REGIODIRECTION OF THE FORMATION OF KETOAMIDES IN THE THERMOLYSIS OF DERIVATIVES OF 2,6-EPIDIOXYPIPERIDINE

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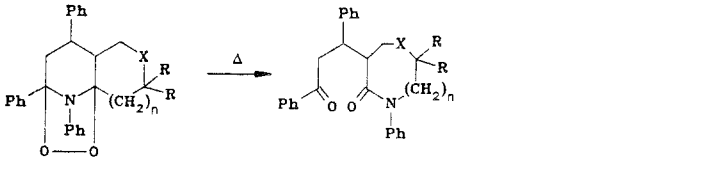
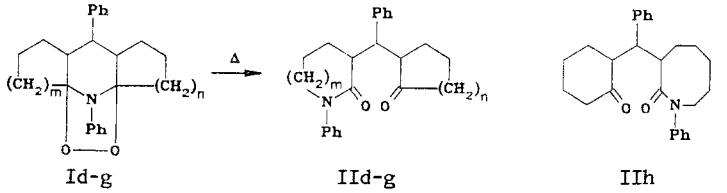
Thermolysis of a series of unsymmetrically substituted bi- and tricyclic derivatives of 2,6-epidioxypiperidine leads to the predominant formation of only one of the possible ketoamides; this is probably associated with the synchronous course of the reaction.

The decomposition of derivatives of 1,2,4-dioxazolidine with the formation of ketones and amides was previously described [1, 2]: the mixture of both possible ketones and both possible amides is formed from the unsymmetrically substituted dioxazolidines under the conditions applied by the author [boiling with the solution of NaOH in methanol or thermolysis at 500°C (160 mm of Hg stem)]. The decomposition of 2,6-epidioxypiperidine derivatives by an analogous scheme may lead to two isomeric ketoamides in the case of the symmetrically substituted derivatives, and to four isomeric ketoamides in the case of the unsymmetrically substituted derivatives. We showed by the investigation of the low-temperature (140-150°C) thermolysis of the symmetrically substituted 2,6-epidioxypiperidine derivatives – 4a,10a-epidioxyperhydroacridines – that the (2-oxocyclohexyl) alkylcaprolactams with the 1,5-disposition of the carbonyl groups are thereby formed; the alternative ketolactams with the 1,6-disposition of the carbonyls were not detected [3].

Continuing the investigation of the regiodirection and regioselectivity of the thermolysis of the cyclic aminoperoxides, we studied the thermolysis of a series of unsymmetrically substituted bicyclic (Ia-c) and tricyclic (Id-f) derivatives of 2,6-epidioxypiperidine, as well as the trans-anti-cis-aminoperoxide (Ig), in which the substituents only differ in their steric disposition.



Ia-c IIa-c



Id-g IId-g IIh

I, II a,b X=CH_2, R=H, c X=O, R=CH_3; a,c,g n=1, b,d n=2; e,f n=3; d,e,g m=1, f m=2

The aminoperoxides (Ia, c, d) were previously described by us [4]. The aminoperoxides (Ib, e, f) were synthesized by schemes including the synthesis of the 1,5-diketones (III) and (Va, b). These were used to obtain the 1,4-dihydropyridine derivatives (IV) and (VIIa, b) [compound (IV) is obtained directly from the diketone (III), and the compounds (VIIa, b) are

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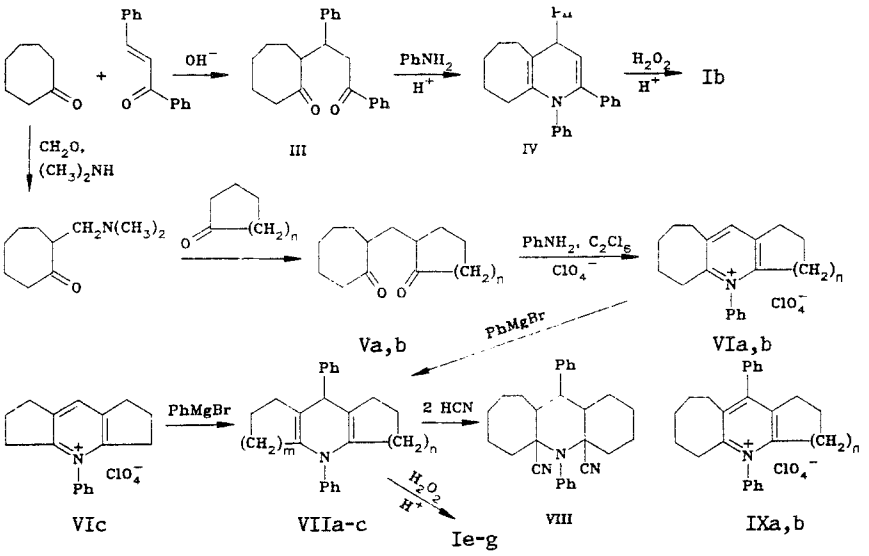
obtained via the pyridinium salts (VIa, b)] with the subsequent addition of hydrogen peroxide to them. The aminoperoxide (Ig) was synthesized from the known [5] pyridinium salt (VIc). The addition of H_2O_2 to the compounds (IV) and (VII) was accomplished without the isolation of the latter, directly after performing the reaction of the diketone (III) with aniline or the salts (VI) with phenylmagnesium bromide; the dicyanide (VIII) was obtained for the characterization of the compound (VIIb). The addition of H_2O_2 to the compounds (VIIa, b) is accompanied by their partial oxidation; small amounts of the pyridinium salts (IXa, b) were isolated as by-products. The tricyclic aminoperoxides (Ie-g) are formed in the form of the mixtures of the trans-syn-trans- and trans-anti-cis-isomers. In the case of (Ie), the predominating trans-syn-trans isomer (the PMR spectrum shows the signal of the proton at the position 4 of the piperidine ring as a triplet at 3.04 ppm with the SSCC of J = 12 Hz) was isolated from the mixture by crystallization. In the case of (If), the 1:1 mixture of the stereoisomers, which is inseparable by crystallization, is formed; this is possibly the molecular compound (the presence in the PMR spectrum of two equally intense signals of the 4-H proton: the triplet at 2.82 ppm with the SSCC of J = 12 Hz, and the quartet at 3.73 ppm with the SSCC of J = 12 and 6 Hz, analogous to the signals of the given protons in the trans-syn-trans- and trans-anti-cis forms correspondingly which were previously described [4] for tricyclic aminoperoxides). The treatment of this mixture with a catalytic amount of HCl at −15°C leads to the quantitative conversion of the mixture to the pure trans-syn-trans isomer. In the case of (Ig), the predominant isomer is the trans-anti-cis isomer (the signal of the 4-H proton in the form of a quartet at 3.33 ppm with the SSCC of J = 11 and 6 Hz); the trans-syn-trans isomer (the signal of the 4-H proton in the form of a triplet with the SSCC of J = 11 Hz at 3.1 ppm) is formed in markedly lower amount. The bicyclic aminoperoxide (Ib) was obtained in the form of one stereoisomer, the configuration of which was not established. The trans-syn-trans isomers of the tricyclic aminoperoxides (Id-f) and the trans-anti-cis-isomer of the aminoperoxide (Ig) were utilized for the thermolysis.



V, VI, IX a $n=1$, b $n=2$; VII a,c $n=1$, b $n=2$; a,b $m=3$, c $m=1$

The thermolysis of the aminoperoxides (I) was performed by boiling them in xylene or DMF. As in the cases previously described [3], only the ketoamides with the 1, 5-disposition of the carbonyl groups are the products of the thermolysis. In the majority of cases, the formation of only one of the two possible isomers of such ketoamides was thereby detected. In the remaining cases, one isomer dominates over the other.

In the thermolysis of the bicyclic aminoperoxides (Ia-c), only the alicyclic (Ia, b) or heterocyclic (Ic) substituent is converted into the amide fragment; the aryl substituent enters into the composition of the ketone fragment, which results in the formation of the 3-(α-phenacylbenzyl) lactams (IIa-c). Significant regioselectivity was also noted for the compounds (Id-g) which have much more structurally similar substituents in the piperidine ring. The side ring with the smaller number of sides is converted into the lactam fragment with the enlargement of the ring during the thermolysis of the compounds (Id-f): this occurs exclusively in the cases of (Id) and (Ie), and preferentially in the case of (If) [the ratio

TABLE 1. Physicochemical Characteristics of the Compounds Synthesized

Compound	Empirical formula	bp, °C, [bp, °C (mm of Hg stem)]	IR spectrum, cm^{-1}	Mass spectrum, m/z (I_{rel}, %)	Yield, %*
Ib	$C_{28}H_{29}NO_2$	147...148	1600, 1585	411 (7), 393 (13), 379 (100)	20
Ie	$C_{25}H_{29}NO_2$	109...110	1600	375 (7), 357 (10), 343 (100), 341 (15)	30
If	$C_{26}H_{31}NO_2$	143...145	1600, 1585	389 (1), 371 (3), 357 (100), 355 (10)	50
Ig**	$C_{23}H_{25}NO_2$	132...133	1595	347 (7), 329 (7), 315 (100), 313 (25)	43
IIa	$C_{27}H_{27}NO_2$	149...150	1674, 1642	397 (18), 292 (30), 278 (28), 250 (14), 189 (100)	69
IIb	$C_{28}H_{29}NO_2$	138...139	1680, 1641	411 (100), 383 (6), 306 (25), 292 (50), 261 (21), 203 (40)	70
IIc	$C_{28}H_{29}NO_3$	192...193	1682, 1647	427 (55), 322 (20), 308 (20), 280 (2), 219 (100)	83
IId	$C_{24}H_{27}NO_2$	154...155	1708, 1652	361 (1), 333 (9), 264 (13), 175 (100)	82
IIe	$C_{25}H_{29}NO_2$	129...130	1692, 1634	375 (2), 347 (2), 264 (14), 175 (100)	81
IIf	$C_{26}H_{31}NO_2$	179...180	1690, 1651	389 (10), 361 (5), 278 (22), 250 (14), 189 (100)	63
α-IIg	$C_{23}H_{25}NO_2$	119...120	1728, 1632	347 (3), 319 (4), 291 (15), 264 (25), 175 (100)	56
β-IIg	$C_{23}H_{25}NO_2$	124...125	1729, 1632	347 (3), 319 (4), 291 (15), 264 (21), 175 (100)	7
IIh	$C_{26}H_{31}NO_2$	209...211	1693, 1641	389 (50), 361 (9), 292 (45), 264 (60), 203 (100)	9
III	$C_{22}H_{24}O_2$	101...102	1692	320 (19), 302 (5), 208 (80), 200 (100)	72
Va	$C_{13}H_{20}O_2$	[135...136 (2)]	1740, 1700	208 (60), 124 (100), 96 (60)	65
Vb	$C_{14}H_{22}O_2$	[146...148 (1)]	1707	222 (100), 124 (83), 110 (100)	69
VIa	$C_{19}H_{22}ClNO_4$	192...193	1600, 1585, 1100		84
VIb	$C_{20}H_{24}ClNO_4$	187...188	1600, 1590, 1100		89
VIII	$C_{28}H_{31}N_3$	231...233	2230, 1600		50
IXa	$C_{25}H_{26}ClNO_4$	226...228	1615, 1595, 1095		6
IXb	$C_{26}H_{28}ClNO_4$	264...266	1620, 1600, 1100		10

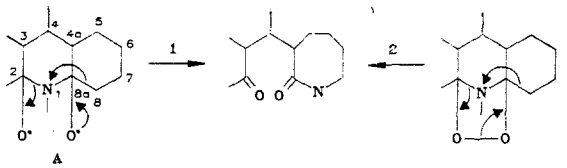
*The yield according to the diketone (III) is presented for compound (Ib). The yield according to the corresponding pyridinium perchlorate (VIa), (IVb) is presented for (Ie, f). The yield according to the cycloheptanone is presented for (Va, b).

**The trans-anti-cis isomer.

of the ketolactams (IIf) and (IIh) is 7: 1]. In the thermolysis of the trans-anti-cis isomer of compound (Ig), which has identical side rings, one ring is however preferentially enlarged: one of the stereoisomeric ketolactams α-(IIg) predominates, whereas the other stereoisomer β-(IIg) is a minor product. The ratio of α-(IIg) to β-(IIg) is 8:1 (in the given case, the differing regiodirection of the thermolysis leads to the formation of stereoisomeric products).

In the IR spectra of the ketolactams (II) (Table 1), the absorption band of the keto group occurs in the region of 1670-1680 cm^{-1} for compounds (IIa-c), 1690-1710 cm^{-1} for compounds (IId-f, h), and 1730 cm^{-1} for the compounds (IIg). The absorption band of the amide carbonyl of the ketolactams (II) occurs in the region of 1630-1650 cm^{-1}, as for the spectra of the ketolactams previously described [3]. The mass-spectrometric fragmentation of the ketolactams (II) (Table 1) is also analogous to the fragmentation of the analogous compounds previously described [3]. The presence of very intense ion peaks for which the m/z equals the mass of the corresponding lactam (N-phenylcaprolactam, N-phenylvalerolactam, etc.) is most characteristic; this characterizes the fragmentation of the compounds with the 1, 5-disposition of the carbonyl groups [3]. It is easily possible to make a selection between alternative structures of the ketolactams [besides the stereoisomeric ketolactams (IIg)] from the value of the m/z of such a peak. There are also characteristic peaks corresponding with the removal of the ketone fragment (the phenacyl or the oxocycloalkyl) from the molecular ion; the ketolactams (IIa-c) also have the peaks of the $(M - 105)^+$ ions (the removal of benzoyl). A series of the ketolactams has the peaks of the $(M - 28)^+$ ions corresponding with the removal of CO from the molecular ion; others have the peaks corresponding with the removal of CO and the ketone fragment. The stereoisomeric ketolactams α-(IIg) and β-(IIg) have virtually the identical picture of mass-spectrometric fragmentation, as well as very similar IR spectra.

The authors of the work [1] proposed a mechanism for the previously described thermolysis of 1, 2, 4-dioxazolidine derivatives (the reaction closest to the one studied by us) including the initial homolysis of the O—O bond, the subsequent fragmentation of the resulting biradical with the breaking of the C—C bond adjoining the C—O bond, and finally the attack of the carbon radical center on the nitrogen atom with the homolysis of the C—N bond and the release of the ketone. The given proposition for the reactions of an analogous mechanism considered by us, i.e., the formation and subsequent two-stage conversion of the biradical A, does not in our view agree with the high regioselectivity of the given reactions observed by us or likewise the structure of the thermolysis products. In particular, when there is a separate stage for the fragmentation of the biradical, the breaking of the $C_{(8a)}—C_{(4a)}$ bond should proceed more readily than that of the $C_{(8a)}—C_{(8)}$ bond; this should lead, on the whole, to the preferred formation of the ketoamine with the 1, 6-disposition of the carbonyl groups. However, such amides were not generally detected. According to our proposition, the thermolysis of the 2, 6-epidioxypiperidine derivatives studied by us includes either the single-stage simultaneous conversion of the biradical A (1) or the completely synchronous rearrangement of the initial aminoperoxide (2).



A

In both cases, the $C_{(8)}—C_{(8a)}$ bond, situated at the side of the reverse "departing" $N—C_{(2)}$ bond, should migrate; this leads to ketolactams with the 1, 5-disposition of the carbonyl groups. The synchronous character of the conversion is in accord with the high regioselectivity of the reactions. The investigation of models of the aminoperoxides (I) confirms the results obtained. In particular, it can be assumed that the thermolysis of the trans-anti-cis aminoperoxide (Ig) proceeds with the predominant conversion of the cis-coupled trimethylene substituent to the lactam fragment.

EXPERIMENTAL

The IR spectra were taken in chloroform using the Specord IR-75 instrument. The mass spectra were taken on the LKB-9000 instrument at the ionization energy of 70 eV. The PMR spectra were taken on a Bruker WM-250 instrument. The monitoring of the course of the reactions and the purity of the compounds obtained was accomplished by TLC on plates of Silufol.

The characteristics of the compounds synthesized are presented in Table 1. The data of the elemental analysis correspond with the calculated data.

1,3-Diphenyl-3-(2-oxocycloheptyl)-1-propanone (III). To the solution of 6.2 g (0.03 mole) of benzalacetophenone in 60 ml of ethnaol are added 3.9 g (0.035 mole) of cycloheptanone and the solution of 2 g of KOH in 5 ml of water. The mixture is left for 3 days at room temperature; the oil which separated out is crystallized with trituration. The diketone is filtered off, washed with water and the 2% solution of HCl, and again with water; it is dried and recrystallized from the 3:1 mixture of hexane–ethyl acetate.

2-(2-Oxocycloalkylmethyl) cycloheptanones (Va, b). The mixture of 22.5 g (0.2 mole) of cycloheptanone, 6.6 g (0.22 mole) of paraformaldehyde, 18 g (0.22 mole) of dimethylamine hydrochloride, and 2 ml of concentrated HCl in 100 ml of isopropanol is boiled for 1 h. The solvent is distilled off under reduced pressure. The residue is dissolved in 50 ml of water and extracted with ether. The aqueous layer is rendered alkaline with a 40% solution of NaOH until an alkaline reaction is obtained, prior to the extraction with ether (3 × 30 ml). The extract is dried with anhydrous potassium carbonate, and the ether is evaporated. The residue is dissolved in 40 ml of the cyclanone [cyclopentanone in the synthesis of the diketone (Va), and cyclohexanone in the synthesis of the diketone (Vb)], and the solution is added dropwise to 100 ml of the corresponding boiling cyclanone in the course of 3 h. The mixture is boiled for 15 h. The excess of the cyclanone is distilled off under reduced pressure, and the residue is distilled in vacuo (1-2 mm of Hg stem).

1-Phenyl-2,3-trimethylene-5,6-pentamethylenepyridinium (VIa) and 1-Phenyl-2,3-tetramethylene-5,6-pentamethylenepyridinium (VIb) Perchlorates. The solution of 0.1 mole of the diketone (Va) or (Vb), 11 g (0.12 mole) of aniline, and 28.5 g (0.12 mole) of hexachloroethane in 200 ml of xylene is boiled with the removal of water for 1 h. The xylene is decanted from the oil which separated out. The oil is dissolved in water, rendered alkaline with Na_2CO_3 to the pH 9, and extracted with ether (2 × 50 ml). To the aqueous layer is added, in small portions, a saturated aqueous solution of NH_4ClO_4 with stirring. The precipitated perchlorate (VIa) or (VIb) is filtered off; it is washed with water, dried, and recrystallized from ethanol.

1,2,4-Triphenyl-5,6-pentamethylene-2,6-epidioxypiperidine (Ib). The solution of 4.8 g (0.015 mole) of the diketone (III), 4 g (0.45 mole) of aniline, and 30 mg of p-toluenesulfonic acid in 50 ml of xylene is boiled with the removal of water for 15 h. The xylene and the excess aniline are distilled off under reduced pressure. The residue is dissolved in 15 ml of ethanol prior to the addition of the solution of 1 g of CH_3COONa in the mixture of 5 ml of CH_3COOH and 5 ml of 30% hydrogen peroxide. The mixture is held for 15 h at 5-10°C. The precipitated aminoperoxide (Ib) is filtered off, washed with ethanol and water, dried, and recrystallized from ethyl acetate.

Synthesis of the Tetracyclic Aminoperoxides (Ie-g). To the solution of the Grignard reagent prepared from 8.6 g (0.055 mole) of bromobenzene and 1.45 g (0.06 mole) of magnesium in 200 ml of THF is added, in portions, 0.027 mole of the finely ground pyridinium perchlorate (Va-c). The mixture is boiled for 30 min, and the THF is distilled off. To the residue is carefully added a 10% aqueous solution of NH_4Cl prior to the extraction with ether. The extract is washed with water, and the ether is evaporated. The residue is dissolved in 100 ml of ether [in the isolation of the peroxide (Ie)] or in the mixture of 30 ml of THF and 20 ml of propanol [in the isolation of the peroxides (If) and (Ig)]. To the solution obtained is added the solution of 5 g of CH_3COONa in the mixture of 15 ml of CH_3COOH and 20 ml of 30% H_2O_2. The mixture is left for 15 h at −10°C. Further, in the isolation of the compound (Ie), the ether solution is washed with water, a solution of Na_2CO_3, and again with water. The ether is distilled off, and the residue is treated with propanol prior to the removal by filtration of 1 g of the pure trans-syn-trans isomer of the aminoperoxide (Ie). In the isolation of the compound (If), the precipitated mixture of the two stereoisomeric forms of the aminoperoxide is filtered off. It is washed with ethanol and dissolved in 60 ml of THF prior to cooling it to −15°C and the addition of 3 drops of concentrated HCl. The mixture is held for 1 h at −15°C. After the neutralization of the solution by the action of Na_2CO_3 and the distillation of the THF, the obtained trans-syn-trans isomer of the aminoperoxide (If) is recrystallized from the 2:1 mixture of ethanol–ethyl acetate. In the case of the isolation of compound (Ig), the precipitated trans-anti-cis isomer is filtered off, washed with ethanol, dried, and recrystallized from ethyl acetate. The filtrate remaining after the separation of the trans-anti-cis isomer is diluted with water prior to the isolation of the trans-syn-

trans isomer of the aminoperoxide (Ig); the yield is 15%, and the mp is 116-117°C (from ethyl acetate).

By-products of the aminoperoxidation reaction – the perchlorates (IXa) and (IXb) – are precipitated on the addition of a saturated solution of NH_4ClO_4 to the aqueous layer after washing the ether solution with water [in the isolation of compound (Ie)] or to the filtrate diluted with water after the separation of the mixture of the isomeric forms of compound (If). The perchlorates are filtered off, washed with water, and recrystallized from ethanol.

1,4-Diphenyl-2,3-tetramethylene-5,6-pentamethylene-2,6-dicyanopiperidine (VIII). The reaction of 2 g of the perchlorate (VIb) with phenylmagnesium bromide is performed as described above until the stage of the distillation of the ether. The residue [unpurified compound (VIIb)] is dissolved in 8 ml of THF prior to the addition of the solution of 1.5 g of NaCN in the mixture of 3 ml of water and 4 ml of CH_3COOH. The mixture is heated for 1 h at 50-60°C and diluted with water. The precipitated dicyanide (VIII) is filtered off and recrystallized from ethanol.

Thermolysis of the Derivatives of 2,6-Epidioxypiperidine (Ia-g). The solution of 1 g of the aminoperoxide (Ia-g) in 20 ml of DMF [for the aminoperoxides (Ie, g)] or xylene (for the remaining aminoperoxides) is boiled for 2-5 h until the disappearance of the spot of the initial aminoperoxide on the TLC. The solvent is evaporated under reduced pressure. In the thermolysis of the aminoperoxides (If, g), the residue is chromatographed on a column with silica gel 100/160; the elution is performed with the 4:1 system of hexane–ethyl acetate. In the remaining cases, the residue is treated with ether, and the individual precipitated ketolactam is filtered off after several hours. The ketolactams (II) obtained are recrystallized from the mixture of hexane–acetone (IIb, e, g) or from ethyl acetate (the remaining ketolactams).

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