

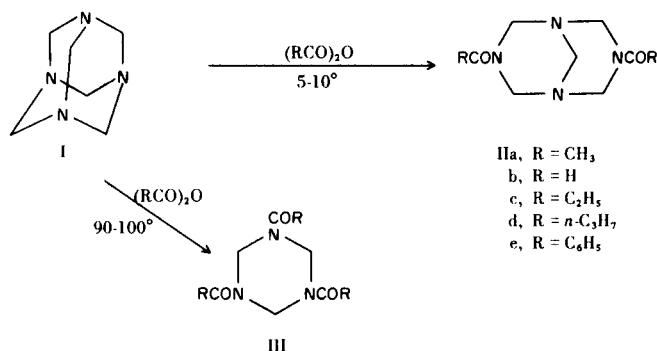
The Preparation of 3,7-Diacyl-1,3,5,7-tetraazabicyclo[3.3.1]nonanes

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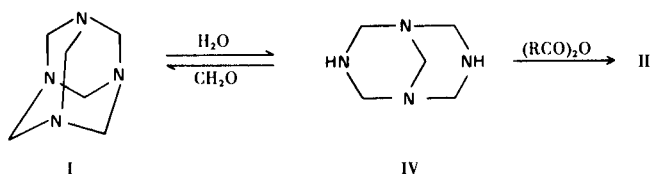
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The reaction of hexamethylenetetramine (I) with acetic anhydride has been studied by several investigators (1,2,3,4,5) always using anhydrous conditions. Prior to a recent report from this laboratory (5), IIa was the only compound noted from this reaction. Our work showed that triacylhexahydro-s-triazines (III) can also be formed. The



yields of IIa varied widely, but never exceeded 45%. We report herein a simple procedure for the preparation of IIa in over 90% yield and the use of this method for the synthesis of four new analogues (IIb-e).

The basic feature of our procedure involves conducting the reaction in the presence of water, the amount of which can be varied widely. Using acetic anhydride, water, and I at $5-10^\circ$, IIa is obtained in 65-73% pure yield based on I. If the reaction is conducted in the presence of an inorganic base equivalent to the acetic acid formed, the yield of pure IIa rises to 80%. Essentially, the latter procedure was used to prepare IIb-e. The yields of these compounds were lower than that of IIa, and no attempt was made to optimize them. The effectiveness of water in promoting the formation of II presumably results from the equilibrium (6). Compound IV is therefore probably the species actually undergoing acylation when water is present.

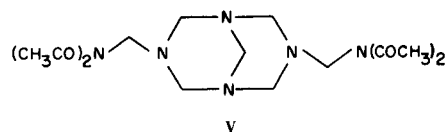


It will be noted that the conversion of I to II implies the loss of a methylene group, presumably as formaldehyde. The expected amount of formaldehyde was in fact isolated as the bismethone derivative. It was then found that the addition of ammonium acetate in an amount at least equivalent to the formaldehyde led to yields of IIa higher than theoretical based on the amount of I used. It thus appears that I is being formed from the ammonium acetate and liberated formaldehyde. This type of reaction has been studied in some detail (7).

It was found that ketene could be substituted for acetic anhydride in the preparation of IIa. Yields of pure IIa as high as 65%, based on I, were obtained, but no attempt was made to optimize this method. Ketene is known to react sufficiently slowly with water to permit its use as a reaction solvent in the acylation of amines (8).

A recent report (9) cites the reaction of trichloroacetyl chloride with I in the presence of aqueous base to yield 5% of the 3,7-di-(trichloroacetyl) analogue of II.

During recrystallization of crude IIa, a small amount of a solid, m.p. 222° , was obtained. The same compound was also obtained upon refluxing I with acetic anhydride and toluene. It was assigned structure V based on analytical, nmr, and molecular weight data. Marked differences in the nmr spectrum at 25° and 55° indicate temperature-dependent hindered rotation.



The formation in small amount of a compound also melting at 222° was likewise noted many years ago (10) to result from the reaction of acetic anhydride and I. On the basis only of analysis for C and H and aqueous hydrolysis to *N,N'*-methylenebisacetamide, the compound was concluded to be *N,N'*-methylenebisdiacetamide. The latter material was not prepared at that time for comparison with the compound melting at 222° and was in fact unknown until later (11). We have prepared it, verified the reported melting point (96°), and noted that it differs in other respects from V. It is therefore concluded that the com-

pound with m.p. 222° is V rather than *N,N'*-methylenbisdiacetamide as reported previously.

EXPERIMENTAL (12)

3,7-Diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (IIa).

a. Using Acetic Anhydride and Sodium Hydroxide.

Compound I (14 g., 0.1 mole) in 50 ml. water was added at 10° over 5 minutes to a cooled and stirred solution of sodium hydroxide (24 g., 0.6 mole) in 120 ml. water. Acetic anhydride (61.2 g., 0.6 mole) was then added at 10° over 60 minutes. The resulting clear solution was stirred for an additional 60 minutes and then evaporated to dryness *in vacuo* at 50°. The solid (83.5 g.) was extracted with 2-200 ml. portions of chloroform. Distillation of the solvent gave 21g. crude IIa, m.p. 185-190° (98% of theoretical). Recrystallization from acetone gave m.p. 192° (lit 193-195° (4); 194° (3)). nmr (deuteriochloroform): δ 5.87-4.12 (m, 8H, ring CH₂); δ 4.24 (s, 2H, endo CH₂); δ 2.07 (s, 6H, CH₃).

b. Using Acetic Anhydride and Ammonium Acetate.

To a slurry comprising I (14 g., 0.1 mole), ammonium acetate (6.2 g., 0.08 mole) and water (7 ml.) was added acetic anhydride (30.6 g., 0.3 mole) dropwise over 60 minutes with stirring and cooling at 5-10°. The solution was then stirred at 10° for 30 minutes and evaporated to dryness, yielding 25.2 g. crude IIa. This represents a 119% yield based on I used. Recrystallization from acetone gave 21.2 g. (100% of theoretical) of pure IIa.

c. Using Ketene.

Ketene (0.94 mole) prepared by the pyrolysis of acetone was passed into a solution of I (14 g., 0.1 mole) and sodium acetate trihydrate (34 g., 0.25 mole) in 175 ml. water at 15-20° with stirring over a 2 hour period. The clear solution was worked up as described above. The yield of pure IIa was 13.5 g., (65% of theoretical).

3,7-Diformyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (IIb).

To a solution of I (70 g., 0.5 mole) and anhydrous sodium acetate (123 g., 1.5 moles) in 500 ml. water was added dropwise with stirring at 0-10° acetic formic anhydride (132 g., 1.5 moles) prepared by a published procedure (13). After stirring 1 hour the solution was evaporated to dryness *in vacuo*. The wet, acidic solid was dissolved in 250 ml. water and the solution made weakly alkaline with sodium carbonate. Evaporation to dryness gave a white solid which was thoroughly dried *in vacuo* over sodium hydroxide. It was extracted with three 900 ml. portions of acetone. The combined extracts were evaporated to 300 ml. and crystallized yielding 24.0 g. of solid. Recrystallization from acetone gave 20.1 g. (22% of theoretical), m.p. 246-251°: nmr (deuteriochloroform): δ 4.21-5.57 (m, 10H, CH₂); δ 7.97 (s, 2H, CHO).

Anal. Calcd. for C₇H₁₂N₄O₂: C, 45.7; H, 6.6; N, 30.1. Found: C, 46.0; H, 6.7; N, 30.1. Mol. wt: Calcd: 184. Found: 212 (osmometric); 184 (mass spectrometric).

3,7-Dipropionyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (IIc).

The procedure described above for the preparation of IIb was followed. The yield was 52% of theoretical, m.p. 131.5-132.5°. nmr (deuteriochloroform): δ 1.08 (t, 6H, CH₃) J \cong 7 cps; δ 2.31 (q, 4H, COCH₂) J \cong 7 cps; δ 4.10-5.87 (m, 10H, ring CH₂).
Anal. Calcd. for C₁₁H₂₀N₄O₂: C, 55.0; H, 8.4; N, 23.3. Found: C, 55.0; H, 8.5; N, 23.0. Mol. wt: Calcd: 240. Found: 263 (osmometric).

3,7-Di-*n*-butyryl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (IIId).

The procedure described above for the preparation of IIb was

followed. The yield was 52% of theoretical, m.p. 84.5-87°: nmr (deuteriochloroform): δ 0.93 (t, 6H, CH₃) J \cong 7 cps; δ 1.30-1.87 (m, 4H, CH₂CH₂) J \cong 7 cps; 2.23 (t, 4H, COCH₂) J \cong 7 cps; δ 4.13-5.38 (m, 10H, ring CH₂). Mol. wt. Calcd: 268. Found: (osmometric) 270.

3,7-Dibenzoyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (IIe).

The procedure described above for the preparation of IIb was followed, except that the reaction temperature was 55°. The yield was 13% of theoretical m.p. 179-181°: nmr (DMSO-d₆): δ 4.25-5.40 (m, 10H, CH₂); δ 7.50 (s, 10H, C₆H₅).

Anal. Calcd. for C₁₉H₂₀N₄O₂: C, 67.8; H, 6.0. Found: C, 66.9; H, 6.1. Mol. wt. Calcd: 336. Found: 335 (osmometric). Calcd: 354. Found: 354.

3,7-Bis(diacetamidomethyl)-1,3,5,7-tetraazabicyclo[3.3.1]nonane (V).

Evaporation of the acetone filtrate from recrystallization of 20 g. crude IIa gave a viscous oil which partially crystallized on standing. Leaching with 5 ml. cold acetone gave 0.7 g. solid. Recrystallization from benzene gave m.p. 222°: Nmr (deuteriochloroform at 55°): δ 3.18 (s, 2H, endo CH₂); δ 4.60 (s, 8H, ring CH₂); δ 5.17 (s, 4H, -CH₂N(COCH₃)₂); δ 2.1 (s, 12H, CH₃). At 25° the spectrum was as follows: δ 3.3 (s, 2H, endo CH₂); δ 4.68, 4.72 (d, 8H, ring CH₂); δ 5.25 (s, 4H, -CH₂N(COCH₃)₂); δ 2.08 (s, 6H, CH₃); δ 2.23 (s, 6H, CH₃).

Anal. Calcd. for C₁₅H₂₆N₆O₄: C, 50.8; H, 7.4; N, 23.7. Found: C, 50.7; H, 7.2; N, 24.0. Mol. wt. (mass spectrometric): Calcd.: 354. Found: 354.

N,N'-Methylenbisdiacetamide.

N,N'-Methylenbisacetamide (14) (30 g., 0.23 mole) and acetic anhydride (140 g., 1.38 mole) were heated 14 hours at 140-145° with slow removal of acetic acid through a fractionating column. After removal of remaining acetic anhydride *in vacuo*, the residue was recrystallized from isopropanol. The yield of *N,N'*-Methylenbisdiacetamide was 16.3 g. (33%) of theoretical, m.p. 96°. The literature (11) claims a 90% yield for this procedure on a tenfold scale, m.p. 96°; nmr (deuteriochloroform): δ 5.38 (s, 2H, CH₂); δ 2.48 (s, 12H, CH₃CO).

Anal. Calcd. for C₉H₁₄N₂O₄: C, 50.5; H, 6.6; N, 13.1. Found: C, 50.6; H, 6.8; N, 13.0. Mol. wt. Calcd: 214. Found: 216 (osmometric).

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