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Synthesis of Analogues of GABA. XII* *cis*- and *trans*-4-Aminotetrahydrofuran-2-carboxylic Acid

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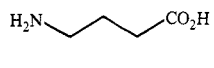
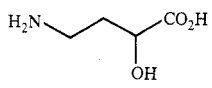
Abstract

cis- and *trans*-4-Aminotetrahydrofuran-2-carboxylic acid have been synthesized as conformationally restricted analogues of GABA and their stereochemistry confirmed by the cyclization of the *cis* isomer to the bicyclic *N*-tosyl lactam.

Oxygen heterocyclic analogues of acetylcholine such as muscarine, which is a substituted tetrahydrofuran derivative, and related dioxalones have provided a vast amount of information regarding the classification and structural requirements of cholinergic receptors in the nervous system.[1] For the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) (1), heteroaromatic analogues such as muscimol and kojic amine are potent GABA agonists,[2] but simple tetrahydrofuran derivatives of GABA have apparently not been investigated. Substitution of the 2 position of GABA with an oxygen substituent as in the hydroxy compound (2) leads to retention of GABA-mimetic activity.[2] If this fact is considered with the high activity of both *trans* and *cis* isomers of the cyclopentane analogues (3),[3] then the tetrahydrofuran derivatives (4) and (5) appear worthy of investigation. Furthermore, these compounds would be useful for structure–activity studies which, by analogy with (3), would predict the *trans* isomer (4) to be more active than the *cis* isomer (5) on GABA receptors.



(1)



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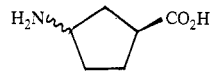

(3)

* Part XI, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2983.

[1] Triggle, D. J., and Triggle, C. R., 'Chemical Pharmacology of the Synapse' p. 311 (Academic Press: London 1976).

[2] Allan, R. D., and Johnston, G. A. R., *Med. Res. Rev.*, 1983, **3**, 91.

[3] Johnston, G. A. R., Allan, R. D., Andrews, P. R., Kennedy, S. M. E., and Twitchin, B., in 'GABA-Neurotransmitters' (Eds P. Krogsgaard-Larsen, J. Scheel-Kruger and H. Kofod) p. 149 (Munksgaard: Copenhagen 1978).

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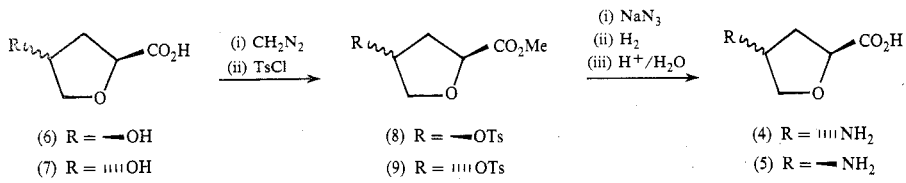
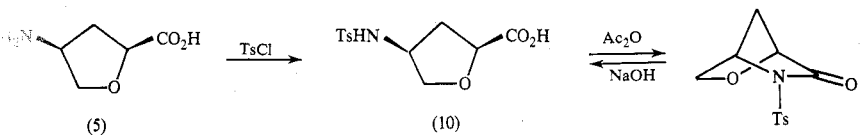
The *cis*- and *trans*-hydroxy acids (6) and (7) are ideal precursors for the amino acids and are available from diethyl allylmalonate by a literature procedure[4,5] involving the separation of the stereoisomers by fractional crystallization.[6] The stereochemistry of (6) and (7) has been assigned from infrared data on intramolecular hydrogen bonding of the methyl ester derivative.[5,6]



(6) R = —OH
(7) R = ⁞⁞⁞OH
(8) R = —OTs
(9) R = ⁞⁞⁞OTs
(4) R = ⁞⁞⁞NH$_2$
(5) R = —NH$_2$

Scheme 1

Each of these hydroxy acids has been converted into an amino acid by the route shown in Scheme 1. The intermediate tosyl methyl esters (8) and (9) each underwent clean displacement reactions with sodium azide to yield, after catalytic reduction and hydrolysis, the required amino acids (4) and (5) respectively. G.l.c. analysis of the crystalline products indicated that in each case contamination by the other isomer was less than 1%. The expected inversion during azide displacement on the tosylates (8) and (9) was proved, as illustrated in Scheme 2, by the reversible cyclization of the *cis*-amino acid (5) which had been formed from the *trans*-hydroxy acid (7). The *N*-tosyl amino acid (10) could be cyclized by refluxing in acetic anhydride for 45 h, while the corresponding *trans*-*N*-tosyl amino acid gave only a trace of the bicyclic compound (11) under the same conditions. Base-catalysed ring opening of (11) gave back the initial *N*-tosyl amino acid (10). Scheme 2 thus proves the assigned stereochemistry of (4) and (5), as well as confirming the previously determined stereochemistry of the hydroxy acids.



(5)
(10)
(11)

Scheme 2

The activity of the two amino acids as GABA-mimetic agents will be reported in detail elsewhere, but briefly, when compared with the *trans*- and *cis*-cyclopentane analogues (3), compounds (4) and (5) are at least 100-fold less active at transiently contracting the isolated guinea-pig ileum, and are also not significantly active at inhibiting the uptake of radiolabelled GABA into rat brain slices at 5×10^{-4} M.[7]

[4] Ichihara, A., Yamanaka, T., and Matsumoto, T., *Bull. Chem. Soc. Jpn*, 1965, **38**, 1165.
[5] Matsumoto, T., and Ichihara, A., *Bull. Chem. Soc. Jpn*, 1960, **33**, 1015.
[6] Yamanaka, T., Ichihara, A., Tanabe, K., and Matsumoto, T., *Tetrahedron*, 1965, **21**, 1031.
[7] Beart, P. M., Johnston, G. A. R., and Uhr, M. L., *J. Neurochem.*, 1972, **19**, 1849.

Experimental

For general directions see ref.[8] R_F values reported are for thin-layer chromatography (t.l.c.) on Merck Kieselgel 60 precoated t.l.c. plates in butan-1-ol/acetic acid/water (4 : 1 : 2), unless otherwise indicated. Amino acid products were analysed by gas–liquid chromatography of *N*-trifluoroacetyl methyl ester derivatives as reported previously.[9] Retention times at 150° were: compound (4) 3 min 20 s and (5) 2 min 28 s. Mass spectral data refer to chemical ionization with methane as reagent gas in a Finnigan 2300E mass spectrometer. Ether refers to diethyl ether.

Methyl 4-Tosyloxytetrahydrofuran-2-carboxylates (*8*) *and* (*9*)

trans-4-Hydroxytetrahydrofuran-2-carboxylic acid (7)[4,6] (0·80 g, 6·1 mmol) was dissolved in methanol and converted into the methyl ester with diazomethane. The solvent was removed and the crude ester was stirred in dry pyridine (3·5 ml), and tosyl chloride (1·73 g, 9·1 mmol) was added portionwise with ice cooling. After 16 h at 4°, the reaction mixture was poured into ice-water and extracted with ether (3 × 40 ml). The organic layer was washed with 1 M HCl, 5% $NaHCO_3$, dried and evaporated without heating to yield a yellow oil which crystallized from hexane with dry ice/acetone cooling (1·4 g, 85%). Recrystallization from chloroform/hexane gave an analytical sample of the *trans*-tosylate (9), m.p. 55–56° (Found: C, 51·65; H, 5·3. $C_{13}H_{16}O_6S$ requires C, 52·0; H, 5·4%). ^{1}H n.m.r. δ ($CDCl_3$) 7·9, 2H, d, *J* 8·5 Hz, ArH; 7·45, 2H, d, *J* 8·5 Hz, ArH; 5·23, 1H, m, H4; 4·67, 1H, t, *J* 8 Hz, H2; 4·05, 2H, m, H5; 3·77, s, 3H, OCH_3; 2·48, s, 3H, $ArCH_3$; 2·75–2·0, 2H, m, H3. ν_{max} 1730, 1360, 1175 cm^{-1}.

The *cis*-hydroxy acid (6) was similarly converted into the *cis*-tosylate (8) (70%), m.p. 56–56·5° (Found: C, 51·9; H, 5·6. $C_{13}H_{16}O_6S$ requires C, 52·0; H, 5·4%). ^{1}H n.m.r. δ ($CDCl_3$) 7·93, 2H, d, *J* 9 Hz, ArH; 7·46, 2H, d, *J* 9 Hz, ArH; 5·1, 1H, m, H4; 4·45, 1H, t, *J* 6·5 Hz, H2; 3·96, 2H, m, H5; 3·64, s, 3H, OCH_3; 2·35, s, 3H, $ArCH_3$; 2·45–2·26, 2H, m, H3. ν_{max} 1740, 1352, 1168 cm^{-1}.

Methyl 4-Azidotetrahydrofuran-2-carboxylates

Sodium azide (0·70 g, 10·7 mmol) in water (6 ml) was heated at reflux with a solution of the *trans*-tosylate (9) (1·6 g, 5·3 mmol) in ethanol (18 ml) for 16 h. After ethanol was removed under reduced pressure, water was added and the product extracted with ether. Washing with water, drying and solvent removal gave the crude cis-*azido methyl ester* in about 75% yield as an oil containing some ethyl ester by n.m.r. spectroscopy. ν_{max} 2090, 1725 cm^{-1}.

The *cis*-tosylate (8) similarly gave the crude trans-*azido methyl ester* in about 70% yield. ν_{max} 2090, 1730 cm^{-1}.

trans- *and* cis-*4-Aminotetrahydrofuran-2-carboxylic Acids* (*4*) *and* (*5*)

The crude *trans*-azido ester (1·13 g) in methanol (16 ml) and 1 M HCl (4 ml) was hydrogenated in the presence of 10% palladium on charcoal (70 mg) at room temperature and atmospheric pressure for 3 h. After filtration, the methanol was removed under vacuum and the residue was refluxed for 30 min in 0·5 M HCl (20 ml). The product was concentrated under reduced pressure, absorbed on a column of Dowex 50(H^+) ion-exchange resin (20 ml), and the amino acid eluted with 1 M pyridine. Evaporation and crystallization from aqueous ethanol gave a product which contained less than 1% of the corresponding *cis*-amino acid by g.l.c. as impurity in the trans-*amino acid* (4) (0·46 g, 53%), m.p. 278–280° (dec.) (Found: C, 45·6; H, 7·2; N, 10·6. $C_5H_9NO_3$ requires C, 45·8; H, 6·9; N, 10·7%). ^{1}H n.m.r. δ (D_2O, external tetramethylsilane) 5·13, 1H, t, *J* 8 Hz, H2; 4·9–4·2, 3H, m, H4 and H5; 3·2–2·8, 2H, m, H3. ν_{max} 2170, 1600, 1560 cm^{-1}. Mass spectrum: *m/e* 132 (MH^+, 100%), 115 (13), 87 (21), 86 (95), 69 (10). R_F 0·17.

A similar procedure converted the *cis*-azido ester (0·70 g) into the cis-*amino acid* (5) with less than 1% of the other isomer by g.l.c. (0·34 g, 63%), m.p. 266–268° (dec.) (Found: C, 45·6; H, 6·9; N, 10·6. $C_5H_9NO_3$ requires C, 45·8; H, 6·9; N, 10·7%). ^{1}H n.m.r. δ (D_2O, external tetramethylsilane) 4·93, 1H, dd, *J* 6, 9 Hz, H2; 4·7–4·4, 3H, m, H4 and H5; 3·65–2·9, 1H,

[8] Allan, R. D., and Fong, J., *Aust. J. Chem.*, 1983, **36**, 601.
[9] Allan, R. D., Johnston, G. A. R., and Twitchin, B., *Aust. J. Chem.*, 1979, **32**, 2517.

m, H3; 2·8–2·3, 1H, m, H3. ν_{max} 2175, 1630, 1575 cm^{-1}. Mass spectrum: *m/e* 132 (MH^+, 76%), 115 (2), 87 (8), 86 (100), 69 (2). R_F 0·17.

cis-*4*-(N-*Tosylamino*)*tetrahydrofuran-2-carboxylic Acid* (*10*)

Tosyl chloride (480 mg, 2·5 mmol) in ether (1·5 ml) was added to a solution of the *cis*-amino acid (5) (100 mg, 0·76 mmol) in 1 M NaOH (5·5 ml), and the mixture was stirred at room temperature for 16 h. After excess tosyl chloride was extracted with chloroform, the aqueous layer was acidified with conc. HCl and extracted with ethyl acetate. Washing with water, drying and solvent removal gave an oil which crystallized from chloroform/hexane yielding the cis-N-*tosyl acid* (10) (180 mg, 83%), m.p. 122–125° (Found: C, 50·4; H, 5·5; N, 4·8. $C_{12}H_{15}NO_5S$ requires C, 50·5; H, 5·3; N, 4·9%). ^1H n.m.r. δ ($CDCl_3$) 8·5, s, COOH; 7·86, 2H, d, *J* 8·5 Hz, ArH; 7·43, 2H, d, *J* 8·5 Hz, ArH; 6·0, 1H, bd, *J* 6 Hz, NH; 4·55, 1H, dd, *J* 4·5, 9 Hz, H2; 3·93, 3H, m, H4 and H5; 2·47, s, $ArCH_3$; 2·4–2·0, 2H, m, H3. ν_{max} 3210, 1750, 1320, 1150 cm^{-1}. Mass spectrum: *m/e* 286 (MH^+, 100%), 268 (2), 240 (60), 172 (56).

A similar procedure on the *trans*-amino acid (124 mg) gave the trans-N-*tosyl acid* (230 mg, 85%), m.p. 130–132° (Found: C, 50·2; H, 5·3; N, 4·9. $C_{12}H_{15}NO_5S$ requires C, 50·5; H, 5·3; N, 4·9%). ^1H n.m.r. δ ($CDCl_3$, CD_3SOCD_3) 8·3, s, COOH; 7·86, 2H, d, *J* 8·5 Hz, ArH; 7·4, 2H, d, *J* 8·5 Hz, ArH; 6·2, 1H, bd, *J* 6 Hz, NH; 4·56, 1H, t, *J* 7 Hz, H2; 4·2–3·54, 3H, m, H4 and H5; 2·45, s, $ArCH_3$; 2·33–2·0, 2H, m, H3. ν_{max} 3240, 1730, 1330, 1160 cm^{-1}. Mass spectrum: *m/e* 286 (MH^+, 100%), 240 (9), 172 (7).

Cyclization of the cis-N-*Tosyl Acid* (*10*)

The *cis-N*-tosyl acid (10) (100 mg) was refluxed in acetic anhydride (5 ml) for 45 h. After solvent removal under vacuum, the solid residue was taken up in ethyl acetate, washed with 10% sodium carbonate and dried (Na_2SO_4). Evaporation of the solvent gave a solid (80 mg, 85%) which was almost pure by n.m.r. spectroscopy. Recrystallization from ether yielded N-*tosyl-2-oxa-5-azabicyclo*[*2.2.1*][*heptan-6-one* (11) (40 mg, 42%), m.p. 127–128° (Found: C, 53·9; H, 4·7; N, 5·0. $C_{12}H_{13}NO_4S$ requires C, 53·9; H, 4·9; N, 5·2%). ^1H n.m.r. δ ($CDCl_3$) 8·05, 2H, d, *J* 8·5 Hz, ArH; 7·43, 2H, d, *J* 8·5 Hz, ArH; 5·7, 1H, m, H1; 4·51, 1H, m, H4; 3·9, 1H, d, *J* 8 Hz, H3; 3·63, 1H, d, *J* 8 Hz, H3; 2·47, s, $ArCH_3$; 2·05, 2H, m, H7. ν_{max} 1760, 1360, 1175 cm^{-1}. Mass spectrum: *m/e* 268 (MH^+, 100%), 240 (2), 112 (15). R_F (chloroform/acetone 5 : 2) 0·80.

Under the same cyclization conditions, the corresponding *trans-N*-tosyl acid gave only trace amounts of the bicyclic compound (11) as detected by t.l.c.

Ring Opening of the Bicyclic Lactam (*11*)

The bicyclic lactam (11) (40 mg) was heated in 1 M NaOH (10 ml) at 70° for 1 h. Normal extractive workup after acidification gave an oil (26 mg, 62%). Two recrystallizations from chloroform/hexane yielded a solid product (10 mg, 23%) which was identical (m.p., i.r., n.m.r., t.l.c.) with a sample of the *cis-N*-tosyl acid (10) prepared as above.

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