Cubane derivatives

3.* Synthesis and antiischemic activity of some nitroxyalkyl derivatives of 1,4-cubanedicarboxylic acid and its diamide

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New *N,N'*-bis- and *N,N,N',N'*-tetrakis-hydroxyalkyl-substituted 1,4-cubanedicarboxamides were synthesized. Nitration of these compounds yielded the corresponding nitrates. The reactions of 1,4-cubanedicarboxylic acid dichloride with ethylene glycol mononitrate and glycerol dinitrate gave esters 1,4-$[R^1R^2CHOC(O)]_2C_8H_6$, where R^1 = H and R^2 = CH_2ONO_2; and R^1 = R^2 = CH_2ONO_2, respectively. The cardiopharmacological activity of some of the synthesized compounds was determined. This allowed us to find for the first time cubane derivatives that exhibit this kind of biological activity. The antiischemic activity of one of these compounds, *N,N'*-bis(2-nitroxyethyl)-1,4-cubanedicarboxdiamide, is higher than that of the well-known Nicorandil.

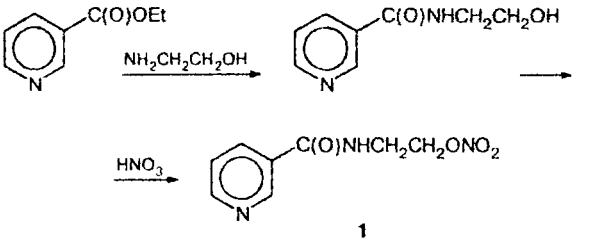
Key words: 1,4-cubanedicarboxylic acid, hydroxy- and nitroxyalkylamides, esters, antiischemic activity, Nicorandil.

Compounds containing the cubane (pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane) fragment attract the attention of scientists not only due to their new original chemistry.[2] High enthalpies of formation and the density of nitro derivatives of cubane gave impetus to a search for high-energy compounds, namely, powerful explosives and components of propellant systems, based on these derivatives.[3,4] Cubane derivatives containing other substituents are characterized by ever wider limits of pharmacological activity. Data on antitumor, anti-HIV, antiviral, and antiulcer activities of cubane derivatives as well as on their antinarcotic action are available in the literature.[3,5–7]

The aim of this work was to synthesize cubane derivatives containing nitrate groups and to carry out the preliminary estimation of their cardiopharmacological antiischemic activity typical of alcohol nitrates. We used the promising antianginal drug, *N*-(2-nitroxyethyl)nicotinamide (Nicorandil) (**1**), which has been produced in Japan since 1984 and introduced to the European market under the commercial name Icorel in recent years, as a reference compound.

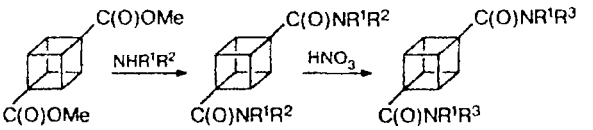
Results and Discussion

Based on a rather simple and well-reproducible procedure for the preparation of compound **1** described in the literature:[8,9]



1

and on a procedure for the synthesis of esters of 1,4-cubanedicarboxylic acid with the use of alkyl sulfates, which we have developed recently,[10] we synthesized a number of substituted diamides of 1,4-cubanedicarboxylic acid **3** and **4** starting from dimethyl ester **2**:



2 **3a–e** **4a–e**

3: R^1 = H; R^2 = $(CH_2)_2OH$ (**a**), R^2 = $(CH_2)_3OH$ (**b**), R^2 = $CHEtCH_2OH$ (**c**), R^2 = CMe_2CH_2OH (**d**), R^1 = R^2 = $(CH_2)_2OH$ (**e**)

4: R^1 = H; R^3 = $(CH_2)_2ONO_2$ (**a**), R^3 = $(CH_2)_3ONO_2$ (**b**), R^3 = $CHEtCH_2ONO_2$ (**c**), R^3 = $CMe_2CH_2ONO_2$ (**d**), R^1 = R^3 = $(CH_2)_2ONO_2$ (**e**)

The reactions of compound **2** with aminoalcohols were carried out in boiling methanol. Methanol and an

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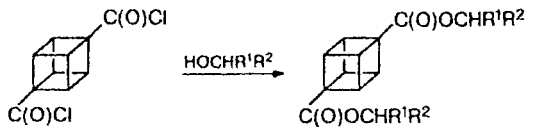
excess of aminoalcohol were distilled off. Hydroxyalkylamides **3** were purified by recrystallization from a suitable solvent and then converted to nitrates **4** by nitration either with an equimolar mixture of HNO_3 and Ac_2O or with solutions of HNO_3 in CH_2Cl_2.

Recently,[1] we have developed a method for preparing 1,4-cubanedicarboxylic acid dichloride (**5**). Its high reactivity was confirmed by the reaction of compound **5** with MeOH. This reaction gave ester **2** in a yield, which was ~15% higher than that obtained in the reaction with methyl sulfate.[10] This is of considerable importance because of the fact that 1,4-cubanedicarboxylic acid is scarcely available. The reactions of **5** with ethylene glycol mononitrate and glycerol dinitrate afforded the desired compounds containing nitrate groups, namely, esters **6**.



5 **6a,b**

6a: $R^1 = H$, $R^2 = CH_2ONO_2$
6b: $R^1 = R^2 = CH_2ONO_2$

The major characteristics of the synthesized substituted amides and esters of 1,4-cubanedicarboxylic acid are given in Table 1.

The antiischemic activity of selected synthesized compounds (Table 2) was determined at the All-Russian Scientific Center of Safety of Biologically Active Compounds of the Russian Health Ministry. The estimation was carried out using the best integral test, namely, by studying the effect of these compounds on the size of the necrotic zone after myocardial infarction induced in non-line white rats with weights of 250—350 g. The effect of the compounds on the size of the necrotic zone was determined within 4 h after occlusion of the coronary artery using the differential indicator method.[11,12] The method was based on separate quantitative determination of sizes of the necrotic and ischemic zones.

The samples were introduced into rats in isotoxic doses. Because of this, the preliminary determination of acute toxicity was required. For this purpose, the compounds were introduced into mice intraperitoneally. From the values of LD_{50} in Table 2 it follows that the acute toxicity of the compounds that contain the cubane fragment is substantially lower than that of Nicorandil and is many times lower than that of nitroglycerine (LD_{50} = 108 mg kg^{-1}).

The results of determination of antiischemic activity of the compounds under study are represented in Table 2 as a ratio between the necrotic and ischemic zones (in %) in comparison with assays in which the drug was not introduced (reference). Table 2 gives also the antiischemic activity of 2-nitroxyethyl nicotinate (**7**), which was prepared according to a standard procedure from nicotinoyl chloride and ethylene glycol mononitrate (m.p. is 45—46 °C from propan-2-ol).

It should be noted that compound **7** does not show reliable statistical differences from the reference, and its antiischemic activity is rather low. The other compounds under study (**1**, **4a**, **4d**, and **6a**) exhibit pronounced antiischemic activity. In these cases, the differences from the reference assays are statistically reliable.[13]

The data in Table 2 allow one to reveal regularities of the changes in the antiischemic activity in relation to the structures of the compounds under study. First, an analog of Nicorandil, compound **4a**, exhibits the highest antiischemic activity in the series of the compounds under study although it is less toxic. This fact proved the great potential of the cubane fragment in the development of cardiopharmacological drugs. Apparently, a search for these drugs among compounds of the cubane series as well as a search for other kinds of pharmaceuticals show promise. A pairwise comparison of the antiischemic activities of compounds **1** and **7** and compounds **4a** and **6a** led us to the same conclusion. The replacement of the amide functional group in compound **1** by the ester group leads to a loss of activity. Although this replacement in compound **4a** results in a decrease in the activity, the activity of compound **6a** that contains the cubane fragment remains relatively high. It is worthy of note that other changes in the chemical structures of the substituents also affect substantially the activity of cubane systems. Thus, the antiischemic activities of compounds **4d** and **6a** are virtually identical in spite of the fact that **4d** contains the amide functional groups, while **6a** contains ester groups.

Experimental

The ^1H NMR spectra were recorded on an NMR spectrometer equipped with a superconducting magnet (294 MHz). The instrument was developed and built at the Institute of Chemical Physics in Chernogolovka of the Russian Academy of Sciences. The IR spectra were measured on a Specord M82 spectrophotometer.

Preparation of hydroxy-substituted 1,4-cubanedicarboxamides (3a—e) (general procedure). A solution of ester **2** (4.5 mmol) and aminoalcohol (13.5 mmol) in ethanol (50 mL) was refluxed for 5 h. After cooling of the reaction mixture to ~20 °C and the removal of the solvent and excess aminoalcohol, a solid product was obtained. The product was recrystallized from ethanol. The yield was 80—90%. The characteristics of products **3a—e** are given in Table 1.

Preparation of nitroxy-substituted 1,4-cubanedicarboxamides (4a—e) (general procedure). Compounds **3a—e** (8 mmol) were slowly added to a cooled 1 : 1 HNO_3—Ac_2O mixture or to a solution of HNO_3 in CH_2Cl_2 (a fivefold excess). The reaction mixture was stirred at 0—5 °C for 15 min, and then dry 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 ethanol.

Table 1. Major characteristics of the synthesized substituted amides and esters of 1,4-cubanedicarboxylic acid

Compound	Molecular formula	Found / Calculated (%) C	H	N	M.p. /°C	^{1}H NMR (Me_4Si, DMSO-d_6, δ, *J*/Hz)	IR spectrum (KBr pellets), ν/cm^{-1}
3a	$C_{14}H_{18}N_2O_4$	59.50 60.42	6.48 6.52	10.22 10.07	226—227	3.14 (q, 4 H, NCH_2, $^3J \approx 6.0$); 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, $^3J \approx 6.0$)	3362, 3329, 3227, 3239 (OH, NH); 2987 (CH cubane); 2927, 2876 (CH_2); 1634 (C=O); 1550 (NH); 1067 (C—OH)
3b	$C_{16}H_{22}N_2O_4$	62.80 62.73	7.30 7.24	9.80 9.14	268—270	1.56 (quintet, 4 H, CCH_2C, $^3J \approx 6.0$); 3.00 (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 (NH); 2993 (CH cubane); 2927, 2867 (CH_2); 1622 (C=O); 1061 (C—OH)
3c	$C_{18}H_{26}N_2O_4$	64.50 64.65	7.92 7.84	8.40 8.38	238—239		3344 (OH); 3240 sh, 1556, 1541, 1532 (NH); 2990 (CH cubane); 2963, 2933, 2879 (CH_3, CH_2); 1622 (C=O); 1055 (C—OH)
3d	$C_{18}H_{26}N_2O_4$	65.18 64.65	7.62 7.84	8.53 8.38	245—246	1.19 (s, 12 H, CCH_3); 3.39 (s, 4 H, OCH_2); 4.00 (s, 6 H, CH); ~4.9 (br.s, 2 H, OH); 6.89 (s, 2 H, NH)	3299 (OH); 3242 sh, 1538 (NH); 2999 (CH cubane); 2972, 2927, 2870 (CH_3, CH_2); 1625 (C=O); 1475, 1451, 1439, 1382, 1361 (CH_3, CH_2); 1073 (C—OH)
3e	$C_{18}H_{26}N_2O_6$	59.60 59.00	7.46 7.15	7.73 7.65	190—191	3.21 (br.t, 4 H, NCH_2-*cis*, ^3J = 5.5); 3.36 (br.t, 4 H, NCH_2-*trans*, ^3J = 5.5); 3.51 (br.t, 4 H, OCH_2-*cis*, ^3J = 5.5); 3.60 (m, 4 H, OCH_2-*trans*); 4.18 (s, 6 H, CH); 4.76 (br.s, 2 H, OH-*cis*); 4.91 (br.s, 2 H, OH-*trans*)	3455, 3380 (OH); 3014, 2999, 2978 (CH cubane), 2942, 2864 (CH_2); 1583 (C=O); 1082, 1078 (C—OH)
4a	$C_{14}H_{16}N_4O_8$	45.44 45.66	4.53 4.38	15.22 15.21	141—142	3.40 (q, 4 H, NCH_2, ^3J = 6.0); 4.02 (s, 6 H, CH); 4.54 (t, 4 H, CH_2ONO_2, ^3J = 6); 8.00 (br.t, 2 H, NH, ^3J = 6.0)	3002, 1349 (CH cubane); 3218, 1538 (NH); 1630 sh (C=O); 1619, 1271, 851 (ONO_2)
4b	$C_{16}H_{20}N_4O_8$			14.28 14.14	167—168		3260, 1552 (NH); 3000, 2990, 1335 (CH cubane); 2930, 2870 (CH_2); 1650 sh (C=O); 1630, 1285, 895, 880 (ONO_2)
4c	$C_{18}H_{24}N_4O_8$	51.50 50.94	5.70 5.70	13.80 13.20	131—132	0.88 (t, 3 H, CH_3, ^3J = 7.0); 1.55 (m, 2 H, $CHCH_2CH_3$); 3.30 (m, 2 H, $NCH+H_2O$); 4.06 (s, 6 H, CH); 4.50 (m, 4 H, CH_2ONO_2, ABX, $\Delta\nu_{AB}$ = 61.0, $\lvert^2J_{AB}\rvert$ = 11.0, $^3J_{AX}$ = 3.8); 7.71 (br.m, 1 H, C(O)NH)	3280, 1532 (NH); 2990 sh (CH cubane); 2970, 2927, 2876 (CH_3, CH_2); 1645 sh (C=O); 1634, 1277, 860 (ONO_2)
4d	$C_{18}H_{24}N_4O_8$	50.75 50.94	6.28 5.70	12.98 13.20	126—127	1.31 (s, 12 H, CCH_3); 4.02 (s, 6 H, CH); 4.75 (s, 4 H, CH_2ONO_2); 7.40 (br.s, 2 H, NH)	3290, 1538 (NH); 3000 sh (CH cubane); 2987, 2930, 2900 (CH_3, CH_2); 1645 sh (C=O); 1634, 1283, 875, 848 (ONO_2)
4e	$C_{18}H_{22}N_6O_{14}$	39.68 39.57	4.06 4.06	15.80 15.38	101—102	3.48 (br.t, 4 H, NCH_2-*cis*, ^3J = 4.4); 3.65 (br.t, 4 H, NCH_2-*trans*, ^3J = 4.4); 4.18 (s, 6 H, CH); 4.61 (br.t, 4 H, CH_2ONO_2-*cis*, ^3J = 4.4); 4.71 (br.t, 4 H, CH_2ONO_2-*trans*, ^3J = 4.4)	3011, 2981 (CH cubane); 2921, 2850 (CH_2); 1650 sh (C=O); 1634, 1286, 863, 851 (ONO_2)
6a	$C_{14}H_{14}N_2O_{10}$	45.70 45.41	3.57 3.81	7.64 7.57	89—90	4.21 (s, 6 H, CH); 4.36 (m, 4 H, OCH_2); 4.75 (m, 4 H, CH_2ONO_2)	3004, 2990, 1316 (CH cubane); 1718 (C=O); 1634, 1283, 857 (ONO_2); 1442 (CH_2); 1214, 1085 (C—O—C)
6b	$C_{16}H_{16}N_4O_{16}$	36.98 36.92	3.00 3.10	10.76 10.77	108—109	4.17 (s, 6 H, CH); 4.67 (m, 8 H, CH_2ONO_2, ABX, $\Delta\nu$ = 38.5, $^3J_{AX}$ = 3.6, $^3J_{BX}$ = 5.9); 5.40 (m, 2 H, OCH, ABX)*	3017, 2994, 1331, 1319 (CH cubane);1730 (C=O); 1655, 1634, 1280, 848 (ONO_2); 1457, 1434 (CH_2); 1214, 1088 (C—O—C)

* CD_3CN.

Table 2. Antiischemic activity of selected synthesized compounds

Compound	LD_{50} /mg kg^{-1}	α* (%) (number of assays)
**	—	68.0±4.3 (17)
1	475	42.0±5.4 (8)
4a	800	36.1±6.2 (6)
4d	750	51.4±7.9 (6)
6a	825	50.3±6.1 (6)
7	>1000	57.4±4.3 (6)

* α is the ratio between the necrotic and ischemic zones. ** Reference compound.

The yield was 90—95%. The characteristics of products **4a—e** are given in Table 1.

Bis(2-nitroxyethyl) 1,4-cubanedicarboxylate (6a). A solution of ethylene glycol mononitrate (1.67 g, 15.6 mmol) in dichloroethane (20 mL) was added with stirring to freshly prepared acid dichloride **5** (1.16 g, 5.2 mmol) at 20 °C. The reaction mixture was refluxed at 80—82 °C for 48 h until liberation of HCl ceased. The solvent and an excess of ethylene glycol mononitrate were removed. The solid compound (1.66 g, 86%) that formed was recrystallized from hexane. The characteristics of product **6a** are given in Table 1.

Bis(2-dinitroxypropyl) 1,4-cubanedicarboxylate (6b). A solution of glycerol 1,3-dinitrate (2.84 g, 15.6 mmol) in dichloroethane (30 mL) was added with stirring to freshly prepared compound **5** (1.16 g, 5.2 mmol) at ~20 °C. The reaction mixture was refluxed at 80—82 °C for 48 h until liberation of HCl ceased. The solvent and an excess of glycerol dinitrate were removed. The solid compound (2.5 g, 92%) that formed was recrystallized from hexane. The characteristics of product **6b** are given in Table 1.

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