7-Nitro-1,3,5-triazaadamantane and Derivatives. Reactions of Azaadamantanes with Anhydrides

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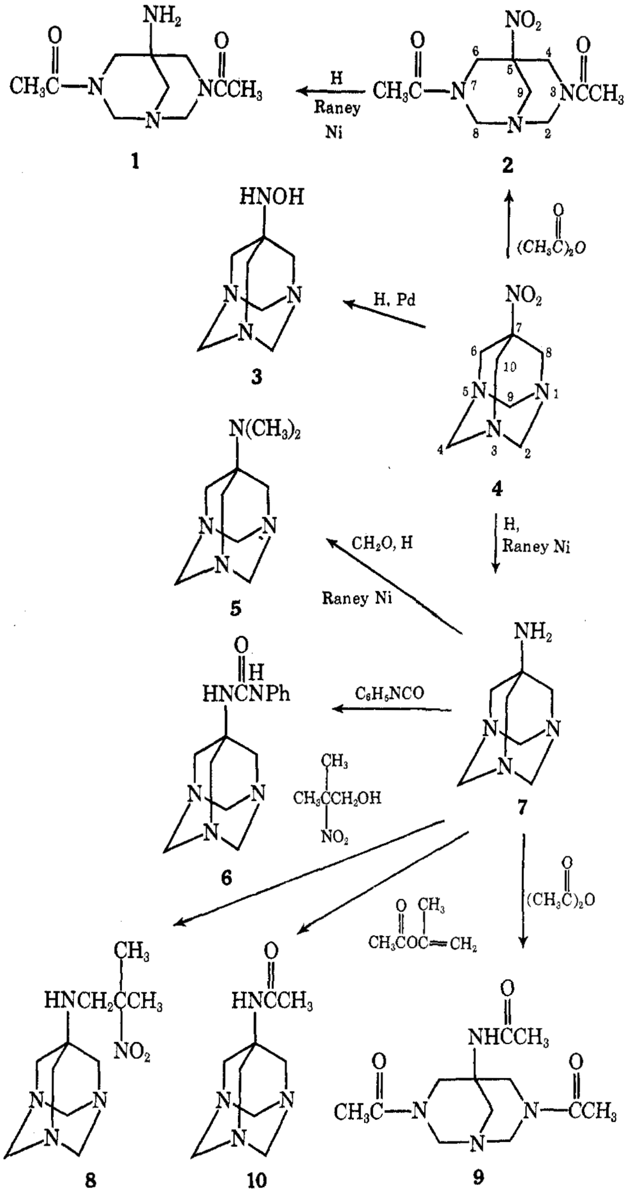
The preparations of 7-nitro-1,3,5-triazaadamantane (**4**) and of 1,3,5-triaza-7-adamantylamine (**7**) are disclosed in a U. S. Patent.[1] We had been studying the preparation and properties of **4** before the cited patent came to our attention, and we wish to submit our results at this time.

Previously,[1] compound **4** was prepared by heating a mixture of ethanol, paraformaldehyde, ammonium acetate, and nitromethane. We found that **4** could also be prepared from tris(hydroxymethyl)nitromethane, ammonium hydroxide, and paraformaldehyde.

Some reactions carried out with **4** are shown in Scheme I. Of these, perhaps the only ones requiring comment are reactions of **4** and of 1,3,5-triaza-7-adamantylamine (**7**) with acetic anhydride and of **7** with isopropenyl acetate. On attempted acetylation of **7** with acetic anhydride, 5-acetamido-3,7-diacetyl-1,3,7-triazabicyclo[3.3.1]nonane (**9**) was isolated rather than the expected 7-acetamido-1,3,5-triazaadamantane (**10**). Compound **10** was finally prepared by long refluxing of **7** in isopropenyl acetate.

SCHEME I



After **9** had been identified, the reaction of **4** with acetic anhydride was studied, and was found to lead to a good yield of 3,7-diacetyl-5-nitro-1,3,7-triazabicyclo-[3.3.1]nonane (**2**). Similar products were formed from benzoic and propionic anhydrides. The bicyclononanes were identified by analysis and by nmr. The formaldehyde formed was identified by its distinctive odor.

The nmr spectrum of **4**, taken in trifluoroacetic acid, is simple, and consists of a sharp peak at δ 4.23 (6 H) and an AB system at δ 4.75 and 5.07 (6 H, J_{AB} = 13 Hz). The single peak is attributed to the six hydrogen atoms on carbon atoms 6, 8, and 10, while the AB system is formed by splitting between the axial and equatorial hydrogen atoms on carbon atoms 2, 4, and 9.

The nmr spectrum of 3,7-diacetyl-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane (**2**), taken in dimethyl-d_6 sulfoxide, is complex, although the methyl peak (6 H) at δ 2.11 is easily identified. Based on six hydrogen atoms for the methyl groups, the rest of the peaks integrate for a total of ten hydrogen atoms.

The course of the reaction forming **2** is not known, but does not involve splitting out formaldehyde as methylene acetate. When methylene acetate was added to a reaction mixture of **4** and acetic anhydride a new peak appeared at δ 5.70 in the nmr spectrum.

The formation of **2** from **4** and acetic anhydride is similar to the reaction of 1,3-diazaadamantane with nitrous acid and tosyl chloride,[2] in which formaldehyde is split out and the corresponding dinitroso and ditosyl derivatives are formed. It is also similar to these and other reactions of hexamethylenetetramine which lead to 3,7 derivatives of 1,3,5,7-tetraazabicyclo[3.3.1]-nonane,[3] and particularly to that of acetic anhydride with hexamethylenetetramine, which was found to lead to a 6.5% yield of 3,7-diacetyl-1,3,5,7-tetraazabicyclo-[3.3.1]nonane.[4]

We have found that the reaction of hexamethylenetetramine and acetic anhydride at room temperature for 4 min gives a 45% yield of 3,7-diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane, but at 90° for 45 min only 9% of the bicyclic product was isolated. Presumably further reaction leading to the tetraacetyltetrazocine occurs, but the bicyclic diacetyl compound crystallizes preferentially. However, with propionic anhydride at 90° for 2 hr, a 39% yield of 1,3,5,7-tetrapropionyloctahydrotetrazocine was isolated. The nmr spectrum ($CDCl_3$) consisted of a strong peak at δ 5.34 (8 H), a quartet at δ 2.60 (8 H), and a triplet at δ 1.15

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[1] N. W. Gabel, U. S. Patent 3,301,854 (Jan 31, 1967).

[2] H. Stettler and R. Merten, *Chem. Ber.*, **90**, 868 (1957).

[3] W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms" Part Two, Interscience, New York, N. Y., 1961, pp 1393–1398.

[4] E. Aristoff, J. A. Graham, R. H. Meen, G. S. Myers, and G. F. Wright, *Can. J. Res.*, **27B**, 520–544 (1949). See also M. Dominikiewicz, *Arch. Chem. Farm.*, **2**, 78 (1935); *Chem. Abstr.*, **30**, 1029[6] (1936).

(12 H). A Dreiding model of this compound indicated it to be a very flexible ring.

Experimental Section

All melting points were taken in open capillary tubes and are uncorrected. The nmr spectra were determined using a Varian A-60A spectrometer, and ir spectra were taken on a Perkin-Elmer Model 21 spectrometer using a KBr disk.

7-Nitro-1,3,5-triazaadamantane (4).—To 150 ml of 28% ammonium hydroxide was added 75.0 g of tris(hydroxymethyl)-nitromethane. The solution was heated in a 40° bath and stirred with a magnetic stirrer. After 30 min seven 15-ml portions of 38% formaldehyde solution were added at 15-min intervals. Cooling and filtration gave 26.0 g of product (28%). This was recrystallized from 700 ml of water using 2.0 g of decolorizing carbon to give 18.9 g of white crystalline product. In a sealed capillary **4** decomposed over the range 260–310° (lit.[1] mp 315°).

Following the procedure in ref 1, a mixture of 125 ml of ethanol, 15 g of nitromethane, 50 g of paraformaldehyde, and 58 g of ammonium acetate was stirred and refluxed for 6 hr. The reaction mixture after 12 hr cooling was filtered to give 8.7 g of product. This is in contrast to the 35 g of sublimed product reported in ref 1.

The above procedure was modified by adding only 23 g of paraformaldehyde to the other ingredients, stirring and refluxing for 1 hr, adding 11 g of paraformaldehyde, stirring and refluxing for 1 hr, adding another 11-g portion of paraformaldehyde, and then stirring and refluxing for 6 hr. Cooling and filtration gave 20.8 g (45%).

1,3,5-Triaza-7-adamantylamine (7).—To 700 ml of methanol was added 100.0 g of **4**. This mixture was reduced for 4 hr at 50° under a hydrogen pressure of 1000 psi in a stainless steel rocking bomb using 30 g of a slurry of Raney nickel in methanol as catalyst. The reaction mixture was cooled, filtered, and evaporated to dryness *in vacuo*. The residue was dissolved in 800 ml of hot benzene, and the solution was concentrated to 300 ml. Cooling and filtration yielded 74 g of product melting at 213–217°. This was recrystallized from 600 ml of benzene to give 58 g of white crystals melting at 218–220° (lit.[1] mp 300–310°). *Anal.* Calcd for $C_7H_{14}N_4$: C, 54.52; H, 9.15; N, 36.33. Found: C, 54.80; H, 9.29; N, 36.11.

1,3,5-Triaza-7-adamantylhydroxylamine (3).—A mixture of 50.0 g of **4**, 600 ml of water, and 1.0 g of 5% palladized carbon was reduced at 30° in a stainless steel rocking bomb for 2 hr under 1000 psi of hydrogen. The mixture was filtered and evaporated to dryness *in vacuo*. Then 600 ml of *n*-butyl alcohol was added, and the solution was concentrated to 100 ml. Cooling for 12 hr followed by filtration gave 39.4 g of product, mp 221–223°. Recrystallization from 90% *n*-butyl alcohol–10% water raised the mp to 227–229°. *Anal.* Calcd for $C_7H_{14}N_4O$: C, 49.39; H, 8.28. Found: C, 49.61; H, 8.17.

1,3,5-Triaza-7-adamantyldimethylamine (5).—To 150 ml of methanol was added 9.2 g of **7**, 9 ml of 37% formaldehyde solution, and about 5.0 g of a suspension of Raney nickel in water. This mixture was reduced for 4 hr at room temperature and 50 psi of hydrogen in a Parr hydrogenation apparatus. After concentration *in vacuo* the residue was dissolved in 50 ml of acetone, mixed with 20 ml of cyclohexane, and then evaporated to 20 ml. Filtration gave 6.3 g, mp 100–108°. Recrystallization from cyclohexane raised the mp to 106–108°. *Anal.* Calcd for $C_9H_{18}N_4$: C, 59.30; H, 9.95. Found: C, 59.12; H, 10.04.

***N*-Phenyl-*N'*-(1,3,5-triaza-7-adamantyl)urea (6).**—The residue from the reduction of 9.2 g (0.05 mol) of **4** with Raney nickel was dissolved in 100 ml of hot benzene. After cooling, 6 ml of phenyl isocyanate were added; the mixture was stirred for 5 hr and then filtered. The product was recrystallized twice from nitromethane to give 5.3 g of product which decomposed above 200°. *Anal.* Calcd for $C_{14}H_{19}N_5O$: C, 61.52; H, 7.01; N, 25.62. Found: C, 61.42; H, 7.00; N, 25.77.

***N*-(2-Nitroisobutyl)-1,3,5-triaza-7-adamantylamine (8).**—To 7.7 g (0.05 mol) of **7** in 150 ml of methanol was added 5.0 g of 2-methyl-2-nitro-1-propanol. The solution was refluxed for 1 hr, then evaporated to dryness. The residue was crystallized from 100 ml of cyclohexane plus 20 ml of ethanol to give 2.9 g, mp 213–216°. *Anal.* Calcd for $C_{11}H_{21}N_5O_2$: C, 51.74; H, 8.30; N, 27.43. Found: C, 51.63; H, 8.32; N, 27.43.

7-Acetamido-1,3,5-triazaadamantane (10).—To 50 ml of isopropenyl acetate was added 6.0 g of **7**, and the mixture was refluxed for 24 hr. After cooling for 12 hr, 5.8 g of product was recovered, mp 182–188°. The ir spectrum of this product was identical with that of a small amount previously prepared using a 6-hr refluxing period. This product melted at 188–191°. *Anal.* Calcd for $C_9H_{16}N_4O$: C, 55.08; H, 8.22; N, 28.55. Found: C, 55.09; H, 8.07; N, 28.71.

5-Acetamido-3,7-diacetyl-1,3,7-triazabicyclo[3.3.1]nonane (9).—A mixture of 10 ml of acetic anhydride and 3.0 g of **7** was heated on the steam bath for 30 min, then mixed with 100 ml of water. The solution was then evaporated to dryness *in vacuo*. The residue was crystallized from 25 ml of isopropyl alcohol to give 0.7 g, mp 232–236°. *Anal.* Calcd for $C_{12}H_{20}N_4O_3$: C, 53.71; H, 7.52; N, 20.88. Found: C, 53.80; H, 7.57; N, 20.73.

3,7-Diacetyl-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane (2).—The previous experiment was repeated using **4** in place of **7**, and crystallizing the product from 40 ml of isopropyl alcohol. This gave 2.9 g of product, mp 158–161°. *Anal.* Calcd for $C_{10}H_{16}N_4O_4$: C, 46.87; H, 6.29. Found: C, 46.92; H, 6.57.

5-Amino-3,7-diacetyl-1,3,7-triazabicyclo[3.3.1]nonane (1).—**2** (10 g) was reduced for 4 hr at 50 psi and room temperature in 150 ml of methanol using about 5 g of a suspension of Raney nickel in water. Recrystallization from methanol plus acetone gave 4.4 g, mp 180–182°. *Anal.* Calcd for $C_{10}H_{18}N_4O_2$: C, 53.08; H, 8.02; N, 24.76. Found: C, 53.20; H, 8.03; N, 25.00.

5-Nitro-3,7-dipropionyl-1,3,7-triazabicyclo[3.3.1]nonane.—To 50 ml of propionic anhydride was added 10 g of **4**, and the mixture was heated for 45 min on the steam bath. It was then stirred with 200 ml of ice water and concentrated to dryness *in vacuo*. The residue was crystallized twice from isopropyl alcohol (100 ml and 75 ml) to give 10.6 g, mp 145–147°. *Anal.* Calcd for $C_{12}H_{20}N_4O_4$: C, 50.69; H, 7.09. Found: C, 50.89; H, 7.22.

3,7-Dibenzoyl-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane.—A mixture of 9.2 g of **4** and 19.6 g of benzoic anhydride was heated for 4 hr on the steam bath. The mixture was then treated with 50 ml of hot isopropyl alcohol and filtered. Addition of 40 ml of water to the filtrate, followed by cooling overnight, gave 8.2 g of crystals, mp 160–189°. Recrystallization from aqueous isopropyl alcohol gave 5.1 g, mp 239–240°. *Anal.* Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30. Found: C, 62.95; H, 5.53.

1,3,5,7-Tetrapropionyloctahydrotetrazocine.—A mixture of 50 ml of propionic anhydride and 10 g of hexamethylenetetramine was heated for 2 hr on the steam bath. It was then cooled and mixed with 200 ml of water. After 30 min this mixture was concentrated *in vacuo*, and the residue was crystallized twice from 50 ml of isopropyl alcohol to give 7.3 g, mp 152–154°. *Anal.* Calcd for $C_{16}H_{28}N_4O_4$: C, 56.46; H, 8.29; N, 16.46. Found: C, 56.56; H, 8.35; N, 16.37.

3,7-Diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane.—To 50 ml of acetic anhydride was added 10 g of hexamethylenetetramine. The solution was heated on the steam bath for 15 min, then mixed with 200 ml of ice water. This mixture was then concentrated *in vacuo*, and the residue was taken up in 100 ml of hot ethyl acetate. On cooling and filtering 2.2 g of crystals were obtained, mp 190–196°. Recrystallization from an ethanol–ethyl acetate solution raised the mp to 193–195°. Similar experiments with reaction times of 45 min (steam bath) and 4 min (room temperature) gave, respectively, 1.4 and 6.8 g. *Anal.* Calcd for $C_9H_{16}N_4O_2$: C, 50.92; H, 7.60. Found: C, 51.17; H, 7.60.

Registry No.—**1**, 32515-99-4; **2**, 32516-00-0; **3**, 28820-72-6; **4**, 14612-28-3; **5**, 32476-16-7; **6**, 32476-17-8; **7**, 14707-75-6; **8**, 32476-19-0; **9**, 32516-01-1; **10**, 32476-20-3; 5-nitro-3,7-dipropionyl-1,3,7-triazabicyclo[3.3.1]nonane, 32516-02-2; 3,7-dibenzoyl-5-nitro-1,3,7-triazabicyclo[3.3.1]nonane, 32516-03-3; 1,3,5,7-tetrapropionyloctahydrotetrazocine, 32516-04-4; 3,7-diacetyl-1,3,5,7-tetraazobicyclo[3.3.1]nonane, 32516-05-5.

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