Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 3, pp. 363-370, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $6.00+0.00

0957-4166(94)E0046-D

NEW ASYMMETRIC SYNTHESIS OF (-)-ESERMETHOLE

M.Pallavicini[a*], E.Valoti[a*], L.Villa[a] and I.Resta[b]

[a] Istituto di Chimica Farmaceutica e Tossicologica, Universita' di Milano, viale Abruzzi 42, I-20131 Milano, Italia.

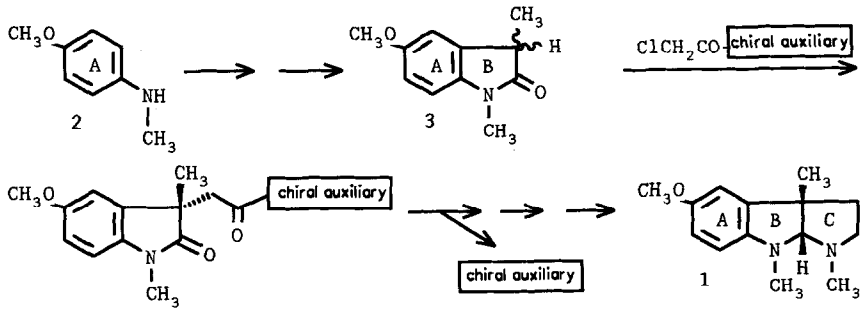
[b] Biochimica Opos S.p.a., via delle Industrie 84, I-20041 Agrate Brianza (Milano), Italia.

Abstract. A new synthesis of (-)-esermethole, based on the asymmetric alkylation at C(3) of racemic 1,3-dimethyl-5-methoxyoxindole (**3**), is described. The chloroacetyl derivatives of (-)-menthol and (S)-N-methyl-(1-phenylethyl) amine were chosen as chiral alkylating agents and used under different reaction conditions (temperature, solvent and base). In particular, the latter reacted with **3** in toluene at 10°C, in the presence of *t*-butyllitium, giving (3S,1'S)-N-methyl-N-(1'-phenylethyl)-1,3-dimethyl-5-methoxyoxindol-3-ilacetamide (**10**) with a 63% d.e.. This intermediate was easily separated from the undesired minor (3R,1'S) diastereomer (**11**) and converted to (-)-esermethole (99.6% e.e.) in two steps.

In our previous communication[1] we had described a new synthesis of (-)- and (+)-esermethole , penultimate intermediates to (-)- and (+)-physostigmine respectively, *via* chemical resolution of their precursor 1,3-dimethyl-3-(2-aminoethyl)-5-methoxyoxindole with optically active tartaric acids. As a continuation of our studies we searched for an alternative asymmetric synthesis of (-)-esermethole (**1**). The synthetic plan is outlined briefly in Scheme I. Key features of the approach, as revealed in this summary, included (1) the preparation of 1,3-dimethyl-5-methoxyoxindole **3** from N-methyl-*p*-anisidine **2**, (2) the asymmetric alkylation at C(3) of the indolic intermediate **3** with the chloroacetyl derivative of the appropriate chiral auxiliary, (3) the removal of the latter and (4) the formation of the cis-fused pyrrolidine

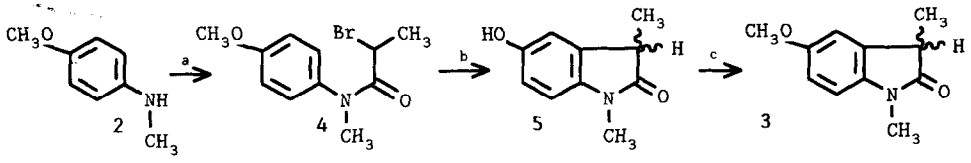
ring C.

Scheme I



Intermediate **3** was prepared according to the procedure described by Julian and Pikl[2] for the corresponding 5-ethoxy derivative with some minor modifications (Scheme II).

Scheme II



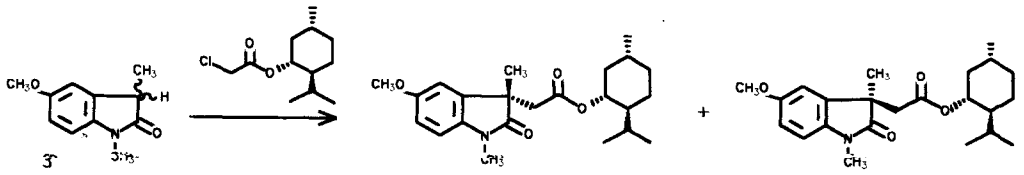
a) 2-bromopropionylbromide, $(CH_2Cl)_2$; b) $AlCl_3$; c) $(CH_3)_2SO_4$, aq KOH.

In order to accomplish the asymmetric alkylation at C(3), menthol was initially selected as stoicheiometric chiral auxiliary, both its enantiomers being cheap and readily available. In particular, the initially chosen laevorotatory isomer was esterified with chloroacetyl chloride and used to alkylate **3**. The results of the diastereoselective alkylation are compiled in Table I, where the different reaction conditions (solvent, temperature, deprotonating agent) are specified with the corresponding yields and diastereomeric excesses.

As shown in this summary, only moderate degrees of stereoselectivity were achieved. Moreover, the two diastereomers were not easily separable by silica gel chromatography; on the other hand, the oily consistency of their isolated mixture precluded further diastereomeric enrichment by selective crystallization. On account of these disadvantages, the use of (-)-menthol as chiral auxiliary was discarded as well as successive multistep conversion to optically active esermethole. Therefore the induced absolute configuration of C(3), assignable on the basis of the above conversion, was not determined.

1-Phenylethylamine was then selected as alternative chiral auxiliary. The

Table I. Alkylation of 3 with (1R,2S,5R)-menthyl chloroacetate [a]

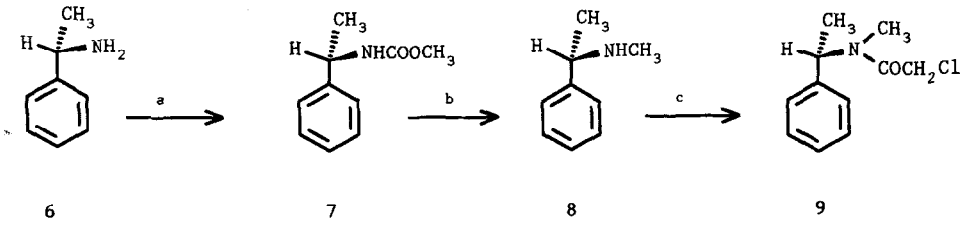


Entry	Deprotonating agent	Solvent	T [°C]	yield, % [b]	d.e., % [c]
1	NaOH (TBAB as phase transfer catalyst)	CH_2Cl_2 aq NaOH (15%)	25	35	1
2	$(CH_3)_3CO^-K^+$	*t*-butanol	25	38	30
3	"	toluene	5	50	49
4	"	"	10	55	37
5	$(CH_3)_3CLi$	"	25	74	32

a) Obtained as a white solid in quantitative yield by reaction of (–)-menthol with chloroacetyl chloride in refluxing benzene. The ^1H NMR spectrum agreed with the assigned structure. b) Isolated yield, after flash chromatography on silica gel (el., hexane/EtOAc 7:3), of the diastereomeric mixture. ^1H NMR analysis confirmed that the isolated mixture consisted of two diastereomeric menthyl 1,3-dimethyl-5-methoxyoxindol-3-ilacetates. c) Determined by HPLC on chiral stationary phase (Chiralcel OJ column from Daicel, 250x4.6 mm I.D.) using hexane/2-propanol 92:8 (flow-rate 0.6 ml/min). The first-eluting isomer (t_R 9 min) always exceeded the second (t_R 11.3 min). The HPLC diastereomeric excesses were consistent with those evaluated via ^1H NMR analysis on the basis of the relative intensities of the two distinct doublets due to C(5)CH_3 of the menthyl residue.

chloroacetamide of its N-methylated S isomer **9** was prepared from (S)-(1-phenylethyl)amine **6** *via* conversion to carbamate **7**, successive reduction to (S)-N-methyl-(1-phenylethyl)amine **8** and final reaction with chloroacetyl chloride, as outlined in Scheme III. According to ^1H NMR analysis performed at 20°C in three different solvents (DMSO-d_6, methyl-d_3 alcohol-d, acetone-d_6), intermediate **9** consisted of a mixture of two rotamers in a ratio 3:1. In fact, the two methyl groups and the methylene and methine protons were all represented by two distinct signals, showing identical multiplicity and relative intensity consistent with the above mentioned ratio (see "Experimental Section"). Moreover, it is to be noted that this doubling of the signals disappeared when NMR analysis was performed at higher temperature (80°C). The observations are a consequence of hindered rotation about the amidic bond owing to its partial double

Scheme III



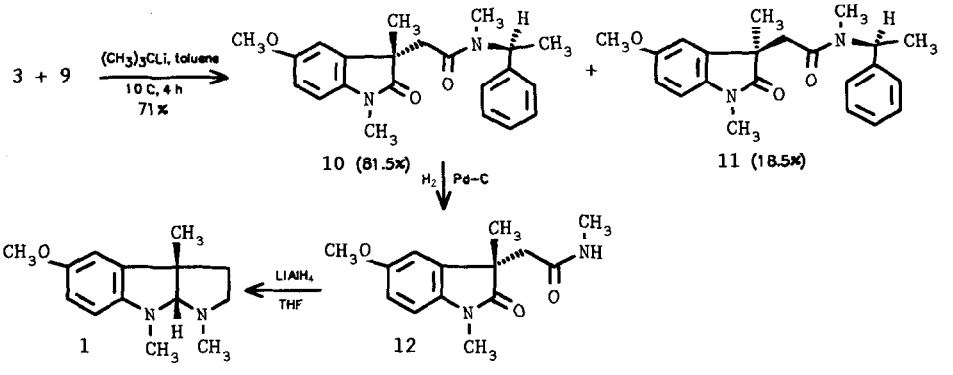
6 7 8 9

a) $ClCOOCH_3$, Et_3N; b) $LiAlH_4$, THF; c) $ClCH_2COCl$, benzene.

bond character which leads to steric interaction.

The use of the chiral derivative **9** entailed a slight modification of the strategy shown in Scheme I. In fact, it was expected that **9** would asymmetrically alkylate the intermediate **3**, and construct, after removal of phenylethyl fragment and reductive cyclization, the N-methylated pyrrolidine ring C of esermethole. Obviously, such an approach precluded the final recovery of the chiral auxiliary, but, on the other hand, it could result in a shortened synthetic sequence, as outlined in Scheme IV.

Scheme IV



Crude **10**, obtained with a 63% d.e. by reaction of **3** with **9** in toluene in the presence of *tert*-butyllitium at 10°C , was easily separated from its 3R epimer **11** by chromatography on silica gel. ^1H NMR analysis of isolated **10** indicated the presence of two rotamers in a ratio 2:1, due to the hindered rotation about the amidic bond, analogously to what had been observed in the case of intermediate **9** (see "Experimental Section"). The subsequent two step conversion to (-)-esermethole, *via* hydrogenolytic removal of the phenethyl fragment and reductive cyclization, proved the feasibility of the above synthetic strategy and allowed the assignment of

the S configuration to the C(3) of **10**.

Chiral HPLC analyses of **12** and **1** showed enantiomeric excesses greater than 99.5% indicating that the hydrogenolysis and the subsequent reduction did not affect the optical purity of intermediate **10**.

Alkylation of intermediate **3** with (R)-N-methyl-N-(1-phenylethyl)chloroacetamide afforded the enantiomer of **10** in analogous chemical and optical yields. Subsequent two step conversion to (+)-esermethole confirmed the opposite asymmetric induction at C(3) of the indolic nucleus.

In summary, we have demonstrated that alkylation of oxindole **3** with the chloroacetyl derivative of the appropriate chiral auxiliary proceeds with a good degree of stereoselectivity. In particular, the chloroacetamide of N-methylated (S)-(1-phenylethyl)amine alkylated intermediate **3** with the highest diastereoselectivity (63% d.e.). The major component of the resultant diastereomeric mixture could be easily separated from its epimer and readily converted to enantiomerically pure (-)-esermethole.

Experimental Section

Melting points are uncorrected. Optical rotations were measured in a 1-dm cell of 1 ml capacity using a Perkin-Elmer 241 polarimeter. IR spectra were determined on a Perkin-Elmer 1310 instrument. ^{1}H NMR spectra were recorded on a Bruker AC 200 instrument. Mass spectra were recorded on a Finnigan TSQ-70 mass spectrometer. HPLC analyses were performed on Chiralcel columns (250x4.6 mm I.D.) from Daicel using a Waters 510 pump and a Pye Unicam PU 4025 UV detector (analytical wavelength 254 nm). Chromatographic data were collected and processed on a Waters 740 Data Module.

N-(4-methoxyphenyl)-N-methyl-2-bromopropionylamide (4). 2-Bromopropionyl bromide (12 ml, 114.6 mmol) was added dropwise to a stirred solution of N-methyl-*p*-anisidine (15 g, 109.3 mmol) in dichloroethane (100 ml) at room temperature. The reaction mixture was heated under reflux until evolution of HBr had ceased (2 h) and, after cooling to room temperature, added with EtOAc (100 ml) and washed, in sequence, with 4 N H_2SO_4 (2x50 ml), 4 N NaOH (2x50 ml) and aq NaCl (30%, 2x50 ml). The organic phase was dried with Na_2SO_4 and concentrated in vacuo to give **4** (29.4 g, 99%) as a tick brown oil: ^{1}H NMR ($CDCl_3$) δ 1.7 (d, 3 H), 3.25 (s, 3 H), 3.85 (s, 3 H), 4.3 (q, 1 H), 6.9 (d, 2 H), 7.2 (d, 2 H).

1,3-Dimethyl-5-hydroxyoxindole (5). To N-(4-methoxyphenyl)-N-methyl-2-bromopropionylamide **4** (25.6 g, 93.9 mmol) $AlCl_3$ (22 g) was added. The mixture was heated at 200°C for 1 h, while stirring. The resulting

liquefied mass was poured while hot into a mortar and allowed to solidify. After pulverizing, the brownish solid was treated with crushed ice, removed by filtration from the resulting aqueous suspension and crystallized from ethanol to give **5** (14.1 g, 85%): mp 211-213°C; ^{1}H NMR (DMSO) δ 1.35 (d, 3 H), 3.1 (s, 3 H), 3.45 (q, 1 H), 6.65-6.85 (m, 3 H), 9.1 (s, 1 H).

1,3-Dimethyl-5-methoxyoxindole (3). To a stirred solution of 1,3-dimethyl-5-hydroxyoxindole **5** (10 g, 56.4 mmol) in aq KOH (5%, 70 ml) dimethyl sulfate (7.2 ml, 76.1 mmol) was added dropwise at room temperature. After warming to 90 °C for 30 min, the reaction mixture was allowed to cool to room temperature and extracted with EtOAc. The organic phase was concentrated and the oily brownish residue distilled in vacuo (bp 170°C, 0.3 mbar) yielding a yellow oil, which solidified upon standing. Recrystallization from Et_2O gave **3** (4.3 g, 40%) as white crystals: mp 84-86°C; IR (KBr) 3000, 2950, 2900, 1700, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5 (d, 3 H), 3.2 (s, 3 H), 3.4 (q, 1 H), 3.8 (s, 3 H), 6.7-6.9 (m, 3 H); MS *m/z* (relative intensity) 191 (M, 100), 176 (75). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.11; H, 6.91; N, 7.26.

(S)-N-Methoxycarbonyl-(1-phenylethyl)amine (7). Methyl chloroformate (6.8 ml, 88 mmol) was added to a stirred solution of (S)-(1-phenylethyl)amine **6** (10 g, 82.5 mmol) and Et_3N (13 ml, 93.3 mmol) in CH_2Cl_2 (150 ml) at 5°C. The reaction mixture was allowed to warm to room temperature over 1 h. After rinsing with 3N HCl (50 ml) and water (3x50 ml), the organic layer was concentrated and the resulting residue taken up in Et_2O. The formed white precipitate was removed by filtration and the solvent evaporated, yielding a solid residue which was crystallized from Et_2O-hexane to give **7** (8.21 g, 56%) as white crystals: mp 56-57°C; $[\alpha]_D^{20}$ -105 (c 1, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.5 (d, 3 H), 3.7 (s, 3 H), 4.7-5.1 (m, 2 H), 7.2-7.4 (m, 5 H).

(S)-N-Methyl-(1-phenylethyl)amine (8). A solution of (S)-N-methoxycarbonyl-(1-phenylethyl)amine **7** (7.5 g, 41.8 mmol) in THF (30 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (3.18 g) in THF (150 ml) at 5°C. The reaction mixture was heated under reflux for 1 h and, after cooling to 10°C, added with ice, filtered through a Celite pad and concentrated in vacuo. The residue was taken up in EtOAc (150 ml) and extracted with 3N HCl (80 ml). The acidic aqueous phase was basified with NaOH and extracted with EtOAc (3x100 ml). The combined organic extracts were washed with water (3x50 ml), dried (Na_2SO_4) and concentrated. The oily residue was distilled yielding **8** (4.25 g, 75%) as a pale yellow oil: bp 80°C/15 mmHg; $[\alpha]_D^{20}$ -67 (c 1, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3 H),

1.45 (s, 1 H), 2.3 (s, 3 H), 3.65 (q, 1 H), 7.15-7.4 (m, 5 H).

(S)-N-Methyl-N-(1-phenylethyl)chloroacetamide (9). Chloroacetyl chloride (2.95 ml, 37 mmol) was added dropwise to a stirred solution of (S)-N-methyl-(1-phenylethyl)amine **8** (10 g, 74 mmol) in benzene (150 ml) at 15°C. The reaction mixture was allowed to warm to room temperature over 30 min. EtOAc (100 ml), ice and 3N HCl (80 ml) were added. The organic phase was separated, washed with water (2x70 ml), dried (Na_2SO_4) and concentrated to give **9** (7.4 g, 94.5% calculated on chloroacetyl chloride) as a pale yellow oil: $[\alpha]_D^{20}$ -178 (c 1, EtOH); IR (neat) 3020, 2950, 1650, 1450 cm^{-1}; ^1H NMR (DMSO) δ 1.43 (d, 2.25 H), 1.56 (d, 0.75 H), 2.51 (s, 0.75 H), 2.70 (s, 2.25 H), 4.44 (AB quartet, 1.5 H), 4.54 (AB quartet, 0.5 H), 5.19 (q, 0.25 H), 5.76 (q, 0.75 H), 7.22-7.43 (m, 5 H); MS *m/z* (relative intensity) 211 (M, 42), 176 (94), 134 (65), 119 (100), 105 (83). Anal. Calcd for $C_{11}H_{14}ClON$: C, 62.41; H, 6.67; Cl, 16.75; N, 6.62. Found: C, 62.19; H, 6.71; Cl, 16.83; N, 6.58.

(3S,1'S)-N-Methyl-N-(1'-phenylethyl)-1,3-dimethyl-5-methoxyoxindol-3-il-acetamide (10). (S)-N-Methyl-N-(1-phenylethyl)chloroacetamide **9** (2.2 g, 10.4 mmol) was dissolved in toluene and added dropwise to a mixture of 1,3-dimethyl-5-methoxyoxindole **3** (2 g, 10.4 mmol) and *tert*-butyllitium (1.7 M solution in pentane, 6.1 ml) in toluene at 10°C. The mixture was stirred at this temperature for 4 h and then diluted with EtOAc, washed with water, dried (Na_2SO_4) and concentrated to give an oily residue. HPLC analysis (Chiralcel OD from Daicel; eluent: hexane-2-propanol-H_2O-Et_2NH, 88:12:0.4:0.08; flow-rate 1.4 ml/min) of this residue showed the presence of two prevalent components, namely the desired product **10** (t_R 5.86 min) and the 3R epimer **11** (t_R 7.02 min), with a 63% d.e. of the former. Column chromatography on silica gel (eluent: EtOAc-hexane, 55:45) allowed to isolate, in sequence, **10** (2.2 g, 58%) and **11** (0.4 g), both as white solids. **10**: mp 234-235°C; $[\alpha]_D^{20}$ -138 (c 1.8, EtOH); d.e. 99.68 (HPLC under the above mentioned conditions); IR (KBr) 3040, 2950, 1700, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (d, 2 H), 1.58 (d, 1 H), 1.31 (s, 1 H), 1.39 (s, 2 H), 2.54 (s, 1 H), 2.60 (s, 2 H), 2.98 (AB quartet, 1.3 H), 3.11 (AB quartet, 0.7 H), 3.27 (s, 3 H), 3.78 (s, 3 H), 5.12 (q, 0.3 H), 5.95 (q, 0.7 H), 6.64-6.85 (m, 3 H), 7.12-7.44 (m, 5 H); MS *m/z* (relative intensity) 366 (M, 100), 204 (48), 190 (47), 134 (94), 105 (59). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.29; H, 7.20; N, 7.58. Comparison of the ^1H NMR spectrum of the second-eluting minor product **11** with that of the desired major product **10** confirmed that the former was a diastereomer of the latter, the same signals being observable, with some small differences in chemical shifts and coupling costants.

(S)-N-Methyl-1,3-dimethyl-5-methoxyoxindol-3-ilacetamide (12). A solution of (3S,1'S)-N-methyl-N-(1'-phenylethyl)-1,3-dimethyl-5-methoxyoxindol-3-ilacetamide **10** (4 g, 10.9 mmol) in EtOH (200 ml) was poured into a stainless steel autoclave and added with 10% palladium-charcoal (700 mg). After pressurizing to 4 atm with hydrogen, the mixture was vigorously shaken at 100°C for 20 h. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to give **12** (2.86 g, 100%) as a white solid: e.e. 99.6% (HPLC under the same conditions adopted to determine the d.e. of **10**); ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 3 H), 2.55-2.8 (m, 5 H), 3.2 (s, 3 H), 3.8 (s, 3 H), 6.55 (br s, 1 H), 6.7-6.9 (m, 3 H).

(-)-Esermethole (1). (S)-N-Methyl-1,3-dimethyl-5-methoxyoxindol-3-ilacetamide **12** (2.65 g, 10.1 mmol) was dissolved in THF and added dropwise to a stirred suspension of $LiAlH_4$ (1.85 g) in THF at room temperature. The mixture was heated at 50°C for 8 h and then cooled to 10°C. Crushed ice was cautiously added while diluting with more THF to ensure a vigorous stirring. After filtering through a Celite pad, the solvent was evaporated. The residue was dissolved in Et_2O and extracted with 1 N HCl. The aqueous acidic phase was separated, washed with Et_2O, basified with Na_2CO_3 and extracted with EtOAc. The organic extract was concentrated to give a residue which was chromatographed on silica gel eluting with a 20% 2-propanol-hexane mixture. The eluant was concentrated yielding **1** (0.95 g, 40.5%) as an oil, which crystallized on standing: mp 53-54°C; $[\alpha]_D^{20}$ -137.5 (c 0.35, benzene) [Lit.[3] $[\alpha]_D$ -136.7 (c 0.35, benzene)]; 99.6% e.e. (determined by HPLC on the chiral stationary phase Chiralcel OJ (Daicel), using hexane-2-propanol 95/5, flow-rate 0.6 ml/min); ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 3 H), 1.95 (m, 2 H), 2.55 (s, 3 H), 2.6-2.8 (m, 2 H), 2.9 (s, 3 H), 3.75 (s, 3 H), 4.05 (s, 1 H), 6.4 (dd, 1 H), 6.65 (m, 2 H).

References

(1) Pallavicini,M.; Valoti,E.; Villa,L.; Lianza,F. *Tetrahedron Asymmetry* **1994** (in press).
(2) Julian,P.L.; Pikl,J. *J.Am.Chem.Soc.* **1935**, *57*, 563.
(3) Lee,T.B.K.; Wong,G.S.K. *J.Org.Chem.* **1991**, *56*, 872.

(*Received in UK* 20 *December* 1993; *accepted* 21 *January* 1994)