INTRAMOLECULAR AMIDATION OF ARYLALKYLHYDROXAMIC ACIDS

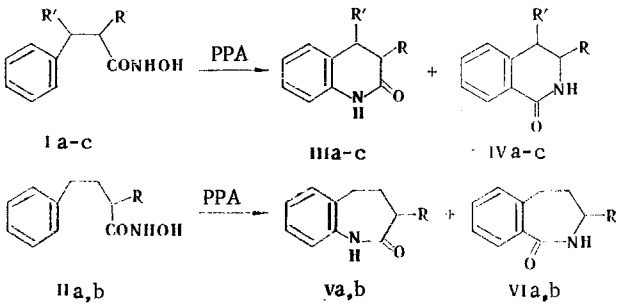
V. M. Potapov, V. M. Dem'yanovich,
O. E. Vendrova, and V. A. Khlebnikov

UDC 547.831.8'333.7'891.2:542.952:543.422

It is shown that mixtures of two isomeric benzolactams, viz., compounds of the benzamide and anilide type, are formed in the intramolecular amidation of arylalkylhydroxamic acids under the influence of polyphosphoric acid (PPA). A general reaction scheme that includes three pathways, viz., direct amidation, Lossen rearrangement of the hydroxamic acids with subsequent cyclization of the isocyanates, and Beckmann rearrangement of the oximes of the cyclic ketones formed in the thermal cleavage of the starting hydroxamic acids in PPA, is proposed on the basis of a study of racemic and optically active arylalkylhydroxamic acids.

Many methods for the synthesis of benzolactams with different types of conjugation in the molecule, viz., anilide and benzamide conjugation, have been described [1-5]. However, most of these methods cannot be used for the synthesis of optically active compounds of this type. In principle, the intramolecular amidation of arylalkylhydroxamic acids in polyphosphoric acid (PPA) is suitable for the synthesis of optically active benzolactams with an α-asymmetric carbon atom; the literature data on this reaction [6-9] provide evidence for the isolation of benzolactams only of the anilide type from the reaction mixtures.

In contrast to this, we have established that two isomeric benzolactams, viz., compounds of the anilide (IIIa-c, Va,b) and benzamide (IVa-c, VIa,b) type, are formed in the cyclization of arylalkylhydroxamic acids Ia-c and IIa,b in PPA. We have also obtained optically active benzolactams of the anilide type (IIIb and Vb) by this method for the first time.



I, III, IV a R = R′ = H; b R = CH_3, R′ = H; c R = H, R′ = CH_3; II, V, VI a R = H; b R = CH_3

The yields of isomeric benzolactams and their ratios under various reaction conditions were determined by gas—liquid chromatography (GLC) with the aid of squalane as the internal standard. In the analysis of the reaction mixtures in all cases we observed chromatographic peaks of the corresponding cyclic ketones, the percentages of which in the reaction mixtures (∿10% of the overall weight) decreased as the temperature and time were increased. In addition, in a number of cases we detected the presence of trace amounts of cyclic ketone oximes.

To determine the optimum (in a preparative respect) reaction conditions we used the method of mathematical experiment planning, which made it possible to determine the conditions for the maximum yields and ratios of the isomeric benzolactams over the temperature range 90 to 130°C and times ranging from 0.3 to 5 h (Tables 1 and 2). The dependence of the yield of six-membered benzolactam (±)-IIIb, obtained from Ib, on the reaction temperature and time is presented in Fig. 1.

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 655-660, May, 1983. Original article submitted July 20, 1982.

 0009-3122/83/1905-0528$07.50

TABLE 1. Conditions for Obtaining the Maximum Yields of the Benzolactams

Starting compound	Reaction conditions		Yield (overall), %	Isomer ratio
	temp., °C	time, h		
Ia	125—130	4—5	58	IIIa/IVa ≥ 15*
(±)-Ib	115	2,5	60	(±)-IIIb/(±)-IVb=5
(±)-Ic	115	2,5	68	(±)-IIIc/(±)-IVc=2
IIa	120	2,5	44	Va/VIb ≥ 15
(±)-IIb	115	3	29	(±)-Vb/(±)-VIb=7
VII	115	4,5	75	(±)-IIIb/(±)-IVc=4
VIII	125—130	1—5	95	†

*It was established by calibration GLC analyses that the error in the determination of the percentage of the lesser component becomes indeterminately large for isomer ratios ≥15. The overall yield of benzolactams in this case is set equal to the yield of the component present in larger amounts.
†An isomer of the benzamide type was not detected chromatographically under any of the investigated rearrangement conditions.

Similar dependences were ascertained for the reaction of hydroxamic acids Ia,c and IIa, b; the ranges of the maximum yields of the benzolactams in the latter three cases are shifted somewhat to increased temperatures and times.

Thus a study of the intramolecular amidation of racemic hydroxamic acids Ia-c and IIa,b confirmed the previously observed [10] formation in this reaction of two isomeric benzolactams of the anilide and benzamide type and made it possible to find the optimum conditions for carrying out this reaction and determine the isomer ratios.

To study the stereochemistry of the intramolecular amidation of arylalkylhydroxamic acids and to synthesize optically active six- and seven-membered benzolactams of the anilide type with an α-asymmetric carbon atom we carried out the cyclization in PPA of (—)-(R)-methylbenzylacetohydroxamic acid [(—)-Ib and (—)-(R)-α-methyl-α-(β-phenylethyl)acetohydroxamic acid [(—)-IIb]. (+)-3-Methyl-3,4-dihydro-1H-quinol-2-one [(+)-IIIb] and (—)-3-methyl-3,4-dihydro-2H-isoquinol-1-one [(—)-IVb] were isolated in the cyclization of acid (—)-Ib. We previously obtained (—)-IVb in optically pure form by an independent method [11]. A comparison of the circular dichroism (CD) of the two compounds showed that the optical purity of the dihydroquinolone (—)-IVb obtained in the present research was 29%. The optical purity of dihydroisoquinolone (+)-IIIb (∿38%) was determined by NMR spectroscopy with the aid of the chiral shift reagent europium tris[3-(tert-butoxymethylene)-(+)-camphorate] [Eu(TBC)$_3$] [12].

(+)-3-Methyl-1,2,3,4-tetrahydrobenz[b]azepin-2-one [(+)-Vb] and (—)-3-methyl-2,3,4,5-tetrahydrobenz[c]azepin-1-one [(—)-VIb] were isolated in the cyclization of acid (—)-IIb. We previously obtained (—)-VIb with an optical purity of ∿90% by an independent method [13]. A comparison of the CD of the two compounds showed that ∿100% optically pure lactam (—)-IVb was isolated from the reaction mixture.

The optical purity of lactam (+)-Vb is evidently low. This is evidenced by the small degree of dichroism of this compound as compared with (—)-IVb and the isomeric 4- and 5-methyl-substituted benzolactams of the anilide type, whereas the extinction of lactam (+)-Vb in the UV region is virtually the same as the extinction of these compounds. We were unable to directly determine the optical purity of lactam (+)-Vb because of the absence of splitting of the signals of the enantiotopic protons in its PMR spectrum, as in the spectrum of the racemic analog in the presence of Eu(TBC)$_3$.

We feel that it is possible to explain the data that we obtained by taking into account three competitive pathways of intramolecular amidation of the arylalkylhydroxamic acids in PPA [in the case of (—)-Ib and (—)-IIb].

TABLE 2. Conditions for the Cyclization of Arylalkylhydroxamic Acids in PPA That Ensure Maximum Preponderance of Benzolactams of the Anilide Type

Starting compound	Reaction conditions		Yield (overall), %	Anilide/benzamide isomer ratio
	temp., °C	time, h		
Ia	90—130	0,3—5	10—58	IIIa/IVa ≥ 15
(±)-Ib	125	4	20	(±)IIIb/(±)-IVb = 7
(±)-Ic	90—95	0,3—1	30—55	(±)-IIIc/(±)-IVc = 8
	125—130	4—5		
IIa	90—130	0,3—5	20—44	Va/VIa ≥ 15
(±)-IIb	115	3	29	(±)-Vb/(±)-VIb = 7

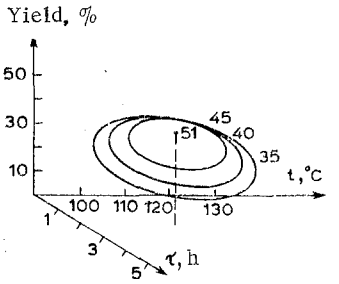
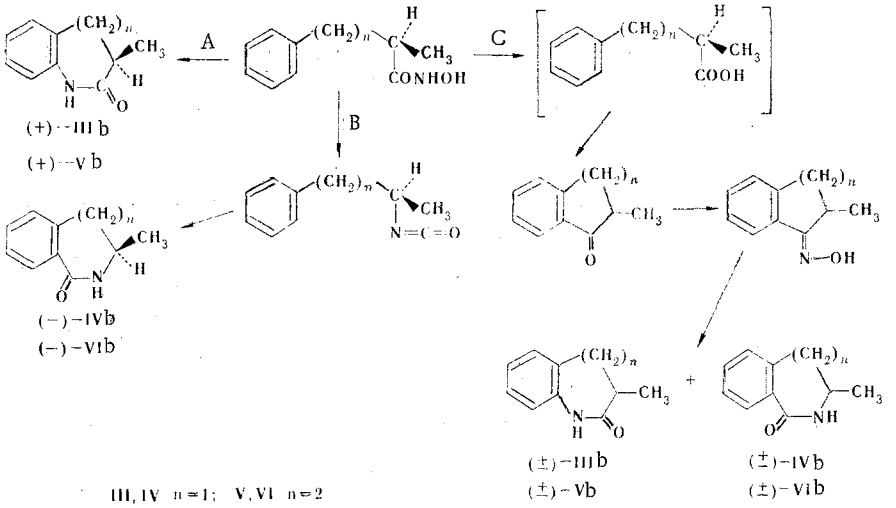


Fig. 1. Temperature—time dependendence of the yield of lactam (±)-IIIb in the cyclization of hydroxamic acid (±)-Ib in PPA.



Direct amidation, which leads to isomers of the anilide type (pathway A), proceeds without involvement of the asymmetric center, and, consequently, the optical purity of benzolactams (+)-IIIb and (+)-Vb, which are formed via this pathway, should correspond to the optical purity of the starting hydroxamic acids (∿100%).

Isomers of the benzamide type (pathway B) are formed in the Lossen rearrangement of hydroxamic acids with subsequent cyclization in PPA of the intermediate isocyanates. Since retention of the configuration of the asymmetric center is a general rule in rearrangements at an electron-deficient nitrogen atom, and in this case the optical purity of benzamides (−)-IVb and (−)-VIb should correspond to the optical purity of the starting hydroxamic acids.

The third possible reaction pathway (pathway C) assumes partial cleavage of the hydroxamic acids in PPA at elevated temperatures to give hydroxylamine and the corresponding optically active carboxylic acids. Cyclization of the latter in PPA proceeds with complete

racemization. The cyclic ketone oximes that are formed in the reaction with hydroxylamine undergo Beckmann rearrangement in PPA, and the same benzolactams of the benzamide and anilide type are again formed but in racemic form. The detection in the reaction mixtures of chromatographic peaks of the corresponding cyclic ketones and their oximes after cyclization of the racemic hydroxamic acids and the preparative isolation from the reaction mixtures of racemic 2-methylindanone and 2-methyltetralone, respectively, after cyclization of optically active hydroxamic acids (—)-Ib and (—)-IIb constitute evidence in favor of pathway C.

To verify the proposed reaction scheme we studied the Beckmann rearrangement in PPA of 2-methylindanone oxime (VII) and 2-methyltetralone oxime (VIII) — the proposed intermediates in the reactions of the hydroxamic acids via pathway C. The rearrangements were carried out under conditions similar to the conditions of cyclization of the hydroxamic acids. The yields of the isomeric benzolactams and their ratios under various reaction conditions were determined by GLC (Table 1).

The results of quantitative analysis of the reaction mixtures in combination with data on the optical purity of the isomeric benzolactams (Table 3) may serve as additional confirmation of the proposed reaction scheme.

It is expedient to further discuss the six-membered and seven-membered benzolactams separately.

Six-Membered Benzolactams. On the basis of the data in Table 3 and knowing the yields (A) and ratios of the isomers, as well as the optical purity of one of them, one can calculate the optical purity of the second isomer. For example, for the (—)-IVb isomer of the benzamide type the optical purity $p_{(-)\text{-IVb}}$ is calculated from the formula

$$p_{(-)\text{-IVb}} = (1 - A_{(\pm)\text{-IVb}}/A_{(-)\text{-IVb}}) \cdot 100 \quad (1)$$

The yield of racemic benzolactam IVb of the benzamide type in the intramolecular amidation of hydroxamic acid (—)-Ib can, in turn, be calculated from data on the optical purity of benzolactam (+)-IIIb of the anilide type [$p_{(+)\text{-IIIb}}$] and the ratio of the racemic products of the Beckmann rearrangement of oxime VII [$A'_{(+)\text{-IIIb}}/A'_{(+)\text{-IVb}}$]:

$$A_{(\pm)\text{-IVb}} = A_{(+)\text{-IIIb}}(1 - 0{,}01p_{(+)\text{-IIIb}})/(A'_{(\pm)\text{-IIIb}}/A'_{(\pm)\text{-IVb}}) \quad (2)$$

Substitution of the numerical data from Table 3 into Eqs. (1) and (2) gives optical purity $p_{(-)\text{-IVb}}$ = 31%, which is in completely satisfactory agreement with the experimentally found optical purity of (—)-IVb (29%).

Seven-Membered Benzolactams. The fact that virtually one isomer of the anilide type is formed under all of the investigated conditions of the Beckmann rearrangement of 2-methyltetralone oxime (VIII) (Table 1) makes it possible to explain the data on the optical purity of seven-membered benzolactams. It may be concluded that the isomer of the anilide type in the rearrangement of arylalkylhydroxamic acids is formed primarily via pathway C, which also explains its low optical purity. However, the (—)-IVb isomer of the benzamide type, which does not develop via pathway C, naturally has high optical purity: The yield of this isomer is determined completely by the second possible reaction pathway (pathway B), and its optical purity is equal to the optical purity of starting hydroxamic acid IIb (∿100%).

EXPERIMENTAL

Analysis by GLC was carried out with a Tsvet-5 chromatograph with a flame-ionization detector; the carrier gas was nitrogen (40 ml/min), the 1 m by 4 mm steel column was filled with 5% Silicon XE-60 on Chromaton NAW silanized with hexamethyldisiloxane, and the column temperature was 170°C. The circular dichroism (CD) spectra were recorded with a JASCO J-20 automatic spectropolarimeter in cuvettes with lengths of 10, 1, and 0.5 mm. The UV spectra were obtained with a Cary-219 spectrophotometer. The IR spectra were obtained with a UR-20 spectrometer. 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 PMR spectra were recorded with a Tesla BS-497 spectrometer with an operating frequency of 100 MHz.

Hydroxamic acids Ia-c, IIa,b, (—)-Ib, and (—)-IIb were obtained as described in [14].

Investigation of the Cyclization of Hydroxamic Acids Ia-c and IIa,b and the Rearrangement of Oximes VII and VIII in PPA. A 0.05-g sample of the hydroxamic acid or oxime was

TABLE 3. Ratios of the Isomeric Benzolactams and Their Optical Purity

Starting compound	Reaction conditions		Product of the anilide type		Product of the benzamide type	
	temp., °C	time, h	yield, %	optical purity, %	yield, %	optical purity, %
(−)-Ib	110	3	(+)-IIIb: 50	38	(−)-IVb: 9	29
VII	110	3	(±)-IIIb: 60	—	(±)-IVb: 12	—
(−)-IIb	115	4	(+)-Vb: 20	Low	(−)-VIb: 4	100
VIII	115	4	(±)-Vb: 75	—	(±)-VIb: —	—

added with stirring to 5 g of PPA, and the mixture was thermostatted at various temperatures (90-130°C) and stirred for a certain period of time (from 0.3 to 5 h). It was then decomposed with ice, and the aqueous mixture was extracted with chloroform. The chloroform extracts were dried with magnesium sulfate, the solvent was removed by distillation, and the residue was analyzed by GLC with squalane as the internal standard (Tables 1 and 2).

Cyclization of Acid (−)-Ib in PPA. A 1-g sample of (−)-Ib [$[\alpha]_D^{20}$ −90.5° (c 4.2, ethanol)] was added with stirring to 100 g of PPA, and the mixture was stirred at 110°C for 3 h and worked up as described above. The solvent was removed by distillation, and the residue was chromatographed with a column filled with L 40/100 silica gel (Czechoslovakian SSR) by elution with a mixture of benzene and acetone (10:1) to give 0.286 g of lactam (+)-IIIb with mp 134°C and M^+ 161. IR spectrum (CCl_4): νCO 1680 cm^{-1} (amide I). The optical purity was 38% [12]. UV spectrum in ethanol, λ_{max}(log ε): 285 (inflection, 3.16) and 250 nm (4.19). Circular dichroism in hexane (c 0.01), −[θ]° (λ, nm): 0 (300), −685 (287), 0 (275), 8440 (250), 0 (244), −1640 (225), and −6180 (205). Also isolated was 0.140 g of lactam (−)-IVb with mp 145°C and M^+ 161. IR spectrum (CCl_4): νCO 1675 cm^{-1} (amide I). The optical purity was 29% [11]. UV spectrum in ethanol, λ(log ε): 280 (inflection, 3.0) and 231 nm (3.91). Circular dichroism in isooctane (c 0.01), −[θ]°(λ, nm): 0 (300), −4029 (270), −2947 (244), 1253 (225), and −2010 (210).

Cyclization of Acid (−)-IIb in PPA. A 1-g sample of (−)-IIb [$[\alpha]_D^{20}$ −38.2° (c, 4.2, ethanol)] was added with stirring to 100 g of PPA, and the mixture was stirred at ∿115°C for 4 h and worked up as described above. The solvent was removed by distillation, and the residue was chromatographed with a column filled with L 40/100 silica gel by elution with a mixture of benzene and acetone (10:1) to give 0.114 g of lactam (+)-Vb with mp 166°C and M^+ 175. IR spectrum (mineral oil): νCO 1680 cm^{-1} (amide I). UV spectrum in ethanol, λ_{max}(log ε): 275 (inflection, 3.0), 268 (3.25), and 239 nm (4.12). Circular dichroism in isooctane (c 0.02), −[θ]°(λ, nm): 0 (290), 71.7 (275), 35.9 (270), 1033 (250), 359 (245), 1434 (240), 0 (233), 0 (233), and −430 (227). Also isolated was 0.040 g of lactam (−)-VIb with mp 165°C and M^+ 175. IR spectrum (mineral oil): νCO 1662 cm^{-1} (amide I). UV spectrum in ethanol, λ_{max}(log ε): 272 (3.26), 226 (4.15), and 220 nm (4.13). Circular dichroism in isooctane (c 0.01), −[θ]°(λ, nm): 0 (300), −583 (284), −3970 (256), −1620 (240), 0 (237), 6800 (222), and 0 (212).

LITERATURE CITED

1. E. R. Blout and D. S. Silverman, J. Am. Chem. Soc., 66, 1442 (1944).
2. P. Camilleri, R. Ellud, A. I. Kirbu, and T. G. Myjahid, J. Chem. Soc., Perkin Trans. II, 12, 1617 (1979).
3. F. Mayer, L. van Zütphen, and W. Phillips, Chem. Ber., 60, 858 (1927).
4. J. Colonge and R. Chambard, Bull. Soc. Chim. Fr., No. 3, 982 (1953).
5. P. T. Lansbury and N. R. Mancuso, J. Am. Chem. Soc., 88, 1205 (1966).
6. F. W. Wassmund and S. J. Padejimas, J. Am. Chem. Soc., 89, 7131 (1967).
7. J. T. Marone, Diss. Abstr. Int., B33, 2532 (1972).
8. J. Suwinski, Zesz. Nauk PS'1. Chem. Pharm. Bull., 19, 1325 (1971).
9. T. Kametani and H. Nemoto, Chem. Pharm. Bull., 19, 1325 (1971).
10. P. B. Terent'ev, L. D. Solov'eva, V. M. Dem'yanovich, O. E. Popova, and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 2, 246 (1979).
11. V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and A. P. Terent'ev, Dokl. Akad. Nauk SSSR, 185, 614 (1969).

12. V. M. Potapov, V. M. Dem'yanovich, O. E. Vendrova, and V. A. Khlebnikov, Dokl. Akad. Nauk SSSR, 285, 624 (1981).
13. V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and O. E. Vendrova, Khim. Geterotsikl. Soedin., No. 5, 675 (1981).
14. V. M. Potapov, V. M. Dem'yanovich, O. E. Vendrova, and V. A. Khlebnikov, Zh. Org. Khim., 18, 1205 (1982).
15. E. S. Wallis and R. D. Dripps, J. Am. Chem. Soc., 55, 1701 (1933).
16. Y. Barry, H. B. Kagan, and G. Snatzke, Tetrahedron, 27, 4737 (1971).