SYNTHESIS AND MASS-SPECTROMETRIC BEHAVIOR OF 1,3,4,5-TETRAHYDROBENZ-[b]AZEPIN-2-ONES

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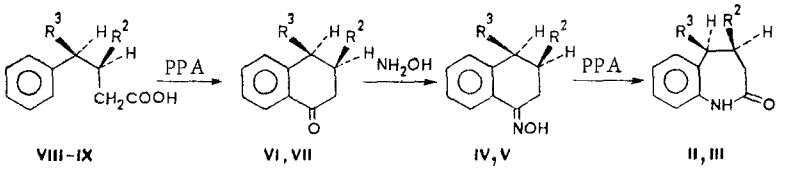
The mass-spectrometric behavior of methyl-substituted 1,3,4,5-tetrahydrobenz[b]-azepin-2-ones was studied. The fragmentation of benzolactams of the aniline type proceeds more selectively than the investigated fragmentations of lactams of the benzamide type. This is evidently associated with the noncoplanarity of the heterocyclic ring. Analysis of the mass spectra of the benzolactams makes it possible to determine both the type of fusion with the aromatic ring and the positions of the alkyl substituents in the heterocyclic ring.

We have previously shown that the processes involved in the dissociative ionization of isomeric methyl-substituted 3,4-dihydroquinolones and 3,4-dihydroisoquinolones differ; this makes it possible by means of the mass spectra to determine both the affiliation of a compound with one or another series and the position of the methyl group in the ring [1]. Similar characteristic differences in the mass-spectrometric behavior have been noted in a number of methyl-substituted 2,3-dihydroisoindolones [2] and 2,3,4,5-tetrahydrobenz[c]azepin-1-ones (lactams of the benzamide type) [2, 3]. In particular, it was established that the most probable pathways of fragmentation of the molecular ions involve cleavage of the saturated heterocyclic ring at the amide N—CO bond and the benzyl C—C bond. It seemed of interest to ascertain whether this character of fragmentation is retained in isomeric methyl-substituted 1,3,4,5-tetrahydrobenz[b]azepin-2-ones (I-III), which are lactams of the anilide type.

R-(+)-3-Methyl-1,3,4,5-tetrahydrobenz[b]azepin-2-one (I) was obtained previously by intramolecular amidation from R-(—)-2-methyl-4-phenylbutyrohydroxamide acid [4].

Benzolactams II and III, which contain an asymmetric atom in the β and γ positions relative to the amido group, were obtained by Beckmann rearrangement of the oximes of the corresponding substituted tetrazoles in polyphosphoric acid (PPA) (IV, V) [5]. The starting compounds for the synthesis of tetralones were optically active γ-phenylbutyric acids (VII, IX) [5].



VIII-IX VI, VII IV, V II, III

II, IV, VI, VIII $R^2=CH_3$, $R^3=H$; III, V, VII, IX $R^3=CH_3$, $R^2=H$

In a mass-spectral study we established that the stabilities of the molecular ions of lactams I-III are appreciably lower as compared with the analogous six-membered lactams [1] and do not exceed 9% and that the position of the methyl group in the heterocyclic ring has virtually no effect on the stabilities (see Table 1). The intensities of the $(M - CH_3)$ ions are very low and also are virtually independent of the position of the methyl group in the ring; this is evidently associated with the noncoplanarity of the seven-membered ring.

The principal fragmentation of the molecular ions of benzolactams of the anilide type (I-III) involves two processes (see the scheme presented below). The first process consists

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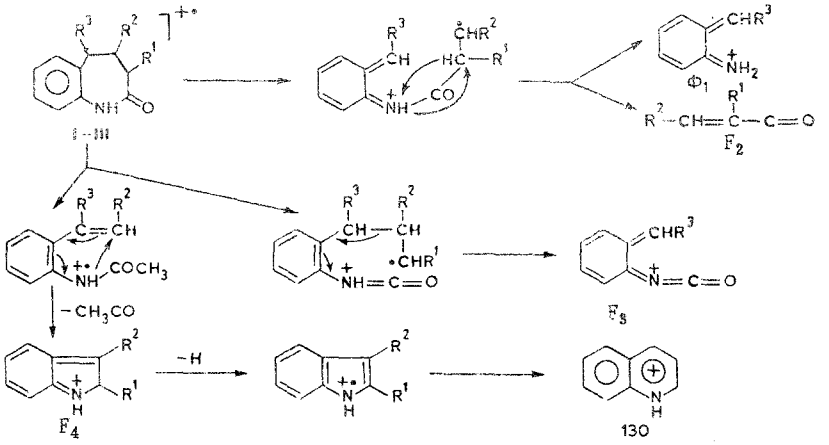
TABLE 1. Intensities of the Characteristic Ions in the Mass Spectra of I-III (% Σ_{40})

Compound	W_M	F_1	F_2	F_3	F_4
I	9,7	30,8	1,2	20,0	2,5
II	9,8	30,6	7,4	2,8	2,5
III	9,6	43,6	2,2	—	0,9

in primary cleavage of the benzyl C—C bond with the formation of conjugated o-methyleneanilinium cation F_1 and splitting out of unsaturated acylium ion F_2. The second fragmentation pathway involves cleavage of the α—β C—C bond with respect to the carbonyl group with subsequent transfer of the amide proton, splitting out of the alkyl radical, and the formation of methylenephenyl isocyanate ion F_3. In addition, one observes a third fragmentation pathway, which is apparently characterized by isomerization of the molecular ion to give an o-alkenylacetanilide with the subsequent elimination of an acetyl group and the formation of isobaric ion F_4. The compositions of the indicated ions were confirmed by the high-resolution mass spectra. The F_4 ion possibly has a heterocyclic structure, inasmuch as it subsequently loses one or two (in the case of I and II) hydrogen atoms, which is characteristic for methylindoles [6].



I $R^1=CH_3$, $R^2=R^3=H$; II $R^1=R^3=H$; $R^2=CH_3$; III $R^1=R^2=H$, $R^3=CH_3$

Let us note that the position of the methyl group in the heterocyclic ring has an appreciable effect on the primary fragmentation pathway. Thus the intensity of the F_1 ion peaks is highest in the case of 5-methyl-substituted III; the mass number of this ion is 14 amu greater than in the mass spectra of the other two isomers. Increased intensity of the F_2 ion peak is characteristic for the 4-methyl-substituted isomer II in connection with the great ease of cleavage of the benzyl C—C bond adjacent to the tertiary carbon atom. However, in the mass spectrum of I, which contains a methyl group in the 3 position, the second most intense peak is the F_3 ion peak; this is also associated with primary cleavage of the C—C bond adjacent to the site of branching. The overall intensity of the F_1-F_4 ions, together with the molecular ion, exceeds 50% of the total ion current, which indicates the high selectivity of fragmentation of benzolactams of the anilide type and is apparently also associated with the noncoplanarity of the heterocyclic ring.

Thus an analysis of the mass spectra of the benzolactams makes it possible to confidently determine both the type of fusion with an aromatic ring and the positions of the alkyl substituents in the heterocyclic ring.

EXPERIMENTAL

The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 50 eV. The high-resolution mass spectra were recorded at an energy of 70 eV with a JEOL JMS-01SG-2 mass spectrometer with automatic data processing. The IR spectra were recorded with a UR-20 spectrometer. Analysis by gas-liquid chromatography (GLC) was carried out with a Tsvet-5 chromatograph with a flame-ionization detector; the carrier gas was nitrogen (flow rate 40 ml/min),

TABLE 2. Mass Spectra of I-III

Compound	m/z values (relative intensities, %)*
I	175 (35), 146 (5), 133 (7), 132 (65), 118 (8), 117 (7), 106 (100), 104 (9), 91 (7), 78 (9), 77 (10)
II	175 (32), 160 (6), 146 (8), 132 (9), 131 (12), 117 (6), 107 (11), 106 (100), 104 (6), 78 (8), 77 (11), 69 (24)
III	175 (22), 120 (100), 97 (7), 69 (5), 57 (7), 55 (5), 43 (5), 41 (6), 39 (5)

*The molecular-ion peak and the peaks of ions with intensities greater than 5% are presented.

the steel column (l = 1m, d = 4 mm) was packed with 5% silicon XE-60 as the liquid phase and Chromaton N-AW as the solid phase (160-200 mesh), and the column temperature was 170°C.

The synthesis of R-(+)-3-methyl-1,3,4,5-tetrahydrobenz[b]azepin-2-one was carried out by the method in [4].

R-(−)-Methyltetralone (VI), with bp 118°C (6 mm) and $[\alpha]_D^{25}$ −12.3° (without a solvent), was obtained in 60% yield by the described method from (+)-3-methyl-4-phenylbutanoic acid (VIII) [5] [literature data: bp 140°C (13 mm) [7]; for the S isomer, $[\alpha]_D^{20}$ 12.4° (without a solvent) [5]].

S-(−)-4-Methyltetralone (VII). This compound, with bp 115°C (6 mm) and $[\alpha]_D^{25}$ −16.4° (without a solvent), was similarly obtained in 58% yield from (+)-4-phenylpentanoic acid (IX) [5] [literature data: bp 110-111°C (1 mm) [7] and $[\alpha]_D^{20}$ −14.5° (without a solvent) [5]].

Cyclic Ketone Oximes. A solution of 0.07 mole of potassium hydroxide in 30 ml of absolute ethanol was added to a mixture of 0.075 mole of hydroxylamine hydrochloride in 200 ml of absolute ethanol, a solution of 0.04 mole of the cyclic ketone in 30 ml of ethanol was added to the resulting solution (the medium was slightly acidic), and the mixture was refluxed for 6 h. It was then cooled and treated with water to dissolve the precipitate, and the solution was extracted with ether. The organic layer was dried with magnesium sulfate, the ether was removed by distillation, and the residue was recrystallized from ethanol. This procedure gave R-(−)-3-methyltetralone oxime, with mp 98°C, M^+ 175, and $[\alpha]_D^{25}$ −0.68° (c 1.0, ethanol), in 90% yield.

S-(−)-4-Methyltetralone Oxime (V). This compound, with mp 58°C, M^+ 175, and $[\alpha]_D^{25}$ −1.2° (c 1.0, ethanol), was obtained in 50% yield.

Benzolactams (II and III). A 0.01-mole sample of the cyclic ketone oxime was heated in polyphosphoric acid (PPA) in a weight ratio of 1:50 for 2-3 h, after which the mixture was cooled, decomposed with ice water, and extracted with chloroform. The extract was washed with water and dried with magnesium sulfate. The chloroform was removed by distillation, and the residue was recrystallized from benzene–isooctane or, if the purification was inadequate, it was chromatographed with a column packed with silica gel by elution with benzene–acetone (10:1). The purity of the compounds was monitored by thin-layer chromatography (TLC) on Silufol and also by means of GLC.

R-(−)-4-Methyl-1,3,4,5-tetrahydrobenz[b]azepin-2-one (II). This compound, with mp 148°C, was obtained in 90% yield from R-(−)-3-methyltetralone oxime (IV) by heating at 105°C for 2 h. IR spectrum (mineral oil): 1680 cm^{-1} (C=O, amide I). Found: C 75.8; H 7.8%. $C_{11}H_{13}NO$. Calculated: C 75.4; H 7.5%.

S-(−)-5-Methyl-1,3,4,5-tetrahydrobenz[b]azepin-2-one (III). This compound, with mp 161-162°C and M^+ 175, was obtained in 70% yield from S-(−)-4-methyltetralone oxime (V) by heating the reaction mixture at 130-140°C for 2.5 h. IR spectrum (mineral oil): 1668 cm^{-1} (C=O, amide I). The mass spectra of I-III are presented in Table 2.

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OXIDATION AND REDUCTION OF SUBSTITUTED 4-HYDROXYAMINO- AND 4-OXIMINOIMIDAZOLIDIN-2-ONES

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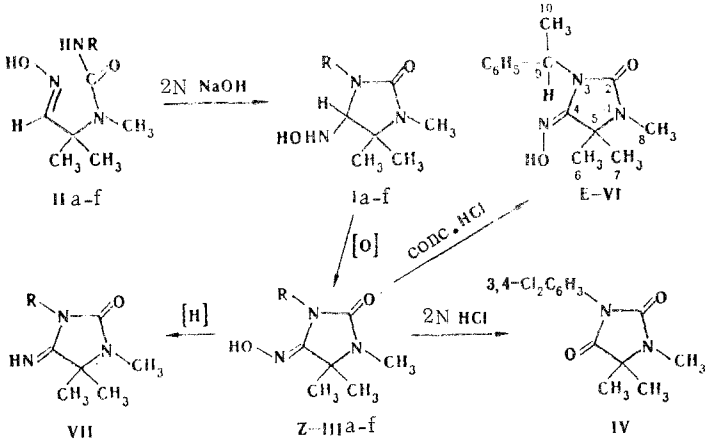
4-Oximino-3-aryl(alkyl)-5,5-dimethylimidazolidin-2-ones were obtained by air oxidation of substituted 4-hydroxyaminoimidazolidin-2-ones in the presence of sodium ethoxide. In hydrochloric acid 4-oximino-3-(3',4'-dichlorophenyl)imidazolidin-2-one gives the corresponding hydantoin, whereas 4-oximino-3-(1'-phenylethyl)-imidazolidin-2-one gives its E isomer with respect to the oxime group. The reduction of 4-oximino-3-alkylimidazolidin-2-ones with Raney alloy in 20% NaOH or hydrogenation on a palladium catalyst leads to 4-imino derivatives, whereas reduction of 4-oximino-3-aryl-5,5-dimethylimidazolidin-2-ones that contain chlorine atoms in their aromatic rings with sodium in liquid ammonia leads to their dehalogenation.

We have found that 4-hydroxyamino-3-aryl(alkyl)-1,5,5-trimethylimidazolidin-2-ones (Ia-e), obtained from the corresponding N-carbamoyl derivatives (IIa-f) of 2-methyl-2-methylaminopropanaldoxime, are easily converted in strongly alkaline media to stable crystalline IIIa-e, which, in contrast to the starting compounds, do not give the colored complexes with 2,3,5-triphenyltetrazolium chloride that are characteristic for unsubstituted hydroxyamino groups.



I, II, III a R=3,4-$Cl_2C_6H_3$, b R=3-ClC_6H_4, c R=4-ClC_6H_4, d R=C_6H_5, e R=$C_6H_5CHCH_3$, f R=CH_3; VII a R=$C_6H_5CHCH_3$, b R=CH_3

The PMR spectra of the compounds (in d_6-DMSO) do not contain the signal of a hydrogen atom in the 4 position of the heteroring. Two intense absorption bands at 1665-1680 and

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