STEREOISOMERISM IN MACROCYCLIC BIS(PIPERIDONES)

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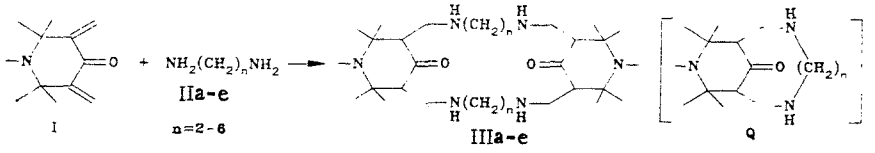
The reaction of a polysubstituted 3,5-dimethylene-4-piperidone with aliphatic diamines leads to macrocyclic products, namely, 3,3',5,5'-di(methylaminoalkylaminomethyl)-bridged bis(piperidones). The latter compounds are formed as mixtures of cis,trans-isomers, and isolated in the form of cis,cis-isomers. ^{13}C-NMR spectral analysis has shown that these compounds also exhibit characteristic syn-anti isomerism associated with the relative orientation of the 3,5-substituents on opposite piperidone rings.

It has previously been shown that reaction of piperidone I with primary amines leads to the formation not only of the products of addition of the amine to the C=C bond, but also to the formation of cleavage products of the piperidone ring [1]. In light of the unusual behavior of polysubstituted 4-piperidones, the addition of amines to piperidone I was subjected to further study.

Reactions of the dimethylene ketone I with aliphatic diamines IIa-e were carried out under high dilution conditions in order to avoid the formation of linear oligomers, and led to the formation of the first type of compounds in quantitative yields. The structures of these compounds were elucidated on the basis of their IR, mass, and ^{1}H- and ^{13}C-NMR spectra, as well as by elemental analysis (Tables 1-3). The functional similarity between the dimeric macrocyclic structure III and the monomeric bicyclic structure Q makes it difficult to distinguish between these two products, both of which result from one reaction pathway, namely, addition of the amine to the double bond without ring opening.



The formation of a mixture of compounds is deduced from PMR spectral evidence, which shows, for each reaction product, two pairs of signals for the gem-dimethyl groups; these signals have varying intensities, but exhibit constant predominance of one compound each in the n = 2-6 series, which gives rise to the central pair of singlets. Those compounds which were present in the greatest amounts could be isolated in 15-30% yields, and were shown by ^{1}H- and ^{13}C-NMR to be homogeneous to within 90-100% (based on the integrated intensities of the α-methyl group signals in the PMR spectra).

Based on mass spectral evidence, the isolated compounds were assigned the macrocyclic structure III (Table 2). One characteristic feature of the mass spectra is that the protonated molecular ion peak $(M + H)^+$ is either very small, or not detectable at all, whereas the ion peak corresponding to half its mass is relatively intense. Nevertheless, any assumptions concerning the formation of compounds of structure Q in mixtures with the corresponding macrocycles III, even in mass spectroscopically detectable amounts, appear to be groundless. Thus, the spectrum of a completely acylated derivative of IIIa (Ac_2O, 20°C, 4 days), which was not subjected to any special purification prior to conversion, showed an intense peak for the molecular ion $(M + H)^+$ of the macrocyclic tetraamide. The presence of two signals for the carbonyl carbon atoms in the ^{13}C-NMR spectra also corroborates the macrocyclic structure for compound IIIa (Table 3).

The highest homolog IIIe differs from the lower members of the series IIIa-d in its fragmentation pattern; the latter compounds are characterized by thermal decomposition and

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TABLE 1. Macrocyclic Bis(piperidones) IIIa-e and IV

Compound	mp, °C	IR spectrum, cm^{-1}		PMR[a] spectrum, δ ppm			Found, %			Molecular formula	Calc., %		
		NH	C=O	$(CH_3)_2$	NCH_3	(CH_2)	C	H	N		C	H	N
IIIa	131—132	3290	1705	0,98; 1,16	2,26	—	66,1	11,0	16,6	$C_{28}H_{54}N_6O_2$	66,4	10,7	16,6
IIIa[b]	119—120			0,77; 0,98; 1,16; 1,37	2,26; 2,30	—	66,2	10,8	16,6	$C_{28}H_{54}N_6O_2$	66,4	10,7	16,6
IIIb	132—133	3300	1700	0,95; 1,13	2,24	1,56	67,3	10,6	15,6	$C_{30}H_{58}N_6O_2$	67,5	10,9	15,7
IIIb[b]				0,75; 0,95; 1,13; 1,32	2,24; 2,31	1,56							
IIIc	117—118	3300	1705	0,94; 1,11	2,23	1,40	68,1	10,9	14,9	$C_{32}H_{62}N_6O_2$	68,4	11,0	14,9
IIIe[b]				0,73; 0,94; 1,11; 1,32	2,23; 2,30	1,40							
IIId	125—126	3300	1705	0,97; 1,16	2,27	1,32	68,9	11,2	14,1	$C_{34}H_{66}N_6O_2$	69,1	11,2	14,2
IIId[b]				0,75; 0,97; 1,16 — [c]	2,27; 2,34	1,32							
IIIe	115—116	3300	1700	0,97; 1,15	2,26	1,33	69,6	11,5	13,5	$C_{36}H_{70}N_6O_2$	69,9	11,3	13,6
IIIe[b]				0,73; 0,97; 1,15; — [c]	2,26; 2,32	1,33							
IVb	>200 (dec.)	—	1710, 1640 amide	0,75; 0,80; 1,34; 1,54	2,16; 2,23	—	63,6	8,9	12,1	$C_{56}H_{62}N_6O_6$	64,0	9,2	12,5

[a]The $N-CH_2$ and CH protons give rise to overlapping multiplets in the region 2.3-3.5 ppm. [b]For a mixture of isomers (without a superscript, for the cis,cis-isomer). [c]The signal is hidden behind signals due to other groups.

TABLE 2. Chemical Ionization Mass Spectra of Macrocyclic Bis-(piperidones) IIIa-e and the Tetraacetyl Derivative of Piperidone IIIa (cis,cis-isomer)[a]

Compound	m/e (relative intensity, %)[b]
IIIa	507 (0,1), 449 (0,1), *447 (0,8)*, 391 (0,3), 345 (0,6), 305 (0,2), 279 (0,2), 268 (0,3), **254 (11,0)**, 235 (1,1), 223 (20,8), 194 (100,0)
IIIb	535 (0,1), *461 (0,8)*, 391 (0,4), 280 (0,3), **268 (1,5)**, 239 (2,1), 222 (1,5), 220 (1,1), 194 (100,0)
IIIc	563 (0,04), *475 (0,4)*, 391 (0,1), 294 (0,1), **282 (2,9)**, 251 (3,9), 211 (2,5), 194 (100,0)
IIId	391 (0,8), **296 (0,7)**, 265 (1,3), 225 (1,0), 194 (100,0)
IIIe	563 (1,0), 549 (1,2), 535 (2,0), 533 (1,1), 521 (1,5), 507 (2,6), 493 (1,6), 479 (1,7), 451 (1,3), 411 (1,2), 401 (1,2), 391 (3,4), 383 (2,8), 369 (3,6), 313 (1,8), 265 (1,4), 257 (5,7), 239 (3,6), 194 (100,0)
Ac_4-IIIa	675 (16,1), 531 (0,1), 340 (1,4), **338 (5,3)**, 289 (1,0), 213 (1,0), 194 (15,5), 183 (3,0), 168 (1,4), 165 (1,9), 145 (100,0)

[a]All peaks having mass greater than M/2 + H are given, along with all lower mass peaks having intensities greater than 1% (with the maximum peak assigned 100%). The reagent gas was NH_3 for bis(piperidones) IIIa-e, and isobutane for Ac_4-IIIa. [b]The ion peak corresponding to thermal decomposition of macrocycles IIIa-c, with loss of one molecule of the starting diamine, is italicized, whereas the ion peak $[M/2 + H]^+$ is written in boldface type.

loss of the starting diamine, whereas piperidone IIIe undergoes decomposition of the hexamethylene chain and elimination of the central methylene units (apparently in the form of olefins having 4, 5, and 6 atoms). This also gives rise to the formation in the mass spectra of relatively intense high molecular ions $[M + H - (CH_2)_n]^+$. If one assumes that the protonated molecular ion $(M + H)^+$ is instead the peak with half the mass, 310 (corresponding to the hypothetical structure Q), then the mass spectrum should also contain fragment ion peaks resulting from similar decomposition of the hexamethylene chain in bicyclic Q. The absence of these peaks establishes the unitary nature of the ion, and also establishes the dimer structure IIIe. The macrocyclic structures of the lowest (n = 2) and highest (n = 6) homologs have thus been proven, and allow us to conclude that the mass spectra of the other members of the series (n = 3-5) also describe macrocyclic bis(piperidones) of structure IIIb-d.

Compounds having the structure described in III can exhibit two types of three dimensional isomerism (Scheme 1): cis-trans isomerism, corresponding to the relative orientations

TABLE 3. ^{13}C-NMR Spectra of Macrocyclic Bis(piperidones) IIIa-e

Compound	Chemical shift, ppm, multiplicity at partial ^{13}C-{^{1}H} decoupling (theoretical number of groups of chemically nonequivalent carbon atoms for the cis,cis-, cis,trans-, and trans,trans-isomersr)									Theoretical sum Σ of groups of chemically nonequivalent carbon atoms for each isomer		
	NCH_3	$(CH_3)_2$	$C_{(2,6)}$	$C_{(3,5)}$	$C_{(4)}$	$C_{(1')}$	$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	cis,cis-	cis,trans-	trans,trans-
IIIa	28,42 q	26,40 q, 23,06 q	60,94 s	58,53 d	213,69 213,86	47,32 t	49,59 t	—	—	16	28	16
	(2,2,2)	(4,8,4)	(2,4,2)	(2,4,2)	(2,2,2)	(2,4,2)	(2,4,2)					
IIIb	28,63 q	26,55 q, 23,26 q	61,31 s	58,72 d	213,60	47,05 t	48,05 t	30,71 t	—	18	30	18
	(2,2,2)	(4,8,4)	(2,4,2)	(2,4,2)	(2,2,2)	(2,4,2)	(2,4,2)	(2,2,2)				
IIIc	28,14 q	26,07 q, 22,86 q	60,67 s	58,23 d	212,99	47,29 t	50,16 t	28,04 t	—	18	32	18
	(2,2,2)	(4,8,4)	(2,4,2)	(2,4,2)	(2,2,2)	(2,4,2)	(2,4,2)	(2,4,2)				
IIId	28,18 q	26,14 q, 22,76 q	60,77 s	58,16 d	213,29	46,72 t	49,42 t	30,29 t	24,93 t	20	34	20
	(2,2,2)	(4,8,4)	(2,4,2)	(2,4,2)	(2,2,2)	(2,4,2)	(2,4,2)	(2,4,2)	(2,2,2)			
IIIe	28,38	26,37, 22,92	61,04	58,76	213,36	47,32	50,40	30,45	27,81	20	36	20
	(2,2,2)	(4,8,4)	(2,4,2)	(2,4,2)	(2,2,2)	(2,4,2)	(2,4,2)	(2,4,2)	(2,4,2)			
IIIa[b]	28,45	30,29, 30,19 26,50, 26,44 23,33, 23,13 16,60, 16,47	63,48[c] 63,31[c] 61,17 60,74	60,80[c] 60,60[c] 59,40 58,83	212,19 210,40	47,59 47,08 45,28 45,21	49,73 49,26 48,86 48,76					

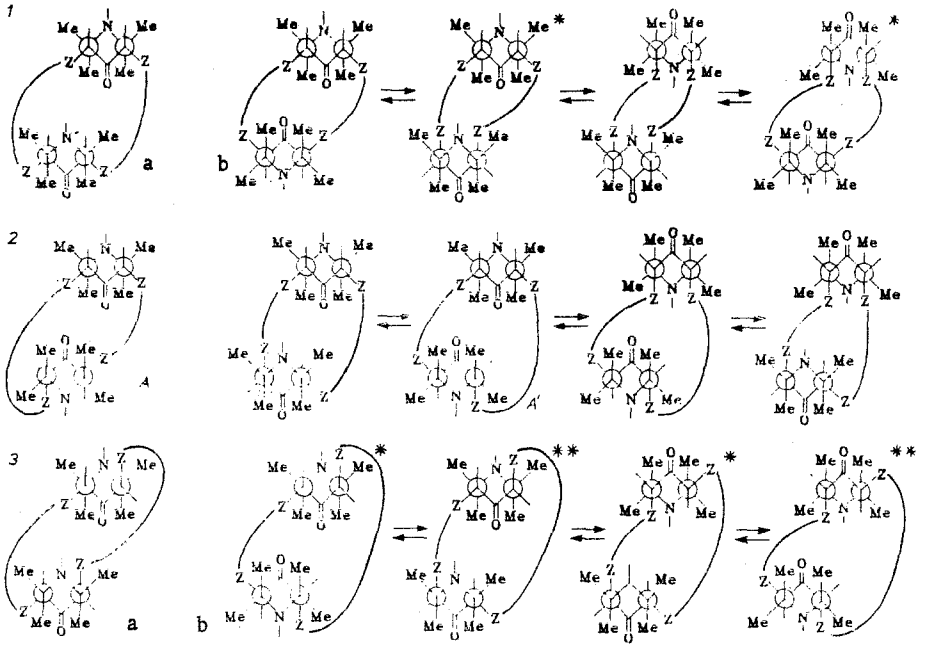
[a]Including syn-anti isomerism. [b]Mixture of the cis,cis-isomer of IIIa and the corresponding cis,trans-isomer (only ancillary signals are given, i.e., signals of the cis,trans-isomer). [c]Tentative assignment.

of the 3,5-substituents in each piperidone ring (cis-cis-, cis-trans-, and trans-trans-isomers) and also isomers corresponding to different relative orientations (syn vs anti) of these substituents on opposing piperidone rings. This type of stereoisomerism is characteristic of systems composed of two noncondensed saturated six-membered rings, such as perhydroanthracene or perhydrophenanthrene. In the case of the bis(piperidones) of type III, it has been found that the independent conformational mobility of the terminal rings and of the central chain in the macrocycle does not lead to interconversion of the syn- and anti-isomers; the relative orientations of the Z substituents on the two different rings do not change upon ring inversion. This indicates that both the cis-cis- and trans-trans-isomers of III can each give rise to two isomers of the syn-anti-type. In the case of the cis-trans-isomers two groups of conformers can be distinguished, and cannot be interconverted by ring inversion into conformers of the other group, but rather are related to them as optical antipodes (pairs from each group). The relative orientation of substituents of the two rings are identical in each enantiomeric pair, i.e., the cis-trans-isomer is a cis-anti-trans-isomer.

It is obvious that cis-trans-isomers should differ more in their physical chemical properties than should syn-anti pairs of isomers, since in the case of the latter isomers, each of the piperidone residues in one isomer differ from the same piperidone ring of its isomer only in terms of the three dimensional arrangement of the distant piperidone ring. As the size of the central macrocycle increases, the similarity in the properties of the syn-anti isomers also increases.

Because of the different internal symmetries of the possible conformers, the cis-cis- and trans-trans-isomers of III differ from the cis-trans-isomer in the absolute number of groups of structurally nonequivalent atoms of one type, and thus in the number of lines expected in their theoretical ^{13}C-NMR spectra (see Scheme 1 and Table 3). The number of groups

Scheme 1



Stereoisomerism and conformational transitions in type III bis(piperidones): 1) cis-cis-isomer (a, syn-isomer; b, anti-isomer); 2) cis-trans-isomer (A and A', enantiomers); 3) trans-trans-isomer (a, syn-isomer; b, anti-isomer). Three dimensionally equivalent structures are denoted by asterisks (* or **).

of atoms of one type is equal to the number of groups of atoms of each type which cannot be interconverted by positional exchange (considering only conformational changes associated with inversion of the six-membered rings). In the case of the cis-cis- and trans-trans-isomers, degeneracy of the conformational transitions and internal symmetry of the conformers leads to equivalency of all of the carbon atoms of one type in each isomer (with the exception of the geminal carbon atoms of the α-methyl groups); at the same time, however, all of the conformers of the cis-trans-isomer are structurally (three-dimensionally) different and do not possess any symmetry elements. As a consequence, the cis-cis- and trans-trans-isomers have the same number of groups of chemically nonequivalent carbon atoms (both of each type and the total number), whereas the cis-trans-isomer has almost twice as many such groups.

The number of signals, 9, 9, 9, 10 and 10, respectively, in the ^{13}C-NMR spectra of the isolated isomers of IIIa-e does not allow us to assign signals to each of the isomers in the cis-trans-series of III. At the same time, however, the presence of two signals for the carbonyl group carbon atoms, of approximately equal intensity, in the spectrum of isomer IIIa indicates that the latter (isolated isomer) consists of a mixture of the cis-syn-cis- and cis-anti-cis-isomers in about equal ratios. The absence of double signals for the other types of carbon atoms in the spectrum of bis(piperidone) IIIa, as well as the absence of corresponding doubling of any of the signals in the spectra of the higher homologs IIIb-e can be explained in terms of the above-mentioned similarity of the syn- and anti-isomers, which increases as the relative separation of the two six-membered rings increases. In these cases one observes degeneracy of the signals for carbon atoms of one type in isomeric pairs, and only the most proximate carbonyl groups of the syn- and anti-isomers of the lowest homolog IIIa exhibit their nonequivalence by ^{13}C-NMR spectroscopy.

The ^{13}C-NMR spectrum of the product mixture resulting from the reaction of piperidone I with diamine IIa, after recrystallization from hexane, contains, in addition to the signals of isomer IIIa, a series of new signals which can be assigned to the cis-trans-isomer of structure III. For each signal of a group of chemically equivalent carbon atoms in compound IIIa (with the exception of the C=O and N-Me groups), one detects four additional signals of lesser intensity, two of which have very similar chemical shift values to the predominant isomer IIIa, and two of which have very different (chemical shift) values (see Table 3).

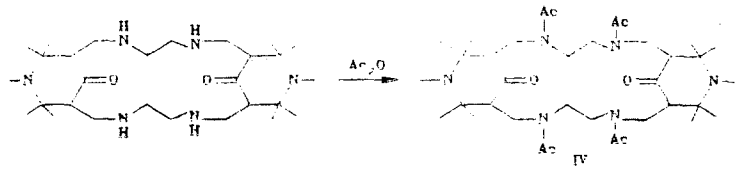
The number of groups of chemically nonequivalent carbon atoms in the cis-trans-isomer of III thus overlaps the number of auxiliary signals observed in the experimental spectrum (auxiliary relative to the signals of isomer IIIa). One can further assume, that the first pair of signals corresponds to one piperidone ring having the same configuration of substituents as both the piperidone rings of IIIa (cis- or trans-), and that the second pair of signals can be attributed to the piperidone residue having the opposite configuration (trans- or cis-). The mutual assignment of several signals of similar chemical shift values is simplified by the relative intensity differences of these signals. The absolute assignment of the two weak-field pairs of signals (of four) to either the $C_{(3,5)}$ or $C_{(2,6)}$ atoms is not significant.

The three dimensional nonequivalence of the two piperidone rings is also supported by the presence of two different signals for the carbonyl group carbon atoms. The signal of one of the N–Me groups is apparently hidden under the signal due to the ring having the same configuration on bis(piperidone) IIIa. The alternative signal assignment for the new signals, i.e., to the cis- or trans-isomers of structure Q, can be ruled out, since a mixture of the latter should lead to half the number of lines actually observed in the spectrum. For the same reasons, assumptions concerning the presence of yet another isomer in the mixture, this one with substituent configurations opposite that of isomer IIIa, either separately or together with isomers of Q, can also be precluded, since they do not agree with the number of auxiliary signals; the assignment of the latter (auxiliary signals) to the cis-trans-isomer should therefore be regarded as unambiguous (taking into account also the results of elemental analysis).

The chemical shift values of the carbon atoms of the piperidone rings were calculated using the incremental values for methyl substituents [2], and the chemical shift value of 1-methyl-4-piperidone as a starting point [3]. The calculated chemical shift values for the $C_{(2,6)}$ atoms of 1,2,2,3,5,6,6-heptamethyl-4-piperidone (61.7 ppm for the cis-isomer and 61.5 ppm for the trans-isomer) are very similar to the chemical shift values observed experimentally in the spectrum of the cis-trans-isomer of III. The corresponding calculated values for the chemical shifts of the $C_{(3,5)}$ atoms (56.9 ppm for the cis-isomer and 54.3 ppm for the trans-isomer) were not detected in the spectrum of the trans-isomer. This demonstrates, above all, that the chair-like conformation of the six-membered rings is partially distorted, and to a greater extent for the trans-ring (the polysubstituted N-oxide piperidone ring which occurs in the composition of formone derivatives also exhibits a twisted chair conformation [4]). At the same time, one of the Z substituents of the trans-ring in the cis-trans-isomer of III may not be purely axial, and thus may not confer the same γ-gauche effect relative to the chemical shift value of the corresponding $C_{(3)}$ or $C_{(5)}$ atom of the ring (in contrast to 3,5-dimethylpiperidine [2]). In such a case, the upfield shift of the signals due to one pair of $C_{(3,5)}$ atoms in the cis-trans-isomer of III relative to the second pair of $C_{(3,5)}$ atoms would not automatically mean that the first pair belongs to the ring having trans-configuration. The difference in chemical shift values between the downfield pair of $C_{(3,5)}$ atoms in the cis-trans-isomer of III and the calculated chemical shift values for analogous atoms in a ring having a cis-configuration is not large, on the order of 2-2.5 ppm, and is even less (1.3-1.8 ppm) in the case of isomers of IIIa-e. This difference can be ascribed to a partially twisted ring conformation, as well as to inadequate modelling of the unknown incremental value of the alkylaminomethyl group by the known increment of a methyl group. If one also takes into account the similarity in chemical shift values for the $C_{(1')}$ carbon atoms of isomers IIIa-e with the chemical shifts of the downfield pair of signals for the corresponding atoms in the cis-trans-isomer of III, i.e., those with 3,5-diequatorial substituents, then the assignment of isomers IIIa-e to the cis-cis series can be made with a higher degree of confidence.

This simplifies the cis-trans-assignment in 1,2,2,6,6-pentamethyl-3,5-dialkylaminomethyl-4-piperidones. Since the α-methyl group signals in the PMR spectra of these compounds are characteristic of cis- and trans-isomers ([1] and Table 1), one can assume that the central pair of methyl signals, with chemical shift differences of less than 0.25 ppm, corresponds to the cis-configuration of 3,5-substituents, and the difference of greater than 0.5 ppm for the pair of terminal singlets corresponds to the trans-configuration. The observed results confirm the isomeric assignment made for similar compounds, which was concluded earlier based on stereochemical considerations [1].

Acylation of the isolated mixture of cis-cis- and trans-trans-isomers of structure III leads to a mixture of isomers of tetraamide IV, with the same ratio as in the precursor isomers (based on integrated intensities of the gem-dimethyl group signals in their PMR spectra).



IV

The conversion of the amino functional groups to amide linkages removes the problem associated with the characteristic chemical shift values of the proton signals due to the α-methyl groups in rings having the cis- and trans-configuration. Simultaneous shielding of one pair of methyl groups and deshielding of the other pair of methyl groups in the cis-piperidinyl residue ($\Delta\delta$ = 0.66 ppm) is the same as in the trans-substituted ring ($\Delta\delta$ = 0.73 ppm).

EXPERIMENTAL

PMR spectra were recorded on a Varian T-60 spectrometer (in $CDCl_3$ versus HMDS); ^{13}C-NMR spectra were obtained on a Bruker WH-250 spectrometer (in $CDCl_3$ versus TMS). IR spectra were obtained on a Perkin-Elmer 580B spectrophotometer using Vaseline mulls, and mass spectra were taken on a Finnigan 4201 spectrometer (chemical ionization with NH_3 or iso-BuH, 0.4 torr, 100 eV, rate of sample heating 100°/min).

1,1',2,2,2',2',6,6,6',6'-Decamethyl-cis-cis-3,3',5,5'-di(methylaminoalkylaminomethyl)-4,4'-bis(piperidones) (IIIa-e). To 500 ml of benzene was added simultaneously over 15 h a solution of 10 mmole of dimethylketone I in 50 ml benzene and a solution of 10 mmole of diamine IIa-e in 50 ml of alcohol; the mixture was then allowed to stand for 12 h. The residue after evaporation was treated with 10 ml of cyclohexane for 10 days at 20°C, and the undissolved portion (bispiperidones IIIa-e) were removed by filtration. Recrystallization of the residue from hexane after evaporation of the reaction mixture resulted in a mixture of the cis-cis- and cis-trans-isomers of structure IIIa.

1,1',2,2,2',2',6,6,6',6'-Decamethyl-3,3',5,5'-di[N,N-diacetyl(methylaminoethylaminomethyl)]-4,4'-bis(piperidone) (mixture of cis-cis and cis-trans-isomers) (IV). A mixture of the cis-cis isomer IIIa and the corresponding cis-trans-isomer (10 mmole) was allowed to stand in excess Ac_2O for 4-5 days; after evaporation an aqueous NaOH solution (pH 10-11) was added, and the mixture was extracted with chloroform (3 × 15 ml) and then dried over $CaCl_2$. The mixture was subjected to chromatography on neutral Al_2O_3 (activity II) (Pharmacia SR 25/45 column, supported in chloroform, eluted with chloroform); the fractions corresponding to absorption peaks at 260 nm were then evaporated to give 8 mmole of the tetraamide IV (80% yield).

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