Syntheses and Properties of Optically Active 2-Substituted Taurines

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The synthesis of nine 2-substituted taurines (**5a**—**i**), including the marine natural product D-cysteinolic acid (**5f**), are described. These involve the successive conversion of *N*-t-butoxycarbonyl(Boc)-protected amino acid esters (**1**) into the *N*-Boc-2-aminoethanols (**2**), their *O*-mesylated derivatives (**3**), the deprotected 2-aminoethyl methanesulphonates (**4**), followed by the replacement of the mesyloxy group by a sulpho group to give the optically active taurines (**5a**—**e**,**g**—**i**). Hydrogenolysis of 2-benzyloxymethyltaurine (**5e**) gives D-cysteinolic acid (**5f**). The structure of another of the products, (**5b**), is also confirmed by an alternative synthesis from *N*-Boc-valine methyl ester (**1b**) *via* two β-bromoethylamine derivatives, (**6b**) and (**7b**).

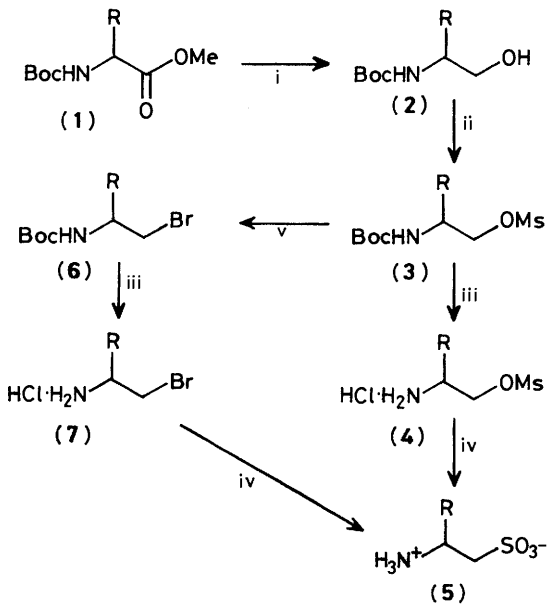
An optically active taurine derivative, D-cysteinolic acid (**5f**), has been isolated from marine micro-organisms[1-3] and its bioactivity has also been reported.[4] However, although the enantiomer of (**5f**) has been prepared,[1] the natural product itself (**5f**) has not been synthesized before. Further, since there have been no simple and general synthetic routes to 2-substituted taurine derivatives (**5**), this has limited studies on the structural properties and structure–activity relationships for compounds of type (**5**).

We earlier reported a general synthetic method leading to taurine-containing dipeptides, *via* an amino acid β-halogenoethylamide without racemization,[5,6] and, more recently, we have shown that C-terminal amino acids in oligopeptides can be converted into taurine derivatives.[7,8] We now report the extension of such a process to the synthesis of 2-substituted taurines: thus, a synthetic route represented by formulae (**1**)—(**5**) in the Scheme, has been evaluated as a general method: it proved remarkably successful.

Syntheses.—2-Substituted taurines (**5**) were synthesized by two routes, namely through the 2-aminoethyl methanesulphonates (**4**) and the halogenoethylamine (**7**). The former shorter method proved better, although in the analogous conversion of a C-terminal amino acid of a peptide into a taurine derivative, the second route proved better.[6,7] First, each α-amino acid methyl ester was converted into the corresponding hydroxyethylamide (**2**) by $LiBH_4$ reduction[8,9] in 80—95% yield. Then each hydroxyethylamide (**2**) was mesylated in 93—99% yield to give the derivative (**3**), which was deprotected to give (**4**) (*ca.* 90—100%), and subsequently allowed to react with sodium sulphite to give a 2-substituted taurine (**5**) (*ca.* 90—100%). Alternatively, the product (**5b**) was prepared from the substrate (**3b**) *via* two bromo intermediates (**6b**) and (**7b**) in 54% yield. The products derived from both syntheses proved identical.

The natural D-cysteinolic acid (**5f**) was obtained quantitatively by a conventional hydrogenation of its benzyl derivative (**5e**), which was synthesized from Boc-L-Ser(Bzl)-OMe (**1e**).

$[\alpha]_D$ *Values and Spectra.*—Each pair of enantiomers (**5a**/**g**), (**5b**/**h**), and (**5c**/**i**) had the same numerical values of opposite sign (Table 2). In the case of (*S*)-2-benzyltaurine, h.p.l.c. analysis after derivatization with a chiral isothiocyanate, 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC),[10] clearly established that racemization was effectively absent: the Figure shows the (*S*)-2-benzyltaurine with the contaminant (*R*)-isomer amounting to <0.5%. In view of the chemical similarity



R	*R*/*S*	R	*R*/*S*
a; Me	*S*	**f**; $HOCH_2$	*S*
b; Pr^i	*S*	**g**; Me	*R*
c; $PhCH_2$	*S*	**h**; Pr^i	*R*
d; Ph	*R*	**i**; $PhCH_2$	*R*
e; $PhCH_2OCH_2$	*S*		

Scheme. i, $LiBH_4$, EtOH; ii, MsCl, Et_3N, CH_2Cl_2; iii, HCl in dioxane; iv, Na_2SO_3, H_2O; v, LiBr, Me_2CO

of the other products and the lack of direct chemical reaction of the asymmetric centre, retention of optical integrity in all cases seemed to be kept. In the ^1H n.m.r. spectra shown in Table 1, the two characteristic methylene protons of the taurine entity were observed at *ca.* δ 2.8 and 3.0, respectively; exceptionally in the case of (**5d**), both protons were shifted towards lower field by the ring current effect of the benzene ring.

Experimental

M.p.s are uncorrected. ^1H N.m.r. spectra were measured in 0.2M NaOD–D_2O solution on a Bruker AM-400 instrument; chemical shifts are δ values from t-butyl alcohol (1.23 p.p.m.) as

Table 1. ^{1}H N.m.r. spectral data for 2-substituted taurines (δ p.p.m., *J*/Hz)

Compd.	α-H (2-H)	β-H (1-H)	H in 2-substituent
(**5a**)	2.86 (1 H, dd, *J* 8, 14) 2.97 (1 H, dd, *J* 4, 14)	3.31—3.39 (m)	1.15 (3 H, d, *J* 6.5)
(**5b**)	2.76 (1 H, dd, *J* 10, 15) 3.06 (1 H, dd, *J* 2, 15)	3.03—3.09 (m)	0.89 (3 H, d, *J* 7), 0.90 (3 H, d, *J* 7), 1.66—1.78 (1 H, m)
(**5c**)	2.85 (1 H, dd, *J* 9, 14) 3.05 (1 H, dd, *J* 3, 14)	3.48—3.55 (m)	2.68 (1 H, dd, *J* 8, 13), 2.86 (1 H, dd, *J* 6, 13), 7.28—7.41 (5 H, m)
(**5d**)	3.23 (1 H, dd, *J* 10, 13) 3.43 (1 H, dd, *J* 6, 13)	4.08 (dd, *J* 6, 10)	7.40—7.46 (3 H, m)
(**5e**)	2.83 (1 H, dd, *J* 8, 14) 3.05 (1 H, dd, *J* 4, 14)	3.42—3.51 (m)	3.42—3.51 (1 H, m), 3.55—3.61 (1 H, m), 4.59 (2 H, s), 7.36—7.46 (5 H, m)
(**5f**)	2.83 (1 H, dd, *J* 9, 14) 3.07 (1 H, dd, *J* 4, 14)	3.23—3.34 (m)	3.51 (3 H, dd, *J* 7, 11), 3.58 (3 H, dd, *J* 6, 11)
(**5g**)	2.86 (1 H, dd, *J* 9, 14) 2.97 (1 H, dd, *J* 3, 14)	3.31—3.39 (m)	1.15 (3 H, d, *J* 6.5)
(**5h**)	2.76 (1 H, dd, *J* 10, 15) 3.06 (1 H, dd, *J* 2, 15)	3.03—3.09 (m)	0.89 (3 H, d, *J* 7), 0.90 (3 H, d, *J* 7), 1.66—1.78 (1 H, m)
(**5i**)	2.85 (1 H, dd, *J* 9, 14) 3.05 (1 H, dd, *J* 3, 14)	3.48—3.55 (m)	2.68 (1 H, dd, *J* 8, 13), 2.86 (1 H, dd, *J* 6, 13), 7.28—7.41 (5 H, m)

Table 2. M.p.s and $[\alpha]_D$ values of 2-substituted taurines

Compd. (Formula)	$[\alpha]_D$ (*c* 1, in H_2O)	M.p. (°C)[a] (decomp.)	Found (%) (Requires) C	H	N
(**5a**)	+18.5°	>330	26.1	6.8	10.3
($C_3H_9NO_3S$)			(25.9)	(6.5)	(10.2)
(**5b**)	+29.8°	325—326	35.9	8.0	8.2
($C_5H_{13}NO_3S$)			(35.9)	(7.8)	(8.4)
(**5c**)	−3.5°	>330	50.4	6.3	6.3
($C_9H_{13}NO_3S$)			(50.2)	(6.1)	(6.5)
(**5d**)	+1.3°	>330	47.8	5.4	7.0
($C_8H_{11}NO_3S$)			(47.8)	(5.5)	(7.0)
(**5e**)	−8.4°	242—243	49.0	5.9	5.8
($C_{10}H_{15}NO_4S$)			(49.0)	(6.2)	(5.7)
(**5f**)	+7.5°[b]	279—281[b]	23.5	6.1	8.9
($C_3H_9NO_4S$)			(23.2)	(5.8)	(9.0)
(**5g**)	−18.3°	>330	26.1	6.8	10.3
($C_3H_9NO_3S$)			(25.9)	(6.5)	(10.2)
(**5h**)	−29.7°	325—326	36.0	7.9	8.7
($C_5H_{13}NO_3S$)			(35.9)	(7.8)	(8.4)
(**5i**)	+3.6°	>330	50.0	6.4	6.5
($C_9H_{13}NO_3S$)			(50.2)	(6.1)	(6.5)

[a] Recrystallized from H_2O–EtOH. [b] Lit.,[1] m.p. 279—282 °C (decomp.), $[\alpha]_D$ +7.0° (*c* 2, in H_2O); lit.,[2] m.p. 278—279 °C (decomp.), $[\alpha]_D$ +6.7° (*c* 0.99, in H_2O)

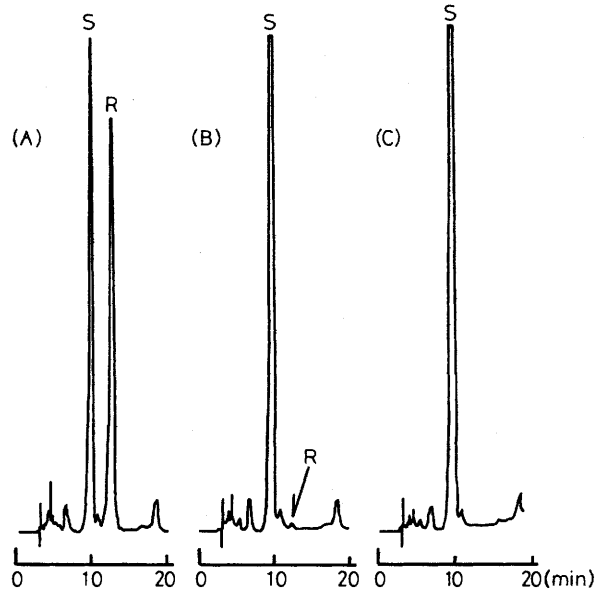


Figure. Analysis of diastereoisomeric thiourea derivatives formed from 2-benzyltaurine with GITC. (A) Equimolar mixture of (*S*)- and (*R*)-isomers. (B) (*S*)-Isomer with 0.5% (*R*)-isomer. (C) (*S*)-Isomer. H.p.l.c. conditions were as follows: column: Deverosil ODS-7 (4.6 × 150 mm); column temp.: room temp.; eluant: methanol–10 mM KH_2PO_4 (pH 2.8; $HClO_4$) (55:45); flow rate: 0.9 ml/min; detect. u.v. (250 nm)

an internal standard. Optical rotations were measured with a JASCO DIP-140 instrument.

2-Substituted N-*2-Butoxycarbonylaminoethanols* (**2a**—**i**).—All known 2-substituted 2-butoxycarbonylaminoethanols (**2**) were prepared from the corresponding *N*-Boc-amino acid methyl esters (**1**) by a known method using $LiBH_4$ in ethanol.[11] Their physicochemical properties were identical with those described in the literature: [(**2a**,**c**,**e**);[12] (**2b**,**g**—**i**);[9] (**2c**)[11]].

Preparation of 2-Substituted 2-t-Butoxycarbonylaminoethyl Methanesulphonates (**3a**—**e**,**g**—**i**).—To an ice-cooled solution of (*S*)-2-t-butoxycarbonylaminopropan-1-ol (**2a**) (50 mmol) and triethylamine (55 mmol) in dichloromethane (200 ml), a solution of methanesulphonyl chloride (52 mmol) in dichloromethane (100 ml) was added dropwise during 30 min; the solvent was then evaporated under reduced pressure and ethyl acetate and water were added to the residue. The organic layer was washed with aqueous 5% $NaHCO_3$ and brine, and dried (Na_2SO_4), and evaporated to give crystalline (S)-2-*t-butoxycarbonylaminopropyl methanesulphonate* (**3a**) (96%), m.p. 75—76 °C, $[\alpha]_D$ −30.2° (*c* 1, in $CHCl_3$) (Found: C, 42.6; H, 7.9; N, 5.4. $C_9H_{19}NO_5S$ requires C, 42.7; H, 7.6; N, 5.5%). Similarly, seven derivatives (**3b**—**e**,**g**—**i**) were prepared: (S)-2-*t-butoxycarbonylamino-3-methylbutyl methanesulphonate* (**3b**) (95%), m.p. 75—77 °C, $[\alpha]_D$ −34.9° (*c* 1, in $CHCl_3$) (Found: C, 47.0; H, 8.3; N, 5.1. $C_{11}H_{23}NO_5S$ requires C, 47.0; H, 8.2; N, 5.0%); (S)-2-*t-butoxycarbonylamino-3-phenylpropyl methanesulphonate* (**3c**) (93%), m.p. 116—117 °C (decomp.), $[\alpha]_D$ −17.4° (*c* 1, in $CHCl_3$) (Found: C, 54.6; H, 7.0; N, 4.5. $C_{15}H_{23}NO_5S$ requires C, 54.9; H, 7.0; N, 4.3%); (R)-2-*t-butoxycarbonylamino-2-phenylethyl methanesulphonate* (**3d**) (98%), m.p. 107—109 °C, $[\alpha]_D$ −11.2° (*c* 1, in $CHCl_3$) (Found: C, 53.1; H, 7.0; N, 4.5. $C_{14}H_{21}NO_5S$ requires C, 53.3; H, 6.7; N, 4.4%); (S)-3-*benzyloxy-2-t-butoxycarbonylaminopropyl meth-*

anesulphonate (**3e**) (99%) (oily substance, which was used for the next reaction without further purification); (R)-2-*t-butoxycarbonylaminopropyl methanesulphonate* (**3g**) (98%), m.p. 75—76 °C, $[\alpha]_D$ + 29.9° (*c* 1, in $CHCl_3$) (Found: C, 42.5; H, 7.6; N, 5.5. $C_9H_{19}NO_5S$ requires C, 42.7; H, 7.6; N, 5.5%): (R)-2-*t-butoxycarbonylamino-3-methylbutyl methanesulphonate* (**3h**) (96%), m.p. 75—76 °C (decomp.), $[\alpha]_D$ +35.0° (*c* 1, in $CHCl_3$) (Found: C, 47.0; H, 8.3; N, 5.1. $C_{11}H_{23}NO_5S$ requires C, 47.0; H, 8.2; N, 5.0%); (R)-2-*t-butoxycarbonylamino-3-phenylpropyl methanesulphonate* (**3i**) (95%), m.p. 116—117 °C (decomp.), $[\alpha]_D$ +18.0° (*c* 1, in $CHCl_3$) (Found: C, 54.6; H, 7.0; N, 4.5. $C_{15}H_{23}NO_5S$ requires C, 54.7; H, 7.0; N, 4.3%).

Preparation of 2-*Substituted* 2-*Aminoethyl Methanesulphonate Hydrochlorides* (**4a—h**).—The *N*-protected mesyl derivative (**3a**) (75 mmol) was treated with 4M HCl in dioxane (150 ml) with stirring for 1 h at room temperature. Evaporation and recrystallization gave (S)-2-*aminopropyl methanesulphonate hydrochloride* (**4a**) (100%), m.p. 132—133 °C (from MeCN), $[\alpha]_D$ +10.3° (*c* 1, in DMF) (Found: C, 25.4; H, 6.6; N, 7.5. $C_4H_{12}ClNO_3S$ requires C, 25.3; H, 6.4; N, 7.4%). Similarly, seven derivatives (**4b—e,g—i**) were prepared: (S)-2-*amino*-3-*methylbutyl methanesulphonate hydrochloride* (**4b**) (99%), m.p. 126—128 °C (from MeCN–Et_2O), $[\alpha]_D$ +6.6° (*c* 1, in DMF) (Found: C, 33.0; H, 7.3; N, 6.4. $C_6H_{16}ClNO_3S$ requires C, 33.1; H, 7.4; N, 6.4%); (S)-2-*amino-3-phenylpropyl methanesulphonate hydrochloride* (**4c**) (100%), m.p. 133—134 °C (from MeCN–Et_2O), $[\alpha]_D$ +7.7° (*c* 1, in DMF) (Found: C, 45.2; H, 6.4; N, 5.3. $C_{10}H_{16}ClNO_3S$ requires C, 45.2; H, 6.1; N, 5.3%); (R)-2-*amino*-2-*phenylethyl methanesulphonate hydrochloride* (**4d**) (100%), m.p. 144—146 °C (from MeCN–Et_2O), $[\alpha]_D$ −9.4° (*c* 1, in DMF) (Found: C, 43.0; H, 5.6; N, 5.7. $C_9H_{14}ClNO_3S$ requires C, 43.0; H, 5.6; N, 5.6%); (S)-2-*amino-3-benzyloxypropyl methanesulphonate hydrochloride* (**4e**) [97% from (**2e**)], m.p. 112—114 °C (from MeCN–Et_2O), $[\alpha]_D$ +3.1° (*c* 1, in DMF) (Found: C, 44.7; H, 6.1; N, 4.8. $C_{11}H_{18}ClNO_4S$ requires C, 44.7; H, 6.1; N, 4.7%); (R)-2-*aminopropyl methanesulphonate hydrochloride* (**4g**) (99%), m.p. 135—136 °C, $[\alpha]_D$ −10.3° (*c* 1, in DMF) (Found: C, 25.6; H, 6.6; N, 7.3. $C_4H_{12}ClNO_3S$ requires C, 25.3; H, 6.4; N, 7.4%); (R)-2-*amino-3-methylbutyl methanesulphonate hydrochloride* (**4h**) (98%), m.p. 129—131 °C (from MeCN–Et_2O), $[\alpha]_D$ −6.7° (*c* 1, in DMF) (Found: C, 32.8; H, 7.6; N, 6.4. $C_6H_{16}ClNO_3S$ requires C, 33.1; H, 7.4; N, 6.4%); (R)-2-*amino*-3-*phenylpropyl methanesulphonate hydrochloride* (**4i**) (100%), m.p. 128—130 °C (from MeCN–Et_2O), $[\alpha]_D$ −7.4° (*c* 1, in DMF) (Found: C, 45.2; H, 6.0; N, 5.2. $C_{10}H_{16}ClNO_3S$ requires C, 45.2; H, 6.1; N, 5.3%).

(S)-2-*Amino*-3-*methylbutanesulphonic Acid* (**5b**).—(*a*) A mixture of the mesyl derivative (**4b**) (40 mmol) and sodium sulphite (60 mmol) in water (80 ml) was stirred for 20 h at room temperature. The reaction mixture was first applied to an IR-120B (H^+ form) and then to a Dowex-11 (acetate form) column. The eluate was evaporated under reduced pressure and the crystalline residue was recrystallized from water–ethanol to give the 2-*substituted taurine* (**5b**) (89%), m.p. 325—326 °C (decomp.) (from H_2O–EtOH) (Tables 1 and 2).

(*b*) A mixture of the bromo derivative hydrochloride (**7b**) (20 mmol) and sodium sulphite (30 mmol) was stirred for 20 h at room temperature to give the same pure product (**5b**) (86%), m.p. 325—326 °C (decomp.).

Similarly, seven other mesyl derivatives (**4**) and sodium sulphite gave the corresponding 2-substituted taurines (**5**) (Tables 1 and 2): (S)-2-*aminopropanesulphonic acid* (**5a**) (82%); (S)-2-*amino*-3-*phenylpropanesulphonic acid* (**5c**) (72%); (R)-2-*amino*-2-*phenylethanesulphonic acid* (**5d**) (79%); (S)-2-*amino*-3-*benzyloxypropanesulphonic acid* (**5e**) (76%); (R)-2-*aminopropanesulphonic acid* (**5g**) (67%); (R)-2-*amino*-3-*methylbutane sulphonic acid* (**5h**) (67%); and (R)-2-*amino*-3-*phenylpropanesulphonic acid* (**5i**) (83%).

(S)-2-*Amino*-3-*hydroxypropanesulphonic Acid* (**5f**).—The benzyloxy derivative (**5e**) (40 mmol) was hydrogenated in the presence of 10% Pd–C (1.0 g) in MeOH–AcOH–H_2O (5:3:6; 140 ml) at room temperature for 20 h. The catalyst was filtered off and the filtrate was evaporated under reduced pressure to give a crystalline residue, which was recrystallized from aqueous ethanol to give the pure D-cysteinolic acid (**5f**) (79%), m.p. 279—281 °C (decomp.) (Tables 1 and 2).

(S)-2-*Amino*-1-*bromo*-3-*methylbutane Hydrochloride* (**7b**).—A mixture of the *N*-protected mesyl derivative (**3b**) (50 mmol) and anhydrous LiBr (140 mmol) in acetone (100 ml) was stirred for 20 h at room temperature. The solvent was evaporated off and the residue was dissolved in ethyl acetate. The solution was washed with water, 5% $NaHCO_3$, and brine and evaporated under reduced pressure to give a crude oily substance which was purified by means of silica gel column chromatography (hexane–AcOEt, 9:1) to give apparently pure material (**6b**) (57%), which was deprotected by 4M HCl in dioxane (100 ml) with stirring for 1 h at room temperature. Evaporation and recrystallization gave the *hydrochloride* (**7b**) [54% from (**3b**)].

Pre-column Treatment of (S)-2- *and/or* (R)-2-*Benzyltaurine with* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranosyl Isothiocyanate* (*GITC*).—A sample of the taurine (5 mg) was dissolved in water (5 ml) containing 0.8% triethylamine and acetonitrile (5 ml); 50 μl of this solution was then heated with a 0.2% solution of GITC in acetonitrile (50 μl) at 55 °C for 30 min. An aliquot (2 μl) was analysed by h.p.l.c. (see Figure).

Acknowledgements

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