Cubane derivatives

6.* Synthesis of some substituted hydrazides of 1,4-cubanedicarboxylic acid

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An efficient procedure was developed for the preparation of 1,4-cubanedicarboxylic acid dihydrazide (**1**). Its reactions with acetic anhydride, aromatic aldehydes, and acetylacetone were studied.

Key words: 1,4-(dimethoxycarbonyl)cubane, 1,4-cubanedicarboxylic acid dihydrazide, hydrazine.

In view of the growing interest in cubane derivatives as potent pharmaceuticals,[1–5] the development of various procedures for the introduction of the cubane fragment into molecules of organic compounds is an urgent problem.

One of the compounds which are of interest from the standpoint of their use in the synthesis of cubane derivatives is 1,4-cubanedicarboxylic acid dihydrazide (**1**). This acid has not yet been described in the literature. A number of compounds which may be of interest both from the viewpoint of chemistry and pharmacology can by prepared by various reactions of the NH_2NH group (for example, acylation, condensation, formation of heterocycles, *etc.*[6–8]).

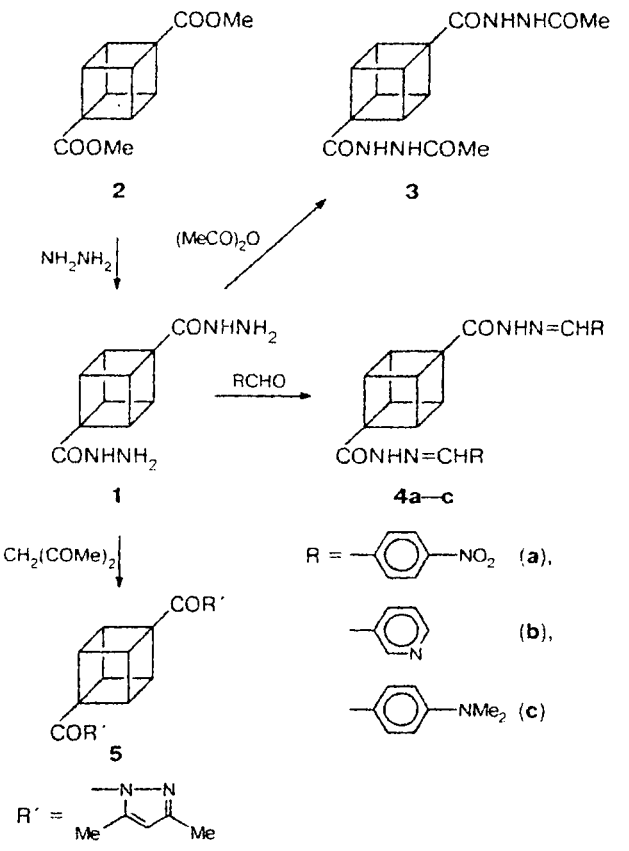
In the present work, we performed the synthesis of compound **1** from methyl 1,4-cubanedicarboxylate (**2**) and studied its reactions with acetic anhydride, aromatic aldehydes, and acetylacetone (Scheme 1).

Compound **1** was prepared according to a procedure reported previously[9] by refluxing acid **2** with an ethanolic solution of hydrazine hydrate. Dihydrazide **1** was obtained in ~90% yield and was readily isolated from the reaction mixture as a precipitate, which did not require additional purification.

The reactions of compound **1** with acetic anhydride, aromatic aldehydes, and acetylacetone afforded products characteristic of reactions of hydrazides, *viz.*, acetylhydrazine, hydrazones, and substituted pyrazole, respectively. Not only do these reactions provide chemical evidence for the structure of compound **1**, but they also substantially extend the range of possibly potent pharmacologically active cubane derivatives.

The reaction of dihydrazide **1** with acetylacetone afforded the target product, pyrazole **5**, in low yield (5.7%), which may be due to the enhanced tendency of compound **5** to undergo hydrolysis because 1,4-cubanedicarboxylic acid was isolated as the major product. Additional experiments demonstrated that dihydrazide **1** did not undergo hydrolysis under these conditions. Thus, prolonged refluxing of compound **1** in acetic acid did not give rise to 1,4-cubanedicarboxylic acid.

Scheme 1



* For Part 5, see Ref. 1.

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All the resulting compounds, except for **5**, are solids poorly soluble in most of the available solvents. Their structures were established by elemental analysis and ^{1}H NMR and IR spectroscopy.

Experimental

The ^{1}H NMR spectra were recorded on an NMR spectrometer equipped with a superconducting magnet (294 MHz), which was developed and built at the Institute of Chemical Physics in Chernogolovka of the Russian Academy of Sciences, and on a Bruker WM-250 instrument (250 MHz) in DMSO-d_6 with respect to Me_4Si. The IR spectra were measured on a Specord M82 spectrophotometer in KBr pellets.

Dimethyl 1,4-cubanedicarboxylate **2** was synthesized according to a known procedure.[10]

1,4-Cubanedicarboxylic acid dihydrazide (1). Ester **2** (2.20 g, 10 mmol) was dissolved in ethanol (100 mL) on heating. Then hydrazine hydrate (10 mL, 200 mmol) was added and the reaction mixture was refluxed on a water bath for 8 h. The precipitate that formed was filtered off, washed with water and ethanol, and dried in air to a constant weight. The yield was 2.0 g (91%), m.p. 284—285 °C (with decomp.). Found (%): C, 54.4; H, 5.5; N, 25.4. $C_{10}H_{12}N_4O_2$. Calculated (%): C, 54.53; H, 5.49; N, 25.44. ^{1}H NMR, δ: 4.10 (s, 10 H, CH of cubane, NH_2); 8.85 (br.s, 2 H, 2 NH). IR, ν/cm^{-1}: 3375, 3325, 3275, 2995, 2975, 2945, 2925, 1610, 1510, 1430, 1380, 1340, 1265, 1225, 1200, 1130, 1085, 970, 960, 915, 850, 830.

1,4-Bis(1′,4′-dioxo-2′,3′-diazapentyl)cubane (3). Dihydrazide **1** (220 mg, 1 mmol) was stirred with an excess of acetic anhydride (5 mL) for 5 h and the reaction mixture was kept overnight. The precipitate that formed was filtered off, washed with water, and dried in air. Compound **3** was obtained in a yield of 295 mg (90%), m.p. 295—296 °C (with decomp.). Found (%): C, 54.7; H, 5.4; N, 18.5. $C_{14}H_{16}N_4O_4$. Calculated (%): C, 55.26; H, 5.30; N, 18.41. ^{1}H NMR, δ: 1.87 (s, 6 H, 2 Me); 4.18 (s, 6 H, CH of cubane); 9.51 (br.s, 4 H, 4 NH). IR, ν/cm^{-1}: 3235, 3040, 3000, 2930, 2920, 2850, 1675, 1605, 1485, 1365, 1335, 1290, 1250, 1200, 1115, 1085, 1035, 1015, 940, 910, 850, 825.

1,4-Bis[4′-(4″-nitrophenyl)-1′-oxo-2′,3′-diazabut-3′-en-1′-yl]cubane (4a), 1,4-bis[1′-oxo-4′-(3″-pyridyl)-2′,3′-diazabut-3′-en-1′-yl]cubane (4b), and 1,4-bis[4′-(4″-dimethylaminophenyl)-1′-oxo-2′,3′-diazabut-3′-en-1′-yl]cubane (4c) were prepared according to a general procedure. A suspension of dihydrazide **1** (440 mg, 2 mmol) in ethanol (50 mL) and acetic acid (10 mL) was heated to boiling. Then the corresponding aldehyde (4.8 mmol; 720 mg of *p*-nitrobenzaldehyde, 520 mg of 3-pyridylcarbaldehyde, or 715 mg of 4-dimethylaminobenzaldehyde) was added with stirring. The reaction mixture was refluxed for 1 h and then cooled to ~20 °C. The precipitate that formed was filtered off, washed with ethanol, and dried in air to a constant weight to obtain compounds **4a**, **4b**, and **4c**, respectively.

Compound 4a. The yield was 890 mg (92%), m.p. 280—281 °C (with decomp.). Found (%): C, 59.6; H, 3.7; N, 17.2. $C_{24}H_{18}N_6O_6$. Calculated (%): C, 59.26; H, 3.73; N, 17.28. ^{1}H NMR, δ: 4.42 (s, 6 H, CH of cubane); 7.84 (d, 4 H, CH arom.); 8.05 (s, 2 H, 2 CH=N); 8.20 (d, 4 H, CH arom.); 11.56 (br.s, 2 H, 2 NH). IR, ν/cm^{-1}: 3440, 3374, 3168, 3065, 2995, 2925, 2850, 1649, 1640, 1605, 1580, 1520, 1502, 1375, 1335, 1245, 1200, 1145, 1105, 1010, 935, 858, 840.

Compound 4b. The yield was 847 mg (95%), m.p. 294—295 °C (with decomp.). Found (%): C, 66.4; H, 4.5; N, 21.0. $C_{22}H_{18}N_6O_2$. Calculated (%): C, 66.32; H, 4.55; N, 21.09. ^{1}H NMR, δ: 4.36 (s, 6 H, CH of cubane); 7.35 (br.s, 2 H, pyridyl); 7.96 (br.s, 4 H, pyridyl); 8.47 (s, 2 H, 2 HC=N); 8.76 (s, 2 H, pyridyl); 11.39 (br.s, 2 H, NH). IR, ν/cm^{-1}: 3440, 3166, 3071, 3000, 2947, 2895, 2856, 2814, 1654, 1608, 1600, 1554, 1528, 1508, 1482, 1446, 1397, 1364, 1312, 1256, 1230, 1184, 1171, 1135, 1065, 1016, 947, 937, 877, 841, 816.

Compound 4c. The yield was 710 mg (89%), m.p. 288—289 °C (with decomp.). Found (%): C, 69.8; H, 6.3; N, 17.8. $C_{28}H_{30}N_6O_2$. Calculated (%): C, 69.69; H, 6.26; N, 17.41. ^{1}H NMR, δ: 2.95 (s, 12 H, 4 Me); 4.30 (s, 6 H, CH of cubane); 6.65 (m, 4 H, CH arom.); 7.42 (m, 4 H, CH arom.); 7.80 (s, 2 H, 2 HC=N); 10.88 (br.s, 2 H, 2 NH). IR, ν/cm^{-1}: 3165, 3071, 2990, 2945, 2925, 2855, 1655, 1610, 1592, 1567, 1534, 1498, 1415, 1371, 1335, 1325, 1255, 1137, 1099, 1016, 939, 872, 841, 815, 802.

1,4-Bis[(3′,5′-dimethylpyrazol-1′-yl)carbonyl]cubane (5). Hydrazide **1** (440 mg, 2 mmol) was dissolved in acetic acid (10 mL) upon heating. Then acetylacetone (1.0 mL, 10 mmol) was added and the reaction mixture was kept overnight. The precipitate that formed (286 mg) was filtered off. The IR spectrum and the melting point of the product are in complete agreement with the corresponding data for 1,4-cubanedicarboxylic acid. Acetic acid was removed *in vacuo* from the mother liquor and the residue was recrystallized from heptane after which compound **5** was obtained in a yield of 40 mg (5.7%), m.p. 168—169 °C. Found (%): N, 16.3. $C_{20}H_{20}N_4O_2$. Calculated (%): N, 16.08. ^{1}H NMR, δ: 2.20 (s, 6 H, 2 Me); 2.53 (s, 6 H, 2 Me); 4.40 (s, 6 H, CH of cubane); 5.91 (s, 2 H, 2 CH=C). IR, ν/cm^{-1}: 3230, 3010, 2950, 2925, 1685, 1610, 1585, 1480, 1455, 1435, 1410, 1370, 1345, 1315, 1245, 1205, 1180, 1140, 1115, 1035, 1025, 985, 960, 865, 845.

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