# Structure and Chemistry of the Aldehyde Ammonias. 3. Formaldehyde–Ammonia Reaction. 1,3,5-Hexahydrotriazine[1]

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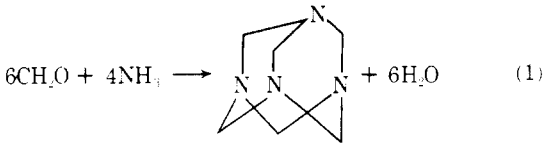
The formaldehyde–ammonia reaction has been examined in $D_2O$ solvent with the aid of $^1H$ and $^{13}C$ NMR spectroscopy. Reaction intermediates, including 1,3,5-hexahydrotriazine (**2**) and 1,3,5,7-tetraazabicyclo[3.3.1]nonane (**6**), are observed, and the mechanisms of their formation and conversion into hexamine are discussed. Solutions previously reported to contain **2** alone have been shown to be complex mixtures.

The formaldehyde–ammonia reaction under appropriate conditions leads quantitatively to hexamine (**1**, eq 1).[3] Despite

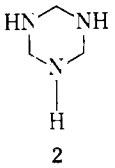


(1)

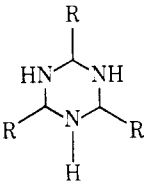
**1**

its importance, it has received limited detailed study; understanding of this complex reaction sequence is tentative. In the present work $^1H$ and $^{13}C$ NMR spectroscopy have been employed to follow the reaction and identify some intermediates.

The most extensive recent study of the formaldehyde–ammonia reaction is that of Richmond, Myers, and Wright.[4] From chemical evidence they concluded that 1,3,5-hexahydrotriazine (**2**) is a reaction intermediate. This result is in



**2**



**3**, R = alkyl
**3a**, R = $CH_3$

agreement with the early reports of Duden and Scharff,[5] who first correctly assigned structure **1** to hexamine. The present study provides NMR evidence for formation of **2**. Our previous studies on reaction of *n*-alkanals with ammonia showed that the ultimate reaction products are usually 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**3**).[1,6] The kinetics of the formaldehyde–ammonia reaction have been examined by several workers.[7]

## Results and Discussion

**$^1H$ and $^{13}C$ NMR Spectra of Formaldehyde–Ammonia Solutions.** In the present work $^1H$ and $^{13}C$ NMR spectra of various $D_2O$ solutions of ammonium-$d_4$ hydroxide and formaldehyde at 25 °C were determined at intervals. The $^1H$ spectra clearly reveal the rapid formation of hexamine and the presence of reaction intermediates (Figure 1). The methylene signals are grouped in two principal regions. Rather broad signals near $\delta$ 4.5 are attributed to $NCH_2O$-type methylenes; compare these signals with those of 1,3-perhydrotriazine (**4**) in which the C-2 methylenes appear at $\delta$ 4.55[8a] (Table I). Sharper, more defined signals appear near $\delta$ 3.5–4.0 and represent $NCH_2N$-type methylenes (with the exception of hexamine itself which appears as a singlet at $\delta$ 4.75).[9] Altering the formaldehyde–ammonia molar ratio from 1:4 to 3:2 provides the same products in each experiment, and their relative distribution at a given time is changed but slightly.

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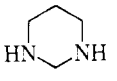
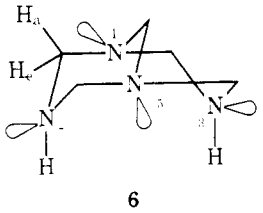


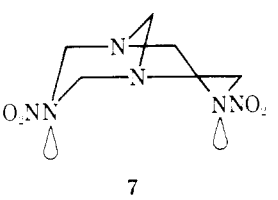
**5**

1,3,5-Hexahydrotriazine (**2**) exhibits a sharp singlet at $\delta$ 3.95. This value may be compared with the C-2 methylene signal of 1,3-hexahydrodiazine (**5**, $\delta$ 3.73)[8b] and the ring methine signal of 2,4,6-trimethyl-1,3,5-hexahydrotriazine [**3a**, $\delta$ 3.80 (q)] in $D_2O$ solvent (Table I). Hexahydrotriazine forms rapidly and ultimately is the principal species present other than hexamine. Initially, its concentration is much greater than that of hexamine, a fact supported by low temperature (−10 °C) $^{13}C$ NMR spectra observations; e.g., the peak height ratio of **2**/**1** equals 3 after 1 h.

Signals attributed to 1,3,5,7-tetraazabicyclo[3.3.1]nonane (**6**) persist in the $^1H$ NMR spectra of formaldehyde–ammonia



**6**



**7**

solutions (Figure 1; other spectra obtained show this more clearly). The concentration of **6** is relatively much lower than that of **2** except in the earlier reaction stages where it appears to be nearly equal. The signals attributed to **6** appear as two single lines: one a collapsed AB quartet of the 2,4,6,8 ring methylene protons centered near $\delta$ 3.86; the second, a singlet of one-fourth relative intensity, is the bridge methylene at $\delta$ 3.81. The constant 4:1 ratio of these peaks is retained as their intensities vary and supports the structure assignment. The $^1H$ NMR spectra of numerous model compounds are similar to that of **6**. For example, 3,7-dinitro-1,3,5,7-tetraazabicyclo[3.3.1]nonane (**7**) exhibits a bridgehead methylene singlet at $\delta$ 4.14; the ring methylenes appear as an AB quartet (Table I).[10]

The conformation of **6** is shown as a flattened chair–chair, which is favored in various heterocyclic bicyclo[3.3.1]nonanes.[10,11] To explain the observed collapsed AB quartet of **6**, the ring axial and equatorial protons are seen as similarly deshielded since both are equidistant from the adjacent nitrogen p lobes, assuming the N-3 and N-7 lobes to be exocyclic to avoid their "rabbit ear" interaction. The N-3 and N-7 hydrogens thereby assume an axial configuration. Thus, the methylene hydrogens and nitrogen lone pair orbitals in **6** appear to be oriented like those in hexamine.

Broad signals near $\delta$ 4.5 are attributed, principally, to *N*-methylol-*O*-*d* derivatives. The breadth of these signals, which persists throughout the reaction, suggests a rapid steady-state turnover of these groups owing to their short half-lives. The intensity of these signals disappears more rapidly than that

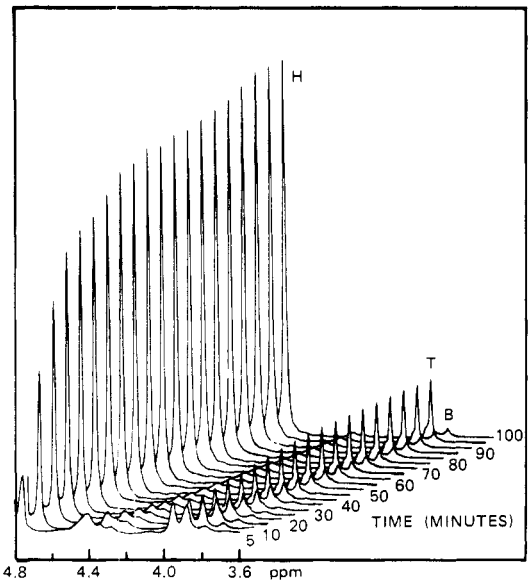



**Figure 1.** $^1H$ NMR spectra of $D_2O$ solution of formaldehyde (1 M) and ammonium hydroxide (1 M) determined at various times after mixing (25 °C): H = hexamine (1); T = 1,3,5-hexahydrotriazine (2); B = 1,3,5,7-tetraazabicyclo[3.3.1]nonane (6).

**Table I. $^1H$ and $^{13}C$ NMR Spectra in $D_2O$ Solvent (25 °C)**

| compd no. | group | chemical shift, $\delta$[a] $^1H$ | $^{13}C$ |
|---|---|---|---|
| 1 | $CH_2$ | 4.75 (s) | 74.5 |
| 2 | $CH_2$ | 3.95 (s) | 61.6 |
| 3a | CH | 3.80 (q, $J$ = 6.5 Hz) | 67.3 |
| 4 | C-2 $CH_2$ | 4.55 (s)[b] | |
| 5 | C-2 $CH_2$ | 3.73 (s)[c] | |
| 6 | C-2,4,6,8 $CH_2$ | 3.86 (q)[d] | 66.6[e] |
| | C-10 $CH_2$ | 3.81 (s) | 69.9[e] |
| 7[f] | C-2,4,6,8 $CH_2$ | 4.96, 5.52 (q, $J$ = 13 Hz) | 68.5 |
| | C-10 $CH_2$ | 4.14 (s) | 64.9 |
| 8 | C-2,2',6,6' $CH_2$ | 3.97 (s)[e] | 67.0[e] |
| | C-4,4' $CH_2$ | 3.95 (s)[e] | 61.4[e] |
| | bridge $CH_2$ | | 68.4[e] |
| 9 | C-2,4 $CH_2$ | | 65.3[e] |
| | C-6,8 $CH_2$ | | 66.3[e] |
| | C-10 $CH_2$ | | 70.1[e] |
| | N-3 *exo*-$CH_2$ | | 70.8[e] |
| 12a | $CH_2$[g] | 6.40 (s) | 55.4 |
| 12b | $CH_2$[g] | 5.77 (s), 6.38 (s), 7.03 (s) | 46.2, 56.8, 65.4 |
| 13a[h] | C-2,8 $CH_2$ | 4.25, 5.81 (q)[g] | 60.7[f] |
| | C-4,6 $CH_2$ | 5.30, 5.49 (q,[g] $J$ = 13 Hz) | 69.4[f] |
| | C-10 $CH_2$ | 4.59 (s) | 68.1[f] |
| 13b[h] | C-4,8 $CH_2$ | 4.33, 5.81 (q)[g] | 59.9[f] |
| | C-2,6 $CH_2$ | 5.30, 5.53 (q,[g] $J$ = 13 Hz) | 70.1[f] |
| | C-10 $CH_2$ | 4.59 (s) | 68.4[f] |

[a] Sodium 3-(trimethylsilyl)propanoate internal reference for $D_2O$ solutions, and tetramethylsilane for others. [b] Reported $\delta$ 4.40 in $CDCl_3$.[8] [c] Reported $\delta$ 3.63 in $D_2O$; reference compound was not stated.[9] [d] Center lines of collapsed AB quartet. [e] Suggested assignments. [f] $(CD_3)_2SO$ solvent; some data are also reported in ref 10a,b. [g] $(CD_3)_2CO$ solvent; some data are also reported in ref 10a,c. [h] Compound prepared by the procedure of Bachmann and Deno.[15]

of **2** and **6** (also observed in the $^{13}C$ NMR spectra).

The proton-decoupled Fourier transform $^{13}C$ NMR spectra of formaldehyde–ammonia solutions in $D_2O$ provide data in agreement with those derived from proton spectra. Near the completion of the reaction, two principal signals persist, those

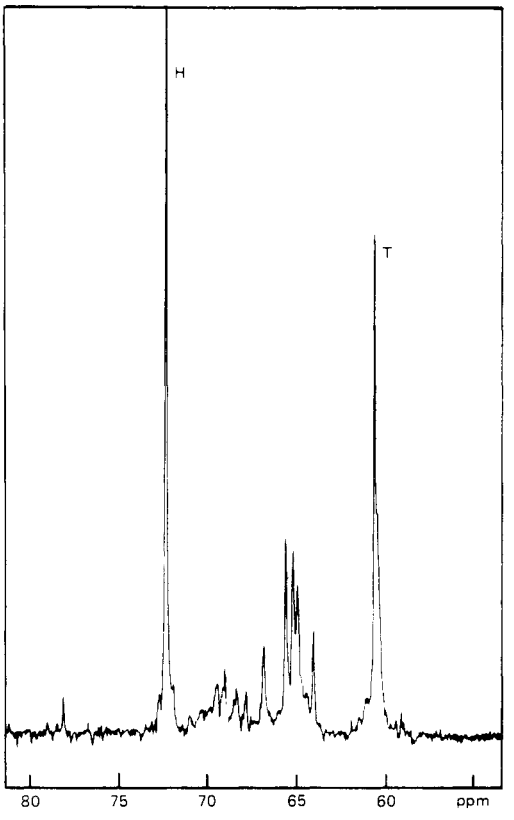
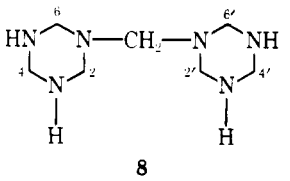
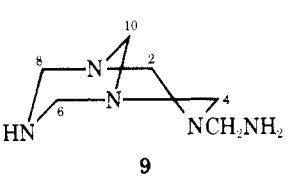



**Figure 2.** Proton-decoupled $^{13}C$ NMR spectrum of $H_2O$–$D_2O$ solution of formaldehyde (5.7 M) and ammonium hydroxide (7.8 M) determined after 24 h elapsed reaction time at −10 °C: H = hexamine (1); T = 1,3,5-hexahydrotriazine (2).

of hexamine (**1**, $\delta$ 74.5) and 1,3,5-hexahydrotriazine (**2**, $\delta$ 61.6). Owing to the required signal-averaging time (~10–15 min), $^{13}C$ spectra obtained at early and intermediate reaction times are observed to be very complex with numerous lines to which it is difficult to match structure assignments. Spectra obtained at later reaction times are simpler and show the intense lines of **1** and **2** in addition to other weaker lines, most of which are grouped as a pattern of nine lines showing estimated relative intensity ratios of 4:4:2:2:2:1:1:1:1. These ratios are retained in three groups (4:1, 4:2:1, and 2:2:1:1) of diminished intensity as the reaction proceeds (Figure 2 shows a typical spectrum). One pair of lines ($\delta$ 66.6, 69.9; 4:1 ratio) is attributed to **6** (Table I). Stable intermediate compounds such as **8** (signal



**8**



**9**

intensity ratio 4:2:1) and **9** (ratio 2:2:1:1) would account for the remaining lines, although certain less plausible and less stable alternative structures could be written. A line at $\delta$ 61.4 (estimated relative intensity 2) seen as a shoulder on the triazine peak (Figure 2) suggests a structure very similar to **2**; the signal of the 4,4' carbons of **8** would be expected to appear near $\delta$ 61.5. [A weak shoulder ($\delta$ 3.97) on the proton spectrum signal of **2** (Figure 1) could correspond to 2,2',6,6' ring methylene signals in **8**.] The spectrum of **9** should closely resemble that of **6** (suggested signal assignments are listed in Table I). The bis(nitramine) **7** has a spectrum similar to that of **6** (lines at $\delta$ 64.9 and 68.5 in $(CD_3)_2SO$ solvent[10b]), although nitro substitution affects the chemical shift values.

**1,3,5-Hexahydrotriazine (2).** The present study shows

1,3,5-hexahydrotriazine formation to occur in ammonia–formaldehyde reactions (Figures 1 and 2). At equilibrium it is the principal minor component in solution; hexamine is the major component. Our efforts to prepare pure **2**, either neat or in solution, were unsuccessful. The material is converted into hexamine under a variety of conditions.

A substance known as **Henry solution**[12] is prepared by passing 1 mol equiv of ammonia gas into a solution of 40% formalin at 0 °C, followed by addition of sufficient solid potassium carbonate to cause separation of a floating oily layer. The oil is treated with additional potassium carbonate, decanted or centrifuged, and stored at low temperature.[4,12] Although the directions of Henry call for a 1:1 molar ratio of formaldehyde and ammonia, Wright[4] observed that this ratio could be varied without altering the chemical properties of the product.

Wright concluded from chemical evidence that Henry solution is largely aqueous 1,3,5-hexahydrotriazine (**2**, 50% by weight).[4] Henry believed his product to be trimethylolamine, $(HOCH_2)_3N$.[12] In the present study it is concluded that Henry solution contains some **2**, in addition to other components, but rapidly changes to hexamine on aging. The $^1H$ and $^{13}C$ NMR spectra of Henry solution and the spectra of aqueous formaldehyde–ammonia solutions at comparable reaction points are virtually indistinguishable and are believed to contain the same components.

By examination of the proton NMR spectra of Henry solution prepared in $D_2O$ and determined at intervals at 25 °C, the relative concentrations of the major components were determined. Figure 3 shows a plot of time vs. the approximate relative molar concentrations of **1**, **2**, and **6** (established by dividing the appropriate peak heights by the number of protons per signal; small amounts of **8** and **9** may be included in the concentration values for **2** and **6**, respectively). It may be observed that after about 2 weeks the molar ratio of the three components is nearly equal and that the concentration of **2** remains high for about 1 month before the relative concentration of hexamine predominates significantly. The rate of reaction is accelerated greatly on warming. It is clear that Henry solution is a dynamic mixture. Wright's conclusion that

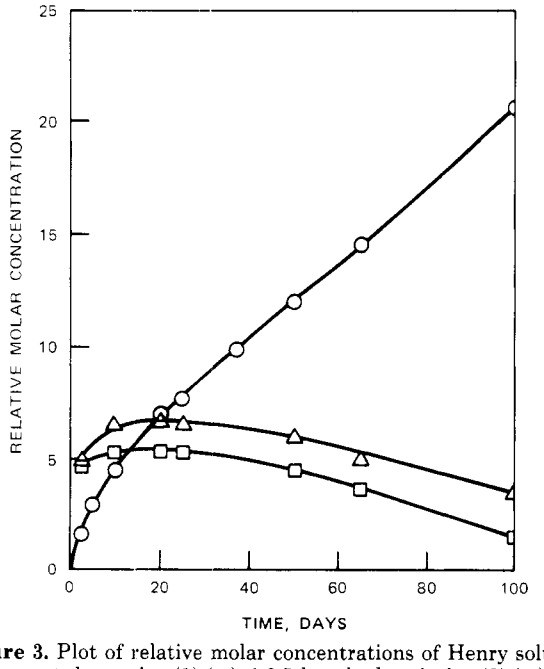



**Figure 3.** Plot of relative molar concentrations of Henry solution components hexamine (**1**) (○), 1,3,5-hexahydrotriazine (**2**) (△), and 1,3,5,7-tetraazabicyclo[3.3.1]nonane (**6**) (□) vs. time (25 °C). Data are calculated from $^1H$ NMR peak heights divided by the number of protons corresponding to the signal to obtain the concentration index.

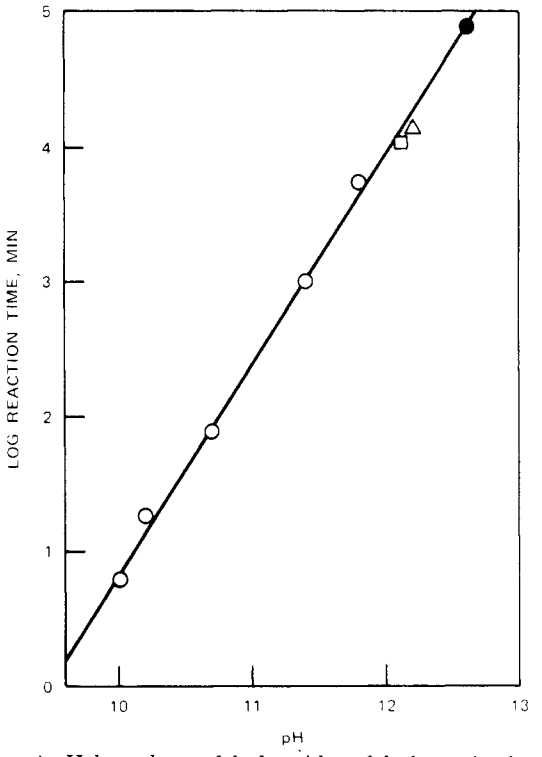



**Figure 4.** pH dependence of the logarithm of the hexamine formation rate (minutes elapsed to $^1H$ NMR peak height ratio of hexamine (**1**)/1,3,5-hexahydrotriazine (**2**) = 4:1): (○) $D_2O$ solutions of $CH_2O$, $ND_4OD$ only; (□) NaOH added; (△) Duden and Scharff solution; (●) Henry solution.

it behaves as 1,3,5-hexahydrotriazine, although partially correct, is applicable only to fresh solutions.

An important misconception regarding Henry solution ("1,3,5-hexahydrotriazine solution") is the failure to recognize its transitory shelf life. Thus, at present several chemical distributors market a product, prepared by Wright's procedure,[4] labeled "hexahydro-*s*-triazine, 50% aqueous solution".[13] It is claimed to have a shelf life of 12–15 months when kept cool, or "several weeks" at ambient temperature.[4,13] Actually, all samples of such materials which we have obtained smell strongly of ammonia and have been found to contain only hexamine (~40% aqueous solution) and ammonium hydroxide. Occasionally crystals of hexamine separate from these solutions. Presumably such solutions have aged or become warm excessively. Use of such samples in chemical reactions can lead to ambiguous results, as in the questionable report of a preparation of 1,3,5-hexahydrotriazinium nitrate.[14]

Henry solution has a much longer shelf life (as measured by its rate of hexamine formation from **2**) than 1:1 formaldehyde–ammonia solutions; compare Figures 1 and 3. This is due to its high ammonia content and high pH (12.6). The effect of pH on a measure of the rate of hexamine formation is seen in Figure 4, which plots the log of time required for the molar ratio of hexamine to hexahydrotriazine to reach 2:1 vs. pH ($D_2O$ solutions; data are in Table II). The pH remains reasonably constant at this stage of the reaction and may be measured quite accurately. The pH was varied by controlling the concentration of reactants or by addition of sodium hydroxide. Henry solution contains traces of potassium carbonate (0.2%), but this base at this low concentration has virtually no effect on the pH in comparison to the large amount of ammonia and amines present (Table II). Addition of formaldehyde or acid to Henry solution results in its rapid conversion to hexamine. Aqueous solutions of hexamine made acidic (pH 1) or basic (pH 12) revealed only the hexamine peak in NMR spectra after several hours. However, vigorous acid

**Table II. Formaldehyde–Ammonia Reactions in $D_2O$ at 25 °C: pH–Rate Profile Data**

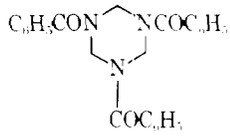
| reactant concentration, M[a] | | reaction time,[b] | |
|---|---|---|---|
| $[CH_2O]$ | $[NH_3]$ | min | pH[c] |
| 0.50 | 0.50 | 6 | 10.0 |
| 0.50 | 0.50[d] | 10 | 10.1 |
| 0.67 | 0.67 | 18 | 10.2 |
| 0.50 | 1.00 | 90 | 10.7 |
| 4.7 | 4.7 | 1030 | 11.4 |
| 3.0 | 6.0 | 5700 | 11.8 |
| 2.8 | 2.8[e] | 11 000 | 12.1 |
| 2.8 | 2.8[f] | 13 400 | 12.2 |
| 15 | 15[g] | 72 000 | 12.6 |

[a] Concentration of reactants in solution after initial mixing. [b] Time required for ratio of peak heights of $^1H$ NMR signals of hexamine and 1.3,5-hexahydrotriazine, respectively, to reach 4:1. [c] pH measured when peak height ratio of hexamine to 1,3,5-hexahydrotriazine signals = 4:1. [d] Solution 0.07 M in $K_2CO_3$. [e] Solution 0.28 M in NaOD. [f] Duden and Scharff solution. [g] Henry solution; concentrations of reactants calculated from data of ref 4; solution ~0.01 M in $K_2CO_3$.

treatment of hexamine (reflux several hours) results in complete degradation to formaldehyde and ammonia.[7a,g]

Attempts were made to isolate pure 1,3,5-hexahydrotriazine (**2**). Freshly prepared Henry solution was concentrated to dryness at near 0 °C to yield a white solid, aliquots of which were extracted with various cold solvents. When reconstituted in $D_2O$ its $^1H$ NMR spectrum was very similar to that of the original, except for some slight decrease in the triazine peak intensity. Extraction with cold $CDCl_3$ produced similar results, except that the triazine peak was diminished considerably. Extractions into carbon tetrachloride or benzene-$d_6$ gave solutions showing the spectrum of hexamine only; **2** would be expected to be less soluble in these solvents. These preliminary results suggest that **2** exhibits thermal instability like that of 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**3**),[1,6] most of which decompose rapidly at ambient temperatures. Based on observed relative NMR peak intensities, the bicyclotetramine **6** present in the reconstituted Henry solution appears to be relatively more stable than **2**.

**Duden and Scharff solution**[5] is prepared by addition of 40% formalin to aqueous ammonium hydroxide prepared by addition of a molar excess of sodium hydroxide to aqueous ammonium chloride solution. These authors concluded that their solution contained 1,3,5-hexahydrotriazine since it reacted with benzoyl chloride to form the 1,3,5-tribenzoyl derivative **10**, in addition to the acyclic product **11**. These



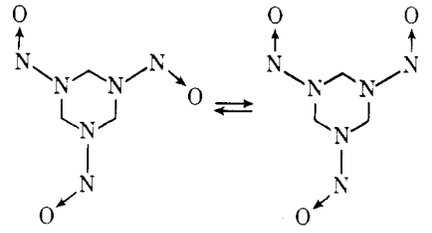
**10**

$C_6H_5CONHCH_2NHCH_2NHCOC_6H_5$

**11**

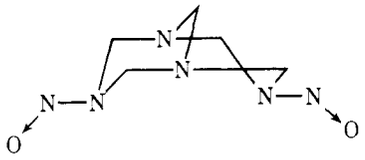
results were confirmed by Wright.[4] Duden and Scharff solution differs from Henry solution in that it is less concentrated in amine products and contains sodium chloride and sodium hydroxide. It forms hexamine more slowly than unmodified 1:1 formaldehyde–ammonia solutions of the same molarity and more rapidly than Henry solution. Wright attributed these rate differences to the greater amine (not ammonia) concentration in Henry solution.[4] We have now established that it is the presence of excess sodium hydroxide which accounts for the enhanced stability of Duden and Scharff solution since it raises the pH to a value (12.2) where hexamine formation is quite slow (Figure 4). Solutions of 1:1 formaldehyde–ammonia to which sodium hydroxide has been added to cause a pH increase also form hexamine very slowly (Figure 4). Added sodium chloride exhibits no significant salt effect on the observed hexamine formation rate, in agreement with the kinetic data of Ogata and Kawasaki.[7g,i]

The chemical behavior of 1,3,5-hexahydrotriazine solutions (Henry and Duden and Scharff solutions) differs in some, but not all, respects from that of solutions of pure hexamine. The subject has been reviewed and studied by Wright.[4] For example, the preparation of 1,3,5-tribenzoyl-1,3,5-hexahydrotriazine (**10**) from fresh Henry solution contains little 1,3,5-tribenzoyl-1,3,5-triazapentane (**11**), whereas the preparation of **10** from hexamine contains larger amounts of the latter substance. Hexamine solution reacts with diazotized *m*-nitroaniline to yield 3,7-bis(3-nitrophenyldiazo)-1,3,5,7-tetraazabicyclo[3.3.1]nonane, whereas freshly prepared Henry solution does not.[4,5] Chemical behavior as an assay of **2** in solution cannot be considered conclusive, however. Henry solution, Duden and Scharff solution, and formaldehyde–ammonia solutions of various molar ratios, as well as hexamine solutions, all react with nitrous acid at pH 1 to form 1,3,5-trinitroso-1,3,5-hexahydrotriazine (**12**) irreversibly in con-

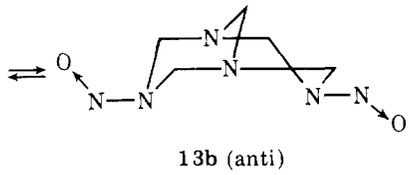


**12a** **12b**

sistent yields of 25–30% based on methylene. The report by Wright[4] that his yield of **12** from Henry solution is 52% based on methylene is incorrect; calculated from the data which he reports, his correct yield is 26.6%; his yield from hexamine is 24%, as reported. The incorrect report is often cited in the secondary literature to support the high assay of **2** in Henry solution.[3] At higher pH (3–6) Henry solution as well as hexamine solutions react with nitrous acid to yield 3,7-dinitroso-1,3,5,7-tetraazabicyclo[3.3.1]nonane (**13**, 70–75%). As



**13a** (syn)

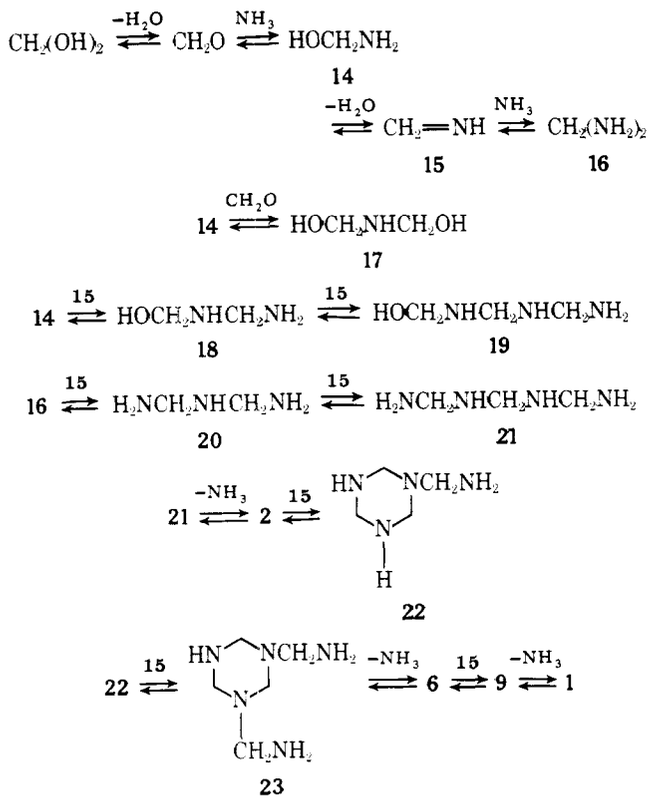


**13b** (anti)

explained by Bachmann,[15] the product distribution of **12** and **13** is dependent on the pH of the reaction medium. Their formation is an acid-catalyzed nitrosation of hexamine. Hexamine formation from **2** at pH 1 is evidently faster than nitrosation of **2** to form **12**.

The high-resolution $^1H$ NMR spectrum of **12** in $(CD_3)_2CO$ reveals four methylene singlets, corresponding to a nearly statistical distribution of the symmetrical and asymmetrical forms **12a** and **12b** (1:3 ratio). The results are in agreement with the $^{13}C$ spectrum and an earlier report of proton spectra by Urbanski and co-workers, although their reported signals of the two forms were not completely resolved.[10c] The dinitroso compound **13** exhibits $^1H$ and $^{13}C$ NMR spectra at 30 °C corresponding to nearly equal amounts of syn and anti forms

Scheme I



13a and 13b, in agreement with previous reports[10a] (data in Table I).

**Mechanism of Hexamine Formation.** Mechanisms of hexamine formation from formaldehyde and ammonia have been discussed by others in several reports.[3-5,7] The present work and recent studies on aldehyde–ammonia and aldehyde–amine reactions, coupled with earlier information, now provide a better understanding of this complex reaction. For example, several extensive recent studies have elucidated detailed mechanisms of carbinolamine and imine formation.[16-21]

The kinetics of formaldehyde and ammonia consumption have been shown to be third order: first order in ammonia and second order in formaldehyde.[7] The data could be explained by a rate-limiting reaction of hemiaminal **14** with formaldehyde to form dimethylolamine (**17**, Scheme I). The pH–rate profile of this reaction reported by Kawasaki[7g,i] (maximum rate at pH 9.8) is of the same type observed by Abrams and Kallen for N-methylolation of amines.[19] The methylolation of ring-substituted anilines indicates hydronium, solvent, and hydroxide terms in the rate law; significant imine formation is not observed, nor is there a salt effect.[18] Abrams and Kallen also observed that the rate of monomethylolation was much faster than the rate of addition of the second *N*-methylol group. The $^1$H NMR peak observed in the initial stage of the formaldehyde–ammonia reaction near $\delta$ 4.5 may be attributed to **17** (at 1 min elapsed reaction time, this signal appears as one intense, broad singlet, stronger in relative intensity than the one revealed in Figure 1 at 5 min).

The only kinetic study of the measured rate of hexamine formation from formaldehyde and ammonia is that of Winkler and co-workers.[7c,d] The rate law for this process differs from that of the initial consumption of reactants in being more complex. Formation of an unspecified byproduct was indicated by the data.

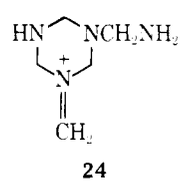
Scheme I describes an oversimplified mechanism for hexamine formation from formaldehyde and ammonia. It represents a summary of one possible reaction route which is in agreement with present knowledge. It is recognized that oxygen may be exchanged for nitrogen in some of the structures to represent additional species probably present. However, equilibria lead ultimately to heterocyclic products containing ring nitrogen only. For example, intermediates such as dimethylolamine (**17**) are probably consumed by retrogression to reactants rather than by direct participation in the reaction sequence(s). Methylenimine (**15**) is assumed to be the reactive aminomethylation intermediate, although its concentration is negligible relative to aminals **14** and **16**.

Reaction intermediates of Scheme I are of acyclic and cyclic types. Acyclics include monomers (**14, 15, 16**), dimers (**17, 18**), and trimers (**19, 20, 21**). As discussed above, there exists kinetic and NMR evidence for hemiaminal monomer **14**. The very labile homologous aldehyde ammonias, $RCH(OH)NH_2$, derived from alkanals have been isolated.[6] The instability and solubility of these are greatest when R is a small group ($CH_3$, $C_2H_5$). Dissociation to aldimines, RCH=NH, or retrogression to reactants occurs very readily; thus, the parent homologue (**14**) would be expected to be extremely reactive and labile. Acetaldimine ($CH_3CH$=NH), derived from $CH_3CH(OH)NH_2$ but not isolated, trimerizes very rapidly compared to its higher homologues;[6] owing to its low steady-state concentration, methylenimine (**15**) would be expected to be undetectable spectroscopically but to trimerize very rapidly to hexahydrotriazine **2**.

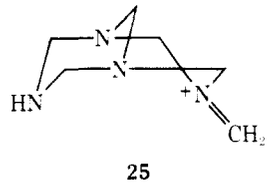
Acyclic dimers **17** and **18** and trimer **19** could be represented by broad $NCH_2O$ peaks seen near $\delta$ 4.5 (Figure 1). Good NMR and kinetic evidence for dimers $CH_3CH(OH)NHCH(OH)CH_3$ and $CH_3CH(NH_2)NHCH(OH)CH_3$ formed in the acetaldehyde–ammonia reaction has been reported.[22]

1,3,5-Hexahydrotriazine (**2**) represents the most abundant stable formaldehyde–ammonia reaction product other than hexamine (Figures 1 and 2). In the reaction of alkanals with ammonia, 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**3**) are formed exclusively and in high yield.[1,6] Although labile compounds, they are more stable than **2** and do not react further with alkanal and ammonia to form *C*-alkyl derivatives of hexamine.

The linear pH dependence of the conversion rate **2** → **1** (Figure 4) suggests solvent-mediated proton-transfer steps. Although a detailed description of this process is not possible with present knowledge, a concerted route rather than discrete iminium ion participation is favored.[21,23] Ring closure of completely developed exocyclic iminium intermediates such as **24** → **6** and **25** → **1** would be sterically less favored than



**24**



**25**

nonplanar transition states. Similar acid-catalyzed processes thought to proceed through discrete methylene iminium ion intermediates, such as methylenebisamine formation,[24] and epimerization of 2,4,6-trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes,[25] may also be concerted. The chemistry of methylene iminium salts has been reviewed.[26]

Near the completion of the reaction leading to **1** the solution becomes depleted in formaldehyde and monomers **14–16**. These reactants, required for the subsequent conversion of intermediates to **1**, are made available by acid-catalyzed retrogression of the intermediates to **15**. Solutions containing **2** and ammonia are observed to react rapidly upon addition of formaldehyde, or acetic acid, to produce only hexamine as **2, 6,** and other intermediates disappear. A rate-limiting, acid-catalyzed retrogression of **2** (to **15** and other products)

could thus account for the rate dependence observed in Figure 4. Ultimately, all intermediates are consumed to form **1**, its retrogression rate in acidic medium being slower than any of its precursors.

## Experimental Section

$^1H$ NMR and $^{13}C$ NMR spectra were determined on a Varian XL-100 spectrometer with a Transform Technology TT-100 pulsed Fourier transform system. Chemical shift measurements were determined at ~30 °C unless otherwise stated and are referenced to sodium 3-(trimethylsilyl)propanesulfonate ($H_2O$ or $D_2O$ solutions).

**Formaldehyde–Ammonium-$d_4$ Hydroxide-$d$ Solution in $D_2O$.** A mixture of 8.4 g of paraformaldehyde (95% assay), sodium bicarbonate (0.1 g), and $D_2O$ (11.6 mL) was heated on the steam bath (~20 min) to obtain a clear solution. The solution contained 40% formaldehyde by weight as determined by reaction of an aliquot portion with dimedone.

Ammonia gas (5 g) was bubbled into 50 mL of $D_2O$ at 0 °C. The resulting solution was distilled into 25 mL of $D_2O$ until the total volume was 55 mL (6.0 M ammonium-$d_4$ hydroxide-$d$ stock solution assayed by titration with 1 N NaOH solution).

The stock formaldehyde and $ND_4OD$ solutions were diluted with $D_2O$ and mixed as required to obtain various formaldehyde–ammonia ratios. $^1H$ and $^{13}C$ NMR spectra were determined at various intervals. Figure 1 shows $^1H$ spectra for a solution prepared from equal volumes of 1 M formaldehyde and $ND_4OD$ solutions. Solutions were prepared in the same manner at various concentrations and various formaldehyde–ammonia ratios. No significant differences in NMR spectra were observed, although rates of hexamine formation were faster in dilute, formaldehyde-rich solutions (see Table II). A solution prepared (0.5 M in formaldehyde and $NH_3$) containing potassium carbonate (final concentration 0.07 M) revealed a rate of conversion to hexamine virtually unchanged from those containing no added potassium carbonate (Table II).

Proton-decoupled Fourier transform $^{13}C$ NMR spectra were determined at intervals at −10 °C since the reaction was too rapid at higher temperatures to accommodate the required signal-averaging times (500 scans, 15 min). The relative peak heights at various times for hexamine and 1,3,5-hexahydrotriazine, respectively, at −10 °C were the following: 2, 6 (1 h); 9, 15 (2.5 h); 11, 17 (3 h); 14, 18.5 (3.8 h); 15, 20 (4.5 h); 22, 14 (24 h). The spectrum obtained at 24 h is shown in Figure 2. The $^{13}C$ spin–lattice relaxation time, $T_1$, for aqueous hexamine, determined by the two-pulse inversion-recovery method, was found to be 0.65 s. This is sufficiently short to justify the assumption that the methylene carbon signal intensity is an accurate measure of hexamine concentration under the experimental conditions used (50° pulse repeated at 2.5-s intervals).[27]

Measurements of pH were determined at intervals on aliquot portions with a Beckman Model G glass electrode pH meter, calibrated with stock $NH_4OH$ solutions. Peak heights of $^1H$ NMR spectra hexamine and triazine signals were also determined at intervals (from curves similar to those of Figure 1). As an arbitrary measure of the extent of reaction, a point was taken where the peak height ratio of hexamine to triazine was 4:1 (molar ratio = 2:1); pH was also determined at this point (pH was observed to be very constant near this point in the reaction). The pH of the solution was varied by initially adjusting the ammonia–formaldehyde ratio and reactant concentrations, or by addition of sodium hydroxide (Table II summarizes the data). A plot of pH vs. the log of the time at the occurrence of the specified peak height ratios is seen in Figure 4.

**Henry Solution in $H_2O$.** Samples of Henry solution were prepared by the procedure of Henry[12] as modified by Richmond, Myers, and Wright.[4] It is a clear, colorless liquid with a strong ammoniacal odor. $^1H$ and $^{13}C$ NMR spectra were determined at intervals on the original solution and on solutions diluted with an equal volume of $D_2O$. $^1H$ NMR spectra were determined at several temperatures between −10 and 80 °C. After 0.5 h at 80 °C or 3 h at 60 °C, all of the peaks except those of hexamine and water had disappeared.

A 1.0-g sample of freshly prepared Henry solution was concentrated to dryness at 5–15 °C (0.1 mm) to yield 0.5 g of white solid. Aliquot portions of this residue were extracted, separately, with $D_2O$, $CDCl_3$, $CCl_4$, and $C_6D_6$, and $^1H$ NMR spectra of the extracts were determined (discussion in text). Another aliquot was treated with concentrated sulfuric acid, followed by ignition in a crucible, to form an ash calculated to correspond to 0.18% potassium carbonate (~0.01 M in the original Henry solution).

**Henry Solution in $D_2O$.** A mixture of paraformaldehyde (3.0 g, 0.1 mol), $D_2O$ (4.5 mL), and sodium bicarbonate (0.1 g) was heated on the steam bath until a clear solution resulted (~20 min). After chilling to 0 °C, ammonia gas (1.7 g, 0.1 mol) was passed into the solution during 15 min, keeping the temperature below 10 °C. Potassium carbonate (5 g) was added in portions with stirring during 10 min, keeping the temperature below 3 °C. After standing at 0 °C for 20 min, the top layer (4.3 g) was separated and stored at 0 °C. $^1H$ NMR spectra of an aliquot sample stored at 25 °C were determined at intervals. Peak heights of signals for hexamine (**1**, $\delta$ 4.75), 1,3,5-hexahydrotriazine (**2**, $\delta$ 3.95), and 1,3,5,7-tetraazabicyclo[3.3.1]nonane (**3**, $\delta$ 3.86; nonbridgehead methylenes only) were determined at intervals. The peak heights were each divided by the number of methylene groups corresponding to the signal, 6, 3, and 4, respectively, in order to obtain the relative molar concentration of each of the three components. Data are plotted in Figure 3. The Henry solution–$D_2O$ solvent NMR spectra were similar to those of the Henry solution–$H_2O$ solvent except for a weaker $H_2O$ signal. Changing the original ratio of reactants formaldehyde/ammonia from 1:1 to 3:2 did not significantly alter the spectra of the final solution.

**Duden and Scharff Solution in $D_2O$.** Solution A: paraformaldehyde (3.16 g, 95% assay, 0.1 mol), sodium bicarbonate (0.1 g), and $D_2O$ (4.5 g) were warmed on the steam bath until a clear solution resulted (about 20 min). Solution B: to a solution of ammonium chloride (5.35 g, 0.1 mol) in 20 mL of warm $D_2O$ was added 4.4 g (0.11 mol) of sodium hydroxide. A portion of solution A (0.75 g, 0.01 mol of formaldehyde) was added slowly to a portion of solution B (3.2 g, 0.01 mol of ammonium chloride and 0.011 mol of sodium hydroxide) with ice-bath cooling, keeping the temperature below 15 °C during the addition. NMR and pH measurements were determined at intervals (data are in Table II). Owing to the high sodium ion concentration of the solution (2.8 M), accurate pH measurements could not be made with the glass electrode employed; a group of pH indicator papers was used. A "synthetic" Duden and Scharff solution was prepared by addition of 0.75 g of formaldehyde solution A, above (0.01 mol of formaldehyde), to a solution containing 1.56 mL of 6.4 M $ND_4OD$ in $D_2O$, 1.0 mL of 0.1 M NaOD in $D_2O$, and 0.585 g of NaCl. Its properties, as expected, were identical with those of the Duden and Scharff solution prepared above.

**1,3,5-Trinitroso-1,3,5-hexahydrotriazine (12).** A mixture of paraformaldehyde (4.74 g, 95% assay, 0.15 mol), water (9.0 mL), and sodium bicarbonate (0.05 g) was heated on the steam bath to obtain a clear solution. To the solution, chilled to −10 °C in an ice–salt bath, was added cold concentrated ammonium hydroxide (10.0 mL, 0.15 mol) with stirring, keeping the temperature below 0 °C during the addition (15 min). After being stored at 0 °C for 6 h, the solution was poured into 200 mL of cold water (3 °C). To this solution was added simultaneously a solution of sodium nitrite (17.8 g, 97% assay, 0.25 mol) in 50 mL of water and a second solution of concentrated sulfuric acid (8.4 mL) in 50 mL of water with stirring, keeping the temperature below 4 °C; the sulfuric solution was added fast enough to keep the solution at pH 1 throughout the addition period (total time 20 min). After addition was complete, the mixture was stirred at 3 °C for 45 min; filtration, followed by washing with water, gave 2.53 g (29%) of pure **12**, mp 105–106 °C (lit.[15] mp 106–107 °C), identical with an authentic sample. The $^1H$ and $^{13}C$ NMR spectra of the product [$(CD_3)_2CO$ solvent] revealed the absence of impurities, including **13** (data are in Table I).

**Registry No.**—**1**, 100-97-0; **2**, 110-90-7; **3a**, 638-14-2; **4**, 14558-49-7; **5**, 505-21-5; **6**, 281-19-6; **7**, 949-56-4; **8**, 69470-04-8; **9**, 69470-05-9; **12**, 13980-04-6; **13**, 101-25-7; formaldehyde, 50-00-0; ammonia, 7664-41-7; nitrous acid, 7782-77-6.

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# Synthesis, Stereochemistry, and Rearrangement of 9-Alkylthioxanthene *N*-(*p*-Toluenesulfonyl)sulfilimines

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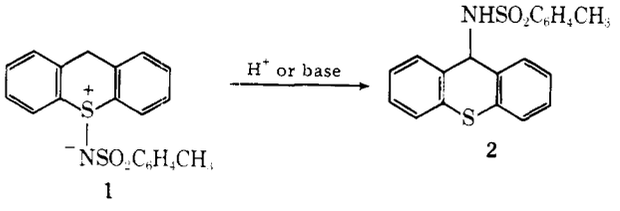
*cis*- and *trans*-9-Methyl- (**6a**), *cis*- and *trans*-9-ethyl- (**6b**), and *trans*-9-isopropylthioxanthene *N*-(*p*-toluenesulfonyl)sulfilimines (**6c**) were synthesized by two routes: (i) tosylation of 10-aminothioxanthenium mesitylenesulfonates, which were prepared by the reaction of the corresponding thioxanthenes with *O*-mesitylenesulfonylhydroxylamine; and (ii) reaction of the thioxanthenes with chloramine T. The stereochemistry of the sulfilimines **6a–c** was ascertained by a comparison of the NMR spectra of **6a–c** with those of the corresponding sulfoxides, whose stereochemistry has been well established, and by the thermal equilibration of **6a–c**. When refluxed in dioxane containing small amounts of concentrated hydrochloric acid, **6a–c** were reduced to the corresponding thioxanthenes. Upon treatment with DBU in benzene *cis*- and *trans*-**6a,b** and *trans*-**6c** rearranged to the corresponding 9-alkyl-9-(*N*-*p*-toluenesulfonamido)thioxanthenes. The rates of the rearrangement decreased in the order *trans*-**6a** > *trans*-**6b** > *cis*-**6a** > *cis*-**6b** > *trans*-**6c**.

Thioxanthene *N*-(*p*-toluenesulfonyl)sulfilimine (**1**) undergoes acid- and base-catalyzed rearrangement to 9-*N*-(*p*-toluenesulfonamido)thioxanthene (**2**).[1,2] We have now examined the effect of the 9-alkyl substituents on this rearrangement. In this paper the synthesis and stereochemistry of 9-alkylthioxanthene *N*-(*p*-toluenesulfonyl)sulfilimines (**6a–c**), and their behavior toward acid and base, are described.




## Results and Discussion

**Synthesis.** 9-Alkylthioxanthene *N*-(*p*-toluenesulfonyl)-sulfilimines (**6a–c**) were synthesized by two routes as shown in Scheme I: (method A) tosylation of 10-aminothioxanthenium mesitylenesulfonates (**4a–c**),[3] which were prepared by the reaction of the thioxanthenes **3a–c** with *O*-mesitylenesulfonylhydroxylamine (MSH);[4] and (method B) reaction of **3a–c** with chloramine T.

Treatment of the thioxanthenes **3a–c** with 1 equiv of MSH in methylene chloride at room temperature gave the corresponding *S*-amine salts **4a–c**. Thus, 9-methylthioxanthene (**3a**) afforded two isomeric *S*-amine salts **4a** in a cis/trans ratio of ~3:5 (by NMR spectroscopy), which could be separated by fractional recrystallization. Tosylation of each isomer gave pure *cis*- and *trans*-**6a** in 8 and 19% overall yields, respectively. 9-Ethylthioxanthene (**3b**) also gave a mixture of cis and trans isomers of the *S*-amine salts **4b**. This mixture was directly converted into two isomeric *N*-(*p*-toluenesulfonyl)-sulfimines **6b**, which were separated by column chromatography to give pure *cis*- and *trans*-**6b** in 9 and 31% overall yields, respectively. 9-Isopropylthioxanthene (**3c**) produced exclusively the trans isomer of the *S*-amine salt **4c** in 73% yield. Passing an ethanolic solution of *trans*-**4c** through a

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