

CLEAVAGE OF ENANTIOMERS OF METHANO-1H-CYCLOOCT[b]INDOL-9-OL AND THEIR ABSOLUTE CONFIGURATION

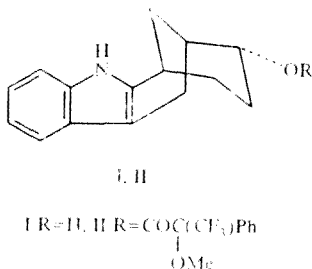
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Chiral [6R and 6S-(6 α , 9 α , 10 α)]methano-1H-cyclooct[b]indol-9-ols were segregated into enantiomers through diastereomeric esters with (R)- α -methoxy- α -trifluoromethylphenylacetic acid. The absolute configuration of the enantiomers was established by the NMR method using the shift reagent Eu(fod)₃ and the circular dichroism spectra.

Derivatives of methano-1H-cyclooct[b]indole that we had synthesized earlier are chiral structures [1]. Compounds containing the indole chromophore have recently become the objects of stereochemical investigations using the circular dichroism method [2, 3].

The pathway to enantiomeric methanocyclooct[b]indoles lies through the use of chiral carbonyl derivatives of bicyclo[3.3.1]nonane in the indolization reaction or segregation of a racemate of the condensed heterocyclic structure I. Since the initial structure I contains a hydroxyl group, we undertook an attempt to segregate the racemate I using the chloride of (+)-(R)- α -methoxy- α -trifluoromethylphenylacetic acid (MTPA). The synthesis and segregation of the racemic (+)-(R)-MTPA were accomplished according to the well known procedures [4, 5].

Diastereomeric esters of cyclooctaindol-9-ol I with the (+)-(S)-chloride of MTPA were produced by the reaction of the reactants in anhydrous pyridine at room temperature. The levorotatory ester (–)-II with $[\alpha]_D -51.5^\circ$ (s, 0.33, chloroform) was isolated in a yield of 20% by double crystallization from ether. The compound (+)-II with $[\alpha]_D +56.7^\circ$ (s, 1.08, chloroform) was produced by repeated crystallization of the evaporated mother liquor after isolation of the (–)-enantiomer.



To establish the enantiomeric excess and absolute configuration of the secondary alcohols we used the same (+)MTPA, since diastereotopic signals of the methyl and trifluoromethyl groups of the esters are observed in the NMR spectra [6]. The signals of the proton of the methyl group in the ¹H NMR spectra have different chemical shifts (0.03...0.13), depending on the configuration of the hydroxyl group, and the integral intensities of these signals permit a determination of the ratio of enantiomers. However, only one signal of the protons of the methoxy group at 3.58 ppm is observed in the ¹H NMR spectrum of compound (–)-II. The difference in the chemical shifts of the diastereotopic protons can be increased by using lanthanide shift reagents [7]. In the case of successive addition of Eu(fod)₃ to a solution of compound (–)-II, a doubling of the resonance signals is observed in the NMR spectrum. The magnitude of the induced shifts and their difference increase with increasing Eu(fod)₃ concentration. The dependence of the magnitude of the induced shifts of the diastereotopic protons of the methoxy group on the concentration ratio of the compound Eu(fod)₃/(±)-II is presented in Fig. 1. A comparison of the intensity of the signals of the methoxyl protons permitted a determination of the diastereomeric frequency of the ester (–)-II, which is 92.5%.

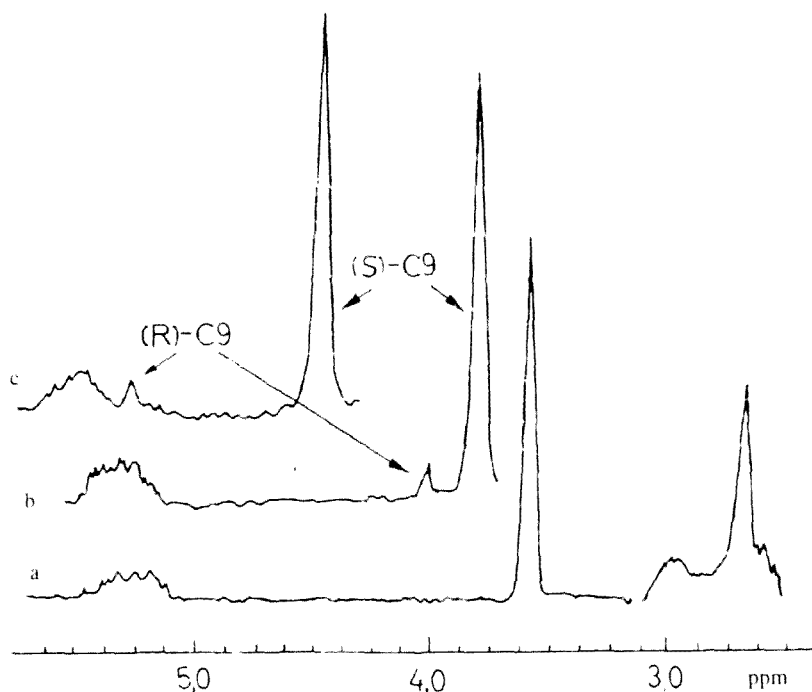


Fig. 1. Fragment of the ^1H NMR spectrum of compound $(-)\text{-II}$ in the absence of $\text{Eu}(\text{fod})_3$ (a) and with its addition in molar ratios $\text{Eu}(\text{fod})_3/(-)\text{-II}$ 0.08 (b); 0.24 (c).

One signal of the methoxyl protons, which is shifted in the weak-field direction with the addition of $\text{Eu}(\text{fod})_3$, is also observed in the NMR spectrum of the ester $(+)\text{-II}$; however, it is not split even at a rather high ratio of $\text{Eu}(\text{fod})_3/(+)\text{-II}$; however, it is not split even at a rather high ratio of $\text{Eu}(\text{fod})_3/(+)\text{-II}$. Thus, the ester $(+)\text{-II}$ can be considered enantiomerically pure, and the value obtained $[\alpha]_D +56.7^\circ$ corresponds to the pure enantiomer.

The absolute configuration of the chiral center at the hydroxyl group can be established according to the ^1H NMR spectra in the presence of shift reagents. It was established that the signals of the methoxyl protons undergo a stronger induced shift in the case of an (R) configuration of the chiral atom [8]. In the NMR spectra of the ester $(-)\text{-II}$ in the presence of $\text{Eu}(\text{fod})_3$ (Fig. 1), the signal of the protons of the methoxyl group of the predominant diastereomer has a smaller induced shift in comparison with the signal of the other diastereomer. Thus, the absolute configuration of the compound $(-)\text{-II}$ is $[6R-(6\alpha, 9\alpha, 10\alpha)]$. The configuration of the compound $(+)\text{-II}$ is determined as $[6S-(6\alpha, 9\alpha, 10\alpha)]$.

The corresponding chiral compounds I were produced by hydrolysis of the esters II by KOH in benzene. The absolute configuration of the compounds $(-)\text{-I}$ and $(+)\text{-I}$ follow from the configurations of the esters II and were assigned as $[6R-(6\alpha, 9\alpha, 10\alpha)]$ and $[6S-(6\alpha, 9\alpha, 10\alpha)]$, respectively. In the circular dichroism (CD) spectrum of the compound $(-)\text{-I}$, weak absorption bands are observed at 270 and 300 nm, corresponding to 1L_a and 1L_b transitions of the indole chromophore (Fig. 2). The CD spectrum between 200 and 230 nm consists of the strong positive absorption of the transition 1B_b of the indole chromophore at 230 nm and a negative minimum below 200 nm of the indole transition 1B_a .

The authors would like to express gratitude to Dr. B. Bossenbroek from Chemical Abstract Service for aid in constructing the names of the compounds I.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in liquid petrolatum. The UV spectra on a Spectromom 202 spectrometer is 96% ethanol. The ^1H NMR spectra were recorded on a BS 487C spectrometer with working frequency 80 MHz, internal standard TMS. In the recording of the NMR spectra with $\text{Eu}(\text{fod})_3$, the shift reagent, freshly sublimed and dried under vacuum over P_2O_5 , was added in portions to a solution of 0.35...0.4 mole of the substrate, and the mixture was shaken thoroughly. The circular dichroism spectra were recorded on a Jasco Model J-500A spectropolarimeter in ethanol solution. The optical rotation of the solutions was measured in a cuvette with optical path length 10 cm on a Perkin-Elmer 141 polarimeter at the D-line of a sodium lamp.

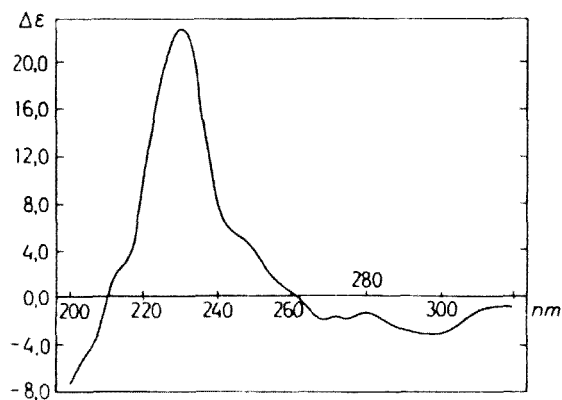


Fig. 2. Circular dichroism spectrum of the compound (–)-I.

The data of elementary analysis of the compounds synthesized for C, H, and N correspond to the calculated values.

[6R-(6 α , 9 α , 10 α)]Methano-1H-cyclooct[b]indol-9-ol Ester of (R)- α -Methoxy- α -trifluoromethylphenylacetic Acid (–)-(II). To 4.8 ml of absolute piperidine we successively added 1.14 g (4.5 mmoles) (S)-(+)-chloride of MTPA, 9.8 ml of CCl_4 , and 0.73 g (3.2 mmoles) of a racemic mixture of I. The mixture was kept at room temperature for 24 h, then water was added to the reaction mixture until the precipitate dissolved, and it was extracted with ether. The ether extracts were washed with dilute HCl, with solutions of Na_2CO_3 and NaCl, and dried with MgSO_4 . The solvent was evaporated, and the residue was recrystallized twice from absolute ether. We obtained 0.52 g (26% yield) of the compound (–)-II with mp 167...169°C. $[\alpha]_D -51.5^\circ$ (s, 0.33, chloroform). NMR spectrum (CDCl_3): 0.75...2.75 (10 H, m, methylene protons of the alicyclic skeleton), 3.58 (3 H, s, OCH_3), 5.25 (1 H, m, $\text{C}_9\text{-H}$), 7.0...7.7 (10 H, s, aromatic protons, and NH).

[6S-(6 α , 9 α , 10 α)]Methano-1H-cyclooct[b]indol-9-ol Ester of (R)- α -Methoxy- α -trifluoromethylphenylacetic Acid (+)-(II). The ether mother liquors from the crystallization of the compound (–)-II were combined, and the solvent was evaporated. Repeated crystallization from absolute ether and then toluene yielded 0.14 g (7%) of the compound (+)-II, possessing a constant angle of rotation of polarized light. mp 164...165°C. $[\alpha]_D +56.7^\circ$ (s, 1.08, chloroform). The NMR spectrum was identical with the spectrum of the compound (–)-II described above.

[6R-(6 α , 9 α , 10 α)]Methano-1H-cyclooct[b]indol-9-ol (–)-(I). To a solution of 0.52 g (1.2 mmoles) of the ester (–)-II in 10 ml of benzene we added a solution of 0.3 g KOH in 25 ml of ethanol and boiled on a water bath for 24 h. Then water was added to the reaction mixture, and it was left until crystals separated out. The crystals that precipitated were washed with water and with 50% ethanol, yielding 0.15 g (58%) of the compound (–)-I. mp 219...220°C. $[\alpha]_D -16^\circ$ (s, 0.2, chloroform), enantiomeric excess 82.3%. IR spectrum: 3300 (NH), 297 (–6.93). UV spectrum, λ_{max} (ϵ): 283 (8000). CD spectrum, λ_{max} ($\Delta\epsilon$): 230 (+22.85), 297 (–6.93). NMR spectrum [$(\text{CF}_3\text{CO})_2\text{O}$]: 0.75...2.6 (10 H, m, protons of the alicyclic skeleton), 3.2 (1 H, m, $\text{C}_9\text{-H}$), 4.7 (1 H, br.s., OH), 6.5...7.2 (4 H, m, aromatic protons), 7.4 (1 H, br.s., NH).

[6S-(6 α , 9 α , 10 α)]Methano-1H-cyclooct[b]indol-9-ol (+)-(I). To a solution of 0.12 g (0.27 mmole) of the ester (+)-II in 5 ml of benzene we added a solution of 0.09 g KOH in 15 ml of ethanol and boiled on a water bath for 24 h. Then water was added to the mixture, and it was left until crystals separated. The precipitated crystals were washed with water and with 50% ethanol, yielding 0.058 g (96.6%) of the compound (+)-I mp 219...219.5°C. $[\alpha]_D +17^\circ$ (s, 0.47, chloroform). The IR and UV spectra were identical with the spectra of the compound (–)-I.

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