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SYNTHESIS AND CHIRAL-OPTICAL PROPERTIES OF SOME BENZOLACTAMS*

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Five- and seven-membered benzolactams — (-)-S-2, 3-dimethyl-2, 3-dihydroisoindolone and (+)-S-5-methyl-2, 3, 4, 5-tetrahydrobenz[c]azepin-1-one — were synthesized. A study of their chiral-optical properties and comparison with the previously studied six-membered lactam (-)-S-4-methyl-3, 4-dihydroisoquinol-1-one showed that their circular dichroism spectra are similar: The spectra contain dichroic absorption bands due to $\pi \rightarrow \pi^*$ transitions in the aromatic chromophore (~270 and ~220 nm) and a band of charge transfer in the benzamide chromophore at 240-250 nm. The magnitude of the Cotton effect due to the charge-transfer band increases as the lactam ring becomes larger (five-membered < six-membered < sevenmembered benzolactam). The change in the magnitude of the Cotton effect is explained by the development of a strictly dissymetric chromophore.

The spectral and chiral-optical properties of simple cyclic amides have been studied quite thoroughly. A strong transition (log ε 4.0), which masks the weaker long-wave $n \rightarrow \pi^*$ transition, is observed in the UV spectra of lactams at ~190 nm [2]. However, Chen and Swenson [2] were able to establish the position of the $n \rightarrow \pi^*$ transition - 233 nm for cislactams and 227-230 nm for trans-lactams - by breaking down the observed absorption band into its Gaussian components.

Cotton effects (CE) due to the $n \rightarrow \pi^*$ transition at 230-225 nm and the $\pi \rightarrow \pi^*$ transition at ~190 nm are observed in the circular dichroism (CD) spectra of a number of one-ring and two-ring lactams in conformity with their UV spectra (for example, see [3-5]).

Much less study has been devoted to benzolactams containing an aromatic chromophore fixed in a ring and conjugated with the amide grouping. Thus a study of the chiral-optical properties of the previously synthesized (+)-S-3-methyl- (I) [6] and (-)-S-4-methyl-3,4-dihydroisoquinol-1-one (II) [7] showed that they differ from aliphatic lactams with respect to their spectropolarimetric behavior.



In the present research we synthesized and studied five- and seven-membered lactams - (-)-S-2,3-dimethyl-2,3-dihydroisoindolone (III) and (+)-S-5-methyl-2,3,4,5-tetrahydrobenz-*Communication XLVI from the series "Stereochemical studies." See [1] for communication XLV.

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[c]azepin-1-one (IV) — and compared them with the previously studied [7] six-membered lactam II, which, like the five- and seven-membered benzolactams described in this paper, has an asymmetric carbon atom bonded to an aromatic ring.

 $(-)-2, 3-Dimethyl-2, 3-dihydroisoindolone was synthesized from <math>(-)-N-methyl-\alpha-phenylethyl-amine via the scheme proposed by Hauser [8] for the synthesis of N-substituted 2,3-dihydroiso-indolones$



Metallation of (-)-N-methyl- α -phenylethylamine with butyllithium in the presence of tetramethylethylenediamine leads to organic dilithio compound VI, which is converted to the corresponding acid VII by the action of dry ice. The acid was cyclized to lactam III without further purification by heating.

The structure of III was confirmed by both the low- and high-resolution mass spectra. It was found that the molecular ion undergoes fragmentation of the "amide type" [9] with the elimination of either a methyl group or a hydrogen atom and the formation of stable fragments at 160^{4} (see Scheme 1). The data from the high-resolution spectra make it possible to establish that the ion at 146 in all likelihood undergoes partial rearrangement to the iso-quinolinium form, since ejection of an HCNH fragment is observed in addition to elimination of a CH₃NCH group.

Tetrahydrobenzazepinone IV was obtained from $(+)-\gamma$ -phenylbutylamine (VIII) [10] via the scheme that we used previously in the synthesis of (-)-4-methyl-3,4-dihydroisoquinol-l-one (II) [7]:

^{*}The intensities in percent of the maximum ion are presented in parentheses. +The fraction of the given ion in the doublet is given in brackets.

[‡]Here and subsequently, the m/e values are given for the ion peaks.



In addition to an intense molecular ion, a relatively low-intensity $(M - CH_3)^+$ ion was observed in the mass spectrum of IV; this indicated the presence of a methyl group. The spectrum also contained peaks of intense ions formed by elimination of CH_2NH (146) and C_2H_4NH (132) groupings from the molecular ion, which confirmed the presence of a polymethyleneamide ring in the molecule. Finally, elimination of a CHO group by the molecular ion indicated the presence of an amide group. The general scheme of the fragmentation with an indication of the elementary compositions of the ions is presented in Scheme 2.

An α band of local excitation of the aromatic chromophore, which is responsible for the appearance of a negative CE in the CD spectra (Fig. 2) for II and III, appears in the UV spectra of all of the investigated lactams (Fig. 1). This CE is positive for IV.

A positive CE is observed at about 220 nm for the five-membered benzolactam, whereas a strong negative CE is observed for seven-membered lactam IV; both of these effects are due to the p absorption band of the aromatic chromophore. This CE could not be measured for the six-membered lactam, but it is apparent from the trend of the curve that it is positive [7].

A complex CE due to the α -absorption band of the aromatic chromophore is observed for dihydroisoindolone III and dihydroisoquinoline II. It is partially masked by a second





Fig. 1. UV spectra of (→)-2,3-dimethyl-2,3-dihydroisoindolone (1), (-)-4-methyl-3,4-dihydroisoquinoll-one (2), and (+)-5-methyl-2,3, 4,5-tetrahydrobenz[c]azepin-1-one (3) in isooctane.



Fig. 2. Circular dichroism spectra of (-)-2, 3-dimethyl-2, 3-dihydroisoindolone (1), (-)-4-methyl-3, 4-dihydroisoquinol-1-one (2), and (+)-5-methyl-2, 3, 4, 5-tetrahydrobenz[c]azepin-1-one (3) in isooctane.

stronger negative CE centered at 240 nm. From the position of this CE and the high intensity of the corresponding absorption band in the UV spectrum [for III, λ_{max} 243 nm (log ε 3.8)] it may be assumed that this CE is due to charge transfer in the C₆H₄CONH chromophore.

In the case of seven-membered lactam IV the CE of the charge-transfer band (CTB) is observed at 250 nm and is positive. However, there are no corresponding absorption bands in the UV spectra of the six- and seven-membered lactams; they are evidently masked by the strong p band of the local excitation of the aromatic chromophore at about 220 nm.

Thus a comparison of the five- (III) and seven-membered (IV) lactams that we synthesized with the previously studied six-membered compound (II) shows that their CD spectra are similar: the spectra contain dichroic absorption bands due to $\pi \rightarrow \pi^*$ transitions in the aromatic chromophore (~270 and ~220 nm) and a CTB at 240-250 nm.

However, the signs of the observed CE are the same for the five- and six-membered lactams (III and II) but differ from the sign of the seven-membered lactam (IV).

The CE due to the CTB (240-250 nm) increases as the size of the lactam ring increases (five membered < six-membered < seven-membered benzolactam). This change in the CE may be associated with the fact that the C_6H_4CONH chromophore grouping undergoes distortion as the lactam ring becomes larger, and this leads to the appearance of a strictly dissymmetric chromophore, which also causes an increase in the CE. This disruption of the conjugation should also be simultaneously reflected in the intensity of the corresponding absorption band in the UV spectra of the investigated compounds; it might be expected that the intensity of the absorption band at 240 nm should decrease on passing successively from the five-membered to six- and seven-membered lactams, since the conjugation of the amide group and the aromatic chromophore decreases in this order.

It is apparent from Fig. 1 that over the examined range the intensity of the absorption of seven-membered benzolactam IV [λ_{max} 250 nm (ε 3000)] is actually lower than the intensity of the absorption of benzolactams II and III.

On the other hand, the possibility that the increase in the CE at 240-250 nm on passing from the five-membered lactam to the six- and seven-membered benzolactams is due to the fact that an additional contribution to rotation due to the disymmetry of the ring, as observed in a series of β -, γ -, and δ -aliphatic lactams [11-13], develops as the lability of the ring increases, even in the case of retention of the conjugation in the chromophore grouping, is not excluded. Thus the sign of the CE due to the $n \rightarrow \pi^*$ transition in the amide chromophore of β -lactams with planar structures [11] is determined by the Casym configuration. The greater lability of the five- and six-membered lactams (γ - and δ -lactams, respectively) forced one to take into account not only the Casym configuration but also the chiral character of the ring [12, 13]; in this case it was shown that the A and C conformations give positive CE, while the B and E conformations give negative CE:



This approach also explains why the smallest CE in our case is observed for fivemembered benzolactam III, which has a planar structure. In addition, since the contribution due to the disymmetry of the ring rather than to the C_{asym} configuration evidently becomes the determining factor on passing from five- and six-membered benzolactams, the change in the signs of the CE in the case of the seven-membered benzolactam also becomes understandable. Despite the fact that all of the investigated lactams have an asymmetric carbon atom with an S configuration, the five- and six-membered benzolactams give negative CE, and the seven-membered benzolactam gives a positive CE.

Thus benzolactams with a conjugated benzamide chromophore give two CE due to the α and p bands of the local excitation of the aromatic chromophore. The magnitude and sign of the CE at 240-250 nm due to charge transfer in the benzamide chromophore, like the magnitude and sign of the CE due to an $n \rightarrow \pi^*$ transition in the amide chromophore of aliphatic lactams, depend on the size and, consequently, the lability of the lactam ring.

EXPERIMENTAL

The optical rotatory dispersion (ORD) and the circular dichroism (CD) of the compounds were measured with a Jasco J-20 automatic spectropolarimeter in 10- and 1-m long cuvettes. The UV spectra were recorded with a Cary-15 spectrophotometer. The IR spectra were obtained with an IKS-22 spectrometer. The PMR spectra of solutions of the compounds in CCl_3CN were recorded with a Perkin-Elmer 12 spectrometer (60 MHz) with hexamethyldisiloxane as the external standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source; the ionizing-electron energy was 50 eV, the temperature was 40°C, the emission current was 1.5 mA, and the accelerating voltage was 2 kV. The high-resolution mass spectra were recorded with a JEOL JMS-01-SG-2 spectrometer with double focusing at an ionizing-electron energy of 75 eV.

The synthesis and separation of α -phenylethylamine into its antipodes were carried out by the methods described in [14]. The following values were obtained: $[\alpha]^{20}_{D} -41^{\circ}$ (without a solvent) and $[\alpha]^{20}_{D} +40.8^{\circ}$ (without a solvent) according to [14], $[\alpha]^{20}_{D} -40.8^{\circ}$ (without a solvent) and $[\alpha]^{20}_{D} +40.8^{\circ}$ (without a solvent).

<u>N-Formyl-(-)- α -phenylethylamine by Formylation of (-)- α -Phenylethylamine with 85% Formic Acid [15]. N-Formyl-(-)- α -phenylethylamine, with bp 150-151°C (1 mm) [bp 180-185°C (14 mm) (for the racemate)], was obtained in 95% yield.</u>

<u>N-Methyl-(-)- α -phenylethylamine</u>. This compound, with bp 63-65°C (7 mm) [bp 87°C (18 mm) [16]], was obtained in 90% yield by reduction of N-formyl-(-)- α -phenylethylamine with LiAlH in absolute ether.

(-)-2, 3-Dimethyl-2, 3-dihydroisoindolone [8]. A total of 140 ml of an 0.74 M solution of n-butyllithium in hexane was added dropwise to 6.8 g (0.05 mole) of N-methyl-(-)- α -phenylethylamine and 2.9 g (0.025 mole) of N,N,N',N'-tetramethylenediamine in 200 ml of absolute ether, and the mixture was stirred for 5 h and allowed to stand overnight. Dry ice was added gradually to the resulting solution at -60°C, and the white suspension was stirred for about 30 min and poured into 100 ml of 10% hydrochloric acid solution. The acidic mixture was extracted with ether, and the ether extract was dried with magnesium sulfate. The ether was removed by distillation to give 0.1 g of (-)-2, 3-dimethyl-2, 3-dihydroisoindolone.

The aqueous acid fraction was evaporated, and the solid residue was heated at $120-130^{\circ}$ C until foaming ceased. Water was added, and the mixture was extracted with benzene. The benzene extract was dried with magnesium sulfate, and the benzene was removed by distillation to give another 0.6 g of (-)-2,3-dimethyl-2,3-dihydroisoindolone, which was purified by preparative chromatography on aluminum oxide coated plates in a chloroform-ethyl acetate system (10:1) to give a substance with mp 140°C (benzene-isooctane) in 15% yield [based on the

converted N-methyl-(-)- α -phenylethylamine]. IR spectrum: 1690 cm⁻¹ (ν_{CO}). PMR spectrum: 1.7 (d, 3H, 3-CH₃), 3.3 (s, 3H, NCH₃), 4.6 (q, 1H, 3-H), and 7.7 ppm (m, 4H, C₆H₄). UV spectrum in ethanol, λ_{max} (log ε): 278 (3.15), 269 (3.40), 237 (3.86), 229 (4.05), 220 nm (4.06). Circular dichroism in alcohol (c 0.043) $[\theta]^{\circ}$ (λ , nm): 0 (280), -711 (277), -323 (275), -1809 (270), -969 (266), -1744 (263), -891 (260), -1560 (250), -1857 (243), -966 (235), 0 (232), +3937 (218), +3417 (216), +5052 (214), +6834 (206), +4754 (202). Circular dichroism in isooctane (c 0.015) [θ]° (λ , nm): 0 (257), -2140 (250), -2990 (243), 0 (234), +8540 (228), +8110 (226), +10040 (222), +10680 (216), +9610 (210), +3840 (205).

 $(+)-\gamma$ -Phenylbutylamine. This compound was obtained from $(+)-\beta$ -methylhydrocinnamic acid by the scheme described in [10].

 $N-[(+)-\gamma-Phenylbutyl]$ urethane. This compound, with bp 137-139°C (12 mm), was obtained in 80% yield from $(+)-\gamma$ -phenylbutylamine by condensation with ethyl chlorocarbonate in alkaline medium [7]. Found, % : C 70.8; H 8.8. C13H19NO2. Calculated, %: C 70.6; H 8.7. UV spectrum in ethanol, λ_{max} (log ϵ): 268 (2.22), 264 (2.25), 258 (2.40), 252 (2.27), 248 (2.15). [M]³₃₅₀ +271 (c, 0.12, ethano1).

(+)-5-Methyl-2,3,4,5-tetrahydrobenz[c]azepin-1-one. A mixture of 7 g (0.03 mole) of $N-[(+)-\gamma-phenylbutyl]$ urethane and 120 g of polyphosphoric acid was stirred at 110-120°C for 3 h, after which it was cooled and decomposed with ice. The aqueous mixture was extracted with ether, and the ether extract was washed successively with water, sodium carbonate solution, and water and dried with magnesium sulfate. The ether was removed by distillation, and the residue was recrystallized to give a product with mp 109-111°C (benzene-heptane) in 10% yield. Found, %: C 75.7; H 7.5. C11H13NO. Calculated, %: C 75.4; H 7.5. IR spectrum: 1650 cm⁻¹ (v_{CO}). PMR spectrum: 1.6 (d, 3H, 5-CH₃), 1.9 (m, 2H, 4-CH₂), 3.5 (m, 3H, 5-H, 3-CH₂), and 7.6 ppm (m, 4H, C₆H₄). UV spectrum in ethanol, λ_{max} (log ϵ): 276 (2.95), 269 (3.03), 218-221 nm (4.00). Circular dichroism in ethanol (c 0.005), $[\theta]^{\circ}$ (λ , nm): -280 (285), -5320 (276), 0 (267), +28000 (250), +32200 (243), 0 (230), -39080 (221), 0 (212). Circular dichroism in isooctane (c 0.002) $[\theta]^{\circ}$ (λ , nm): +425 (295), +2130 (275), 467 (277), +32200 (250), 0 (232), -416-0 (222), 0 (213), +17000 (210).

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