

Synthesis, chiroptical properties and absolute configuration of spiro[1,3-benzodioxole-methanocyclooct[*b*]indole]

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The synthesis of chiral 1'*H*-spiro[1,3-benzodioxole-2,12'-[6',10']methanocyclooct[*b*]indole] **3**, a fused polycyclic structure derived from bicyclo[3.3.1]nonane, was accomplished *via* the Fisher indolization reaction. Enantiomers of this structure were obtained by chiral HPLC enantiomer separation on a swollen microcrystalline triacetylcellulose column. Chiroptical properties of the resolved enantiomers containing indole and 1,2-methylenedioxybenzene chromophores were studied. Application of the sector rule to the 1,2-methylenedioxybenzene chromophore to establish the absolute configuration of this polycyclic structure did not lead to an unequivocal conclusion which is likely to be due to the transannular interaction of the chromophores. The enantiospecific synthesis from enantiomerically enriched (–)-(1*R*,5*S*)-bicyclo[3.3.1]nonane-2,9-dione **1** was performed to prove unequivocally the (+)-(6'*R*,10'*S*)-configuration of the title structure. This study demonstrates that semiempirical rules should be applied cautiously to the determination of the absolute configuration of molecules containing several chromophores.

Introduction

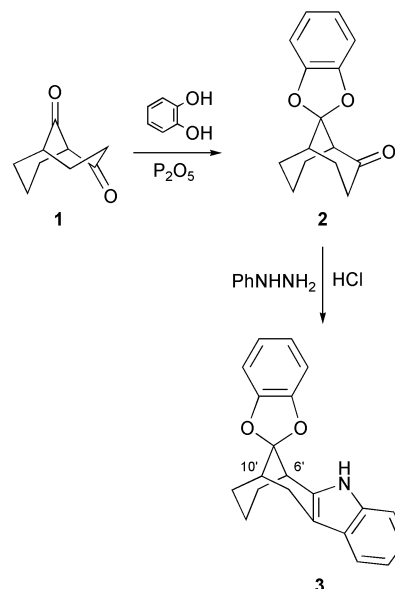
The indole ring is a strong planar chromophore, which, in a chiral molecular structure, is of considerable interest in circular dichroism (CD) spectroscopic studies of various natural and synthetic chiral molecules.¹ Since the indole ring system is a constituent of many naturally occurring molecules, including the essential amino acid tryptophan, indoles are present in many peptides and other natural systems.² The chirality of molecules containing the indole ring arises as a result of substitution with groups having stereogenic centers,³ by incorporation of the indole into a polycyclic ring system.⁴ The absolute configuration of a number of chiral indoles has been studied by CD spectroscopy though the absolute configuration could not be established using any reliable rule for correlation of the sign and magnitude of the observed absorption with the absolute configuration. Recently we reported on the CD spectra of chiral polycyclic methanocyclooct[*b*]indole structures and the intensity of the CD spectrum of the (+)-(*S,S*)-diindole could not be explained by theoretical treatment.⁵ The interchromophoric interaction of the two indole rings in that structure was suggested to account for the unusual intensity of the spectrum. Two problems should be considered when two alike or different chromophores are present in a molecule. Firstly, the interchromophoric interaction may change not only the intensity of the CD spectra⁶ but also the sign of the Cotton effect (CE).⁷ Secondly, a particular interest is associated with the applicability of a definite rule for the correlation of absolute configuration with the sign of the CE effect.

Thus further insight into understanding the rules relating the signs of the Cotton effect to absolute configurations could be obtained by a study of functionalized chiral bridged bicyclic compounds containing the appropriate chromophores in a well-defined spatial relationship. Such structures are also of interest in view of the study of possible interactions between non-conjugated chromophores (transannular interactions). Therefore, the aim of this work was the synthesis of chiral 1'*H*-spiro[1,3-benzodioxole-2,12'-[6',10']methanocyclooct[*b*]indole] exhibiting a single spatial orientation of indole and 1,2-methylenedioxybenzene chromophores, enantiomer separation, a study of the CD spectra and the determination of the absolute configuration of the enantiomers.

Results and discussion

Synthesis of 1'*H*-spiro[1,3-benzodioxole-2,12'-[6',10']methanocyclooct[*b*]indole] **3** and enantiomer separation by HPLC

Benzenediol protected ketone **2** was the starting compound for the construction of chiral bicyclononane fused with the indole ring *via* the Fisher indolization reaction. The synthesis of monoacetal **2** was accomplished by regioselective protection of the carbonyl group at position C-9 in diketone **1** by a reaction with benzene-1,2-diol (Scheme 1).⁸



Scheme 1

The reaction of the monoacetal **2** with phenylhydrazine in the presence of a catalytic amount of hydrochloric acid afforded indole derivative **3** in excellent yield. The structure of the latter was assigned on the basis of spectroscopic and elemental analysis data. The characteristic signal for NH of the indole ring in the ¹H NMR spectrum and the disappearance of the C=O absorption in the IR spectrum were diagnostic.

In recent years optically active compounds have been available thanks to development of chromatographic methods for resolution of enantiomers.⁹ HPLC is used to obtain the enantiomers of various structures on a semipreparative scale, and a number of bicyclic structures have been successfully resolved.¹⁰ We performed enantiomer separation of indole derivative **3** by chromatography on a swollen microcrystalline triacetylcellulose column with the equipment described previously¹¹ using 95% aqueous ethanol as the mobile phase. The efficiency of enantiomer resolution is expressed by selectivity factor $\alpha = k'_2/k'_1$, where k'_1 and k'_2 are retention factors for the first and second eluted enantiomers, respectively. The first eluted enantiomer of **3** showed a positive rotation and the chromatogram showed rather well separated peaks in both the polarimeter and UV trace. The efficiency of separation was sufficiently high ($k'_1 = 0.89$ and $k'_2 = 1.82$, $\alpha = 2.04$) to obtain practically enantiomerically pure enantiomers of **3**.

Circular dichroism spectra and chiroptical properties of **3**

The circular dichroism (CD) spectra were recorded and analysed in order to determine the absolute configuration of the resolved enantiomers of spiro[1,3-benzodioxole-methanocyclooct[*b*]indole] **3**. The chiroptical methods and, in particular, CD have proved an indispensable tool for studying the absolute configuration of organic compounds.¹² The absolute configuration of chiral compounds containing definite chromophores can be settled from the analysis of CD spectra.¹³ The enormous number of applications of CD measurements led to the formulation of semiempirical rules for the correlation of the signs and magnitudes of observed Cotton effects with the absolute configurations of chiral structures. However, the use of rules in the determination of the absolute configuration of molecules has a number of limitations; for example, some of the rules appear to have a weak theoretical basis, and for some chromophores, including the indole chromophore, no general rule for the analysis of their CEs exists.

The enantiomers of the resolved chiral molecule include two chromophores, namely indole and 1,2-methylenedioxybenzene. As has been mentioned, no general rule for analysis of CEs for the indole chromophore exists. The other chromophore of interest in the studied molecule is the 1,2-methylenedioxybenzene chromophore having C_{2v} symmetry. The 1L_b transition, the so called α -band, of the 1,2-methylenedioxybenzene chromophore is observed at *ca.* 290 nm and is due to the interference of the $\pi \rightarrow \pi^*$ aromatic transitions and $n \rightarrow \pi^*$ transitions of the oxygen atoms. The empirical rule, like the octant rule, for the 1L_b transition was proposed in the study of chiroptical properties of lycorine and related compounds.¹⁴ This empirical rule served well for the determination of the absolute configuration of monoacetal **2** and the corresponding diastereomeric *exo*- and *endo*-hydroxy derivatives obtained from the latter.¹⁵

The CD spectrum of first eluted enantiomer (+)-**3** in ethanol exhibited the positive band at around 290 nm, a positive shoulder at *ca.* 217 nm and a positive band below 210 nm (Fig. 1). The (–)-enantiomer gave the reversed CD spectrum.

However, the interpretation of the experimental CD spectrum and the assignment of observed CE's to particular electronic transitions are rather complicated due to the fact that both indole and 1,2-methylenedioxybenzene chromophores exhibit transitions at the same wavelength. Namely, for the indole chromophore bands at *ca.* 300 nm (1L_b transition), *ca.* 290 nm (1L_a), *ca.* 230 nm (1B_b) and below 210 nm (1B_a) are observed,¹⁶ whereas the 1,2-dioxophenylene chromophore exhibit bands at *ca.* 285 nm (α -band), *ca.* 240 nm (β -band) and *ca.* 220 nm.¹⁴ Thereby the superposition of the above mentioned bands of the same or opposite signs give resultant positions and magnitudes of the Cotton effects in the CD spectrum of **3**. In agreement with this, the UV spectrum of **3** in

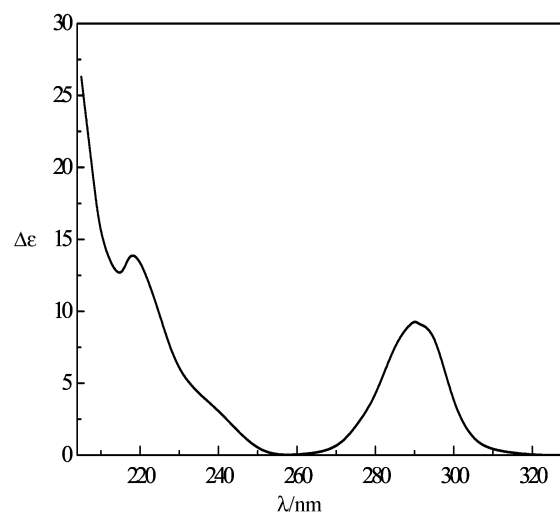


Fig. 1 CD spectrum of the first eluted (+)-enantiomer of **3** in EtOH ($\Delta\epsilon_{290} +9.53$, $\Delta\epsilon_{217} +14.13$ (sh)).

ethanol shows three bands at 322, 266 and 236 nm, respectively. It is not obvious which transition, namely 1L_b and 1L_a bands of the indole chromophore or the α -band of the 1,2-methylenedioxybenzene chromophore, is responsible for a positive CE at 290 nm. Consequently, the sign and the magnitude of the CE corresponding to the α -band of the 1,2-methylenedioxybenzene chromophore could not be established from the experimental CD spectrum securely. Nevertheless, we attempted to assign the absolute configuration of **3** using the empirical rule for the 1L_b transition of the 1,2-methylenedioxybenzene chromophore.

The preferred conformation of **3** has to be known to predict the absolute configuration. The fusion of the bicyclic framework with the indole ring notably reduces the conformational flexibility of the molecule. Only two lowest energy conformers were obtained with SPARTAN Pro using the Monte-Carlo method and MMFF94 force field.¹⁷ The most stable was found to be the double chair conformation, the six-membered ring bearing the indole ring being considerably flattened. The next conformation, *i.e.* the twist boat–twist chair was calculated to be of much higher energy ($\Delta E = 6.85$ kcal mol⁻¹).

The projection of (6'*S*,10'*R*)-**3** into octants with the 1,2-methylenedioxybenzene chromophore at the origin of coordinates is presented in Fig. 2. A third nodal surface perpendicular

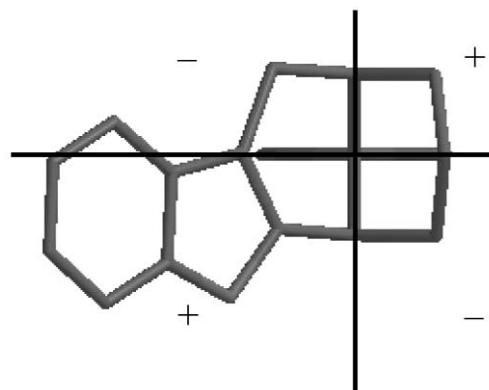


Fig. 2 Projection of (6'*S*,10'*R*)-**3** into octants with the 1,2-methylenedioxybenzene chromophore at the origin of coordinates (signs of the front octants are indicated).

to and bisecting the benzene ring is definitely not planar although the detailed form of it is not known.¹⁴ Fortunately, the rest of the molecule **3** probes front octants and the asymmetry of the molecule and consequently the sign and magnitude of the CE are determined by the contribution of the indole ring. In accordance with the CE effect in the CD spectrum of (+)-**3** the

(6'*S*,10'*R*) absolute configuration may initially be assigned to this enantiomer. However the final conclusion could be reached only by applying another independent method, *e.g.* chemical correlation or theoretical calculations.

Enantiospecific synthesis of (+)-3 and proof of the absolute configuration

The unequivocal proof of the absolute configuration of enantiomers obtained by HPLC separation could be secured by an independent method. Hence there was an objective to synthesize the title compound in the enantiomerically pure form. The starting diketone **1** is readily available in enantiomerically enriched form *via* asymmetric cyclization of cyclohexanone enamines in the reaction with propenoyl chloride.¹⁸ Starting from (–)-(1*R*,5*S*)-bicyclo[3.3.1]nonane-2,9-dione **1** (ee 70%), the (+)-1'*H*-spiro[1,3-benzodioxole-2,12'-[6',10']methanocyclooct[*b*]indole] **3** was obtained. The absolute configuration of (+)-**3** is predetermined by the configuration of starting (–)-(1*R*,5*S*)-diketone **1** since the configuration of the bridgehead atoms does not change during the acetalization and the subsequent indolization reactions. The measurement of the rotation angles and the CD spectrum unequivocally proved the absolute configuration of (+)-**3** as (6'*R*,10'*S*). This result is in disagreement with the configuration deduced from the octant rule for the 1,2-methylenedioxybenzene chromophore. The failure to predict the correct sign of the CE could possibly be accounted for by the dominant input of ¹L_b and ¹L_a transitions of the indole chromophore to the sign and magnitude of the CE at 290 nm and the likely transannular interaction of the chromophores. The latter interactions have been evidenced in appropriate structures by photoelectron spectroscopy, NMR, CD, and other methods.¹⁹ This study clearly demonstrates that the prediction of the CE sign using empirical rules should be made with precaution when two alike or different chromophores are present in the molecule.

Conclusions

The synthesis of chiral 1'*H*-spiro[1,3-benzodioxole-2,12'-[6',10']methanocyclooct[*b*]indole, a fused polycyclic structure, was accomplished *via* the Fisher indolization reaction. Enantiomers of this structure were obtained by chiral HPLC enantiomer separation and the chiroptical properties of the resolved enantiomers containing indole and 1,2-methylenedioxybenzene chromophores were studied. Application of the octant rule to the 1,2-methylenedioxybenzene chromophore to establish the absolute configuration of the enantiomers did not lead to an unequivocal conclusion due to the likely transannular interactions of the chromophores. Enantiospecific synthesis of **3** was performed from enantiomerically enriched (–)-(1*R*,5*S*)-bicyclo[3.3.1]nonane-2,9-dione **1** to prove unequivocally the title structure has the (+)-(6'*R*,10'*S*)-configuration in contrast to the assignment based on the analysis of the CD spectrum. This interesting structure clearly demonstrates that semiempirical rules should be applied cautiously in the determination of the absolute configuration of structures containing several chromophores.

Experimental

General

Melting points were recorded on a Kofler melting apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on a BS-587A 80 MHz "Tesla" spectrometer in DMSO-*d*₆, and are reported in δ ppm downfield from the internal reference TMS. IR spectra were obtained on a Perkin Elmer Spectrum BX spectrometer.

CD spectra were recorded with a Jasco Model J-500 A spectropolarimeter and the UV spectra were recorded on a Cary

2290 spectrophotometer using spectral grade ethanol. Optical rotations were measured at the sodium D line on a Perkin-Elmer 141 and at 546 nm on a Polamat-A polarimeter; $[\alpha]$ values are given in 10⁻¹ deg cm² g⁻¹. Enantiomer separation was performed on a swollen microcrystalline triacetylcellulose (TAC) column using the equipment described previously¹¹ with 95% aqueous ethanol as the mobile phase.

Chromatography was performed using silica gel Kieselgel 60 (0.040–0.063 mm) for flash chromatography and Kieselgel 60 F₂₅₄ plates for TLC. Molecular mechanics calculations were performed using the SPARTAN Pro program package.¹⁷

Synthesis of (±)- and (+)-3

Racemic spiro[1,3-benzodioxole-2,9'-bicyclo[3.3.1]nonan]-2'-one **2** and (–)-(1*R*,5*S*)-bicyclo[3.3.1]nonane-2,9-dione **1** were obtained as described in ref. 8 and 18, respectively.

1'*H*-Spiro[1,3-benzodioxole-2,12'-[6',10']methanocyclooct[*b*]indole] **3**

Spiro[1,3-benzodioxole-2,9'-bicyclo[3.3.1]nonan]-2'-one **2** (0.20 g, 0.82 mmol) and phenylhydrazine (0.11 g, 1.02 mmol) were dissolved in methanol (8 ml). The reaction mixture was acidified with hydrochloric acid (0.1 ml) and heated under reflux for 3.5 hours. The reaction mixture was cooled and left to crystallize. The crystals were filtered, washed (MeOH : H₂O 1 : 1) and dried to give **3** (0.25 g, 97%), mp 265–267 °C. ¹H NMR δ : 10.76 (1H, NH), 7.4–6.6 (8H), 3.2–1.2 (10H); ¹³C NMR δ : 146.65, 146.54, 136.16, 133.38, 126.01, 121.40, 121.22, 120.30, 119.33, 118.35, 117.48, 111.05, 108.6 (two C), 107.98, 35.55, 31.64, 30.33, 27.30, 25.65, 16.42; IR (KBr): 3399 (NH), 1067 (C–O), 742 (disubst. arom.) cm⁻¹. Anal. calcd for C₂₁H₁₉NO₂: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.15; H, 6.05; N, 4.36%.

Data for the first eluted (+)-**3** enantiomer after HPLC separation: $[\alpha]_D^{25} = 308$ (*c* 0.0029, EtOH); $\Delta\epsilon_{290} = +9.53$ dm³ mol⁻¹ cm⁻¹, $\Delta\epsilon_{217} = +14.13$ (sh); UV, λ_{max}/nm (log (ϵ /dm³ mol⁻¹ cm⁻¹)): 322 (4.11), 266 (4.66), 236 (4.84).

(+)-(6'*R*,10'*S*)-1'*H*-Spiro[1,3-benzodioxole-2,12'-[6',10']methanocyclooct[*b*]indole] **3**

Phosphorus pentoxide (0.04 g, 0.26 mmol) was added to a solution of (–)-(1*R*,5*S*)-bicyclo[3.3.1]nonane-2,9-dione **1** (0.02 g, 0.31 mmol, ee 70%) and benzene-1,2-diol (0.022 g, 0.197 mmol) in dry toluene (5 ml). The reaction mixture was heated under reflux for 2.5 h, cooled and the solution decanted from P₂O₅. The remaining solid was washed with toluene (2 × 5 ml), combined solutions were washed with water, aqueous NaHCO₃, dried and evaporated. The remaining solid was chromatographed through a short plug of silica gel (toluene : EtOAc 5 : 1), the collected fractions were concentrated and the remaining solid (0.018 g) was used for further transformations. The obtained spiro[benzo-1,3-dioxole-2,9'-bicyclo[3.3.1]nonan]-2'-one and phenylhydrazine (0.01 g, 0.09 mmol) were dissolved in methanol (4 ml). The reaction mixture was acidified with hydrochloric acid (0.05 ml) and heated under reflux for 2 hours. The reaction mixture was concentrated to dryness and the remaining solid suspended in tetrachloromethane and filtered. The filtrate was concentrated and the remaining solid subjected to column chromatography (chloroform) to give (+)-**3** (0.018 g, ee 70%, 43%), mp 267–269 °C. $[\alpha]_{546}^{16} = 288$ (*c* 0.125, EtOH), $[\alpha]_{546}^{16} = 106$ (*c* 1.2, CHCl₃). ¹H NMR, IR and elemental analysis data are identical with the racemic sample as presented above.

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