PECULIARITIES OF THE REACTION OF N,N'-SUBSTITUTED DIPHTHALIMIDES WITH AMINES

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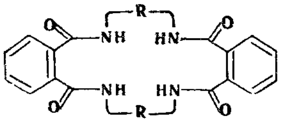
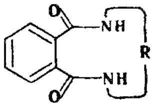
Macrocyclic phthalic acid diamides were obtained by the reaction of N,N'-substituted diphthalimides with polyoxyethylenediamines, while the corresponding tetraamides were obtained with primary aliphatic amines. It is shown that the reaction is a thermodynamically controlled process.

Interest in macrocyclic compounds and their acyclic analogs that contain other functional groups in addition to ether groups has grown in recent years [1, 2]. In order to obtain and study macrocyclic amides of phthalic acid we examined the reaction of N,N'-substituted diphthalimides with various amines.

It is known that the phthalimide ring of N-alkylphthalimides opens up under the influence of amines to give the corresponding phthalic acid amides [3, 4]. The formation of rings of the I or II type is possible when diamines and N,N'-substituted diphthalimides are used:

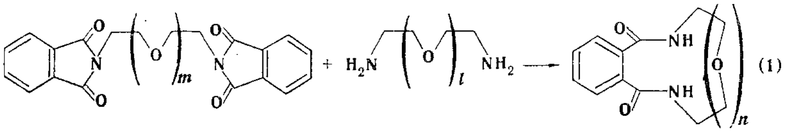


I



II

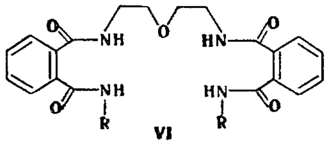
We have observed [5] that macrocyclic phthalic acid diamides Va-d are obtained in the reaction of diphthalimides III, which contain a polyoxyethylene fragment, with diamines IV (m = 1):



III IV Va-d

V a n=1; b n=2; c n=3; d n=4

To ascertain the peculiarities of the reaction under consideration we treated diphthalimides III with various amines. Primary aliphatic amines with an amino group attached to a primary carbon atom have different effects on different diphthalimides. Thus a number of compounds with structures VIa-e were obtained when 3-oxapentane-1,5-diphthalimide (III, m = 1) was treated with primary aliphatic amines.



VI

VI a $R=C_4H_9$; b $R=C_8H_{17}$; c $R=C_9H_{19}$; d $R=C_{12}H_{25}$; e $R=C_{16}H_{33}$

Treatment of 3,6-dioxaoctane-1,8-diphthalimide (III, m = 2) with butyl- and octylamine leads to the formation of only phthalic acid N,N'-dibutyl- and N,N'-dioctylamides.

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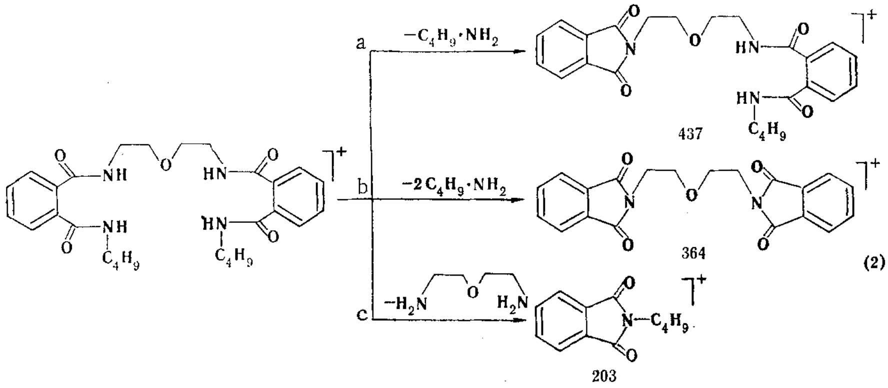
The behavior of VI under electron impact and their thermal fragmentation are in agreement and, together with other data, confirm their structure. Thus the mass spectrum of VIa contains intense peaks of ions with m/z 437, 364, and 203, which correspond to the elimination of butylamine, 3-oxapentane-1,5-diamine, and two molecules of butylamine.



(2)

The mass spectra of VIb and VId are similar to the mass spectrum of VIa.

Thermolysis of VIa at 250°C leads to the formation of butylamine and 3-oxapentane-1,5-diphthalimide [i.e., only a pathway corresponding to reaction (2b)], while thermolysis of VIe leads to 3-oxapentane-1,5-diamine and cetylphthalimide [reaction (2c)], and VIb gives 3-oxapentane-1,5-diphthalimide and octylphthalimide, as well as a difficult-to-separate mixture of 3-oxapentane-1,5-diamine and octylamine. Thus thermolysis and ionization lead to similar fragmentation of VI; however, in the case of thermolysis a lower-boiling amine is primarily split out, despite the differences in the basicities.

Secondary (diethyl- and dibutyl-) and tertiary (triethyl- and tributyl-) amines, as well as primary amines with an amino group attached to a tertiary carbon atom (tert-butyl- and tert-pentylamine), do not react with III (m = 1 and 2), which can be explained by steric hindrance.

Attempts to obtain compounds that contain a polymethylene fragment (dimethylene and hexamethylene) instead of a polyoxyethylene fragment under the conditions of reaction (1) do not lead to cyclic products, in agreement with the data in [4]. These differences in the ability to undergo cyclization are probably explained by the presence of ether bonds in III-V. The fact that Va-d could not be obtained when water was absent constitutes evidence in favor of this assumption. It is known that substances that contain oxyethylated links react with water to form oxinium complexes, which change the geometry of the polyoxyethylene chain, converting the rectified "zigzag" form to the twisted "sinuous" form [6]. Thus the role of water in the reaction under consideration evidently consists in the creation of favorable conformational conditions for cyclization.

To ascertain the role of diamines in the reaction under discussion we examined the reaction of diphthalimides III with various diamines IV. We established that treatment of 3-oxapentane-1,5-diphthalimide (III, m = 1) with 3,6-dioxaoctane-1,8-diamine (IV, $l = 2$), 3,6-dioxaoctane-1,8-diphthalimide (III, m = 2) with 3-oxapentane-1,5-diamine (IV, $l = 1$), and 3,6,9-trioxaundecane-1,11-diphthalimide (III, m = 3) with 3,6-dioxaoctane-1,8-diamine (IV, $l = 2$) gives the same cyclic diamide Vb. It is apparent from these transformations that diamines IV act both as bases, which cleave phthalimide ring III, and as structural elements in the formation of macrocycles V. In addition, the enumerated transformations constitute evidence that the reaction evidently is a thermodynamically controlled process. To confirm this assumption we treated macrocycles Va and Vc with 3,6-dioxaoctane-1,8-diamine (IV, $l = 2$) under the conditions of reaction (1). Transamidation occurred in both cases, and diamide Vb was obtained.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Perkin-Elmer 580 B spectrometer. The PMR spectra were recorded with a Tesla BS-467 spectrometer with tetramethylsilane as the external standard. The mass spectra were obtained with an LKB-9000 spectrometer at an ionizing voltage of 70 eV with direct introduction of the samples into the source; the sample vaporization temperature was 40-100°C, and the ionization-chamber tempera-

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	R_f	IR spectrum, ν, cm^{-1}			N found, %	Empirical formula	N calc. %	M^+	Yield, %
			NH	CO	COC					
IIId	94—95	0.55*	—	1770 1710	1115	4,5	$C_{26}H_{28}N_2O_8$	4,5		73
Va	215—216	0.42†	3310	1635	1135	12,1	$C_{12}H_{14}N_2O_3$	12,0	234	10
Vb	189—190	0.32†	3290	1660	1115	10,9	$C_{14}H_{18}N_2O_4$	10,9	278	38
Vc	166—167	0.26†	3280	1635	1135	8,8	$C_{16}H_{22}N_2O_5$	8,7	322	7
Vd	129—130	0.22†	3295	1640	1110	7,0	$C_{18}H_{26}N_2O_6$	7,0	366	9
VIa	105—106	0.1*	3250	1660	1125	11,0	$C_{28}H_{38}N_4O_5$	11,0	510	31
VIb	133—134	0.29*	3240	1660	1125	9,0	$C_{36}H_{54}N_4O_5$	9,0	622	44
VIc	134—135	0.3*	3250	1660	1125	8,6	$C_{38}H_{58}N_4O_5$	8,6		42
VId	124—125	0.35*	3250	1660	1125	7,6	$C_{44}H_{70}N_4O_5$	7,6		49
VIe	109—110	0.71*	3250	1660	1125	6,6	$C_{52}H_{86}N_4O_5$	6,6		37

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*Acetone—hexane (1:1).

†Acetone.

ture was 220°C. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in an acetone—hexane system (1:0-1:5) with development in UV light and with ninhydrin. N,N'-Substituted diphthalimides III were obtained by the method in [7]. The characteristics of IIId are presented in Table 1.

Polyoxyethylenediamines IV. Compounds IVa and IVb were obtained by treatment of 0.2 mole of imide IIIa or IIIb with a eutectic [8] mixture of 0.4 mole of sodium hydroxide and 0.4 mole of potassium hydroxide prepared in the form of a 70% aqueous solution with subsequent removal of the aqueous amine from the reaction mixture by distillation at up to 260°C. The amine was dried with sodium hydroxide and distilled under reduced pressure. Amine IVa was obtained in 77% yield, while IVb was obtained in 72% yield. The constants were in agreement with the data in [7]. Compounds IVc and IVd were obtained by the method in [7]. Compound IVd had bp 167-168°C (3 mm) and n_D^{20} 1.4636.

Macrocyclic Phthalic Acid Diamides V (Table 1). These compounds were obtained by the method in [5]. The compounds obtained by the various methods were identified from mixed-melting-point determinations, their chromatographic behavior, and a comparison of the PMR and IR spectra of the described substances with the spectra of the substances obtained by the method in [5]. In the PMR spectra (CF_3COOH and $CDCl_3$) the chemical shifts of the phenyl protons are found at 7.53-7.57 and 7.83 ppm, the chemical shifts of the protons attached to the amide nitrogen atom are found at 8.27-8.53 and 7.46-7.67 ppm, and the chemical shifts of the methylene protons are found at 3.8 and 3.87-3.93 ppm, respectively.

Tetraamides VI (Table 1). A mixture of 0.01 mole of 3-oxapentane-1,5-diphthalimide (III, m = 1), 10 ml of water, 250 ml of methanol, and 0.02 mole of the corresponding amine, which was obtained by the method in [9], was heated at 40-50°C until the imide dissolved completely. The methanol was removed by distillation under reduced pressure, and the residue was crystallized from acetone. Phthalic acid N,N'-dibutylamide (60%), with mp 103-104°C, and phthalic acid N,N'-dioctylamide (64%), with mp 128-129°C (in agreement with the melting points in [10]), were obtained when imide III (m = 2) was used. In the PMR spectra (CF_3COOH) of VI the chemical shift of the protons of the phenyl group is 7.57 ppm, the chemical shift of the protons of the NH groups is 8.13 ppm, the chemical shift of the bridge protons is 3.76 ppm, and the chemical shifts of the CH_3, CH_2CH_2, and CH_2N substituents are, respectively, 0.73, 1.17, and 3.43 ppm. The integral intensities of the groups of protons correspond to the formulas presented above with an accuracy of 4%.

Thermolysis of Tetraamides VI. A 0.01-mole sample of tetraamide VI was heated on a metal bath to 250°C, during which the amine that was distilled from the mixture was collected. The residue was crystallized. In the case of tetraamide VIa we obtained butylamine (in 75% yield; the hydrochloride had mp 214-215°C, in agreement with the data in [9]) and 3-oxapentane-1,5-diphthalimide [in 62% yield with mp 155-156°C (from acetic acid), in agreement with the data in [7]; the IR spectrum was identical to the IR spectrum of the genuine imide]. In the case of VIb we obtained a difficult-to-separate mixture of 3-oxapentane-1,5-diamine and octylamine. In the case of VIe we obtained 3-oxapentane-1,5-diamine [in 47% yield with bp 63-64°C (4 mm); the hydrochloride had mp 226-227°C [11]] and N-cetylphthalimide [in 34% yield with mp 74-75°C (from ethanol) [12]].

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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS.

8.* EFFECT OF C-SUBSTITUENTS ON THE N-METHYLATION OF 1,4-DIAZABICYCLO[2.2.2]OCTANES AND THE DEMETHYLATION OF THEIR BISQUATERNARY SALTS

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The introduction of substituents with various inductive constants in the 2 position of the diazabicyclo]2.2.2]octane ring gives rise to a change in the pK_a values and affects the ease of introduction of a methyl group in the 1 and 4 positions, as well as the rate of demethylation of the bisquaternary salts from the 1 position. When 1,4-diazabicyclo[2.2.2]octane is treated with a sufficiently strong nucleophile, the ring is opened to give a piperazine derivative.

The nucleophilicity of 1,4-diazabicyclo[2.2.2]octane (Ia) has been studied in the case of a large number of different reactions [2]. However, the literature does not contain data on the effect of C-substituents, other than alkyl groups, on the ability of this bicyclic heteroring to give quaternary salts. In addition, the previously described [3, 4] methods for the synthesis of C-substituted bicyclic system Ia lead only to bis(methylbromides), and it therefore becomes necessary to demethylate them. Taking this into account, we felt it was expedient to evaluate the effect of substituents on the N-methylation of C-substituted bicyclic system Ia and the ability of their bisquaternary salts to undergo demethylation.

Bases Ia-e react smoothly with an equimolar amount of methyl iodide in nonpolar solvents to give monoquaternary derivatives IIa-e. On the basis of the great difference in the basicities of the nitrogen atoms it can be assumed that the reaction takes place at the nitrogen atom in the 4 position. We were unable to detect an appreciable effect of the substituents on the course of the reaction (Table 1). An appreciable effect is displayed when a second N-methyl group is introduced. Bisquaternary salts IIIa-c are easily obtained, whereas an attempt to obtain a bisquaternary salt from base If by prolonged refluxing in methanol with excess methyl iodide leads only to IIf. Bisquaternary salt IIIe was obtained only after prolonged heating of ester Ie or the sodium salt of acid Ig with dimethyl sulfate. Bisquaternary

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*See [1] for communication 7.

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