Observations on the Synthesis and Characterization of *N,N',N''*-Tris-(dimethylaminopropyl)hexahydro-*s*-triazine and isolable intermediates

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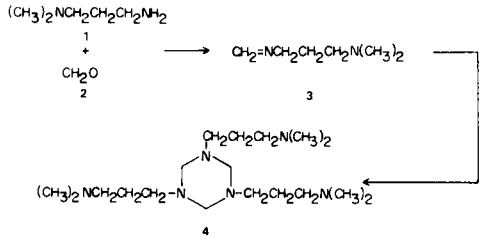
The trimerization of isocyanates utilizing tertiary amine catalysts is well known and has been employed industrially in the manufacture of isocyanurate foams and resins. The patent literature describes the use of *N,N',N''*-tris (dimethylaminopropyl)hexahydro-*s*-triazine (**4**, abbreviated HHT) in such applications (1-6). This heterocyclic tertiary amine (**4**) is claimed to be a more efficient trimerization catalyst than other commerical amine catalysts (7).

A literature search uncovered only one reference (8) containing the physical constant of HHT (**4**) and its methiodide derivative. This paper describes some of our observations concerning the synthesis and characterization of HHT (**4**) and is particularly directed toward the identification and characterization of several novel intermediates.

It has been reported that compound **4** is prepared by the addition of *N,N*-dimethylaminopropylamine (**1**) to aqueous formaldehyde (**2**). It is believed that this reaction of primary amines and formaldehyde involves initially the formation of the respective aldimine (**3**) which in turn rapidly trimerizes (9) (Scheme 1).

Scheme 1



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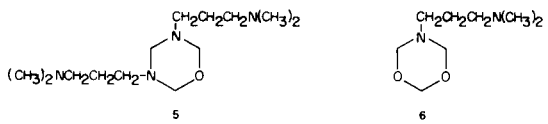
We have isolated HHT (**4**) in 80-90% yield using this procedure. Compound **4** had a boiling point of 135-140° at 0.01 mm and the elemental analysis, molecular weight, and spectroscopic data were consistent with the assigned structure. Two picrate derivatives have also been prepared and analyzed. The nmr of the major picrate (m.p. 175-176°) in DMSO-d_6 solution indicated a ratio of one picric acid to one propyl group, corresponding to three picric acids per HHT (**4**) molecule. Satisfactory elemental analysis has been obtained for this picrate structure. A second picrate (m.p. 217-220°) was obtained but not successfully characterized.

We have also succeeded in isolating the intermediate aldimine (**3**) by thermally cracking (9) purified HHT (**4**). This was accomplished by refluxing HHT (**4**) at 150°/0.01 mm and condensing the volatile aldimine (**3**) in a trap cooled to -70°. The trapped aldimine (**3**) was mixed with carbon tetrachloride and its nmr spectrum recorded at low temperature. The spectrum obtained (Figure 1) was consistent with the aldimine (**3**) structure. Upon warming to room temperature, conversion of the aldimine (**3**) to HHT (**4**) was observed.

The yield of HHT (**4**) was observed to be slightly higher and the crude product less contaminated when the reaction was conducted by reverse addition; that is formaldehyde (**2**) added to the amine (**1**). In the experiments where the amine (**1**) was added to formaldehyde (**2**), impurities were observed in the nmr analysis of the crude product. If an excess of formaldehyde was employed in these reactions, the amount of by-products increased. Two other compounds have been isolated and characterized from these reaction mixtures and can be postulated to arise from incorporation of formaldehyde (**2**) in the aldimine (**3**) trimerization process.

The major product (**5**) corresponds to a 2:1 adduct of the aldimine (**3**) and formaldehyde (**2**): 3,5-bis(*N,N*-dimethylaminopropyl)-1,3,5-tetrahydro-oxadiazine (**5**). This material (**5**) has been isolated in 60% yield when two moles of amine (**1**) are reacted with three moles of formaldehyde (**2**). This material had a boiling point of 100-110°/0.01 mm and the elemental analysis, molecular weight, and spectroscopic data are consistent with the assigned structure. Even after repeated distillation of the

Scheme 2



5 6

2:1 adduct (**5**), small quantities of HHT (**4**) were observable by nmr analysis. Because of this observation, the thermal stability of the 2:1 adduct (**5**) was investigated

by nmr in *o*-dichlorobenzene solvent. At 100°, the 2:1 adduct (**5**) decomposed to HHT (**4**) and paraformaldehyde at a rate of 25% per hour. A by-product (≈ 2%) was detected by nmr analysis, and ir analysis indicated possible carbon-nitrogen double bond formation. The structure of this product was not determined. When the 2:1 adduct (**5**) was distilled under conditions of short exposure (flash distillation), analytically pure material was obtained.

A second compound was also observed in the nmr analysis, but in low yield. If a large excess of formaldehyde was employed in the synthesis, the yield of this compound could be increased to 20%. This compound has been tentatively identified as the 1:2 adduct of the aldimine (**3**) and formaldehyde (**2**): 5-(*N*,*N*-dimethylaminopropyl)-1,3,5-dihydrodioxazine (**6**). Elemental analysis, molecular weight, and spectroscopic data are consistent with the assigned structure. A similar dioxazine compound has been reportedly isolated from the reaction products of ethylamine and aqueous formaldehyde (10). The thermal stability of the 1:2 adduct (**6**) was also investigated by nmr in *o*-dichlorobenzene solvent. In contrast to the 2:1 adduct (**5**), the 1:2 adduct (**6**) was stable at 100° even over a period of two hours.

An attempt was made to determine whether the adducts (**5**) and (**6**) would react with starting amine (**1**) to produce HHT (**4**) under our reaction conditions. A mixture of adducts (**5**) and (**6**) was treated with excess amine (3) in the presence and absence of water at 55° for three hours. Analysis by nmr indicated no reaction had occurred (see Experimental). Under these conditions, adducts (**5**) and (**6**) are not reactive intermediates in the synthesis of HHT (**4**).

However, the reported synthesis (8) of HHT (**4**) was conducted at 100°, a condition under which the adduct (**5**) can be considered to be a potential reactive intermediate. Such cyclic intermediates may be involved in the synthesis of other hexahydro-*s*-triazines. The effectiveness of these heterocyclic tertiary amines (**5** and **6**) as isocyanate trimerization catalysts is now being determined.

EXPERIMENTAL

The *N*,*N*-dimethylaminopropylamine was obtained from Aldrich Chemical Company and used without further purification. Formaldehyde was obtained as a 37% aqueous solution (ACS Certified) from Fisher Scientific Company. Melting points and boiling points are uncorrected. Elemental analysis and molecular weight determinations were performed by Galbraith Laboratories, Knoxville, Tennessee. Infrared spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. The nmr spectra were determined on a Japan Electron Optics Lab. 4H-100 spectrometer using TMS as internal standard and solvents where indicated.

N,*N*',*N*''-Tris(dimethylaminopropyl)hexahydro-*s*-traizine (**4**).

To a stirred solution of 37% aqueous formaldehyde (**2**) (115 g., 1.42 moles) was added *N*,*N*-dimethylaminopropylamine (**1**) (150 g., 1.47 moles) at a rate to keep the temperature between 50-55°. The addition was complete after 3 hours and the reaction stirred for an additional hour. The reaction mixture was then cooled in an ice bath and potassium hydroxide (115 g.) added such that the temperature did not exceed 25°. The organic layer was separated and subjected to vacuum distillation resulting in the isolation of *N*,*N*',*N*''-tris(dimethylaminopropyl)hexahydro-*s*-triazine (4) (140 g., 0.41 mole), b.p. 135-140°/0.01 mm; nmr (carbon tetrachloride): δ 3.21 (S, 6 H), 2.39 (t, 6 H, J = 7.0 Hz), 2.22 (t, 6 H, J = 7.0 Hz), 2.12 (S, 18 H), 1.50 (m, 6 H).

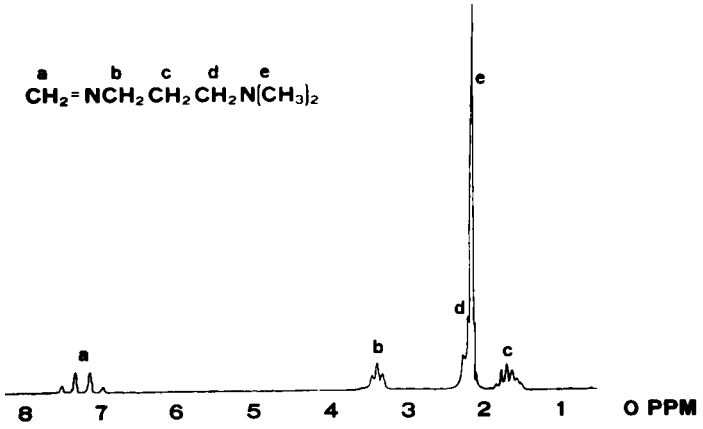


Figure 1

Anal. Calcd. for $C_{18}H_{42}N_6$: C, 63.11; H, 12.36; N, 24.53; molecular weight 342.6. Found: C, 63.35; H, 12.27; N, 24.33; molecular weight 347.

Picrate of *N*,*N*',*N*''-Tris(dimethylaminopropyl)hexahydro-*s*-triazine.

The free base (**4**, 1.03 g.) was added to a hot solution of picric acid (2.5 g.) in 60 ml. of 2-propanol. The initial orange, viscous oil converted into an orange solid. Filtration of the cooled slurry gave 3.0 g. of picrate with a m.p. of 160-165°. Recrystallization from ethanol gave 0.9 g. of picrate with a m.p. of 175-176°. The nmr analysis in DMSO-d_6 indicated three picric acid molecules per molecule of HHT (**4**).

Anal. Calcd. for $C_{36}H_{51}N_{15}O_{21}$: C, 41.90; H, 4.98; N, 20.55. Found: C, 41.87; H, 4.99; N, 20.30.

Treatment of the heated filtrate with additional picric acid (2.1 g. in 35 ml. 2-propanol), cooling the turbid solution after continued heating for 5 minutes and filtration gave 0.4 g. of yellow powder with a m.p. of 210-212°. Recrystallization from ethanol raised the m.p. to 217-220°. The nmr analysis as described above indicated four picric acid molecules per molecule of HHT (**4**).

Anal. Calcd. for $C_{42}H_{54}N_{18}O_{28}$: C, 40.07; H, 4.32; N, 20.02. Found: C, 42.89; H, 4.96; N, 19.97.

3-(*N*,*N*-Dimethylamino)propylformaldimine (**3**).

Previously distillled **4** was heated under reflux at 150°/0.01 mm for four hours and the volatile formaldimine was condensed in a dry-ice trap inserted between the pump and the refluxing **4**. The pressure was raised to atmospheric and carbon tetrachloride was introduced into the trap. The carbon tetrachloride solution was warmed to -20° and transferred to an nmr tube cooled in a dry ice bath. The spectra were then recorded at various temperatures (see Figure 1); nmr (carbon tetrachloride): δ 7.25

(AB Quartet, 2 H), 3.39 (t, 2 H), 2.20 (t, 2 H), 2.12 (S, 6 H), 1.70 (m, 2 H).

The temperature was raised to 25° and, after 1 hour, the original aldimine (**3**) spectrum had disappeared, and a spectrum of trimer (**4**) was obtained. The ir spectrum was identical with that obtained for HHT (**4**).

3,5-Bis(*N,N*-dimethylaminopropyl)-1,3,5-tetrahydro-oxadiazine (**5**).

Dimethylaminopropylamine (**1**) (102 g., 1.0 mole) was added dropwise with stirring to a 37% solution of aqueous formaldehyde (125 g., 1.5 moles) such that the temperature did not exceed 50°. The addition required 1.5 hours after which the reaction mixture was allowed to stand for an additional 1.5 hours. The solution was then cooled in an ice bath and a total of 40 g. of potassium hydroxide was added such that the temperature did not exceed 25°. The organic layer was separated and subjected to vacuum distillation resulting in the isolation of **5** (77.5 g., 0.3 mole), b.p. 100-110°/0.01 mm; nmr (carbon tetrachloride): δ 4.25 (S, 4 H), 3.58 (S, 2 H), 2.62 (t, J = 7.5 Hz, 6 H), 2.22 (t, J = 7.5 Hz, 6 H), 2.12 (S, 18 H), 1.50 (m, 6 H).

Anal. Calcd. for $C_{13}H_{30}N_4O$: C, 60.43; H, 11.70; N, 21.68, molecular weight 258.4. Found: C, 60.26; H, 11.90; N, 21.80; molecular weight 270.

5-*N,N*-Dimethylaminopropyl-1,3,5-dihydro-dioxazine (**6**).

Dimethylaminopropylamine (**1**) (20.4 g., 0.2 mole) was added dropwise to a 37% aqueous formaldehyde solution (80 g., 0.98 mole) over a period of one hour. The temperature of the reaction did not exceed 35° during this addition. The reaction was then cooled in an ice bath and 80 g. of potassium hydroxide added such that the temperature did not exceed 25°. The organic layer was separated and subjected to vacuum distillation. The major isolated product was compound **5**, but compound **6** was also isolated (6.5 g., 0.04 mole), b.p. 45°/.01 mm, nmr (carbon tetrachloride): δ 5.52 (S, 2 H), 4.52 (S, 4 H), 3.03 (t, J = 7.5 Hz, 2 H), 2.22 (t, J = 7.5 Hz, 2 H), 2.12 (S, 6 H), 1.55 (m, 2 H).

Anal. Calcd. for $C_8H_{18}N_2O_2$: C, 55.15; H, 10.41; N, 16.08; molecular weight, 174. Found: C, 55.15; H, 10.48; N, 16.04; molecular weight 175.

Attempted Reaction of Adducts (**5**) and (**6**) with *N,N*-Dimethylaminopropylamine (**1**).

a.

A 5 g. mixture of adduct (**5**) (80%) and adduct (**6**) (20%) was added to 10 g. of *N,N*-dimethylaminopropylamine (**1**) and an nmr spectrum recorded immediately in *o*-dichlorobenzene solvent. The remaining reaction mixture was heated at 55° for three hours after which its nmr spectrum was recorded. There was no observable difference between the two indicating no reaction had occurred. The original nmr sample was also heated for three hours at 55° and 30 minutes at 80° in the nmr probe with the same result. The samples were also analyzed after standing 48 hours at 25° with the same result, indicating that adducts (**5**) and (**6**) were stable under these conditions.

b.

A 5 g. mixture of adduct (**5**) (80%) and adduct (**6**) (20%) was added to 10 g. of *N,N*-dimethylaminopropylamine (**1**) and 2 ml. of water. The mixture was heated at 55° for three hours, followed by cooling to room temperature and the addition of 10 g. of potassium hydroxide. The organic layer was separated after one hour and analyzed by nmr. The spectrum was identical to that obtained above indicating no reaction had occurred.

Acknowledgement.

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