Cyclopropanediamines. 5.[1] Ring-Opening and *Cis–Trans* Isomerization of 1,2-Cyclopropanediamines in Aqueous Buffers

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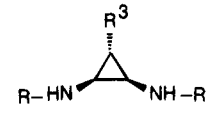
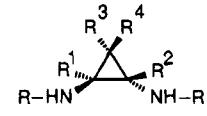
In aqueous phosphate buffer, pH = 5.8, at 25 °C, the *N,N'*-dimethyl-1,2-cyclopropanediammonium dibromides **1b–3b** react rapidly after an initiation phase of several hours to afford methanamine (ca. 1 mol) and traces of pyrroles besides unidentified products. The onset is delayed, and the reactions are slowed down drastically by hydroxylamine. *cis*-**1b**·2HBr partly isomerizes to *trans*-**1b**, which decomposes much more slowly. *trans*-**3a**·2HBr is converted quantitatively to 4-aminobutan-2-one **12a**, and *trans*-**3b**·2HBr partly to **12b**. *Trans*-**4a**·2HBr and *trans*-**5a,b**·2HBr are stable for several days. *trans*-**6a**·2HBr decomposes, while *trans*-**6b**·2HBr and *trans*-**6c**·2HBr form the 2-styrylpyrroles **19b** and **19c**, respectively. The reactions are interpreted in terms of a slow formation of carbonyl compounds during the initiation phase, which react with unchanged cyclopropanediamine to give iminium ions (**8**, **13**, or **16**). These open the cyclopropane ring to yield the crucial intermediates (**9**, **14**, or **17**) which possess both an azomethine ylide and an iminium moiety. These intermediates undergo ring closure to either a cyclopropane ring (**9** → *trans*-**8**) or a dihydropyrrole ring (**17** → **18**). Alternatively, the intermediates are hydrolyzed to Mannich bases (**9** → **10**, **14** → **12**), which in turn react with unchanged cyclopropanediamine, thus completing an autocatalytic cycle.

Introduction

Cope rearrangement to 2,3-dihydro-1,4-diazepines and *cis–trans* isomerization have been observed in the reactions of cyclopropanediamines with aldehydes.[3] Under similar conditions, *N,N'*-dibenzylcyclopropanediamines react with aromatic aldehydes to yield 2-arylpyrroles.[4,5] The present study was undertaken because of the following observations which appeared to be unrelated to these reactions. *cis*-**1a**·2HCl is stable in boiling hydrochloric acid for at least 4 h, while it isomerizes to *trans*-**1a** at room temperature when it is dissolved in deuterium oxide containing the weakly basic NMR standard sodium 3-(trimethylsilyl)propanoate.[6] In practice, some insoluble material did precipitate, but no further products could be detected by proton spectroscopy. Although stereomutations[7] and ring-opening reactions of cyclopropanes[5,8] are well documented, there was no obvious clue to the mechanism of this particular *cis–trans* isomerization. To explore the problem in detail, we prepared the ring-substituted cyclopropanediammonium dibromides **1–6**.[9] An important question is raised by the fate of the amino groups. Ammonia could be smelled when the NMR sample tubes of the experiment described above were opened. Hence at least some cyclopropanediamine seemed to have decomposed with loss of one or both amino groups. In order to address this question, we labeled the amino groups by methyl or benzyl groups and monitored the reactions in aqueous buffers by proton spectroscopy. The *N*-benzyl derivatives of **1–6** generally turned out to be insoluble in aqueous solutions. The experiments with the *N*-methyl compounds, however, resulted in a detailed picture of the reactions of cyclopropanediamines in aqueous solutions. Surprisingly, *cis–trans* isomerization, decomposition, the ring-enlargement affording pyrroles, and the formation of 2,3-dihydro-1,4-diazepines from *trans*-cyclopropanediamines could be traced back to common intermediates, i.e. azomethine ylides.





cis-**1a**, **b**: R^3 = H
cis-**2a**, **b**: R^3 = Me
a: R = H; **b**: R = Me; **c**: R = Bn

	R^1	R^2	R^3	R^4
trans-**1a**, **b**	H	H	H	H
trans-**2a**, **b**	H	H	Me	H
trans-**3a**, **b**	Me	H	H	H
trans-**4a**	Me	Me	H	H
trans-**5a**, **b**	H	H	Me	Me
trans-**6a** - **c**	H	H	Ph	H

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(1) Part 4 of this series: ref [9]. The results are part of the Dissertation of W. von der Saal, University of Würzburg, 1983.

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(3) Quast, H.; von der Saal, W. *Chem. Ber.* **1984**, *117*, 1591.

(4) Quast, H.; von der Saal, W.; Stawitz, J. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 588.

(5) For an excellent review on cyclopropanamines see Vilsmaier, E. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Chapter 22, pp 1341.

(6) Quast, H.; Stawitz, J. *Tetrahedron Lett.* **1976**, 3803.

(7) For leading references see: Baldwin, J. E.; Cianciosi, S. J.; Glenar, D. A.; Hoffman, G. J.; Wu, I.-W.; Lewis, D. K. *J. Am. Chem. Soc.* **1992**, *114*, 9408. Baldwin, J. E.; Selden, C. B. *J. Am. Chem. Soc.* **1993**, *115*, 2239. Getty, J. S.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1992**, *114*, 2085.

(8) Reviews: (a) DePuy, C. H. *Fortsch. Chem. Forsch.* **1973**, *40*, 73; Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66. de Meijere, A. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809. Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. Tsuji, T. Nishida, S. *Acc. Chem. Res.* **1984**, *17*, 56; Salaün, J. R. Y. *Top. Curr. Chem.* **1988**, *144*, 1. Reissig, H. U. *Top. Curr. Chem.* **1988**, *144*, 73. Battiste, M. A.; Coxon, J. M. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1987; Part 1, Chapter 6, pp 255–305; Reissig, H. U. *Ibid.*, Chapter 8, pp 375–443. Verhé, R.; De Kimpe, N. *Ibid.*, Chapter 9, pp 445–564; Boche, G.; Walborsky, H. M. *Ibid.* Chapter 12, pp 701–808. (b) Friedrich, E. C. *Ibid.* Chapter 11, pp 633–700. (c) Salaün, J. R. Y. *Ibid.*, Part 2, Chapter 13, pp 809–878. (d) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

(9) von der Saal, W.; Reinhardt, R.; Seidenspinner, H.-M.; Stawitz, J.; Quast, H. *Liebigs Ann. Chem.* **1994**, 569.

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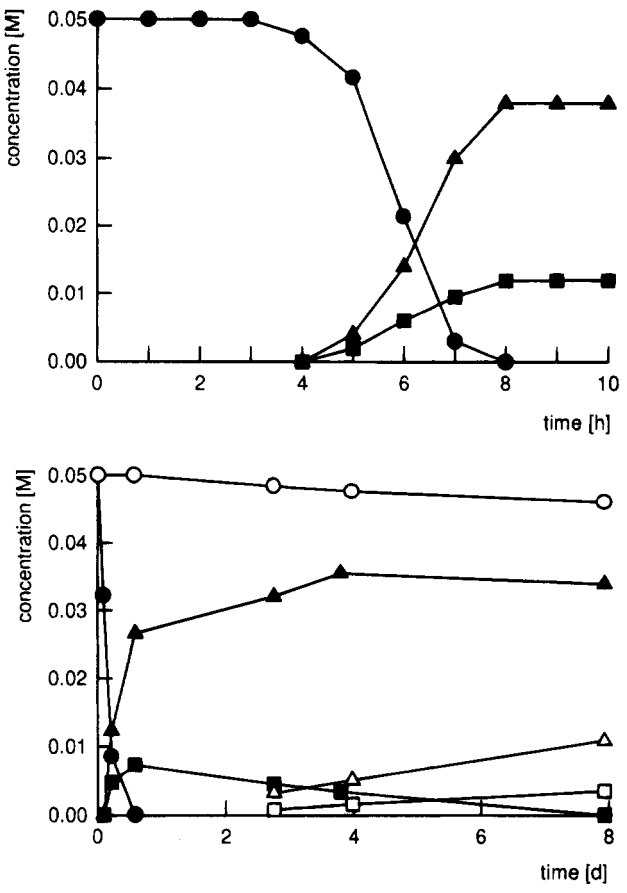


Figure 1. Concentration *vs* time curves for solutions of *cis*-**1b**·2HBr (0.05 M) in aqueous phosphate buffers (0.5 M). The heights of the methyl signals in 400 MHz proton spectra were used to calculate the concentrations of *cis*-**1b** (δ = 2.87 ppm; circles), *trans*-**1b** (δ = 2.90 ppm; squares), and methanamine (δ = 2.70 ppm; triangles). Top: pH = 5.8, 25 °C; Bottom: filled symbols: pH = 6.8, 32 °C; hollow symbols: pH = 6.8, 32 °C; this solution contained hydroxylamine (5 mM).

Results

Ring-Opening and *cis*–*trans* Isomerization of the Cyclopropanediammonium Dibromides 1. Addition of 1 equiv of K_2HPO_4 to a solution of *cis*-**1b**·2HBr in deuterium oxide causes a time-dependent high-field shift of all proton signals. This is due to an increase of the pD value from 5 to 8 during the reaction. To keep the pH reasonably constant (ΔpH = 0.2–0.3) in the following experiments, we used solutions (0.05 M) of the cyclopropanediammonium dibromides in aqueous phosphate buffers (0.5 M). The concentration *vs* time curves for the reaction of *cis*-**1b**·2HBr under these conditions (pH = 5.8, 25 °C) are shown in Figure 1 (top). After a 4 h initiation phase, *cis*-**1b** starts to disappear. At the same time, the signals of *trans*-**1b**, methanamine, and unidentified products appear. The reaction apparently ceases after 8 h, at the time when *cis*-**1b** has disappeared completely. By observing such solutions for more than a week, it became evident, however, that *trans*-**1b** reacts, too, but far more slowly than the *cis* isomer (Figure 1, bottom).

The initiation phase is *not* due to impurities in the starting material. *cis*-**1b**·2HBr that had been recrystallized twice from methanol behaved in exactly the same way. The possibility of an influence of air on any radical reactions[10] was excluded by degassing the buffer solution and saturating it with argon. Addition of a catalytic amount of methanammonium chloride had no effect, but hydroxylamine strongly delayed the onset and greatly retarded the rate of disappearance of *cis*-**1b** (Figure 1, bottom). The amount of methanamine at the end of the conversion is slightly higher than that calculated for a decomposition of *cis*-**1b** with concomitant formation of one molecule of methanamine. When higher concentrations of *cis*-**1b**·2HBr were used, the solutions became turbid at the end of the reaction. Probably, pyrroles or oligomers thereof are also produced, because the solutions gave a positive Ehrlich test.[11] No attempts were made to elucidate the structures of these products.

Table 1. Yields of *trans*-1b Produced from Solutions of *cis*-1b·2HBr (0.05 M) in Aqueous Phosphate Buffers (0.5 M) of Various pH Values and Fractions of the Monoprotonated Cyclopropanediamines under These Conditions

buffer	pH	yields of *trans*-**1b** [%][a]	monoprotonated diamines [%][b] *cis*-**1b**·H$^+$	*trans*-**1b**·H$^+$
acetate	4.6	42	92	10
acetate	5.0	49	96	22
acetate	5.3	40	98	35
phosphate	5.8	20	99	63
phosphate	6.4	16	99	87
phosphate	6.8	13	99	94

[a] Maximum concentration (%) based on the initial concentration of *cis*-**1b** = 100%. [b] Calculated from the pK_a values for *cis*-**1b** (3.56, 8.73) and *trans*-**1b** (5.65, 8.73).[12]

The amounts of *trans*-**1b** produced from *cis*-**1b** depended on the pH value of the buffers (Table 1). The rate of disappearance of *cis*-**1b** reached a maximum around pH 6. Methanamine and pyrroles were detected in all experiments.

The conversion of *cis*-**1a** could not be monitored as precisely, because the proton spectrum of this compound lacks a singlet resonance. Based on the rate of disappearance of the ABX_2 multiplet arising from the cyclopropyl protons, the conversion seemed to proceed with a similar initiation phase.

Reactions of the Ring-Methylated Cyclopropanediammonium Dibromides 2–5. In aqueous phosphate buffer (0.5 M, pH = 5.8, 25 °C), *cis*-**2a**·2HBr and *cis*-**2b**·2HBr (0.05 M) appeared to form products in which the cyclopropane ring had been cleaved in preference to *cis*–*trans* isomerization, although these could not be identified, with the exception of methanamine in the reaction of *cis*-**2b**. The decomposition of *cis*-**2b** affording methanamine resembled that of *cis*-**1b** in that the *cis*-cyclopropanediamine began to disappear after an initiation phase (Figure 2, top). Likewise, *trans*-**4a**·2HBr decomposed into several products, whereas *trans*-**5a**·2HBr and *trans*-**5b**·2HBr were completely stable for several weeks under these conditions. Decomposition occurred only after the solutions were heated to 90 °C.

(10) For cyclopropane stereomutations catalyzed by one-electron oxidants see Dinnocenzo, J. P.; Schmittel, M. *J. Am. Chem. Soc.* **1987**, *109*, 1561; c.f. Boche, G.; Wintermayr, H. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 874.

(11) Fischer, H.; Orth, H. *Die Chemie des Pyrrols*, Akademische Verlagsanstalt: Leipzig, 1934; p 66. In Ehrlich's test, the presence of pyrroles is detected by the red color which forms immediately after the addition of one drop of a solution of 4-(dimethylamino)benzaldehyde (50 mg) in hydrochloric acid (50 mL, 6 M).

(12) pK_a-Values were determined by titration of aqueous solutions of *cis*- and *trans*-**1b**·2HBr with aqueous KOH. Details will be reported elsewhere.

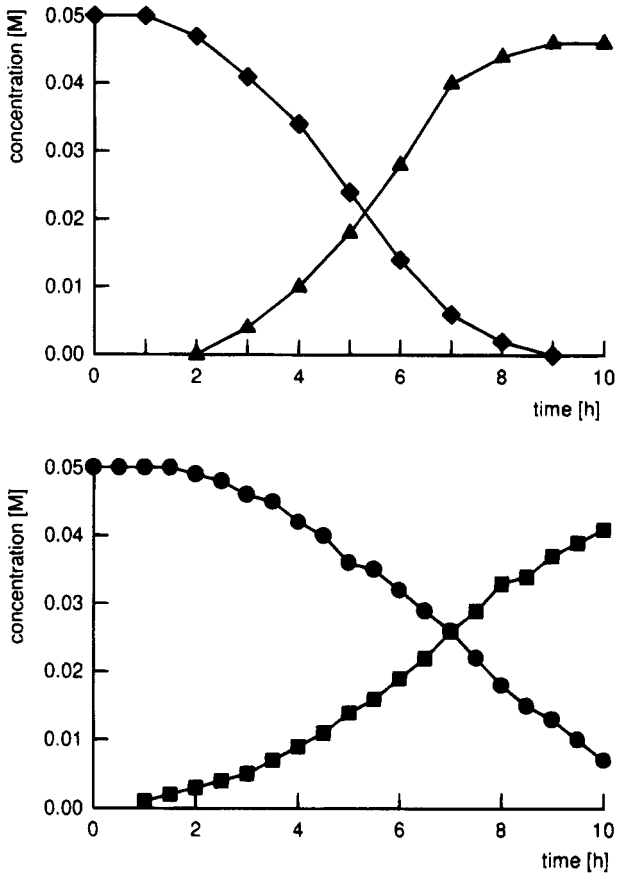


Figure 2. Concentration *vs* time curves for solutions (0.05 M) in aqueous phosphate buffer (0.5 M, pH = 5.8, 25 °C) of *cis*-**2b**·2HBr (top), and *trans*-**3a**·2HBr (bottom). The heights of the *N*-methyl signals in 400 MHz ^{1}H NMR spectra were used to calculate the concentrations of *cis*-**2b** (δ = 2.95 ppm; diamonds) and methanamine (δ = 2.70 ppm; triangles). The heights of the *C*-methyl signals were used for the calculation of the concentrations of *trans*-**3a** (δ = 1.60 ppm; circles) and **12a** (δ = 2.26 ppm; squares).

The 1-methylcyclopropanediamine *trans*-**3a** began to disappear after a similar initiation phase. Unlike the other cases, only a single product was formed in 95–98% yield (Figure 2, bottom). Ehrlich's test for pyrroles gave a negative result. At temperatures above 50 °C or at higher pH values (>9), the product decomposed. Its instability deterred us from attempting its isolation in pure form. Therefore, the assignment of the structure 4-aminobutan-2-one (**12a**) was based on proton and carbon-13 spectra and, in particular, on their comparison with those of the long-known[13] Mannich base 4-(dimethylamino)butan-2-one (Table 2). Furthermore, structure **12a** is corroborated by the pH dependence of the proton spectrum and the results of H/D exchange experiments.

In the high-field proton spectrum, the methylene groups of **12a** and **12c** give rise to two triplets. That at higher field is broadened by a long-range coupling with the methyl protons. The chemical shifts of both methylene groups of **12a** depend on the pH value. The protons in α position of the amino group are shifted by 0.22 ppm to higher field and the β protons by 0.16 ppm, when the pH value is raised from 7.6 to 12, whereas the chemical shift of the methyl group remains constant. Lowering

(13) Mannich, C. *Arch. Pharm.* **1917**, *255*, 261. Spaeth, E. C.; Geissman, T. A.; Jacobs, T. L. *J. Org. Chem.* **1946**, *11*, 399.

Table 2. Chemical Shifts (ppm) and Coupling Constants (Hz) in the Proton Spectra and Chemical Shifts in the Carbon-13 Spectra of 4-Aminobutan-2-one (12a), 4-Methylaminobutan-2-one (12b), and 4-(Dimethylaminobutan-2-one (12c) Dissolved in Aqueous Phosphate Buffers, pH = 7.6 (^{1}H) and 6.8 (^{13}C)

compd	1-H	3-H	4-H	$^3J_{34}$	C-1	C-2	C-3	C-4
12a[a]	2.26	3.02	3.24	6.3	29.33	211.55	39.57	66.39
12b[b]	2.26	3.07	3.27	6.5				
12c[c]	2.29	3.14	3.36	6.8	29.42	210.47	37.22	52.09

[a] $^4J_{13}$ = 0.25 Hz. [b] NCH_3 = 2.73 ppm. [c] $^4J_{13}$ = 0.25 Hz; NCH_3 = 2.71 ppm; NCH_3 = 42.91 ppm.

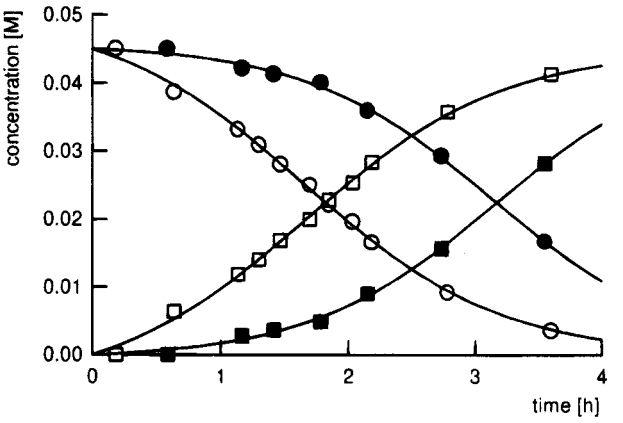


Figure 3. Formation of 4-aminobutan-2-one (**12a**, squares) from solutions of *trans*-**3a** (0.045 M, circles) in aqueous phosphate buffer (0.5 M, pH = 6.3) at 32 °C. Filled symbols: Phosphate buffer (100 μL) was added to a freshly prepared solution of *trans*-**3a**·2HBr (0.05 M, 900 μL). Hollow symbols: A solution of **12a** (0.05 M, 100 μL) in phosphate buffer was added to a freshly prepared solution of *trans*-**3a**·2HBr (0.05 M, 900 μL). The lines were drawn on the basis of the rate constants k_1 and k_2 calculated from a nonlinear fit of the data to eq 2.

the pH value below 7.6 does not change the chemical shift of either methylene triplets. This shows that the product is completely protonated under these conditions. The pH dependence confirms the assignment of structure **12a**. In particular, these experiments exclude the possibility that the product is 4-hydroxybutan-2-one which might have been formed by elimination of ammonia and addition of water. The reaction of *trans*-**3a**·2HBr in deuterium oxide under otherwise identical conditions led to proton spectra in which the singlet and the high-field triplet were missing and the low-field triplet was collapsed into a singlet as expected for a H/D exchange at the α positions of a carbonyl group.

The initiation phase let us suspect that the reaction of *trans*-**3a** started with a slow, spontaneous ring opening, liberating eventually a small amount of ammonia and **12a** which might catalyze the first step. Indeed, small amounts of hydroxylamine strongly retarded the disappearance of *trans*-**3a** by trapping catalytically active carbonyl compounds as in the case of *cis*-**1b**. On the other hand, when small amounts of a solution of **12a**, obtained by complete conversion of *trans*-**3a**, were added to a freshly prepared solution of *trans*-**3a**, the reaction was accelerated significantly (Figure 3). The addition of the same amount of pure buffer solution or of a solution of ammonium chloride in buffer had no effect.

Further evidence for an autocatalysis in the decomposition of *trans*-**3a** came from fitting of the data of Figure 3 to eq 2, which is the integrated form of eq 1. This equation combines a "spontaneous" ring-opening of the

cyclopropanediamine A (*trans*-**3a**) affording the catalyst C (**12a**) with an autocatalytic reaction.[14]

$$A \xrightarrow{k_1} C$$

$$A + C \xrightarrow{k_2} 2C$$

$$\frac{-d[A]}{dt} = k_1[A] + k_2[A][C] \quad (1)$$

$$[A]_t = \frac{[A]_0\{k_1 + k_2([A]_0 + [C]_0)\}}{k_2[A]_0 + (k_1 + k_2[C]_0)e^{\{k_1 + k_2([A]_0 + [C]_0)\}t}} \quad (2)$$

The rate constants k_1 and k_2 for both experiments in Figure 3 were calculated from the experimental data with a Marquardt nonlinear regression algorithm.[15] The starting concentration of *trans*-**3a** ($[A]_0$) was set to 0.045 M, and that of the catalyst **12a** ($[C]_0$) to zero. The lines drawn through the data points in Figure 3 were obtained using eq 2 and the calculated rate constants.

The rate constant k_1 of the "spontaneous" ring opening is 5×10^{-6} [s^{-1}], corresponding to a half-life of 1.5 days. This rate constant is much smaller than the rate constant k_2 of the catalyzed ring opening (8×10^{-3} [mol L^{-1} s^{-1}]). Addition of catalytic amounts of **12a** as described increased k_1 by nearly 1 order of magnitude to 4×10^{-5} [s^{-1}], whereas k_2 remained almost unchanged (7×10^{-3} [mol L^{-1} s^{-1}]).

The *N,N'*-dimethyl derivative *trans*-**3b** reacted much slower than *trans*-**3a**. Methanamine and small amounts of 4-(methylamino)butan-2-one (**12b**) were formed besides several other, unidentified products. Pyrroles were detected by Ehrlich's reagent.

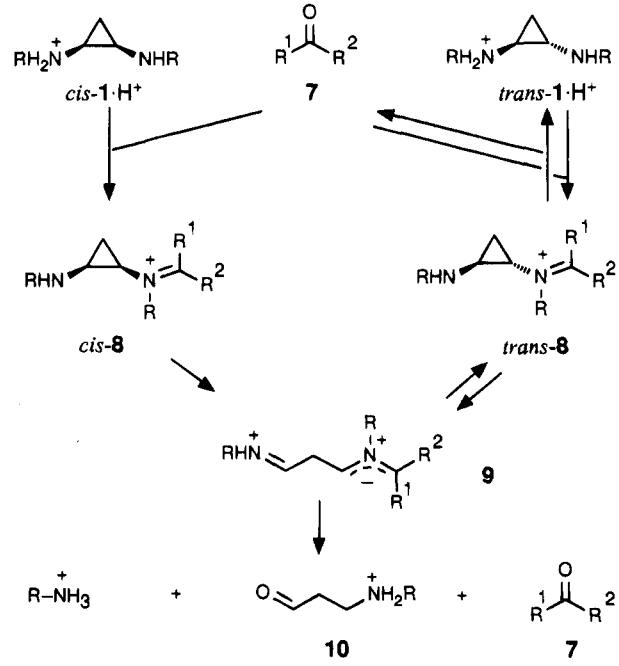
Formation of 2-Styrylpyrroles 19 from the 3-Phenylcyclopropanediammonium Dibromides 6. Immediately after dissolving *trans*-**6b**·2HBr in aqueous phosphate buffer of pH = 6.8, a colorless, crystalline material precipitated, and methanamine was observed by proton spectroscopy. The solution was odorless at the beginning, but soon developed a characteristic odor resembling cinnamaldehyde. The same products were formed in acetate buffered methanol. The styrylpyrrole structure **19b** was assigned to the crystalline material on the basis of proton and carbon-13 spectra and a positive Ehrlich test. When the experiment was repeated in deuterium oxide as solvent, no deuterium was incorporated in the product. The reaction of *trans*-**6a**·2HBr under the same conditions yielded a brown resin, which consisted of several unidentified products. The *N,N'*-dibenzyl compound *trans*-**6c**·2HBr, which was insoluble in aqueous phosphate buffer, yielded the styrylpyrrole **19c** in acetate-buffered methanol.

The substitution pattern of the pyrroles **19b** and **19c** and the *trans* configuration of the styryl double bond follow from the proton coupling constants. That the styryl group is attached at C-2 of the pyrrole ring can be deduced on the basis of a long-range coupling observed between the proton at C-5 and one of the methine protons of the styryl double bond. This type of zig-zag-coupling has been reported for pyrrole-2-carbaldehydes and related systems.[16]

We have shown previously that 1-alkyl-2-arylpyrroles can be prepared in good yields from *N,N'*-dialkylcyclopropanediamines and aromatic aldehydes.[4] Accordingly, the 2-styrylpyrroles **19** appeared as products of an analogous reaction of the 3-phenylcyclopropanediamines with cinnamaldehyde, which itself somehow arose from the cyclopropanediamines. In fact, addition of 2 equiv of cinnamaldehyde to a freshly prepared solution of *trans*-**6c**·2HBr in acetate-buffered methanol did immediately cause the precipitation of the pyrrole **19c**. After 1 h, it was isolated in 71% yield based on *trans*-**6c**.

Discussion

Several remarkable observations and properties of cyclopropanediamines are disclosed in the present work. First, all cyclopropanediamines **1**–**6** are more or less persistent in aqueous buffers for some time. After a few hours in solution, some cyclopropanediamines suddenly start to react rapidly. Second, the substitution pattern and the configuration of the 1,2-cyclopropanediamine determine the types of reactions that occur. These comprise *cis*–*trans* isomerization, decomposition into Mannich bases plus ammonia or alkanamines, and formation of pyrroles in a multistep sequence. Third, in the cases of cyclopropanediamines that engage in more than one type of reaction the reactions commence after the same initiation phase. Fourth, some primary products survive under the reaction conditions, whereas others decompose or react with the unchanged fraction of cyclopropanediamine to furnish further products.



The *cis*–*trans* isomerization of *cis*-**1** and the decomposition of both *cis*- and *trans*-**1** in aqueous buffers require the presence of a carbonyl species, e.g. **7**. This conclusion is inferred from the strong retardation of the reaction rates by hydroxylamine. This traps any ketones or aldehydes already present at the beginning, or arising

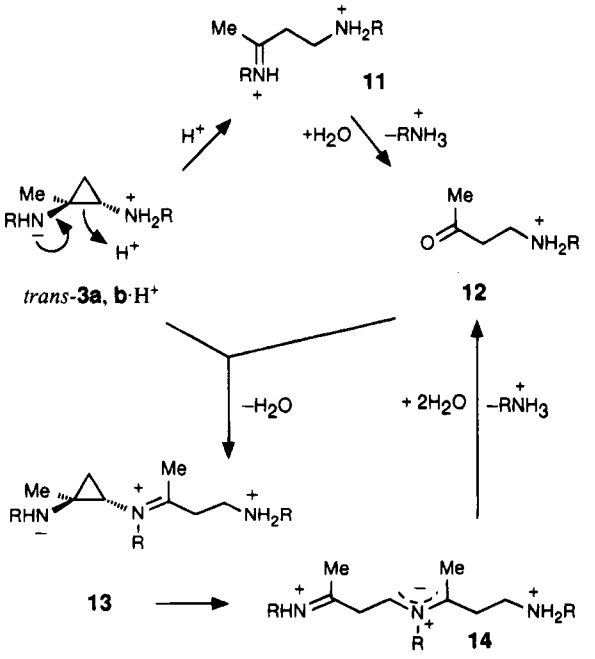
(14) Moore, J. W.; Pearson, R. G. *Kinetics and Mechanism*; Wiley: New York, 1981; p 26.

(15) Marquardt, D. W. *J. Soc. Indust. Appl. Math.* **1963**, *11*, 431. The program used was SigmaPlot from Jandel Scientific, 40699 Erkrath, Germany.

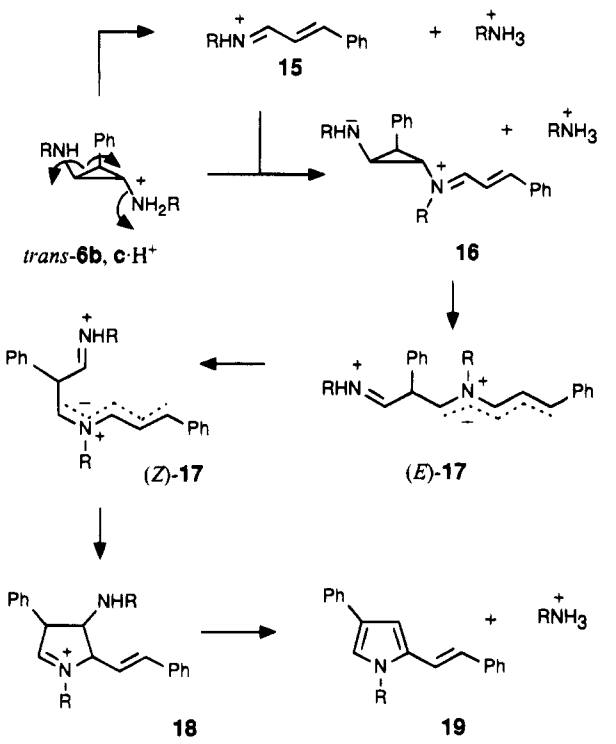
(16) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977; p 472.

from **1**, as unreactive oximes. The origin of **7** remains obscure, but we suspect that it is generated slowly from **1** during the initiation-phase. Considering the pH *vs* rate profile of the reaction, which reaches a maximum between pH 6 and 7, we conclude that the monocation *cis*-**1**·H$^+$, predominating at those pH values, reacts with **7** to produce the imine *cis*-**8**. This may undergo opening of the cyclopropane ring to afford the crucial intermediate **9**, which simultaneously possesses an (electrophilic) iminium and a (nucleophilic) azomethine ylide moiety. The three-membered ring may be closed again to the more stable *trans*-**8**, which eventually is hydrolyzed to regenerate **7**. This sequence is invoked to rationalize the observed *cis*–*trans* isomerization of *cis*-**1**.

The postulated azomethine ylide **9** also provides a clue to the formation of methanamine and to the autocatalytic rate law governing the conversions of the cyclopropanediamines. Both functional groups of **9** may be hydrolyzed to regenerate the original carbonyl species **7** and to produce an amine plus the Mannich base **10**. This carbonyl compound and/or those derived by its cleavage initiate the autocatalytic cycle resulting eventually in the complete decomposition of *cis*-**1** and also of *trans*-**1**. The *trans* isomers are much less reactive, however, probably because formation and ring-opening of *trans*-**8** are slower. It is interesting in this context that the yields of *trans*-**1b** obtained from *cis*-**1b** at different pH values seem to parallel the fraction of *trans*-**1b** that exists in the diprotonated form (Table 1), which is unreactive toward carbonyl compounds. Mannich bases that are derived from acetaldehyde, e.g. **10**, could not be observed because of their instability in the pH range of the experiments. Most likely, they fragment into amine, formaldehyde, and acetaldehyde which may give rise to the formation of the insoluble products observed.



The mechanistic scheme developed for *cis*- and *trans*-**1** is supported by the identification of the acetone-derived Mannich bases **12** as reaction products of the cyclopropanediamines *trans*-**3**. Here again, a slow ring-opening process during the initiation phase may provide the catalyst **12** which initiates the autocatalytic cycle proceeding *via* iminium ion **13** and the azomethine ylide **14**.



In most of the experiments discussed above, pyrroles were detected by a sensitive color test only, but never observed directly. 2-Styrylpyrroles **19** became the main products obtained from 3-phenylcyclopropanediamines **6**, 2 mol of which were involved in product formation. The reaction of *N*,*N*′-dialkylcyclopropanediamines and aromatic aldehydes yields pyrroles.[4] Therefore, it seemed reasonable that the diamines *trans*-**6b** and -**6c** had reacted with cinnamaldehyde or derivatives thereof, e.g. the iminium ions **15**. Formation of the latter may be interpreted in terms of a disrotatory ring opening[8b] of *trans*-**6b** or -**6c** with the protonated amino group in *trans* position to the phenyl ring acting as the leaving group. This process is facilitated by the relief of torsional strain between the phenyl and the *cis* amino group and by the formation of a conjugated system (**15**) in the *trans* configuration. The primary iminium ions **15** may react with the nonencumbered amino group of unchanged *trans*-**6**, either immediately or *via* cinnamaldehyde, to afford the secondary iminium ions **16**. Ring-opening of **16** yields the conjugated azomethine ylides (*E*)-**17**. These prefer a third reaction type rather than reclosure of the cyclopropane ring or hydrolysis, viz. (*E*)/(*Z*) isomerization followed by intramolecular attack of the iminium carbon atom at the azomethine ylide moiety to yield the pyrrolinium ions **18**, which eliminate alkanamine to afford the styrylpyrroles **19**. The formation of **18** from **16** may be regarded as a polar hetero analog of the well-known vinylcyclopropane cyclopentene rearrangement.[8c,17] Most probably, aryl iminium ions obtained from cyclopropanediamines and aromatic aldehydes also follow a conjugated azomethine ylide pathway to pyrroles but not a trimethylene pathway advocated previously.[4] This diradical mechanism operates in the thermal *N*-alkylidenecyclopropanamine 1-pyrroline rearrangement which

(17) Reviews: Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247. Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. Kulinkovich, O. G. *Russ. Chem. Rev.* **1993**, *62*, 839.

brings about the same structural change as the ring-enlargement described here.[18]

Conclusions

A major result of the present study is that various types of reactions, previously thought to be unrelated, of cyclopropanediamines can be traced back to common intermediates, i.e. azomethine ylides. Azomethine ylide intermediates have been invoked before in the formation of 2,3-dihydro-1,4-diazepines from *trans*-cyclopropanediamines.[3]

Cyclopropanediamines are much more stable in neutral, aqueous solutions than hitherto assumed, provided that the solutions do not contain traces of ketones or aldehydes. Any observed instability results from the presence of minute amounts of a carbonyl compound which initiate an autocatalytic decomposition proceeding by hydrolysis of the intermediate azomethine ylides to the corresponding carbonyl compounds and amines. Stability of cyclopropanamines in acidic media and cleavage of the C(1)–C(2) bond to eventually afford ketones under neutral conditions have been observed in many instances before. For example, 1-methyl-2,2-diphenylcyclopropanamine is converted in aqueous sodium bicarbonate at room temperature to 4,4-diphenyl-2-butanone.[19] The homoenamine reactivity of cyclopropanamines is strongly favored by acceptor and conjugating groups.[5] It is the transformation of one amino group into such a functionality, i.e. the iminium moiety, which triggers all reactions of cyclopropanediamines described here.

Experimental Section

General. Reference 9. Phosphate buffers (0.5 M) were prepared from KH_2PO_4 and Na_2HPO_4. 4-(Dimethylamino)-butan-2-one (**12c**) was prepared according to reference 13.

Reactions of the 1,2-Cyclopropanediammonium Dibromides 1–5. Solutions (0.05 M) of **1–5** in aqueous phosphate buffer (0.5 M) were prepared in NMR sample tubes at 25 °C, and the insert of the spectrometer (Bruker WM 400) was kept at the same temperature. Prior to each experiment, the homogeneity of the magnetic field was optimized with the help of acetone-d_6. The proton spectra were recorded without lock. After intervals of 30 min, 80 FIDs were accumulated with an acquisition time of 3.277 s. The resolution was 1.5 Hz.

1-Methyl-4-phenyl-2-styryl-1*H*-pyrrole (19b). *trans*-**6b**·2HBr (500 mg, 1.48 mmol) and K_2HPO_4 (270 mg, 1.55 mmol) were dissolved in water (10 mL). After 3 min, a colorless material began to precipitate, which was collected after 3 h, washed with cold methanol, and dried over P_4O_{10}. Yield: 114 mg (59%), colorless needles, mp 150–151 °C from MeOH/$CHCl_3$ (6:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (CH_3), 6.64 (d, $^4J_{3,5}$ = 1.9 Hz, 3-H), 6.90 (dd, ^3J = 16.2 Hz, ^5J = 0.4 Hz, CH), 6.99 (dd, $^4J_{3,5}$ = 1.9 Hz, ^5J = 0.4 Hz, 5-H), 7.05 (d, ^3J = 16.2 Hz, CH). MS (70 eV), *m*/*z* (rel inten) 259 (M^+, 100), 243 (M–Me, 14). Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 88.21; H, 6.41; N, 5.41.

1-Benzyl-4-phenyl-2-styryl-1*H*-pyrrole (19c). (a) *trans*-**6c**·2HBr (25 mg, 0.05 mmol) and sodium acetate (8 mg, 0.1 mmol) were dissolved in methanol (0.5 mL). After 2 h, a crystalline material began to precipitate, which was collected after 6 h and dried over silica gel: 5.0 mg (60%) colorless crystals, mp 141–142 °C from MeOH/C_6H_6 (1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (CH_2), 6.83 (d, $^4J_{3,5}$ = 1.9 Hz), 6.97 (dd, ^3J = 15.8 Hz, ^5J = 0.4 Hz, CH), 7.07 (d, $^4J_{35}$ = 1.9 Hz, 5-H), 7.07 (d, ^3J = 15.8 Hz, 7-H). MS (70 eV) *m*/*z* (rel inten) 335 (M^+, 76), 244 (M–C_7H_7, 100), 167 (M–C_7H_7–C_6H_5, 12). Anal. Calcd for $C_{25}H_{21}N$: C, 89.51; H, 6.32; N, 4.18. Found: C, 89.63; H, 6.38; N, 4.04.

(b) *trans*-**6c**·2HBr (245 mg, 0.50 mmol), sodium acetate (80 mg, 1.0 mmol), and cinnamaldehyde (132 mg, 1.0 mmol) were dissolved in methanol (3 mL). After 1 min, a colorless material began to precipitate: 119 mg (71%). Mp, ^{1}H NMR, and IR spectra were identical with those taken from the product obtained in experiment a.

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(18) Caramella, P.; Huisgen, R.; Schmolke, B. *J. Am. Chem. Soc.* **1974**, *96*, 2997. *Idem Ibid.* **1974**, *96*, 2999.
(19) Walborsky, H. M., Ronman, P. E. *J. Org. Chem.* **1973**, *38*, 4213.