)
	ν_{OH}	ν_{NH}	$\nu_{C \equiv N}$	$\nu_{C=O}$	δ_{NH}	
VIa	3485	3380, 3345, 3290, 3190	2260	1685, 1660	1620	250 (36), 233 (5), 207 (62), 206 (100), 190 (38), 178 (45), 177 (38), 162 (86), 161 (92), 131 (35), 105 (20)
VIb	3500	3400, 3310, 3240, 3200	2260	1660	1625	264 (57), 247 (10), 221 (84), 220 (96), 204 (51), 203 (22), 193 (83), 192 (100), 190 (92), 175 (96), 162 (63)
VIc	3480	3385, 3340, 3290, 3200	2255	1685, 1660	1615	278 (88), 261 (16), 235 (92), 234 (100), 218 (68), 217 (19), 206 (83), 178 (88), 162 (92), 161 (88), 105 (80)

*Molecular ion peak and the ten strongest peaks of the fragment ions are given.

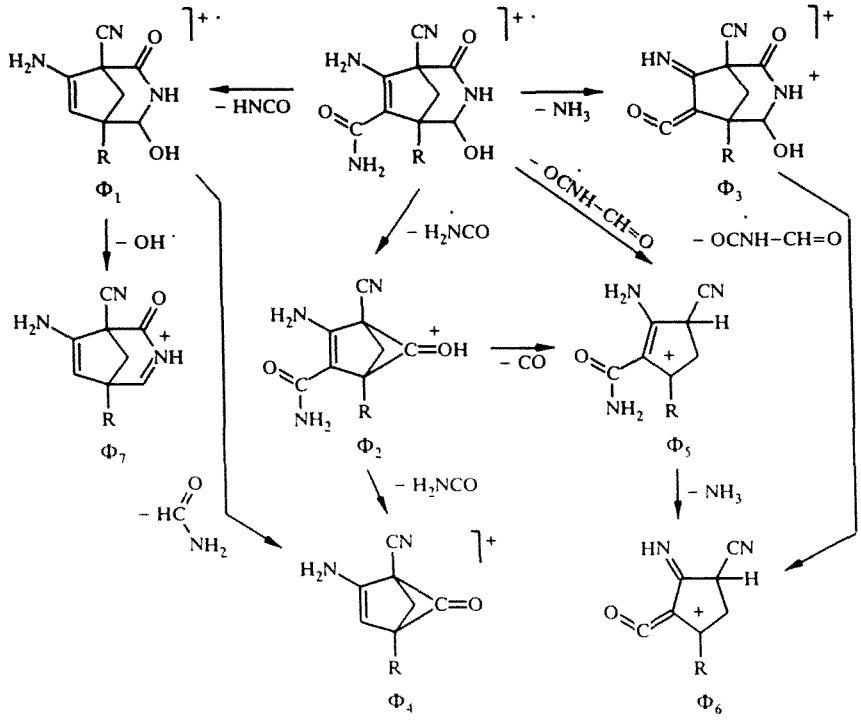

Fig. 2. Fragmentation of compounds (VIa-c) under electron impact.

ionization source at 70 eV. The x-ray crystallographic analysis was carried out on a Siemens P3/PC diffractometer (−120°C, λMoKα, $\theta/2\theta$ scan, θ_{max} = 27°).

5-Alkyl-6-amino-4-hydroxy-7-carbamoyl-2-oxo-1-cyano-3-azabicyclo[3.2.1]oct-6-enes (VIa-c). To a suspension of 2 g (11 mmole) of 2-cyanoethane-1,1,2-tricarboxamide (I) in 25 ml of a 1:2 mixture of water and isopropyl alcohol, while stirring, we added in one portion 30-40 mmole of α-alkylacrolein (IIa-c) and then 0.25 g (2.5 mmole) of triethylamine. The mixture was stirred until the initial substances had completely dissolved. The obtained solution was kept for 24 h [(2 days in the reaction with the aldehyde (IIc)]. The precipitate was filtered off, washed with isopropyl alcohol, and recrystallized from a 1:1 mixture of acetonitrile and water [from water for compound (VIa)]. The constants of the synthesized compounds are given in Table 1.

TABLE 3. Atomic Coordinates ($\times 10^4$) in the Molecule of Compound (VIa)

Atom	x	y	z
$O_{(2)}$	-18815(2)	5341(1)	-1358(1)
$O_{(4)}$	-119(2)	8130(1)	2854(1)
$O_{(71)}$	-1639(2)	10804(1)	-1144(1)
$N_{(3)}$	-1404(2)	6271(2)	945(1)
$N_{(6)}$	-1973(2)	10795(2)	1558(2)
$N_{(11)}$	-6031(2)	6065(2)	-2892(2)
$N_{(71)}$	-2327(2)	8616(2)	-2699(2)
$C_{(1)}$	-3806(2)	7147(2)	-570(2)
$C_{(2)}$	-2256(2)	6153(2)	-368(2)
$C_{(4)}$	-1718(2)	7294(2)	2172(2)
$C_{(5)}$	-3270(2)	8278(2)	1809(2)
$C_{(6)}$	-2706(2)	9416(2)	966(2)
$C_{(7)}$	-3004(2)	8776(2)	-422(2)
$C_{(8)}$	-4697(2)	7263(2)	707(2)
$C_{(11)}$	-5055(2)	6546(2)	-1883(2)
$C_{(51)}$	-3883(2)	8993(2)	3131(2)
$C_{(52)}$	-5001(3)	7923(2)	3718(2)
$C_{(71)}$	-2284(2)	9443(2)	-1438(2)
$O_{(1S)}$	-1891(2)	5377(2)	5753(2)
$O_{(2S)}$	-430(2)	2089(2)	4377(1)
$H_{(3N)}$	-458(25)	5806(20)	1074(18)
$H_{(4)}$	-2032(21)	6676(18)	2813(17)
$H_{(40)}$	453(31)	8528(26)	2270(24)
$H_{(6A)}$	-1665(26)	11088(22)	2456(22)
$H_{(6B)}$	-1578(25)	11364(22)	1023(20)
$H_{(8A)}$	-5786(24)	7755(20)	544(18)
$H_{(51A)}$	-2838(25)	9412(20)	3804(19)
$H_{(51B)}$	-4561(24)	9830(21)	2898(18)
$H_{(52A)}$	-6093(29)	7543(23)	3046(22)
$H_{(52B)}$	-4340(30)	7080(27)	3998(23)
$H_{(52C)}$	-5339(29)	8418(25)	4540(24)
$H_{(71A)}$	-2617(27)	7628(26)	-2888(21)
$H_{(71B)}$	-1672(29)	8960(23)	-3212(22)
$H_{(1SA)}$	-2505(35)	4763(30)	5036(30)
$H_{(1SB)}$	-2064(46)	4997(38)	6490(38)
$H_{(2SA)}$	78(33)	2981(30)	4400(25)
$H_{(2SB)}$	-424(34)	1956(29)	5171(29)

TABLE 4. Intensity of the Peaks of the Characteristic Ions in the Mass Spectra of Compounds (VIa-c) (% Σ_{50})*

Compound	W_m†	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7
VIa	3,37	5,73	9,29	0,5	7,97	4,18	8,5	3,56
VIb	1,22	1,8	2,06	0,22	1,52	2,15	2,06	1,09
VIc	2,55	2,62	2,86	0,45	2,05	2,38	2,74	1,95

*% Σ_{50}) intensity of the relative total current, calculated to the peak with m/z 40, %.
†As in Russian original; no footnote is given — Publisher.

X-Ray Crystallographic Analysis of the Structure of Compound (VIa). The principal crystallographic data were as follows: Triclinic crystals, space group P1, a = 7.705(6), b = 9.037(7), c = 9.964(9) Å, α = 99.65(2), β = 100.78(2), γ = 93.22(2)°, V = 669.2(4) Å^3, $C_{11}H_{14}N_4O_3 \cdot (H_2O)_2$, Z = 2, d_{calc} = 1.428 g/cm^3. The structure was interpreted by the direct method and refined by full-matrix least-squares treatment in anisotropic approximation for the nonhydrogen atoms. The hydrogen atoms, localized objectively in a Fourier difference synthesis, were refined in isotropic approximation. The final divergence factors were R = 0.044 in 3267 unique reflections with $I > 3\delta(I)$. All the calculations were performed on an IBM

PC/AT-286 using the SHELXTL PLUS software. The molecule of (VIa) and the bond lengths are shown in Fig. 1, and the atomic coordinates are given in Table 3. (The atomic coordinates, bond lengths, bond angles, and temperature factors have been deposited at the Cambridge databank of structural data.)

The ^{13}C NMR spectrum of compound (VIc) (DMSO-d_6): 47.50 (46.39) $C_{(1)}$; 167.35 (167.98) $C_{(2)}$; 97.99 (95.56) $C_{(4)}$; 79.14 (79.79) $C_{(5)}$; 162.87 (164.03) $C_{(6)}$; 52.36 (52.56) $C_{(7)}$; 36.35 (41.06) $C_{(8)}$; 118.82 (118.99) CN; 166.99 (167.26) $CONH_2$; 27.87 (29.16) R; 25.57; 23.03 (22.95) ppm. (The splitting of the signals results from the fact that the sample consisted of two isomers.)

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