Studies of Chiral Indoles. Part I. Indoles with Chiral 1- and 3-Substituents. Synthesis and Preparative Enantiomeric Separation by Chromatography on Microcrystalline Triacetylcellulose

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A number of indole derivatives with chiral substituents in position 1 or 3 and with substituents of varying size in position 2 have been prepared. The chiral rotors are 1-N,N-dimethylcarbamoylethyl and N'-methylpiperidin-2'-on-3'-yl and their corresponding thioanalogues, and 1-phenylethyl.

The reaction conditions required to obtain preferential 1- or 3-alkylation are discussed in terms of the HSAB principle and the extent of ion pair formation.
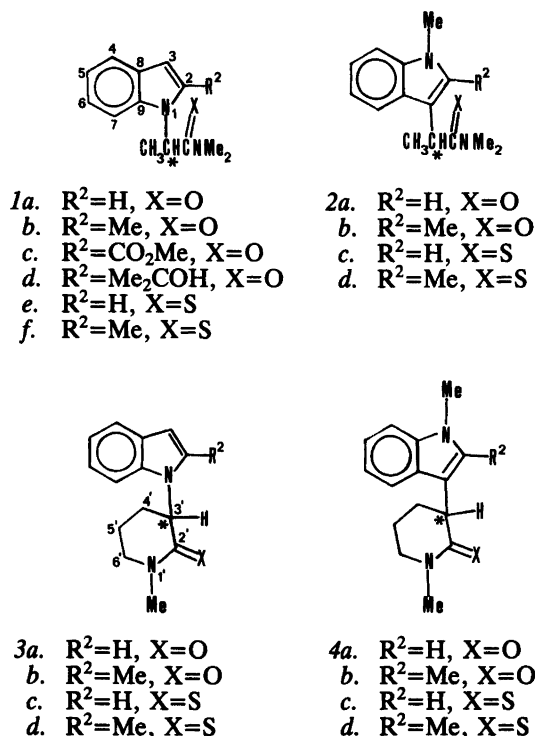
Three 1-(N,N-dimethylcarbamoylethyl-indoles (R^2=H and Me, and R^2=Me, R^3=CO$_2$Me, R^5=OMe) and one 1-(1-phenylethyl)indole (R^2=Me, R^3=CO$_2$Me, R^5=OMe) were obtained optically pure by stereospecific pathways. The other compounds were obtained in racemic forms. Most of the racemic compounds were conveniently resolved by liquid chromatography on swollen, microcrystalline triacetylcellulose (TAC). In some cases rather remarkable separations were obtained.

Attempts were made to prepare the optically active 1- and 3-(N'-methylpiperidin-2'-on-3'-yl)indoles by hydrolysis of the methylthioimmonium salts prepared from chromatographically resolved thioamides. The 3-substituted analogues were partly racemized in this process, while the 1-substituted ones were completely racemized. A possible explanation is proposed.

We are currently studying the circular dichroism (CD) spectra of "nucleoside models" as a function of their well-known [1] *syn-anti* equilibrium around the glycosidic bond. In some of these models we have replaced the base by the indole ring system and the sugar moiety by different rotors containing a chromophore as shown in Scheme 1.

These studies require optically active compounds, and in this work we report on the preparation of the substituted indoles and the often remarkably efficient resolution of the racemic compounds by chromatography on swollen microcrystalline triacetylcellulose (TAC).[2] This technique is undoubtedly the most convenient one for optical resolution in the present case.

In a previous study on 1- and 3-isopropylindoles,[3] the isopropyl group was shown to adopt both a *syn* and an *anti* conformation. The position of the equilibrium between these depends on the size of the substituent in position 2. It has been shown that rotors R of the

1a. R²=H, X=O
 b. R²=Me, X=O
 c. R²=CO₂Me, X=O
 d. R²=Me₂COH, X=O
 e. R²=H, X=S
 f. R²=Me, X=S

2a. R²=H, X=O
 b. R²=Me, X=O
 c. R²=H, X=S
 d. R²=Me, X=S

3a. R²=H, X=O
 b. R²=Me, X=O
 c. R²=H, X=S
 d. R²=Me, X=S

4a. R²=H, X=O
 b. R²=Me, X=O
 c. R²=H, X=S
 d. R²=Me, X=S

Scheme 1. The numbers in the piperidone ring are primed to simplify assignment and in accordance with nucleoside nomenclature.

type CH_3-CH-X with $X=CO_2H$ or CO_2CH_3 behave similarly to isopropyl groups when attached to planar frameworks.[4] Preliminary investigations using the DNMR technique show that a change from an ester to an amide does not cause any significant change in this behaviour, and that ring-closure to the lactam only causes minor changes. Also the 1-phenylethyl group behaves very much like an isopropyl group in these systems.

The piperidonylindoles showed very poor resolution on TAC, whereas the corresponding thioanalogues generally gave much better separation. In order to take advantage of this, we transformed the resolved thio compounds to the corresponding oxo analogues,[5] without affecting the easily oxidized indole ring. The reaction proceeds *via* the methylthioimmonium salt as shown in eqn. 1. The reaction, however, gives varying degree of racemization depending on the substrate.
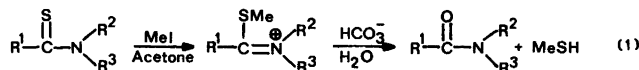
In subsequent articles we intend to report on the generalizations, which can be made with respects to structural effects on the chromatographic separation, and also the results of ^{1}H NMR and CD spectroscopic studies and molecular mechanics calculations.

EXPERIMENTAL

Syntheses. "Flash chromatography"[6] on silica gel (Merck 60, mesh 230−400) with various solvents has been useful in the purification of most of the synthesized compounds. The light petroleum and ligroin are the fractions boiling at 40−60 and 80−100 °C, respectively. $MgSO_4$ was used in all drying procedures.

The enantiomeric purity of compounds prepared by stereospecific pathways and of those resolved by chromatography with R_s value ≤1.3, was checked by the use of chiral shift reagents. The spectra were recorded on a Nicolet Model 360 WB NMR spectrometer. "Pirkle's alcohol",[7] (+)-1-anthryl-2,2,2-trifluoroethanol was used in most cases and $Eu(hfbc)_3$[8] for *5c* and *8*, but they failed for *5a*, *5b*, *5e*, and *6e*. The chiral $Eu(hfbc)_3$-Ag(fod) shift reagent[9,10] was successfully applied in these cases. One molar equivalent of the shift reagent was used unless otherwise stated. The optical purity was determined with an accuracy of ±2 % by visual fitting of the experimental curves to Lorentzian curves. The optical rotation, enantiomeric excess (in the following abbreviated ee) and ^{1}H NMR signals of the diastereomeric complex used to determine the enantiomeric purity follow after ordinary spectral data for each compound. Optical rotations were measured in methanol unless otherwise stated. The [α] values which are above 100° are probably accurate to better than 5 %, but with lower rotations the uncertainty due to weighing errors (small quantities available) and errors in measurement of the rotation may lead to uncertainties in [α] as high as 10 % in unfavourable cases.

(R,S)- *and* (S)-*alanine dimethylamide.* The (S)-form has been described by Freudenberg *et al.*[11] and the (R,S)-form by Guthrie *et al.*[12] The "mixed anhydride method"[13] with pivaloyl chloride in THF and direct conversion of the anhydride into the amide was chosen to make both (R,S)- and (S)-N-carbobenzoxyalanine amide from N-carbobenzoxyalanine.[12]

(R,S)-N-*Methyl-3-bromo-2-piperidone.* 3,3-Dibromo-2-piperidone[14] (20 g, 74 mmol) and bromomethane (35 g, 370 mmol) were dissolved in a cooled solution (−3 °C) of sodium-dried THF (500 ml) and dry DMF (15 ml) under nitrogen atmosphere. Sodium hydride (1.85 g, 77 mmol) was added in portions of 0.3 g with rapid agitation during a period of 8 h. The reaction mixture was allowed to stand overnight at −3 °C, after which time no starting material was observed (GLC: Dexil 300, 130−240 °C, 8 °C/min).

The mixture was evaporated and the remaining paste was dissolved in ether (400 ml). The ethereal solution was extracted with saturated aqueous NH_4Cl solution (3×75 ml), dried, filtered and evaporated. The residue (25 g) which according to GLC contained more than 95 % of the desired product (uncorrected FID response), was used in the next step without purification.

Flash chromatography of a small amount with dichloromethane/ethyl acetate (80:20) followed by recrystallization from ligroin/toluene (75:25) gave colourless needles, m.p. 70−71 °C. MS [IP 70 eV: *m/e* (% rel. int.)]: 273/271/269 (1/2/1, M), 192/190 (17/18, M−Br), 188/186/184 (5/10/6), 164/162 (24/27), 72 (100). ^{1}H NMR (100 MHz, $CDCl_3$, 30 °C): δ 2.06 (2H, m, 5-CH_2), 2.99 (2H, m, 4-CH_2), 3.00 (3H, s, N−CH_3), 3.45 (2H, t, 6-CH_2).

The catalytic debromination was carried out according to Wineman *et al.*[14] and was complete within a few min. By carrying out the reaction in dilute solution (*ca.* 2 g of starting material in 100 ml of glacial acetic acid) bis-debromination was suppressed and the monobrominated product obtained in *ca.* 90 % yield. The slightly yellow oil was used directly in the next synthesis. MS: 193/191 (4/4, M), 112 (100), 108/106 (12/11), 72 (25). ^{1}H NMR (100 MHz, $CDCl_3$, 30 °C): δ 1.76−2.40 (4H, m, 4-CH_2, 5-CH_2), 2.95 (3H, s, N−CH_3), 3.23−3.44 (2H, m, 6-CH_2), 4.48−4.59 (1H, m, 3-C*H*).

(R)-*1-(1-N,N-Dimethylcarbamoylethyl)indole (1a).* To the sodium salt of indole,[3,15] prepared from sodium hydride (1.56 g, 65 mmol) and indole (3.5 g, 30 mmol) in dry DMF (40 ml), (S)-2-bromopropanoic acid[16] (4.9 g, 32 mmol; $[α]_D^{23}=−46.0$ (neat), lit.[17] $[α]_D=−46.2$) was added at such a rate that the temperature in the cooled solution did not exceed 5 °C. After 2 h at room temperature and 2 h at 50 °C the reaction was completed. The solution was chilled, and acidic compounds were separated from non-acidic by extraction with saturated aqueous $NaHCO_3$ solution and ether. Acidification of the aqueous phase with 1 M H_2SO_4 was followed by extraction with ether. The final ethereal solution was extracted four times with 1M H_2SO_4, dried, filtered, and evaporated. Recrystallization of the residue from toluene/ligroin (90:10) followed by ethanol/water (60:40) gave slightly

yellow crystals (yield 48 %) of (R)-1-(1-carboxyethyl)-indole, m.p. 130–132 °C. ^{1}H NMR (60 MHz, CDCl$_3$, 30 °C): δ 1.75 (3H, d, J 7.0 Hz, CH$_3$CH), 5.12 (1H, q, J 7.0 Hz, CHCH$_3$), 6.56 (1H, d, J 3.6 Hz, 3-H), 7.00–7.83 (5H, m).

The mixed anhydride method[13] was used to convert the acid to the amide. (R)-1-(1-Carboxyethyl)indole (1.0 g, 5.3 mmol) and triethylamine (0.55 g, 5.4 mmol) were added to a precooled (−2 °C) solution of sodium-dried THF (20 ml) under an atmosphere of nitrogen and with rapid agitation. Pivaloyl chloride (0.64 g, 5.3 mmol) in THF (10 ml) was added at such a rate that the temperature did not exceed 0 °C. A flocky precipitate was immediately formed. After 1 h at −2 °C, dimethylamine (~0.5 g, 10 mmol), in THF (5 ml) was slowly added at −1 °C with rapid agitation and then the reaction mixture was left at −2 °C over night. The reaction mixture was evaporated after filtration and the remaining oil was dissolved in ether, extracted with saturated aqueous NaHCO$_3$ solution, dried, filtered and evaporated. The slightly yellow oil, almost pure according to NMR (yield 98 %), was finally purified by preparative GLC (OV 101, 230 °C) giving colourless crystals, m.p. 48.5–50 °C. The racemic form was obtained by the same procedure as a colourless oil. Anal. C$_{13}$H$_{16}$N$_2$O: C, H, N. MS: 216 (16, M), 144 (100), 115 (18). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.63 (3H, d, J 6.9 Hz, CH$_3$CH), 2.78, 2.98 (6H, 2s, E,Z-N−CH$_3$), 5.32 (1H, q, J 6.9 Hz, CH$_3$CH), 6.53 (1H, doublet of doublets, J 3.2 Hz, 0.7 Hz, 3-H), 7.12–7.22 (2H, m, 5-H, 6-H), 7.17 (1H, s, J 3.2 Hz, 2-H), 7.36 (1H, m, 7-H), 7.62 (1H, m, 4-H). [α]$_D^{23}$ = +168°, [α]$_{365}^{23}$ = +651°, (C 1.2), ee > 99 %. ^{1}H NMR: δ 1.58, 1.62 (3H, 2d, CH$_3$CH).

(R,S)-and (R)-1-(1-N,N-dimethylcarbamoylethyl)-2-methylindole (1b) was with minor modifications prepared as described for 1a, starting from 2-methylindole. After the addition of the acid the reaction mixture was allowed to stand over night at room temperature. Recrystallization from toluene/ligroin (85:15) gave a 25 % yield of 1-(1-carboxyethyl)-2-methylindole as colourless crystal, m.p. 147.5–150.0 °C (rac., dec.), 149.5–151.5 °C (R, dec.). ^{1}H NMR (60 Mhz, CDCl$_3$, 30 °C): δ 1.65 (3H, d, J 7.0 Hz, CH$_3$CH), 2.32 (3H, s, 2-CH$_3$), 5.07 (1H, q, J 7.0 Hz, CHCH$_3$), 6.25 (1H, s, 3-H), 6.93–7.72 (4H, m).

Flash chromatography of the amide with ether followed by recrystallization from hexane/toluene (90:10) gave colourless crystals, m.p. 116.5–117 °C (rac.), 115–116 °C (R), (yield 95 %). Anal. C$_{14}$H$_{18}$N$_2$O: C, H, N. MS: 230 (14, M), 158 (100), 143 (12), 130 (10), 115 (20). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.59 (3H, d, J 6.9 Hz, CH$_3$CH), 2.41 (3H, d, J 0.9 Hz, 2-CH$_3$), 2.51, 2.96 (6H, 2s, E,Z-N−CH$_3$), 5.12 (1H, q, J 6.9 Hz, CHCH$_3$), 6.27 (1H, quint, J 0.9 Hz, 3-H), 7.04–7.13 (2H, m, 5-H, 6-H), 7.32 (1H, m, 7-H), 7.50 (1H, m, 4-H). [α]$_D^{23}$ = +244°, [α]$_{365}^{23}$ = +924°, (C 0.44), ee > 99 %, ^{1}H NMR: δ 1.51, 1.53 (3H, 2d, CH$_3$CH).

(R,S)-1-(1-N,N-Dimethylcarbamoylethyl)-2-methoxycarbonylindole (1c) was prepared as described for 1a, starting from 3-methoxycarbonylindole, with the following change. After addition of (S)-2-bromopropanoic acid at 10 °C, and 1 h at the same temperature, the reaction mixture was kept at 20 °C for 6 days. Work-up gave 1-(1-carboxyethyl)-2-methoxycarbonylindole as an almost pure amorphous precipitate (yield 59 %), completely racemized. ^{1}H NMR (60 MHz, CDCl$_3$, 30 °C): δ 1.80 (3H, d, J 7.2 Hz, CH$_3$CH), 3.88 (3H, s, O−CH$_3$), 6.11 (1H, q, J 7.2 Hz, CHCH$_3$), 7.02–7.88 (5H, m). The amide was obtained as white needles after flash chromatography with dichloromethane and recrystallization twice from hexane/toluene (85:15) in nearly quantitative yield, m.p. 123–124.5 °C. Anal. C$_{15}$H$_{18}$N$_2$O$_3$: C, H, N. MS: 274 (21, M), 202 (76), 170 (100), 144 (28), 115 (36). ^{1}H NMR (360 MHz, (CD$_3$)$_2$O, 25 °C): δ 1.55 (3H, d, J 6.9 Hz, CH$_3$CH), 2.57, 2.84 (6H, 2s, E,Z-N−CH$_3$), 3.88 (3H, s, O−CH$_3$), 6.68 (1H, q, J 6.9 Hz, CHCH$_3$), 7.01–7.22 (2H, m, 5-H, 6-H), 7.33 (1H, d, 3-H), 7.58–7.61 (2H, m, 4-H, 7-H). [α]$_D^{23}$ = +237°, [α]$_{365}^{23}$ = +1103°, (C 0.27).

(R,S)-1-(1-N,N-Dimethylcarbamoylethyl)-2-(1-methyl-1-hydroxyethyl)indole (1d). 1-(1-Carboxyethyl)-2-methoxycarbonylindole (1.8 g, 7.3 mmol) in dry ether (10 ml) was added under nitrogen atmosphere with cooling (+10 °C) and agitation to a solution of methylmagnesium iodide (30 mmol) in dry ether (25 ml). A pasty precipitate was formed at once, which resisted dissolution on further addition of ether, but became dispersed when sodium-dried THF (75 ml) was added. The temperature was kept at 35 °C for 4 h. Ice-water (10 ml) was added and the resulting mixture was then evaporated until the organic solvents had disappeared. The oil was dissolved in ether (100 ml) and extracted with saturated aqueous NaHCO$_3$ solution (75 ml). The aqueous phase was acidified with 1M HCl and

extracted with ether (3×50 ml). The final ethereal solution was dried, filtered and evaporated, giving a slightly yellow oil (0.7 g, 38 % yield) of *1-(1-carboxyethyl)-2-(1-methyl-1-hydroxyethyl)indole*, which was used without further purification in the next step. However, applying the mixed anhydride method [13] gave in this case not the desired product. Instead, cyclization in almost quantitative yield to a 6-ring lactone, *1,4-dihydro-1,4,4-trimethylindolo[4,5a]-3,9b-oxazine-2-one* (7) occurred. Flash chromatography of the crude oil with dichloromethane, followed by two recrystallizations from aqueous ethanol (96:4) gave colourless crystals, m.p. 108.5–109 °C (rac.). Anal. $C_{14}H_{15}NO_2$: C, H, N. MS: 229 (62, M), 215 (11), 186 (100), 170 (25), 144 (32). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.83, 1.90 (6H, 2s, $(CH_3)_2COH$), 1.90 (3H, d, J 7.2 Hz, CH_3CH), 5.19 (1H, q, J 7.2 Hz, $CHCH_3$), 6.39 (1H, d, J 0.7 Hz, 3-H), 7.16–7.28 (2H, m, 5-H, 6-H), 7.31 (1H, m, 7-H), 7.63 (1H, m, 4-H). IR (KBr): 1735(s), $[\alpha]_D^{23}=+183°$, $[\alpha]_{365}^{23}=+747°$ (C 0.12), ee > 99 %. ^{1}H NMR, 2 eq. Pirkle's alcohol: 1.84, 1.86 (3H, 2d, CH_3CH).

Compound 7 (0.3 g, 1.3 mmol) and dimethyl amine (0.5 g, 11 mmol) were dissolved in toluene (10 ml) and kept at room temperature for 2 days. Evaporation followed by chromatography with ethyl acetate/dichloromethane (70:30) gave *1d* (0.33 g, 90 % yield). Final purification by semipreparative HPLC (silica 60–10 Polygosil 10 μ) with dichloromethane/ethyl acetate after enantiomeric separation on TAC gave a slightly yellow film. MS: 274 (12, M), 202 (23), 184 (38), 158 (100). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.62 (1H, s, OH), 1.72, 1.84 (6H, 2s, $(CH_3)_2COH$), 1.80 (3H, d, J 6.9 Hz, CH_3CH), 2.64, 2.90 (6H, 2s, E,Z-N−CH_3), 6.15 (1H, q, J 6.9 Hz, $CHCH_3$), 6.40 (1H, s, 3-H), 7.03−7.15 (2H, m, 5-H, 6-H), 7.37 (1H, m, 7-H), 7.52 (1H, m, 4-H). The N-methyl resonances are extensively exchange broadened at this temperature, which makes the shift determination somewhat inaccurate. $[\alpha]_D^{23}=+56°$, $[\alpha]_{365}=+152°$ (C 0.086), ee=62 %. ^{1}H NMR: δ 1.79, 1.82 (3H, 2s, CH_3COH). Attempts to prepare *1d* from *1c* by reacting it with methylmagnesium iodide in ether failed. A flocky precipitate was immediately formed which would not be dissolved by further addition of ether or THF, and only starting material was recovered even after prolonged boiling.

(R,S)-3-*(1-N,N-dimethylcarbamoylethyl)indoles* were prepared from (S)-*N,N*-dimethyl-2-bromopropanamide [18] ($[\alpha]_D^{23}=+67.4$, $[\alpha]_{365}^{23}=+300$, (C 0.78, ethanol), ee 84 %) and the appropriate 2-substituted 1-indolylmagnesium iodide according to the route outlined for 3-alkylindoles.[3,19] These compounds were then, after purification by flash chromatography with appropriate solvents, N-methylated with dimethyl sulfate and sodium hydride in DMF.[3] Only yields and solvent combinations in the purification after each synthetic step will be mentioned.

(R,S)-3-*(1-N,N-Dimethylcarbamoylethyl)-1-methylindoles (2a)*. Flash chromatography with dichloromethane/ethyl acetate (85:15) as mobile phase gave pure 3-*(1-N,N-dimethyl-carbamoylethyl)indole* in 75 % yield. ^{1}H NMR (60 MHz, CDCl$_3$, 30 °C): δ 1.52 (3H, d, J 6.9 Hz, CH_3CH), 2.85, 2.91 (6H, 2s, E,Z-N−CH_3), 4.17 (1H, q, J 6.9 Hz, $CHCH_3$), 6.90−7.75 (5H, m), 9.23 (1H, s, N−H). CD analysis showed that the product was completely racemized. Methylation, followed by purification by flash chromatography with dichloromethane/ethyl acetate (80:30) (yield 95 %) and two recrystallizations from ligroin/toluene (90:10) afforded the pure 2a, m.p. 110.5−112 °C. Anal. $C_{14}H_{18}N_2O$: C, H, N. MS: 230 (9, M), 158 (100), 143 (17), 130 (4), 115 (13). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.50 (3H, d, J 6.8 Hz, CH_3CH), 2.94, 2.97 (6H, 2s, E,Z-N−CH_3), 3.73 (3H, s, N(1)−CH_3), 4.19 (1H, q, J 6.8 Hz, $CHCH_3$), 6.94 (1H, s, 2-H), 7.09−7.24 (2H, m, 5-H, 6-H), 7.29 (1H, m, 7-H), 7.64 (1H, m, 4-H). $[\alpha]_D^{23}=+154°$, $[\alpha]_{365}^{23}=+625°$, (C 0.31).

(R,S)-3-*(1-N,N-Dimethylcarbamoylethyl)-1,2-dimethylindole (2b)*. Filtration of the residue, after the anisole had been distilled off, gave an almost pure precipitate of 3-*(1-N,N-dimethylcarbamoylethyl)-2-methylindole* (yield 50 %). ^{1}H NMR (60 NHz, CDCl$_3$, 30 °C): δ 1.47 (3H, d, J 7.0 Hz, CH_3CH), 2.37 (3H, s, 2-CH_3), 2.78, 2.94 (6H, 2s, E,Z-N−CH_3), 4.03 (1H, q, J 7.0 Hz, $CHCH_3$), 6.97−7.73 (5H, m), 8.20 (1H, s, N−H). Methylation followed by column chromatography with dichloromethane/ethyl acetate (90:10) gave 2b in 95 % yield. Recrystallization from ligroin/toluene (70:30) gave colourless needles, m.p. 163.5−164 °C. Anal. $C_{15}H_{20}N_2O$: C, H, N. MS: 244 (8, M), 172 (100), 157 (18), 144 (15), 128 (6). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.45 (3H, d, J 6.8 Hz, CH_3CH), 2.38 (3H, s, 2-CH_3), 2.77, 2.93 (6H, 2s, E,Z-N−CH_3), 3.64 (3H, s, N(1)−CH_3), 4.03 (1H, q, J 6.8 Hz, $CHCH_3$), 7.04−7.17 (2H, m, 5-H, 6-H), 7.24 (1H, m, 7-H), 7.64 (1H,

m, 4-*H*). $[\alpha]_D^{23}=+261°$, $[\alpha]_{365}^{23}=+1170°$, (C 0.30).

The syntheses of the *1-(N'-methylpiperidin-2'-on-3'-yl)indoles* were carried out in THF instead of DMF. For reasons not further investigated, the yield was much lower when the latter solvent was used.

(R,S)-1-(N'-Methylpiperidin-2'-on-3'-yl)indole (3a). To a precooled solution (0 °C) of indolyl sodium (~23 mmol) in sodium-dried THF (40 ml) was added (*R,S*)-3-bromo-*N*-methyl-2-piperidone (~3.8 g, 20 mmol) in THF (30 ml) with rapid agitation under nitrogen atmosphere. After 21 h at 0 °C, the solvent was evaporated. The remaining oil was poured into water (100 ml) and extracted with ether (4×50 ml). The combined ether phases were dried and evaporated. Flash chromatography with dichloromethane/ethyl acetate (60:40) gave an oil (yield 3.6 g, 69 %), which crystallized on prolonged standing, m.p. 90−91 °C (rac.) after recrystallization from ligroin/toluene (80:20). Anal. $C_{14}H_{16}N_2O$: C, H, N. MS: 228 (19, M), 168 (16), 156 (31), 143 (11), 129 (5), 84 (100). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.96−2.08 (2H, m, 5'-C*H*$_2$), 2.26−2.32 (2H, m, 4'-C*H*$_2$), 3.05 (3H, s, N'−C*H*$_3$), 3.38−3.57 (2H, m, 6'-C*H*$_2$), 4.97 (1H, t, *J* 8.1 Hz, 3'-*H*), 6.52 (1H, m, 3-*H*), 7.05 (1H, m, 2-*H*), 7.08−7.20 (2H, m, 5-*H*, 6-*H*), 7.23 (1H, m, 7-*H*), 7.61 (1H, m, 4-*H*). $[\alpha]_{365}^{53}=-47°$, $[\alpha]_{313}^{23}=-242°$, (C 0.078), ee=66 %. ^{1}H NMR: δ 3.03, 3.04 (3H, 2s, N'−C*H*$_3$).

1-(N'-Methylpiperidin-2'-on-3'-yl)-2-methylindole (3b) was obtained in 35 % yield by the same procedure as for *3a*, starting from 2-methylindole. Flash chromatography with dichloromethane/ethyl acetate (80:20) gave an almost pure viscous liquid. Minor impurities were removed by liquid chromatography on TAC. This compound is extremely sensitive towards light and becomes red after short exposure. Decomposition is observed even when it is stored in refrigerator (−18 °C) and in the dark. Anal. Found: C 73.55, H 7.52, N 11.3, Calc. for $C_{15}H_{18}N_2O$: C 74.3, H 7.50, N 11.56. MS: 242 (30, M), 182 (6), 170 (16), 157 (11), 130 (100), 84 (99). ^{1}H NMR (360, MHz, CDCl$_3$, 25 °C): δ 2.01−2.21 (4H, m, 4'-C*H*$_2$, 5'-C*H*$_2$), 2.39 (3H, s, 2-C*H*$_3$), 3.07 (3H, s, N'−C*H*$_3$), 3.38−3.68 (2H, m, 6'-C*H*$_2$), 4.87 (1H, doublet of doublets, 3'-C*H*), 6.25 (1H, m, 3-*H*), 6.97−7.09 (3H, m, 5-*H*, 6-*H*, 7-*H*), 7.49 (1H, m, 4-*H*).

The *3-(N'-methylpiperidin-2'-on-3'-yl)indoles* were prepared as described for the corresponding 3-(1-carbamoylethyl)indoles, starting from (*R,S*)-3-bromo-*N*-methyl-2-piperidone.

3-(N'-Methylpiperidin-2'-on-3'-yl)-1-methylindole (4a). 3-(*N'*-Methylpiperidin-2'-on-3'-yl)indole was obtained in approximately 50 % yield in the first reaction step after flash chromatography with dichloromethane/ethyl acetate (50:50). ^{1}H NMR (60 MHz, CDCl$_3$, 30 °C): δ 1.70−2.27 (4H, m, 4'-C*H*$_2$, 5'-C*H*$_2$), 3.03 (3H, s, N'−C*H*$_3$), 3.20−3.53 (2H, m, 6'-C*H*$_2$), 3.90 (1H, t, *J* 7.0 Hz, 3'-C*H*), 6.47 (1H, d, *J* 2.8 Hz, 3-*H*), 6.90−7.67 (5H, m), 8.40 (1H, s, N−*H*). N−Methylation gave a 50 % yield of *4a* after flash chromatography with dichloromethane/ethyl acetate (80:20), followed by recrystallization from ligroin/toluene (70:30), m.p. 86−87.5 °C. Anal. $C_{15}H_{18}N_2O$: C, H, N. MS: 242 (47, M), 213 (9), 183 (25), 170 (67), 157 (35), 83 (100). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.75−2.01 (2H, m, 5'-C*H*$_2$), 2.08−2.22 (2H, m, 4'-C*H*$_2$), 3.05 (3H, s, N'−C*H*$_3$), 3.34−3.47 (2H, m, 6'-C*H*$_2$), 3.72, (3H, s, N−C*H*$_3$), 3.98 (1H, t, *J* 6.3 Hz, 3'-CH), 6.87 (1H, m, 2-*H*). 7.06−7.22 (2H, m, 5-*H*, 6-*H*), 7.27−7.35 (2H, m, 4-*H*, 7-*H*). $[\alpha]_{365}=-48°$, (C 0.13), ee=90 %. ^{1}H NMR: δ 3.61, 3.64 (3H, 2s, N−C*H*$_3$).

3-(N'-Methylpiperidin-2'-on-3'-yl)-1,2-dimethylindole (4b). The first step gave 3-(*N'*-methylpiperidin-2'-on-3'-yl)-2-methylindole in 59 % yield after flash chromatography with ethyl acetate/dichloromethane (60:40) as eluent. ^{1}H NMR (60 MHz, CDCl$_3$, 30 °C): δ 1.73−2.13 (4H, m, 4'-C*H*$_2$, 5'-C*H*$_2$), 1.83 (3H, s, 2-C*H*$_3$), 3.09 (3H, s, N'−C*H*$_3$), 3.33−3.90 (3H, m, 6'-C*H*$_2$, 3'-C*H*), 6.80−7.30 (4H, m), 8.47 (1H, s, N−*H*).

N-Methylation followed by flash chromatography with dichloromethane/ethyl acetate (60:40) and recrystallization from ligroin/toluene (60:40), gave *4b* as colourless prisms (yield 50 %), m.p. 142−144 °C (rac.). Anal. $C_{16}H_{20}N_2O$: C, H, N. MS: 256 (56, M), 242 (4), 227 (5), 213 (6), 197 (17), 184 (100), 171 (37), 158 (25). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.86−2.09 (4H, m, 4'-C*H*$_2$, 5'-C*H*$_2$), 2.34 (3H,.s, 2-C*H*$_3$), 3.08 (3H, s, N'−C*H*$_3$), 3.38−3.62 (2H, m, 6'-C*H*$_2$), 3.63 (3H, s, N−C*H*$_3$), 3.82 (1H, t, *J* 8.0 Hz, 3'-C*H*), 6.98−7.13 (2H, m, 5-*H*, 6-*H*), 7.20−7.28 (2H, m, 4-*H*, 7-*H*). $[\alpha]_D^{23}=+18°$, $[\alpha]_{365}^{23}=+157°$, (C 0.14), ee=84 %. ^{1}H NMR: δ 2.15, 2.22 (3H, 2s, 2-C*H*$_3$). The conversion of the amides to the corresponding thio analogues was easily achieved by treatment with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-

2,4-diphosphetane-2,4-disulfide, "the Lawesson reagent".[20] This procedure leads to extensive racemization, which is contradictory to the results obtained for dipeptides reported by Clausen et al.[21,22]

(R,S)-*1-(1-N,N-Dimethylthiocarbamoylethyl)indole (1e)* was prepared by gentle reflux of *1a* (2.0 g, 8.7 mmol) and Lawesson reagent (3.57 g, 8.7 mmol) in sodium-dried toluene (25 ml) for 2 h, when all starting material had disappeared as checked by TLC. Evaporation followed by flash chromatography with toluene/dichloromethane (60:40) afforded a crystalline product (yield 78 %), which was finally purified by recrystallization first from ligroin/toluene (85:15), and then from 95 % aqueous ethanol, m.p. 141.4–142 °C (rac.). Anal. $C_{13}H_{16}N_2S$: C, H, N. MS: 232 (19, M), 144 (100), 116 (12), 88 (8). ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ 1.82 (3H, d, J 6.9 Hz, CH_3CH), 3.09 (3H, s, E–N–CH_3), 3.49 (3H, s, Z–N–CH_3), 5.57 (1H, q, J 6.9 Hz, CHCH$_3$), 6.52 (1H, m, 3-*H*), 7.10–7.24 (2H, m, 5-*H*, 6-*H*), 7.33–7.34 (2H, m, 2-*H*, 7-*H*), 7.64 (1H, m, 4-*H*). $[a]_D^{23}=+215°$, $[a]_{405}^{23}=+1205°$, (C 0.30).

(R,S)-*1-(1-N,N-Dimethylthiocarbamoylethyl)-2-methylindole (1f)* was prepared and purified as described for *1e*, starting from *1b* (yield 80 %), m.p. 97–98 °C (rac.). Anal. $C_{14}H_{18}N_2S$: C, H, N. MS: 246 (17, M), 158 (100), 143 (8), 130 (7), 88 (8). ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ 1.86 (3H, d, J 6.8 Hz, CH_3CH), 2.42 (3H, d, J 0.9 Hz, 2-CH_3), 2.77 (3H, s, E–N–CH_3), 3.47 (3H, s, Z–N–CH_3), 5.24 (1H, q, J 6.8 Hz, CHCH$_3$), 6.27 (1H, quint, J 0.9 Hz, 3-*H*), 7.03–7.12 (2H, m, 5-*H*, 6-*H*), 7.48–7.51 (2H, m, 4-*H*, 7-*H*). $[a]_D^{23}=+588°$, $[a]_{405}^{23}=+2451°$, (C 0.13).

3-(1-N,N-Dimethylthiocarbamoylethyl)-1-methylindole (2c). Starting from *2a*, the reaction was completed within 1 h, when carried out as described for *1e*. Flash chromatography with dichloromethane–toluene (80:20) followed by recrystallization from 95 % aqueous ethanol gave colourless prisms (yield 84 %), m.p. 131.5–132.5 °C. Anal. $C_{14}H_{18}N_2S$: C, H. N. MS: 246 (12, M), 158 (100), 143 (16), 130 (4), 115 (11). ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ 1.66 (3H, d, J 6.7 Hz, CH_3CH), 3.19 (3H, s, E–N–CH_3), 3.50 (3H, s, Z–N–CH_3), 3.70 (3H, s, N(1)–CH_3), 4.47 (1H, q, J 6.7 Hz, CHCH$_3$), 7.02 (1H, s, 2-*H*), 7.08–7.23 (2H, m, 5-*H*, 6-*H*), 7.27 (1H, m, 7-*H*), 7.62 (1H, m, 4-*H*). $[a]_D^{23}=+286°$, $[a]_{405}^{23}=+1417°$, (C 0.15), ee > 99 %. ^{1}H NMR, 2 eq. Pirkle's alcohol: δ 3.06, 3.07 (3H, 2s, E–N–CH_3).

3-(1-N,N-Dimethylthiocarbamoylethyl)-1,2-dimethylindole (2d) was prepared and purified as described for *2c*, starting from *2b*. Yield (98 %), m.p. 154.5–155 °C. Anal. $C_{15}H_{20}N_2S$: C, H, N. MS: 260 (7, M), 172 (100), 157 (17), 144 (5). ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ 1.45 (3H, d, J 7.0 Hz, CH_3CH), 2.38 (3H, s, 2-CH_3), 2.77 (3H, s, E–N–CH_3), 2.93 (3H, Z–N–CH_3), 3.64 (3H, s, N(1)-CH_3), 4.03 (1H, q, J 7.0 Hz, CH_3CH), 7.04–7.17 (2H, m, 5-*H*, 6-*H*), 7.24 (1H, m, 7-*H*), 7.64 (1H, m, 4-*H*). $[a]_D^{23}=+598°$, $[a]_{405}^{23}=+2532°$, (C 0.13).

1-(N'-Methylpiperidine-2'-thion-3'-yl)indole (3c) was prepared as described for *1e*, starting from *3a*, with the exception that the temperature was kept at +75 °C. Flash chromatography with dichloromethane/toluene (60:40) afforded an almost pure amorphous product (^{1}H NMR, yield 60 %). Anal. Found: C 66.7, H 6.6, N 11.0. Calc. for $C_{14}H_{16}N_2S$: C 68.81, H, 6.60, N 11.47. MS: 244 (70, M), 211 (5), 168 (54), 156 (28), 143 (32) 122 (37), 55 (100). ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ 1.96–2.35 (4H, m, 4'-CH_2, 5'-CH_2), 3.54 (3H, s, N'-CH_3), 3.56–3.70 (2H, m, 6'-CH_2), 5.36 (1H, doublet of doublets, J 7.4 Hz. 5.5 Hz, 3'-C*H*), 6.52 (1H, d, J ~2.4 Hz, 3-H), 7.02 (1H, d, J ~2.4 Hz, 2-*H*), 7.07–7.20 (2H, m, 5-*H*, 6-*H*), 7.30 (1H, m, 2-*H*), 7.61 (1H, m, 4-*H*). $[a]_D=+20°$, $[a]_{405}^{23}=+416°$, (C 0.15), ee > 99 %. ^{1}H NMR: δ 3.44, 3.46 (3H, 2s, N'-C*H*$_3$).

1-(N'-Methylpiperidine-2'-thion-3'-yl)-2-methylindole (3d) was prepared as described for *3c* starting from *3b*, but the reaction time had to be extended to 6 h at +75 °C and 1 h at +100 °C before all starting material had been consumed. The pure product (yield 67 %) was obtained after flash chromatography with dichloromethane/toluene (85:15), followed by recrystallization from 95 % aqueous ethanol, m.p. 161.5–163.5 °C. Anal. $C_{15}H_{18}N_2S$: C, H, N. MS: 258 (43, M), 225 (16), 182 (16), 168 (13), 130 (47), 55 (100). ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ 2.05–2.50 (4H, m, 4'-CH_2, 5'-CH^2), 2.45 (3H, s, 2-CH_3), 3.55 (3H, s, N'-CH_3), 3.62–3.82 (2H, m, 6'-CH_2), 5.13 (1H, doublet of doublets, J 10.8 Hz, 6.2 Hz, 3'-C*H*), 6.27 (1H, s, 3-H), 6.92 (1H, m, 7-*H*), 6.97–7.07 (2H, m, 5-*H*, 6-*H*), 7.50 (1H, m, 4-*H*). $[a]_{405}^{23}=-347°$, (C 0.076), ee > 99 %. ^{1}H NMR: δ 3.49, 3.51 (3H, 2s, N'-C*H*$_3$).

3-(N'-Methylpiperidine-2'-thion-3'-yl)-1-methylindole (4c) was obtained in quantitative yield within 35 min by converting *4a* by the same procedure as for *3c*. Flash chromatography with chloroform/toluene (92:8) followed by recrystallization from 95 % aqueous ethanol afforded the pure compound, m.p. 140.5–141.5 °C. Anal. $C_{15}H_{18}N_2S$: C, H, N. MS: 258 (100, M), 243 (3), 225 (20), 201 (18), 183 (62), 170 (56), 157 (96). ^1H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.74–2.19 (4H, m, 4'-CH_2, 5'-CH_2), 3.47–3.66 (2H, m, 6'-CH_2), 3.59 (3H, s, N'-CH_3), 3.73 (3H, s, N–CH_3), 4.72 (1H, t, J 4.2 Hz, 3'-CH), 6.80 (1H, s, 2-H), 7.07–7.22 (2H, m, 5-H, 6-H), 7.28 (1H, m, 7-H), 7.51 (1H, m, 4-H). $[\alpha]_D^{23}=-73°$, $[\alpha]_{405}^{23}=-213°$, (C 0.12).

3-(N'-Methylpiperidine-2'-thion-3'-yl)-1,2-dimethylindole (4d) was prepared as described for *4c*, in 86 % yield, starting from *4b*. Flash chromatography with dichloromethane/toluene (80:20) followed by two recrystallizations from 95 % aqueous ethanol and one from ligroin/toluene (70:30) afforded the pure compound, m.p. 177–179 °C. Anal. $C_{16}H_{20}N_2S$: C, H, N. MS: 272 (26, M), 239 (4), 197 (15), 184 (22), 182 (28), 171 (29), 144 (100). ^1H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.84–2.12 (4H, m, 4'-CH_2, 5'-CH_2), 2.36 (3H, s, 2-CH_3), 3.61 (3H, s, N'-CH_3), 3.59–3.77 (2H, m, 6'-CH_2), 3.65 (3H, s, N–CH_3), 4.44 (1H, t, J 6.0 Hz, 3'-CH), 6.97–7.12 (2H, m, 5-H, 6-H), 7.17–7.23 (2H, m, 4-H, 7-H). $[\alpha]_D^{23}=+48°$, $[\alpha]_{365}^{23}=+732°$, (C 0.13).

1-and 3-(1-Phenylethyl)indoles. The racemic 1- and 3-(1-phenylethyl)indoles were obtained as mixtures, when prepared as described for 1-isopropyl-2,3-dimethylindole,[3] from the sodium salts of the corresponding 2-substituted indoles and 1-phenyl-1-bromoethane in DMF. Separation of the 1- and 3-analogues was easily achieved by flash chromatography. In some cases additional chromatographic purification was necessary to remove other impurities, mainly the corresponding 1,3-di-(1-phenylethyl)indoles. Only deviations from the original procedure and purification methods will be mentioned.

1-(1-Phenylethyl)indole (5a). Flash chromatography with toluene–light petroleum (80:20) gave *5a* in 54 % yield. Final purification was achieved by preparative GLC (OV 101, 220 °C), m.p. 50–51 °C. Anal. $C_{16}H_{15}N$: C, H, N. MS: 221 (14, M), 117 (86), 105 (100). ^1H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.91 (3H, d, J 7.2 Hz, CH_3CH), 5.67 (1H, q, J 7.2 Hz, CHCH$_3$), 6.56 (1H, d, 3-H), 7.05–7.30 (9H, m), 7.62 (1H, m, 4-H). $[\alpha]_D^{23}=+110°$, $[\alpha]_{365}^{23}=+549°$, (C 0.13), ee>99 %. ^1H NMR: δ 2.23, 2.38 (3H, 2d, CH_3CH).

1-Methyl-3-(1-phenylethyl)indole (6a). 3-(1-Phenylethyl)indole (yield *ca.* 18 %), was methylated as described for *2a* (yield 95 %). Repeated flash chromatography with light petroleum/toluene (80:20), followed by recrystallization from methanol gave the pure compound, m.p. 70–72 °C. Anal. $C_{17}H_{17}N$: C, H, N. MS: 235 (43, M), 220 (100), 204 (8), 178 (9), 158 (22). ^1H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.69 (3H, d, J 7.2 Hz, CH_3CH), 3.74 (3H, s, N–CH_3), 4.36 (1H, q, J 7.2 Hz, CHCH$_3$), 6.82 (1H, s, 2-H), 6.96–7.31 (8H, m), 7.36 (1H, m, 4-H). $[\alpha]_D^{23}=+111°$, $[\alpha]_{365}^{23}=+463°$, (C 0.14).

2-Methyl-1-(1-phenylethyl)indole (5b). Two consecutive purifications by flash chromatography with toluene/light petroleum (80:20) and toluene/light petroleum (90:10) gave *5b* (yield 15 %). Recrystallization from methanol gave colourless crystals, m.p. 89.5–92 °C. Anal. $C_{17}H_{17}N$: C, H, N. MS: (18, M), 131 (72), 105 (100). ^1H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.94 (3H, d, J 7.2 Hz, CH_3CH), 2.36 (3H, s, 2-CH_3), 5.75 (1H, q, J 7.2 Hz, CHCH$_3$), 6.28 (1H, s, 3-H), 6.94–7.32 (8H, m), 7.51 (1H, m, 4-H). $[\alpha]_D^{23}=-44°$,
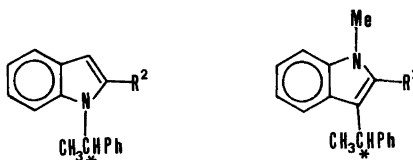
5a.	R^2=H		*6a.*	R^2=H
b.	R^2=Me		*b.*	R^2=Me
c.	R^2=CO$_2$Me		*c.*	R^2=CO$_2$Me
d.	R^2=Me$_2$COH		*d.*	R^2=Me$_2$COH
e.	R^2=MeC=CH$_2$		*e.*	R^2=MeC=CH$_2$

$[\alpha]_{365}^{23} = -122°$, (C 0.13), ee > 99 %. ^{1}H NMR: δ 2.61, 2.68 (3H, 2s, 2-CH_3).

1,2-Dimethyl-3-(1-phenylethyl)indole (6b). 2-Methyl-3-(1-phenylethyl)indole (yield 50 %), was methylated as described for *2a* in quantitative yield. Recrystallization from methanol gave slightly yellow crystals, m.p. 95–97 °C. Anal. $C_{18}H_{19}N$: C, H, N. MS: 249 (42, M), 234 (100), 218 (9), 172 (28), 157 (12). ^{1}H NMR (100 MHz, CDCl$_3$, 30 °C): δ 1.76 (3H, d, *J* 7.2 Hz, CH_3CH), 2.28 (3H, s, 2-CH_3), 3.56 (3H, s, N–CH_3), 4.43 (1H, q, *J* 7.2 Hz, CHCH$_3$), 6.85–7.44 (9H, m). $[\alpha]_D^{23} = -14°$, $[\alpha]_{365}^{23} = -109°$, (C 0.17).

2-Methoxycarbonyl-1-(1-phenylethyl)indole (5c). The reaction time was extended to 66 h. Dichloromethane/toluene (80:20) as eluent in the chromatography afforded *5c* (yield 50 %). Recrystallization from ligroin/toluene (90:10) gave colourless crystals, m.p. 61–63.5 °C. Anal. $C_{18}H_{17}NO_2$: C, H, N. MS: 279 (9, M), 175 (49), 143 (46), 105 (100). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.95 (3H, d, *J* 7.2 Hz, CH_3CH), 3.90 (3H, s, COOCH_3), 6.95–7.30 (8H, m), 7.37 (1H, m, 3-H), 7.62–7.67 (2H, m, 4-H, 7-H). $[\alpha]_D^{23} = +75°$, $[\alpha]_{365}^{23} = +421°$, (C 0.18), ee > 99 %. ^{1}H NMR: δ 2.03, 2.04 (3H, 2d, CH_3CH).

1-Methyl-2-methoxycarbonyl-3-(1-phenylethyl)indole (6c). 2-Methoxycarbonyl-3-(1-phenylethyl)indole (yield 10 %) was methylated in quantitative yield as described for *2a* and purified as *5c*, m.p. 129–131 °C. 2-Methoxycarbonyl-3-(1-phenylethyl)indole was also obtained by reacting either the sodium salt of 2-methoxycarbonylindole at 20 °C for 48 h, or the lithium salt at +45 °C for 6 h with 1-phenylbromoethane both in THF. In the latter case only the 3-substituted analogue was formed (yield *ca.* 25 %) but in the former case the C(3)/N(1) ratio was 2.4 (total yield *ca.* 30 %). Anal. $C_{19}H_{19}NO_2$: C, H, N. MS: 293 (48, M), 278 (100), 261 (24), 246 (21). ^{1}H NMR (100 MHz, CDCl$_3$, 30 °C): δ 1.80 (3H, d, *J* 7.4 Hz, CH_3CH), 3.87 (3H, s, COOCH_3), 3.93 (3H, s, N–CH_3), 5.23 (1H, q, *J* 7.4 Hz, CHCH$_3$), 6.83–7.42 (9H, m). $[\alpha]_D^{23} = +178°$, $[\alpha]_{365}^{23} = +823°$, (C 0.11), ee > 99 %. ^{1}H NMR, 2 eq. Pirkle's alcohol: 3.897, 3.904 (3H, 2s, COOCH_3).

2-(1-Methyl-1-hydroxyethyl)-1-(1-phenylethyl)indole (5d) was prepared by addition of *5c* (5.0 g, 18 mmol) in dry ether (30 ml) to a solution of methylmagnesium iodide (50 mmol) in dry ether (50 ml) at 0 °C. 1 h at 0 °C and 14 h at +10 °C completed the reaction. Work-up gave a yellow oil, which was subjected to flash chromatography with dichloromethane–toluene (90:10) to remove minor amounts of 2-(1-methylethenyl)-1-(1-phenylethyl)indole (*5e*). Recrystallization first from methanol and then from light petroleum gave colourless crystals (yield 4.0 g, 80 %), m.p. 103–104 °C. Anal. Found: C 81.0, H 7.71, N 4.77. Calc. for $C_{19}H_{21}NO$: C 81.6, H 7.58, N 5.01. MS: 279 (3, M), 261 (20), 246 (5), 157 (65), 105 (100). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.76, 1.82 (6H, 2s, (CH_3)$_2$COH), 1.85 (1H, s, (CH$_3$)$_2$COH), 1.97 (3H, d, *J* 7.1 Hz, CH_3CH), 6.43 (1H, s, 3-H), 6.63 (1H, q, *J* 7.1 Hz, CH$_3$CH), 6.79 (1H, m, 7-H), 6.87–7.10 (2H, m, 5-H, 6-H), 7.15–7.30 (5H, m), 7.54 (1H, m, 4-H). $[\alpha]_D^{23} = -32°$, $[\alpha]_{405}^{23} = -58°$, (C 0.17), ee = 86 %. ^{1}H NMR, 2 eq. Pirkle's alcohol: δ 1.76, 1.72 (3H, 2s, COHCH_3).

1-Methyl-2-(1-methyl-1-hydroxyethyl)-3-(1-phenylethyl)indole (6d) was prepared essentially as described for *5d*, starting from *6c*. The temperature was, however, raised to +20 °C and the reaction time extended to 150 h, after which time all starting material had been consumed. Flash chromatography with dichloromethane–toluene (40:60) gave an orange-coloured oil, almost pure according to ^{1}H NMR, which crystallized on standing (yield 42 %). Recrystallization from light petroleum gave slightly yellow crystals, m.p. 94.5–96 °C. Compound *6d* decomposes easily (turns yellow) when exposed to light, and it also eliminates water when heated although not as readily as *5d*. Anal. $C_{20}H_{23}NO$: C, H, N. MS: 293 (33, M), 278 (9), 275 (14), 260 (80), 245 (14), 200 (35), 105 (100). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.79, 1.82 (6H, 2s, (CH_3)$_2$COH), 1.80 (3H, d, *J* 7.1 Hz, CH_3CH), 1.87 (1H, s, OH), 3.96 (3H, s, N–CH_3), 4.97 (1H, q, *J*7.1 Hz, CHCH$_3$), 6.87 (1H, m, 5-H), 7.10–7.34 (8H, m). $[\alpha]_D^{23} = -116°$, $[\alpha]_{365}^{23} = -616°$, (C 0.11), ee > 99 %. ^{1}H NMR, 2 eq. Pirkle's alcohol: δ 3.86, 3.88 (3H, 2s, N–CH_3).

2-(1-Methylethenyl)-1-(1-phenylethyl)indole (5e). Enantiomeric separation of *5d* on TAC and subsequent evaporation of the eluent (aqueous ethanol (96:4)) with warming (*ca.* 40 °C) afforded *5e*. Preparative TLC on silica (Merck 60, F254, with dichloromethane/toluene (90–10)) afforded the pure compound as a slightly yellow oil. MS: 261 (14, M), 157 (59), 142 (6), 105 (100). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.90 (3H, d, *J* 7.1 Hz, CH_3CH), 2.17 (3H, m, CH_3C=C), 5.14 (1H, m, *Z*–CH$_3$C=CH), 5.34 (1H, quint, *J* 1.6 Hz, *E*–CH$_3$C=CH), 5.89 (1H, q, *J* 7.1 Hz, CHCH$_3$), 6.46 (1H, s, 3-H), 6.87 (1H, m, 4-H),
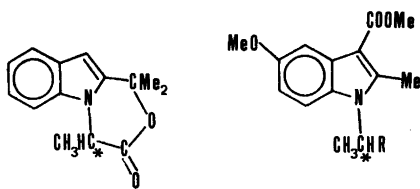
7.

8.   X=Ph
9.   X=CON(CH$_3$)$_2$

6.90−7.03 (2H, m, 5-H, 6-H), 7.20−7.33 (5H, m), 7.55 (1H, m, 4-H). $[\alpha]_D^{23}=-26°$, $[\alpha]_{365}^{23}=-31°$, (C 0.14), ee=94 %. ^{1}H NMR: δ 2.26, 2.30 (3H, 2s, C=C−CH_3).

1-Methyl-2-(1-methylethenyl)-3-(1-phenylethyl)indole (6e) was prepared from *6d* essentially as described for *5e*. However, addition of a few drops of 1M HCl was necessary to complete the dehydration in reasonable time (*ca.* 2 h), in preference to decomposition. Preparative TLC as for *5e* gave the pure compound as slightly yellow amorphous material. MS: 275 (49, M), 260 (100), 245 (28), 230 (8), 198 (20), 185 (25). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.77 (3H, d, J 7.3 Hz, CH_3CH), 2.04 (3H, doublet of doublets, J 1.4 Hz, 1.0 Hz, CH_3=CH), 3.64 (3H, s, N−CH_3), 4.41 (1H, q, J 7.3 Hz, CHCH), 5.11 (1H, m, Z−CH$_3$C=CH), 5.52 (1H, m, E−CH$_3$C=CH), 6.92−7.14 (2H, m, 5-H, 6-H), 7.21−7.38 (7H, m). $[\alpha]_D^{23}=-53°$, $[\alpha]_{365}^{23}=-408°$, (C 0.037), ee>99 %. ^{1}H NMR: δ 3.76, 3.81 (3H, 2s, N−CH_3). The racemic forms of *5e* and *6e* were also prepared from racemic *5d* and *6d* in order to determine the enantiomeric purity.

The Nenitzescu reaction[23] is a potential way to obtain optically active N-substituted indole derivatives from optically active aminocrotonates and *p*-benzoquinone. This reaction was successful with 3-aminocrotonates to give *8* and *9*, whereas attempts to prepare the 2-H analogues of *8* and *9* failed, because no suitable enaminocarboxylate could be obtained.

(R,S)-and (S)-Methyl-3-(1-phenylethyl)aminocrotonate were prepared by dissolving (*R,S*)- or (*S*)-1-phenylethylamine (6.05 g, 50 mmol), and methyl acetoacetate (6.38 g, 50 mmol) in dry ether. A few mg of *p*-toluenesulfonic acid and molecular sieve (3 Å, 10 g) were added. After 24 h at room temperature the solution was rapidly extracted with small portions of aqueous saturated NaHCO$_3$ solution, dried, filtered, and evaporated. The enamine (yield 93 %, almost pure according to ^{1}H NMR) was used without further purification. ^{1}H NMR (60 MHz, CDCl$_3$, 30 °C): δ 1.40 (3H, J 6.8 Hz, CH_3CH−N), 1.65 (3H, s, CH_3C=C), 3.56 (3H, s, COOCH_3), 4.43 (1H, s, H−C=C), 4.54 (1H, quint, J 6.8 Hz, CH$_3$CHN), 7.10−7.40 (5H, m), 8.94 (1H, d, J 6.8 Hz, N−H).

(R,S)-and (S)-Methyl-3-(1-N,N-dimethylcarbamoylethyl)aminocrotonate were prepared from (*R,S*)- or (*S*)-alanine N,N-dimethylamide and methyl acetoacetate in toluene with azetropic distillation and a few mg of *p*-toluene sulfonic acid as catalyst. The reaction was complete in 2.5 h. After work-up as described above, the crude oil was used directly in the next synthetic step (yield *ca.* 70 %). ^{1}H NMR (60 MHz, CDCl$_3$, 30 °C): δ 1.37 (3H, J 6.8 Hz, CH_3CHN), 1.88 (3H, s, CH_3C=C), 2.98, 3.05 (6H, 2s, E,Z-N−CH_3), 3.61 (3H, s, COOCH_3), 4.49 (1H, s, H−C=C), 4.50 (1H, m, CH$_3$CHN), 8.99 (1H, d, J *ca.* 7.6 Hz, N−H).

(R,S)-and (S)-2-Methyl-5-methoxy-3-methoxycarbonyl-1-(1-phenylethyl)indole (8). The 5-hydroxy precursor was prepared essentially according to Poletto and Weiss,[24] starting from 1,4-benzoquinone and methyl-3-(1-phenylethyl)aminocrotonate. The best result was obtained when the initial temperature was 60 °C, and the enamine was added with agitation at such a rate that the heat of reaction maintained the temperature at approximately 60 °C. Increased amounts of tarry products were obtained if the reaction was carried out at elevated temperature. After an additional 0.5 h at 60 °C, the mixture was evaporated, neutralized with aqueous saturated NaHCO$_3$ solution, and extracted with several portions of ether. The ether solution was dried, filtered and evaporated, and the resulting precipitate was recrystallized from toluene, affording a colourless powder (yield 50 %), m.p. 198.5−200 °C (rac.). MS: 309 (12, M), 205 (21), 105 (100). ^{1}H NMR (100 MHz, CDCl$_3$, CD$_3$OD (70:30), 30 °C): δ 1.91 (3H, d, J 7.0 Hz, CH_3CH), 2.70 (3H, s, 2-CH_3), 3.89 (3H, s, COOCH_3), 5.81 (1H, q, J 7.0 Hz, CHCH$_3$), 6.49−7.75 (8H, m). The methylation was

carried out with dimethyl sulfate in DMSO-NaOH at 70 °C. After work-up followed by repeated flash chromatography (dichloromethane) a pure liquid product was obtained in 80 % yield. Anal. Found: C 73.4, H 6.57, N 4.35, O 14.6. Calc. for $C_{20}H_{21}NO_3$: C 74.3, H 6.55, N 4.33, O 14.8. MS: 323 (10, M), 292 (2), 219 (21), 204 (6), 105 (100). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.94 (3H, d, J 7.2 Hz, CH_3CH), 2.76 (3H, s, 2-CH_3), 3.84, 3.94 (6H, 2s, 5-OCH_3, 3-COOCH_3), 5.83 (1H, q, J 7.2 Hz, CH$_3$CH), 6.67 (1H, doublet of doublets, J 8.9, 2.6 Hz, 6-H), 6.87 (1H, d, J 8.9 Hz, 7-H), 7.13−7.32 (5H, m, Ph−H), 7.65 (1H, d, J 2.6 Hz, 4-H). $[\alpha]_D^{23}=+83°$, $[\alpha]_{405}^{23}=+204°$, (C 0.29), ee > 99 %. ^{1}H NMR: δ 2.12, 2.14 (3H, d, CH_3CH).

(R,S)-and   (S)-1-(1-N,N-*Dimethylcarbamoylethyl)-2-methyl-5-methoxy-3-methoxycarbonylindole (9)* were prepared mainly as described for *8*, starting from methyl-3-(1-*N,N*-dimethylcarbamoylethylaminocrotonate and 1,4-benzoquinone. The reaction was, however, not as exothermic as for *8*, and external heating was necessary to maintain the temperature at 60 °C during the reaction. After 45 min the solution was cooled and worked up by extraction with chloroform. Gradient column chromatography, starting with dichloromethane and gradually mixing with up to 20 % ether, gave an oil, which was used directly in the methylation step. After work-up of the reaction mixture from methylation, flash chromatography with dichloromethane/ethyl acetate (70:30) followed by preparative TLC on silica (Merck 60 F254, dichloromethane/ethyl acetate (90:10) gave an oil, which crystallized when diluted in cold ether. Recrystallization from ligroin/toluene (80:20) afforded colourless crystals, m.p. 103.5−105.5 °C (rac.), 128−131 °C (*S*). Anal. $C_{17}H_{22}N_2O_4$: C, H, N. MS: 318 (21, M), 246 (100), 214 (23). ^{1}H NMR (360 MHz, CDCl$_3$, 25 °C): δ 1.63 (3H, d, J 6.9 Hz, CH_3CH), 2.46 (3H, s, 2-CH_3), 2.77, 2.95 (6H, 2s, *E,Z*-N−CH_3), 3.87, 3.93 (6H, 2s, 3-COOCH_3, 5-O−CH_3), 5.15 (1H, q, J 6.9 Hz, CHCH$_3$), 6.83 (1H, doublet of doublets, J 9.2, 2.6 Hz, 6-H), 7.28 (1H, d, J 9.2 Hz, 7-H), 7.63 (1H, d, J 2.6 Hz, 4-H). $[\alpha]_D^{23}=+201°$, $[\alpha]_D^{365}=+857°$, (C 0.23).

General procedure for the transformation of a thioamide to an amide. The thioamide (0.1 mmol) and methyl iodide (*ca.* 0.3 mmol) were dissolved in acetone (analytical grade, 5 ml) and allowed to stand at room temperature for 3 h. The excess of methyl iodide and solvent were evaporated, and the methylthioimmonium salt was again dissolved in acetone (5 ml) and water (5 ml). Saturated aqueous NaHCO$_3$ solution (0.5 ml) was added, and the temperature was raised to 60 °C. The reaction was interrupted when the methylthioimmonium salt was consumed (30 min − 3 h), as checked by TLC. After evaporation the amide was dissolved in ether and the ethereal solution dried, filtered and evaporated. Purification by preparative TLC (silica 60, F254) with appropriate eluents gave the pure amide. The optical purity for *4a* and *4b* was 90 % and 25 %, respectively, whereas *3a* and *3b* were completely racemized.

Chromatographic resolution of enantiomers. The analytical and preparative resolutions were performed by liquid chromatography on swollen microcrystalline triacetylcellulose. This method seems to be one of the most general ones for preparative resolution and has been successfully applied to many different classes of organic compounds.[25−28]

A glass column (30×2.5 cm) was packed with approximately 90 g of triacetylcellulose (particle size 20−30 μm) according to the procedure described by Hesse and Hagel.[2] The eluent was in all cases 96 % aqueous ethanol. The pump equipment was a FMI Model PPSY working in the range of 0−900 ml/h and connected to a pulse dampener. The non-retained volume was determined by the use of 1,3,5-tri-*t*-butylbenzene[29] to 101±1.5 ml/h independent of the flow rate in the range of 150−300 ml/h. The eluate was monitored by an LKB UV detector Model 4700 working at 254 nm, and a Perkin Elmer Model 241 MC polarimeter working at 365 nm with a flow cell, working in series. The output from the detectors was fed to a 2-channel recorder.

To obtain comparable separation factors, single runs with analytical samples were performed with a flow rate of approximately 270 ml/h (pressure 2.3 kg cm^{-2}) and at room temperature. The results from the analytical runs are shown in Table 1. The separation factors for *4a, 5b, 5d,* and *5e* were estimated by visual fitting of the experimental chromatograms to skewed overlapping Gaussian curves.[30] The separation factors for *1d, 3a, 3d,* and *4b* were roughly estimated by reinjection of the enriched enantiomers in series. The observed retention volumes were assumed to be linearly related to those of the individual enantiomers [eqns. (2) and (3)].

$$n_{11}V_1 + n_{12}V_2 = V_{11} \tag{2}$$

$$n_{21}V_1 + n_{22}V_2 = V_{22} \tag{3}$$

V_1 and V_2=Real retention volumes
n=Molar fractions
V_{11} and V_{22}=Observed retention volumes, when the first, respectively, the last enantiomer is enriched

The validity of this assumption for small separations was readily demonstrated by computer simulation, using Gaussian curves.

The samples in the preparative separations in each run varied between 10 and 200 mg in 1 to 4 ml eluent, depending on the separation and solubility. In cases where the separation was good, absolute ethanol was used, and sometimes a small amount of THF was added to increase the solubility of the sample before injection. As has been often observed,[31] this always resulted in distorted peaks and diminished separations. The compounds *1c, 3a, 3d,* and *4b* were preparatively enriched by using recycling technique on TAC. The enantiomers were further purified by recrystallization when appropriate. To avoid dehydration, the solutions of *5d* and *6d* were, after enantiomeric separation, collected in a vessel chilled with dry ice/ethanol, diluted with ice-water and aqueous NaCl solution, and extracted with cold ether (0 °C). After drying, filtration and evaporation of the cold (0 °C) ethereal solution, the compounds were finally purified by preparative TLC (silica plates Merck 60 F254, dichloromethane/toluene (90:10)). Compound *1d* was finally purified by semipreparative HPLC (silica 60–10, Polygocil 10 μ, dichloromethane, ethyl acetate (80:20)) after enantiomeric separation. The purity was generally checked by GLC (Dexil 300, OV 101), TLC (silica Merkc 60 F254) or ^{1}H NMR (360 MHz) before the CD measurements.

RESULTS AND DISCUSSION

Syntheses. The ambient nucleophilic character of the indolyl anion, and the rules and reaction conditions which govern its selectivity, have been extensively studied.[32,33]

The reaction between (R)-2-bromopropionate and indolylsodium in DMF resulted in the expected *N*-alkylation.[15] The anion exists as a free ion in this solvent and reacts preferentially with its hard *N*-center, the substrate being a fairly hard electrophile.

The reaction proceeds by a stereospecific pathway when R^2=H and R^2=Me, while when R^2=CO$_2$Me, a completely racemic product was obtained. The only difference except the R^2 substituent was the reaction time. The yield decreased drastically, to <10 %, if the reaction with 2-methoxycarbonylindole was performed at elevated temperature (*ca.* 50 °C).

When 1-phenyl-1-bromoethane was the substrate, both *N*- and *C*(3)-alkylation occurred under conditions that otherwise were similar to those used in the reaction with (R)-2-bromopropionate, and which then strongly favour *N*-alkylation. The *N/C*(3) ratio is 3:1 for indole, 1:3.3 for 3-methylindole and 5:1 for 2-methoxycarbonylindole. The *C*(3)-alkylation has been interpreted in terms of varying degree of S$_N$1-character[15,34–36] of the reaction. As the ionizing tendency of the alkyl halide increases, the proportion of *C*(3)-alkylation is increased. Alternatively, the result may be discussed in terms of hard-soft interactions.[37] The soft electrophile will react with the soft *C*(3)-nucleophile even if the hard *N*-nucleophile is a free ion, and *C*(3)-alkylation requires loss of conjugation in the transition state.

The change from R^2=H to R^2=Me gives reversed *N/C*(3) ratios in this reaction. This tendency was also observed when *N,N*-dimethyl-2-bromopropanamide was reacted with the indolylsodium salt in THF. When R^2=H the reaction gave no *C*(3)-substitution but when

R^2=Me a small amount (*ca.* 4 %, GLC) of 3-(1-*N,N*-dimethylcarbamoylethyl)-2-methylin-dole was obtained. This is probably due to increased electron density at $C(3)$ when R^2=Me.

R^2=COOMe favours *N*-alkylation more strongly than R^2=H. In the former indolylso-dium salt, we have π-electron delocalization into the methoxycarbonyl group, which will affect $C(3)$ more than N, since the attacking electron pair on the nitrogen does not participate in the conjugated system, whereas that at $C(3)$ does. The preponderance for *N*-alkylation for R^2=COOMe in DMF with 1-phenyl-1-bromoethane was easily reversed by changing the solvent to THF ($C(3)/N$=2.4). Lithium as the counter ion in THF gave a further increase in the amount of $C(3)$-alkylation (>99 % of $C(3)$). Both changes are ascribed to the effect of more tightly bound ion pairs.[15,38]

The stereospecific reaction between (S)-2-bromopropionate and indolylsodium (R^2=H and R^2=Me) may occur with inversion or retention of configuration. Cowdrey *et al.*[39] showed that, depending on the concentration, 2-bromopropionate gave on reaction with methoxide ion in methanol either inversion or retention of configuration. Because the reaction conditions used here were quite different, no prediction about the stereochemistry could be made.

To solve this problem *1a was prepared from (S)*−*N,N*-dimethyl-2-bromopropanamide and indolylsodium in THF. This reaction, which is likely to proceed with inversion, gave *1a* with the same configuration as when prepared from (S)-2-bromopropionate, and implies that (S)-2-bromopropionate reacts with an ordinary S_N2-substitution.

3-(1-Carboxyethyl)indole has been synthesized and resolved previously.[40,41] Surprising-ly, however, no other derivative of this acid is to our knowledge reported, despite the considerable interest in 3-indoleacetic acids, its higher homologues, and derivatives because of their plant growth regulation properties.

The convenient method to prepare 3-alkylindoles from indolylmagnesium halides and alkyl halides in anisole,[3,19,42] was successfully applied to the synthesis of 3-(1-*N,N*-dimethylcarbamoylethyl)-indoles and the 3-(3'-piperidin-2'-onyl)indoles. The superiority of anisole as the solvent[42] over *e.g.* ether and THF was well established. It has been suggested that this is due to an effect on the solubility of the reagent,[42] and was presumably the reason why previous workers,[43,44] when reacting 5-benzyloxy-2-(R)-indolylmagnesium reagent and *N,N*-dialkylchloroacetamides, performed it in the absence of solvent. Although the yields reported were somewhat higher than ours, the conditions are much more severe and the molar amount of the indolylmagnesium halide was much higher.

$C(3)$-Alkylation is exclusively observed, and is either due to the formation of an intimate ion pair as in THF,[45,56] or perhaps even covalent character of the N−Mg bond as in ether,[47] which effectively prevents *N*-alkylation.

The reaction gives different stereochemistry for the indolylmagnesium halide compared to indolylsodium in THF, when reacted with *N,N*-dimethyl-2-bromopropanoic amide. The first reaction gives a completely racemic product, while the second proceeds stereospecifical-ly. A possible explanation is a difference in the nucleophilicity *versus* basicity of the reagent. The completing acid-base reaction is faster than product formation when M=MgBr, while product formation is faster when M=Na as shown in eqn. 4. Racemization may also occur in the product.

The transformation of a thioamide to an amide connected to an indole ring is an intricate problem. The reagents used to transform a thioamide to an amide are often oxidizers.[48] However, indole is autoxidized by air and light, and readily oxidized by a variety of reagents.[49] As an example, the use of NO^+[48] gave a number of yellow and red products, but

$$(4)$$

M = Na or MgBr
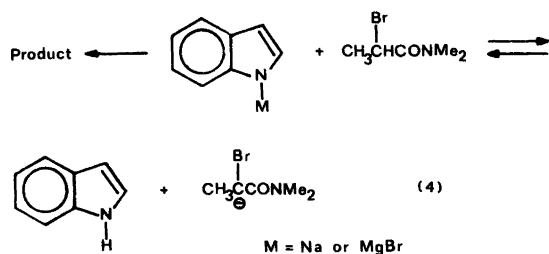
not the desired one. Dibenzylselenoxide[50] and trimethyl phosphite,[51] which are weak oxidants, neither oxidized the indole ring, nor transformed the thioamide. Silver nitrate[52] gave the product in small quantities but the reaction proceeded slowly. The transformation *via* the methylthioimmonium[5] salt (eqn. 5) is, in our opinion, a very smooth general way, although it caused different degrees of racemization for these compounds. The difference in stereoselectivity between the 1- and 3-(piperidine-2'-thion-3'-yl)indoles is probably due to the difference in electronegativity between N and $C(3)$. The contribution to the acidity of the methine hydrogen of the more electronegative nitrogen is sufficient to favour elimination, a possibility also suggested by Mukherjee,[5] as shown in eqn. 5 and results in a completely racemic product.

$$(5)$$
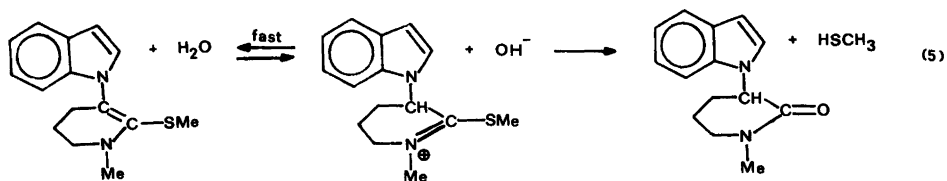
Chromatographic separations. The most striking observation is perhaps the difference in enantiomer separation between the carbonyl analogues of 1- ad 3-(1-carbamoylethyl)indoles *1* and *2* on one hand and 1- and 3-(3-piperidonyl)indoles *3* and *4* on the other (Table 1). While *1* and *2* give excellent separation, with *1b* as an extreme, *3* and *4* show very modest separations, and *3b* no separation at all. Although *1b* does not give the largest α-value (12.7), it is the compound with the largest absolute enantiomeric separation (ΔR_T ca. 11 h at a flow rate of 260 ml/h). It is amazing that *1b* and *3b*, which in solution have very similar *syn-anti* equilibria, give such remarkably different separations. This may indicate a difference in the orientation of the amide group, which could lead to different interaction with the chiral cavity for each enantiomer, which is of vital importance for the separation.

Other striking observations are the difference in separation between the compounds with R^2=H or Me and the consequence of changing the amide to a thioamide. These results can be generalized in the following way. Compounds *1* and *2* show better separation when R^2=Me, no matter whether it is an amide or a thioamide, and substitution of a carbonyl by a thiocarbonyl group results in diminished separation. Compounds *3* and *4* on the other hand exhibit increased separation when the carbonyl is substituted by a thiocarbonyl group, and separation for R^2=H is better than for R^2=Me. The piperidonyls also show regularity when comparing the carbonyl analogues among themselves and the thiocarbonyl analogues among themselves, the order of enantiomer separation being *4a>4b≥3a>3b*. This order is maintained for the thioanalogues, where *4c>4d>3c>3d*.

Table 1. Separation factors for compounds *1−7*.

Compound	$k_1'^a$	k_2'	α^b	R_s^c
1a	1.43	4.04	2.83	2.7
1b	2.51	31.84	12.7	6.4
1c	0.68	3.36	4.9	2.7
1d	0.22	0.24	<1.08	<0.1
1e	1.70	2.87	1.7	1.7
1f	1.97	6.64	3.4	3.7
2a	0.77	2.86	2.9	2.9
2b	0.79	7.36	9.3	5.2
2c	1.19	1.90	1.6	1.3
2d	2.04	7.76	3.8	3.3
3a	1.09	1.17	<1.08	<0.25
3b	0.72	0.72	1.0	0
3c	1.54	2.03	1.3	0.7
3d	1.25	1.34	1.07	0.2
4a	0.48	0.63	1.31	0.56
4b	0.56	0.61	<1.09	<0.25
4c	1.07	17.6	16.7	6.0
4d	1.13	4.48	3.9	2.9
5a	1.86	2.54	1.4	1.1
5b	2.26	2.75	1.22	0.48
5c	0.66	1.63	2.5	1.1
5d	0.17	0.30	1.71	0.51
5e	0.89	1.08	1.21	0.50
6a	1.43	2.68	1.9	1.8
6b	1.56	3.52	2.3	2.2
6c	0.81	1.15	1.4	0.8
6d	0.36	0.77	2.1	1.3
6e	0.64	2.66	4.2	3.7
7	1.59	2.05	1.3	0.8

$$^a\ k_1' = \frac{V(R_1) - V(R_o)}{V(R_o)} \quad ^b\ \alpha = \frac{k_2'}{k_1'} \quad ^cR_s = \frac{V(R_2) - V(R_1)}{\frac{1}{2}(W(b_1) + W(b_2))}$$

$V(R_1)$=Retention volume of the first eluted enantiomer.
$V(R_o)$=Non-retained volume.
$W(b_1)$=Volume at the basis of the triangulated peak of the first eluted enantiomer.

We have observed that the ease of thionation of the piperidonylindoles (*3,4*) with the Lawesson reagent parallels the separation factors. The reaction of *4a* and *4b* was completed within $\frac{1}{2}$ h at +70 °C and of *3a* within $1\frac{1}{2}$ h, while *3b* had to be warmed for 6 h at +70 °C and 1 h at 100 °C. This may reflect the accessibility of the carbonyl group both in the reaction with the Lawesson reagent and in the differentiating enantiomeric interactions with TAC.

Another peculiar fact is the drastically diminished separations for the N−H analogues of *2a*, *2b*, and *6c* (not shown in Table 1).

The 1- and 3-phenylethylindoles (*5, 6*) show less variation in separation factors, and no regularities have been observed.

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