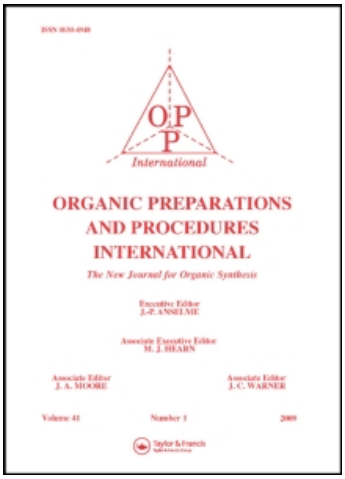

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1-ALKYLIDENE(ARYLIDENE)AMINO-2-AMINOETHANES AND THEIR TAUTOMERIZATION TO IMIDAZOLIDINES

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1-ALKYLIDENE(ARYLIDENE)AMINO-2-AMINOETHANES AND THEIR TAUTOMERIZATION TO IMIDAZOLIDINES

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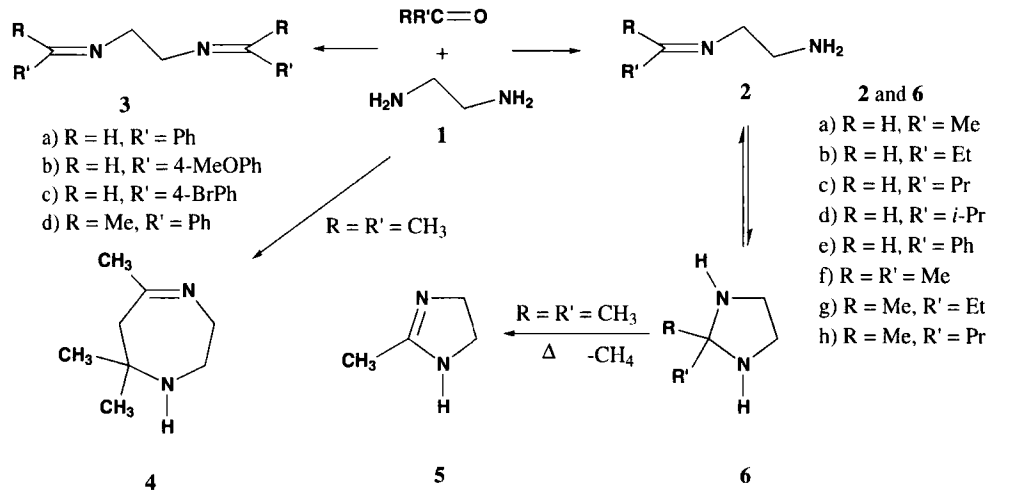
In theory, the interaction of ethylenediamine (**1**) with aldehydes and ketones could lead to the corresponding mono-imines (**2**). In practice, however, the *bis*-imines are actually obtained with aromatic[1-4] and aliphatic aldehydes,[4] aliphatic ketones,[2,5] acetophenone[2] and benzophenone.[2] The mono-imines have been isolated only with cyclohexanone and its homologues. The formation of mono-mines has been claimed with formaldehyde[9] and acetone[6] but no products were isolated. The instability of these mono-imines has been ascribed to their tendency toward hydrolysis and polymerization. Chromatographic methods and vacuum distillation are not useful for isolation because of the decomposition of these substances on the adsorbent surface, even at relatively low temperatures.[5]

We carried out several PMR-monitored experiments of the reaction mixtures of diamine **1** with typical carbonyl compounds, such as benzaldehyde and acetone, in order to devise a synthetic path to 1-monoalkylidene derivatives **2**. The *bis*-derivative **3a** predominates in the reaction mixture of benzaldehyde with ethylenediamine in a 1:1 proportion. Although 1-arylideneamino-2-aminoethane (**2e**) is present in less than 10%, it becomes the only product when the proportion

benzaldehyde:diamine is equal 1:10 and was isolated after extraction with pentane or hexane and removal the solvent under vacuum at room temperature (Tables 1 and 2). However, all attempts at further purification by precipitation from heated solutions led to its complete disproportionation to the *bis*-derivative **3a**. Under the same conditions, the mono-(*p*-anisylidene) and (*p*-bromobenzylidene) derivatives were spontaneously converted into *bis*-adducts (**3b,c**) during solvent removal. Therefore it is recommended to use freshly prepared 1-arylydeneamino-2-aminoethanes in solutions for subsequent transformations without purification.

5,7,7-Trimethyl-2,3,6,74-tetrahydro-1H-1,4-diazepine (**4**) was obtained in the reaction of ethylenediamine with an excess of acetone. Its formation can be explained by the aldolization of acetone in basic medium and subsequent condensation of the intermediate with ethylenediamine. Diazepine **4** has been found in the reaction mixture (less than 10%) when the acetone:diamine proportion was 1:2; however, the mono-derivative **2f** became the main product. It can be isolated after extraction of the reaction mixture (acetone:diamine proportion is equal 1:5) with pentane (Tables 1 and 2). Attempted further purification by vacuum distillation failed because of its easy decomposition into 2-methylimidazohne (**5**) even upon moderate heating.



Based on this information, we obtained simple mono-alkylidene(arylidene) derivatives of ethylenediarnine **2** and **6a-h** (Tables 1 and 2) in excellent yields (nearly 100%). This method was unsuitable for the synthesis of the corresponding products of condensation with branched ketones (pinacoline, acetophenone). These last two ketones require acid catalysis and heating resulting in the formation of the *bis*-derivatives, although the presence of mono-adducts (30-40%) in the reaction mixtures was observed by ^{1}H NMR spectroscopy. The *bis*-derivative **3d** with acetophenone was isolated. Compounds **2** and **6a-h** are liquids (with the exception of solid **6a**, mp. 48°, lit.[10] mp. 46-49°). No changes were observed after one week in the cold.

The structure of compounds **2** in solution was investigated by means of NMR spectroscopy (Tables 1 and 2). The signal of H-C=N at δ 7.79-8.27 for aldehyde derivatives or the signal of the methyl group at δ 1.65-1.90 in the ^{1}H NMR spectra for methylketones and the signal of sp^2 carbon

atom at δ 164.0-174.0 in the ^{13}C NMR spectra correspond to the linear tautomer **2**. The peak of the C-2 carbon atom (δ 71.1-80.3) in ^{13}C NMR spectra and the signal of H-2 (δ 3.74-4.16) for aldehyde derivatives or the signal of methyl groups (δ 0.95-1.21) in ^{1}H NMR spectra for methylketones belong to the cyclic form **6**.

Although the ring-chain tautomerism of 1,3-O,N-[11-13] and 1,3-S,N-heterocycles[11,12] as well as of alkylidene derivatives of C- and N-substituted ethylenediamines has been fairly well studied, less is known about the ring-chain equilibrium of compounds **2**. Tautomerism was suggested for (1-pentametyleneamino)-2-aminoethane but later it was established that this compound and some its homologs exist in the imidazolidine form **6**.[8]

TABLE 1. ^{1}H NMR of Products of Reaction of Ethylenediamine with Aldehydes and Ketones

Compd,%	R	R'	CH_2N	NH
6a, 100	4.16(q)	1.38(d)	3.10[a]	1.72(s)
6b, 100	3.98(t)	1.82(q), 1.29(t)	3.20[a]	2.06(s)
6c, 100	3.90(t)	1.74(m), 1.23(t)	3.15[a]	2.63(s)
2d, 5	7.79(d)	1.60-2.08(m), 1.17(d)	3.68(t), 3.26(t)	3.73(s)
6d, 95	3.74(d)	1.60-2.08(m), 1.05(d)	3.14a	2.29(s)
2e, 100	8.27(s)	7.08-7.36(m)	3.67(t), 3.03(t)	3.99(s)
2f, 30	1.90(s)	1.84(s)	3.06(t), 2.83(t)	3.43(s)
6f, 70	1.21(s)	1.21(s)	2.94(s)	1.72(s)
	2.09(q), 0.82(t)	1.65(s) - E-form		
2g, 35	2.07(q), 0.80(t)	1.68(s) - Z-form	3.20(t), 2.94(t)	3.46(s)
6g, 65	1 55(q),[b] 0.96(t)	1.20(s)	2.90(s)	2.40(s)
	2.18(t), 0.96(t)	1.80(s) - E-form		
2h, 40	2.15(t), 0.94(t)	1.82(s) - Z-form	3.38(t), 2.89(t)	3.47(s)
6h, 60	0.92(t)[c]	1.21(s)	2.94(s)	2.40(s)

a) A_2B_2-system. b) CH_2 of ethyl group is AB-part of ABX_3-system at 1.14-1.42 ppm in DMSO-d_6.
c) Other CH_2 signals located at 1.47-1.86 ppm.

We found that the products (**6a-c**) of condensation of diamine **1** with *n*-alkanals do not contain detectable amounts of the linear form (**2**), but branching of alkyl substituent R' (in **6d**) increases the portion of the linear form **2d** up to 5%. The introduction of a phenyl group increased the amount of the open-chain tautomer **2e** to such an extent that the cyclic form was undetectable. The ketone derivatives of ethylenediamine exhibit the ring-chain tautomerism resulting in comparable amounts of both tautomers. Equilibration occurs immediately after solution. The contents of isomer **6** decreases with increasing size on the position of a substituent R'. The nature of the solvent and the temperature have practically no influence on position of the equilibrium **2-6**. The tautomers **2g** and **2h** are a mixtures of E,Z-isomers relative to the C=N bond, causing the doubling of all signals of this form in ^{1}H NMR and ^{13}C NMR spectra.

It is known that 1-alkilydene(arylidene)amino-3-diaminopropanes exist in the cyclic hexahydropyrimidine form.[16,17] The latter tendency for ethylenediamine derivatives to form the cyclic tautomer in comparison with compounds derived from 1,3-diaminopropane is in accordance with the Baldwin rules since the 1,3-diazolidine formation represents an unfavored 5-*endo-trig*-process.[18]

Compounds **2** are prospective synthons, in particular as new ligands N-isopropylethylenediamine was prepared by reduction of compound 2f.[6,25] This synthesis appears to be a simpler method for preparing these compounds than alkylating procedures employing alkyl halides. The 1,3-anionic cycloreversion of N-lithioimidazolidines is known to be a new route to 2-azaallyl anions[25] and its cycloaddition to give a convenient method for the synthesis of pyrrolidines.[26]

TABLE 2. ^{13}C NMR of Products of Reaction of Ethylenedimine with Aldehydes and Ketones

Compd	C=N, $C^{(2)}$	$C^{(4)}$-$C^{(5)}$	Other signals
6a	71.1	45.8	19.8
6b	74.7	43.5	8.1, 25.8
6c	74.1	44.6	12.7, 18.4, 36.3
2d, 6d	164.0, 80.3	45.4	18.4, 32.5, 33.0, 41.5, 60.0
2e	160.8	-	60.5, 63.5, 127.0, 127.5, 129.5, 135.1
2f, 6f	165.5, 74.6	44.6	16.6, 25.7, 27.2, 50.7, 52.5
2g, 6g	170.6 (E-form), 169.0 (Z-form), 77.9	45.1	8.2, 9.6, 11.2, 23.8, 32.2, 34.3, 41.7, 43.1, 51.2, 52.9
2h, 6h	174.0 (E-form), 169.0 (Z-form), 76.6	44.5	12.1, 12.8, 14.8, 15.6, 16.5, 17.3, 18.0, 23.4, 39.2, 41.6, 43.1, 43.8, 46.1, 47.0, 49.9, 53.1

The pharmacology of different 1,3-diazolidines is of current interest. Some diazolidines show endocrine stimulatory activity[19], while others display antitrypanosomal effects,[20] antiviral and tuberculostatic action. The data on the ring-chain equilibrium's of simple alkylidene derivatives of ethylenediamine are useful for the understanding of transformations of the co-factor N^5,N^{10}-methylenetetrahydrofolic acid containing a 1,3-diazolidine ring that undergoes ring-chain tautomerism.

EXPERIMENTAL SECTION

The ^1H NMR (100 MHz) and ^{13}C NMR (20.41 MHz) spectra were recorded with Tesla-BS497 spectrometer using HMDS as internal standard, solvent $CDCl_3$. The elemental analysis data (C, H, N) of the new compounds are in agreement with calculated values within 0.2%.

Compounds 2 and 6. General Procedure.- A solution of the carbonyl compound (0.1 mole) in 50 mL $CHCl_3$ was added slowly to the anhydrous diamine (60 g, 1 mole) at 0°. After one day, chloroform was removed under vacuum at room temperature and the residue was extracted with three portions hexane or pentane (150, 150 and 100 mL). The combined extract was dried for 24 hours over anhydrous Na_2SO_4 (compound **2e**) or over K_2CO_3 (other compounds) and the solvent removed under vacuum at room temperature. Compound **6a**, yield 83%, **6b**, yield 87%, **6c**, yield 86%, **2** and **6d**, yield

85%, **2e**, yield 75%, **2** and **6f**, yield 90%, **2** and **6g**, yield 93%, **2** and **6h**, yield 98%.

Compounds 3a-c.- Anhydrous 1,2-diaminoethane (30 g, 0.5 mole) was added under cooling to 1 mole of an appropriate aldehyde. The reaction mixture was kept at room temperature overnight. Then the reaction mixture was extracted with three portions hexane or pentane (150, 150 and 100 mL). The combined extract was dried over anhydrous Na_2SO_4 for one day. The white crystals formed after removal of the solvent under vacuum were recrystallized from methanol.

1,2-*bis*(Benzylydeneamino)ethane (3a), mp. 52°, lit.[3] mp. 53-54°; ^{1}H NMR spectra ($CDCl_3$, δ): *8.25* (s, CH=N); 7.33-7.73 (m, Ar); 3.92 (s, CH_2).

1,2-*bis*(*p*-Methoxybenzylydeneamino)ethane (3b), mp. 110°, lit.[3] mp. 112-114°.^{1}H NMR spectra ($CDCl_3$, δ): 8.12 (s, CH=N); 6.76-7.70 (m, Ar); 4.02 (s, CH_2); 3.69 (s, CH_3).

1,2-*bis*(p-Bromobenzylydeneamino)ethane (3c), mp. 157°, lit.[4] mp. 157-158°.^{1}H NMR spectra ($CDCl_3$, δ): 8.17 (s, CH=N); 7.46-7.68 (m, Ar); 4.02 (s, CH_2).

1,2-*bis*(1-Phenylethylydeneamino)ethane (3d).- 1,2-diaminoethane (30 g, 0.5 mole) and acetophenone (6,0 g, 0.05 mole) were heated at reflux in 100 mL of benzene, using a Dean-Stark flask to remove the water formed. The reaction mixture was extracted with three portions of hexane (150, 150 and 100 mL). The combined extract was dried over Na_2SO_4. The white crystals formed after removal of the solvent under vacuum were recrystallized twice from hexane. Yield 81%, mp. 110°, lit.[2] mp. 112.5°.^{1}H NMR spectra ($CDCl_3$, δ): 7.13-7.71 (m, Ar); 3.76 (s, CH_2); 2.05 (s, CH_3).

5,7,7-Trimethyl-2,3,6,7-tetrahydro-1H-1,4-diazepine (4).- 1,2-Diaminoethane (3 g, 0.05 mole) and acetone (29 g, 0.5 mole) were boiled during two hours. The oily substance which was formed after removal of acetone in vacuum was distilled to give 5.2 g (71%) of a red liquid, bp. 59-61° (2 mm), lit.[22] bp. 60-61° (3 mm). ^{1}H NMR spectra ($CDCl_3$, δ): 3.31 (t, CH_2N=); 2.52 (t, CH_2N); 2.26 (s, CH_2); 2.08 (s, NH); 2.05 (s, CH_3); 0.85 (s, $2CH_3$).

2-Methylimidazoline (5). The white crystals of compound **5** formed during the attempt to distill compounds **2** and **6f-g**, were recrystallized from a $CHCl_3$-dioxane mixture, (2:5). Yield of product 50%, mp. 105°, lit.[24] mp. 103-105°. ^{1}H NMR spectra ($CDCl_3$, δ): 6.48 (s, NH); 3.52 (s, $2CH_2$); 1.93 (s, CH_3).[24]

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