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SYNTHESIS AND CONVERSIONS OF POLYHEDRAL COMPOUNDS

17.* CONVERSION OF 1,3-DIAZA- AND 1,3,5-TRIAZAADAMANTANES TO NITROGEN-CONTAINING PENTACYCLIC COMPOUNDS

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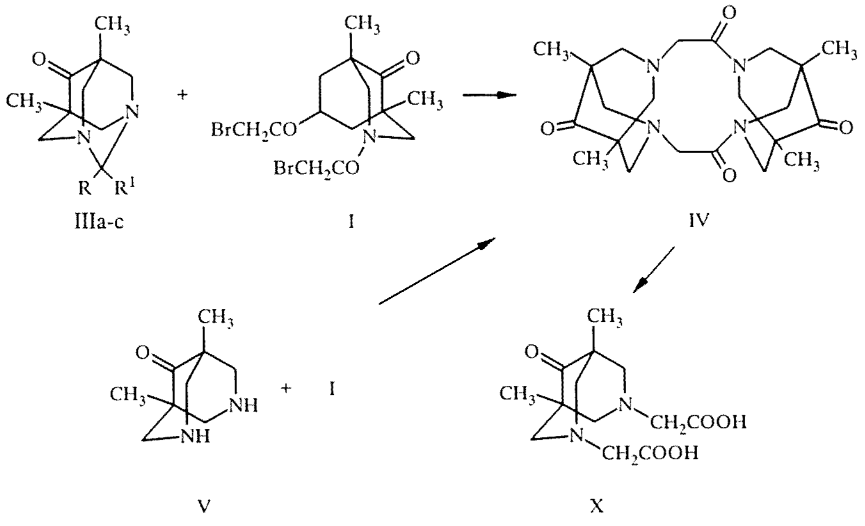
It has been shown that derivatives of 1,3-diaza- and 1,3,5-triazaadamantanes, and also derivatives of 3,7-diazabicyclo[3.3.1]nonane, interact with 3,7-bis(bromoacetyl)-3,7-diaza- and 3,7-bis(bromoacetyl)-1,3,7-triazabicyclo[3.3.1]nonanes in the presence of bases to form previously unknown types of heteropolyhedral structures — nitrogen-containing pentacyclic compounds.

We had found previously that when derivatives of 1,3-diaza- and 1,3,5-triazaadamantanes interact with 1,2-dibromoethane, the CH_2 group in their methylenediamine fragment is replaced by CH_2CH_2, forming derivatives of 1,4-diaza- and 1,3,6-triazahomoadamantanes [2].

Here we are reporting on a study of the possiblity of using in this reaction, instead of 1,2-dibromoethane, certain α,ω-dihalides of bicyclic compounds, in particular 3,7-bis(bromoacetyl)-3,7-diaza-1,5-dimethyl-9-oxo- and 3,7-bis(bromoacetyl)-7-nitro-1,3,7-triazabicyclo[3.3.1]nonanes (I and II); these reactions would presumably yield new, previously unknown types of heteropolyhedral structures.



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*For Communication 16, see [1].

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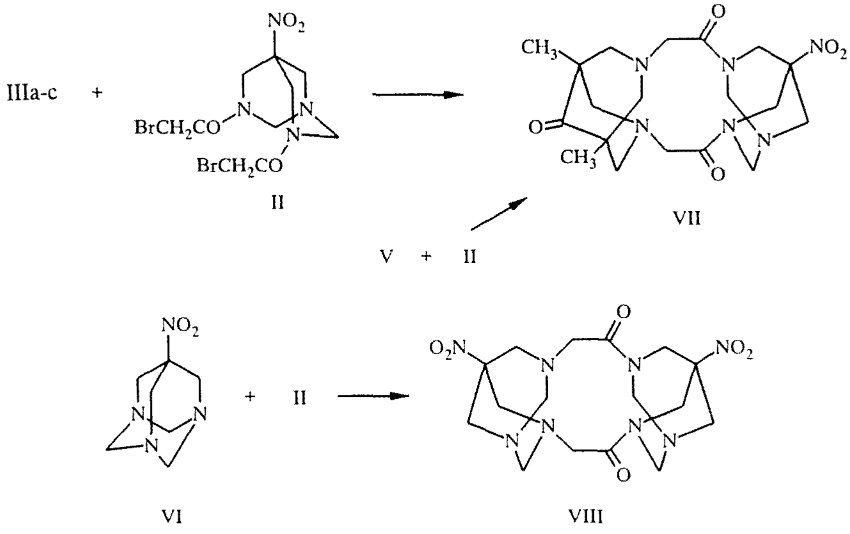
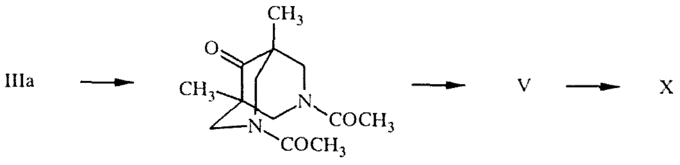


IIIa R = R^1 = H, b R = R^1 = CH$_3$, c R = H, R^1 = C$_2$H$_5$

We have established that the interaction of equimolar quantities of 5,7-dimethyl-6-oxo-1,3-diazaadamantane (IIIa) with the diazabicylononane (I) [3] in boiling ethanol at high dilution in the presence of triethylamine affords a tetraazapentacyclic compound - 6,8,15,17-tetramethyl-2,7,12,16-tetraoxo-1,4,10,13-tetraazapentacyclo[13.3.1.1^{4,8}.1^{6,10}.1^{13,17}]docosane (IV); i.e., the CH$_2$ group in the methylenediamine fragment of the diazaadamantane IIIa is replaced by a bis(bromoacetyl)diazabicyclo-nonane group I. Compound IV is also obtained by the action of the dibromide I on the diazaadamantanes IIIb and IIIc, which contain an alkylated CH$_2$ group, and also by the action of the dibromide I on 1,5-dimethyl-9-oxo-3,7-diazabicyclo-[3.3.1]nonane (V). Analogously, through the interaction of the diazaadamantanes IIIa-c or the diazabicyclononane V with the triazabicyclononane II, and through the interaction of 7-nitro-1,3,5-triazaadamantane (VI) with the triazabicyclononane II, pentaaza- and hexaazapentacyclic compounds are obtained: 8,10-dimethyl-17-nitro-4,9,14-trioxo-1,3,6,12,15-pentaazapentacyclo[13.3.1.1^{3,17}.1^{6,10}.1^{8,12}]docosane (VII) and 10,17-dinitro-4,14-dioxo-1,3,6,8,12,15-hexaazapentacyclo-[13.3.1.1^{3,17}.1$^{6.10}$. 1^{8,12}]docosane (VIII), respectively. In these cases, the CRR^1 group of the methylenediamine fragment of the diazaadamantanes IIIa-c or the CH$_2$ group of the triazaadamantane VI are replaced by a residue of bis(bromoacetyl)triazabicyclononane II.

The dibromide II was obtained by the interaction of the triazaadamantane VI with bromoacetyl chloride under conditions that we had worked out previously for the synthesis of 3,7-diacyl-1,3,7-triazabicyclo[3.3.1]nonanes [4]. The diazabicyclononane V was synthesized by hydrolysis of 3,7-diacetyl-1,5-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane (IX), which was obtained in turn by the interaction of the diazaadamantane IIIa with acetyl chloride. This method of synthesis of the diacetyldiazabicyclononane IX, in contrast to the known method of its preparation using acetic anhydride [5], does not require heating or any large consumption of the original substances, and the process goes forward rapidly.



IX

The structures of the synthesized compounds were confirmed by spectroscopic methods. The mass spectra of the products IV and VII-IX include peaks of the molecular ions; the spectrum of the triazabicyclononane II contains a peak of the ion $(M - NO_2)^+$. In the IR spectra of compounds II, IV, and VII-IX we observe absorption bands that are characteristic for the amide group (1630-1670 cm^{-1}); and in the spectrum of the bis(carboxymethyl)diazabicyclononane (X) (obtained as described below), we observe bands at 1700 and 3360-3400 cm^{-1}, confirming the presence of the carboxyl group. In the IR spectrum of the diazabicyclononane V, in contrast to the original diacetyl derivative IX, there is a Bohlman band in the 2750-2850 cm^{-1} region. Characteristic for the UV spectrum of compound V is a bathochromic shift of the carbonyl group absorption maximum in the 247 nm region, due to the interaction of the unshared electron pair of the nitrogen atoms with the π-electrons of the carbonyl group (see also [6]). In the PMR spectrum of compound IV, the signals of the protons of the diazabicyclononane framework form two doublets (AB system), in contrast to the diacetyl derivative IX, where they form four doublets (two AB systems), and also in contrast to the analogous spectrum of 3,7-dibenzyl-1,5-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane [5]. The PMR spectra of the pentacyclic compounds, as should be expected, are complex and difficult to interpret, owing to superposition of the signals of the methylene group protons. In establishing the structure of the pentacyclic compounds, we used chemical methods as well as physicochemical methods (IR and mass spectrometry, elemental analysis). Thus, acid hydrolysis of compound IV gave high yields of the diazabicyclononane V and 3,7-bis(carboxymethyl)-1,5-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane (X). The latter compound was also obtained by counter-synthesis – by the interaction of the diazabicyclononane V with bromoacetic acid in the presence of a base.

EXPERIMENTAL

The IR spectra were taken in UR-20 and Specord IR-75 spectrometers, in white mineral oil. The UV spectra were taken in a Specord instrument in 96% ethanol, the mass spectra in MKh-1320 instruments with direct introduction of the sample into the ion source. The ionizing electron energy was 60 eV. The PMR spectra were obtained in a Varian T-60 instrument in $CDCl_3$, with TMS internal standard. Melting points were determined on a Boetius microblock. The course of the reaction and the purity of the substances were monitored by TLC on Silufol UV-254 plates in the solvent systems 7:3 propanol–water (a), 1:1 acetone–hexane (b), or butanol saturated with aqueous ammonia (c), or on KSK-gips silica gel in a 7:3 propanol–water system (d). The developer was iodine vapor.

The results of elemental analysis of the synthesized compounds for contents of C, H, Br, Cl, and N matched the calculated contents.

6,8,15,17-Tetramethyl-2,7,12,16-tetraoxo-1,4,10,13-tetraazapentacyclo[13.3.1.1^{4,8}.1^{6,10}.1^{13,17}]docosane (IV, $C_{22}H_{32}N_4O_4$). A. A solution of 1.8 g (0.01 mole) of the diazaadamantane IIIa, 4.1 g (0.01 mole) of the dibromide I [3], and 2.5 g (0.025 mole) of triethylamine in 500 ml of ethanol was refluxed while stirring for 8 h. The solvent was removed under vacuum, and the residue was washed with water and recrystallized from methanol: mp 267-268°C, R_f 0.5 (a). IR spectrum, cm^{-1}: 1650, 1670 (C=O amide), 1720 (C=O ketone). M^+ 416. Yield 2.2 g (53%).

B. Compound IV was obtained as described above from 0.84 g (0.005 mole) of the diazabicyclononane V, 2 g (0.005 mole) of the dibromide I, and 1.5 g (0.015 mole) of triethylamine, with a reaction time of 6 h. Yield 0.9 g (45%).

C. Compound IV was obtained as described above from 0.21 g (0.001 mole) of the diazaadamantane IIIb or IIIc and 0.41 g (0.001 mole) of the dibromide I. Yield 46-47%.

The samples of compound IV obtained from the different starting materials were completely identical, as established by melting point and TLC.

1,5-Dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane (V, $C_9H_{16}N_2O$). A solution of 5.2 g (0.02 mole) of the diacetyldiazabicyclononane IX in 50 ml of 5 N HCl was refluxed for 5 h, after which the solution was reduced to one-third volume under vacuum and then cooled. The precipitated crystals were filtered off and dissolved in 20 ml of water. To this solution, a 60% aqueous NaOH solution was added dropwise to bring the pH up to 10; then the solution was cooled, and the residue was filtered off, dried, and recrystallized from ethyl acetate: mp 66-68°C, R_f 0.47 (d). IR spectrum, cm^{-1}: 1705 (C=O ketone), 3170-3360 (NH). UV spectrum, λ_{max}, nm (and ε): 205 (2000), 247 (830). PMR spectrum, ppm (and J, Hz): 0.78 (6H, s, $2CH_3$); 2.9 (4H, d, J = 12 Hz, 4-CH_a–N); 3.13 (2H, s, 2NH); 3.35 ppm (4H, d, J = 12 Hz, 4-CH_e–N). M^+ 168. Yield 2 g (60%).

Dihydrochloride ($C_9H_{16}N_2O \cdot 2HCl$): mp 221-222°C (decomp., from 5:1 ethanol–water), R_f 0.6 (a).

3,7-Bis(bromoacetyl)-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane (II, $C_{10}H_{14}Br_2N_4O_4$). A. To a solution of 9.2 g (0.05 mole) of the triazaadamantane VI and 8.4 g (0.013 mole) of $NaHCO_3$ in 300 ml of THF and 80 ml of water, 18.9 g (0.12 mole) of bromoacetyl chloride was added (while stirring) over the course of 4 h. The reaction mixture was stirred for 1 h additional, and the organic layer was then separated and evaporated under vacuum. The residue was taken up in 100 ml of water and extracted with ethyl acetate (3 × 80 ml). The extract was washed with water and dried with $MgSO_4$, and the solvent was driven off. The residue was crystallized by adding ether and recrystallized from ethyl acetate: mp 164-168°C (decomp.), R_f 0.55 (b). IR spectrum, cm^{-1}: 1560 (NO_2), 1670 (C=O amide). $(M - NO_2)^+$ 366, 368, 370. Yield 17 g (82%).

B. To a solution of 1.84 g (0.01 mole) of the triazaadamantane VI in a mixture of 150 ml of dioxane and 30 ml of water, 3.9 g (0.025 mole) of bromoacetyl chloride was added dropwise with stirring. After adding half of the acid chloride, the solution was neutralized with 1.3 g (0.013 mole) of triethylamine, the second half of the acid chloride was added, and the solution was again neutralized with 1.3 g (0.013 mole) of triethanolamine, after which the solvent was removed under vacuum. The subsequent treatment was as described above. Yield 18 g (87%). Samples of the product II obtained by the two different methods were identical, as evidenced by melting point and TLC.

8,10-Dimethyl-17-nitro-4,9,14-trioxo-1,3,6,12,15-pentaazapentacyclo[13.3.1.1^{3,17}.1^{6,10}.1^{8,12}]docosane (VII, $C_{19}\cdot H_{28}N_6O_5$). A. A solution of 0.9 g (0.005 mole) of the diazaadamantane IIIa, 2.1 g (0.005 mole) of the dibromide II, and 1.5 g (0.015 mole) of triethylamine in 50 ml of dioxane was held for 10 h at 80°C. The solvent was removed under vacuum, and the residue was washed with water and then recrystallized from a 1:1 dioxane–water mixture: mp 274-275°C, R_f 0.45 (a). IR spectrum, cm^{-1}: 1340, 1540 (NO_2), 1645 (C=O amide), 1715 (C=O ketone). M$^+$ 420. Yield 1.1 g (52%).

Compound VII was obtained analogously from the diazomethines IIIb and IIIc. Yield 48-50%.

B. A solution of 0.84 g (0.005 mole) of the diazabicyclononane V, 2.1 g (0.005 mole) of the dibromide II, and 1.5 g (0.015 mole) of the triethylamine in 50 ml of dioxane was refluxed for 8 h. The subsequent treatment was as described above. Yield 1.2 g (57%). Samples of the product VII obtained by the above methods were identical, as evidenced by melting point and TLC.

10,17-Dinitro-4,14-dioxo-1,3,6,8,12,15-hexaazapentacyclo[13.3.1.1^{3,17}.1^{6,10}.1^{8,12}]docosane (VIII, $C_{16}H_{24}N_8O_6$). A 1.84-g quantity (0.01 mole) of the triazaadamantane VI and 4.14 g (0.01 mole) of the dibromide II in 100 ml of dioxane was refluxed with stirring for 8 h. Then, a solution of 0.8 g (0.02 mole) of NaOH in 15 ml of water was added to the reaction mixture, and refluxing was continued for an additional 1 h. The solvent was removed under vacuum, and the residue was washed with water and recrystallized from a 1:1 DMF–water mixture: mp 255-257°C, R_f 0.4 (c). IR spectrum, cm^{-1}: 1630 (C=O amide), 1545 (NO_2). M$^+$ 424. Yield 2.5 g (59%).

3,7-Bis(carboxymethyl)-1,5-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane (X, $C_{13}H_{20}N_2O_5$). A mixture of 1.7 g (0.01 mole) of the diazabicyclononane V, 2.8 g (0.02 mole) of bromoacetic acid, and 2.8 g (0.07 mole) of NaOH in 50 ml of ethanol was refluxed for 6 h. Then the solvent was removed under vacuum, and the residue was dissolved in 30 ml of water. To the resulting solution, 10 N HCl was added dropwise to bring the pH down to 7, after which the precipitate was filtered off and recrystallized from acetone: mp 225-227°C, R_f 0.75 (a). IR spectrum, cm^{-1}: 1700 (C=O acid), 1710 (C=O ketone), 3360-3400 (OH acid). Yield 2.5 g (88%).

3,7-Diacetyl-1,5-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane (IX, $C_{13}H_{20}N_2O_3$). To a mixture of 0.9 g (0.005 mole) of the diazaadamantane IIIa, 1.3 g (0.015 mole) of $NaHCO_3$, 2 ml of water, and 20 ml of dioxane, a solution of 1.2 g (0.015 mole) of acetyl chloride in 5 ml of dioxane was added dropwise. The reaction mixture was stirred for 1 h, after which the solvent was removed under vacuum. Then 10 ml of cold water was added to the residue, and the insoluble material was filtered off and recrystallized from water: mp 264-265°C [5], R_f 0.55 (a). IR spectrum, cm^{-1}: 1650 (C=O amide), 1730 (C=O ketone). UV spectrum, λ_{max}, nm (and ε): 204 (6330), 231 (3160). PMR spectrum, ppm (and J, Hz): 0.93 (6H, s, 2CH_3); 2.0 (6H, s, 2CH_3CO); 2.67 (2H, dd, J = 14, J = 3 Hz, 2,6-CH_a–); 3.15 (2H, dd, J = 13, J = 3 Hz,, 4,8-CH_a–N); 4.0 (2H, dd, J = 13, J = 3 Hz, 4,8-CH_e–N); 4.97 ppm (2H, dd, J = 14, H = 3 Hz, 2,6-CH_e–N). M$^+$ 252. Yield 0.7 g (56%).

Hydrolysis of Tetraazapentacyclodocosane (IV). A solution of 2.1 g (0.005 mole) of compound IV in 30 ml of 5 N HCl was refluxed for 5 h. The solution was cooled to room temperature and neutralized with 10% NaOH to pH 7. The precipitate was filtered off, dried, and recrystallized from acetone. Obtained the bis(carboxymethyl)diazabicyclononane X: mp 225-227°C, R_f 0.75 (a). Yield 1 g (70%).

To the aqueous filtrate, a 10% aqueous NaOH solution was added to pH 12; the precipitate was filtered off and recrystallized from ethyl acetate. Obtained the diazabicyclononane IV: mp 66-68°C, R_f 0.47 (d). Yield 0.7 g (83%).

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