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PREPARATION OF OPTICALY ACTIVE 3-(1-METHYL-1-PHENYLPROPYL)INDOLE AND INVESTIGATION OF ITS CHIRAL-OPTICAL PROPERTIES

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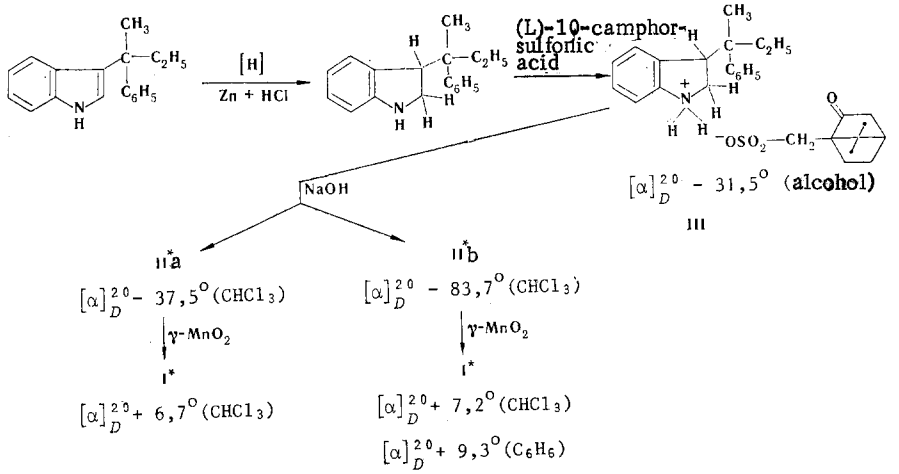
Optically active 3-(1-methyl-1-phenylpropyl)indole was obtained by dehydrogenation of the resolved [by means of (L)-10-camphorsulfonic acid] 3-(1-methyl-1-phenylpropyl)indoline. The chiral-optical properties of this product were investigated, and the possibility of the use of circular dichroism data for the identification of the chiral indole chromophore was demonstrated.

We have previously investigaged the prototropic isomerization of 3-alkyl(aryl)indoles [1] and expressed the assumption that the process is intramolecular in character. To confirm this, it was necessary to synthesize 3-(1-methyl-1-phenylpropyl)indole (I), which contains a chiral substituent in the 3 position of the indole molecule. The investigation of the chiral-optical properties of this 3-alkylindole is of independent interest for the study of the stereochemistry of complex natural indole compounds.

Racemic indole I was obtained by alkylation with methylethylphenylchloromethane in the presence of dipyridinezinc chloride in metromethane [2]. We proposed to obtain optically active indole I* by the following sequence of transformations: reduction of indole to indoline, separation of the latter into its antipodes by means of (L)-10-camphorsulfonic acid, and, finally, production of the chiral 3-alkylindole by dehydrogenation of the optically active indoline.



Indoline II was isolated in 17% yield in the reduction of racemic indole I with zinc in hydrochloric acid. A new asymmetric center develops in the case of reduction in the 3 position of the indole molecule, and one therefore should have expected the formation of two pairs of diastereomeric salts.

The less soluble indoline salt III with specific rotation $[\alpha]_D^{20}$ −24.6° (alcohol) was isolated when equimolar amounts of racemic indoline II and (L)-10-camphorsulfonic acid were

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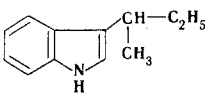
mixed in acetone. The specific rotation increased to −31.5° after three recrystallizations from ethanol–water.

Alkaline decomposition of this salt led to a mixture of diastereomers of indoline II* with $[\alpha]_D^{20}$ −6.5° ($CHCl_3$), two recrystallizations of which from hexane yielded the less soluble indoline IIa* with $[\alpha]_D^{20}$ −37.5° ($CHCl_3$); workup of the mother liquid gave indoline IIb* with $[\alpha]_D^{20}$ −83.7° ($CHCl_3$).

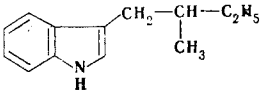
The same indole I* enantiomer with $[\alpha]_D^{20}$ +6.7° ($CHCl_3$) and $[\alpha]_D^{20}$ +7.2° ($CHCl_3$), the structure of which was confirmed by PMR data, was obtained in the case of dehydrogenation of each of indolines IIa* and IIb* by means of γ-MnO_2.

The literature contains only one report [4] of the synthesis of optically active 3-alkylindoles, and the starting compound in this case was (S)-1-chloro-2-methylbutane. The S configuration of the asymmetric center in the 3 position was assigned for the synthesized optically active indoles IV and V by the method of stereochemical correlation.



$[\alpha]_D^{25}$ + 12.98° (c 7.7; CCl_4)

IV



$[\alpha]_D^{25}$ + 9,96° (c 2,2; $CHCl_3$)

V

We assume that the optically active 3-(1-methyl-1-phenylpropyl)indole (I*) that we obtained, which has, as compared with the described indoles IV and V, both the same sign and order of specific rotation, evidently also has an S configuration of the asymmetric center.

To study the chiral-optical properties of the indole chromophore for indole I* we recorded the circular dichroism (CD) curves in solvents with varying polarities. The information in the literature regarding the chiral indole chromophore is limited. Circular dichroism data are available for a number of yohimbine alkaloids [5]; these data are characterized by the existence of one long-wave cotton effect (CE) at 250-300 nm, in comformity with which we assumed that the manifestation of only one optically active ^1L_B electron transition is characteristic for indole alkaloids.

In a later paper [6] on the magnetic circular dochroism (MCD) of indole alkaloids there was a report of the appearance in the MCD spectrum of two B terms with opposite signs at 250-300 nm associated with ^1L_B and ^1L_A electron transitions of the heteroaromatic chromophore; the CE of the long-wave ^1L_B transition is positive. Good agreement between the trends of the MCD curves of yohimbine and serotonin derivatives was observed, and this makes it possible to identify the chiral indole chromophore from the MCD spectrum of serotonin [6].

It is apparent from Fig. 1 that a similar CD pattern is also observed for indole I* in heptane: a positive ^1L_B transition at 270 nm, a negative ^1L_A transition at 220 nm, and a positive ^1B_a band at 210 nm. The trend of the CD curve in ethanol is similar; the maximum of all of the CE undergo the bathochromic shift that is characteristic for a π–π^* transition. The data for the UV spectra are in good agreement with the CD data in the corresponding solvents. The CD data obtained for indole I* can be used for the identification of chiral indole chromophores.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in benzene were recorded with an XL-100 spectrometer with tetramethylsilane as the internal standard. The UV spectra were recorded with an AR-25 spectrophotometer. The specific rotations were measured with a JASCO J-20 automatic spectropolarimeter in a 1-cm long cuvette. The CD spectra were recorded with a Cary-61 spectrometer at room temperature.

3-(1-Methyl-1-phenylpropyl)indole (I). This compound was obtained by the method in [2].

3-(1-Methyl-1-phenylpropyl)indoline (II). A 9-g (36 mmole) sample of indole I was refluxed for 60 h in 50 ml of n-butanol, during which small portions (6.5 g of Zn and 80 ml of concentrated HCl) were added every 6 h. The mixture was then made alkaline with ammonia and extracted with ether. The extract was dried with K_2CO_3, and the solvent was removed to give 1.6 g (17%) of indoline II with mp 120-122°C (from aqueous acetone). UV spectrum, λ_{max} (log ε): 246 (3.9) and 303 nm (3.3). PMR spectrum: 0.56 (t, 3H, CH_2CH_3), 1.12 (s, 3H, CCH_3),

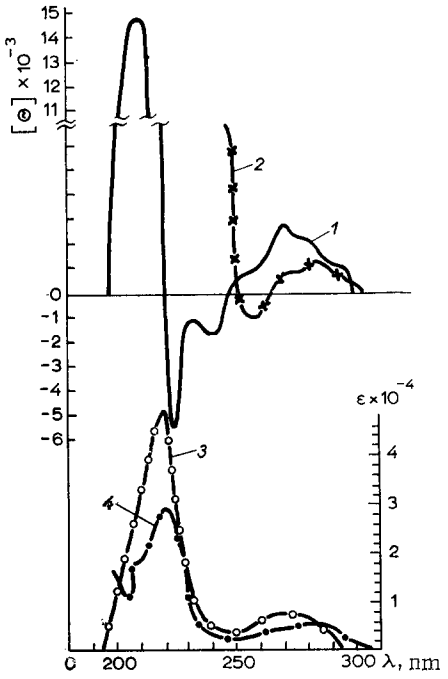


Fig. 1. Circular dichroism (CD) spectra of 3-(1-methyl-1-phenylpropyl)indole in heptane (1) and in alcohol (2); UV spectra in heptane (3) and in alcohol (4).

1.3-1.8 (m, 2H, CH_2CH_3), 2.7 (m, 1H, NH), 3.16-3.24 (m, 2H, 2-H), and 3.46-3.64 ppm (m, 1H, 3-H). Found: C 84.4: H 8.5; N 5.7%. $C_{18}H_{21}N$. Calculated: C 84.4; H 8.2; N 5.5%.

Resolution of 3-(1-Methyl-1-phenylpropyl)indoline (II). (L)-10-camphorsulfonic acid with specific rotation $[\alpha]_D^{20}$ −33.8° (c 6.5; alcohol) was obtained by the method in [7]. A solution of 12.2 g (52.5 mmole) of (L)-10-camphorsulfonic acid in 70 ml of acetone was added to 13.2 g (52.5 mmole) of indoline II in 100 ml of acetone. After 2 h, the mixture was filtered to give 9.5 g (37.5%) of the less soluble (in acetone) salt III with mp 197-200°C and $[\alpha]_D^{20}$ −24.6° (c 5.7; alcohol). Three recrystallizations from ethanol–water (1:2) gave 7.2 g (28%) of salt III with mp 189-193°C and $[\alpha]_D^{20}$ −31.5° (c 3.3; alcohol). Decomposition of the total amount of this salt with sodium hydroxide yielded 2.56 g (19%) of indoline II* with mp 121-123°C and $[\alpha]_D^{20}$ −6.5° (c 0.8; $CHCl_3$). Recrystallization of optically active indoline II from hexane led to a change in the specific rotation. Two recrystallizations from hexane yielded the less soluble indoline IIa*, and workup of the mother liquor gave IIb*, the signals of which in the PMR spectrum were absolutely identical to those of racemic indoline II; however, their specific rotations differed. This procedure gave 0.24 g (2%) of the less soluble IIa , with mp 121-123°C and $[\alpha]_D^{20}$ −37.5° (c 4.8; $CHCl_3$), and well as 0.24 g (2%) of IIb* with mp 122-124°C and $[\alpha]_D^{20}$ −83.7° (c 5.5; $CHCl_3$).

Optically Active 3-(1-Methyl-1-phenylpropyl)indole (I*). A 0.24-g (0.9 mmole) sample of indoline IIa* was stirred for 18 h with 0.31 g (3.6 mmole) of γ-MnO_2 [3] in 25 ml of dry benzene at room temperature. An additional 0.1 g (1.2 mmole) of γ-MnO_2 was added, and the mixture was stirred for another 2 h. The completion of the reaction was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in benzene. The manganese dioxide was removed by filtration and washed successively with 20% hydrochloric acid and water. The filtrate was dried with $MgSO_4$, and the benzene was removed to give 170 mg (71%) of crude indole I*, which was purified with a column filled with SiO_2 (L 40/100) by elution with benzene–hexane (1:1) to give 137 mg of crystalline indole I* with mp 97-99°C and $[\alpha]_D^{20}$ +6.7 (c 2.1: $CHCl_3$). Similarly, from 240 mg of indoline IIb* we obtained 200 mg (76%) of optically active indole I* with mp 98-100°C, $[\alpha]_D^{20}$ +7.2° (c 5.9; $CHCl_3$), and $[\alpha]_D^{20}$ +9.3° (c 3.3; C_6H_6). PMR spectrum: 0.78 (t, 3H, CH_2CH_3), 1.64 (s, 3H, CCH_3), and 2-2.4 ppm (m, 2H, CH_2CH_3). UV spectrum, λ_{max} (log ε): 220 (4.7) and 270 mm (3.8).

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SYNTHESIS AND INTRAMOLECULAR ELECTRON INTERACTIONS IN TETRACHLORO-4-PYRIDYLCARBONIMIDOYL DICHLORIDE AND ITS DERIVATIVES

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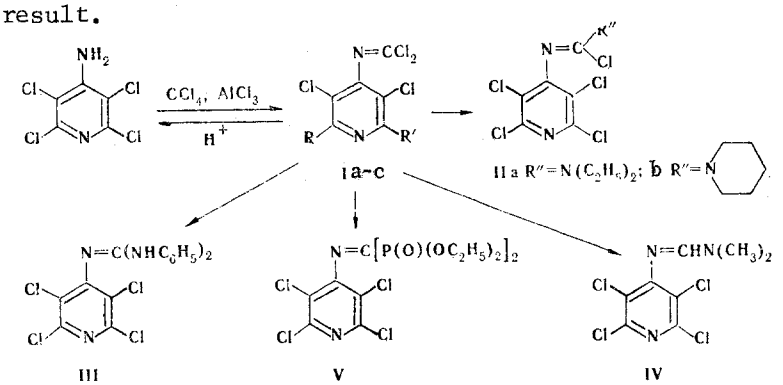
Tetrachloro-4-pyridylcarbonimidoyl dichloride was synthesized, and products of the reaction of the latter with amines, triethyl phosphite, and dimethylformamide (DMF) were obtained; acid hydrolysis was also carried out. The character of the intramolecular interactions beteen the π system of the pyridine ring and the C=N bond was investigated by IR spectroscopy.

It is known that the amino group in aminopolyhalopyridines has low nucleophilicity and in most cases is not involved in reactions. This inertness can be overcome by converting the amines to reactive iminothionyls [1] or to imidoyl dichlorides. In the present paper we describe a simple method for the preparation of polychloropyridylcarbonimidoyl dichlorides (Ia-c). We also investigated some properties of the compounds obtained.

The reaction of 4-amino-2,3,5,6-tetrachloropyridine with refluxing CCl_4 in the presence of $AlCl_3$ leads to the formation of Ia in high yield. Imidoyl dichloride Ia reacts readily with amines at room temperature to give IIa,b. It should be noted that only one chlorine atom undergoes substitution upon reaction with diethylamine and N-trimethylsilylpiperidine. We were unable to carry out the reaction at two chlorine atoms at higher temperatures and in excess amounts of these amines. However, disubstitution product III was obtained by the action of aniline on imidoyl dichloride Ia at room temperature. We were unable to obtain a monosubstitution product using aniline hydrochloride or even N-trimethylsilylaniline.

The known formamidine IV is formed when Ia is heated in dimethyl formamide (DMF); however, no reaction occurs with dimethyl sulfoxide (DMSO) under similar conditions.

The reaction of imidoyl chloride Ia with triethyl pnosphite proceeds quite smoothly and leads to the formation of a product of the Arbuzov reaction (V). The acidic hydrolysis of Ia takes place readily upon heating in alcohol, and the startingg4-amino-2,3,5,6-tetrachloropyridine is formed as a result.



I a R=R¹=Cl; b R=Cl, R¹=CCl_3; c R=H, R¹=CCl_3

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