Synthesis of Analogues of γ-Aminobutyric Acid. Part 11.[1] Unsaturated and Saturated Tetronic Acid [Furan-2,4(3*H*,5*H*)-dione] Derivatives

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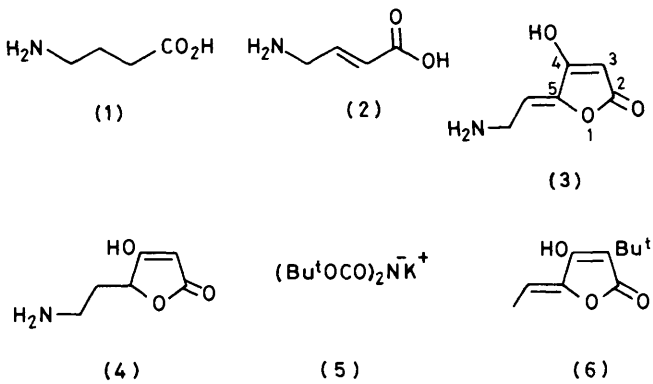
5-(2-Aminoethylidene)-4-hydroxyfuran-2(5*H*)-one (3) and the corresponding reduced 5-(2-aminoethyl) derivative (4) have been synthesised as conformationally restricted analogues of the neurotransmitter GABA. The use of the t-butyl protected reagents bis(t-butoxycarbonyl)amine and 5-ethylidene-4-t-butoxyfuran-2(5*H*)-one (7b) allowed generation of the required amino compounds under mild acidic deprotection conditions in the final step.

γ-Aminobutyric acid (GABA) (1) is believed to be the major inhibitory neurotransmitter within the mammalian central nervous system and pharmacological intervention in the GABA system is the goal of many medicinal chemistry investigations.[2] Neurotransmitter analogues of restricted conformation can provide considerable information on particular ' active conformations ' of the neurotransmitter which are involved in various processes such as receptor activation, cellular uptake, or enzymic transamination.[3,4] On examining the structures of active GABA analogues it is apparent that particular functionalities as well as molecular shape are consistent with high activity on GABA systems.[5] Among these ' active ' functional groups are carbon–carbon double bonds [as in *trans*-4-aminocrotonic acid (2)],[6] hydroxy substituents at C-2 or -3,[5] and oxygen-containing heterocyclic rings (as in muscimol [7] and kojic amine [8]). These considerations, taken with the perplexing question of whether both or only one of the carboxylate oxygens of (2) are of major importance for receptor activation, lead to the suggestion that derivatives such as (3) and (4) may be important GABA analogues.



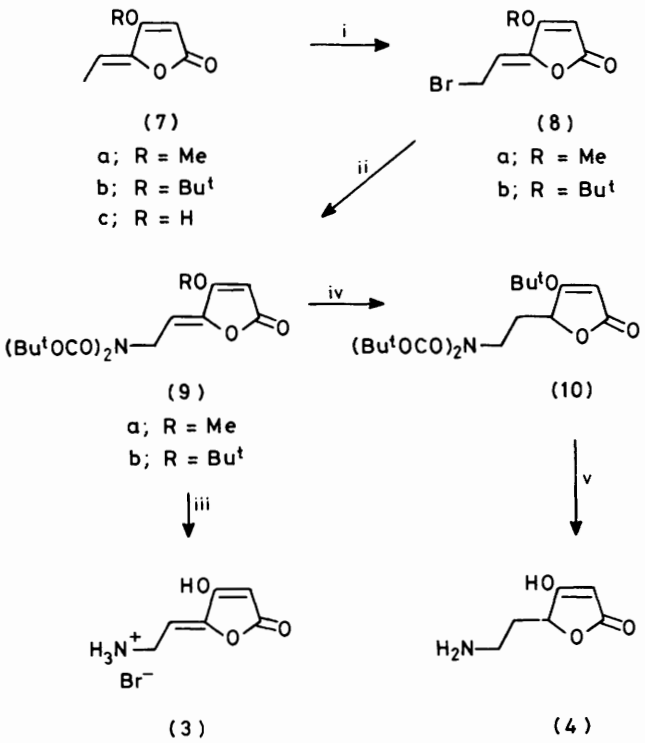
Tetronic acids [furan-2,4(3*H*,5*H*)-diones],[9,10] although present in natural products [11] and of comparable acidity to carboxylic acids,[9] appear not to have been exploited as bioisosteric replacements for carboxylic acids in drug molecules. This paper reports the synthesis of (3) as a GABA analogue with the carbons of the GABA backbone constrained to be coplanar, as well as that of the considerably more flexible saturated derivative (4).

In a previous synthesis of GABA analogues containing allylic amino groups we have demonstrated the expedience and generality of the route involving allylic bromination of unsaturated acids and esters with *N*-bromosuccinimide (NBS) followed by displacement with nitrogen nucleophiles such as ammonia, azide, and phthalimide.[12] Earlier work on the synthesis of penicillic acid by Raphael [13] showed that a tetronic acid methyl ether related to (7a) underwent the required allylic bromination on the side chain and that the bromine was readily displaced with triethylamine.

Initial experiments were performed on the readily obtained unsaturated tetronic acid (7c). NBS reacted readily but the first two equivalents gave bromination at the unsubstituted carbon in the heterocyclic ring and no allylic substitution could be induced on the ethylidene group of the resultant dibromoketolactone. However the methyl ether (7a) readily gave the required compound (8a) as shown in the Scheme.

The retention of the (*Z*) stereochemistry as depicted in (7) [14] in the proposed structures of (8), (9), and (3) is supported by ^{1}H n.m.r. spectroscopy whereby the proton, 3-H, in (7), (8), and (9) appears as a sharp singlet showing no long range coupling greater than 0.4 Hz. The 4-methoxymethylamino analogue of (7) has been reported to show a long range coupling of 1 Hz between the two olefinic protons in the (*E*)-isomer only.[15] Furthermore the methyl ether (7a) was unchanged on refluxing with catalytic quantities of NBS, indicating that the configuration is thermodynamically more stable. These reaction conditions rapidly isomerise thermodynamically less stable but-2-enoic acid derivatives to equilibrium (*E*)–(*Z*) mixtures.[16] Reaction of the bromo tetronic acid ether (8a) with ammonia gave no isolable product. This is consistent with a high susceptibility to ring opening of the tetronic acid ether under basic conditions. A modified Gabriel reagent that could be readily deprotected to give a primary amino group under mild acid conditions was therefore required. The potassium salt (5) of the rarely exploited bis(t-butoxycarbonyl)amine [17,18] fitted these requirements extremely well. Although the salt prepared in the same manner as potassium phthalimide could not be obtained with well defined stoicheiometry, it could be used as a stable crystalline material which reacted with the allylic bromide (8a) in *N*-methylpyrrolidine at 50 °C to give the protected amine (9a).

Despite the fact that the methyl protecting group of (7a) was cleanly removed by treatment with concentrated aqueous HBr [19] for 24 h at room temperature, (3) could not be isolated by similar treatment of the diprotected amino tetronic acid (9a). Similarly trimethylsilyl iodide deprotected compound (7a) but failed with (9a), and thiolate deprotection could not be controlled to give demethylation without concurrent addition to the product. The problem was overcome by the use of the t-butyl protecting group on the tetronic acid. The tetronic acid t-butyl ether (7b) was generated from (7c) and isobutene at room temperature by sulphuric acid catalysed esterification, albeit in low yield but in reasonable conversion. These conditions have not been optimised but it was found



Scheme. *Reagents:* i, NBS; ii, $(Bu^tOCO)_2N^-K^+$; iii, HBr–AcOH; iv, H_2,Pd–C; v, HBr–AcOH, then ion exchange resin

that higher temperatures (40 °C) or the use of the BF_3–H_3PO_4 complex [20] resulted in the isolation of the *C*-substituted t-butyl derivative (6).

As shown in the Scheme the sequence (7b) ⟶ (8b) ⟶ (9b) ⟶ (3) successfully generated the crystalline hydrobromide of (3), the last step being carried out under the mild conditions of HBr–acetic acid at room temperature. Catalytic hydrogenation of (9b) followed by deprotection gave the reduced compound (4) which could not be obtained crystalline either from its hygroscopic salts or its neutral form.

Experimental

M.p.s were measured on a Reichert hot-stage apparatus, and are uncorrected. Microanalyses were determined by the Australian Microanalytical Service, Melbourne. U.v. spectra were recorded on a Perkin-Elmer 124 spectrophotometer and i.r. spectra from Nujol mulls on a Perkin-Elmer 177 spectrophotometer. ^1H and ^{13}C N.m.r. spectra were recorded on a JEOL FX-90Q spectrometer unless otherwise indicated, in $CDCl_3$ with $SiMe_4$ as internal standard. Mass spectral data refer to chemical ionisation using methane as reagent gas on a Finnigan 2300E mass spectrometer. Ether refers to diethyl ether.

4-t-Butoxy-5-ethylidenefuran-2(5H)-one (7b).—5-Ethylidene-4-hydroxyfuran-2(5*H*)-one (7c) [21] (3.0 g) in t-butyl alcohol (10 ml) and dichloromethane (90 ml) was stirred with ice-cooling in a 250-ml pressure bottle. Liquid isobutene (27 ml) and concentrated sulphuric acid (2 ml) were added and the vessel sealed with a rubber bung secured with wire. After being stirred at room temperature (20—30 °C) for 3 days, the solution was cooled on ice and poured into water (6 ml). The dichloromethane layer was washed with aqueous sodium carbonate, dried and evaporated to dryness yielding a crude crystalline product (1.38 g, 32%). Recrystallisation from hexane gave the *t-butyl ether* (7b) (23%), m.p. 97—98 °C (Found: C, 65.7; H, 7.5. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.7%); $\lambda_{max.}$ (EtOH) 259 nm (log ε 4.24); $\nu_{max.}$ 3 120 (CH), 1 750, 1 695, and 1 600 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 5.48 (q, *J* 7.4 Hz, =C*H*CH_3), 5.18 (br s, 3-H), 1.88 (d, *J* 7.5 Hz, =CHCH_3), and 1.50 (s, CMe_3); δ_C (22.5 MHz; $CDCl_3$) 169.7, 164.7, 146.3, 104.9, 90.5, 83.3, 27.5, and 11.1 p.p.m.; *m/z* 183 (MH^+, 3%) and 127 ($MH^+ - C_4H_8$, 100).

Acidification and extraction with ethyl acetate of the combined aqueous sodium carbonate washings led to recovery of the starting hydroxyfuranone (7c) (1.95 g, 65%), identified by its n.m.r. spectrum.

5-Ethylidene-4-hydroxy-3-t-butylfuran-2(5H)-one (6).—5-Ethylidene-4-hydroxyfuran-2(5*H*)-one (7c) (2.0 g) was treated in the same way as described above except that the mixture was heated in water at 40 °C for 1 h and was then left at room temperature for 16 h. The major product was separated by acidification and extraction of the aqueous sodium carbonate washings which gave the crude *3-t-butylfuranone* (6) (2.2 g, 76%), m.p. 149—150 °C (from aqueous EtOH) (Found: C, 65.8; H, 7.6. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.7%); $\lambda_{max.}$ (EtOH) 313 (log ε 3.97) and 249 nm (4.12); $\lambda_{max.}$ (HCl) 269 nm (log ε 4.17); $\nu_{max.}$ 3 250 (OH), 1 720, and 1 630 cm^{-1}; δ_H [$CDCl_3$, 2 drops $(CD_3)_2SO$] 5.69 (q, *J* 7.5 Hz, =C*H*CH_3), 1.87 (d, *J* 7.5 Hz, =CHCH_3), and 1.35 (s, CMe_3); δ_C [$CDCl_3$, 2 drops $(CD_3)_2SO$] 169.8, 160.6, 144.4, 110.2, 103.8, 31.4, 29.0, and 11.1 p.p.m.; *m/z* 183 (MH^+, 100%) and 127 ($MH^+ - C_4H_8$, 75).

5-(2-Bromoethylidene)-4-t-butoxyfuran-2(5H)-one (8b).—A solution of the t-butyl ether (7b) (2.0 g, 11 mmol) and *N*-bromosuccinimide (2.35 g, 13.2 mmol) in carbon tetrachloride (60 ml) was refluxed under a tungsten iodide floodlight (800 W) for 13 h. The solution was cooled, filtered, washed with water, dried and evaporated to dryness to give the crude solid bromo derivative (8b) (3.0 g) which was used in the next step without purification. Chromatography on silica gel with light petroleum–benzene gave the pure *bromo t-butyl ether* (8b) (31%), m.p. 105—106 °C (from light petroleum–benzene) (Found: C, 45.8; H, 4.8. $C_{10}H_{13}BrO_3$ requires C, 46.0; H, 5.0%); $\lambda_{max.}$ (EtOH) 267 nm (log ε 4.28); $\nu_{max.}$ 3 120 (CH), 1 770, and 1 600 cm^{-1}; δ_H ($CDCl_3$) 5.66 (br t, *J* 9 Hz, =C*H*CH_2-Br), 5.26 (s, 3-H), 4.20 (d, *J* 9 Hz, =CHCH_2Br), and 1.51 (s, CMe_3); δ_C ($CDCl_3$) 168.1, 164.4, 147.6, 103.7, 91.8, 84.1, 27.4, and 23.6; *m/z* 263, 261 (MH^+, 1%) 207, 205 ($MH^+ - C_4H_8$, 80), and 125 ($MH^+ - C_4H_8$ – HBr, 100).

A similar procedure on the methoxy compound (7a) [14] gave the bromo methyl ether (8a) (44%), m.p. 132—133 °C, δ_H (60 MHz; $CDCl_3$) 5.73 (t, *J* 8 Hz, =C*H*CH_2Br), 5.35 (s, 3-H), 4.2 (d, *J* 8 Hz, =CHCH_2Br), and 3.96 (s, OMe).

Crude Potassium Bis(t-butoxycarbonyl)aminide (5).—A solution of potassium hydroxide (2.4 g) in ethanol (10 ml) was added to bis(t-butoxycarbonyl)amine (9 g) in ethanol (10 ml) with stirring. Addition of ether (40 ml) gave a crystalline product which was filtered and washed with ether. The vacuum dried salt (7 g) was used without further purification.

Reaction of the Bromo t-Butyl Ether (8b) *with Potassium Bis(t-butoxycarbonyl)aminide* (5).—Potassium bis(t-butoxycarbonyl)aminide (3.5 g, 13.7 mmol) was added in portions to an ice-cold solution of the crude bromo t-butyl ether (8b) (3.1 g, 11.9 mmol) in dry *N*-methylpyrrolidone (8 ml) and then stirred at 50 °C for 3.5 h. After cooling and dilution with water, the product was extracted into ethyl acetate, washed thoroughly with water, dried, and evaporated to give a solid residue (7.2 g). Chromatography on basic

alumina with light petroleum–dichloromethane gave a crude product (4.3 g) suitable for deprotection followed by work-up on ion exchange resin. The contaminant bis(t-butoxycarbonyl)-amine could be removed by repeated crystallisation to give the pure 5-[2-*bis*(*t-butoxycarbonyl*)*aminoethylidene*]-4-*t-butoxy-furan*-2(5H)-*one* (9b) (0.74 g, 16%), m.p. 160—161 °C (Found: C, 60.4; H, 7.75; N, 3.3. $C_{20}H_{31}NO_7$ requires C, 60.4; H, 7.85; N, 3.5%); $\lambda_{max.}$ (EtOH) 259 nm (log ε 4.26); $\nu_{max.}$ 3 120 (CH), 1 770, 1 730, 1 700, and 1 600 cm^{-1}; δ_H($CDCl_3$) 5.4 (t, *J* 6.8 Hz, =C*H*CH_2N); 5.2 (br s, 3-H), 4.5 (d, *J* 6.8 Hz, =CHCH_2N), and 1.5 (27 H, s, CMe_3); δ_C ($CDCl_3$) 168.9, 164.7, 152.1, 146.0, 105.0, 91.0, 83.6, 82.8, 42.1, 28.0, and 27.4 p.p.m.; *m/z* 298 ($MH^+ - CO_2C_4H_8$, 6%), 242 (298 − C_4H_8, 100), and 186 (242 − C_4H_8, 28).

A similar procedure gave the *N*-protected methyl ether (9a) (71%), m.p. 83—85 °C; δ_H (60 MHz; $CDCl_3$) 5.45 (t, *J* 6.5 Hz, =C*H*CH_2N), 5.23 (s, 3-H), 4.47 (d, *J* 6.5 Hz, =CHCH_2N), 3.9 (s, OMe), and 1.5 (18 H, s, CMe_3).

Reduction of the N-*Protected Ether* (9b).—The *N*-protected ether (9b) (200 mg, 0.5 mmol) in ethyl acetate (10 ml) was hydrogenated at atmospheric pressure over 10% palladium-on-carbon (27 mg) for 30 min. Filtration, evaporation of the solvent, and crystallisation from light petroleum–ethyl acetate yielded 5-[2-*bis*(*t-butoxycarbonyl*)*aminoethyl*]-4-*t-butoxyfuran*-2(5H)-*one* (10) (176 mg, 87%), m.p. 154—156 °C (Found: C, 60.2; H, 8.3; N, 3.3. $C_{20}H_{33}NO_7$ requires C, 60.1; H, 8.3; N, 3.5%); $\lambda_{max.}$ (EtOH) 223 nm (log ε 4.13); $\nu_{max.}$ 3 116 (CH), 1 750, 1 730, 1 690, and 1 620 cm^{-1}; δ_H ($CDCl_3$) 5.1 (s, 3-H), 4.66 (dd, *J* 8.5, 3.5 Hz, 5-H), 3.75 (t, *J* 7 Hz, CH_2N), 2.3—1.7 (m, CH_2CH_2N), 1.51 (s, 2 × CMe_3), and 1.48 (s, CMe_3); δ_C ($CDCl_3$) 176.8, 173.3, 152.3, 90.1, 83.9, 82.6, 78.2, 42.6, 31.9, 28.1, and 27.4 p.p.m.; *m/z* 300 ($MH^+ - CO_2C_4H_8$, 10%), 244 (300 − C_4H_8, 14), and 188 (244 − C_4H_8, 100).

5-(2-*Aminoethylidene*)-4-*hydroxyfuran*-2(5H)-*one Hydrobromide* (3).—The crude *N*-protected ether (9b) (2.53 g) was dissolved in 45% w/v hydrogen bromide in acetic acid (14 ml) for 15 min at room temperature. This solvent was removed under reduced pressure and the product dissolved in water (7 ml), washed with ethyl acetate and absorbed on a column of Dowex 50 (H^+) ion exchange resin (25 ml). Elution with 1M-pyridine gave an oily product (0.5 g, 55%) after evaporation. Addition of hydrogen bromide in acetic acid (0.4 ml) yielded the crystalline *unsaturated hydrobromide* (3) (0.21 g, 15%), m.p. 184—186 °C (decomp.) (Found: C, 32.4; H, 3.7; N, 6.5. $C_6H_8BrNO_3$ requires C, 32.45; H, 3.6; N, 6.3%); $\lambda_{max.}$ (EtOH) 306 (log ε 3.87) and 241 nm (log ε 4.10), $\lambda_{max.}$ (HCl) 251 (log ε 4.15); $\nu_{max.}$ 3 110 (CH), 1 735, 1 690, 1 620, and 1 580 cm^{-1}; δ_H (D_2O; external Me_4Si) 6.15 (t, *J* 7 Hz, =C*H*CH_2-N), and 4.39 (d, *J* 7 Hz, =CHCH_2N) (the 3-H exchanges immediately); δ_C (D_2O–H_2O, 6 : 1; external Me_4Si) 173.5 (s, C-2 or -4), 170.7 (s, C-4 or -2), 149.4 (s, C-5), 101.1 (d, =C*H*CH_2NH_2), 91.4 (d, C-3), and 36.1 p.p.m. (t, =C*H*CH_2-NH_2); *m/z* 142 (MH^+, 50%) and 125 ($MH^+ - NH_3$, 100).

5-(2-*Aminoethyl*)-4-*hydroxyfuran*-2(5H)-*one* (4).—The saturated *N*-protected ether (9b) (140 mg) was deprotected as above except that the 1M-pyridine eluant from the ion exchange resin was freeze dried to give the *saturated* 4-*hydroxyfuranone* (4) as a hygroscopic amorphous powder (35 mg, 69%) (Found: M^+, 143.057. $C_6H_9NO_3$ requires *M*, 143.058); $\lambda_{max.}$ (EtOH) 249 nm (log ε 4.16); $\lambda_{max.}$ (HCl) 223 cm^{-1} (log ε 3.98); $\nu_{max.}$ 1 670 (br) and 1 550 (br) cm^{-1}; δ_H (D_2O, external Me_4Si) 5.06 (dd, *J* 7 Hz, 4 Hz, 5-H), 3.55 (t, *J* 7 Hz, CH_2N), and 2.9—2.0 (m, CH_2CH_2N) (the 3-H exchanges immediately); δ_C (D_2O–H_2O, 10 : 1) 196.4 (s, C-2 or -4), 183.6 (s, C-4 or -2), 82.8 (d, C-3), 81.3 (d, C-5), 37.5 (t, $CH_2CH_2NH_2$), and 30.2 (t, $CH_2CH_2NH_2$); *m/z* 144 (MH^+, 77%), 126 ($MH^+ - H_2O$), and 102 (base peak).

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References

1 Part 10, R. D. Allan and J. Fong, *Aust. J. Chem.*, 1983, **36**, 1221.
2 P. Krogsgaard-Larsen, *J. Med. Chem.*, 1981, **24**, 1377.
3 G. A. R. Johnston, R. D. Allan, S. M. E. Kennedy, and B. Twitchin, in ' GABA-Neurotransmitters,' ed. P. Krogsgaard-Larsen, J. Scheel-Kruger, and H. Kofod, Munksgaard, Copenhagen, 1978, p. 149.
4 P. Krogsgaard-Larsen and E. Falch, *Mol. Cell. Biochem.*, 1981, **38**, 129.
5 R. D. Allan and G. A. R. Johnston, *Med. Res. Rev.*, 1983, **3**, 91, and refs. cited therein.
6 G. A. R. Johnston, D. R. Curtis, P. M. Beart, C. J. A. Game, R. M. McCulloch, and B. Twitchin, *J. Neurochem.*, 1975, **24**, 157.
7 P. Krogsgaard-Larsen, L. Brehm, and K. Schaumburg, *Acta Chem. Scand., Ser. B*, 1981, **35**, 311.
8 J. G. Atkinson, Y. Girard, J. Rokach, and C. S. Rooney, *J. Med. Chem.*, 1979, **22**, 99.
9 L. J. Hayes and J. R. Plimmer, *Q. Rev.*, 1960, **14**, 292.
10 Y. S. Rao, *Chem. Rev.*, 1976, **76**, 625.
11 G. Pattenden, *Fortsch. Chem. Org. Naturst.*, 1978, **35**, 133.
12 R. D. Allan and B. Twitchin, *Aust. J. Chem.*, 1978, **31**, 2283; R. D. Allan, *Aust. J. Chem.*, 1979, **32**, 2507; R. D. Allan, G. A. R. Johnston, and B. Twitchin, *Aust. J. Chem.*, 1981, **34**, 2231.
13 R. A. Raphael, *J. Chem. Soc.*, 1948, 1508.
14 N. G. Clemo and G. Pattenden, *Tetrahedron Lett.*, 1982, **23**, 581.
15 G. Jones and J. R. Phipps, *J. Chem. Soc., Perkin Trans. 1*, 1975, 458.
16 R. D. Allan, G. A. R. Johnston, and B. Twitchin, *Aust. J. Chem.*, 1980, **33**, 1115.
17 L. A. Carpino, *J. Org. Chem.*, 1964, **29**, 2820.
18 C. T. Clarke, J. D. Elliot, and J. H. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1088.
19 T. Yamada, H. Hagiwara, and H. Uda, *J. Chem. Soc., Chem. Commun.*, 1980, 838.
20 H. C. Beyerman and G. J. Heiszwolf, *Recl. Trav. Chim. Pays-Bas*, 1965, **84**, 203.
21 T. P. C. Mulholland, R. Foster, and D. B. Haydock, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1225.

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