Cyclopropanediamines, 7[◇]

Pyrroles from 1,2-Cyclopropanediamines and Aldehydes

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Received March 25, 1998

Keywords: Azomethine ylides / Nitrogen heterocycles / Ring expansion / Small ring systems / Synthetic methods

Mechanistic investigations by means of proton spectroscopy detected intermediates and uncovered the course of reactions in acetate-buffered [D_4]methanol of primary cyclopropanediamines *cis*- and *trans*-**2a** with benzaldehyde (**3a**) or 2,2-dimethylpropanal (**3b**), of secondary cyclopropanediamines *cis*- and *trans*-**2b** with **3b**, and of the ring-methylated cyclopropanediamine *trans*-**14a** and the aromatic aldehydes **3a** and **c**. This study provided the basis of an expedient synthesis of pyrroles which takes place under exceptionally mild conditions. Irrespective of the configuration, primary (**2a**·2HBr) and secondary cyclopropanediammonium dibromides **2b** and **c**·2HBr that are devoid of ring substituents react with aromatic aldehydes **3a**, **e**–**h**, cinnamic aldehyde (**3i**), and **3b** to afford 2-substituted (**8a**, **b**) and 1,2-disubstituted pyrroles (**8c**–**i**), respectively. The 3-substituted secondary *trans*-cyclopropanediammonium dibromides **24**·2HBr furnish 1,2,4-trisubstituted pyrroles **25**. While the primary 1-methylcyclopropanediammonium dibromide *trans*-**14a**·2HBr reacts regioselectively with **3a** and **c** to produce only 2,3-substituted pyrroles **19a**, **c**, the corresponding secondary dibromide *trans*-**14c**·2HBr gives rise to the formation of mixtures of 1,2,3- (**22**) and 1,2,5-trisubstituted pyrroles **23**. The key step of pyrrole formation from 1,2-cyclopropanediamines and aldehydes is the ring expansion of intermediate monoiminium ions of type **5** via azomethine ylides (*E,Z*)-**6** to yield dihydropyrrolium ions **7**.

Introduction

Various reactions of 1,2-cyclopropanediammonium dibromides in aqueous or methanol buffers proceed via common intermediates, i.e. azomethine ylides. These reactions comprise the *cis*-*trans* isomerization of *cis*-cyclopropanediammonium dibromide (*cis*-**2a**·2HBr)[1], the autocatalytic and ketone-catalyzed conversion of 1-methyl-*trans*-cyclopropanediammonium dibromide (*trans*-**14a**·2HBr) into 4-aminobutanone (**20**)[2], the formation of *cis*-2,3-substituted 2,3-dihydro-1*H*-1,4-diazepines (**11**) from cyclopropanediamines and aromatic aldehydes[3], and the formation of 2-aryl-1-benzylpyrroles from *N*,*N*′-dibenzylcyclopropanediamines and aromatic aldehydes[1][4]. We observed, using proton spectroscopy, that solutions in [D_4]methanol of *cis*- or *trans*-**2a**·2HBr, benzaldehyde (**3a**, 2 mol), and sodium acetate (2 mol) equilibrated within seconds at room temperature to afford identical mixtures consisting mainly of the dihydrodiazepinium ion **11a**·H^+ and the *trans*-bisimine *trans*-**4a**[5]. The results were interpreted in terms of the reactions and equilibria depicted in Scheme 1.

There are only two irreversible steps involved, viz. the intramolecular nucleophilic attack in (*E*,*Z*)-**6** of the azomethine ylide moiety at the imine carbon atom to yield the dihydropyrrole **7**, and the Cope rearrangement of (*s*-*cis*)-*cis*-**4** to dihydrodiazepine **10**. An intriguing observation was that benzaldehyde reacted with the *primary* cyclopropanediammonium dibromides *cis*- or *trans*-**2a**·2HBr in acetate-buffered methanol at room temperature to give diphenyldihydrodiazepine **11a** in 47% yield, while, under identical conditions, the (*secondary*) *N*,*N*′-dibenzyl derivative *trans*-**2c**·2HBr gave 1-benzyl-2-phenylpyrrole (**8d**) in 78% yield[4]. No dihydrodiazepines were found under the conditions of pyrrole formation, most probably because the *N*,*N*′-dibenzylbisiminium dication, required as precursor for a Cope rearrangement, did not arise in the nearly neutral medium. Likewise, no trace of a pyrrole was detected under the conditions of dihydrodiazepine formation. This result is probably due to a dramatic difference in rates of the two irreversible steps, of which the Cope rearrangement of (*s*-*cis*)-*cis*-**4a** is much faster than the cyclization of azomethine ylide (*E*,*Z*)-**6a** to dihydropyrrole **7a**.

Scheme 1 offered opportunities to test this assumption: The route, which eventually would lead to dihydrodiazepines, might be redirected to pyrrole formation if it were possible to reduce the rate of the Cope rearrangement without affecting the rate of pyrrole formation. This can be conceived in two ways, either by reducing the concentration of the *cis*-bisimine *cis*-**4**, or by lowering the rate constant of the Cope rearrangement. Here we report that both strategies can be used to favor the formation of pyrroles. These observations not only confirmed Scheme 1, but also uncovered an expedient method for the preparation of such pyrroles in good yields under very mild conditions.

[◇] Part 6: Ref.[2]. The results are part of the dissertations by J. Stawitz, **1978**, W. von der Saal, **1983**, and R. Reinhardt, **1985**, University of Würzburg.

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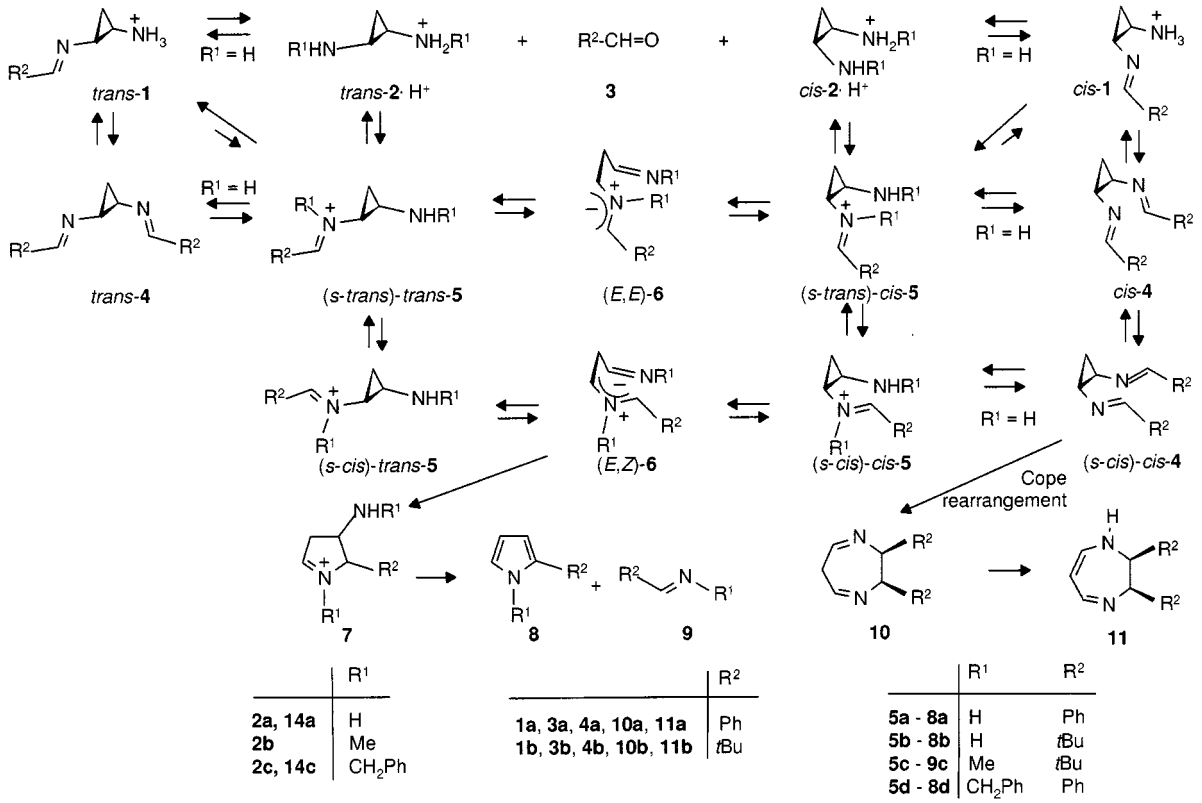
Scheme 1. Equilibria and irreversible reactions to pyrroles **8** and dihydrodiazepines **11** of 1,2-cyclopropanediammonium dibromides **2**·2HBr and aldehydes **3**



Mechanistic Results

Reactions at Low Concentrations of Benzaldehyde: 2-Phenylpyrrole From Primary Cyclopropanediamines

Scheme 1 suggested that pyrrole **8a** might be formed if the concentration of *cis*-bisimine *cis*-**4a** is lowered relative to those of the monoimines **5a**. We envisaged that this could be achieved by reducing the concentration of benzaldehyde. In previous experiments, we employed *two* moles of an aromatic aldehyde and *one* mol of a cyclopropanediammonium dibromide because two moles of the aldehyde are included in the dihydrodiazepines **11**, and two moles are consumed in the pyrrole forming reactions as well, viz. one for the pyrroles **8** themselves, and the second one for the Schiff bases **9**, which accompany the pyrroles. Since Schiff bases equilibrate with aldehydes and amines, pyrrole formation is conceivable to occur with just one mol of aldehyde, however, which eventually is completely incorporated in the pyrrole.

For scrutiny of the dihydrodiazepine/pyrrole competition, we monitored the reaction of *cis*- and *trans*-**2a** with benzaldehyde by proton spectroscopy. This was possible because the proton spectra of *cis*- and *trans*-**2a**[6], *trans*-**4a**[3], and **11a**[3] were known from previous work, while that of **8a** was recorded from an authentic sample (Table 2). In the spectra taken from the reaction mixtures, the signals of the cyclopropane protons were clearly separated and this allowed the assignment of structures to some intermediates.

Three phases could be distinguished. The first ended five minutes after mixing *trans*-**2a**·2HBr, benzaldehyde, and sodium acetate in [D_4]methanol in the ratio 1:2:2. Dihydrodiazepine **11a** was the predominating species and the cyclopropanediamines had equilibrated to yield a ratio of *trans*-**2a**/*cis*-**2a** of 4:1 which did not change anymore. Signals of pyrrole **8a** were not yet observable but those of two transient species which are most probably the imines *trans*- and *cis*-**1a**. They are characterized by singlets at $\delta = 8.6$ and 8.7 (CH of benzylidene groups) and unresolved multiplets at $\delta = 1.5$ and 2.9 from intact cyclopropane rings. After the end of the second phase, viz. fifteen minutes, these signals had disappeared and the mixture consisted mainly of unchanged *trans*-**2a** (40%) and dihydrodiazepine **11a** (40%). Minor components were the diastereomerized diamine *cis*-**2a** (10%) and indeed 2-phenylpyrrole (**8a**, 10%). Bisimines **4a** were never detected.

When *trans*-**2a**·2HBr was exchanged for its *cis* isomer *cis*-**2a**·2HBr, the resulting mixtures had exactly the same composition. A third experiment started from bisimine *trans*-**4a** dissolved in [D_4]methanol to which hydroxylamine hydrochloride, sodium acetate, and acetic acid were added. The rationale behind this experiment was trapping of benzaldehyde as oxime and thus producing monoimine *trans*-**5a** from bisimine *trans*-**4a**. Indeed the resulting mixtures closely resembled those of the first two experiments.

During the slowest phase (twelve hours), the relative amounts of the cyclopropanediamines decreased further and the proton signals of **8a** changed slightly: those of the phenyl protons increased, but the signals of both 3-H and 5-H were overlaid with doublets (J = 2.7 Hz), while the signal of 4-H remained unchanged. Obviously, a new, isotopomeric pyrrole emerged with 4-H exchanged for deuterium, viz. 4-[D]**8a**. The final mixture consisted of **11a**, *trans*-**2a**, 4-[D]**8a**, **8a**, and *cis*-**2a** in the ratio 4:2:2:1:1.

These experiments confirm Scheme 1. The reactions between cyclopropanediamines **2a** and benzaldehyde afford mainly dihydrodiazepine **11a**. At the onset, it arises fast, but finally, when there is only a small fraction of the aldehyde left in form of the monoimines **1a/5a**, then pyrrole formation can compete with the route via the Cope rearrangement. This observation led to the development of a convenient synthesis of 2-arylpyrroles (vide infra).

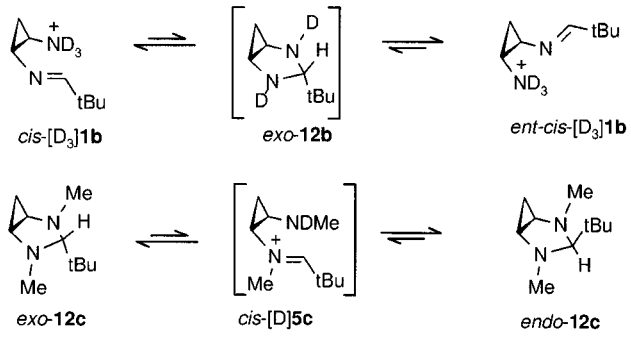
The slow formation of 4-[D]**8a** is indicative of the intermediate dihydropyrrolium ion **7a**, whose low concentration precluded observation by proton spectroscopy. Control experiments showed that the proton 4-H of **8a** is *not* exchanged under the reaction conditions during a period of time as long as two weeks. Neither is deuterium incorporated at the carbon atoms of equilibrating cyclopropanediamines *trans*- and *cis*-**2a** or dihydrodiazepine **11a**. Evidently, H/D exchange occurs exclusively at the α position of the iminium group of **7a**, which eventually becomes C-4 of pyrrole **8a**. Apparently, elimination of ammonia from **7a** to afford **8a** is slow enough to allow the H/D exchange under the conditions employed.

Lowering the Rate of the Cope Rearrangement − 2-*tert*-Butylpyrrole From Primary Cyclopropanediamines and 2,2-Dimethylpropanal

A second way to favor the formation of pyrroles is offered by retardation of the Cope rearrangement with the help of steric strain. The Cope rearrangement of *cis* bisaryldeneamines *cis*-**4** is so fast that their isolation from the reaction of *cis*-cyclopropanediamines and aromatic aldehydes is impossible. In contrast, the encumbered aldehyde 2,2-dimethylpropanal (**3b**) affords *cis*-bisimine *cis*-**4b** and its Cope rearrangement to **10b** occurs only at temperatures above 100°C[7]. Under these conditions, *trans*-**4b** does not rearrange. The dramatic decrease in the rate constant may be anticipated because formation of the new bond C2−C3 of **10b** requires an eclipsed conformation of the two *tert*-butyl groups, which is strongly destabilized[8]. As before, we monitored the conversions by proton spectroscopy (Table 2).

Solutions of *trans*-**2a**·2HBr and 2,2-dimethylpropanal in acetate-buffered [D_4]methanol yielded immediately the rapidly equilibrating pair of tautomers *trans*-**1b** and *trans*-**5b** (ABXY spectrum of cyclopropane ring protons), of which the former is greatly favored[9], and bisimine *trans*-**4b**. After one day, the fraction of *trans*-**4b** had increased and some *cis*-**2a** had formed as well as two new products. One was pyrrole **8b**, the other an unknown compound characterized by an ABX_2-type spectrum of cyclopropane ring protons with a broadened X_2 part. Neither this unknown product nor *trans*-**1b** or *cis*-**2a** were present when the amount of 2,2-dimethylpropanal had been doubled. In that case mainly bisimine *trans*-**4b**, the hemiacetal of the aldehyde and the solvent[10], and a small amount of pyrrole **8b** were observed after one day. As expected, the signals of dihydrodiazepine **11b** never emerged in these experiments.

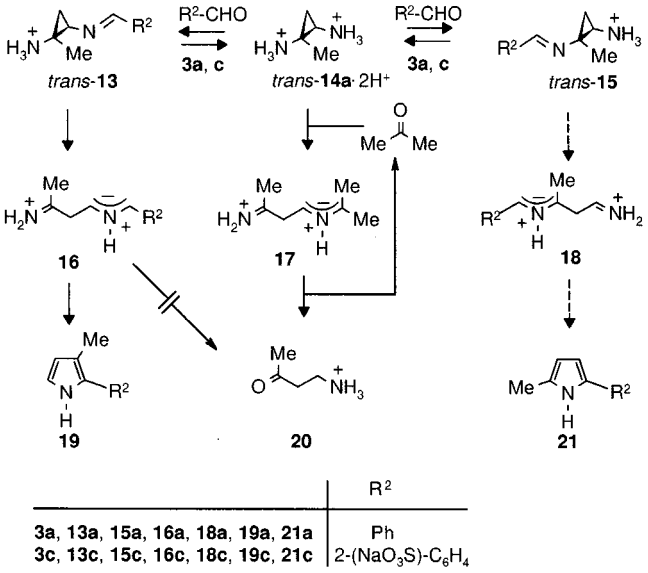
The broadened X_2 part of the ABX_2 multiplet of the unknown compound is indicative of an exchange process. Because the ^{1}H-NMR parameters resemble those of *cis*-**4b**, the unknown compound is most probably the *cis* imine *cis*-**1b** undergoing a degenerate rearrangement via 2,4-diazabicyclo[3.1.0]hexane **12b**. An additional broadening of the signal of the aldimine proton (δ = 7.57) suggests the presence of some **12b** equilibrating rapidly with *cis*-**1b**, most probably the *exo* diastereomer *exo*-**12b**. The overall dynamic process is a two-site exchange for the methylene protons and the methine protons C*Ht*Bu, but a three-site exchange for the cyclopropane methine protons. This is yet another example of the ring-chain equilibria involving imidazolidines, which have been thoroughly investigated by proton spectroscopy[11] and kinetic measurements[12].



2-*tert*-Butyl-1-methylpyrrole From Secondary Cyclopropanediamines and 2,2-Dimethylpropanal

Treatment of the *N*,*N*′-dimethylcyclopropanediammonium dibromide *trans*-**2b**·2HBr with 2,2-dimethylpropanal yielded in one hour pyrrole **8c**, small amounts of *trans*- and *cis*-**2b**, and two new products in the ratio 7:3. The proton spectrum of each compound exhibits an ABX_2 multiplet characteristic of the cyclopropane protons of a free *cis*-1,2-cyclopropanediamine[6] and a singlet from two equivalent *N*-methyl groups. Furthermore, the proton spectrum of the major product shows the singlet of a methine proton (δ = 2.70), which is apparently obscured by other signals in the spectrum of the minor product. On the basis of the ^{1}H-NMR evidence we assigned the bicyclic structures *exo*- and *endo*-**12c** to the new compounds. After one day, the main products were pyrrole **8c** and imine **9c**. Two moles of the aldehyde gave rise to essentially the same results. Treatment of *cis*-**2b**·2HBr with 2,2-dimethylpropanal produced immediately large amounts of only *exo*-**12c**, which exhibited very broad signals. After one hour, signals of *endo*-**12c** emerged at higher field but remained much less intense than those of *exo*-**12c** (10:1). In addition, *trans* diamine *trans*-**2b**, pyrrole **8c**, and imine **9c** were detected.

In contrast to the reactions of the *primary* cyclopropanediamines *cis*- and *trans*-**2a** with 2,2-dimethylpropanal, the analogous conversions of the *secondary* cyclopropanediamines *cis*- and *trans*-**2b** did not allow detection of monoimines, e.g. *cis*- and *trans*-**5c**, as intermediates en route to the observed bicyclic products **12c**. According to the face of the aldimine carbon atom of *cis*-**5c**, which is attacked by the methylamino group, either *exo*- or *endo*-**12c** is produced. The major diastereomer is assigned the *exo* configuration because the *endo* configuration should be disfavored by steric interaction between the *tert*-butyl group and the *endo* proton 6-H.



2-Aryl-3-methylpyrroles From the Primary 1-Methylcyclopropanediamine *trans*-14a and Aromatic Aldehydes

Formation of 2,4-diazabicyclo[3.1.0]hexanes **12** in the experiments described above was not unexpected since bicyclic compounds often result as byproducts in reactions of *cis*-1,2-substituted cyclopropanes. They may even predominate if the cyclopropanes bear additional substituents at C-1 and/or C-2[13]. For example, we observed previously that the carboxy groups of 1-methyl- and 1,2-dimethyl-*cis*-cyclopropanedicarboxylic acid (or derivatives thereof) interact more readily than those of *cis*-cyclopropanedicarboxylic acid itself[6]. It appeared, therefore, interesting to study the reaction of 1-*methyl*cyclopropanediamine *trans*-**14a** with benzaldehyde.

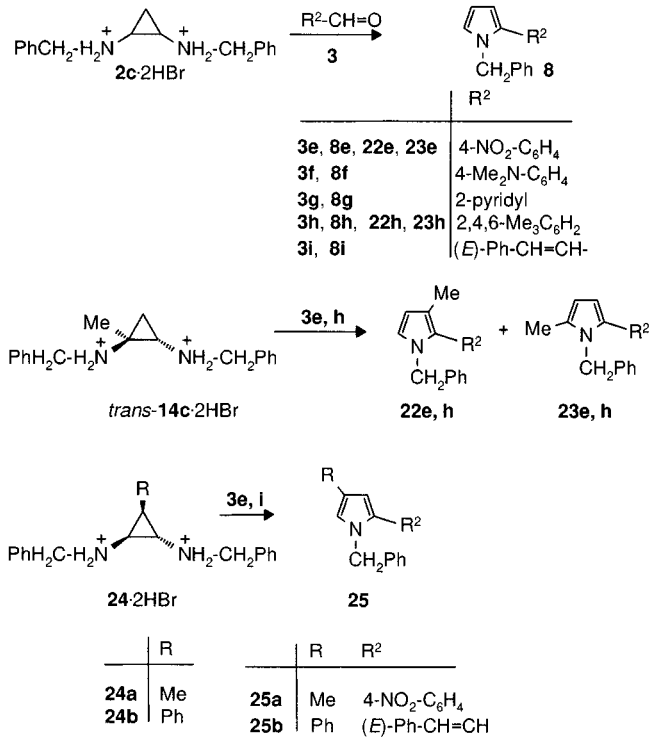
We expected to observe formation of a 2,4-diazabicyclo[3.1.0]hexane of type **12**, which is a derivative of the hitherto unknown cyclopropanediamine *cis*-**14a**. Surprisingly, 3-methyl-2-phenylpyrrole (**19a**) had formed quantitatively already after five minutes. No trace of a dihydrodiazepine nor of the isomeric pyrrole, viz. 5-methyl-2-phenylpyrrole (**21a**), was detected. This result may be rationalized in terms of an initial rapid equilibration of *trans*-**14a** and benzaldehyde with the imines *trans*-**13a** and *trans*-**15a**[14]. Only the former eventually yields a pyrrole (**19a**) via cyclization of an intermediate azomethine ylide (**16a**). Obviously, this ring closure is much faster than the hypothetical recyclization **16a** → *cis*-**13a**, which would result in a *trans*→*cis* isomerization.

The lack of pyrrole **21a** in this multistep scenario becomes plausible if one considers the relative stabilities of the azomethine ylides **16a** and **18a**. Strain introduced by the methyl group into the planar azomethine ylide moiety and the higher energy of the aldiminium group render **18a** less stable than **16a** and hence disfavor this reaction channel. Similar results were observed in the autocatalytic and ketone-catalyzed reactions of *trans*-**14a**·2HBr in aqueous buffers which eventually led to 4-aminobutanone (**20**). Also in this study, the final result was dominated by the relative stabilities of the two ketimines, derived from the ketone and *trans*-**14a**, and their acyclic isomers, namely azomethine ylides such as **17**, which was hydrolyzed to afford **20**[2]. In the present experiments, performed in [D_4]methanol as solvent, this hypothetical hydrolysis product of **16a** was *not* observed, however, although the presence of small amounts of deuterium oxide could not be excluded.

The implied dramatic difference in the reactivities between the deceptively similar azomethine ylides **16a** and **17** became obvious, when *trans*-**14a**·2HBr was treated with the water-soluble aromatic aldehyde **3c** in a buffered *aqueous* medium which should facilitate hydrolysis of **16c**. When the concentrations of the reactants and of sodium acetate were kept similar to those used in [D_4]methanol solution, only pyrrole **19c** formed immediately but no trace of 4-aminobutanone (**20**) or pyrrole **21c**. In a competition experiment, the concentration of aldehyde **3c** was lowered to a fifth of the concentration of *trans*-**14a**·2HBr. The resulting solution consisted of pyrrole **19c** and the hydrolysis product **20** (1:4). Obviously, the aldehyde **3c** and the corresponding fraction of the diamine *trans*-**14a**·2HBr reacted quickly to give pyrrole **19c**, and the remaining diamine was converted more slowly into **20**.

Preparative Results

Treatment of *N*,*N*′-dibenzylcyclopropanediammonium dibromides *cis*- and *trans*-**2c**·2HBr with aromatic aldehydes **3a**, **e**−**h** or cinnamic aldehyde **3i** in acetate-buffered methanol or ethanol at ambient temperature afforded the 2-substituted *N*-benzylpyrroles **8d**−**8i**[4]. In the reactions of the *primary* cyclopropanediamines *cis*- and *trans*-**2a** with 2,2-dimethylpropanal, pyrrole **8b** was only a minor product, but *N*,*N*′-*dimethyl*cyclopropanediamine *trans*-**2b** gave mainly *N*-methylpyrrole **8c** which was isolated in 32% yield. Unlike the *primary* 1-methylcyclopropanediammonium dibromide *trans*-**14a**·2HBr, which gave a *single* pyrrole with benzaldehyde (**3a** → **19a**) and with the *ortho*-sulfonic acid derived thereof (**3c** → **19c**, vide supra), the corresponding *N*,*N*′-*dibenzyl* derivative *trans*-**14c**·2HBr reacted with aromatic aldehydes (**3e**, **h**) to furnish a *mixture* of isomeric pyrroles, viz. **22e**, **h** (major isomers) and **23e**, **h** (minor isomers)[4]. This demonstrates that combinations of subtle effects tune the delicate balance between the various reaction paths. The 3-substituted cyclopropanediamines **24** gave exclusively the corresponding 1,2,4-substituted pyrroles **25**.



The experimental technique employed in the preparation of pyrroles from *secondary* cyclopropanediamines, viz. simple addition of an excess of the aldehyde to solutions of cyclopropanediammonium dibromides in acetate-buffered methanol, fails in the case of *primary* cyclopropanediamines. Instead of pyrroles, dihydrodiazepines **11** arise exclusively except for 2,2-dimethylpropanal (**3b**) which affords bisimines **4b**. The mechanistic study detailed above showed, however, that, *at low concentrations of benzaldehyde*, *cis*- and *trans*-**2a** yielded a small amount of pyrrole **8a** besides dihydrodiazepine **11a**. These observations were now exploited for a convenient synthesis of 2-phenylpyrrole (**8a**) by keeping the concentration of benzaldehyde low throughout the reaction period: After a dilute solution of benzaldehyde in methanol had been added very slowly to a solution of *trans*-**2a**·2HBr in acetate-buffered methanol, pyrrole **8a** could be isolated in 64% yield.

Discussion

The present study revealed several parameters which govern the ultimate fate of 1,2-cyclopropanediammonium dibromides in the reactions with aldehydes in methanol buffers. (i) The ratio of monoimines **5** and *cis* bisimines *cis*-**4** determines the observed ratio of pyrrole **8** vs. dihydrodiazepine **11**. The observation that both, pyrrole **8a** and dihydrodiazepine **11a**, arise simultaneously from *trans*-cyclopropanediamine (*trans*-**2a**) under certain conditions indicated that both are formed via a common intermediate, i.e. an azomethine ylide (**6**). It also suggested the opportunity to direct the multistep sequence either toward formation of 2-arylpyrroles **8** or toward formation of dihydrodiazepines **11**, simply by keeping the concentration of the aromatic aldehyde low or high, respectively. (ii) The second factor is the rate of the Cope rearrangement of the *cis* bisimines *cis*-**4** → **10**. The encumbered bisimine *cis*-**4b** rearranges to **10b** only at high temperature. Accordingly, in acetate-buffered methanol at room temperature, *trans*-**2a** reacted with 2,2-dimethylpropanal to give, among other products, pyrrole **8b** but no trace of dihydrodiazepine **11b**. (iii) The third parameter is rooted in the substitution pattern of the 1,2-cyclopropanediamines. The *N,N′*-dimethyl derivatives **2b** reacted more rapidly than their primary analogs **2a** with 2,2-dimethylpropanal to form a pyrrole (**8c**). The ring-methylated derivative *trans*-**14a** reacted even faster. Only one of two possible pyrroles, i.e. **19a**, arose via azomethine ylide **16a**. No dihydrodiazepine was observed. This observation allowed the connection of the present study with a previous one, carried out in aqueous buffers, where the hydrolysis product 2-aminobutanone (**20**) was formed from the similar azomethine ylide **17**. Azomethine ylides **16** that are derived from an aromatic aldehyde undergo ring closure to a five-

Table 1. Starting material and experimental conditions in the synthesis of pyrroles from 1,2-cyclopropanediammonium dibromides and aldehydes in acetate-buffered methanol; yields, melting points, solvents used for recrystallization, and boiling points

Compound	Starting material		Time	Yield [%]	M.p. [°C] (Solvent)	B.p. [°C][a] /Torr	Ref.
8a	*trans*-**2a**·2HBr	**3a**	16 h	64	135	$90-110/10^{-2}$	[b]
8c	*trans*-**2b**·2HBr	**3b**	4 d	32		$30/10^{-3}$	[b]
8d	*trans*-**2c**·2HBr	**3a**	4 h	78		$103-105/10^{-3}$	[b]
8e	*trans*-**2c**·2HBr	**3e**	2 d	51[c]	104−105 (1. MeOH, 2. hexane)		[4]
8f	*trans*-**2c**·2HBr	**3f**	4 h	75	125 (MeOH)		[4]
	cis-**2c**·2HBr	**3f**	3 h	65			[4]
8g	*trans*-**2c**·2HBr	**3g**	22 h	55		$90/10^{-2}$	[4]
8h	*trans*-**2c**·2HBr	**3h**	3 d	95	67−68		[4]
8i	*trans*-**2c**·2HBr	**3i**	2.5 h	54		oil[d]	[b]
22h, **23h** (7:3)	*trans*-**14c**·2HBr	**3h**	2 d	57		$90/10^{-2}$	[4]
22e	*trans*-**14c**·2HBr	**3e**	2 d	38	79−80 (petroleum ether)		[4]
23e				29	119−120 (petroleum ether)		[4]
25a	**24a**·2HBr	**3e**	4 h	62		$110/10^{-2}$	[4]
25b	**24b**·2HBr	**3i**	1 h	71	141−142 ($MeOH/C_6H_6$)		[1]

[a] Bath temperature during distillation in a sublimation apparatus with a cold finger (−78 °C). − [b] This work. − [c] Yield after fractionating crystallization; the yield of the mixture of **8e** and **9e** ($R^1 = CH_2Ph$, $R^2 = 4\text{-}NO_2\text{-}C_6H_4$) was 94%. − [d] Purified by preparative TLC.

membered ring so fast that hydrolysis cannot compete even in aqueous buffers.

The synthesis of pyrroles presented here is related to the pyrrole formation from 1-(1-piperidino)cyclopropyl ketimines which is catalyzed by tetrafluoroboric acid[15]. Despite a wealth of methods for the preparation of pyrroles[16] there is a continued interest in novel approaches in general and especially for 2-arylpyrroles[17]. The present synthesis compares favorably to existing methods as far as it converts aldehydes into pyrroles under very mild, neutral conditions, viz. in buffered methanol solutions at room temperature. These conditions render it ideal for use in combinatorial chemistry[18].

Financial support of this work by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie*, Frankfurt am Main, is gratefully acknowlegded.

Experimental Section

General: Starting material, yields, and physical data: Table 1. − ^{1}H NMR: Table 2. − ^{13}C NMR: Table 3. − Molecular formulae and masses and elemental analyses: Table 4. − ^{1}H NMR: Bruker WM 400 and Varian EM 390. Spectra that were recorded for solutions in acetate-buffered [D_4]methanol were standardized with sodium 3-(trimethylsilyl)propanesulfonate (0.3 mg)[19]. The parameters of spectra of higher order were optimized with the program LAOCOON III[20]. − ^{13}C NMR: Bruker WM 400. − MS (70 eV): Varian MAT CH 7.

Starting Material and Reference Compounds

3a was distilled prior to use. **3b** was purified via the bisulfite adduct and distilled[10]. 1,2-Cyclopropanediammonium dibromides *cis*- and *trans*-**2a**−**c**·2HBr, *trans*-**14a**, **c**·2HBr, **24a**, **b**·2HBr were prepared as described[6].

cis-N,N′-Bis(2,2-dimethylpropylidene)-1,2-cyclopropanediamine (*cis*-**4b**): Aqueous KOH (42%, 30 ml) was added to a suspension of *cis*-**2a**·2HBr (7.02 g, 30.0 mmol) in diethyl ether (50 ml). The ether layer was separated, and the aquous layer was extracted with ether (10 × 50 ml). The combined organic layers were dried with powdered KOH for 15 min, and **3b** (6.03 g, 70 mmol) was added. The solution was kept for 19 h at 20°C, the solvent was distilled in vacuo, and the residue (yellow oil) at 20−30°C/10^{-5} Torr to yield a colorless oil (4.31 g, 69%), which was stored at −25°C. − IR (film) ν = 1660 cm^{-1} (C=N). − ^{13}C NMR ($CDCl_3$): δ = 14.4 (CH_2), 27.1 (*C*Me_3), 36.1 (Me), 46.1 (CH), 170.5 (N=CH). − MS; *m/z* (%): 208 (0.2) [M^+], 151 (1) [$M^+ - C_4H_9$], 83 (100).

trans-N,N′-Bis(2,2-dimethylpropylidene)-1,2-cyclopropanediamine (*trans*-**4b**) was prepared, as described for *cis*-**4b**, from *trans*-**2a**·2HBr in 79% yield as colorless oil. − IR (film): ν = 1655 cm^{-1} (C=N). − MS; *m/z* (%): 208 (0.5) [M^+], 151 (78) [$M - C_4H_9$], 83 (100).

Attempted Thermolysis of trans-**4b**: *trans*-**4b** (200 mg, 1 mmol) was distilled (40°C, 10^{-5} Torr) into a vial, which was sealed at 10^{-5} Torr and heated to 100°C for 4 d. *Trans*-**4b** was recovered unchanged (GC, IR, ^{1}H NMR).

cis-2,3-Dihydro-2,3-diphenyl-1H-diazepine (**11a**): A mixture of *trans*-**2a**·2HBr (9.59 g, 41.0 mmol), sodium acetate (7.38 g, 90.0 mmol), and **3a** (9.66 g, 91.0 mmol) in methanol (320 ml) was stirred for 3 d at 20°C. The solvent was distilled in vacuo. The residue was dissolved in CH_2Cl_2 (150 ml), and the solution was extracted with aq. NaOH (2 M, 100 ml). The organic layer was dried with Na_2SO_4, and the solvent was distilled in vacuo to yield colorless crystals (10.5 g, 47%), m.p. 180−182°C (from methanol) (ref.[3] 182−183°C). − No trace of **8a** could be detected with Ehrlich's pyrrole test[21] and proton spectroscopy in the residue, which was obtained by addition of water to the mother liquor, acidification to pH = 5 and extraction with CCl_4 followed by distillation of the solvent and some **3a** at 40°C/10^{-2} Torr.

Thermolysis of cis-**4b** − *cis-2,3-Di-tert-butyl-2,3-dihydro-1H-diazepine* (**11b**): Under Ar, a solution of *cis*-**4b** (252 mg, 1.20 mmol) in dry toluene (15 ml) was heated under reflux for 4 d. The solvent was distilled in vacuo until the final volume was 3 ml. Cooling of the solution at 0°C yielded a crystalline precipitate which was collected by filtration and recrystallized from toluene to give colorless needles (124 mg, 49%), m.p. 203−205°C (subl. above 180°C). The mother liquors contained mainly unchanged *cis*-**4b**. − IR (Nujol): ν = 3190 cm^{-1} (NH), 1610 (C=N). − UV (tetrahydrofuran): λ_{max} (ε) = 301 nm (6600). − ^{1}H NMR (CF_3CO_2D, which provides the cation 1,4,6-[D_3] **11b**$^+$): δ = 1.10 (*t*Bu), 1.25 (*t*Bu), 3.13 (3-H), 4.43 (2-H), 7.61 (5-H), 7.73 (7-H). − MS; *m/z* (%): 208 (4) [M^+], 193 (11) [M − Me] 151 (11) [$M - C_4H_9$], 81 (100).

Mechanistic Experiments

1,2-Cyclopropanediammonium Dibromides and Aldehydes in Acetate-Buffered [D4]Methanol: Cyclopropanediammonium dibromide (0.10 mmol) and sodium acetate (*a* mmol) were dissolved in [D_4]methanol (0.7 ml) in 5 mm NMR sample tubes, followed by addition of the aldehydes (*b* mmol). − (a) *cis*- or *trans*-**2a**·2HBr; *a* = 0.21; **3a**, *b* = 0.091. − (b) *cis*- or *trans*-**2a**·2HBr or *cis*- or *trans*-**2c**·2HBr; *a* = 0.22; **3b**, *b* = 0.10 or 0.20. − (c) *trans*-**14a**·2HBr; *a* = 0.21; **3a** or **3c**, *b* = 0.22.

trans-**4a** (22.1 mg, 0.089 mmol), sodium acetate (16.3 mg, 0.20 mmol), and hydroxylamine hydrochloride (6.0 mg, 0.09 mmol) were dissolved in [D_4]methanol (0.7 ml). The reaction was initiated by the addition of acetic acid (5 µl, 0.09 mmol).

Preparative Experiments

2-Phenylpyrrole (**8a**): A solution of **3a** (1.09 g, 10.0 mmol) in methanol (100 ml) was added dropwise during 9 h to a stirred solution of *trans*-**2a**·2HBr (2.34 g, 10.0 mmol) and sodium acetate (1.64 g, 20.0 mmol) in methanol (100 ml). After 16 h, the solvent was distilled in vacuo, and the residue was extracted with diethyl ether (4 × 50 ml). The solvent was distilled in vacuo, and the solid residue was sublimated at 90−110°C bath temp./10^{-2} Torr at a cold finger (10°C), colorless crystals, m.p. 135°C (ref.[22] m.p. 137°C).

2-(1,1-Dimethylethyl)-1-methylpyrrole (**8c**): A solution of *trans*-**2a**·2HBr (4.00 g, 15.3 mmol), sodium acetate (2.71 g, 33.0 mmol), and **3b** (2.63 g, 30.5 mmol) in methanol (120 ml) was stirred for 4 d in the dark and poured into sat. aq. KH_2PO_4 (250 ml). The mixture was extracted with CH_2Cl_2 (5 × 100 ml). The combined organic layers were dried with K_2CO_3. The solvent was distilled in vacuo and the residue sublimed at 30°C bath temp./10^{-3} Torr at a cold finger (−50°C) to yield a yellow oil, which was purified by bulb-to-bulb condensation at 30°C bath temp./10^{-3} Torr to afford a colorless oil. − ^{13}C NMR ($CDCl_3$): δ = 30.3 (Me), 31.8 (*C*Me_3), 36.5 (NMe), 105.0 (C-3), 105.7 (C-4), 123.5 (C-5), 141.1 (C-2). − MS; *m/z* (%): 137 (30) [M^+], 122 (100) [M − Me], 107 (16) [$M - C_2H_6$], 94 (14) [$M - C_3H_7$].

Synthesis of Pyrroles − General Procedure: Solutions of cyclopropanediammonium dibromide (6 mmol), sodium acetate (16 mmol) and aldehyde (**3**, 13 mmol) in 30 ml methanol were stirred

Table 2. Chemical shifts (δ values) and coupling constants (*J*, [Hz]) in 400-MHz proton spectra

Compound	Alkyl groups		CH=N	Ring protons							
				1-H, 2-H	3-H	3′-H[a]	^2J	$^3J_{cis}$	$^3J_{trans}$	$^3J_{1,2}$	[b]
cis-**2a**				2.54	1.02	0.57	−7.1	7.8	4.4		M
trans-**2a**				2.63	1.01		[c]				M
cis-**2b**	Me	2.60		2.55	1.02	0.68	−7.1	7.6	4.5		M
trans-**2b**	Me	2.58		2.61	1.07		−7.2	8.3	4.9	2.2	M
cis-**4b**	*t*Bu	1.01	7.58	3.08	1.12	1.43	−6.1	7.3	5.1		T
trans-**4b**	*t*Bu[d]		7.72	3.11	1.27		[c]				M
		1.03	7.64	3.07	1.25		[c]				T
cis-**1b**	*t*Bu[d]		7.57 (br.)	3.02 (br.)	1.29	1.10[e]	−7.2	7.6	4.4	2.1	M
trans-**1b**	*t*Bu[d]		7.81	2.82, 3.18	1.29	1.27	−11.5	[f]	[f]		M
				1-H, 5-H	3-H	6-H	6′-H				
exo-**12c**	*t*Bu	0.90		3.02	2.70	0.12	[g]	−6.2	6.0	3.0		M
	Me	2.49									
endo-**12c**	*t*Bu	0.82		2.90	[g]	−0.09	[g]	−6.7	5.8	2.9		M
	Me	2.31									
			Aryl-H		3-H	4-H	5-H	$^3J_{34}$	$^4J_{35}$	$^3J_{45}$	
8a			[g]		6.44	6.13	6.79	3.4	1.5	2.7	M
			7.20 (1H), 7.35 (2H), 7.45 (2H)		6.51	6.28	6.71	3.5	1.5	2.7	T
8b	*t*Bu[g]				5.73	5.87	6.48	3.4	1.8	2.8	M
ref.[23]		1.27			5.76	5.91	6.45	3.5	1.5	2.75	C
8c	*t*Bu	1.32			5.80	5.82	6.46	3.6	2.0	2.8	M
	Me	3.71									
8i	CH_2Ph	5.16	6.8−7.3[h]		6.56	6.23	6.71	3.7	1.7	2.7	T
	(*E*)-PhCH=CH										
19a	Me	2.22	7.2−7.4			5.99	6.70			2.4	M
19c	Me	2.15	7.2−7.6			6.02	6.74			2.4	M

[a] 3′-H and 6′-H are *trans* to 1-H. − [b] Solvent: M = acetate-buffered [D_4]methanol, T = [D]trichloromethane, C = tetrachloromethane. − [c] Coupling constants could not be determined (unresolved multiplet). − [d] The signal of the *tert*-butyl group was not unambiguously identified. − [e] The ABX_2 spectrum of the cyclopropane ring protons is the result of rapid exchange via diazabicyclo[3.1.0]hexane **12b**. − [f] $^3J_{cis}$:$^3J_{1,3}$ = 8.8, $^3J_{2,3'}$ = 8.8, $^3J_{trans}$:$^3J_{1,3'}$ = 4.2, $^3J_{2,3}$ = 4.4 Hz. − [g] The signal was obscured. − [h] Including the vinyl protons.

Table 3. Chemical shifts (δ values) in carbon-13 spectra

Compound	Cyclopropane ring							Alkyl groups		[a]
	CH_2			CH	C=N					
trans-**4b**	17.5			50.1	169.6			*t*Bu	35.8, 27.0	T
cis-**4b**	14.4			46.1	170.5			*t*Bu	36.1, 27.1	T
	pyrrole ring				phenyl					
	C-2	C-3	C-4	C-5	=CH−[b]		*i*-C			
8a	133.4	106.6	110.4	120.3	125.0	130.1	135.5			D
					126.9					
8c	141.1	105.0	105.7	123.5				*t*Bu	31.8, 30.3	T
								NMe	36.5	
8d	141.1	109.6	110.3	124.7	127.8	129.6	130.5	CH_2	51.9	T
					128.3	129.8	135.4			
					128.6	130.2				
8f	139.4	107.4	107.8	126.8	112.1	129.0	120.6	NMe	39.7	D
					122.2		134.3	CH_2	49.6	
					128.3		149.2			
8i	131.9	107.1	108.9	117.1	123.3	127.6	137.8	CH_2	50.6	T
					125.9	128.6	138.1			
					126.4	128.8				
					126.9					
25b	138.7	103.9	123.7	125.2	117.0	126.5	132.1	CH_2	49.5	D
					120.8	126.7	135.0			
					124.2	127.2	137.2			
					125.4	128.5				
					125.8					

[a] Solvent: T = [D]trichloromethane; D = [D_6]dimethyl sulfoxide. − [b] The vinyl carbon atoms of **8i** and **25b** are included.

during the periods of time listed in Table 1. The conversions were monitored by TLC [Al_2O_3, petroleum ether (50−70°C)]. The solvent was distilled in vacuo. The residue was extracted with diethyl ether. The organic layer was dried with $MgSO_4$ and the solvent

Table 4. Molecular formulae and masses, and elemental analyses

Compound	Formula	Mol. mass	Elemental analyses	C	H	N
cis-**4b**	$C_{13}H_{24}N_2$	208.4	calcd.	74.95	11.71	13.45
			found	74.89	11.60	13.48
trans-**4b**			found	75.00	11.60	13.68
11b			found	74.82	11.70	13.56
8a	$C_{10}H_9N$	143.2	calcd.	83.88	6.34	9.78
			found	83.54	6.45	9.89
8c	$C_9H_{15}N$	137.2	calcd.	78.78	11.02	10.21
			found	78.91	11.28	10.12
8d	$C_{17}H_{15}N$	233.3	calcd.	87.52	6.46	6.00
			found	87.84	6.68	6.04
8e	$C_{17}H_{14}N_2O_2$	278.3	calcd.	73.36	5.07	10.07
			found	72.87	5.25	9.93
8f	$C_{19}H_{20}N_2$	276.4	calcd.	82.57	7.29	10.14
			found	81.70	7.48	9.87
8g	$C_{16}H_{14}N_2$	234.3	calcd.	82.02	6.02	11.96
			found	82.11	5.98	11.29
8h	$C_{20}H_{21}N$	275.4	calcd.	87.23	7.69	5.08
			found	87.22	7.86	5.05
8i	$C_{19}H_{17}N$	259.4	calcd.	87.99	6.61	5.40
			found	87.66	6.73	5.33
22h, **23h** (7:3)	$C_{21}H_{23}N$	289.4	calcd.	87.15	8.01	4.84
			found	86.83	8.11	4.95
22e	$C_{18}H_{16}N_2O_2$	292.3	calcd.	73.95	5.52	9.58
			found	74.25	5.59	9.56
23e			found	74.61	5.97	9.40
25a			found	73.30	5.11	9.31
25b	$C_{25}H_{21}N$	335.4	calcd.	89.51	6.31	4.18
			found	89.63	6.38	4.04

distilled in vacuo. Purification of the residue by preparative TLC or flash chromatography was followed by distillation or sublimation of the product at a cold finger (−78°C) and/or recrystallization from the solvents listed in Table 1.

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