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SYNTHESES AND CONVERSION OF POLYHEDRAL COMPOUNDS. 26.* SYNTHESIS OF NEW HETEROPOLYHEDRAL COMPOUNDS BY HETEROCYCLIZATION OF CERTAIN 3,7-DISUBSTITUTED DERIVATIVES OF 3,7-DIAZA- AND 1,3,7-TRIAZABICYCLO-[3.3.1]NONANES

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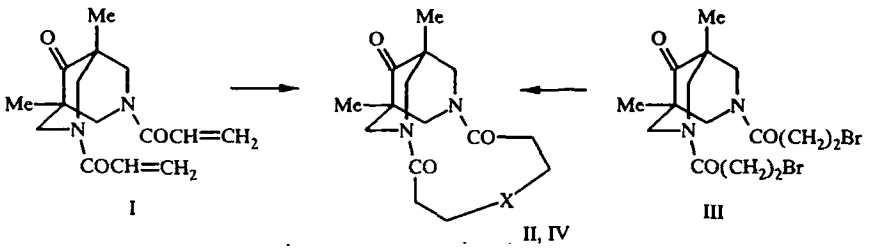
The following heterocyclization reactions have been carried out: heterocyclization of 3,7-diacryloyl-3,7-diazabicyclo[3.3.1]nonane by benzylamine, heterocyclization of 3,7-diacryloyl-, 3,7-bis(β-bromopropionyl)-, and 3,7-bis(β-chloroethyl)-3,7-diazabicyclo[3.3.1]nonanes by hydrogen sulfide, and heterocyclization of 3,7-bis(bromoacetyl)- and 3,7-diacryloyl-1,3,7-triazabicyclo[3.3.1]nonanes by benzylamine and hydrogen sulfide. New compounds were obtained, based on previously unknown thiadiaza-, triaza-, and tetraazatricyclic systems.

The heterocyclization of 3,7-bis(haloacetyl)-3,7-diazabicyclo[3.3.1]nonanes by ammonia or primary amines leads to the corresponding derivatives of 1,4,7-triazatricyclo[7.3.1.$1^{7,11}$]tetradecane [2, 3]. With the aim of obtaining new heteropolyhedral compounds and studying their biological properties, we have investigated the possibility of heterocyclization of derivatives of 3,7-diazabicyclo[3.3.1]nonane and 1,3,7-triazabicyclo[3.3.1]nonane by benzylamine and/or hydrogen sulfide in an alkaline medium.

It was established that refluxing of equimolar quantities of 3,7-diacryloyl-1,5-dimethyl-9-oxo-3,7-diazabicyclo-[3.3.1]nonane (I) [4] and benzylamine in ethanol results in the formation of 1,5,9-triazatricyclo[9.3.1.$1^{9,13}$]hexadecane (II). Heterocyclization was also accomplished successfully when starting with solutions of 3,7-diacryloyl- (I) and 3,7-bis(β-bromopropionyl)-1,5-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane (III) [4], in hydrogen sulfide-saturated methanol and dioxane, respectively, by the action of a 28% aqueous solution of sodium hydroxide. As a result of this treatment, we obtained a derivative of 5-thia-1,9-diazatricyclo[9.3.1.$1^{9,13}$]hexadecane (IV).



I II, IV III

II) X = $NCH_2C_6H_5$, IV) X = S

*For Communication 25, see [1].

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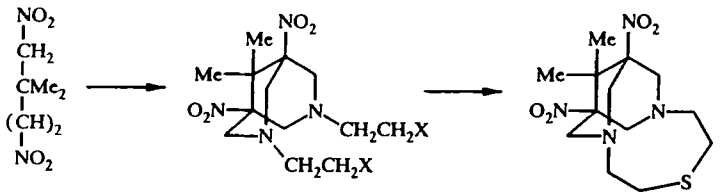
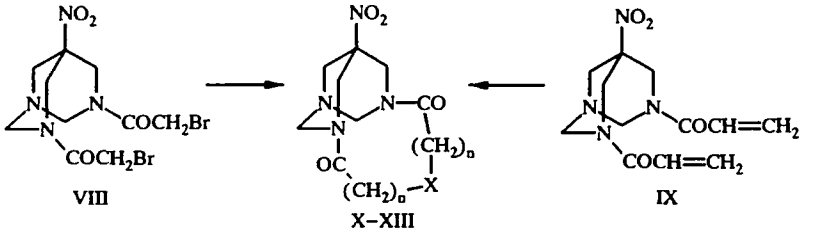
Analogously, by refluxing a solution of 3,7-bis(β-chloroethyl)-9,9-dimethyl-1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (V) in dioxane with hydrogen sulfide in an alkaline medium, we synthesized a derivative of 4-thia-1,7-diazatricyclo-[7.3.1.$1^{7,11}$]tetradecane (VI). The original dichloride V was obtained by the action of thionyl chloride on 3,7-bis(β-hydroxyethyl)-9,9-dimethyl-1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (VII), which in turn was synthesized by the Mannich reaction from 2,2-dimethyl-1,3-dinitropropane, monoethanolamine, and paraformaldehyde.



V, VII VI

V) X = Cl, VII) X = OH

We were able to use benzylamine and also hydrogen sulfide in an alkaline medium to accomplish the heterocyclization of 3,7-bis(bromoacetyl)- (VIII) and 3,7-diacryloyl-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane (IX) [5]. In the case of compound VIII, we also used sodium sulfide for this reaction. As a result, we obtained derivatives of 1,3,6,9-tetraazatricyclo-[7.3.1.$1^{3,11}$]-tetradecane(X), 1,3,7,11-tetraazatricyclo[9.3.1.$1^{3,13}$]hexadecane(XI), 6-thia-1,3,9-triazatricyclo[7.3.1.$1^{3,11}$]-tetradecane(XII), and 7-thia-1,3,11-triazatricyclo[9.3.1.$1^{3,13}$]hexadecane (XIII).



VIII X-XIII IX

X) a = 1, X = $NCH_2C_6H_5$; XI) n = 2, X = $NCH_2C_6H_5$;

XII) n = 1, X = S; XIII) n = 2, X = S

Thus, as a result of the above-described heterocyclization of derivatives of 1,7-diaza- and 1,3,7-triazabicyclo-[3.3.1]nonanes, we have synthesized new heteropolyhedra that differ in the size of one of the rings and also in the number, character, and position of the heteroatoms.

The structures of these compounds were established on the basis of elemental analyses and IR and mass spectra, and in a number of cases by PMR spectra (see Experimental). The mass spectra of all of the synthesized compounds contain peaks of the respective molecular ions. In the PMR spectra of compounds II-VII there is a singlet signal of methyl-group protons in the 1.00-1.35 ppm region. The spectrum of the benzyl-substituted product II also contains a singlet signal of protons of the phenyl group at 7.55 ppm, while the signal of the CH_2 groups has the form of a broad multiplet in the 3.00-5.30 ppm region. The PMR data are more informative in the case of compounds IV-VII. In the spectrum of IV, for example, we can clearly distinguish triplets of CH_2CO and CH_2S groups at 2.70 and 3.30 ppm, respectively (SSCC = 5.5 Hz); however, the signal of the CH_2N groups is manifested in the form of a broad multiplet in the 2.80-5.00 ppm region. The clearest picture is observed for compounds V and VII and the product VI that was obtained from them. In addition to triplet signals of the groups CH_2O (VII), CH_2Cl (V), and CH_2S (VI) at 3.65, 3.60, and 3.40 ppm, respectively (SSCC = 5.5-6.0 Hz), the spectra contain well-resolved triplets of CH_2N groups of the side chains (V, VII) or the heterocycle formed from these groups (VI), in the 2.70-2.90 ppm region (SSCC = 5.5-6.00 Hz), as well as doublets of axial and equatorial protons of CH_2N groups of six-membered heterocycles at 2.95-3.20 and 3.70-3.75 ppm, respectively (SSCC = 11-12 Hz). The PMR spectra of the derivatives of tetraazatricyclic compounds (X, XI) and thiatriazatricyclic compounds (XII, XIII), as would be expected by analogy with the PMR spectra of 3,7-diacyl-1,3,7-triazabicyclononanes [6] are complex and difficult to decipher. The purities of the compounds were established by TLC data.

EXPERIMENTAL

The IR spectra were taken in white mineral oil in a UR-20 spectrometer, the PMR spectra in a Varian T-60 instrument with TMS internal standard. The molecular masses were determined by mass spectrometry in an MKh-1320 instrument with direct introduction of the sample into the ion source. The ionizing electron energy was 60 eV. The course of the reaction and the purity of the substances were monitored by TLC on Silufol UV-254 plates in systems consisting of 7:3 n-propanol–water (*a*), 3:1:1 n-butanol–acetic acid–water (*b*), or on aluminum oxide (degree II activity) in a system consisting of 7:3 n-propanol–water (*c*).

The elemental analyses of compounds III-VII and X-XIII for C, H, N, S, and Cl matched the calculated values (see below).

5-Benzyl-11,13-dimethyl-2,8,12-trioxo-1,5,9-triazatricyclo[9.3.1.1^{9,13}]hexadecane (II). A solution of 3.6 g (13 mmoles) of the diazabicyclononane I and 1.4 g (13 mmoles) of benzylamine in 100 ml of ethanol was refluxed 5 h. The solvent was removed under vacuum, and 50 ml of water was added to the residue. The precipitate was filtered off, dried, and recrystallized from ethanol. Obtained 4.0 g (81.6%) of compound II, mp 222-224°C (ethanol), R_f 0.44 (*a*). IR spectrum, cm^{-1}: 1605 (C=C arom.), 1630-1645 (C=O amide), 1720 (C=O ketone). PMR spectrum (CF_3COOH) ppm: 1.25 (6H, s, $2CH_3$); 3.0-5.3 (18H, m, $9CH_2$); 7.55 (5H, s, H_{arom}). M^+ 383. Found, %: C 69.0; H 8.0; N 11.6. $C_{22}H_{29}N_3O_3$. Calculated, %: C 68.9; H 7.6; N 11.0.

11,13-Dimethyl-2,8,12-trioxo-5-thia-1,9-diazatricyclo[9.3.1.1^{9,13}]hexadecane (IV). ***A.*** A mixture of 0.5 g (18 mmoles) of the diazabicyclononane I and 2 ml of hydrogen sulfide-saturated 28% aqueous NaOH solution in 50 ml of methanol was refluxed 5 h. The precipitate was filtered off, and the filtrate was evaporated under vacuum. Water was added to the residue, and the resulting crystals were filtered off, washed with water, dried, and recrystallized from isopropanol. Obtained 0.3 g (53.6%) of compound IV, mp 158-159°C (isopropanol), R_f 0.32 (*a*). IR spectrum, cm^{-1}: 720 (C–S–C), 1640 (C=O amide), 1710 (C=O ketone). PMR spectrum ($CDCl_3$), ppm: 1.00 (6H, s, $2CH_3$); 2.70 (4H, t, J = 5.5 Hz, $2CH_2CO$); 3.30 (4H, t, J = 5 Hz, $2CH_2S$); 2.80-5.00 (8H, m, $4CH_2N$). M^+ 310. Found, %: C 57.6; H 7.1; N 8.9; S 10.3. $C_{15}H_{22}N_2O_3S$. Calculated, %: C 58.1; H 7.1; N 9.0; S 10.3.

B. To a solution of 1.2 g (2.8 mmoles) of the diazabicyclononane III in 50 ml of dioxane, 4 ml of hydrogen sulfide-saturated 28% aqueous NaOH solution was added, and the mixture was stirred 20 h at room temperature. The dioxane was driven off, and 30 ml of water was added to the residue; the precipitate was filtered off and recrystallized from isopropanol. Obtained 0.7 g (81%) of compound IV, identical to the sample obtained by method A (mp, R_f).

3,7-Bis(β-hydroxyethyl)-9,9-dimethyl-1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (VII). To a solution of 4.8 g (30 mmoles) of 2,2-dimethyl-1,3-dinitropropane in 50 ml of ethanol, there were added successively, with mixing, 3.7 g (60 mmoles) of monoethanolamine, 3 ml of acetic acid, and 3.4 g (120 mmoles) of paraformaldehyde, after which the mixture was refluxed on a water bath for 6 h. The solvent was driven off, and 10 ml of water was added to the residue, along with a 40% NaOH solution to bring the pH to 12. The resulting mixture was extracted with benzene (3 × 30 ml), the benzene was driven off, and the residue was extracted with boiling water (3 × 50 ml). When the combined extract was cooled, yellow crystals separated out; these were recrystallized from a 3:1 water–methanol mixture. Obtained 2.8 g (28.1%) of compound VII, mp 162-163°C: (3:1 water–methanol), R_f 0.57 (*a*). IR spectrum, cm^{-1}: 1550 (C–NO_2), 3340-3420 (OH). PMR spectrum ($CDCl_3$), ppm: 1.35 (6H, s, $2CH_3$); 2.70 (4H, t, J = 5.5 Hz, $2CH_2N$); 3.20 (4H, d, J = 12 Hz, $4CH_aN$); 3.65 (4H, t, J = 5.5 Hz, $2CH_2O$); 3.70 (4H, d, J = 12 Hz, $4CH_eN$); 4.20 (2H, s, 2OH). M^+ 332. Found, %: C 47.4; H 7.3; N 16.5. $C_{13}H_{24}N_4O_6$. Calculated, %: C 47.0; H 7.2; N 16.8.

3,7-Bis(β-chloroethyl)-9,9-dimethyl-1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (V). To a mixture of 0.7 g (2.1 mmoles) of the diazabicyclononane VII, 6 ml of chloroform and 2.5 g (21 mmoles) of thionyl chloride were added; the resulting mass was stirred and refluxed for 1 h. The solvent was driven off, and the residue was washed with ether and dried; then 10 ml of water was added, and the solution was neutralized with 10% NaOH to an alkaline reaction. The precipitate was filtered off, washed with water, dried, and recrystallized from isopropanol. Obtained 0.5 g (64.9%) of compound V, mp 87-88°C (isopropanol), R_f 0.57 (*b*). IR spectrum, cm^{-1}: 1555 (C–NO_2). PMR spectrum ($CDCl_3$), ppm: 1.30 (6H, s, $2CH_3$); 2.90 (4H, t, J = 6 Hz, $2CH_2N$); 3.00 (4H, d, J = 12 Hz, $4CH_aN$); 3.60 (4H, t, J = 6 Hz, $2CH_2Cl$); 3.70 (4H, d, J = 12 Hz, $4CH_eN$). M^+ 368, 370, 372. Found, %: C 42.3; H 5.5; N 14.9; Cl 19.0. $C_{13}H_{22}N_4O_4Cl_2$. Calculated, %: C 42.3; H 5.9; N 15.2; Cl 19.2.

10,10-Dimethyl-9,11-dinitro-4-thia-1,7-diazatricyclo[7.3.1.1^{7,11}]tetradecane (VI). To a solution of 2.7 g (7.3 mmoles) of the diazabicyclononane VII in 70 ml of dioxane, 9 ml of a hydrogen sulfide-saturated 28% NaOH solution was

added. The mixture was refluxed and stirred 15 h and then cooled. The organic layer was decanted, the dioxane was removed under vacuum, and 30 ml of water was added to the residue and then extracted with chloroform (3 × 20 ml). After driving off the chloroform, the residue was crystallized from water. Obtained 1.5 g (62.5%) of compound VI, mp 165-166°C (propanol), R_f 0.72 (*b*). IR spectrum, cm^{-1}: 1555 (C-NO_2). PMR spectrum ($CDCl_3$), ppm: 1.30 (6H, s, $2CH_3$); 2.90 (4H, t, J = 6 Hz, $2CH_2N$); 2.95 (4H, d, J = 11 Hz, $4CH_aN$); 3.40 (4H, t, J = 6 Hz, $2CH_2S$); 3.75 (4H, d, J = 11 Hz, $4CH_eN$). M^+ 330. Found, %: C 47.2; H 7.2; N 16.9; S 10.0. $C_{13}H_{22}N_4O_4N$. Calculated, %: C 47.0; H 7.2; N 17.0, S 9.7.

6-Benzyl-4,8-dioxo-11-nitro-1,3,6,9-tetraazatricyclo[7.3.1.1^{3,11}]tetradecane (X). To a solution of 4.14 g (10 mmoles) of the triazabicyclononane VIII in 45 ml of ethyl acetate, 3.2 g (0.030 mmole [sic]) of benzylamine in 20 ml of ethyl acetate was added with stirring over the course of 3 h. The reaction mass was stirred 8 h, and the precipitated crystals were filtered off and then washed with 200 ml of water and 40 ml of ethyl acetate. Obtained 3 g (83.6%) of compound X, mp 238-240°C (1:1 dioxane–water), R_f 0.73 (*a*). IR spectrum, cm^{-1}: 1550 (C-NO_2), 1610 (C=C arom.), 1650, 1670 (C=O amide). M^+ 359. Found, %: C 57.0; H 6.0; N 19.0. $C_{17}H_{21}N_5O_4$. Calculated, %: C 57.0; H 5.8; N 19.3.

7-Benzyl-4,10-dioxo-13-nitro-1,3,7,11-tetraazotricyclo[9.3.1.1^{3,13}]hexadecane (XI). To a solution of 2.8 g (10 mmoles) of the triazabicyclononane IX in 150 ml of methanol, 1.07 g (10 mmoles) of benzylamine in 40 ml of methanol was added with stirring over the course of 12 h. The reaction mass was stirred 15 h, and the precipitated crystals were filtered off and washed with water, then with methanol. Obtained 2.5 g (64.6%) of compound XI, mp 195-196°C (2:3 DMF–water), R_f 0.18 (*a*). IR spectrum, cm^{-1}: 1540 (C-NO_2), 1600 (C=C arom.), 1640 (C=O amide). M^+ 387. Found, %: C 58.6; H 6.2; N 18.3. $C_{19}H_{25}N_5O_4$. Calculated, %: C 58.9; H 6.5; N 18.1.

4,8-Dioxo-11-nitro-6-thia-1,3,9-triazatricyclo[7.3.1.1^{3,11}]tetradecane (XII). ***A***. A stirred and nitrogen-blanketed solution of 4.14 g (10 mmoles) of the triazabicyclononane VIII and 2 g of NaOH in 2 liters of methanol was bubbled with a moderate flow of hydrogen sulfide for 1 h. The precipitated crystals were filtered off and washed with water to neutral reaction and then with methanol. Obtained 2.3 g (80.4%) of compound XII, mp 262-264°C (decomp.) (1:1 DMF–water), R_f 0.35 (*c*). IR spectrum, cm^{-1}: 670 (C-S-C), 1560 (C-NO_2), 1660 (C=O amide). M^+ 286. Found, %: C 41.8; H 5.0; N 20.0; S 11.4. $C_{10}H_{14}N_4O_4S$. Calculated, %: C 41.9; H 4.9; N 19.7: S 11.2.

B. To a solution of 0.4 g (1 mmole) of the triazabicyclononane VIII in 200 ml of methanol, 0.24 g (1.5 mmoles) of $Na_2S \cdot 9H_2O$ in 50 ml of water was added with stirring over the course of 30 min. The reaction mass was stirred 2 h; then the precipitated crystals were filtered off, washed with water, and recrystallized from a 1:1 DMF–water mixture. Obtained 0.25 g (87%) of compound XII, mp 264-265°C (1:1 DMF–water), R_f 0.35 (*c*).

4,10-Dioxo-13-nitro-7-thia-1,3,11-triazatricyclo[9.3.1.1^{3,13}]hexadecane (XIII). To a solution of 2.8 g (0.01 mole) of the triazabicyclononane IX in 150 ml of methanol, 5 ml of a hydrogen sulfide-saturated 28% NaOH solution was added with stirring over the course of 3 h. The reaction mass was stirred another hour, and the precipitated crystals were filtered off, washed with water to neutral reaction, and then washed with methanol. Obtained 2.3 g (73.2%) of compound XIII, mp 208-209°C (decomp.) (1:1 DMF–water), R_f 0.18 (*a*). IR spectrum, cm^{-1}: 680 (C-S-C), 1550 (C-NO_2), 1670 (C=O amide). M^+ 314. Found, %: C 46.1; H 5.2; N 18.0; S 10.5. $C_{12}H_{18}N_4O_4S$. Calculated, %: C 46.1; H 5.2; N 18.0; S 10.3.

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