REACTIONS OF N-(β-AMINOETHYL)PIPERAZINE AND ITS DERIVATIVES

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The alkylation, cyanoethylation, and heterocyclization reactoins of N-(β-amonoethyl)piperazine and its derivatives, dicarboxylic acid imides, have been investigated. A new method has been proposed for the synthesis of 1,4-diazobicyclo[2.2.2]octane via pyrolytic cleavage of N,N'-bis[piperazinoethyl]ethylenediamine.

One of the side products in the industrial preparation of ethylenediamine via ammonolysis of dichloroethane is N-(β-aminoethyl)piperazine (I). The available resources of this compound are quite large, which makes it important or advisable to search for new pathways for its rational application [1,2].

We have studied the alkylation, cyanoethylation, and heterocyclization reactions of compounds Ia, IIa, IIa-d, and VIIIa. Compound IIa was prepared by condensation of compound Ia with acetonylacetone, while imides IIIa-d were obtained from compound Ia and the corresponding anhydrides.

There are no reports in the literature concerning the alkylation of compound Ia, with the exception of the introduction of a decyl substituent [3]. We have found that alkylation of compound Ia takes place first at the primary amino group. Thus reaction of equivalent amounts of compound Ia and allyl chloride gave N-(β-allylaminoethyl)piperazine (Ib), whose structure was confirmed both based on its IR spectral data as well as by the lack of reaction between compound Ib and acetonylacetone.

Reaction of compound Ia with methallyl chloride in a 1:2 ratio led to the formation of N-methallyl-N'-(β-methallylaminoethyl)piperazine (Ic). Reaction of Ia with chloroacetic acid occurs readily and smoothly in refluxing toluene. Depending on the reagent ratio, either di- or tricarboxylic acids Id, e are obtained. Chloroacetic acid also readily alkylates pyrrole IIa and imides IIIa-d, giving compounds IIb and IVa-d. Triamines VIa-d were obtained via reduction of the imidopiperazine derivatives IIIa-d with $LiAlH_4$. Condensation of pyrrolo- and imidopiperazino acids

TABLE 1. Physical Characteristics of Compounds I-X

Compound	Empirical formula	mp, °C*	Yield, %	Compound	Empirical formula	mp, °C*	Yield, %
Ib	$C_9H_{19}N_3$	165...170 (20)	75	VIa	$C_{14}H_{21}N_3\times\times3(COOH)_2$	212...213	72
Ic	$C_{14}H_{27}N_3$	177...178	61				
Id	$C_{10}H_{19}N_3O_4$	118...119	88	VIb	$C_{14}H_{25}N_3$	209...210	74
Ie	$C_{12}H_{21}N_3O_6$	217...218	95	VIc	$C_{17}H_{27}N_3$	230...235 (5)	66
If	$C_9H_{18}N_4$	178...180 (5)	95	VId	$C_{15}H_{25}N_3\times\times3(COOH)_2$	222...223	69
Ig	$C_{15}H_{24}N_6$	104...105	99				
IIb	$C_{14}H_{23}N_3O_2$	150...151	88	VIIa	$C_{17}H_{20}N_4O_2$	116...117	98
IIc	$C_{20}H_{27}N_5$	152...154	66	VIIb	$C_{17}H_{24}N_4O_2$	163...164	94
IId	$C_{15}H_{24}N_4$	68...69	98	VIIc	$C_{18}H_{26}N_4O_2\times\times2HCl$	162...163	94
IIIa	$C_{14}H_{17}N_3O_2$	161...162	93				
IIIb	$C_{14}H_{21}N_3O_2$	80...81	95	VIId	$C_{18}H_{26}N_4O_2\times\times2HCl$	197...199	88
IIIc	$C_{15}H_{23}N_3O_2\times\times2HCl$	174...176	92				
				VIIIa	$C_{14}H_{32}N_6$	76	
IIId	$C_{15}H_{23}N_3O_2\times\times2HCl$	157...158	90	VIIIc	$C_{26}H_{44}N_{10}\times\times6HCl$	218...219	95
IVa	$C_{16}H_{19}N_3O_4$	124...125	91	IXa	$C_{15}H_{30}N_6O$	178...180	94
IVb	$C_{16}H_{23}N_3O_4$	79...80	87	IXb	$C_{15}H_{30}N_6S$	138...140	88
IVc	$C_{17}H_{25}N_3O_4$	108...110	93	IXc	$C_{21}H_{36}N_8OS\times\times4(CO_2H)$	216...218	92
IVd	$C_{17}H_{25}N_3O_4$	134...135	94				
Va	$C_{22}H_{23}N_5O_2$	305...310	52	IXd	$C_{21}H_{36}N_8S\times\times4(COOH)_2$	210...212	84
Vb	$C_{22}H_{27}N_5O_2$	146...147	61,6				
Vc	$C_{23}H_{29}N_5O_2$	232...233	72,8	Xa	$C_{21}H_{36}N_6$	248...252 (12)	78
Vd	$C_{23}H_{29}N_5O_2$	177...178	61	Xb	$C_{27}H_{42}N_8$	280...282 (10)	96

*The boiling points (p, mm Hg) are given for compounds Ib, f, VIc, and Xa, b.

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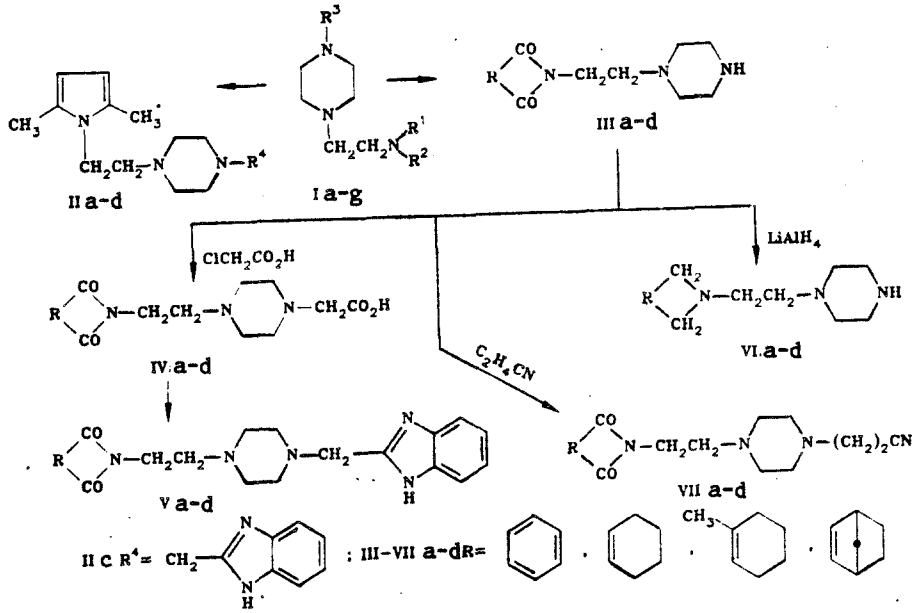
IIb, IVa-d with o-phenylenediamine led to the formation of benzimidazole derivatives IIc, Va-d in yields of 52-73% (Table 1).

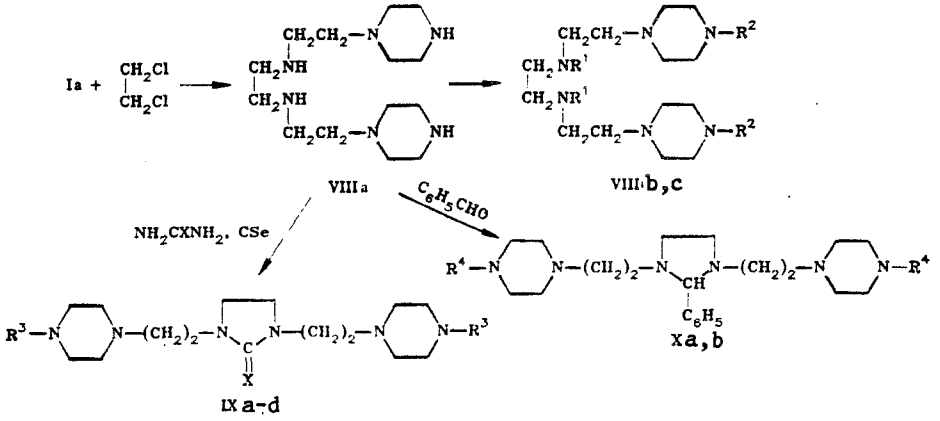
The UV spectra of compounds IIc and Va-d contain absorption bands with maxima at 243, 276, and 274 nm, which are characteristic of benzimidazole derivatives [4].

In contrast to alkylation, cyanoethylation of compound Ia takes place first at the nitrogen atom in the piperazine ring, leading to the formation of N-cyanoethyl-N'-(β-aminoethyl)piperazine (If). The latter undergoes facile condensation with acetonylacetone to give N-cyanoethyl-N-(β-piperazinoethyl)-2,5-dimethylpyrrole (IId), which can also be prepared in quantitative yield by cyanoethylation of compound IIa. Only one compound, namely N-cyanoethyl-N'-(β-dicyanoethylaminoethyl)piperazine (Ig), is obtained upon exhaustive cyanoethylation of compound Ia. Cyanoethylation of imides IIIa-d also proceeds readily; the latter are converted to their cyanoethyl derivatives VIIa-d.



I a $R^1=R^2=R^3=H$; b $R^1=CH_2CH=CH_2$, $R^2=R^3=H$; c $R^1=R^3=CH_2(CH_3)C=CH_2$, $R^2=H$; d $R^1=R^3=CH_2CO_2H$, $R^2=H$; e $R^1=R^2=R^3=CH_2CO_2H$; f $R^1=R^2=H$, $R^3=(CH_2)_2CN$; g $R^1=R^2=R^3=(CH_2)_2CN$; II a $R^4=H$, b $R^4=CH_2CO_2H$; d $R^4=(CH_2)_2CN$

We have also succeeded in preparing a new type of piperazine derivatives from N,N'-bis(piperazinoethyl)ethylenediamine (VIIIa), which was itself easily generated via reaction of compound Ia with dichloroethane in a 1:2 ratio. The structure of compound VIIIa was established based on its PMR spectral data as well as on its chemical reactivity. Condensation of compound VIIIa with urea gave N,N-bis(β-piperazinoethyl)imidazolidin-2-one (IXa). The corresponding imidazolidine-2-thione IXb could be prepared by reaction of either thiourea or carbon disulfide with compound VIIIa.



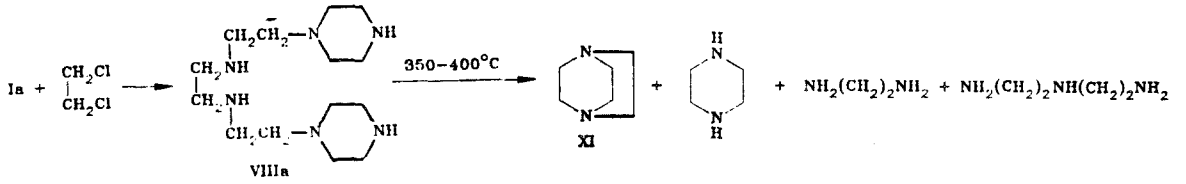
VIII b $R^1=H$, $R^2=C_2H_4CN$; c $R^1=R^2=C_2H_4CN$; IX a $R^3=H$, X=O; b $R^3=H$, X=S; c $R^3=R_2H_4CN$, X=O; d $R^3=C_2H_4CN$, X=S; X a $R^4=H$; b $R^4=C_2H_4CN$

Cyanoethylation of compound VIIIa with 2 moles of acrylonitrile takes place first at the nitrogen atom in the piperazine ring. This results in the formation of compound VIIIb, which can be condensed further, without prior isolation, with urea, thiourea, and carbon disulfide to generate the corresponding imidazolidin-2-one IXc and imidazolidine-2-thione IXd derivatives. Compounds IXc, d are also readily available from reaction of acrylonitrile with compounds IXa, b. Exhaustive cyanoethylation of compound VIIIa led to the formation of the tetracyanoethylated derivative VIIIc.

Compound VIIIa also reacts readily with benzaldehyde to give imidazolidine Xa which, in turn, easily adds to acrylontrile to form the dicyanoethyl derivative Xb.

The IR spectra of compounds If, g, VIIa-d, VIIIc, IXc, d, and Xb all contain absorption ands at 2230 cm^{-1} characteristic of the presence of the nitrile functional group (see bottom of page 310).

An interesting transformaton takes place with compound VIIIa upon pyrolysis. Distillation of compound VIIIa under a weak vacuum at 350-400°C led to the formation of a mixture containing 30% 1,4-diazabicyclo[2.2.2]octane (XI). The other components of the mixture were piperazine, ethylenediamine, and deithylenetriamine. Diazabicyclooctane XI is generally prepared in low yield by catalytic deamination of compound Ia [5, 6].



EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer using a thin film of the sample or nujol mull suspensions; PMR spectra were obtained on a Tesla BS-487B (80 MHz) spectrometer using solutions in CCl_4 versus HMDS as internal standard.

Chromatography was performed on an LKhM-7A chromatograph equipped with a catharometer detector at 175°C; the helium carrier gas flow rate was 3.5 liter/h, the column length 5 m, which was filled with 4-Fluoroplast (coated) with E-301 silicone elastomer as the stationary phase.

The results of C, H, and N elemental analysis for compounds I-X agreed with calculations.

N-(β-Aminoethyl)piperazine (Ia). Isolated by rectificaton (fractional distillation) of the mixture of polyethylene-polyamines obtained as side products in the manufacture of ethylenediamine. bp 216-218°C, n_D^{20} 1.4998, d_{20}^4 0.9842 g/cm^3. The product purity or composition according to GLC analysis is 99.3%.

N-[(β-2,5-Dimethyl-1-pyrrolyl)ethyl]piperazine (IIa, $C_{12}H_{21}N_3$). Compound Ia (12.9 g, 0.1 mole) and acetonylacetone (11.4 g, 0.1 mole) were heated for 5 min at 150°C; the mixture was then distilled under vacuum. Yield 19.3 g (93%) of compound IIa, bp 178-180°C (17 mm Hg), mp 42=43°C, n_D^{20} 1.5298. IR spectrum: 750 cm^{-1} (pyrrole).

N-(β-Piperazinoethyl)imides IIIa-d. A mixture of equimolar amounts of compound Ia and the appropriate anhydride was heated for 3 h at 180-200°C; the imides were crystallized from alcohol using a mixture of acetone—petroleum ether, 1:1. IR spectrum: 1720, 1780 cm^{-1} (imide).

N-(β-Allylaminoethyl)piperazine (Ib). A mixture of 12.9 g (0.1 mole) compound Ia and 7.6 g (0.1 mole) allyl chloride in 50 ml methanol was refluxed for 2 h, 5.6 g (0.1 mole) KOH was added, and the resulting potassium chloride precipitate was removed by filtration. After solvent evaporation the product compound Ib was distilled under vacuum. n_D^{20} 1.4930. IR spectrum: 1570 cm^{-1} (NH).

N-Methallyl-N'-(β-methallylaminoethyl)piperazine (Ic). This was prepared in an analogous manner from Ia and methallyl chloride in a 1:2 mole ratio. n_D^{20} 1.4830. IR spectrum: 1570 cm^{-1} (COOH).

N-Methoxycarbonyl-N'(β-methoxycarbonylaminoethyl)piperzine (Id). A solution of 12.9 g (0.1 mole) compound Ia and 18.9 g (0.2 mole) chloroacetic acid in 200 ml toluene was refluxed for 4 h. The resulting hydrochloride product was separated by filtration and treated with 11.2 g (0.2 moles) of alcoholic KOH. The potassium chloride precipitate was removed by filtration and the alcohol solution was evaporated todryness; the dicarboxylic acid product Id was purified by reprecipitation from acetone solution with hexane. IR spectrum: 1550 cm^{-1} (COOH).

N-Methoxycarbonyl-N'-(β-dimethoxycarbonylaminoethyl)piperazine (Ie). Prepared in an analogous manner from 12.9 g (0.1 mole) compound Ia and 28.4 g (0.3 moles) chloroacetic acid; purified by crystallization from acetone.

Alkylation of Bases IIa, IIIa-d with Chloroacetic Acid. A solution of 0.1 mole base IIIa-d and the appropriate amount of chloroacetic acid in 50 ml toluene was refluxed for 5 h. The resulting hydrochloride product was separated by filtration and treated with an equimolar amount of alcoholic KOH solution. Potassium chloride was removed by filtraton and the acids were purified by crystallization from a 2:1 mixture of acetone—hexane.

Reduction of N-(β-piperazinoethyl)phthalimides IIIa-d. To a suspension of 1.9 g (0.05 moles) $LiAlH_4$ in 50 ml absolute dioxane was added a solution of 0.01 mole of the corresponding imide in 40 ml dioxane, and the mixture was refluxed for 3 h. The reaction mixture was cooled and excess lithium aluminum hydride was destroyed by reaction with water; the resulting precipitate was removed by filtration. The dioxane solvent was distilled off, and the reaction products VIa-d were isolated by vacuum distillation.

Condensaton of Acids IIb, IVa-d with o-Phenylenediamine. A mixture of equimolar amounts of pyrrolo acid IIb, imidopiperazino acids IVa-d, and o-phenylenediamine was heated for 4-6 h at 170-190°C. The reaction products, N-benzimidazolylmethyl-N'-[β-2,5-dimethyl-1-pyrrolyl)ethyl]piperazine (IIc) and N-benzimidazolylmethyl-N'-[(β-piperazinoethyl)imides] Va-d, were purified by crystallization from a 2:1 mixture of acetone—hexane.

Cyanoethylation of Compound Ia. A solution of 12.9 g (0.1 mole) compound Ia and 5.3 g (0.1 mole) acrylonitrile in 50 ml benzene was refluxed for 6 h; compound If was then isolated either by distillation or crystallization, for its free base and salt, respectively.

Compounds **IIa, IIIa-d, VIIIa, IXa, b, and Xa** can be cyanoethylated in an analogous manner.

N,N'-Bis[piperazinoethyl]ethylenediamine (VIIIa). A solution of 25.8 g (0.2 mole) Ia and 9.9 g (0.1 mole) dichloroethane in 100 ml dry methanol was refluxed for 8 h; KOH (11.2 g, 0.2 moles) was then added wth stirring, and the resulting potassium chloride precipitate was removed by filtration, the methanol solvent evaporated, and the product distilled under vacuum. Yield 27.2 g (96%) of compound VIIIa, bp 258-260°C (10 mm Hg). IR spectrum: 1570 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 205 nm (4, 130). PMR spectrum: 1.72 (4-NH), 2.47 (10-CH_2) of these 8-CH_2 in the piperazine rings, 2.74 ppm (4-CH_2, m, ethylenediamine fragment). PMR spectrum (CF_3COOH): 3.45 ppm (2-CH_2, weakly split m, ethylenediamine protons).

N,N'-Bis[β-piperazinoethyl]imidazolidin-2-one (IXa). A mixture of 28.4 g (0.1 mole) compound VIIIa and 6 g (0.1 mole) urea in 50 ml ethanol was heated at 45-100°C until NH_3 evolution had ceased (~8 h); the alcohol solvent and NH_3 were distilled or evaporated off in sequence, and the reaction mixture was then heated an additional 40 min at 240°C. Compound IXa was crystallized from acetone. IR spectrum: 1640 cm^{-1} (CO).

N,N'-Bis[β-piperazinoethyl]imidazolidine-2-thione (IXb). A. A mixture of 28.4 g (0.1 mole) compound VIIIa and 7.6 g (0.1 mole) thiourea in 50 ml butanol was refluxed for 3 h. Compound IXb was crystallized from acetone.

B. A solution of 28.4 g (0.1 mole) compound VIIIa and 7.6 g (0.1 mole) carbon disulfide in 50 ml absolute ethanol was refluxed for 2 h. Compound IXb was purified by crystallization from acetone.

C. In an analogous manner from VIIIb and urea, thiourea, or CS_2 imidazolidinone IXc and imidazolidinethione IXd were obtained.

N,N'-Bis[β-piperazinoethyl]-2-phenylimidazolidine (Xa). A mixture of 2.84 g (0.01 mole) compound VIIIa and 1.1 g (0.01 mole) benzaldehyde was heated for 6 h at 150-170°C; the product was isolated by vacuum distillation. PMR spectrum: 1.85 (2-CH_2, imidazolidine protons); 2.12 (2H, s, NH); 2.33 (8-CH_2, attached to >N—); 2.66 (4-CH_2, attached to 2>NH); 3.20 (1H, s, >N—CH—N<); 7.12 ppm (5H, m, arom. protons).

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