Aust. J. Chem., 1985, **38**, 1647–50

Synthesis of Analogues of GABA. XIII*
An Alternative Route to (*Z*)-4-Aminocrotonic Acid

Robin D. Allan, Graham A. R. Johnston and Rymantas Kazlauskas

Department of Pharmacology, University of Sydney, N.S.W. 2006.

Abstract

(*Z*)-4-Aminocrotonic acid can be conveniently prepared via crystalline phthalimido protected intermediates.

(*Z*)-4-Aminocrotonic acid [(*Z*)-4-aminobut-2-enoic acid, (1) in Scheme 1] and the more readily available (*E*) isomer have previously been synthesized as conformationally restricted analogues of the neurotransmitter GABA (γ-aminobutyric acid).[1] In conventional assays of GABA-mimetic activity, the (*E*) isomer and GABA are more potent than (*Z*)-4-aminocrotonic acid at receptors at which the alkaloid bicuculline acts as an antagonist,[1–3] while the (*Z*) isomer has some bicuculline-insensitive depressant activity.[1] Not all GABA receptors are sensitive to bicuculline,[4] and $GABA_B$ receptors have been defined as bicuculline-insensitive receptors activated by the agonist baclofen.[5] Recently (*Z*)-4-aminocrotonic acid has been investigated as a selective agonist for a new class of bicuculline-insensitive GABA receptors.[6]

For this reason it was important to have a ready supply of (1) in which contamination by the thermodynamically more stable (*E*) isomer was minimal. In the original synthesis, (1) was prepared from 4-aminotetrolic acid which is difficult to purify,

* Part XII, *Aust. J. Chem.*, 1984, **37**, 1123.

[1] Johnston, G. A. R., Curtis, D. R., Beart, P. M., Game, C. J. A., McCulloch, R. M., and Twitchin, B., *J. Neurochem.*, 1975, **24**, 157.

[2] Allan, R. D., Curtis, D. R., Headly, P. M., Johnston, G. A. R., Lodge, D., and Twitchin, B., *J. Neurochem.*, 1980, **34**, 652.

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

[4] Johnston, G. A. R., in 'GABA in Nervous System Function' (Eds E. Roberts, T. N. Chase and D. B. Tower) p. 394 (Raven Press: New York 1976); Johnston, G. A. R., in 'Receptors in Pharmacology' (Eds J. R. Smythies and R. J. Bradley) p. 295 (Dekker: New York 1978).

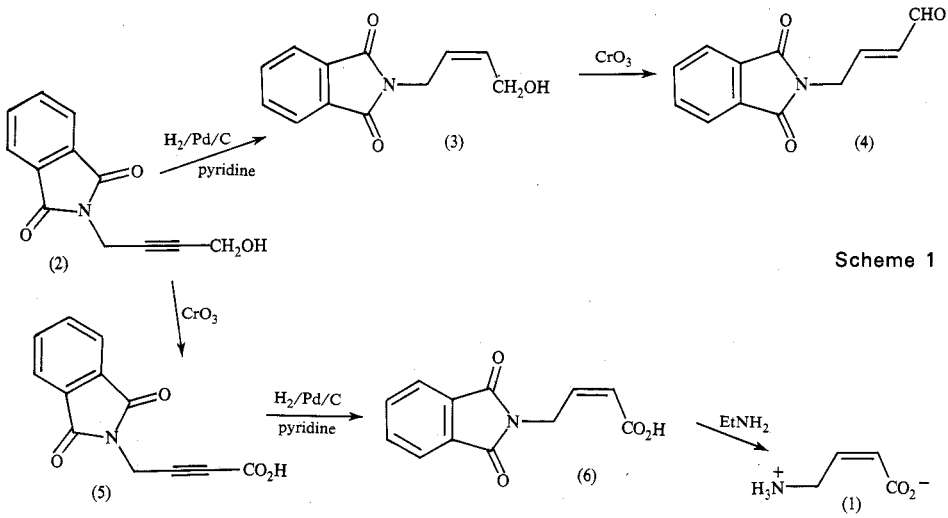
[5] Bowery, N. G., Hill, D. R., Hudson, A. L., Doble, A., Midlemiss, D. N., Shaw, J., and Turnbull, M. J., *Nature (London)*, 1980, **283**, 92; Bowery, N. G., Hill, D. R., and Hudson, A. L., *Br. J. Pharmacol.*, 1983, **78**, 191.

[6] Johnston, G. A. R., and Allan, R. D., *Neuropharmacology*, 1984, **23**, 831; Johnston, G. A. R., Allan, R. D., Benton, A. D., Chen Chow, S., Drew, C. A., Hiern, B. P., Holan, G., Kazlauskas, R., Rzeznicczak, H., and Weatherby, R. P., *Proc. 9th Int. Congr. Pharmacol.*, 1984, **3**, 179; Drew, C. A., Johnston, G. A. R., and Weatherby, R. P., *Neurosci. Lett.*, 1984, **52**, 317.

0004-9425/85/111647$02.00

and was isolated by ion-exchange chromatography of an amino acid mixture.[1] We report here an alternative synthesis of (1) via its crystalline phthalimido protected derivative, which can be purified and deprotected under mild conditions that do not lead to isomerization. This synthesis should also permit convenient preparation of (1) labelled with tritium to high specific activity for ligand binding studies.

The phthaloyl-protected acetylenic amino alcohol (2), prepared from 4-chlorobut-2-yn-1-ol,[7] was easily hydrogenated with no overreduction, in pyridine in the presence of palladium/charcoal catalyst, to the (*Z*) alcohol (3). However, subsequent oxidation with Jones reagent resulted in complete isomerization of the double bond. Attempts to control the isomerization at 0° gave the (*E*) aldehyde (4); this indicated a facile addition–elimination type isomerization of the (*Z*) aldehyde.



Scheme 1

Oxidation of the acetylenic alcohol (2) to the acid (5) before catalytic reduction overcame this problem. Hydrogenation of this intermediate (5) in pyridine could be controlled by careful monitoring of hydrogen uptake. Recrystallization of the product gave the required phthaloyl-protected (*Z*) isomer (6) containing no (*E*) isomer. Deprotection of (6) was achieved with ethanolic ethylamine to afford the desired (*Z*)-4-aminocrotonic acid (1) with less than 0·5% of the (*E*) isomer as determined by t.l.c. and 90-MHz Fourier-transform n.m.r. spectroscopy.

Experimental

General experimental conditions are as reported previously.[8] 60-MHz n.m.r. spectra were run on a Varian EM360A spectrometer and 90-MHz n.m.r. spectra were obtained on a Jeol FX90Q instrument. Mass spectral data refer to chemical ionization with methane as the reagent gas in a Finnigan 2300E mass spectrometer.

[7] Allan, R. D., Johnston, G. A. R., and Twitchin, B., *Aust. J. Chem.*, 1980, **33**, 1115.
[8] Allan, R. D., and Fong, J., *Aust. J. Chem.*, 1983, **36**, 601.

*(Z)-4-Phthalimidobut-2-en-1-ol (3)**

4-Phthalimidobut-2-yn-1-ol (2)[7] (5 g) in pyridine (40 ml) was hydrogenated over 5% palladium/charcoal catalyst (100 mg) for 24 h. The mixture was filtered through Celite, and the filtrate was evaporated to give the *alcohol* (3) as an oil which solidified below 0° and which was used directly in the next step without further purification. ^{1}H n.m.r. δ ($CDCl_3$) 7·90, 4H, m, ArH; 6·00, 1H, dt, *J* 11, 6 Hz, CH_2CH=CH; 5·60, 1H, dt, *J* 11, 6 Hz, CH_2CH=CH; 4·50, 4H, d, *J* 6 Hz, CH_2CH=CH.

Oxidation of Alcohol (3)

To crude (*Z*) alcohol (3) (0·5 g) in acetone (50 ml) was added excess Jones reagent at 0°. After stirring at this temperature for 1 h, water (10 ml) was added and the acetone evaporated in vacuum at low temperature. More water (10 ml) was added and the resulting precipitate was filtered to give a white solid which was identified as the (*E*) isomer of *4-phthalimidobut-2-enal* (4) by n.m.r. spectroscopy and was therefore not investigated further. ^{1}H n.m.r. δ [$(CD_3)_2SO/CDCl_3$ 1 : 3] 9·68, 1H, d, *J* 7 Hz, CHO; 8·00, 4H, s, ArH; 7·06, 1H, dt, *J* 16, 5 Hz, CH_2CH=CH; 6·13, 1H, dd, *J* 7, 16 Hz, CH=CHCHO; 4·63, 2H, d, *J* 5 Hz, CH_2CH=.

(Z)-4-Phthalimidocrotonic Acid (6)

4-Phthalimidobut-2-ynoic acid (5)[7] (3·5 g) was dissolved in pyridine (50 ml) and warmed to 40°. The catalyst, palladium/charcoal (200 mg), was added and the mixture hydrogenated until 1·1 molar equiv. of hydrogen were taken up (after this time the rate of uptake was greatly reduced). The catalyst was removed by filtration through a small amount of Celite, and the dark brown solution evaporated to an oil. This was dissolved in ethyl acetate, and addition of light petroleum gave a slowly separating oil. After standing, the clear solution was decanted from a small amount of red oil which was discarded, and this process repeated three times. The resulting pale orange solution deposited the crystalline product (2 g, 57%) which on one further recrystallization gave the protected *acid* (6) as pale yellow needles, m.p. 179–181° (Found: C, 62·1; H, 4·0; N, 5·7. $C_{12}H_9NO_4$ requires C, 62·3; H, 3·9; N, 6·1%). ν_{max} 3600–2400, 1765, 1700br, 1640, 1255, 1230, 1120, 950, 855, 825, 790, 750, 720 cm^{-1}. ^{1}H n.m.r. δ [$(CD_3)_2SO/CDCl_3$ 1 : 2] 7·88, 4H, s, ArH; 6·22, 1H, dt, *J* 5, 12 Hz, CH_2CH=CH; 5·88, 1H, dt, *J* 1·5, 12 Hz, CH_2CH=CH; 4·82, 2H, dd, *J* 1·5, 5 Hz, CH_2CH=CH. ^{13}C n.m.r. 167·6 (2C, s), 167·1 (s), 143·6 (d), 134·1 (2C, d), 131·8 (2C, s), 123 (2C, d), 122·2 (d), 36·9 (t) ppm. Mass spectrum *m/z* 232 (10%, M+H), 215 (12), 214 (100), 186 (5).

(Z)-4-Aminocrotonic Acid (1)

To (*Z*)-4-phthalimidocrotonic acid (6) (1·3 g) in ethanol (20 ml) was added ethylamine (3 ml of 30% solution in ethanol), and the mixture was allowed to stand at room temperature for 18 h. The solvent was evaporated, and the residue dissolved in water (20 ml) and applied to a column of Dowex 50W (H^+) ion-exchange resin (25 ml). After washing with three bed volumes of water to neutral pH, the amino acid was eluted with aqueous pyridine (100 ml, 1 M), and on evaporation of the solvent a pale brown crystalline solid was obtained. This was recrystallized from water/ethanol/ether to give (*Z*)-4-aminocrotonic acid (1) (210 mg, 37%), m.p. 144–145° (gas evolution) (lit.[1] 145–148°). T.l.c. on silica gel with butanol/water/pyridine 4 : 1 : 1 and developing the plate twice before visualization with ninhydrin did not show any (*E*) isomer in this sample while giving good separation of (*Z*)-4-aminocrotonic acid (R_F 0·25) from (*E*)-4-aminocrotonic acid (R_F 0·16) and γ-aminobutyric acid (R_F 0·16) standards (Found: C, 47·3; H, 6·9; N, 13·5. Calc. for $C_4H_7NO_2$: C, 47·5; H, 7·0; N, 13·9%). ν_{max} 3600–2300, 2200, 1650br, 1520br, 1260, 1160, 900, 890, 845, 835, 823, 745, 725 cm^{-1}. ^{1}H n.m.r. δ (D_2O, 90 MHz, external $SiMe_4$ as standard) 6·59, 1H, d, *J* 11·5 Hz, CH=CHCO$_2$H; 6·37, 1H, dt, *J* 11·5, 5 Hz, CH_2CH=CH; 4·31, 2H, d, *J* 5 Hz, CH_2CH= [cf. 4·16 for the (*E*) isomer]. ^{13}C n.m.r. (D_2O, 90 MHz, external $SiMe_4$) 175·0 (s), 133·4 (d), 130·6 (d), 38·3 (t). Mass spectrum *m/z* 102 (23%, M+H), 84 (77), 85 (100).

* Best name for indexing purposes: (*Z*)-2-(4-hydroxybut-2-enyl)-1*H*-isoindole-1,3(2*H*)-dione.

Acknowledgments

We are grateful to the National Health and Medical Research Council for funding this project, to the Department of Pharmacy, University of Sydney, for mass spectral measurements, and to the University of Sydney for an equipment grant for the Jeol FX90Q n.m.r. spectrometer.

Manuscript received 3 June 1985