EFFECT OF THE POSITION OF THE ASYMMETRIC CENTER ON THE CHIRAL-OPTICAL PROPERTIES OF SEVEN-MEMBERED BENZOLACTAMS

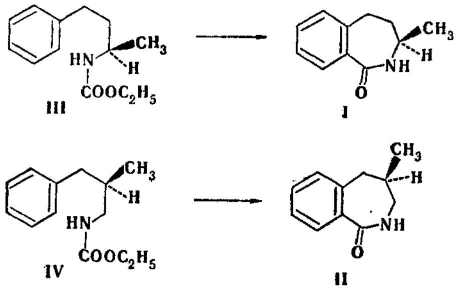
V. M. Potapov, V. M. Dem'yanovich,
L. D. Solov'eva, and O. E. Vendrova

UDC 541.653.547.892

The synthesis and chiral-optical properties of (+)-3-methyl- and (+)-4-methyl-2,3,4,5-tetrahydro-1H-benz[c]azepin-1-ones are described. A weak Cotton effect (CE) at 270 nm and a more intense positive CE are observed for both compounds in the 250 nm region. The considerably lower CE at 250 nm in the case of the 4-methyl isomer as compared with the 3-methyl isomer is explained by the remoteness of the asymmetric center in the 4-methyl isomer from the conjugated benzamide chromophore and the absence of the preferred conformation, which determines the sign of the CE.

During a study of the chiral-optical properties of benzolactams with different sizes of the lactam ring and an identical orientation of the asymmetric carbon atom relative to the aromatic chromophore [1] it was established that the magnitude of elliptical character in the region of the absorption band of the benzamide chromophore increases as the size of the lactam ring increases on passing from a five-membered lactam to a six-membered lactam and then to a seven-membered ring. This was explained by the possibility of the formation of a strictly disymmetrical chromophore due to distortion of the benzamide chromophore.

In order to ascertain the effect of the position of the asymmetric center in seven-membered benzolactams on their chiral-optical properties we synthesized new benzolactams, viz., (+)-3-methyl- (I) and (+)-4-methyl-2,3,4,5-tetrahydro-1H-benz[c]azepin-1-ones (II), by cyclization of, respectively, N-[(+)-1-methyl-3-phenylpropyl]urethane (III) and N-[(+)-2-methyl-3-phenylpropyl]urethane (IV) under the influence of polyphosphoric acid (PPA):



Urethanes III and IV were obtained from (+)-1-phenyl-3-aminobutane (V) and (+)-2-methyl-3-phenylpropylamine (VI) and ethyl chlorocarbonate. Amine V was obtained as we described in [2]. Amine VI was synthesized from (—)-(R)-2-methyl-3-phenylpropanoic acid through the acid chloride and the amide. It is known that racemization is possible in the step involving the preparation of an acid chloride that has an asymmetric center in the α position relative to the carboxy group. We therefore carried out the determination of the optical purity of the resulting (+)-2-methyl-3-phenylpropylamine from the PMR spectrum of N-[(—)-1-phenylethyl]-N'-(2-methyl-3-phenylpropyl)urea (VII), which was obtained by the action of (—)-α-phenylethyl isocyanate with 100% optical purity on amine VI. The ratio of the enantiomers was determined from the ratio of the areas of the peaks of the protons of the diastereotopic methyl groups of the α-phenylethyl fragment. The optical purity of 2-methyl-3-phenylpropylamine with $[M]_{300}^{20}$ + 86.5° (c 0.24, alcohol) was 88%.

The structures of benzolactams I and II were proved by data from the IR and mass spectra. The mass-spectral behavior of 3- and 4-methyl-2,3,4,5-tetrahydrobenzazepin-1-ones

---

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 675-677, May, 1981. Original article submitted July 21, 1980.

0009-3122/81/1705-0498$07.50 © 1981 Plenum Publishing Corporation

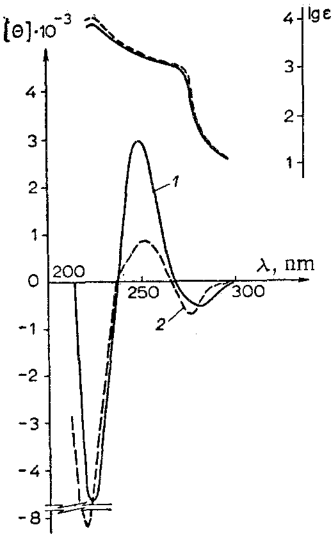


Fig. 1. UV and CD spectra in alcohol of (+)-3-methyl- (I) (1) and (+)-4-methyl-2,3,4,5-tetrahydro-1H-benz[c]azepin-1-one (II) (2).

(I and II) is similar to the fragmentation of the previously described 5-methyl analog (VIII) [1]: The molecular ion (M^+) undergoes primary fragmentation at the amide bond with subsequent elimination from the open form of CH_3, NH_2, and CH_2NH fragments (II) and a CH_3NH fragment (I). The subsequent fragmentation of these ions takes place with the elimination of a CO molecule and the formation of hydrocarbon ions. It should be emphasized that in the mass spectrum of II, as in the mass spectrum of 5-methyl-2,3,4,5-tetrahydro-1H-benz[c]azepin-1-one (VIII), the $M-CH_3$ ion peak has very low intensity. However, in the mass spectrum of I its intensity, as compared with the molecular ion, increases appreciably, similar to what we observed in a comparison of the mass spectra of 3-methyl- and 4-methyl-3,4-dihydroisoquinol-1-ones [3].

We measured the UV spectra and the circular dichroism (CD) in alcohol and isooctane of benzazepinones I and II (Fig. 1). The UV spectra of the two compounds are virtually identical: They contain an inflection at 269-275 nm and an increase in the absorption in the shorter-wave region. The CD spectra of I and II show a negative Cotton effect (CE) in the 275 nm region and a strong negative CE in the 220 nm region, which are associated, respectively, with the ^1L_b and ^1L_a absorption bands of an aromatic chromophore. In addition, a strong positive CE, the reason for which is a charge transfer band in the conjugated benzamide chromophore, is observed at ∿250 nm. The corresponding band does not appear in the UV spectrum. The magnitude of this CE in the case of 4-methyl isomer II ($[\theta]_{255}$ + 870°) is considerably smaller than for 3-methyl isomer I ($[\theta]_{248}$ + 2980°). This difference in the CE cannot be explained by the different optical purities of benzolactams I and II, since the starting amines had close optical purities (90-100%), whereas racemization does not occur in the last steps of the formation of urethanes and their cyclization.

The considerably smaller CE of 4-methyl isomer II as compared with 3-methyl isomer I and the previously investigated 5-methyl isomer VIII may be due to the remoteness of the asymmetric carbon atom from both ends of the conjugated benzamide chromophore, whereas in the latter two isomers the asymmetric center is located next to either the amide part of the benzamide chromophore (I) or the aromatic chromophore (VIII). In addition, the reason for the very small CE of II may be the existence of several conformations of the lactam ring, the contributions of which mutually cancel out one another. At the same time, the greater CE in the case of the 3- and 5-methyl isomers (I and VIII) make it possible to assume that in these compounds there is a preferred conformation, which also determines the sign and magnitude of the observed CE.

EXPERIMENTAL

The CD measurements were made with a JASCO J-20 automatic spectropolarimeter in cuvettes with lengths of 10, 1, and 0.1 mm. The UV spectra were recorded with a Cary-15 spectrophotometer. The IR spectra were recorded with a UR-10 spectrometer. The mass spectra were recorded with a JEOL-JMS-01-SG-02 spectrometer at an ionizing-electron energy of 75 eV and a temperature of 110°C.

The amide, with mp 116°C and $[M]_{300}$ − 870° (c 0.04, alcohol), was obtained in 70% yield from (−)-2-methyl-3-phenylpropanoyl chloride [4]. Found: C 73.3; H 8.0%. $C_{10}H_{13}NO$. Calculated: C 73.6; H 8.0%.

(+)-2-Methyl-3-phenylpropylamine (VI). This compound, with bp 114°C (18 mm) and $[M]_{300}$ 86.5° (c 0.24, alcohol), was obtained in 80% yield by reduction of (−)-2-methyl-3-phenylpropanoic acid amide with lithium aluminum hydride. The hydrochloride had mp 184°C (from ethyl acetate). Found: C 64.4; H 8.6%. $C_{10}H_{15}N \cdot HCl$. Calculated: C 64.6; H 8.7%.

Determination of the Optical Purity of (+)-2-Methyl-3-phenylpropylamine (VI). A 0.005-mole sample of (−)-α-phenylethyl isocyanate with 100% optical purity [5] was added to a heptane solution of 0.005 mole of amine VI, and the mixture was maintained at room temperature for 24 h. The precipitate was removed by filtration and dried, and the PMR spectrum of the resulting N-[(−)-1-phenylethyl]-N'-(2-methyl-3-phenylpropyl)urea (VII) in CD_3OD was measured (the PMR spectrum was measured with a Varian XL-100-15 spectrometer with hexamethyldisiloxane as the internal standard). The chemical shifts of the protons of the diastereotopic methyl groups of the α-phenylethyl fragment were as follows: 1.30 [doublet of the (+)-R isomer] and 1.26 ppm [doublet of the (−)-S isomer]. The ratio of the diastereomers was determined by the weight method from the ratio of the areas of the signals of the protons of the diastereotopic methyl groups of the α-phenylethyl fragment. It amounted to 94:6, which corresponds to an optical purity of 88%.

(S)-(+)-1-Phenyl-3-aminobutane (V). This compound was obtained by the method described in [2] and had bp 101°C (16 mm) and $[\alpha]_D^{20}$ 18.76°C (without a solvent). The optical purity of the amine was 87% [6]. According to the literature data, this compound has bp 101-102°C (14 mm) and $[\alpha]_D^{26}$ 10.1°C (without a solvent) [7].

The corresponding urethanes were obtained by the action of ethyl chlorocarbonate on (+)-2-methyl-3-phenylpropylamine and (+)-1-phenyl-3-aminobutane in an alkaline medium [8].

N-[(+)-1-Methyl-3-phenylpropyl]urethane (III). This compound was obtained in 80% yield and had bp 158°C (3 mm) and $[M]_{300}$ 15°C (c 3.0, alcohol). Found: C 70.9; H 8.8%. $C_{13}H_{19}NO_2$. Calculated: C 70.6; H 8.7%.

N-[(+)-2-Methyl-3-phenylpropyl]urethane (IV). This compound was obtained in 80% yield and had bp 160°C (7 mm) and $[M]_{300}$ 139°C (c 1.02, alcohol). Found: C 70.7; H 8.6%. $C_{13}H_{19}NO_2$. Calculated: C 70.6; H 8.7%.

(S)-(+)-3-Methyl- (I) and (S)-(+)-4-Methyl-2,3,4,5-tetrahydro-1H-benz[c]azepin-1-one (II). These compounds were obtained by the method in [1] by cyclization of the corresponding urethanes in PPA at 135-140°C in 3 h.

(S)-(+)-3-Methyl-2,3,4,5-tetrahydro-1H-benz[c]azepin-1-one (I). This compound, with mp 165°C, was obtained in 10% yield. IR spectrum (mineral oil): $\nu C{=}O$ 1662 cm^{-1} (amide I). Mass spectrum, m/e*: 175 (27), 160 (7), 133 (21), 132 (13), 131 (8), 105 (7), 104 (13), 103 (7), 92 (8), 91 (100), 78 (7), 77 (9). Circular dichroism in isooctane (c 0.02): $[\theta]_\lambda^\circ$ 189 (287 nm, 0 (276), 2740 (252), 0 (234), −4450 (219), 0 (210). Found: M^+ 175. $C_{11}H_{13}NO$. Calculated: M 175.2.

(S)-(+)-4-Methyl-2,3,4,5-tetrahydro-1H-benz[c]azepin-1-one (II). This compound, with mp 103°C, was obtained in 15% yield. IR spectrum (mineral oil): $\nu C{=}O$ 1660 cm^{-1}. Mass spectrum, m/e*: 175 (67), 146 (42), 145 (39), 132 (12), 118 (18), 117 (33), 116 (8), 115 (25), 105 (8), 104 (7), 103 (18), 97 (21), 91 (32), 90 (15), 89 (19), 78 (7), 77 (24). Circular dichroism in isooctane (c 0.02): $[\theta]_\lambda^\circ$ 62 (300 nm), 340 (283), 0 (274), 1780 (254), 0 (230), −5430 (223), 0 (215). Found: M^+ 175. $C_{11}H_{13}NO$. Calculated: M 175.2.

LITERATURE CITED

1. V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, T. N. Nedorezova, and P. B. Terent'ev, Khim. Geterotsikl. Soedin., No. 5, 656 (1978).

---

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

2. V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and N. L. Ermolova, Vestnik MGU, Ser. Khim., No. 6, 714 (1976).
3. P. B. Terent'ev, L. D. Solov'eva, O. A. Popova, V. M. Dem'yanovich, and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 2, 246 (1979).
4. V. M. Potapov, V. M. Dem'yanovich, G. F. Lelyak, and T. N. Maksimova, Zh. Org. Khim., 8, 2319 (1972).
5. A. P. Terent'ev, R. A. Gracheva, and V. T. Bezruchko, Dokl. Akad. Nauk SSSR, 172, 622 (1967).
6. V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and O. E. Vendrova, Zh. Org. Khim., 14, 882 (1978).
7. Y. Yamamoto, J. Oda, and Y. Inouye, Bull. Chem. Soc. Jpn., 48, 3744 (1975).
8. V. M. Potapov, V. M. Dem'yanovich, L. D. Solov'eva, and G. F. Lelyak, Zh. Org. Khim., 5, 1979 (1969).

STRUCTURES OF THE PRODUCTS OF CONDENSATION OF PHTHALAZONE HYDRAZONES WITH MESITYL OXIDE

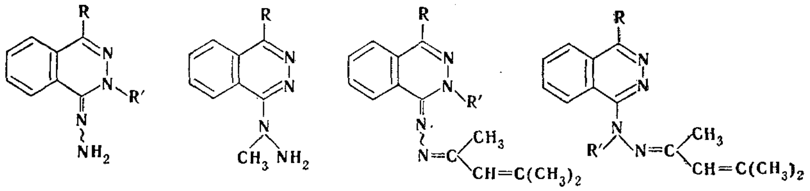
N. N. Bystrykh, B. I. Buzykin,
A. P. Stolyarov, S. A. Flegontov,
and Yu. P. Kitaev

UDC 547.852.7'792:542.953

It was established on the basis of data from the UV and PMR spectra, the dipole moments, and the synthesis of fixed structures that the products of the condensation of phthalazone hydrazones with mesityl oxide have the structures of mixed phthalazone azines and mesityl oxide rather than the phthalazinylhydrazone structure that was previously assumed for them.

We have recently shown [1] that the products of condensation of phthalazone and 4-chlorophthalazone hydrazones (Ia, b) (they were previously assigned 1-hydrazinophthalazine structures IIa, b [2]) with aliphatic and aromatic aldehydes and ketones have phthalazone alkyl(aryl) ylidenehydrazone structures (mixed azines of the phthalazone and carbonyl compound). We then proposed [1] that the product of condensation of Ia with mesityl oxide also has a mixed azine structure (IIIa) rather than the mesityl oxide phthalazinylhydrazone structure (IVa), which was established for it by Moroi and co-workers [3, 4].

In order to confirm this assumption and to ascertain the reasons for the discrepancies in the conclusions drawn in [1] and [3, 4] we used the fixed-structure method. By condensation of mesityl oxide with hydrazones Ia, b we obtained a product described in [3] as hydrazone IVa (the hypotensive preparation "budralazine") and its 4-chloroderivative (in correspondence with [3, 4] it should have the IVb structure), whereas with hydrazones Ic, d we obtained 2-methyl- and 2-methyl-4-chlorophthalazone (1,3-dimethyl-bunten-2-ylidene)hydrazones (IIIc, d), and with 1-methyl-1-(4-R-phthalazin-1-yl)hydrazines (IIc, d) [2, 5] we obtained mesityl oxide N-methyl-N-(4-R-phthalazin-1-yl)hydrazones (IVc, d); we studied their IR, UV, and PMR spectra and measured their dipole moments. We isolated the more stable A isomer,



Ia-d IIa-d IIIa-d IVa-d

I-IV a R=R'=H; b R=Cl, R'=H; c R=H, R'=CH_3; d R=Cl, R'=CH_3

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Branch of the Academy of Sciences of the USSR, Kazan 420083. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 678-683, May, 1981. Original article submitted September 19, 1980.

0009-3122/81/1705-0501$07.50 © 1981 Plenum Publishing Corporation