Notes

2-(Alkylthio)-*N*-hydroxytryptophans from 3-(Alkylthio)indoles†

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Received June 15, 1983

In recent years tryptopan derivatives, having an α-functionality in addition to the amino and carboxy groups have been found as characteristic structural elements of several naturally occurring compounds. It has been suggested[2] that the biogenetic relationship between protein amino acids and α-substituted or dehydro amino acids might proceed via *N*-hydroxy amino acid derivatives, as indicated in Scheme I for tryptophan derivatives.[2] Furthermore, we demonstrated[1] that *N*-hydroxy amino acid derivatives (**2**) not only deserve attention as possible biosynthetic precursors but also as synthons in the preparation of natural products having **3** or **4** as structural elements. One of the approaches we explored successfully for the synthesis of the *N*-hydroxytryptophan derivative **2** starts with the cycloaddition[3] of a transient nitroso olefin **6** to the C(2)–C(3) double bond of indole **7** to yield **10** (X = H, Scheme II). Base-catalyzed ring opening (→**11**, X = H) followed by rearomatization afforded **12**.

As part of a further exploration of this reaction we report now a new rearrangement that was observed in the cycloaddition of **6** with indoles having a 3-alkylthio substituent (**8** and **9**). These reactions gave products **13** and **14**, in which the thioalkyl group had migrated from C(3) to C(2). This rearrangement is noteworthy for several reasons. It occurs in good yield (ca. 70%) under mild conditions (room temperature, CH_2Cl_2, Na_2CO_3), whereas the well-documented[4] rearrangement of alkyl- or aryl-substituted indoles requires a strong acid and elevated temperatures. Furthermore, this rearrangement prompts a reinvestigation of the mechanism proposed so far for the introduction of 2-alkylthio substituents into 3-alkylindoles (vide infra). Finally, this rearrangement opens a new approach to 2-(*S*-cysteinyl)tryptophan derivatives, which are characteristic structural elements of the toxic principles of members of the genus *Amanita*.[5]

The 3-(alkylthio)indoles **8** and **9** were prepared according to the method described by Tomita et al.[6,7] Reaction of **8** or **9** with the nitroso olefin **6**, prepared in situ[1] from **5**, gave adducts in about 70% yields. The UV spectra of the adducts showed a bathochromic shift in comparison with the spectra of **8** and **9**, which is a characteristic difference between 3-(alkylthio)- and 2-(alkylthio)indoles.[8] Further evidence for the substitution pattern of the products, i.e., **13** and **14**, was obtained by recording their ^1H NMR spectra in trifluoroacetic acid.[9] Protonation at the indole's C(3) position yielded an indolenine derivative whose spectrum exhibited a triplet for the C(3) proton (δ 5.0, J = 8 Hz) and a doublet for the adjacent methylene protons (δ 3.7).

Chemical proof of the adduct's structures was come by as indicated in Scheme III. Direct desulfurization of **14** failed; treatment with Raney nickel catalyst, zinc/acetic acid,[7] or nickel boride[10] caused complete decomposition. A similar decomposition was observed in desulfurization experiments with the *N*-hydroxytryptophan derivative **16**, obtained from **14** by selective reduction with $Me_3N{\cdot}BH_3$.[11] These failures can be attributed to free-radical reactions involving the *N*-hydroxy function.

Therefore, the oxime **14** was subjected to selective O-benzylation by reaction with benzyl bromide and potassium *tert*-butoxide. Treatment of the resulting product **17** with Raney nickel gave now a desulfurization product (**18**). NMR analysis clearly indicated the presence of a C(3) substituent; the indole's C(2) protons was at δ 6.9 ppm, a value that is characteristic for the C(2) proton in 3-alkylindoles (δ 6.6–6.9);[12] the signals of C(3) protons in 2-alkylindoles are invariably at higher field (δ 6.0–6.3).[12]

The ^1H NMR spectrum of **18** showed small differences with respect to that of the product **21**, obtained by reaction of indole-3-pyruvic acid **20** with *O*-benzylhydroxylamine hydrochloride and ethanol;[1] the benzylic methylene and ethyl protons of **18** were shifted downfield ($\Delta\delta$ 0.1 ppm) as compared with **21**. Reduction of **18** and **21** with $Me_3N{\cdot}BH_3$ gave, however, the same *N*-(benzyloxy)tryptophan ester **19**. The spectral differences between **18** and **21** point to Z/E isomers; in the synthesis of **21** from **20**, the thermodynamically more stable Z isomer will be formed, whereas the pathway to **18**, starting with the cycloaddition of **6** and **9**, will afford the E isomer.

† Dedicated to Professor Dr Th. Wieland on the occasion of his 70th birthday.

(1) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147 and references cited therein.

(2) So far *N*-hydroxytryptophan derivatives have not been found in natural products. However, the biosynthetic pathway for tryptophan glucosinolates is considered to proceed from *N*-hydroxytryptophan; see: Møller, B L. In "Cyanide in Biology"; Vennesland, B., Conn, E. E., Knowles, C. J., Westley, J., Eds.; Academic Press: London, 1981; p 197.

(3) This versatile cycloaddition has been described for the first time by Gilchrist, T. L.; Longham, D. A.; Roberts, T. G. *J. Chem. Soc., Chem. Commun.* **1979**, 1089.

(4) See, e.g.: "The Chemistry of Heterocyclic Compounds", Indoles Part 1; Houlihan, W. J., Ed.; Wiley Interscience: New York, 1972; p 91, 135.

(5) Wieland, Th. In "Progress in the Chemistry of Natural Products"; Zechmeister, L., Ed.; Springer Verlag: New York, 1967; Vol. 25, p 214.

(6) Tomita, K.; Terada, A.; Tachikura, R. *Heterocycles* **1976**, *4*, 729.

(7) (a) Compound **11** was also isolated as a side product (20%) in the synthesis of 2-(α,α-dimethylallyl)-3-(ethylthio)indole according to the method of: (b) Tomita, K.; Terada, A.; Tachikawa, R. *Heterocycles* **1976**, *4*, 733.

(8) Wieland, Th.; Weiberg, O.; Fischer, E.; Hoerlein, G. *Justus Liebigs Ann. Chem.* **1954**, *587*, 146. Wieland, Th.; Freter, K.; Gross, E. *Ibid.* **1959**, *626*, 154. Wieland, Th.; Grimm, D. *Chem. Ber.* **1965**, *98*, 1727.

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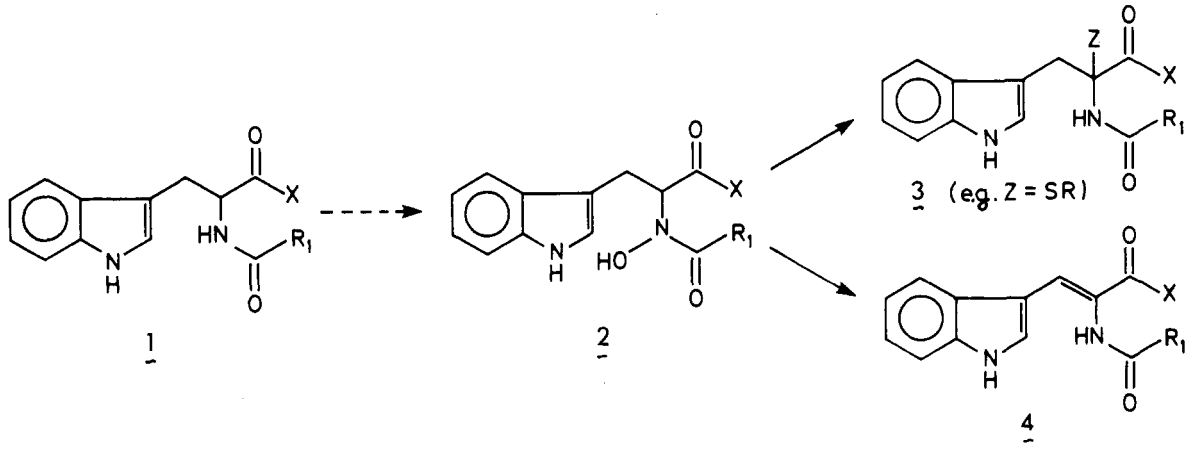
(10) Schut, J.; Engberts, J. B. F. N.; Wijnberg, H. *Synth. Commun.* **1972**, *2*, 415.

(11) Bonner, W. A.; Grimm, R. A. In "The Chemistry of Organic Sulfur Compounds"; Kharasch, N., Myers, C. Y., Eds.; Pergamon Press: New York, 1966; Vol. 2, pp 35–71 and 410–413.

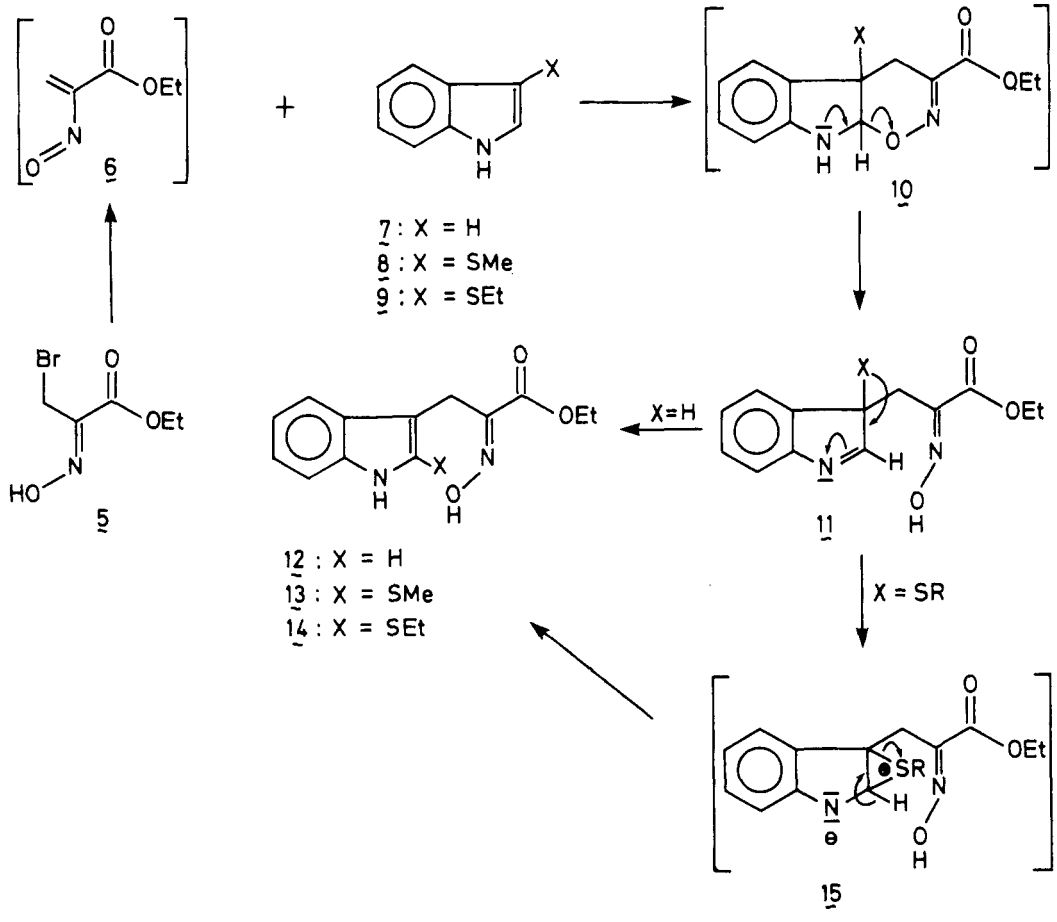
(12) See, e.g.: Cohen, L. A.; Daly, J. W.; Kny, H.; Witkop, B. *J. Am. Chem. Soc.* **1960**, *82*, 2184. Ganellin, C. R.; Ridley, H. F. *J. Chem. Soc. C* **1969**, 1837.

0022-3263/84/1949-0540$01.50/0

Scheme I



Scheme II



The rearrangement during the formation of **13** and **14** can be rationalized as represented in Scheme II. Cycloaddition of **6** and the 3-(alkylthio)indoles **8** or **9** yields **10**, from which the indolenine derivative **11** arises via base-catalyzed ring-opening. Subsequent formation of the episulfonium **15**, followed by rearomatization yields **13** and **14**.

For the application of the cycloaddition of **6** to indoles in the synthesis of sporidesmins,[1] the isolation of the primarily formed cycloadduct **10** is desirable. We anticipated that replacement of the sulfide by a sulfoxide function would render **10** more stable. The sulfoxides, obtained from **8** and **9** by treatment with sodium periodate in acetonitrile, did not react, however, with **6**. This failure may be due to a decrease of the electron density of the indole double bond as well as to increased steric hindrance.

The rearrangement **11** (X = SR) → **13**, **14** (Scheme II) may also occur in the most widely used method[8,13] for the formation of 2-(alkylthio)-3-alkylindoles, i.e., thioalkylation of 3-alkylindoles (**22** → **24**, Scheme IV). Surprisingly, all authors assume that this reaction takes place by nucleophilic attack at the C(2) position. Our results may suggest that the formation of **24** from **22** involves initial formation of a C(3)-disubstituted indolenine derivative (**23**) followed by migration of the thioalkyl group and concomitant rearomatization. A future report will be devoted to the conversion of 3-(*S*-cysteinyl)indoles into tryptathionines,[14]

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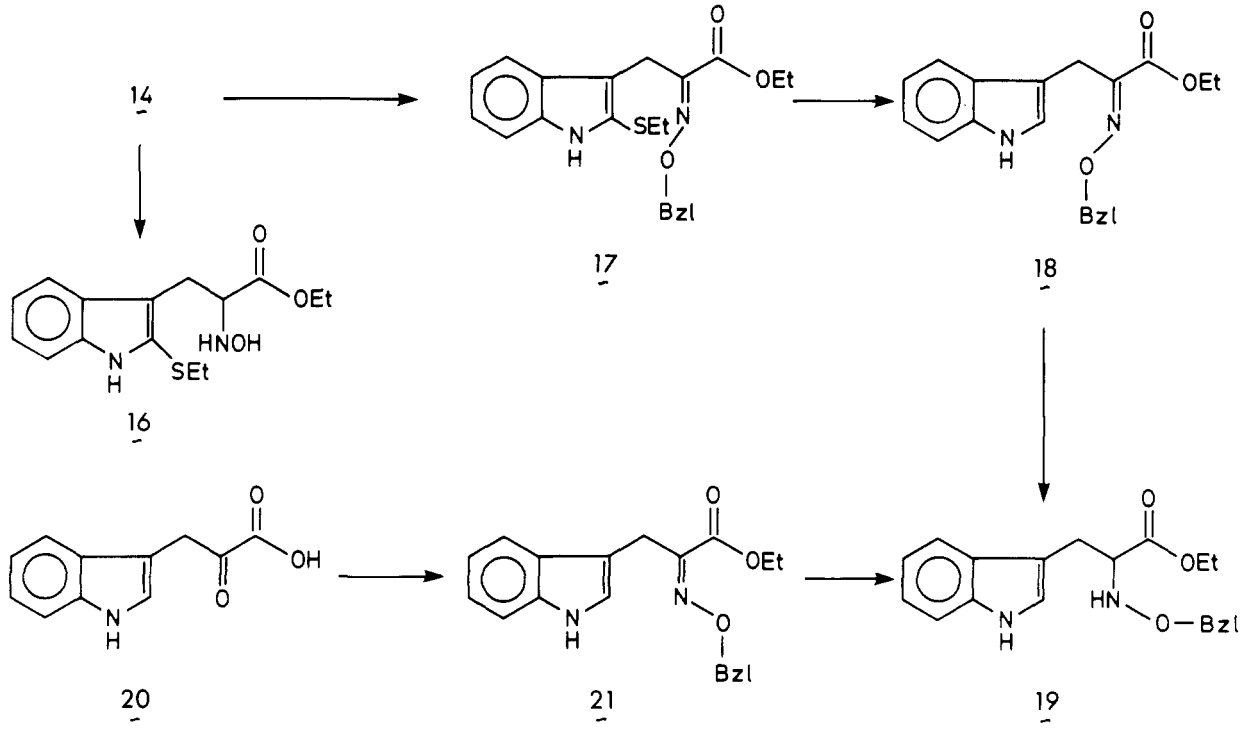
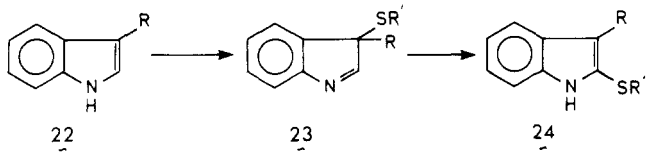
Scheme III



Scheme IV



which are 2-(*S*-cysteinyl)tryptophan derivatives.

Experimental Section

Melting points were taken on a Köfler hot stage (Leitz–Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer Model 555 spectrometer. Proton magnetic resonance spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent. Mass spectra (EI) were obtained with a double-focusing Varian Associates SMI-B spectrometer. Thin-layer chromatography (TLC) was carried out by using Merck precoated silicagel F-254 plates (thickness 0.05 mm). Spots were visualized with a UV hand lamp, iodine vapor, Cl_2–TDM,[15] cinnamaldehyde/HCl for indole detection,[16] or $AgNO_3/Na_2Cr_2O_7$ for the detection of sulfides.[17]

A miniprep LC (Jobin Yvon) was used for preparative HPLC; as stationary phase, Merck silica gel H (type 60) was used.

Ethyl α-(Hydroxyimino)-β-[2-(methylthio)indol-3-yl]-propanoate (13). A solution of **5**[1] (10 mmol, 1.63 g) in dry dichloromethane (50 mL) was added dropwise to a well-stirred solution of 3-(methylthio)indole[6] (**8**, 10 mmol, 2.10 g) and Na_2CO_3 (20 mmol, 2.14 g) in dry dichloromethane (25 mL) at room temperature under nitrogen; the mixture was stirred for 18 h at room temperature. To remove Na_2CO_3 and NaBr, the mixture was filtered through a thin layer of silicagel Merck 60. The resulting solution was washed with 1 N HCl and with brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was subjected to HPLC, eluent 2:98 (v/v) $MeOH/CH_2Cl_2$, to yield 1.93 g of **13** (66%, oil), which was homogeneous on TLC (R_f 0.6; 6:94 (v/v) $MeOH/CH_2Cl_2$). Compound **13** gave on TLC the characteristic yellow spots for sulfur-containing compounds upon spraying with a 2% $AgNO_3$ (w) solution in water–ethanol (4:1, v/v) and 0.1 N $K_2Cr_2O_7/CH_3COOH$ (1:1, v/v). Upon spraying with cinnamaldehyde/concentrated HCl/EtOH solution (1:1:50, v/v/v),[16] only slightly brownish spots were obtained: high-resolution mass spectrum, exact mass calcd for $C_{14}H_{16}N_2O_3S$ *m/e* 292.0881, found 292.0871. UV (methanol) λ_{max} 220, 280, 288, 298 nm, ^1H NMR δ 8.9 (br s, 1 H, NOH), 8.4 (br s, 1 H, NH), 7.7–6.9 (m, 4 H, indole C(4)–C(7)H), 4.2 (s, 2 H, indole C(3) CH_2), 4.2 (q, 2 H, OCH_2CH_3), 2.3 (q, 3H, SCH_3), 1.2 (t, 3 H, OCH_2CH_3).

Ethyl α-(Hydroxyimino)-β-[2-(ethylthio)indol-3-yl]-propanoate (14). Compound **14** was prepared from **9**[6] (1.25 mmol, 263 mg), **5**[1] (1.25 mmol, 222 mg), and Na_2CO_3 (2.5 mmol, 265 mg) as described above for the preparation of **13**. The product **14** obtained in 74% (280 mg, oil) yield was homogeneous on TLC (R_f 0.3; 2:98 (v/v) $MeOH/CH_2Cl_2$): high-resolution mass spectrum, exact mass calcd for $C_{15}H_{18}N_2O_3S$ *m/e* 306.1038, found 306.1031; UV (methanol) λ_{max} 220, 282, 288, 298 nm; ^1H NMR δ 9.0 (br s, 1 H, NOH), 8.4 (br s, 1 H, NH), 7.8–7.0 (m, 4 H, indole C(4)–C(7)H), 4.2 (s, 2 H, indole C(3)–CH_2–), 4.2 (q, 2 H, OCH_2CH_3), 2.8 (q, 2 H, SCH_3), 1.2 (t, 3 H, OCH_2H_3), 1.2 (5, 3 H, SCH_2CH_3).

Ethyl α-(Hydroxyamino)-β-[2-(ethylthio)indol-3-yl]-propanoate (16). A solution of HCl in ethanol (5 mL of a 7 N solution) was added at once to a stirred solution of **14** (1.15 mmol, 352 mg) and $(CH_3)_3N{\cdot}BH_3$ (Aldrich Chemical Co., 1.2 mmol, 88 mg) in ethanol (10 mL) at room temperature. Stirring was continued for 24 h. The mixture was then concentrated to dryness, dissolved in CH_2Cl_2, washed with 5% $NaHCO_3$ solution and with brine, and dried over Na_2SO_4. Evaporation of the solvent and HPLC of the residue (2:98 (v/v) $MeOH/CH_2Cl_2$) gave **16** in 80% (281 mg) yield as a solid material, which was homogeneous on TLC (R_f 0.33; 4:96 (v/v) $MeOH/CH_2Cl_2$): mp 142–144 °C dec (CH_2Cl_2/*n*-hexane); high-resolution mass spectrum, exact mass calcd for $C_{15}H_{20}N_2O_3S$ *m/e* 308.1195, found 308.1165; UV (methanol) λ_{max} 220, 288, 298 nm; ^1H NMR δ 8.5 (br s, 1 H, NH), 7.7–7.0 (m, 4 H, indole C(4)–C(7)H), 6.0 (br s, 2 H, NHOH), 4.15 (q, 2 H, OCH_2CH_3), 4.0 (X part of ABX spectrum, 1 H, indole C(3)–CH_2CH), 3.3–3.1 (m, 2 H, AB part of ABX spectrum CH_2CH), 2.7 (q, 2 H, SCH_2CH_3), 1.15 (t, 3 H, SCH_2CH_3), 1.15 (t, 3 H, OCH_2CH_3). Anal. Calcd for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; N, 9.08. Found: C, 58.24; H, 6.51; N, 9.08.

Ethyl α-(Benzyloximino)-β-[2-(ethylthio)indol-3-yl]-propanoate (17). A solution of benzyl bromide (4.1 mmol, 700 mg) in dimethoxyethane (5 mL) was added dropwise to a stirred solution of **14** (4 mmol, 1.24 g) and potassium *tert*-butoxide (4(4.1 mmol, 450 mg) in dimethoxyethane (20 mL) at room temperature.

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(16) "Anfärbereagentine für Dünnschichtchromatographie", Fa. Merck, 1970, 108.
(17) Knight, R. H.; Young, L. *Biochem. J.* **1958**, *70*, 111.

Stirring in a nitrogen atmosphere was continued for 2 h at room temperature. Then the solvent was removed in vacuo. A solution of the residue in CH_2Cl_2 was washed with 1 N HCl and with brine and subsequently dried over Na_2SO_4. The residue obtained by evaporation of the solvent was subjected to HPLC (1:1 (v/v) hexane/CH_2Cl_2) to give **17** in 79% (1.25 g, oil) yield, which was homogeneous by TLC (R_f 0.55, CH_2Cl_2): high-resolution mass spectrum, exact mass calcd for $C_{22}H_{24}N_2O_3S$ m/e 396.1507, found 396.1497; UV (methanol) λ_{max} 220, 288, 298 nm; ^1H N mR δ 8.2 (br s, 1 H, indole NH), 7.2 (s, 5 H, C_6H_5), 7.6–6.9 (m, 4 H, indole C(4)–C(7)H), 5.25 (s, 2 H, $CH_2C_6H_5$), 4.2 (s, 2 H, indole C(3)–CH_2–), 4.15 (q, 2 H, OCH_2CH_3), 2.7 (q, 2 H, SCH_2CH_3), 1.2 (t, 3 H, OCH_2CH_3), 1.2 (t, 3 H, SCH_2CH_3).

Ethyl α-((*E*)-Benzyloximino)-β-(indol-3-yl)propanoate (18). Raney nickel catalyst (Merck-Schuchard, Darmstadt, FRG) was added portionwise to a solution of **17** (1 mmol, 396 mg) in ethanol (5 mL), which was stirred at room temperature under an atmosphere of nitrogen. The addition of the catlayst was stopped upon completion of the reaction, which was monitored by TLC (R_f 0.5, CH_2Cl_2). The reaction mixture was then filtered, and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL), washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave **18** (306 mg, oil) in 91% yield, which was homogeneous on TLC (R_f 0.6, CH_2Cl_2): high-resolution mass spectrum, exact mass calcd for $C_{20}H_{20}N_2O_3$ m/e 336.1474, found 336.1487; UV (methanol) λ_{max} 220, 280, 288 nm; ^1H NMR δ 8.1 (br s, 1 H, NH), 7.7–7.0 (m, 4 H, indole C(4)–C(7)H), 7.25 (s, 5 H, C_6H_5), 6.9 (d, 1 H, indole C(2)H), 5.3 (s, 2 H, $CH_2C_6H_5$), 4.2 (q, 2 H, OCH_2CH_3), 4.05 (s, 2 H, indole C(3) CH_2), 1.2 (t, 3 H, OCH_2CH_3).

Ethyl α-(Benzyloxamino)-β-(indol-3-yl)propanoate (19). A solution of HCl in ethanol (5 mL of a 7 N solution) was added to a stirred solution of **18** (0.45 mmol, 150 mg) and trimethylamine borohydride complex (Aldrich Chemical Co., 0.9 mmol 66 mg) in ethanol (5 mL) at room temperature. Stirring was continued for 24 h at room temperature. The mixture was then concentrated to dryness in vacuo and the residue positioned between CH_2Cl_2 and water. The organic layer was washed twice with water, dried over Na_2SO_4, and then concentrated in vacuo. The residue was subjected to HPLC (eluent CH_2Cl_2) to yield 98 mg (65%, oil) of **19**, which was homogeneous on TLC (R_f 0.2, CH_2Cl_2). The ^1H NMR spectrum is identical with that of the product obtained from **20** (Scheme III).[1]

3-(Methylsulfinyl)indole. To a stirred and cooled (0 °C) solution of the thioether **8**[6] (5 mmol, 815 mg) in acetonitrile (10 mL) was added dropwise a solution of sodium metaperiodate (5 mmol, 1070 mg) in water (10 mL). Stirring of the reaction mixture was continued at room temperature until completion of the reaction (ca. 3 h) as was monitored by TLC (R_f 0.25, 4:96 (v/v) MeOH/CH_2Cl_2). The precipitate consisting of sodium iodate was removed by filtration, and CH_2Cl_2 was added to the filtrate. The organic layer was washed with brine and dried with Na_2SO_4. Evaporation of the solvent in vacuo and recrystallization from CH_2Cl_2/*n*-hexane gave the product in 91% (814 mg) yield: mp 117–120 °C; high-resolution mass spectrum, exact mass calcd for C_9H_9NOS m/e 179.0405, found 179.0400; UV (methanol) λ_{max} 210, 265, 276, 282 nm; ^1H NMR δ 10 (br s, 1 H, NH), 7.9–6.9 (m, 5 H, indole C(2)H, C(4)–C(7)H), 2.9 (s, 3 H, $-SOCH_3$). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.15; H, 5.06; N, 7.70.

3-(Ethylsulfinyl)indole. This compound was prepared from **9**[6] (5 mmol, 885 mg) and sodium metaperiodate (5 mmol, 1070 mg) as described for 3-(methylsulfinyl)indole. It was obtained in 87% (840 mg) yield: mp 142–143 °C dec (CH_2Cl_2/hexane); high-resolution mass spectrum, exact mass calcd for $C_{10}H_{11}NOS$ m/e = 193.0561, found 193.0550; UV (methanol) λ_{max} 210, 265, 276, 282 nm; ^1H NMR δ 10 (br s, 1 H, NH), 7.9–6.7 (m, 5 H, indole C(2)H, C(4)–C(7)H), 3.15 (q, 2 H, $SOCH_2$), 1.05 (t, 3 H, $SOCH_2CH_3$). Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.11; H, 5.72; N, 7.22.

Registry No. **5**, 73472-94-3; **6**, 87497-88-9; **8**, 40015-10-9; **9**, 1484-16-8; **13**, 87843-25-2; **14**, 87843-26-3; **16**, 87843-27-4; **17**, 87843-28-5; **18**, 87843-29-6; **19**, 81095-85-4; 3-(methylsulfinyl)indole, 86925-06-6; 3-(ethylsulfinyl)indole, 87843-30-9; benzyl bromide, 100-39-0.

Synthesis of the Enantiomeric Forms of α- and β-Alkoxy Carbonyl Compounds from the (2*S*,3*R*)-2,3-Diol Prepared in Fermenting Bakers' Yeast from α-Methylcinnamaldehyde

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Received June 22, 1983

One of the major problems faced in the use of components of the set of readily available, optically active products produced by Nature ("pool of chirality"[1]) as starting materials in the synthesis of enantiomerically pure forms of natural products is that most of these materials are usually accessible in only one enantiomeric form. Attempts to overcome this drawback involve, amongst others, the chemical conversion of abundant natural products into the unnatural form of structurally related materials (e.g., natural tartaric acid into unnatural malic acid[2]), the production of the enantiomeric forms of a chiral synthon by microbial transformulations of nonconventional substrates using microorganisms acting on the same substrate with opposite stereochemistry (e.g., (*R*)- and (*S*)-3-hydroxybutyrate from ethyl 3-oxobutyrate using *Geotrichum candidum* and bakers' yeast, respectively[3]), and preparation of the two enantiomers from suitably functionalized chiral synthons (e.g., the conversion of (*S*)-3-hydroxy-2-methylpropionic acid into (*R*)- and (*S*)-3-*tert*-butoxy-2-methyl-1-propanol[4]).

In this context we report now the preparation of the chiral carbonyl compounds 14–17 and of their enantiomers from the (2*S*,3*R*)-2,3-diol **1**, obtained from fermenting bakers' yeast and α-methylcinnamaldehyde.[5] The procedure takes advantage of the possibility of preparing regioselectively from **1** the 2- and 3-*O*-tosylates **2** and **4**, from which the enantiomeric epoxides **5** and **6** are obtained. To this end, the diol **1**, reacted with 1 mol equiv of 4-toluenesulfonyl chloride in CH_2Cl_2–pyridine, afforded the 2-*O*-tosylate **2** in high yield. ^1H NMR studies on **1** and **2** support the regiospecificity of the reaction: the H-2 signal is shifted from δ 4.08 in **1** to δ 4.75 in **2**. Compound **2** gave rise on basic treatment to the (2*R*,3*R*)-2,3-epoxide **5**. The same epoxide **5** was obtained when the diol **1** was treated with 4-toluenesulfonyl chloride, 1,2-dimethoxyethane, and KOH,[6] thus indicating the regiospecificity of this one-pot conversion of **1** to **5**. On reaction with diisobutylaluminum hydride in THF at −50 °C or with $LiAlH_4$ in diethyl ether at O °C, compound **5** gave rise to the alcohol **7**, which converted, in turn, to the *O*-benzyl ether **8** in ca. 70% overall yield. The latter material on

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