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SYNTHESIS AND CHIROOPTICAL PROPERTIES OF SOME TERTIARY AMINES CONTAINING A PYRIDINE RING

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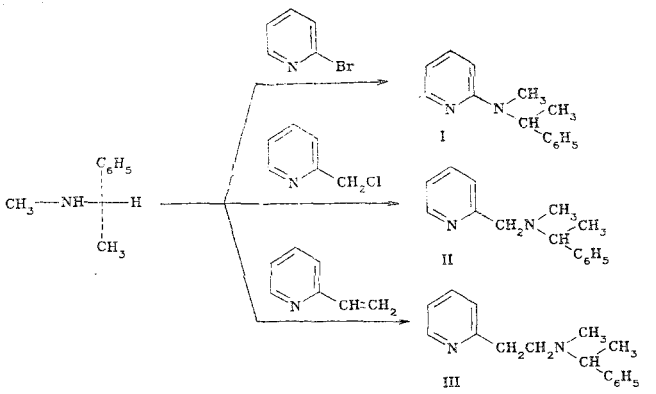
Tertiary amines of the pyridine series containing an α-phenylethylamine residue have been synthesized. The IR spectra and circular dichroisms of these amines have been measured in the 400-200 nm interval, and an assignment of the bands has been made. It is suggested that the long-wave absorption band in the 315 nm region for N-methyl-N-[2-(pyridin-2-yl)ethyl]-α-phenylethylamine and the Cotton effect corresponding to it are due to an intramolecular CTC.

Tertiary amines are catalysts of many acyl transfer reactions that are important from the synthetic point of view. Some derivatives of pyridine and, in particular, its dialkylamino derivative, have proved to be particularly effective in this role [1, 2]. In view of this it appears of interest to obtain chiral tertiary amine derivatives of pyridine in order to study them as chiral catalysts in reactions of this type. In the present investigation, from optically active N-methyl-α-phenylethylamine we have synthesized a number of tertiary amines of the pyridine series (I-III):



(S)(−)-N-methyl-α-phenylethylamine

The synthesis of N-methyl-N-(pyridin-2-yl)-α-phenylethylamine (I) in two stages from 2-fluoropyridine N-oxide has been described previously [3]. For this purpose we used the nucleophilic substitution of a halogen atom directly in the pyridine ring: The amine (I) was obtained

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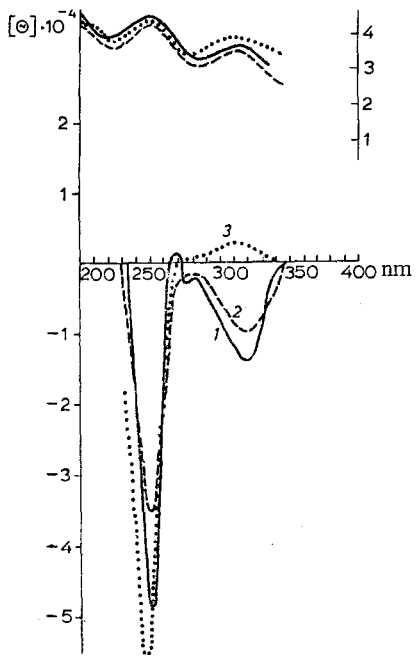

Fig. 1

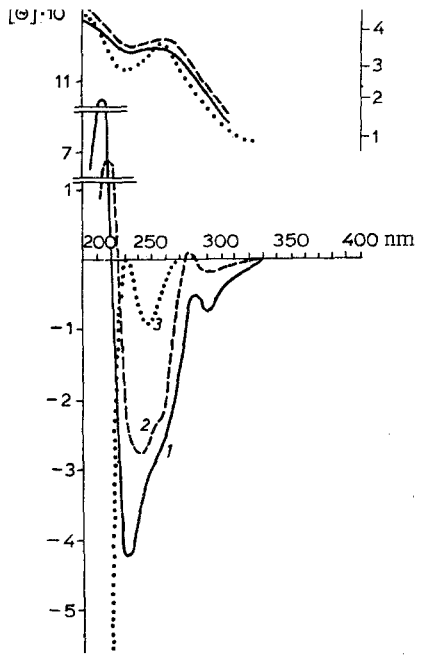

Fig. 2

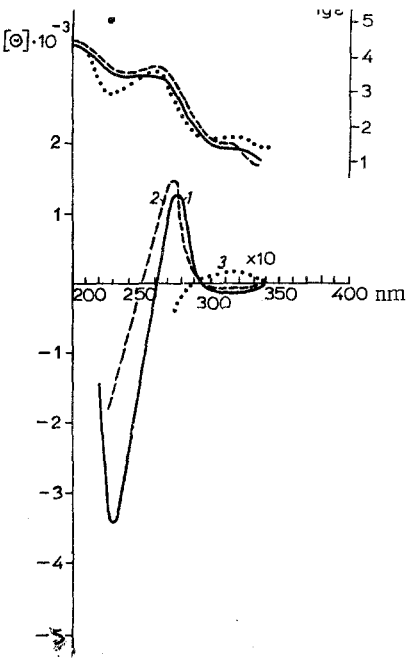

Fig. 3

Fig. 1. UV and CD spectra of the amine (I): 1) in isooctane; 2) in ethanol; 3) in ethanol with the addition of 1 equiv. of HCl.

Fig. 2. UV and CD spectra of the amine (II): 1) in isooctane; 2) in ethanol; 3) in ethanol with the addition of 1 equiv. of HCl.

Fig. 3. UV and CD spectra of the amine (III): 1) in isooctane; 2) in ethanol; 3) in ethanol with the addition of 1 equiv. of HCl (enlarged tenfold).

by heating 2-bromopyridine with (S)(−)-N-methyl-α-phenylethylamine. The reaction was carried out in dimethylformamide and not in an aqueous or aqueous alcoholic medium as described for other N,N-dialkylaminopyridines [2].

N-Methyl-N-(pyridin-2-yl-methyl)-α-phenylethylamine (II) was obtained by boiling 2-chloromethylpyridine with (S)(−)-N-methyl-α-phenylethylamine in ethanol.

N-Methyl-N-[2-(pyridin-2-yl)ethyl]-α-phenylethylamine (III) was synthesized by the addition of (S)(−)-N-methyl-α-phenylethylamine to 2-vinylpyridine by the general method of pyridinylethylation [4].

This is the first time that compounds (II) and (III) have been obtained in the optically active form. Of the constants for (R)(+)-(I) in [3], only the specific rotation at the sodium D line and also the circular dichroism (CD) spectrum in the 400-300 nm region are given in [3]; thus, its chirooptical properties have scarcely been studied.

We have measured the UV and CD spectra of the amines (I-III) in ethanol and in isooctane in the 400-200 nm region (Figs. 1-3). For all the compounds, the CD spectra depend little on the solvent if one disregards the increase in the Cotton effects (CEs) in the case of the amines (I) and (II) on passing from ethanol to isooctane. It must be mentioned that the molecules of the amines under investigation contained two aromatic chromophoric groupings: the benzene and the pyridine rings. The closeness of the spectral characteristics of these chromophores [5, 6] leads to a superposition of the CEs belonging to each of them, which complicates the interpretation of the CD spectra.

For the amine (I), three CEs are observed (Fig. 1). The negative CE in the 320-nm region is apparently connected with a charge-transfer band in the aminopyridine chromophore. The strong negative CE in the 250-nm region represents the superposition of two CEs caused by the ^1L_b absorption band of the benzene ring and the ^1L_a absorption band of the aminopyridine chromophore. The weak negative CE in the 270-nm region appearing only in isooctane is probably due to the ^1L_b absorption band of the benzene ring.

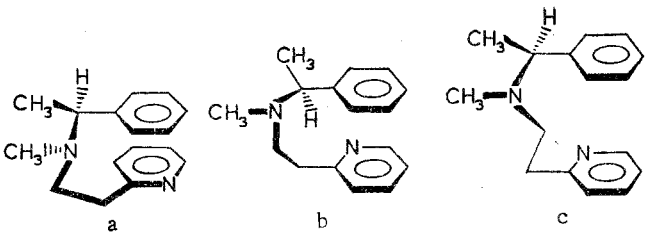

Fig. 4. Conformations of the CTC of (S)(–)-N-methyl-N-[2-(pyridin-2-yl)ethyl]-α-phenylethylamine (III).

The amine (II) shows a complex negative CE in the 250-270 nm region (Fig. 2) which is due to the ^1L_b absorption bands of both chromophores. This effect is partially masked by a strong negative CE in the 240-nm region which we assign to the ^1L_a absorption band of the pyridine chromophore. A strong positive CE in the 210-nm region is probably caused by the ^1L_a band of the benzene chromophore.

The large difference between the CD spectra of the compounds (–)-(I) and (–)-(II) is evidently caused by the different natures of the chromophoric groupings containing a pyridine ring: in the amines (I) there is conjugation between the amino group and the pyridine ring, i.e., here there is an aminopyridine chromophore the spectral characteristics of which differ strongly from the pyridine chromophore in compounds (II) and (III) (Figs. 1-3, UV spectra).

In the CD spectrum of the amine (III) (Fig. 3), a positive CE appears in the 270-nm region and a negative CE in the 230-nm region which can probably be assigned, respectively, to the ^1L_b and ^1L_a bands in the aromatic and pyridine chromophores.

On passing from (S)(–)-(II) to (S)(–)-(III), the CE at 250 nm disappears completely. A comparison of the CD spectra of the amines under investigation with the known characteristics of (S)(–)-N,N-dimethyl-α-phenylethylamine [7] permits the conclusion that the strong CE at 250 nm is due mainly to electronic transitions in the pyridine chromophore. The absence of this CE for the amine (–)-(III) may be connected with the remoteness of the pyridine ring from the asymmetric center and/or its compensation by another, but positive, CE due to electronic transitions in the benzene ring.

Furthermore, for the compound (S)(–)-(III), a weak negative CE is observed at 315 nm. The corresponding absorption band also appears in the UV spectrum. The nature of this CE can apparently be explained if we assume the formation of an intramolecular charge-transfer complex (CTC) where the pyridine ring acts as the acceptor and either the tertiary amino group of the side chain or the benzene ring of the phenylethylamine fragment as the donor. A consideration of molecular models indicates a preferential nature of the interaction of the two aromatic rings. Figure 4 shows some of the possible conformations of such a complex differing by the distance between the interacting aromatic rings. In conformation *a*, the nitrogen atoms of the pyridine ring and of the side chain are remote from one another. Conformations in which the nitrogen atoms are close because of free rotation of the pyridine ring are less suitable because of the repulsion of the free electron pairs of the nitrogen atoms but they will possibly be stabilized on monoprotonation, when the two nitrogen atoms will possess one proton in common (to the extent that this is possible for such conformationally mobile compounds). In favor of such a hypothesis is the increase in the intensity of absorption in the UV spectrum at 315 nm after the addition of 1 equivalent of acid. Here the inflection with ε 30 is converted into a well-resolved absorption band with ε 50.

As can be seen from Figs. 1-3, protonation has a great influence on the CD spectra, the changes mentioned being observed on the addition of one equivalent of acid to the amines under investigation, while the subsequent addition of an excess of acid does not affect the spectrum. This possibility indicates that under the given conditions no addition of a second proton with the formation of a dication takes place.

The CE in the 315-320-nm region for the amines (–)-(I) and (–)-(III) proved to be the most sensitive to protonation. For these CEs a change in sign to positive and an approximately threefold decrease in amplitude was observed. In the case of the compounds (–)-(I) and (–)-(II) for the CE in the 250-nm region the effect of protonation was expressed mainly in a change of amplitude.

The fact that changes in the CE in the 315-nm region on protonation had the same nature for the amines (I) and (III) can be interpreted as evidence in favor of a complex nature of this CE which, in its turn, presupposes an interaction of the pyridine ring with the free electron pair of the nitrogen atom in the amine (III) through space. However, this hypothesis is hardly valid, since the basicities of the two nitrogen atoms in the amine (III) must differ far more than in the amine (I) and this, in its turn, must lead to different types of protonation of these two compounds. Consequently, without an accurate determination of the position of protonation the CD and UV spectra are insufficient for a definitive conclusion concerning the structure of the CTC.

EXPERIMENTAL

The optical rotation measurements were performed on a VNIÉKIprodmash A-1 EPO polarimeter in cells 5 and 2.5 cm long. CD spectra were taken on a JASCO J-20 spectropolarimeter in cells 1 and 0.1 cm long. UV spectra were measured on a Specord UV-Vis spectrophotometer, and PMR spectra for solutions in $CDCl_3$ with TMS as internal standard were taken on a Tesla BS-497 (100 MHz) spectrometer. Protonation: For monoprotonation, to 10 ml of an ethanolic solution of amine (10^{-2} M) was added 0.1 ml of 1 N aqueous HCl. After the recording of the CD spectrum, 2-3 drops of concentrated HCl was added to the same solution and the spectrum was recorded again.

(S)(–)-N-Methyl-N-(pyridin-2-yl)-α-phenylethylamine (I). A mixture of 7.9 g (0.05 mole) of 2-bromopyridine and 13.5 g (0.1 mole) of (S)(–)-N-methyl-α-phenylethylamine in 20 ml of carefully purified and dried DMFA was boiled for 70 h. Then the mixture was poured into water and after alkalinization with NaOH the oily layer was separated off and the aqueous layer was extracted with ether. The ethereal extracts were dried with sodium sulfate, the ether was distilled off, and the residue was distilled in vacuum with an efficient reflux condenser, a fraction with bp 174-175°C (11 mm) being collected. Yield 2.8 g (26%), n_D^{18} 1.5978; $[\alpha]_D^{20}$ –259 (c 1, benzene). PMR spectrum, δ, ppm: 1.55 (3H, d, J = 7 Hz, CH_3); 2.72 (3H, s, N–CH_3); 6.15 (1H, q, J = 7 Hz, CH); 6.53 (2H, m, 3'- and 5'-H); 7.3 (5H, m, C_6H_5); 7.45 (1H, m, 4'-H); 8.21 (1H, m, 6'-H). UV spectrum, λ_{max} (cm^{-1}, log ε): ethanol: 315 (3.64), 250 (4.37), 204 (4.23); isooctane: 313 (3.72), 250 (4.46). CD [θ] (λ, nm); in ethanol (c 10^{-2} M): –9800 (319), –1800 (280), –36,200 (250); in isooctane, (c 10^{-2} M): –14,000 (320), –2200 (280), –3300 (275), 0 (272), +1400 (270), 0 (263), –49,200 (250). Found: C 78.8; H 7.6%. $C_{14}H_{16}N_2$. Calculated: C 79.3; H 7.6%.

(S)(–)-N-Methyl-N-(pyridin-2-ylmethyl)-α-phenylethylamine (II). A mixture of 3.2 g (0.025 mole) of freshly distilled 2-chloromethylpyridine [8] and 3.4 g (0.025 mole) of (S)(–)-N-methyl-α-phenylethylamine in 25 ml of absolute ethanol was boiled in a current of argon for 2 h. Then the mixture was poured into 100 ml of water and extracted with ether and the ethereal extracts were dried with sodium sulfate. The ether was evaporated off and the amine was distilled in a current of argon; yield 1.9 g (34%), bp 118-119°C (1 mm); n_D^{18} 1.5586; $[\alpha]_D^{20}$ –23.9° (c 1, benzene). The compound was fairly unstable and rapidly darkened in the air. PMR spectrum, ppm: 1.43 (3H, d, J = 7 Hz, CH_3); 2.21 (3H, s, N–CH_3); 3.58 and 3.75 (2H, d, J = 14 Hz, diastereotopic CH_2 protons); 3.70 (1H, q, J = 7 Hz, CH); 7.3 (8H, m, C_6H_5, 3'-, 4'-, and 5'-H); 8.5 (1H, m, 6'-H). UV spectrum, λ_{max} (cm^{-1}; log ε); ethanol: 260 (3.65); isooctane: 260 (3.58). CD [θ] (λ, nm): in ethanol (c 10^{-2} M): –200 (285), 0 (279), +70 (276), 0 (270), –2800 (240), 0 (223), +7000 (218); in isooctane (c 10^{-2} M): –790 (288), –520 (279), –4300 (230), 0 (221), 11,700 (214). Found: C 79.9; H 8.1%. $C_{15}H_{18}N_2$. Calculated: C 79.7; H 8.0%.

(S)(–)-N-Methyl-N-(pyridin-2-yl)ethyl]-α-phenylethylamine (III). A mixture of 6.3 g (0.06 mole) of freshly distilled 2-vinylpyridine, 8.1 g (0.06 mole) of (S)(–)-N-methyl-α-phenylethylamine and 3.76 g (0.06 mole) of glacial acetic acid was boiled for 2 h and was then poured into water and the resulting mixture was made strongly alkaline with NaOH and was extracted with benzene. The benzene extracts were dried with sodium sulfate, the benzene was evaporated off, and the residue was distilled in vacuum with an effective reflux condenser. Yield 5.1 g (35%); bp 174-175°C (6 mm): n_D^{19} 1.5557; $[\alpha]_D^{20}$ –31.3° (c 1, benzene). PMR spectrum, δ, ppm: 1.33 (3H, d, J = 7 Hz, CH_3); 2.28 (3H, s, N–CH_3); 2.8 (4H, m, CH_2CH_2); 3.60 (1H, q, J = 7 Hz, CH); 7.2 (7H, m, C_6H_5, 3'- and 5'-H); 7.5 (1H, m, 4'-H); 8.5 (1H, 6'-H). UV spectrum, λ_{max} (cm^{-1}; log ε); in ethanol: 312 (shoulder, 1.48), 262 (3.67), 204 (shoulder, 4.27); in isooctane: 310 (shoulder, 1.40), 260 (3.59), 204 (shoulder, 4.26). CD [θ] (λ, nm): in ethanol (c 10^{-2} M): –40 (320), 0 (299), 1500 (275), 0 (250), –2000 (225); in isooctane (c 10^{-2} M): –60 (318), 0 (292), 1300 (276), 0 (263), –3500 (230). Found: C 79.5; H 8.6%. $C_{16}H_{20}N_2$. Calculated: C 80.0; H 8.4%.

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INFLUENCE OF STRUCTURE ON THE CIRCULAR DICHROISM OF METHYL-SUBSTITUTED 1,3,4-TETRAHYDROBENZ[b]AZEPIN-2-ONES

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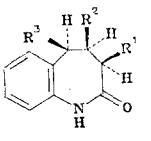
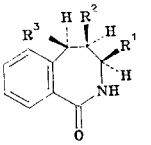
The chirooptical properties of methyl-substituted 1,3,4,5-tetrahydrobenz[b]azepin-2-ones have been studied. A considerable increase in the intensity of the Cotton effect (CE) in the 240-250 nm region with an enlargement of the lactam ring has been observed. The sign of this CE for seven-membered benzolactams correlates with the type of conformation of the lactam ring. A change in the nature of the conjugation (passage from lactams of the benzamide type $-C_6H_4-CO-NH-$ to lactams of the anilide type $-C_6H_4-NH-CO-$) leads to an inversion of the signs of the CEs in the 230-250-nm region.

The chirooptical properties of cyclic amides — lactams — have been described in fairly great detail in the literature (see, for example, [1-3]), unlike the benzolactams containing an aromatic chromophore (of the benzamide or anilide type) fixed to the ring and conjugated with the amide chromophore. We have previously studied a number of compounds of the benzamide type [4] with different sizes of the lactam ring [5] and different positions of the asymmetric center in seven-membered benzolactams [6].

In the present investigation, in order to establish the influence of the type of conjugation on the chirooptical properties of the benzolactams, we have studied the UV spectra and the circular dichroism (CD) of seven-membered benzolactams of the anilide type with different positions of the asymmetric center: R-(+)-3-methyl-, R-(−)-4-methyl-, and S-(−)-5-methyl-1,3,4,5-tetrahydrobenz[b]azepin-2-ones (I, II, and III, respectively), the synthesis of which we have described in preceding papers [7, 8].



I–III



IV–VI

R-(+)-I $R^1=CH_3$, $R^2=R^3=H$; *R*-(−)-II $R^2=CH_3$, $R^1=R^3=H$; *S*-(−)-III $R^3=CH_3$, $R^1=R^2=H$; *R*-(−)-IV $R^1=CH_3$, $R^2=R^3=H$; *R*-(+)-V $R^2=CH_3$, $R^1=R^3=H$; *S*-(+)-VI $R^3=CH_3$, $R^1=R^2=H$

When the CD spectra of the benzolactams obtained were measured in ethanol and in isooctane, it was found that the sign and magnitude of the observed Cotton effects (CEs) did not depend on the polarity of the solvent.

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