Cubane derivatives
8.* Synthesis of nitroxyalkyl-substituted cubane-1,4-dicarboxamides and 4-bromocubanecarboxamides

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New substituted cubane-1,4-dicarboxamides and 4-bromocubanecarboxamides containing the nitroxyl group and amino acid fragments along with the cubane skeleton were synthesized. The cardiac pharmacological activity (both the effect on aorta relaxation and the calcium channel blocking activity) of most of nitroxyalkyl derivatives is equal to or higher than that of *N*-(2-nitroxyethyl)nicotinamide (nicorandil).

Key words: cubane-1,4-dicarboxylic acid, 4-bromocubanecarboxylic acid, oxy- and nitroxyalkylamides, β- and *d*,*l*-alanine, γ-aminobutyric acid, esters, X-ray diffraction analysis, cardiac pharmacological activity.

Cubane (pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane) was synthesized in 1964. Nevertheless, this compound and its derivatives continue to attract interest. Earlier, it has been expected that these structurally strained molecules would be unstable. However, these compounds proved to be stable and simultaneously have huge energy. Along with the possibility of the use of these compounds as energetic materials, some of them are considered as potential sources of drugs. Anticancer, anti-HIV, antiviral, and antiulcer activities of cubane derivatives, as well as their effect on the narcotic dependence, were documented.[2—6] We have demonstrated[7] that some derivatives of cubane-1,4-dicarboxylic acid exhibit high antiischemic activity. This confirms that the cubane fragment has high potential in the design of cardiac pharmacological drugs. The introduction of the bromine atom and an amino acid fragment, which play a great role in the functioning of organisms, into cubane derivatives would be expected to increase the biological activity of these compounds.

The aim of the present study was to synthesize derivatives containing the cubane fragment along with the amide and nitroxyl groups and fragments of different amino acids (glycine, β- and *d*,*l*-alanine, or γ-aminobutyric acid) based on cubane-1,4-dicarboxylic (**1**) and 4-bromocubanecarboxylic (**2**) acids and to preliminary estimate their cardiac pharmacological activity.

* For Part 7, see Ref. 1.

Results and Discussion

Earlier, we have developed[7] a procedure for the synthesis of substituted diamides of cubane-1,4-dicarboxylic acid. Based on this procedure, we used the reactions of dimethyl cubane-1,4-dicarboxylate (**3**) with 2-aminoethanol or 3-aminopropanol for the synthesis of *N*,*N*′-bis(2-hydroxyethyl)diamide (**4a**) and *N*,*N*′-bis(3-hydroxypropyl)diamide of cubane-1,4-dicarboxylic acid (**4b**), respectively. The latter compounds were transformed into *N*,*N*′-bis(2-nitroxyethyl)diamide (**5a**) and *N*,*N*′-bis(3-nitroxypropyl)diamide of cubane-1,4-dicarboxylic acid (**5b**), respectively, by nitration with a solution of HNO_3 in CH_2Cl_2 (Scheme 1).

N-(2-Hydroxyethyl)amide (**8a**) and *N*-(3-hydroxypropyl)amide of 4-bromocubanecarboxylic acid (**8b**) and the corresponding nitroxy derivatives **9a,b** were synthesized according to the same scheme with the use of 4-bromo-1-carbomethoxycubane (**7**), which was prepared by the Hunsdiecker reaction from monomethyl cubane-1,4-dicarboxylate (**6**).

Derivatives of **1** and **2** with amino acids (glycine, β- and *d*,*l*-alanine, and γ-aminobutyric acid) were synthesized by several procedures.

Attempts to synthesize amido derivatives by the reactions of methyl (or ethyl) esters of **1** and **2** with γ-aminobutyric acid failed in spite of varying the reaction

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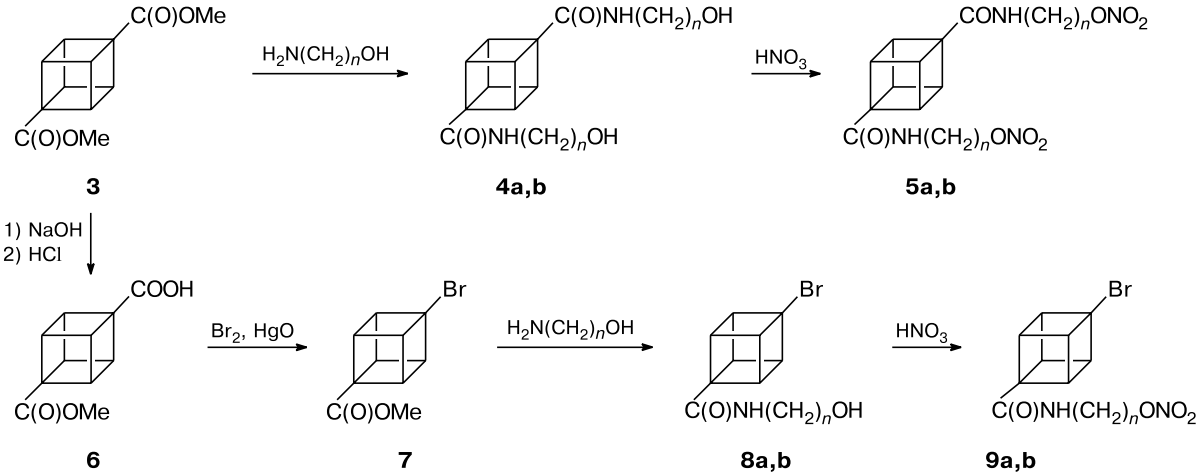
Scheme 1



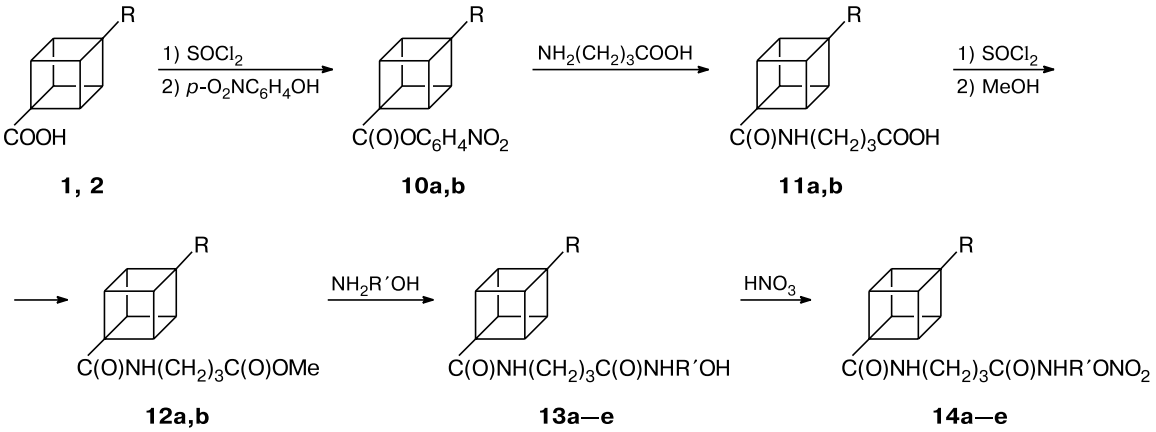
n = 2 (**a**), 3 (**b**)

conditions (temperature, the reaction time, solvents, or catalysts). The condensation was successfully performed only with the use of *p*-nitrophenyl esters of **1** and **2** (Scheme 2).

This fact can be attributed only to the dependence of the formation rate of amide on both the nature of the amino component and ester. It should be noted that the presence of groups having a negative inductive effect in the alcohol component of esters results in an increase in the activity of the esters and, consequently, in an increase in the condensation rate, and the alcohol residue of these esters is readily subjected to the exchange. The *p*-nitrophenyl group is one of the best leaving groups in esters.

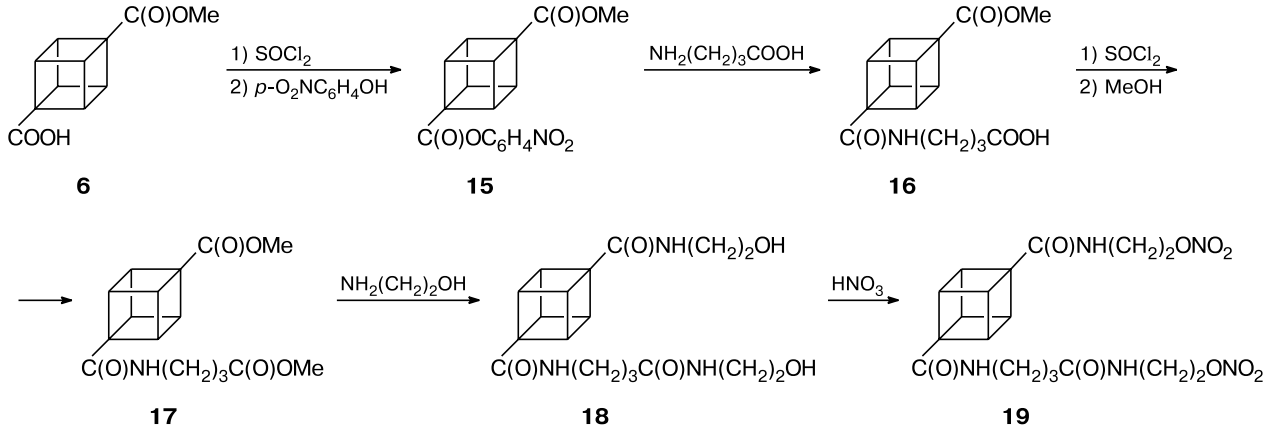
When synthesizing *N*,*N*′-bis(3-carboxypropyl)diamide of cubane-1,4-dicarboxylic acid (**11a**) (and the analogous derivative of 4-bromocubanecarboxylic acid (**11b**)), we run into the following problem. The —NH—$(CH_2)_3$—CO— group is a very flexible fragment of the molecule, which can undergo cyclization at a temperature higher than 5 °C. Hence, we performed the reaction with $SOCl_2$ at ≤0 °C, and the resulting acid chloride was immediately used for the synthesis of methyl ester with preventing it from warming. The reactions of esters of amido derivatives **1** with monoaminoethanol or other amino alcohols, for example, with 3-aminopropanol, 2-amino-2-methylpropan-1-ol, or 2-aminobutan-1-ol, produced the corresponding alcohols, and the subsequent reaction with nitric acid gave their nitrates (see Scheme 2). Derivatives of 4-bromocubanecarboxylic acid were synthesized analogously.

Scheme 2



R is a symmetrical radical (**a**, **c**—**e**) or Br (**b**)
R′ = $(CH_2)_2$ (**a**, **b**), $(CH_2)_3$ (**c**), $CH(Et)CH_2$ (**d**), Pr^iCH_2 (**e**)

Scheme 3



Analogously, *N*-(4-oxo-5-aza-7-nitroxyheptyl)-*N*′-(2-nitroxyethyl)diamide of cubane-1,4-dicarboxylic acid (**19**) was synthesized according to Scheme 3.

In the reaction with aminoacetic acid (glycine), even the use of *p*-nitrophenyl esters of **1** and **2** did not give the desired results. Apparently, this reaction is hindered because glycine is an inner salt, whose carboxy group is involved in the ionic bond with the ammonium nitrogen atom of the $H_3N^+—CH_2—COO^-$ fragment.

Good results were achieved with the use of the presynthesized hydrochloric salts of amino acid methyl (or ethyl) esters as the acylating agent. The reactions were carried out in dichloroethane at room temperature in the presence of triethylamine. This procedure was used for the synthesis of amido derivatives of **1** and **2** with glycine, β- and *d*,*l*-alanines, and γ-aminobutyric acid (Scheme 4).

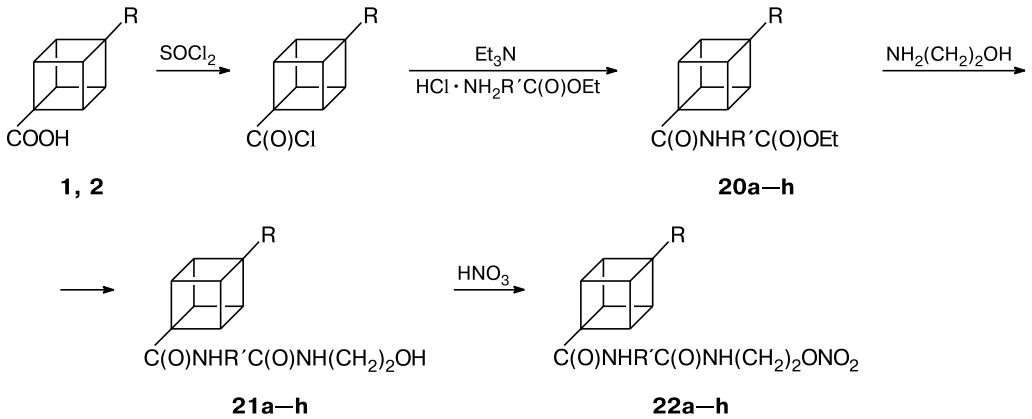
All intermediates and final products were characterized by elemental analysis, IR spectroscopy, and ^1H and ^{13}C NMR spectroscopy. Principal characteristics of the resulting compounds are given in Table 1.

Compound **9a**, which showed the highest cardiac pharmacological activity, was studied by X-ray diffraction (Fig. 1). There are two crystallographically independent molecules per asymmetric unit. These molecules are structurally similar and differ only by rotation of the terminal nitrate groups in the amidonitroxyethyl chains.

The cardiac activity of some of these compounds was studied in the National Research Center for Biologically Active Compounds (Staraya Kupavna, Moscow Region). The effect of these compounds on aorta relaxation and the activity of calcium channels of blood vessel cells was studied in comparison with nicorandil (*N*-(2-nitroxyethyl)nicotinamide) as the reference compound.

The effect on aorta relaxation was investigated in isolated samples (strips) of rat aorta. The relaxation of rat aorta strips contracted with noradrenaline was recorded after the introduction of the tested compound. The concentrations of the tested compounds and nicorandil, which provided the 50% relaxation, were compared. The effect of all tested compounds on aorta relaxation appeared to

Scheme 4



R is a symmetrical radical (**a**, **c**, **e**, **g**) or Br (**b**, **d**, **f**, **h**)
R′ = CH_2 (**a**, **b**), $(CH_2)_2$ (**c**, **d**), $(CH_2)_3$ (**e**, **f**), MeCH (**g**, **h**)

Table 1. Principal physicochemical characteristics of compounds*

Compound	M.p./°C	NMR (DMSO-d_6 + CCl_4), δ (*J*/Hz)		IR, ν/cm^{-1}
		^1H	^{13}C	
2	209—210	~4.25 (s, 6 H, CH_{cub}); 12.38 (br.s, 1 H, COOH)	47.0 (s, 3 C, $\underline{C}H_{cub}C(O)$); 54.0 (s, 3 C, $\underline{C}H_{cub}CBr$); 56.0 (s, 1 C, $\underline{C}_{cub}C(O)$); 63.5 (s, 1 C, $C_{cub}Br$); 171.8 (s, 1 C, C(O))	2920, 2852, 2569, 2524, 1442, 1376, 1365 (OH); 1683, 1618 (C=O); 3005, 1199 (CH_{cub}); 844, 822, 805 (C—Br)
4a	226—227	3.14 (q, 4 H, NCH_2, $^3J_{CH_2CH_2} \cong {}^3J_{CH_2NH_2} \cong 6.0$); 3.40 (br.t, 4 H, OCH_2); 4.02 (s, 6 H, CH); 4.68 (br.s, 2 H, OH); 7.68 (br.t, 2 H, NH, $^3J_{NHCH_2} \cong 6.0$)	—	3416 (OH); 3269 (NH); 2927, 2867 (CH_{cub}); 1622 (C=O); 1541, 848 (NH); 1433 (CH_2); 1259 (C—N); 1061 (C—OH)
4b	268—270	1.56 (quint, 4 H, CCH_2C, $^3J_{CHCH} \cong 6.0$); 3.00 (br.m, 4 H, NCH_2); 3.38 (br.t, 4 H, OCH_2); 4.02 (s, 6 H, CH); 4.42 (br.s, 2 H, OH); 7.68 (br.t, 2 H, NH)	—	3416 (OH); 3269, 1541, 848 (NH); 2993 (CH_{cub}); 2927, 2867, 1433 (CH_2); 1622 (C=O); 1259 (C—N); 1061 (C—OH)
5a	141—142	3.40 (q, 4 H, NCH_2, $^3J_{CHNH} = {}^3J_{CHCH} = 6.0$); 4.02 (s, 6 H, CH); 4.54 (t, 4 H, CH_2ONO_2, $^3J_{CHCH} = 6.0$); 8.00 (br.t, 2 H, NH, $^3J_{NHCH} = 6.0$)	—	1619, 1271, 851 (ONO_2); 3218, 1538 (NH); 1630 (C=O), (C(O)NH); 3002, 1349 (CH_{cub})
5b	167—168	1.82 (quint, 4 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 6.0$); 3.15 (q, 4 H, $NHC\underline{H}_2CH_2$, $^3J_{CH_2NH} \approx {}^3J_{CH_2CH_2} \approx 6.0$); 4.06 (s, 6 H, CH); 4.50 (t, 4 H, $CH_2C\underline{H}_2ONO_2$, $^3J_{CH_2CH_2} = 6.0$); 7.76 (br.t, 2 H, NH, $^3J_{NHCH_2} = 6.0$)	—	3257, 1553 (NH); 2998, 2987 (CH_{cub}); 1652 (C=O); 1625, 1286, 1250, 881 (ONO_2); 1553 (NH)
7	118—120	$\underline{CDCl}_3$: 3.71 (s, 3 H, OMe); ~4.27 (m, 3 H, $C\underline{H}CBr$, A part of AA´A″BB´B″ system, $\Delta\nu_{AB} \approx 11.0$); ~4.30 (m, 3 H, $C\underline{H}CC(O)$, B part of AA´A″BB´B″ system)	$\underline{CDCl}_3$: 47.7 (s, 3 C, $\underline{C}H_{cub}C(O)$); 51.7 (s, 1 C, OMe); 54.5 (s, 3 C, $\underline{C}H_{cub}CBr$); 55.7 (s, 1 C, $\underline{C}_{cub}C(O)$); 63.1 (s, 1 C, $\underline{C}_{cub}Br$); 172.0 (s, 1 C, C(O))	1720, 1230, 1096 (C(O)O); 838, 825 (C—Br); 2996, 1331 (CH_{cub}); 2955, 2851, 1440 (CH_2)
8a	188—189	3.52 (m, 2 H, $NHC\underline{H}_2CH_2$); ~3.8 (m, 2 H, $C\underline{H}_2OH$); 4.31 (m, 6 H, CH, AA´A″BB´B″ system, $\Delta\nu \approx 6.0$); ~6.0 (br.m, 1 H, C(O)NH)	—	3339 sh, 1069, 1062, 1042 (OH); 3310, 1540, 1621 (C(O)NH); 838 (C—Br); 2995, 1316 (CH_{cub}); 2943, 2879, 1451 (CH_2)
8b	180—183	—	—	3275, 1606, 1552 (C(O)NH); 3459, 1040 (OH); 834 (C—Br); 3007, 2994, 1348 (CH_{cub}); 2940, 2880, 1480 (CH_2)
9a	130—132	$\underline{CDCl}_3$: 3.64 (m, 2 H, $NHC\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 5.0$, $^3J_{CH_2NH} \approx 5.0$); 4.29 (m, 6 H, CH, AA´A″BB´B″ system, $\Delta\nu \approx 5$); 4.55 (t, 2 H, CH_2ONO_2, $^3J_{CH_2CH_2} \approx 5.0$); 5.97 (br.t, 1 H, C(O)NH)	—	1630 sh, 1270, 847 (ONO_2); 3211, 1540, 1622 (C(O)NH); 826 (C—Br); 2999, 1345 (CH_{cub}); 2943, 2879, 1451 (CH_2)

(*to be continued*)

Table 1 (*continued*)

Compound	M.p./°C	NMR (DMSO-d_6 + CCl_4), δ (*J*/Hz)		IR, ν/cm^{-1}
		^{1}H	^{13}C	
9b	153—154	DMSO-d_6 + CCl_4 + $CDCl_3$: 1.85 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2}$ = 6.3); 3.19 (q, 2 H, $NHC\underline{H}_2CH_2$, $^3J_{CH_2NH} = {}^3J_{CH_2CH_2}$ = 6.3); 4.22 (m, 6 H, CH, AA´A″BB´B″ system, $\Delta\nu_{AB} \approx 12$); 4.50 (t, 2 H, $CH_2C\underline{H}_2ONO_2$, $^3J_{CH_2CH_2}$ = 6.3); 7.78 (br.t, 1 H, $N\underline{H}CH_2$, $^3J_{NHCH_2} \approx 6.3$)	DMSO-d_6 + CCl_4 + $CDCl_3$: 171.2 (0) (s, 1 C, C(O)); 72.1 (−) (s, 1 C, CH_2ONO_2); 64.5 (0) (s, 1 C, $\underline{C}_{cub}Br$); 58.5 (0) (s, 1 C, $\underline{C}_{cub}C(O)$); 54.7 (+) (s, 3 C, $\underline{C}H_{cub}CBr$); 48.0 (+) (s, 3 C, $H_{cub}CC(O)$); 35.7 (−) (s, 1 C, $NH\underline{C}H_2CH_2$); 27.3 (−) (s, 1 C, $CH_2\underline{C}H_2CH_2$)	1618, 1279, 1037, 875, 757 (ONO_2); 3342, 1626 sh, 1534 (C(O)NH); 829 (C—Br); 3013, 2990, 1322 (CH_{cub}); 2940, 2880, 1446 (CH_2)
10a	214—215	—	—	1745, 1101, 1054 (C(O)O); 1320, 1346 (NO_2); 3001, 1315 (CH_{cub}); 3115, 3087, 1591, 1491, 850 (Ar)
10b	158—160	—	—	1741, 1207, 1055 (C(O)O); 1525, 1349 (NO_2); 833 (C—Br); 2997, 2977, 1315 (CH_{cub}); 3110, 3082, 3046, 1617, 1592, 1491, 861 sh (Ar)
11a	222—224 (decomp.)	1.64 (quint, 4 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \cong 7.0$); 2.21 (t, 4 H, $C\underline{H}_2C(O)$, $^3J_{CH_2CH_2} \cong 7.0$); ~3.08 (m, 4 H, $NHC\underline{H}_2$, $^3J_{CH_2CH_2} \cong 7.0$, $^3J_{CH_2NH} \cong 5.5$); ~3.60 ($C(O)O\underline{H}$ + H_2O from solvent); 4.04 (s, 6 H, CH); 7.80 (br.t, 2 H, C(O)NH, $^3J_{NHCH_2} \cong 5.5$)	—	1626 (C=O); 3287, 1552, 1552 (NHC(O)NH); 1701 (C=O), 2980 br (OHCOOH); 2995, 1333 (CH_{cub}); 2954, 2876, 1451, 1430 (CH_2)
11b	179—181 (decomp.)	—	—	3340, 1613, 1557 (C(O)NH); 2880, 2715, 2665, 2533, 1706, 1198, 1037 (COOH); 836 (C—Br); 3012, 2989, 1343 (CH_{cub}); 2962, 2935, 1452, 1445 (CH_2)
12a	174—175	—	—	3281, 1542, 1622 (C(O)NH); 1736, 1231, 1174 (C(O)O); 2995, 1334 (CH_{cub}); 2949, 2873, 1445, 1371 (Me, CH_2)
12b	130—133		—	737, 1290, 1041 (C(O)O); 3275, 1620, 1550 (C(O)NH); 3001, 1341 (CH_{cub}); 2954 sh, 2925, 2885, 1440, 1432 (Me, CH_2)
13a (**21e**)	206—208	1.60 (m, 4 H, $CH_2C\underline{H}_2CH_2$); 2.80 (m, 4 H, $CH_2C(O)$); 3.10 (m, 8 H, $NHC\underline{H}_2$); 3.37 (m, 4 H, CH_2OH); 4.04 (s, 6 H, CH); ~4.76 (br.s, 2 H, OH); 7.83 (br.m, 2 H, C(O)NH); 7.92 (br.m, 2 H, C(O)NH)	—	3392, 1078 (OH); 3298, 3252, 1552, 1622 (C(O)NH); 3001, 1336 (CH_{cub}); 2943, 2879, 1467, 1444 (CH_2)

(*to be continued*)

Table 1 (*continued*)

Compound	M.p./°C	NMR (DMSO-d_6 + CCl_4), δ (*J*/Hz)		IR, ν/cm^{-1}
		^1H	^{13}C	
13b (**21f**)	125—127	1.62 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 7.2$); 2.06 (t, 2 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 7.2$); 3.02 (m, 2 H, $NHC\underline{H}_2CH_2CH_2$); 3.08 (m, 2 H, $NHC\underline{H}_2CH_2OH$); 3.37 (t, 2 H, $C\underline{H}_2OH$, $^3J_{CH_2CH_2} \approx 6.0$); 4.23 (m, 6 H, CH, AA′A″BB′B″ system, $\Delta\nu_{AB} \approx 7.0$); 7.83, 7.85 (both br.t, 1 H each, $C(O)N\underline{H}$, $^3J_{NHCH_2} \approx 5.0$)	171.8, 169.9 (both 0) (both s, 1 C each, C(O); 64.0 (0) (s, 1 C, CBr); 59.8 (−) (s, 1 C, CH_2OH); 57.5 (0) (s, 1 C, $\underline{C}C(O)$; 53.7 (+) (s, 3 C, $\underline{C}HCBr$); 47.0 (+) (s, 3 C, $\underline{C}HCC(O)$); 41.4 (−) (s, 1 C, NCH_2); 38.0 (−) (s, 1 C, NCH_2); 32.8 (−) (s, 1 C, $\underline{C}H_2C(O)$); 25.2 (−) (s, 1 C, $CH_2\underline{C}H_2CH_2$)	3302, 1076 (OH); 3248, 1624, 1618, 1556 (C(O)NH); 840, 833 (C—Br); 3003, 1337 (CH_{cub}); 2945, 2901, 2860 sh, 1465, 1445 (CH_2)
13c	190—191	—	—	3392, 1078 (OH); 3298, 3252, 1552, 1622 (C(O)NH); 3001, 1336 (CH_{cub}); 2943, 2879, 1467, 1444 (CH_2)
13d	206—207	~0.90 (t, 6 H, Me); ~1.50 (m, 4 H, $CH_2C\underline{H}_2CH_3$); ~1.60 (m, 4 H, $CH_2C\underline{H}_2CH_2$); ~2.10 (m, 4 H, $CH_2C(O)$); ~3.00 (m, 4 H, $NHC\underline{H}_2CH_2$); ~3.30 (m, 4 H, $C\underline{H}_2OH$, AB part of ABX system); ~3.60 (m, 2 H, $NHC\underline{H}(CH_2)_2$, X part of ABX system); ~4.10 (s, 6 H, CH); ~7.45 (d, 2 H, $C(O)N\underline{H}CH$); ~7.70 (m, 2 H, $C(O)N\underline{H}CH_2$)	171.6, 170.6 (both 0) (both s, 2 C each, C(O)); 63.0 (−) (s, 2 C, CH_2); 52.0 (+) (s, 2 C, CH of substituent; 45.7 (+) (s, 6 C, CH_{cub}); 37.6, 33.2, 25.6, 23.6 (all −) (all s, 2 C each, CH_2); 10.1 (+) (s, 2 C, CH_3C)	3420, 1060 (OH); 3275, 1546, 1647 sh, 1618 (C(O)NH); 2995, 1337 (CH_{cub}); 2960, 2931, 2879, 1456, 1377 (Me, CH_2)
13e	192—193	1.19 (s, 12 H, MeC); 1.62 (quint, 4 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 7.0$; 2.04 (t, 4 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 7.0$); 3.34 (br.s, 4 H, $C\underline{H}_2OH$); 4.05 (s, 6 H, CH); 4.85 (br.s, 2 H, OH); 7.26 (br.s, 2 H, C(O)NH); 7.67 (br.t, 2 H, $C(O)N\underline{H}CH_2$, $^3J_{NHCH_2} \approx 6.0$)	—	3207, 1060 (OH); 3285, 1632, 1541 (C(O)NH); 2990, 1335 (CH_{cub}); 2981 sh, 2934, 2868, 1452, 1384, 1364 (Me, CH_2)
14a (**22e**)	154—155	1.63 (m, 4 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \cong 7.3$); 2.08 (t, 4 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \cong 7.3$); 3.04 (m, 4 H, $NHC\underline{H}_2CH_2$); 3.40 (m, 4 H, $NHC\underline{H}_2CH_2ONO_2$); 4.05 (s, 6 H, CH); 4.52 (t, 4 H, CH_2ONO_2, $^3J_{CH_2CH_2} \cong 5.3$); 7.82 (br.t, 2 H, C(O)NH, $^3J_{NH-CH_2} \cong 5.5$); 8.18 (br.t, 2 H, C(O)NH, $^3J_{NH-CH_2} \cong 5.5$)	—	1640, 1278, 863 (ONO_2); 3273, 1543, 1620 (C(O)NH); 2995, 1337 (CH_{cub}); 2938, 2876, 1445 (CH_2)

(*to be continued*)

Table 1 (*continued*)

Compound	M.p./°C	NMR (DMSO-d_6 + CCl_4), δ (*J*/Hz)		IR, ν/cm^{-1}
		^1H	^{13}C	
14b (**22f**)	128—130	$\underline{CDCl_3}$: 1.89 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 6.0$); 2.31 (t, 2 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 6.0$); 3.38 (dt, 2 H, $NHC\underline{H}_2$, $^3J_{CH_2CH_2} \approx 6.0$; $^3J_{CH_2NH} \approx 6.8$); 3.66 (dt, 6 H, $NHC\underline{H}_2CH_2ONO_2$, $^3J_{CH_2CH_2} \approx$ $^3J_{CH_2NH} \approx 5.0$); 4.31 (m, 6 H, CH, AA´A″BB´B″ system, $\Delta\nu_{AB} \approx 5.0$); 4.61 (t, 2 H, CH_2ONO_2, $^3J_{CH_2CH_2} \approx 5.0$); 6.25, 6.84 (both br.t, 1 H each, C(O)NH)	$\underline{CDCl_3}$: 71.5 (–) (s, 1 C, CH_2ONO_2); 65.5 (0) (s, 1 C, CBr); 58.0 (0) (s, 1 C, $\underline{C}C(O)$); 54.1 (+) (s, 3 C, $\underline{C}HCBr$); 47.6 (+) (s, 3 C, $\underline{C}HCC(O)$); 38.8, 37.0 (both –) (both s, 1 C each, CH_2N); 33.7 (–) (s, 1 C, $\underline{C}H_2C(O)$); 22.4 (–) (s, 1 C, $C\underline{C}H_2C$)	3328, 1618, 1536 (C(O)NH); 1641, 1278, 865 (ONO_2); 840 (C—Br); 3007, 2984, 1329 (CH_{cub}); 2925, 2855, 1457, 1434 (CH_2)
14c	148—150	1.63 (quint, 4 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \cong 6.6$); 1.79 (quint, 4 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \cong 6.2$); 2.05 (t, 4 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \cong 6.6$); 3.04 (m, 4 H, $NHC\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \cong 6.6$; $^3J_{CH_2NH} \cong 6.0$); 3.13 (m, 4 H, $NHC\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \cong 6.2$; $^3J_{CH_2NH} \cong 6.0$); 4.06 (s, 6 H, CH); 4.50 (t, 4 H, CH_2ONO_2, $^3J_{CH_2CH_2} \cong 6.2$); 7.70 (t, 2 H, $C(O)N\underline{H}CH_2$, $^3J_{NHCH_2} \cong 6.0$); 7.91 (t, 2 H, $C(O)N\underline{H}CH_2$, $^3J_{NHCH_2} \cong 6.0$)	171.8, 170.5 (both 0) (both s, 2 C each, $C\underline{C}(O)NH$); 71.4 (–) (s, 2 C, $\underline{C}H_2ONO_2$); 45.7 (+) (s, 6 C, $\underline{C}H_{cub}$); 38.0, 34.7 (both –) (both s, 2 C each, $NH\underline{C}H_2CH_2$); 32.9 (–) (s, 2 C, $CH_2\underline{C}H_2C(O)$); 26.4 (–) (s, 2 C, $CH_2\underline{C}H_2CH_2$); 25.3 (–) (s, 2 C, $CH_2\underline{C}H_2CH_2$)	1642, 1280, 879 (ONO_2); 3269, 1549, 1617 (C(O)NH); 2995, 1339 (CH_{cub}); 2943, 2879, 1451 (CH_2)
14d	138—140	~0.90 (t, 6 H, Me); ~1.50 (m, 4 H, $CHC\underline{H}_2CH_3$); ~1.60 (m, 4 H, $CH_2C\underline{H}_2CH_2$); ~2.10 (m, 4 H, $CH_2C(O)$); ~3.10 (m, 4 H, $NHC\underline{H}_2CH_2$); ~4.00 (s, 6 H, CH); ~4.10 (m, 2 H, $NHC\underline{H}(CH_2)_2$, X part of ABX system); ~4.40 (m, 4 H, CH_2ONO_2, AB part of ABX system); ~7.70, ~7.80 (both m, 2 H each, $C(O)N\underline{H}CH$)	—	1634, 1279, 854 (ONO_2); 3277, 1542, 1661 sh, 1627 (C(O)NH); 2989 (CH_{cub}); 2971, 2932, 2881, 1460, 1380 (Me, CH_2)
14e	135—136	1.29 (s, 12 H, MeC); 1.62 (quint, 4 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx$ 7.0); 2.04 (t, 4 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 7.0$); 3.05 (m, 4 H, $NHC\underline{H}_2$, $^3J_{CH_2CH_2} \approx 7.0$, $^3J_{CH_2NH} \approx 6.0$); 4.05 (s, 6 H, CH); 4.67 (s, 4 H, CH_2ONO_2); 7.65 (br.t, 2 H, $C(O)N\underline{H}CH_2$, $^3J_{NHCH_2} \approx 6.0$); 7.67 (br.s, 2 H, C(O)NH)	—	1644 sh, 1281, 873 (ONO_2); 3321 sh, 3274, 1627, 1541 (C(O)NH); 2990, 1337 sh (CH_{cub}); 2981 sh, 2934, 2870 sh, 1456, 1384, 1366 (Me, CH_2)

(*to be continued*)

Table 1 (*continued*)

Compound	M.p./°C	NMR (DMSO-d_6 + CCl_4), δ (*J*/Hz)		IR, ν/cm^{-1}
		^1H	^{13}C	
15	142—143	$\underline{CDCl_3}$: 3.76 (s, 3 H, C(O)OMe); 4.41 (m, 6 H, CH, AA´A″BB´B″ system, $\Delta\nu_{AB} \approx 8.0$); 7.30 (d, 2 H, CH=CO, A part of AX system, $^3J_{CHCH} \approx 7.0$); 8.29 (d, 2 H, $CH{=}CNO_2$, X part of AX system, $^3J_{CHCH} = 7.0$)	—	1734, 1194, 1055 (—C(O)O—C_6H_4); 1708, 1225, 1091 (—C(O)O—Me); 1528, 1343 (NO_2); 3001, 1317 (CH_{cub}); 3113, 3075, 3026, 1616, 1595 (Ar); 2947, 2853, 1430 (Me)
16	177—180	1.63 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 6.8$); 2.20 (t, 2 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 6.8$); 3.08 (dt, 2 H, $NHC\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 6.8$; $^3J_{CH_2NH} \approx 6.0$); 3.62 (s, 3 H, OCH_3); 4.11 (s, 6 H, CH); 7.72 (br.t, 1 H, C(O)NH, $^3J_{NHCH_2} \approx 6.0$); ~12.0 (br.s, 1 H, C(O)OH)	174.1, 171.1, 170.2 (all 0) (all s, 1 C each, C(O)O or C(O)N); 57.2, 54.9 (both 0) (both s, 1 C each, $\underline{C}_{cub}$); 51.1 (+) (s, 1 C, OMe); 46.2, 45.9 (both +) (both s, 3 C each, $\underline{C}H_{cub}$); 37.7, 31.0, 24.6 (all –) (all s, 1 C each, CH_2)	3392, 1592, 1553 (C(O)NH); 2709, 2628, 2517, 1709 (COOH); 1715, 1210, 1094 (C(O)O); 3007 sh, 2989, 1324 (CH_{cub}); 2954, 2931 sh, 2867, 1451, 1437 (Me, CH_2)
17	111—112	1.70 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 7.0$); 2.30 (t, 2 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 7.0$); 3.59, 3.64 (both s, 3 H each, OMe); 4.15 (s, 6 H, CH); 7.79 (br.t, 1 H, C(O)NH, $^3J_{NHCH_2} \approx 6.0$)	172.8, 171.0, 170.2 (all 0) (all s, 1 C each, C(O)O or C(O)N); 57.2, 54.9 (both 0) (both s, 1 C each, $\underline{C}_{cub}$); 51.1 (+) (s, 2 C, OMe); 46.3, 45.9 (both +) (both s, 3 C each, $\underline{C}H_{cub}$); 37.7, 30.8, 24.5 (all –) (all s, 1 C each, CH_2)	1731, 1716 sh, 1250, 1210, 1174, 1086 (C(O)O); 3339, 1626, 1536 (C(O)NH); 3000, 2989, 1321 (CH_{cub}); 2949, 2849, 1454 sh, 1434, 1366 (Me, CH_2)
18	168—172	1.62 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 7.0$); 2.06 (t, 2 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 7.0$); 2.92—3.24 (m, 6 H, $NH\underline{CH}_2$); 3.24—3.51 (m, 4 H, $C\underline{H}_2OH$); 4.04 (s, 6 H, CH); 4.61 (br.s, 2 H, OH); 7.63, 7.70, 7.79 (all br.t, 1 H each, C(O)NH, $^3J_{NHCH_2} \approx 5.0$)	—	3374 sh, 1053 (OH); 3284, 1625, 1543 (C(O)NH); 2995, 1336 (CH_{cub}); 2934, 2877, 1430 (CH_2)
19	134—135	$\underline{CD_3OD}$: 1.80 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 7.0$); 2.23 (t, 2 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 7.0$); 3.23 (t, 2 H, $HNC\underline{H}_2CH_2CH_2C(O)$, $^3J_{CH_2CH_2} \approx 7.0$); 3.52, 3.55 (both t, 2 H each, $NHC\underline{H}_2CH_2ONO_2$, $^3J_{CH_2CH_2} \approx 5.0$); 4.16 (s, 6 H, CH); 4.55, 4.57 (both t, 2 H each, CH_2ONO_2, $^3J_{CH_2CH_2} \approx 5.0$); 4.86 (br.s, C(O)NH + H_2O + OH of methanol)	$\underline{CD_3OD}$: 176.0 (0) (s, 1 C, C(O)); 175.0 (0) (s, 2 C, C(O)); 72.9, 72.8 (both –) (both s, 1 C each, CH_2ONO_2); 48.2 (+) (s, 1 C, 6 C, CH); 39.7 (–) (s, 1 C, $NH\underline{C}H_2CH_2$); 37.9 (–) (s, 2 C, $NH\underline{C}H_2CH_2ONO_2$); 34.2 (–) (s, 1 C, $\underline{C}H_2C(O)$); 26.7 (–) (s, 1 C, $CH_2\underline{C}H_2CH_2$)	1644, 1279, 863 (ONO_2); 3292, 1541, 1641 (C(O)NH); 2989, 1337 (CH_{cub}); 2931, 2865 sh, 1432 (CH_2)
20a	234—235 (decomp.)	3.86 (s, 6 H, OMe); 3.80 (d, 4 H, CH_2, $^3J_{CH_2NH} \approx 5.0$); 4.15 (s, 6 H, CH); 8.20 (br.t, 2 H, C(O)NH, $^3J_{NHCH_2} \approx 5.0$)	—	1620, 3339, 1522 (C(O)NH); 1752, 1741, 1213, 1140 (C(O)O); 3000, 1330 (CH_{cub}); 2954, 2939, 2849, 1452, 1442, 1420, 1369 (Me, CH_2)

(*to be continued*)

Table 1 (*continued*)

Compound	M.p./°C	NMR (DMSO-d_6 + CCl_4), δ (*J*/Hz)		IR, ν/cm^{-1}
		^1H	^{13}C	
20b	156—157	3.78 (s, 3 H, OMe); 4.07 (d, 2 H, CH_2, $^3J_{CH_2NH} \approx 5.4$); 4.29 (m, 6 H, CH, AA′A″BB′B″ system, $\Delta\nu_{AB} \approx 8.0$); 6.09 (br.m, 1 H, C(O)NH)	$\underline{C}DCl_3$: 171.0, 170.4 (both 0) (both s, 1 C each, C(O)N or C(O)O); 63.1 (0) (s, 1 C, $\underline{C}_{cub}Br$); 57.8 (0) (s, 1 C, $\underline{C}_{cub}C(O)NH$); 54.2 (+) (s, 3 C, $H_{cub}CBr$); 52.5 (+) (s, 1 C, OMe); 47.6 (+) (s, 3 C, $\underline{C}H_{cub}CC(O)NH$); 40.9 (–) (s, 1 C, $C(O)\underline{C}H_2N$)	3344, 1629, 1530 (C(O)NH); 1752, 1213, 1041 (C(O)O); 830 (C—Br); 2992 (CH_{cub}); 2949, 2924, 2844, 1452, 1429, 1373 (Me, CH_2)
20c	190—191	1.20 (t, 6 H, Me, $^3J_{MeCH_2} \approx 7.0$); 2.44 (t, 4 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 7.0$); 3.27 (m, 4 H, $NHC\underline{H}_2$); 4.02 (s, 6 H, CH); 4.06 (q, 4 H, $OC\underline{H}_2CH_3$, $^3J_{CH_2Me} \approx 7.0$); 7.78 (br.t, 2 H, C(O)NH, $^3J_{NHCH_2} \approx 5.7$)	171.1, 170.6 (both 0) (both s, 2 C each, C(O)); 59.7 (–) (s, 2 C, OCH_2); 56.8 (0) (s, 2 C, $\underline{C}C(O)$); 45.7 (+) (s, 6 C, CH); 34.5 (–) (s, 2 C, NCH_2); 33.8 (–) (s, 2 C, $CH_2C(O)$); 14.0 (+) (s, 2 C, Me)	3301, 1624, 1546 (C(O)NH); 1727, 1188, 1022 (C(O)O); 2995, 1336 (CH_{cub}); 2948, 2925, 2870, 2851, 1451, 1363 (Me, CH_2)
20d	155—156.5	3.41 (m, 2 H, $NHC\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx {}^3J_{CH_2NH} \approx 5.0$); 3.64 (d, 2 H, $NHC\underline{H}_2C(O)$, $^3J_{CH_2NH} \approx 6.0$); 4.25 (m, 6 H, CH, AA′A″BB′B″ system, $\Delta\nu \approx 8.0$); 4.51 (t, 2 H, CH_2ONO_2, $^3J_{CH_2CH_2} \approx 5.0$); 8.06, 8.08 (both br.t, 1 H each, C(O)NH)	170.3, 169.3 (both 0) (both s, 1 C each, C(O)N); 72.1 (–) (s, 1 C, $\underline{C}H_2ONO_2$); 63.9 (0) (s, 1 C, $\underline{C}_{cub}Br$); 57.4 (0) (s, 1 C, $\underline{C}_{cub}C(O)NH$); 53.9 (+) (s, 3 C, $\underline{C}H_{cub}CBr$); 47.1 (+) (s, 3 C, $\underline{C}H_{cub}CC(O)NH$); 41.7 (–) (s, 1 C), $NH\underline{C}H_2C(O)$); 36.0 (–) (s, 1 C, $NH\underline{C}H_2CH_2$)	3459, 3292, 1693, 1676, 1618, 1564, 1517 (C(O)NH); 1643, 1282, 892 (ONO_2); 839 (C—Br); 3008, 2991, 1326 (CH_{cub}); 2945, 2894, 1424, 1381 (CH_2)
20f	121—122	$\underline{C}DCl_3$: 1.26 (t, 3 H, Me, $^3J_{MeCH_2} \approx 7.1$); 1.85 (quint, 2 H, $CH_2C\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 6.9$); 2.38 (t, 2 H, $CH_2C(O)$, $^3J_{CH_2CH_2} \approx 6.9$); 3.31 (dt, 2 H, $NHC\underline{H}_2CH_2$, $^3J_{CH_2CH_2} \approx 6.9$; $^3J_{CH_2NH} \approx 5.8$); 4.13 (q, 2 H, $OC\underline{H}_2CH_3$, $^3J_{CH_2Me} \approx 7.1$); 4.26 (m, 6 H, CH, AA′A″BB′B″ system, $\Delta\nu_{AB} \approx 7.0$); 6.15 (br.t, 1 H, C(O)NH, $^3J_{NHCH_2} \approx 5.8$)	$\underline{C}DCl_3$: 173.8 (0) (s, 1 C, C(O)O); 171.1 (0) (s, 1 C, C(O)N); 63.3 (0) (s, 1 C, CBr); 60.7 (–) (s, 1 C, OCH_2); 58.1 (0) (s, 1 C, $\underline{C}C(O)$); 54.1 (+) (s, 3 C, $\underline{C}HCBr$); 47.5 (+) (s, 3 C, $\underline{C}HCC(O)$); 39.0 (–) (s, 1 C, NCH_2); 32.0 (–) (s, 1 C, $\underline{C}H_2C(O)$); 24.3 (–) (s, 1 C, $C\underline{C}H_2C$); 14.2 (+) (s, 1 C, Me)	3287, 1624, 1556 (C(O)NH); 1737, 1230, 1199, 1179, 1035 (C(O)O); 842, 831 (C—Br); 3001, 1346 (CH_{cub}); 2949, 2925, 2902, 2853, 1474, 1445, 1431, 1411, 1372 (Me, CH_2)
20g	217—218	1.20 (t, 6 H, $C\underline{H}_3CH_2$, $^3J_{MeCH_2} \approx 7.1$); 1.30 (d, 6 H, $C\underline{H}_3CH$, $^3J_{MeCH} \approx 7.3$); 4.07 (q, 4 H, $OC\underline{H}_2CH_3$, $^3J_{CH_2Me} \approx 7.1$); 4.08 (s, 6 H, CH); 4.23 (m, 2 H, $NC\underline{H}(CH_3)$); 8.08 (d, 2 H, C(O)NH, $^3J_{NHCH} \approx 7.0$)	172.5, 170.5 (both 0) (both s, 2 C each, C(O)); 60.2 (–) (s, 2 C, OCH_2); 56.5 (0) (s, 2 C, $\underline{C}C(O)$); 47.3 (+) (s, 2 C, NCH); 45.8 (+) (s, 6 C, CH); 16.6, 14.0 (both +) (both s, 2 C each, Me)	3351, 1629, 1521 (C(O)NH); 1745, 1207, 1196, 1160 (C(O)O); 2989 (CH_{cub}); 2943, 2980, 2855, 1454, 1369 (Me, CH_2)
20h	160—165	—	—	3223, 1622, 1537 (C(O)NH); 1750, 1211, 1200 sh, 1040 (C(O)O); 836 (C—Br); 2994, 1321 (CH_{cub}); 2952, 2929, 2851, 1450, 1359 (Me, CH_2)

(*to be continued*)

Table 1 (*continued*)

Compound	M.p./°C	NMR (DMSO-d_6 + CCl_4), δ (*J*/Hz)		IR, ν/cm^{-1}
		^1H	^{13}C	
21a	210—211 (decomp.)	3.12 (dt, 4 H, NHC<u>H</u>$_2$CH$_2$, $^3J_{CH_2CH_2} \approx {}^3J_{CH_2NH} \approx 6.0$); 3.39 (t, 4 H, CH$_2$<u>H</u>$_2$OH, $^3J_{CH_2CH_2} \approx 6.0$); 3.64 (d, 4 H, NHC<u>H</u>$_2$C(O), $^3J_{CH_2NH} \approx 6.0$); 4.10 (s, 6 H, CH); ~4.50 (br.s, 2 H, OH); 7.78, 7.92 (both br.t, 2 H each, C(O)NH, $^3J_{NHCH_2} \approx 6.0$)	—	3386, 3298, 1657, 1622, 1555, 1545 (C(O)NH); 3269, 1068 (OH); 2985, 1352 (CH_{cub}); 2952, 2870, 1428 (CH_2)
21b	182—184	—	—	3345, 1685, 1672, 1634, 1580, 1526 (C(O)NH); 3303, 1068, 1045 (OH); 829 (C—Br); 2994 (CH_{cub}); 2936, 2909, 2859, 1461, 1446, 1428 (CH_2)
21c	240—241 (decomp.)	2.24 (s, 4 H, CH$_2$C(O), $^3J_{CH_2CH_2} \approx 7.0$); 3.02—3.44 (m, 8 H, NHC<u>H</u>$_2$); 4.02 (s, 6 H, CH); 4.60 (br.m, 2 H, OH); 7.72, 7.84 (both br.t, 2 H each, C(O)NH, $^3J_{NHCH_2} \approx 5.7$)	170.6, 170.3 (both 0) (both s, 2 C each, C(O)); 59.8 (–) (s, 2 C, <u>C</u>H$_2$OH); 56.9 (0) (s, 2 C, <u>C</u>C(O)); 45.6 (+) (s, 6 C, CH); 41.3, 35.3, 35.2 (all –) (all s, 2 C each, C(O)<u>C</u>H$_2$ + NCH$_2$)	3409, 1068 (OH); 3269, 1652 sh, 1624, 1541 (C(O)NH); 3001, 1335 (CH_{cub}); 2937, 2879, 2879, 1451, 1431 (CH_2)
21d	191—194	2.23 (t, 2 H, CH$_2$C(O), $^3J_{CH_2CH_2} \approx 7.0$); 3.10 (dt, 2 H, NHC<u>H</u>$_2$CH$_2$OH, $^3J_{CH_2CH_2} \approx 5.8$, $^3J_{CH_2NH} \approx 6.0$); 3.24 (dt, 2 H, NHC<u>H</u>$_2$CH$_2$C(O), $^3J_{CH_2NH} \approx 7.0$, $^3J_{CH_2NH} \approx 6.0$); 3.38 (t, 2 H, CH$_2$<u>H</u>$_2$OH, $^3J_{CH_2CH_2} \approx 5.8$); 4.21 (s, 6 H, CH); 7.80, 7.82 (both br.t, 1 H each, C(O)NH, $^3J_{NHCH_2} \approx 6.0$)	170.3, 169.9 (both 0) (both s, 1 C each, C(O)); 66.3 (–) (s, 1 C, CH$_2$OH); 63.9 (0) (s, 1 C, CBr); 59.9 (–) (s, 1 C, NCH$_2$); 57.5 (0) (s, 1 C, <u>C</u>C(O)); 53.8 (+) (s, 3 C, <u>C</u>HCBr); 47.0 (+) (s, 3 C, <u>C</u>HCC(O)); 41.4 (–) (s, 1 C, CH$_2$N); 35.5 (–) (s, 1 C, <u>C</u>H$_2$C(O))	3421, 1080 (OH); 3345, 1629, 1530 (C(O)NH); 837 (C—Br); 3001, 1332 (CH_{cub}); 2943, 2925 sh, 2873, 1457, 1423 (Me, CH_2)
21g	244—245 (decomp.)	—	—	3350 sh, 1665, 1618, 1564 sh, 1536 (C(O)NH); 3298, 1058 (OH); 2995, 2984 (CH_{cub}); 2931, 2884, 1468, 1382 (Me, CH_2)
21h	210—212	1.19 (d, 3 H, C<u>H</u>$_3$CH, $^3J_{MeCH} \approx 7.3$); 3.10 (m, 2 H, NHC<u>H</u>$_2$, $^3J_{CH_2CH_2} \approx 6.0$; $^3J_{CH_2NH} \approx 5.5$); 3.38 (t, 2 H, CH$_2$<u>H</u>$_2$OH, $^3J_{CH_2CH_2} \approx 6.0$); 4.13—4.34 (m, 7 H, CH_{cub} + C<u>H</u>(CH$_3$)); 4.63 (br.s, 1 H, OH); 7.82 (br.t, 1 H, C(O)N<u>H</u>CH$_2$, $^3J_{NHCH_2} \approx 5.5$); 7.87 (br.d, 1 H, C(O)N<u>H</u>CH, $^3J_{NHCH} \approx 7.7$)	172.1, 169.6 (both 0) (both s, 1 C each, C(O)); 63.9 (0) (s, 1 C, CBr); 59.7 (–) (s, 1 C, <u>C</u>H$_2$OH); 57.3 (0) (s, 1 C, <u>C</u>C(O)); 53.8 (+) (s, 3 C, <u>C</u>HCBr); 47.8 (+) (s, 1 C, <u>C</u>H(CH$_3$)); 47.1 (+) (s, 3 C, <u>C</u>HCC(O)); 41.3 (–) (s, 1 C, N<u>C</u>H$_2$); 18.0 (+) (s, 1 C, Me)	3297 sh, 1040 (OH); 3250, 1662, 1621, 1539 sh, 1521 (C(O)NH); 836 (C—Br); 2989, 1338 (CH_{cub}); 2972, 2937, 2879, 1451, 1366 (Me, CH_2)

(*to be continued*)

Table 1 (*continued*)

Compound	M.p./°C	NMR (DMSO-d_6 + CCl_4), δ (*J*/Hz)		IR, ν/cm^{-1}
		^{1}H	^{13}C	
22a	164—165 (decomp.)	3.45 (dt, 4 H, NHC$\underline{H}_2$$CH_2$, $^3J_{CH_2CH_2} \approx {}^3J_{CH_2NH} \approx 5.0$); 3.68 (d, 4 H, NHC$\underline{H}_2$C(O), $^3J_{CH_2NH} \approx 5.7$); 4.12 (s, 6 H, CH); 4.54 (t, 4 H, CH_2ONO_2, $^3J_{CH_2CH_2} \approx 5.0$); 7.97 (br.t, 2 H, N$\underline{H}$$CH_2$C(O), $^3J_{NHCH_2} \approx 5.7$); 8.10 (br.t, 2 H, N$\underline{H}$$CH_2CH_2$, $^3J_{NHCH_2} \approx 5.0$)	72.1 (–) (s, 2 C, CH_2ONO_2); 45.9 (+) (s, 6 C, $\underline{C}H_{cub}$); 41.8, 36.0 (both –) (both s, 2 C each, CH_2N)	1640, 1279, 887 (ONO_2); 1693, 1624, 3393, 3305, 1561, 1504 (C(O)NH); 3004 (CH_{cub}); 2925, 2853, 1437 (CH_2)
22b	155—156.5	3.41 (m, 2 H, NHC$\underline{H}_2$$CH_2$, $^3J_{CH_2CH_2} \approx {}^3J_{CH_2NH} \approx 5.0$); 3.64 (d, 2 H, NHC$\underline{H}_2$C(O), $^3J_{CH_2NH} \approx 6.0$); 4.25 (m, 6 H, CH, AA´A″BB´B″ system, Δν ≈ 8.0); 4.51 (t, 2 H, CH_2ONO_2, $^3J_{CH_2CH_2} \approx 5.0$); 8.06, 8.08 (both br.t, 1 H each, C(O)NH)	170.3 (0) (s, 1 C, C(O)N); 169.3 (0) (s, 1 C, C(O)N); 72.1 (–) (s, 1 C, $\underline{C}H_2ONO_2$); 63.9 (0) (s, 1 C, $\underline{C}_{cub}$Br); 57.4 (0) (s, 1 C, $\underline{C}_{cub}$C(O)NH); 53.9 (+) (s, 3 C, $\underline{C}H_{cub}$CBr); 47.1 (+) (s, 3 C, $\underline{C}H_{cub}$CC(O)NH; 41.7 (–) (s, 1 C, NH$\underline{C}H_2$C(O)); 36.0 (–) (s, 1 C, NH$\underline{C}H_2CH_2$)	3459, 3292, 1693, 1676, 1618, 1564, 1517 (C(O)NH); 1643, 1282, 892 (ONO_2); 839 (C—Br); 3008, 2991, 1326 (CH_{cub}); 2945, 2894, 1424, 1381 (CH_2)
22c	175—176 (decomp.)	2.25 (t, 4 H, CH_2C(O), $^3J_{CH_2CH_2} \approx 7.0$); 3.13—3.47 (m, 8 H, NHC$\underline{H}_2$); 4.01 (s, 6 H, CH); 4.50 (t, 4 H, CH_2ONO_2, $^3J_{CH_2CH_2} \approx 5.2$); 7.73, 8.15 (both br.t, 2 H each, C(O)NH, $^3J_{NHCH_2} \approx 5.5$)	170.7, 170.6 (both 0) (both s, 2 C each, C(O)); 72.2 (–) (s, 2 C, CH_2ONO_2); 56.9 (0) (s, 2 C, $\underline{C}$C(O)); 45.7 (+) (s, 6 C, CH); 35.9, 35.3 (both –) (both s, 2 C each, NCH_2); 35.1 (–) (s, 2 C, $\underline{C}H_2$C(O))	3322, 1624, 1541 (C(O)NH); 1649, 1279, 850, 847 (ONO_2); 2984, 1343 (CH_{cub}); 2937, 2856 sh, 1431 (CH_2)
22d	144—146	2.24 (t, 2 H, CH_2C(O), $^3J_{CH_2CH_2} \approx 7.0$); 3.25 (dt, 2 H, NHC$\underline{H}_2CH_2$C(O), $^3J_{CH_2CH_2} \approx 7.0$, $^3J_{CH_2NH} \approx 6.0$); 3.40 (dt, 2 H, NH$\underline{C}H_2CH_2ONO_2$, $^3J_{CH_2CH_2} \approx 5.2$, $^3J_{CH_2NH} \approx 5.3$); 4.21 (m, 6 H, CH, AA´A″BB´B″ system, $\Delta\nu_{AB} \approx 5.0$); 4.50 (t, 2 H, CH_2ONO_2, $^3J_{CH_2CH_2} \approx 5.2$); 7.83 (br.t, 1 H, C(O)N$\underline{H}$$CH_2CH_2ONO_2$, $^3J_{NHCH_2} \approx 5.3$); 8.14 (br.t, 1 H, C(O)N$\underline{H}$$CH_2CH_2$C(O), $^3J_{NHCH_2} \approx 6.0$)	170.7 (0) (s, 2 C, C(O)); 72.2 (–) (s, 1 C, CH_2ONO_2); 62.6 (0) (s, 1 C, CBr); 57.4 (0) (s, 1 C, $\underline{C}$C(O)); 53.8 (+) (s, 3 C, $\underline{C}$HCBr); 47.0 (+) (s, 3 C, $\underline{C}$HCC(O)); 35.7 (–) (s, 1 C, $\underline{C}H_2N$); 35.2 (–) (s, 2 C, $\underline{C}H_2$C(O) + $\underline{C}H_2$N)	3327, 1616, 1528 (C(O)NH); 1652, 1279, 883, 759 (ONO_2); 841 (C—Br); 3000, 2980, 1353 (CH_{cub}); 2956, 2923, 2852, 1469, 1420 (CH_2)
22g	192—193 (decomp.)	1.21 (d, 6 H, C$\underline{H}_3$CH, $^3J_{CH_2CH} \approx 7.1$); 3.40 (br.m, 4 H, NCH_2); 4.07 (s, 6 H, CH); 4.25 (m, 2 H, NC$\underline{H}$$CH_3$); 4.51 (br.m, 4 H, CH_2ONO_2); 7.81 (br.d, 2 H, C(O)N$\underline{H}$CH, $^3J_{NHCH} \approx 7.5$); 8.11 (br.t, 2 H, C(O)N$\underline{H}$$CH_2$)	172.8, 170.4 (both 0) (both s, 2 C each, C(O)); 72.0 (–) (s, 2 C, CH_2ONO_2); 56.6 (0) (s, 2 C, $\underline{C}$C(O)); 47.8, 45.9 (+) (s, 6 C, CH); 36.0 (–) (s, 2 C, NCH_2); 17.8 (+) (s, 2 C, Me)	3316, 1665, 1630, 1557, 1536, 1521 (C(O)NH); 1624, 1279, 865 (ONO_2); 2984, 1343 (CH_{cub}); 2937, 2880 sh, 2855 sh, 1436, 1369 (Me, CH_2)

(*to be continued*)

Table 1 (*continued*)

Compound	M.p./°C	NMR (DMSO-d_6 + CCl_4), δ (*J*/Hz)		IR, ν/cm^{-1}
		^{1}H	^{13}C	
22h	158—160	1.20 (d, 3 H, C<u>H</u>$_3$CH, $^3J_{MeCH} \approx 7.0$); 3.39 (m, 2 H, NHC<u>H</u>$_2$CH$_2$); 4.13—4.36 (m, 7 H, CH$_{cub}$ + C<u>H</u>Me); 4.50 (t, 2 H, CH$_2$ONO$_2$, $^3J_{CH_2CH_2} \approx$ 5.3); 7.93 (br.d, 1 H, C(O)N<u>H</u>CH, $^3J_{NHCH} \approx 7.5$); 8.11 (br.t, 1 H, C(O)N<u>H</u>CH$_2$, $^3J_{NHCH_2} \approx 5.7$)	172.6, 169.7 (both 0) (both s, 1 C each, C(O); 72.0 (–) (s, 1 C, CH$_2$ONO$_2$); 63.9 (0) (s, 1 C, <u>C</u>Br); 57.3 (0) (s, 1 C, <u>C</u>C(O)); 53.9 (+) (s, 3 C, <u>C</u>HCBr); 47.9 (+) (s, 1 C, <u>C</u>H(CH$_3$)); 47.1 (+) (s, 3 C, <u>C</u>HCC(O)); 36.0 (–) (s, 1 C, N<u>C</u>H$_2$); 17.7 (+) (s, 1 C, Me)	3339, 3263, 1670, 1618 sh, 1541 (C(O)NH); 1636, 1279, 870, 759 (ONO$_2$); 847, 834 (C—Br); 3001, 2985, 1335 (CH$_{cub}$); 2954, 2937, 2890, 2850 sh, 1451 sh, 1441, 1425, 1374 (Me, CH$_2$)

* The results of DEPT experiments are given in parentheses: (+) refers to signals of positive polarity (from CH or CH$_3$), (–) refers to signals of negative polarity (from CH$_2$), (0) means the absence of signals (quaternary C atoms).

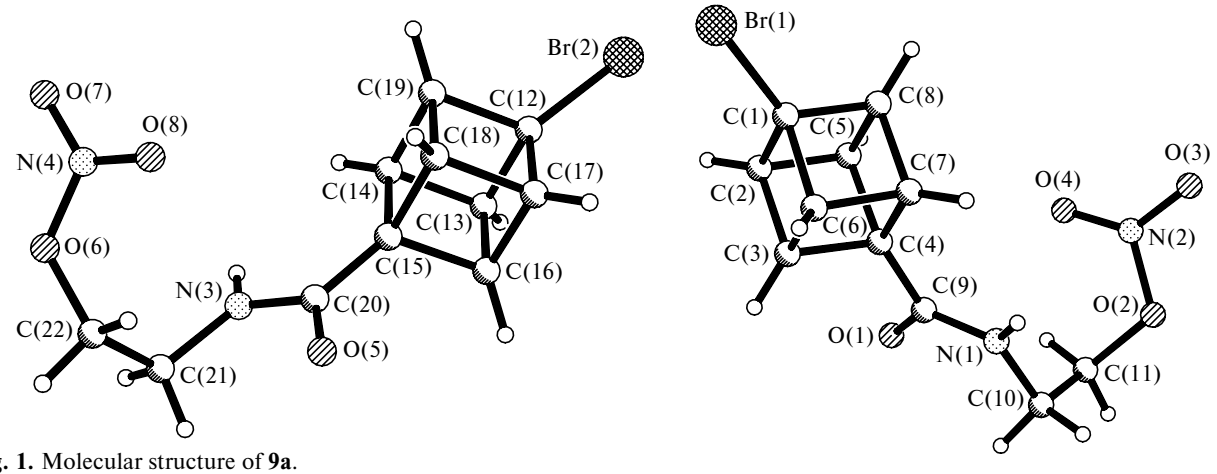


Fig. 1. Molecular structure of **9a**.

be equal to or higher than that of nicorandil. Compounds **9a**, **22b**, and **22h** exhibited the highest activity, which is higher than that of nicorandil by a factor of 10.5, 3.5, and 1.5, respectively.

The effect on the activity of slow calcium channels, *e.g.*, on the calcium channel blocking activity, was studied also in isolated rat aorta strips. In control experiments, the strips were contracted with a calcium chloride solution without the use of the tested compound, the contraction of the strip length being taken as 100%. In experiments with the addition of the tested compound, the contraction of the strip length decreased for 10 min before the treatment with calcium chloride. The amplitude of contraction of the strip length expressed in percentage with respect to the control experiments was taken as the activity of the compounds. It was found that the blocking activity of many tested compounds with respect to both K-ATP-sensitive and calcium channels is comparable (in some cases, even higher) with that of nicorandil (the effect of the decrease in the contraction is 70—80%).

Experimental

The ^{1}H (200.13 MHz) and ^{13}C (50.3 MHz) NMR spectra were recorded on a Bruker DPX-200 spectrometer with respect to Me_4Si as the internal standard. The ^{1}H and ^{13}C NMR experiments were carried out for the same samples. A DMSO-d_6 + + CCl_4 (25 vol.%) + Me_4Si (0.1 wt.%) mixture was used as the solvent. The assignment of the signals was made taking into account the data for related compounds, which have been obtained in our earlier studies[7,8] and also by other authors,[9] the types of multiplets, the integrated intensities, and ^{13}C{^{1}H}DEPT experiments. The IR spectra were recorded on a Specord M-82 spectrophotometer (KBr pellets).

Compounds **1**, **3**, and **6** were synthesized according to known procedures.[8—10] Characteristics of the compounds are summarized in Table 1.

Methyl 4-bromocubanecarboxylate (7). A mixture of ester **6** (1 g, 0.005 mol), HgO (1.2 g), and CH_2Br_2 (25 ml) was heated to 90 °C. Then a solution of Br_2 (1.2 g, 0.015 mol) in CH_2Br_2 (15 mL) was added dropwise at this temperature for 20 min. The reaction mixture was refluxed for 3 h and cooled. Then the solvent and excess Br_2 were removed, and the residue was

washed with a small amount of water and recrystallized from 50% MeOH. The yield was 1.0 g (85%), m.p. 120—121 °C (*cf.* lit. data[9]: m.p. 120.5—122 °C).

4-Bromocubanecarboxylic acid (2). A solution of NaOH (0.2 g, 0.005 mol) in MeOH (2 mL) was added with stirring to a solution of compound **7** (1.2 g, 0.005 mol) in THF (15 mL). The reaction mixture was stirred at ~20 °C for 5 h, the solvent was removed under reduced pressure, the precipitate was dissolved in water (10 mL), and the solution was acidified with concentrated HCl to pH = 3. A white powder of **2** was filtered off, washed with a small amount of water, and dried *in vacuo* to constant weight. The yield was 1.1 g (96%), m.p. 215—216 °C (*cf.* lit. data[9]: m.p. 213.5—216.5 °C).

***N*,*N*′-Bis(3-hydroxyethyl)diamide of cubane-1,4-dicarboxylic acid (4a), *N*,*N*′-bis(3-hydroxypropyl)diamide of cubane-1,4-dicarboxylic acid (4b), *N*-(2-hydroxyethyl)amide of 4-bromocubane-1-carboxylic acid (8a), and *N*-(3-hydroxypropyl)amide of 4-bromocubane-1-carboxylic acid (8b) (general procedure).** A solution of ester **3** (0.005 mol) or compound **7** (0.01 mol) and a threefold excess of amino alcohol in EtOH (50 mL) was refluxed for 5 h. After cooling of the reaction mixture to ~20 °C followed by the removal of the solvent and excess amino alcohol, the resulting solid product was recrystallized from EtOH. The yields were 80—90%.

***N*,*N*′-Bis(2-nitroxyethyl)diamide of cubane-1,4-dicarboxylic acid (5a), *N*,*N*′-bis(3-nitroxypropyl)diamide of cubane-1,4-dicarboxylic acid (5b), *N*-(2-nitroxyethyl)amide of 4-bromocubane-1-carboxylic acid (9a), and *N*-(3-nitroxypropyl)amide of 4-bromocubane-1-carboxylic acid (9b) (general procedure).** Compounds **4a,b** (2.5 mmol) or compounds **8a,b** (5 mmol) were slowly added to a mixture of concentrated HNO_3 (1.0 mL, 0.025 mol) and Ac_2O (2.3 mL, 0.025 mol) cooled to 0 °C or to a solution of HNO_3 (1.0 mL, 0.025 mol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 0—5 °C for 15 min, and then dry Et_2O (25 mL) was added. The precipitate that formed was filtered off, washed with water, dried in a vacuum desiccator over P_2O_5, and recrystallized from EtOH. The yields were 90—95%.

Bis(*p*-nitrophenyl) cubane-1,4-dicarboxylate (10a), *p*-nitrophenyl 4-bromocubanecarboxylate (10b), and 1-carbo-*p*-nitrophenoxy-4-carbomethoxycubane (15). Thionyl chloride (10 mL) was added to compound **1** (0.005 mol), **2** (0.01 mol), or **6** (0.01 mol), and the reaction mixture was kept at 50—60 °C for 3 h. Excess $SOCl_2$ was distilled off *in vacuo*. Acid chloride was obtained in quantitative yield. The latter compound was immediately used for the further synthesis. A mixture of the freshly prepared acid chloride, $CHCl_3$ (10 mL), and *p*-nitrophenol (1.6 g, 0.011 mol) was refluxed with stirring for 2 h. Then the reaction mixture was cooled, and the solvent was removed under reduced pressure. The solid residue was washed with hot water to remove excess *p*-nitrophenol and then with diethyl ether and recrystallized from chloroform. The yields were 80—90%.

***N*,*N*′-Bis(3-carboxypropyl)diamide of cubane-1,4-dicarboxylic acid (11a), *N*-(3-carboxypropyl)amide of 4-bromocubanecarboxylic acid (11b), and *N*-(3-carboxypropyl)amide of 4-carbomethoxycubanecarboxylic acid (16).** A mixture of compound **10a** (0.005 mol), **10b** (0.01 mol), or **15** (0.01 mol), anhydrous dioxane (50 mL), and γ-aminobutyric acid (1.6 g, 50% excess) was refluxed for 5 h. After cooling, the solid residue was filtered off, washed with water and diethyl ether, and recrystallized from EtOH. The yields were 90—95 %.

***N*,*N*′-Bis(3-carbomethoxypropyl)diamide of cubane-1,4-dicarboxylic acid (12a), *N*-(3-carbomethoxypropyl)amide of 4-bromocubanecarboxylic acid (12b), and *N*-(3-carbomethoxypropyl)amide of 4-carbomethoxycubanecarboxylic acid (17).** Cold $SOCl_2$ (30 mL) was added to compound **11a** (0.005 mol), **11b** (0.01 mol), or **16** (0.01 mol). The reaction mixture was stirred at 0—2 °C for 2 h. Excess $SOCl_2$ was distilled off *in vacuo* at ≤5—10 °C. Precooled MeOH (30 mL) was added to the resulting acid chloride, and the reaction mixture was stirred at 0—2 °C for 2 h. The solvent was distilled off, and the precipitate was dried. The yields were 85—90%.

***N*,*N*′-Bis(4-oxo-5-aza-7-hydroxyheptyl)diamide of cubane-1,4-dicarboxylic acid (13a), *N*-(4-oxo-5-aza-7-hydroxyheptyl)amide of 4-bromocubanecarboxylic acid (13b), *N*,*N*′-bis(4-oxo-5-aza-8-hydroxyoctyl)diamide of cubane-1,4-dicarboxylic acid (13c), *N*,*N*′-bis(4-oxo-5-aza-6-ethyl-7-hydroxyheptyl)diamide of cubane-1,4-dicarboxylic acid (13d), *N*,*N*′-bis(4-oxo-5-aza-6,6-dimethyl-7-hydroxyheptyl)diamide of cubane-1,4-dicarboxylic acid (13e), and *N*-(4-oxo-5-aza-7-hydroxyheptyl)-*N*′-(2-hydroxyethyl)diamide of cubane-1,4-dicarboxylic acid (18) (general procedure).** A solution of ester **12a** (0.005 mol), **17** (0.005 mol), or **12b** (0.01 mol) and a threefold (with respect to theoretical) amount of amino alcohol in EtOH (25 mL) was refluxed for 10—20 h. The course of the reaction was monitored by IR spectroscopy based on a decrease in the intensities of the stretching bands of the carbonyl group of the ester fragment in the corresponding ester **12a,b** or **17** and an increase in the intensities of the bands of the carbonyl group of the amide fragment. The reaction was terminated when the IR spectrum showed that the ester group virtually disappeared in the reaction mixture. After completion of the reaction, the mixture was cooled to ~20 °C, the solvent and excess amino alcohol were removed under reduced pressure, and the resulting solid product was recrystallized from ethyl acetate. The yields were 80—90%.

***N*,*N*′-Bis(4-oxo-5-aza-7-nitroxyheptyl)diamide of cubane-1,4-dicarboxylic acid (14a), *N*-(4-oxo-5-aza-7-nitroxyheptyl)amide of 4-bromocubanecarboxylic acid (14b), *N*,*N*′-bis(4-oxo-5-aza-8-nitroxyoctyl)diamide of cubane-1,4-dicarboxylic acid (14c), *N*,*N*′-bis(4-oxo-5-aza-6-ethyl-7-nitroxyheptyl)diamide of cubane-1,4-dicarboxylic acid (14d), *N*,*N*′-Bis(4-oxo-5-aza-6,6-dimethyl-7-nitroxyheptyl)diamide of cubane-1,4-dicarboxylic acid (14e), and *N*-(4-oxo-5-aza-7-nitroxyheptyl)-*N*′-(2-nitroxyethyl)diamide of cubane-1,4-dicarboxylic acid (19) (general procedure).** Compound **13a,c,d,e** (2.5 mmol), **18** (2.5 mmol), or **13b** (5 mmol) was slowly added to a mixture of concentrated HNO_3 (1.0 mL, 0.025 mol) and Ac_2O (2.3 mL, 0.025 mol) cooled to 0 °C or to a solution of HNO_3 (1.0 mL, 0.025 mol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 0—5 °C for 15 min, and then dry diethyl ether (25 mL) was added. The precipitate that formed was filtered off, washed with water, dried in a vacuum desiccator over P_2O_5, and recrystallized from EtOH. The yields were 90—95%.

***N*,*N*′-Bis(carbethoxymethyl)diamide of cubane-1,4-dicarboxylic acid (20a), *N*-(carbethoxymethyl)amide of 4-bromocubanecarboxylic acid (20b), *N*,*N*′-bis(2-carbethoxyethyl)-diamide of cubane-1,4-dicarboxylic acid (20c), *N*-(2-carbethoxyethyl)amide of 4-bromocubanecarboxylic acid (20d), *N*,*N*′-bis(3-carbethoxypropyl)diamide of cubane-1,4-dicarboxylic acid (20e), *N*-(3-carbethoxypropyl)amide of 4-bromocubanecarboxylic acid (20f), *N*,*N*′-bis(1-methyl-1-carbethoxymethyl)diamide of cubane-1,4-dicarboxylic acid (20g), and *N*-(1-methyl-1-carbethoxy-**

methyl)amide of 4-bromocubanecarboxylic acid (20h) (general procedure). Thionyl chloride (10 mL) was added to compound **1** (1.0 g, 0.005 mol) or compound **2** (2.3 g, 0.01 mol), and the reaction mixture was kept at 50—60 °C for 3 h. Excess $SOCl_2$ was distilled off *in vacuo*. An equimolar amount of the hydrochloric salt of amino acid methyl (or ethyl) ester was added to a solution of the freshly prepared acid chloride in CH_2ClCH_2Cl (30 mL), and the reaction mixture was stirred at 30—40 °C until it became homogeneous. Then the mixture was cooled to 10—15 °C, and a solution of Et_3N in CH_2ClCH_2Cl was slowly added dropwise to pH = 8. After the addition of the required amount of Et_3N, the reaction mixture was stirred at ~20 °C for 1 h, water was added until the precipitate was dissolved, the organic layer was separated, and the aqueous layer was extracted with CH_2ClCH_2Cl (3×10 mL). The combined dichloroethane solutions were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The physicochemical characteristics of products **20a—h** (after recrystallization from ethyl acetate) are given in Table 1. The yields were 65—75%.

***N*,*N*′-Bis(2-oxo-3-aza-5-hydroxyamyl)diamide of cubane-1,4-dicarboxylic acid (21a), *N*-(2-oxo-3-aza-5-hydroxyamyl)amide of 4-bromocubanecarboxylic acid (21b), *N*,*N*′-bis(3-oxo-4-aza-6-hydroxyhexyl)diamide of cubane-1,4-dicarboxylic acid (21c), *N*-(3-oxo-4-aza-6-hydroxyhexyl)amide of 4-bromocubanecarboxylic acid (21d), *N*,*N*′-bis(4-oxo-5-aza-7-hydroxyheptyl)diamide of cubane-1,4-dicarboxylic acid (21e), *N*-(4-oxo-5-aza-7-hydroxyheptyl)amide of 4-bromocubanecarboxylic acid (21f), *N*,*N*′-bis(1-methyl-1-carbethoxymethyl)diamide of cubane-1,4-dicarboxylic acid (21g), and *N*-(1-methyl-2-oxo-3-aza-5-nitroxyamyl)amide of 4-bromocubanecarboxylic acid (21h) (general procedure).** A solution of ester **20a,c,e,g** (0.005 mol) or **20b,d,f,h** (0.01 mol) and a threefold (with respect to theoretical) amount of monoethanolamine in EtOH (25 mL) was refluxed for 10—20 h. The course of the reaction was monitored by IR spectroscopy. The reactions were performed until the bands of the C(O)O group of the corresponding ester **20a—h** completely disappeared by analogy with the synthesis of compounds **13a—e** and **18**. After completion of the reaction, the reaction mixture was cooled to ~20 °C, the solvent and excess amino alcohol were removed under reduced pressure, and the resulting solid product was recrystallized from ethyl acetate. The yields were 80—90%. The physicochemical characteristics of compounds **21e,f** are identical to those of compounds **13a,b**.

***N*,*N*′-Bis(2-oxo-3-aza-5-nitroxyamyl)diamide of cubane-1,4-dicarboxylic acid (22a), *N*-(2-oxo-3-aza-5-nitroxyamyl)-amide of 4-bromocubanecarboxylic acid (22b), *N*,*N*′-bis(3-oxo-4-aza-6-nitroxyhexyl)diamide of cubane-1,4-dicarboxylic acid (22c), *N*-(3-oxo-4-aza-6-nitroxyhexyl)amide of 4-bromocubanecarboxylic acid (22d), *N*,*N*′-bis(4-oxo-5-aza-7-nitroxyheptyl)diamide of cubane-1,4-dicarboxylic acid (22e), *N*-(4-oxo-5-aza-7-nitroxyheptyl)amide of 4-bromocubanecarboxylic acid (22f), *N*,*N*′-bis(1-methyl-2-oxo-3-aza-5-nitroxyamyl)diamide of cubane-1,4-dicarboxylic acid (22g), and *N*-(1-methyl-2-oxo-3-aza-5-nitroxyamyl)amide of 4-bromocubanecarboxylic acid (22h) (general procedure).** Compound **21a,c,e,g** (2.5 mmol) or compound **21b,d,f,h** (5 mmol) was slowly added to cooled 90—95% HNO_3 (1 mL, fivefold excess) at 0—5 °C. The reaction mixture was stirred at this temperature for 30 min and poured into ice water. The precipitate that formed was filtered off, washed with water, dried in a vacuum desiccator over P_2O_5, and recrystallized from ethyl acetate or ethanol. The yields were 90—95%.

Table 2. Crystallographic parameters of compound **9a**

Parameter	Characteristics
Molecular formula	$C_{11}H_{11}BrN_2O_4$
Molar weight/g mol^{-1}	315.13
Crystal system	Orthorhombic
Space group	$Pna2_1$
a/Å	9.379(2)
b/Å	6.3930(15)
c/Å	39.484(9)
V/Å^3	2367.5(10)
Z	8
d_{calc}/g cm^{-3}	1.768
μ/mm^{-1}	3.481
Number of measured reflections	7408
Number of reflections with $I > 2\sigma(I)$	3290
R_1	0.0529
wR_2	0.1180

The physicochemical characteristics of compounds **22e,f** are identical to those of compounds **14a,b**.

X-ray diffraction study. The experimental X-ray diffraction data for compound **9a** were collected on an automated Bruker AXS SMART diffractometer equipped with a CCD detector (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, 120 K, ω-scanning technique with a step of 0.3°, exposure time per frame was 30 s) using a standard procedure.[11] The structure of compound **9a** was solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for all nonhydrogen atoms. The H atoms were located in difference Fourier maps and refined isotropically using a riding model. The calculations were carried out using the SHELX-97 program package.[12,13] The crystallographic parameters and the refinement statistics for compound **9a** are given in Table 2.

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