ACYLATION OF AZA CROWN ETHERS WITH N-SUBSTITUTED ISOPHTHALIMIDES

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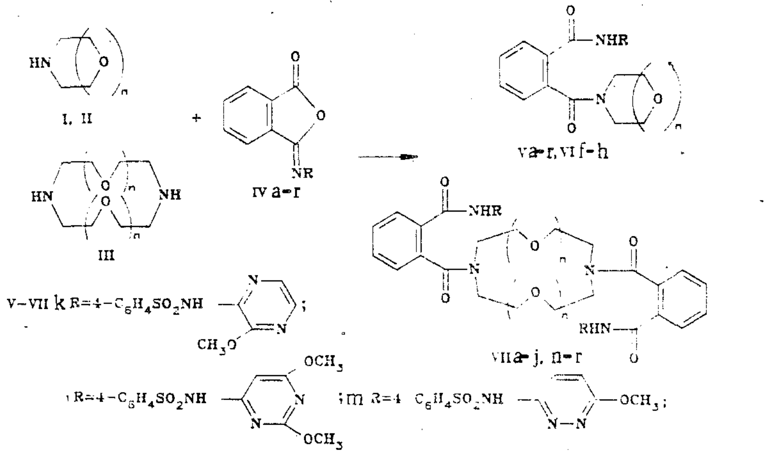
Acylated aza crown ethers containing fragments of N-substituted phthalamic acids in the side chain were obtained by the reaction of monoaza-15-crown-5, monoaza-18-crown-6, and diaza-18-crown-6 with N-substituted isophthalimides.

Interest has recently grown relative to modification of simple macrocyclic systems by introduction into the side chains of substituents that are capable of lipophilic [1], complexing [2,3], biological [4,5], and other properties of the starting crown ethers. Aza crown ethers and various synthetic methods that ensure the formation of a bond between the substituent and the nitrogen atom of the crown ether are often used as the starting compounds.

To search for convenient reagents that ensure modification of aza crown ethers with a rather extensive set of substituents we directed our attention to the possibility of the use of N-alkylphthalimides, which readily acylate primary [6] and sterically unhindered secondary [7] amines. However, an attempt to acylate monoaza-15-crown-5 with N-butyl- and N-octylphthalimide was unsuccessful, evidently as a consequence of steric hindrance of both the amino group in the aza crown ether and of the carbonyl groups in the phthalimides [8]. Isophthalimides in which the carbonyl group is not sterically hindered with respect to nucleophilic attack of the amino group of the aza crown ether are more promising acylating reagents. In this connection, we carried out the reaction of aza crown ethers I-III with N-substituted isophthalimides IV in benzene or chloroform at 25°C and obtained modified aza crown ethers V-VII.



I, IVa-r, Va-r, n=4; II, VI f-h, n=5; III, VIIa-j, n-r, n=2; V—VII a $R=C_6H_5$; b $R=4\text{-}C_2H_5O—C_6H_4$; c $R=4\text{-}C_2H_5OOC—C_6H_4$; d $R=4\text{-}Br—C_6H_4$; e $R=4\text{-}Cl—C_6H_4$; f $R=4\text{-}C_6H_5N{=}NC_6H_4$; g $R=C_8H_{17}$; h $R=C_{12}H_{25}$; i $R=C_2H_5OC_2H_4$; j $R=C_6H_5OC_2H_4$; n $R=(-)C_6H_5(CH_3)CH$; o $R=(+)C_6H_5(CH_3)CH$; p $R=CH_3OOCCH_2$; q $R=D,L\text{-}CH_3OOC(CH_8)CH$; r $R=D,L\text{-}CH_3OOC[CH_2CH(CH_3)_2]CH$

The proposed method is quite general and makes it possible, under mild conditions, to introduce into an aza crown ether molecule fragments of N-substituted phthalamic acids that contain aromatic, aliphatic, and hydroxyethyl (including optically active and pharmacophoric) groups and amino acid fragments as substituents.

Starting isophthalimides IVk-m are not formed by the method in [9]. We were able to accomplish their synthesis from phthaloyl chloride and the corresponding slightly basic and

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TABLE 1. N-Substituted Isophthalimides IVb-r

Compound	mp, °C	R_f	IR spectrum, ν, cm^{-1}		N found, %	Empirical formula	N calc., %	$M^{+\bullet}$*	Yield, %
			C=O	C=N					
IVb	119—120	0,44	1795	1695	5,2	$C_{16}H_{13}NO_3$	5,2	267	72
IVc	112—113	0,44	1800	1710	4,6	$C_{17}H_{13}NO_4$	4,7	295	74
IVd	163—164	0,48	1830	1710	4,5	$C_{14}H_8BrNO_2$	4,6	303	82
IVe	161—162	0,48	1830	1710	5,6	$C_{14}H_8ClNO_2$	5,4		86
IVf	160—161	0,45	1820	1710	13,0	$C_{20}H_{13}N_3O_2$	12,8	327	68
IVg	17—17,5	0,55	1800	1710	5,4	$C_{16}H_{21}NO_2$	5,4	259	82
IVh	46—47	0,62	1800	1720	4,5	$C_{20}H_{29}NO_2$	4,4	315	75
IVi	Oil	0,43	1815	1725	6,6	$C_{12}H_{13}NO_3$	6,4		87
IVj	83—84	0,40	1800	1725	5,3	$C_{16}H_{13}NO_3$	5,2		72
IVk	173—174	0,21	1830	1725	13,7	$C_{19}H_{14}N_4O_5S$	13,7	410	55
IV*l*	164—165	0,19	1830	1700	12,9	$C_{20}H_{16}N_4O_6S$	12,7	440	48
IVm	205—206	0,14	1830	1700	13,8	$C_{19}H_{14}N_4O_5S$	13,7	410	57
IVn	Oil	0,56	1810	1720	5,7	$C_{16}H_{13}NO_2$	5,6		83
IVo	Oil	0,56	1815	1730	5,8	$C_{16}H_{13}NO_2$	5,6	251	77
IVp	71—72	0,28	1810	1720	6,4	$C_{11}H_9NO_4$	6,4	219	55
IVq	78—79	0,34	1810	1720	6,1	$C_{12}H_{11}NO_4$	6,0		42
IVr	Oil	0,43	1830	1730	5,0	$C_{15}H_{17}NO_4$	5,1		51

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*By mass spectrometry.

slightly soluble sulfanilamides in chloroform in the presence of pyridine. Isoimides IVp-r were obtained from the hydrochlorides of the methyl esters of racemic amino acids without intermediate isolation of the free bases.

Intense absorption bands due to the stretching vibrations of C=O and C=N groups at 1795-1830 and 1695-1730 cm^{-1}, respectively, are present in the IR spectra of IV (Table 1). The presence of intense absorption bands of stretching vibrations of NH, C=O, and C—O—C groups at 3290-3400, 1600-1665, and 1110-1185 cm^{-1}, respectively, is characteristic for the IR spectra of V-VII (Table 2).

EXPERIMENTAL

The IR spectra of KBr pellets were recorded with an IKS-29 spectrometer. The molecular masses were determined by mass spectrometry with a Varian MAT-112 spectrometer at an ionizing voltage of 70 eV with direct introduction of the samples into the source. Measurements of the rotation of the plane of polarization of IV, V, and VIIn,o were made with an SM-2 polarimeter in benzene at a solution concentration of 0.2 g/cm^3, 25°C, and 589 nm. The course of the reactions and the individuality of the compounds were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates with development in UV light (extinction) and with ninhydrin (red spots). Acetone—hexane (1:2) was used as the eluent for IV, and acetone—hexane (1:1) was used as the eluent for V-VII. The end of the reaction was established by TLC [elution with acetone—hexane (1:2-2:1)] from the complete conversion of isophthalimides IV and the formation of modified aza crown ethers, the R_f values of which (Table 2) lie between the R_f values of IV (Table 1) and the R_f values of starting aza crown ethers I-III (for which the R_f values are zero in the indicated system). Column chromatography of V-VII was carried out on silica gel L 40/100 (Czechoslovakia) with elution with acetone—hexane (1:1 and 2:1). Monoaza-15-crown-5 and monoaza-18-crown-6 were obtained by the method in [10], diaza-18-crown-6 was obtained by the method in [11], and (—)- and (+)-α-phenylethylamines were obtained by the method in [12] and were 98% and 95% optically pure, respectively.

N-Substituted Isophthalimides IV. Compounds IVa-j,n,o were obtained by the reaction of phthaloyl chloride with the corresponding primary amines in the presence of triethylamine in benzene in analogy with the method in [9]. The constants of IVa were in agreement with those presented in [9]. The specific rotations for isophthalimides IVn,o were —100.2° and 97.0°, respectively.

Compounds IVk-m were obtained by a modified method [9]. A 10-mmole sample of 2-(4-aminobenzenesulfonamido)-3-methoxypyrazine (sulfalene), 6-(4-aminobenzenesulfonamido)-2,4-dimethoxypyrimidine (sulfadimethoxine), or 3-(4-aminobenzenesulfonamido)-6-methoxypyridazine (sulfapyridazine) was dissolved by heating in 15 ml of pyridine, and 300 ml of chloroform was added to the solution. A 200-ml sample of a chloroform solution containing 10 mmole of phthaloyl chloride was added rapidly with stirring at 15°C, and the resulting mixture was maintained at 20°C for 30 min, after which it was washed successively with 3% hydrochloric acid until the wash

TABLE 2. Modified Aza Crown Ethers V-VII

Compound	mp, °C	R_f	IR spectrum, ν, cm^{-1}			N found, %	Empirical formula	N calc., %	Yield, %
			N—H	C=O	C—O—C				
Va	149—150	0,40	3315	1650	1145	6,4	$C_{24}H_{30}N_2O_6$	6,3	74
Vb	Oil	0,25	3310	1650	1140	5,8	$C_{26}H_{34}N_2O_7$	5,8	48
Vc	Oil	0,32	3290	1605	1125	5,5	$C_{27}H_{34}N_2O_8$	5,4	42
Vd	132—133	0,36	3315	1625	1150	5,3	$C_{24}H_{29}BrN_2O_6$	5,4	55
Ve	134—135	0,45	3300	1630	1140	5,8	$C_{24}H_{29}ClN_2O_6$	5,9	62
Vf	165—166	0,29	3315	1645	1145	10,4	$C_{30}H_{34}N_4O_6$	10,3	65
Vg	Oil	0,36	3345	1635	1140	6,1	$C_{26}H_{42}N_2O_6$	5,9	72
Vh	Oil	0,46	3360	1650	1140	5,3	$C_{30}H_{50}N_2O_6$	5,2	70
Vi	Oil	0,33*	3450	1650	1140	6,4	$C_{22}H_{34}N_2O_7$	6,4	58
Vj	Oil	0,57*	3360	1650	1125	5,8	$C_{26}H_{34}N_2O_7$	5,8	54
Vk	204—205	0,17	3400	1645	1185	11,3	$C_{29}H_{35}N_5O_9S$	11,1	25
V*l*	195—196	0,20	3270	1610	1150	10,7	$C_{30}H_{37}N_5O_{10}S$	10,6	18
Vm	139—140	0,39*	3300	1605	1155	11,0	$C_{29}H_{35}N_5O_9S$	11,1	22
Vn	Oil	0,28	3345	1650	1150	6,0	$C_{26}H_{34}N_2O_6$	5,9	68
Vo	Oil	0,28	3300	1655	1130	5,8	$C_{26}H_{34}N_2O_6$	5,9	55
Vp	119—120	0,13	3300	1610	1125	6,6	$C_{21}H_{30}N_2O_8$	6,4	45
Vq	Oil	0,19	3330	1650	1140	6,2	$C_{22}H_{32}N_2O_8$	6,2	47
Vr	Oil	0,31	3350	1625	1140	5,6	$C_{25}H_{38}N_2O_8$	5,7	39
VIf	123—124	0,20	3300	1640	1140	9,7	$C_{32}H_{38}N_4O_7$	9,5	57
VIg	Oil	0,27	3345	1635	1130	5,4	$C_{28}H_{46}N_2O_7$	5,4	70
VIh	Oil	0,37	3350	1630	1130	4,7	$C_{32}H_{54}N_2O_7$	4,8	63
VIIa	109—110	0,34	3300	1610	1120	7,8	$C_{40}H_{44}N_4O_8$	7,9	56
VIIb	Oil	0,22	3330	1630	1135	7,1	$C_{44}H_{52}N_4O_{10}$	7,0	43
VIIc	Oil	0,24	3300	1620	1120	6,5	$C_{46}H_{52}N_4O_{12}$	6,6	40
VIId	154—155	0,40	3330	1610	1115	6,4	$C_{40}H_{42}Br_2N_4O_8$	6,5	52
VIIe	129—130	0,38	3285	1620	1110	7,4	$C_{40}H_{42}Cl_2N_4O_8$	7,2	50
VIIf	129—130	0,19	3300	1605	1140	12,3	$C_{52}H_{52}N_8O_8$	12,2	45
VIIg	Oil	0,32	3330	1620	1130	7,2	$C_{44}H_{68}N_4O_8$	7,2	53
VIIh	94—95	0,47	3340	1665	1135	6,3	$C_{52}H_{84}N_4O_8$	6,3	48
VIIi	Oil	0,18*	3360	1650	1130	7,9	$C_{36}H_{52}N_4O_{10}$	8,0	56
VIIj	69—70	0,55*	3360	1650	1130	6,8	$C_{44}H_{52}N_4O_{10}$	7,0	50
VIIn	79—80	0,21	3300	1600	1110	7,2	$C_{44}H_{52}N_4O_8$	7,3	57
VIIo	86—87	0,21	3300	1600	1115	7,3	$C_{44}H_{52}N_4O_8$	7,3	53
VIIp	68—70	0,12*	3400	1610	1125	8,1	$C_{34}H_{44}N_4O_{12}$	8,0	40
VIIq	Oil	0,31*	3400	1635	1130	7,8	$C_{35}H_{48}N_4O_{12}$	7,7	37
VIIr	Oil	0,24	3330	1635	1130	6,8	$C_{42}H_{60}N_4O_{12}$	6,9	35

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*In acetone—hexane (2:1).

water was acidic and with water until the wash water was neutral. The chloroform was evaporated at 80-100 mm (mercury column). Isophthalimide IVk was crystallized from benzene, and IV*l*,m were crystallized from acetone.

Compounds IVp-r were obtained via the following method. A 10-mmole sample of the hydrochloride of the methyl ester of glycine, D,L-alanine, or D,L-leucine was dissolved in 100 ml of chloroform containing 80 mmole of triethylamine, and 100 ml of a chloroform solution containing 10 mmole of phthaloyl chloride was added rapidly with stirring at 20°C. The reaction mixture was then washed successively with 1% hydrochloric acid until the wash water was acidic and with water until the wash water was neutral. The chloroform was evaporated at 80-100 mm (mercury column). Isophthalimides IVp,q were crystallized from hexane, and IVr was isolated by extraction with pentane.

The properties of IVa-d are presented in Table 1.

Modified Aza Crown Ethers V-VII. A 10-20% solution (in benzene or chloroform, respectively) of 11 mmole of monoaza crown ether I or II or 4.9 mmole of diaza crown ether III was added at 25°C to a 5-20% solution of 10 mmole of IVa-j,n-r in benzene or IVk-m in chloroform, and the mixture was allowed to stand at 20°C for 1-5 days until the conversion of isoimide IV was virtually complete (according TLC). Compounds V-VII were isolated by column chromatography by elution with acetone—hexane in the ratio indicated in Table 2 in the R_f column. The $[\alpha]_{589}^{25}$ values of Vn and VIIn were —43.2° and —64.0°, as compared with 41.8° and 58.8° for Vo and VIIo, respectively. The molecular masses of Va,i,j,n,q and VIIn were confirmed by mass spectrometry.

The characteristics of V-VII are presented in Table 2.

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ESTABLISHMENT OF THE CONFIGUATIONS OF HEXAHYDRO-4-(4-ETHOXYCARBONYLBUTYL)-3*a*-HYDROXY-2-OXO-1H-THIENO[3,4-d]IMIDAZOLES FROM PMR SPECTRAL DATA

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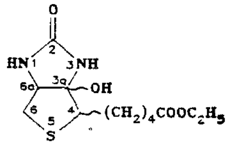
The configurations of isomeric hexahydro-4-(4-ethoxy-carbonylbutyl)-3*a*-hydroxy-2-oxo-1H-thieno[3,4-d]imidazoles were determined by PMR spectroscopy by means of angular and temperature dependences of the vicinal spin—spin coupling constants (SSCC).

It is known that α,γ- and α,β-ureido(thioureido) aldehydes or ketones can have ring or open forms and can exist in solutions in the form of tautomeric mixtures [1]. We have established that hexahydro-4-(4-ethoxycarbonylbutyl)-3*a*-hydroxy-2-oxo-1H-thieno[3,4-d]imidazoles I and II have ring structures, according to data from the IR spectra (the presence in the spectra of characteristic absorption for a hydroxy group) and the mass spectra (the absence of fragmentation that is characteristic for oxo compounds [2]). The peak of a molecular ion (m/z 288), from which a molecule of water (m/z 270) and the side aliphatic chain are ejected with the formation of an ion with mass 141, the peak of which is the maximum peak in the spectrum, is observed in the mass spectrum of I. The presence of peaks of ions with m/z 228 and 245 is due to fragmentation of the urea grouping. It was found by PMR spectroscopy that this compound is a mixture of two isomers that differ with respect to the orientation of the hydroxy group attached to the $C_{(3a)}$ atom with respect to the aliphatic chain attached to the $C_{(4)}$ atom. One of these isomers (I) was isolated in pure form and had mp 136-138°C (Found, %: C 50.0, H 6.6, N 9.5. Calculated: C 50.0, H 7.0, N 9.7). Isomer II could not be isolated in pure form, and this compound was therefore studied in the mixture with isomer I.



I cis(R and OH trans), II trans (R and OH cis).

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