Acid-Catalyzed Ring-Chain Tautomerism in 1,3-Diazolidines

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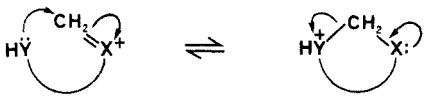
Ring-chain tautomerism has been studied in 2-substituted and 1,3-disubstituted diazolidines. In trifluoroacetic acid, these heterocycles are in equilibrium with the open-chain iminium ion. For materials lacking 2 substitution, 5–10% of the chain form is present at room temperature. Because of resonance stabilization of the positive charge, 2-aryl-substituted systems have about 30% of the chain form. All of these ring and chain forms undergo interconversion on the NMR time scale with a free energy of activation of 16–18 kcal/mol.

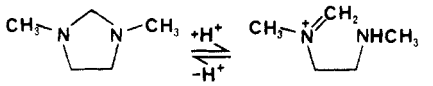
Ring-chain tautomerization involves the reversible addition of a heteroatom to a heteropolar double bond to form a heterocycle.[2] The reaction is usually acid catalyzed and is an important component in the study of five- or six-membered 1,3-heterocycles containing oxygen, nitrogen, or sulfur (eq 1). The process of eq 1 is related to hemi-



(1)

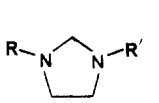
acetal formation in carbohydrates, in which the ring possesses only a single heteroatom. The ring of eq 1 possesses two heteroatoms, because the chain is attached to the C=X through the heteroatom X. In carbohydrates the chain is attached through C. Thus the process of eq 1 is endo-trig, whereas hemiacetal formation in carbohydrates is exo-trig. Ring-chain tautomerism of these types is important not only in organic reactions such as acetal formation but also in biochemical processes such as the thymidylate synthetase reaction.[3]

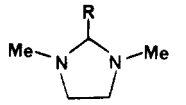
We have recently discovered that ring-chain tautomerism is one of the few examples of nucleophilic addition that may be studied on the NMR time scale.[4] We studied the particular case of 1,3-diazolidine and closely related materials (eq 2). 1,3-Dimethyl-1,3-diazolidine showed



(2)

distinct resonances for the ring and chain forms at room temperature in trifluoroacetic acid. The respective resonances coalesced reversibly at high temperatures ($T_c \sim$ 90 °C) with a free energy of activation of 16.9 ± 0.3 kcal/mol. The molecule of eq 2 has a number of limiting structural features: no substitution on ring carbons, identical substituents on nitrogen, and only *N*-alkyl substituents. In contrast, the diazolidine ring in the cofactor N^5,N^{10}-methylenetetrahydrofolic acid contains C substituents, nonidentical N substituents, and *N*-aryl substituents. In order to broaden our earlier study, we have carried out dynamic NMR studies of 1,3-diazolidines with these latter characteristics. We report herein the NMR studies of diazolidines **1–8**, which include C substitution (**6–8**), unsymmetrical N substitution (**2**, **3**, **5**), and *N*-aryl substitution (**4**, **5**).





1, R = R′ = $PhCH_2$
2, R = CH_3; R′ = $PhCH_2$
3, R = CH_3; R′ = CH_3CH_2
4, R = R′ = Ph
5, R = Ph, R′ = $PhCH_2$

6, R = Ph
7, R = *p*-$CH_3OC_6H_4$
8, R = *p*-$CH_3(CO)NHC_6H_4$

Results and Discussion

There has been no general method for making unsymmetrically 1,3-disubstituted 1,3-diazolidines, so we developed a simple procedure that starts from diethyl oxalate.[5] Stepwise treatment of the diester with 1 mol each of the appropriate primary amines produces an N,N′-disubstituted oxamide. A symmetrically disubstituted oxamide may be obtained in a similar fashion by treatment of the diester with 2 mol of a single primary amine. Reduction of the oxamide with lithium aluminum hydride gives the symmetrical or unsymmetrical 1,2-diaminoethane, which cyclizes on reaction with an aldehyde (formaldehyde for **1–5**; benzaldehydes for **6–8**) to give the desired 1,3-diazolidine.

1,3-Dibenzyl-1,3-diazolidine (1). All spectra were taken at 270 MHz in trifluoroacetic acid (TFA). The spectra of **1** as a function of temperature are given in Figure 1 for the range 40–120 °C. At 40 °C, the NCH_2N, $PhCH_2$, and NCH_2CH_2N protons for the predominant ring form are found respectively at δ 5.2, 4.8, and 4.2. The small peak at δ 8.4 comes from the aldehyde-like CH_2=N protons of the chain form, determined by integration to be present to the extent of about 5%. As the temperature is raised, all the resonances broaden and resharpen on approach to the fast exchange limit. Most dramatic is the nearly complete disappearance of the δ 5.2 resonance, as it apparently coalesces with the δ 8.4 resonance. Coalescence of these peaks occurs at about 100 °C, corresponding to a free energy of activation at coalescence of 16.3 kcal/mol, essentially identical with that for 1,3-dimethyl-1,3-diazolidine.[4] The sharp peaks at δ 3.9 and 4.7 appear irreversibly at high temperature and come from hydrolysis or acetylation of the diazolidine to form $PhCH_2NHCH_2CH_2NHCH_2Ph$ (or its acetylated derivative).

We had not previously looked at low temperature processes in these systems.[4] Figure S-1[6] shows the spectra of the same sample (**1**) in TFA down to −15 °C. There is a very rapid decoalescence of the resonances at δ 5.2 and 4.2, the ring protons. The benzyl protons remain unaffected.

(1) This work was supported by the National Science Foundation (Grant CHE83-12285).

(2) Katritzky, A. R.; Lagowski, J. M. *The Principles of Heterocyclic Chemistry*; Methuen: London, 1966; p 158.

(3) Suckling, C. J. *Enzyme Chemistry*; Chapman and Hall: New York, 1984; p 122.

(4) Lambert, J. B.; Majchrzak, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3588–3591.

(5) Lambert, J. B.; Huseland, D. E.; Wang, G.-t. *Synthesis* **1986**, 657–658.

(6) Figures S-1 to S-7 are found only in the archival version of this paper.

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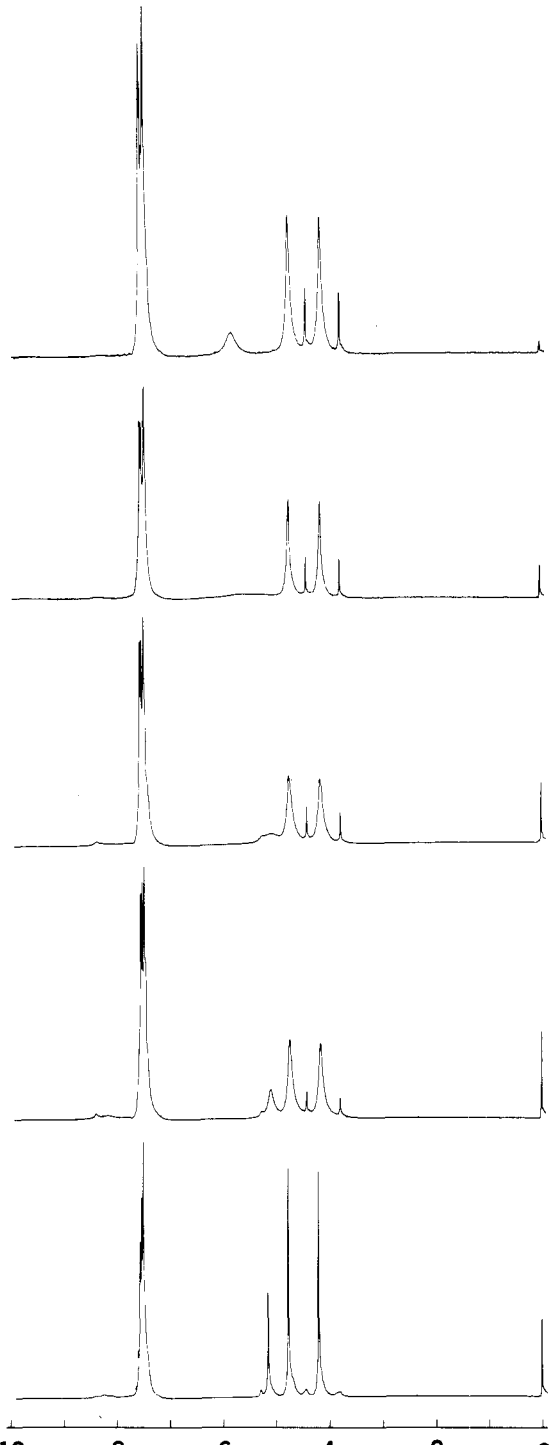
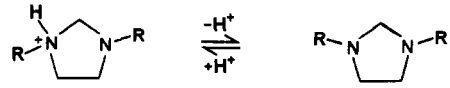


Figure 1. NMR spectrum (270 MHz) of 1,3-dibenzyl-1,3-diazolidine (**1**) in TFA as a function of temperature (bottom to top): 40, 70, 80, 100, and 120 °C.

To produce these more complicated spectra, either proton exchange (eq 3, R = $PhCH_2$) or atomic inversion must



(3)

become slow on the NMR time scale. The unprotonated heterocycle in $CDCl_3$ failed to show spectral changes to −80 °C, in agreement with Anet and Yavari,[7] so that slow nitrogen inversion is not a likely cause of the spectral changes

(7) Anet, F. A. L.; Yavari, I. *Org. Magn. Reson.* **1979**, *12*, 363–364.

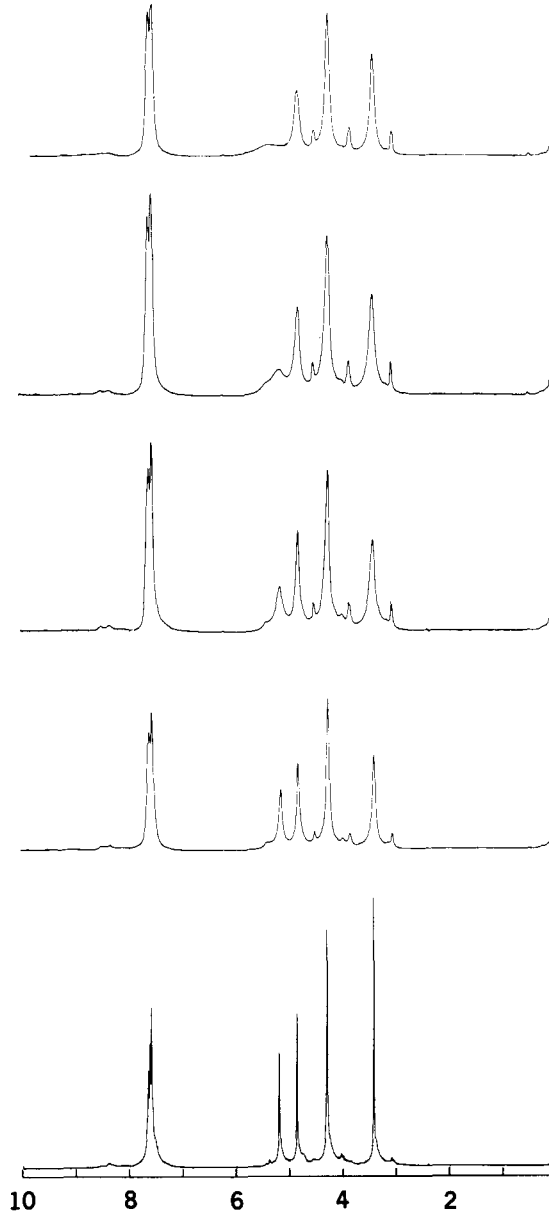
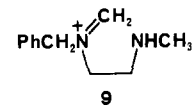


Figure 2. NMR spectrum (270 MHz) of 1-benzyl-3-methyl-1,3-diazolidine (**2**) in TFA as a function of temperature (bottom to top): 40, 80, 90, 100, and 115 °C.

in Figure S-1. We conclude that slowing of proton exchange produced these spectral changes. Since this process has been well studied, we did not examine it further.

1-Benzyl-3-methyl-1,3-diazolidine (2). The more complex spectra of **2** are given in Figure 2. We assign the resonances at δ 5.2, 4.9, 4.3, and 3.4 respectively to the NCH_2N, $PhCH_2$, NCH_2CH_2N, and CH_3 protons. The aldehyde-like resonance occurs as a doublet at δ 8.3 and 8.5, possibly being due to the two conceivable chain forms, **9** and **10**, and amounting to about 6%. Coalescence pro-



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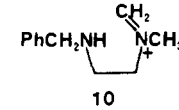

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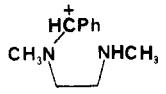
ceeds as the temperature is raised, but is not fully achieved by 115 °C. If a T_c of 120 °C is assumed, the free energy of activation would be 17.3 kcal/mol. Low temperature spectra showed a similar set of decoalescences to those of **1** (Figure S-2),[6] attributed to slowing of proton exchange.

1-Ethyl-3-methyl-1,3-diazolidine (3). The high temperature spectra of **3** are given in Figure S-3.[6] The ethyl

resonances are easily discernible at δ 1.6 and 3.8. The remaining resonances parallel those in **2**. Again, two resonances are visible in the aldehyde-like region. Coalescence is not quite achieved at 120 °C, so that the free energy of activation should be about 17 kcal/mol. The spectrum at the top was taken at 40 °C after the heating cycle, to demonstrate that spectral changes were essentially reversible. Complex changes at low temperatures (Figure S-4)[6] may be attributed to slowing of proton exchange.

***N*-Aryl-Substituted Diazolidines.** Compounds **4** and **5** reacted irreversibly with TFA and produced complex, uninterpretable spectra.

2-Substituted Diazolidines. The chain form composes only 5–10% of the equilibrium mixture for the materials described up to now. An increase in the proportion of the chain form may be brought about by resonance stabilization. Examination of the structures **9** and **10** shows positive charge on the iminium nitrogen. An alternative resonance structure may be drawn with the charge on the primary carbon. This structure presumably is not important for **9** and **10**. When a substituent is introduced at the 2 position, the charge on carbon is stabilized by polarization and hyperconjugation for alkyl groups and by resonance for aryl groups (**11** and **12**). This added delocalization may increase the proportion of the chain form. Consequently, we prepared three examples of 2-aryl-substituted 1,3-diazolidines **6**–**8** and examined their NMR spectra.



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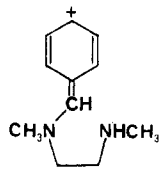

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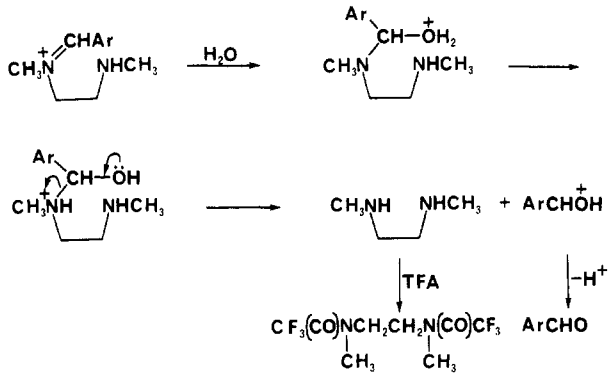
Figure S-5[6] shows the high temperature spectra of 1,3-dimethyl-2-phenyl-1,3-diazolidine (**6**). At 30 °C, the chain form represents about 28% of the mixture, so indeed it has been stablilized with respect to the ring form. The sharp peaks at 30 °C in the region δ 3–5 show little temperature dependence and result from an irreversibly formed byproduct (possibly hydrolysis or acetylation). The nearly overlapping ring-proton resonances enter into a coalescence process, best seen in the resonance at δ 4.8. Coalescence has not been achieved by 125 °C, so that $\Delta G^{\ddagger} > 17$ kcal/mol. It is noteworthy that there are two unequal resonances in the aldehyde region. This duplicity may be the result of syn/anti isomerism, since the phenyl ring may assume two stereochemically distinct positions. In an attempt to stop the irreversible hydrolysis reaction, a sufficient portion of trifluoroacetic anhydride was added to the solution to react with any water present. Unfortunately, the anhydride reacted quickly and irreversibly with the substrate, giving rise to extremely complex ^{1}H spectra.

Further stabilization of the chain form may be achieved by placing a resonance donor at the para position (see **12**). Figure S-6[6] shows the spectra of 1,3-dimethyl-2-(*p*-methoxyphenyl)-1,3-diazolidine (**7**). Again decomposition products make interpretation difficult, but the large size of the iminium resonance is evident. The chain form appears to account for about 40% of the ring/chain peaks. There was little sign of coalescence by 115 °C.

Stabilization of positive charge on the phenyl ring also may be achieved with an acetamido group, as in 1,3-dimethyl-2-(*p*-acetamidophenyl)-1,3-diazolidine (**8**), Figure S-7.[6] The two peaks in the δ 9.4 region correspond to about 33% of the mixture. Coalescence is in progress above 100 °C. The three sharp peaks at high temperatures again are from irreversibly formed decomposition products.

Scheme I



Because of the large amount of decomposition observed in the 2-substituted compounds, we carried out a product study. After reflux in TFA and addition of water, two solids were isolated upon evaporation of the solvents. They were identified as *p*-acetamidobenzaldehyde and *N,N'*-dimethyl-*N,N'*-bis(trifluoroacetyl)ethylenediamine based on their melting points, spectra, and comparison with authentic samples. These products may be accounted for by nucleophilic attack by water on the iminium double bond in the chain form, Scheme I.[8]

Conclusions

Under the conditions studied, alkyl substitution on nitrogen has little influence on the ring-chain equilibrium. Thus, dimethyl, dibenzyl, benzyl methyl, and ethyl methyl all have about 5% of the chain present n TFA and a similar $\Delta G^{\ddagger}$ for tautomerization. Two different chain forms are possible in the unsymmetrical cases. Placement of aryl directly on nitrogen brings about decomposition. Placement of aryl groups at the 2 position stabilizes the chain form through resonance delocalization. It also promotes a side reaction probably involving attack by water on the iminium double bond.[8]

Experimental Section

NMR spectra were taken on a JEOL FX270 spectrometer. The preparation of **1**–**5** has been described elsewhere.[5]

1,3-Dimethyl-2-phenyl-1,3-diazolidine (6) was prepared by the reaction of 1,2-dimethylethylenediamine with benzaldehyde according to our earlier procedure:[5] bp 68–70 °C (0.7 mmHg); ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 5, Ar), 3.2 (s, 1, NCHN), 3.3 and 2.6 (m, 4, CH_2CH_2), 2.2 (s, 6, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.7, 127.3, 126.4, 126.0 (Ar), 90.4 (NCHN), 51.4 (CH_2), 37.3 (CH_3). Anal. Calcd for $C_{11}H_{16}N_2$: C, 75.00; H, 9.09; N, 15.90. Found: C, 74.89; H, 9.31; N, 15.65.

1,3-Dimethyl-2-(*p*-methoxyphenyl)-1,3-diazolidine (7) was prepared in the same way: bp 98–99 °C (1.5 mmHg); ^{1}H NMR ($CDCl_3$) δ 6.8–7.4 (m, 4, Ar), 4.8 (s, 3, OCH_3), 3.2 (s, 1, NCHN), 3.4 and 2.4 (2 q, 4, CH_2CH_2), 2.2 (s, 6, NCH_3). Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.80; H, 8.73; N, 13.57. Found: C, 69.31; H, 8.39; N, 12.27.

1,3-Dimethyl-2-(*p*-acetamidophenyl)-1,3-diazolidine (8) was prepared in the same way: mp 172–174 °C; ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 4, Ar), 3.2 (s, 1, NCHN), 3.4 and 2.5 (m, 4, CH_2CH_2),

(8) A referee has suggested an alternative mechanism of decomposition, whereby initial attack at the =CHAr carbon is by the solvent TFA rather than by water. This reaction would produce $ArCH(OCOCF_3)_2$ and $CH_3NHCH_2CH_2NHCH_3$. Reaction of the diamine with TFA would give the observed acetylated product and water. This water might then hydrolyze $ArCH(OCOCF_3)_2$ to the observed second product, ArCHO. The failure of our attempt to remove all water from the solvent TFA with the use of trifluoroacetic anhydride prohibited our testing this mechanism.

2.2 (s, 10, CH_3 and NH); IR (KBr) ν(C=O) 1665 cm^{-1}. Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.93; H, 8.21; N, 18.00. Found: C, 66.16; H, 8.17; N, 17.37.

Product Study of 8. Substrate 8 (1 g, 4.3 mmol) was dissolved in 50 mL of trifluoroacetic acid. The resulting orange solution was refluxed for 1 h. Water (2 mL) was added and the solvents were removed by rotary evaporation. Treatment of the resulting solid with $CHCl_3$ resulted in the precipitation of one solid. A second solid was obtained by removal of the solvent, and both solids were recrystallized from CH_3OH. Solid I (*N,N'*-dimethyl-*N,N'*-bis(trifluoroacetyl)ethylenediamine): 1.2 g, mp 59-65 °C; ^1H NMR (CD_3OD) δ 3.4 (s, 4), 2.8 (s, 6); IR (KBr) ν(C=O) 1665 cm^{-1}; ^{13}C NMR (CD_3OD) δ 163.5 (C=O, q from splitting by CF_3, J = 60 Hz), 137.6, 132.7, 128.0, 123.2 (q, J = 315 Hz, CF_3), 45.7 (s, CH_2), 34.0 (s, CH_3). Solid II (*p*-acetamidobenzaldehyde): 0.55 g, mp 145-147 °C; ^1H NMR ($CDCl_3$) δ 9.9 (s, 1), 7.5-7.9 (m, 5, Ar, NH), 2.2 (s, 3, CH_3); IR (KBr) ν(C=O) 1690, ν(NC=O) 1678 cm^{-1}.

Supplementary Material Available: Figures S-1 through S-7 (8 pages). Ordering information is given on any current masthead page.

A Potassium Amide Induced Ring Transformation of 1,2,4-Triazines into 1,2,4-Triazoles and 1,3,5-Triazines[1]

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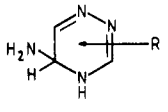
5-Phenyl- and 3,5-diphenyl-1,2,4-triazine, when treated with potassium amide in liquid ammonia, are converted into a mixture of phenyl derivatives of 1,2,4-triazole and amino-1,3,5-triazines. The ring contraction of the 1,2,4-triazine ring into the 1,2,4-triazole ring has been explained by an initial addition of the amide ion to C-6, ring opening by fission of the N1-C6 bond and ring closure (ANRORC-mechanism). The transformation of the 1,2,4-triazine ring into the 1,3,5-triazine ring has been studied by means of ^{15}N-labeled potassium amide. It was found that the nitrogen of the amide ion becomes one of the ring nitrogen atoms in the 1,3,5-triazine ring and that the exocyclic amino group is *un*labeled. Based on these ^{15}N-labeling studies, it is proposed that this ring transformation starts with an initial addition of the amide ion to C-5, ring opening between C-5 and C-6, a dehydrogenative rearrangement of the open-chain intermediate 1-amino-2,4,5-triazahexatriene into 1-amino-4-cyano-2,4-diaza-1,3-butadiene, and ring closure.

Recently we reported[2] on a new procedure for the introduction of an amino group into the 1,2,4-triazine ring via a nucleophilic displacement of hydrogen. The method is based on the potassium permanganate oxidation of 5-amino-4,5-dihydro-1,2,4-triazines (1), being formed in situ by covalent addition of liquid ammonia to 1,2,4-triazines, having an unoccupied C-5 position. Sound evidence for the intermediary existence of these C-5 adducts **I** was provided by ^1H and ^{13}C NMR spectroscopy.[3]



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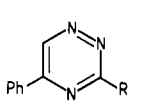
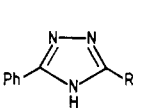
By NMR spectroscopy it was further shown that covalent addition of liquid ammonia to 1,2,4-triazines does not take place when position 5 is blocked by the presence of a substituent. This result was confirmed by the fact that all attempts to convert 5-phenyl-1,2,4-triazine (**2a**) or 3,5-diphenyl-1,2,4-triazine (**2b**) into amino derivatives by oxidation of solutions of **2a** or **2b** in liquid ammonia with potassium permanganate failed.

In view of earlier observations that increase of the nucleophilicity of the aminating agent may change the reaction course,[4,5] we studied the behavior of 1,2,4-triazines **2a** and **2b** toward potassium amide, being a stronger nucleophile than liquid ammonia. We found indeed that **2a** as well as **2b** does react with potassium amide in liquid ammonia, although slowly, however, not leading to the formation of amino derivatives of **2a** or **2b**: but to ring transformation products, i.e., 1,2,4-triazoles and 1,3,5-triazines.



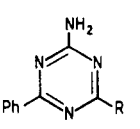
2

a) R = H
b) R = Ph



3

a) R = H
b) R = Ph



4

a) R = H
b) R = Ph
c) R = NH_2

Thus, treatment of **2a** with 4 equiv of potassium amide in dry liquid ammonia at -33 °C for 24 h results in the formation of 3-phenyl-1,2,4-triazole (**3a**, 21%) and 2,4-diamino-6-phenyl-1,3,5-triazine (**4c**, 23%), along with a trace of 2-amino-4-phenyl-1,3,5-triazine (**4a**). 3,5-Diphenyl-1,2,4-triazine (**2b**) reacts similarly, yielding 3,5-

(1) Part 35 in Ring transformations of Heterocycles. For part 34, see: van der Plas, H. C.; Marcelis, T.; van den Ham, D. M. W.; Verhoeven, J. W. *J. Org. Chem.* **1985**, *51*, 4070.
(2) Rykowski, A.; van der Plas, H. C. *Synthesis* **1985**, 884.
(3) Rykowski, A.; van der Plas, H. C.; van Veldhuizen, B. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 273.
(4) Simig, G.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 125.
(5) Breuker, J.; van der Plas, H. C. *J. Org. Chem.* **1979**, *44*, 4677.

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