Aust. J. Chem., 1983, **36**, 601–8

Synthesis of Analogues of GABA. VIII* Selective α-Alkylation and γ-Halogenation of the Dianion from α,β-Unsaturated Nipecotic Acid Derivatives

Robin D. Allan and Joyce Fong

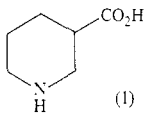
Department of Pharmacology, University of Sydney, N.S.W. 2006.

Abstract

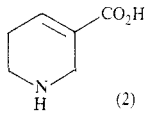
1,2,3,6-Tetrahydropyridine-3-carboxylic acid (3), the β,γ-unsaturated derivative of the GABA uptake inhibitor nipecotic acid (1), has been synthesized by deconjugation via the dilithium salt of the *N*-t-butyloxycarbonyl-protected intermediate (6). Substitution of the intermediate with alkylating agents or an aldehyde gave predominantly α-alkylated products but chlorination with *N*-chlorosuccinimide provided a route to the γ-substituted unsaturated amino acid (13a).

Introduction

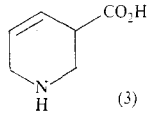
Nipecotic acid (piperidine-3-carboxylic acid) (1)[1-4] is a selective and potent inhibitor of the neuronal uptake of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). For structure–activity studies, the *cis*-4-hydroxy[4] and *cis*-5-hydroxy[5] derivatives as well as the α,β-unsaturated analogues 1,2,5,6-tetrahydropyridine-3-carboxylic acid (guvacine)[6] (2), arecaidine[7] (*N*-methylguvacine), and 5-methylguvacine[4] have been synthesized. Results from these and other heterocyclic analogues[8] indicate that a carbon–carbon double bond or a hydroxyl functional group at the 4-position of (1) is consistent with activity as an uptake inhibitor.



(1)



(2)



(3)

* Part VII, *Aust. J. Chem.*, 1981, **34**, 2641.

[1] Johnston, G. A. R., Krogsgaard-Larsen, P., and Stephanson, A., *Nature (London)*, 1975, **258**, 627.
[2] Krogsgaard-Larsen, P., and Johnston, G. A. R., *J. Neurochem.*, 1975, **25**, 797.
[3] Akkerman, A. M., Jongh, D. K. de, and Veldstra, H., *Recl Trav. Chim. Pays-Bas*, 1951, **70**, 899.
[4] Krogsgaard-Larsen, P., Thyssen, K., and Schaumburg, K., *Acta Chem. Scand., Ser. B*, 1978, **32**, 327.
[5] Jacobsen, P., Schaumburg, K., Larsen, J., and Krogsgaard-Larsen, P., *Acta Chem. Scand., Ser. B*, 1981, **35**, 289.
[6] McElvain, S. M., and Stork, G., *J. Am. Chem. Soc.*, 1946, **68**, 1049.
[7] Boyland, E., and Nery, R., *Biochem. J.*, 1969, **113**, 123.
[8] Krogsgaard-Larsen, P., Brehm, L., and Schaumburg, K., *Acta Chem. Scand., Ser. B*, 1981, **35**, 311.

0004-9425/83/030601$02.00

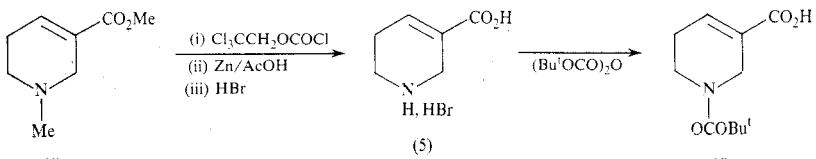
To further these structure–activity studies, we wished to synthesize other piperidine-carboxylic acids with a double bond at the 4-position, especially 1,2,3,6-tetrahydropyridine-3-carboxylic acid (3). Deconjugated acids have previously been synthesized by way of (i) the ene reaction,[9] (ii) the nitrile displacement of an allylic halide followed by hydrolysis,[10] and (iii) the kinetically controlled deconjugation of salts of acids and esters.[11] Our attempts to synthesize (3) by the ene reaction with diethyloxomalonate on the *N*-methoxycarbonyl, *N*-benzoyl and *N*-tosyl derivatives of 1,2,3,6-tetrahydropyridine, or by allylic bromination of the same derivatives were unrewarding. Past studies on the deconjugation method have shown that the alkylation reactions on sodium and/or lithium salts of unsaturated acids or esters favour α-substitution[12–14] while copper salts,[15] *O*-silyl dienyl ethers, or use of an α-silyl substituent[16] favour γ-substitution.

We report here that alkylation of unsaturated piperidine ester or acid enolates results in mainly α-substitution to give the desired deconjugated amino acids, but with *N*-chlorosuccinimide γ-halogenation predominates; this gives a new route to 5-functionalized tetrahydropyridine-3-carboxylic acids.

Results and Discussion

The Preparation of the Enolate Salts

(A) Guvacine has previously been synthesized by various methods.[4,6] We now report a convenient synthesis from the commercially available methyl *N*-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (arecoline) hydrobromide (Scheme 1). Demethylation



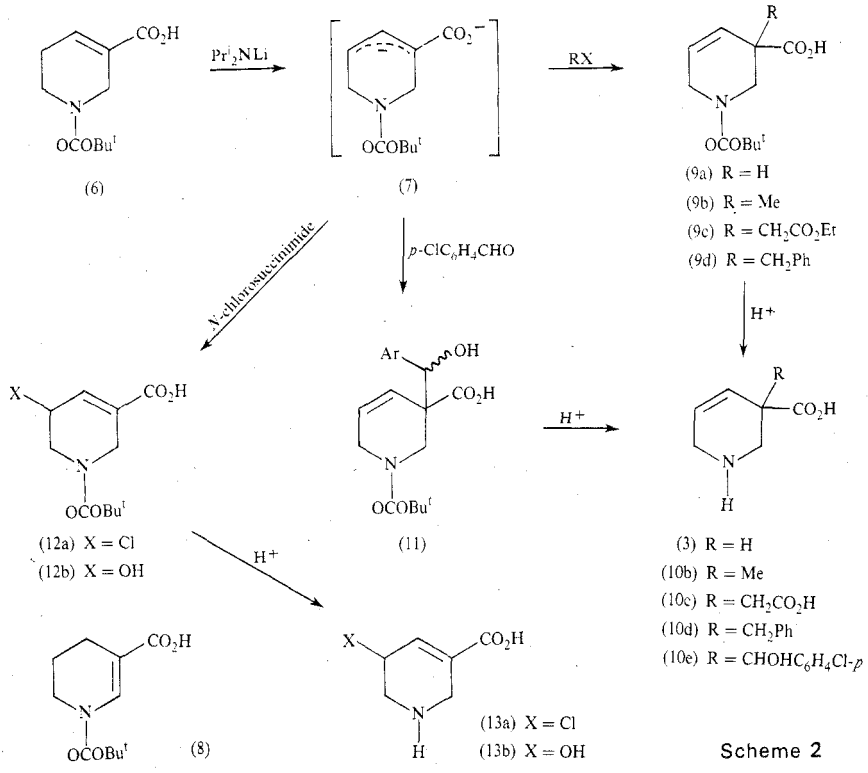
Scheme 1

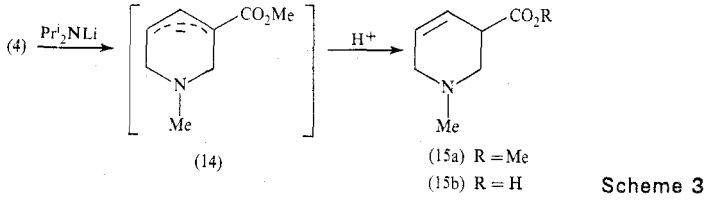
of the free amine (4) was readily achieved by using 2,2,2-trichloroethyloxycarbonyl chloride,[17,18] and the resulting carbamate ester was deprotected with zinc–acetic acid.[19] Acid hydrolysis yielded the hydrobromide (5) without isolation of the intermediates. Treatment of this salt with di-t-butyl dicarbonate and base yielded the *N*-t-butyloxycarbonyl-protected key intermediate (6). The dilithium enolate salt (7) (Scheme 2) was readily generated from (6) with lithium diisopropylamide in tetrahydrofuran at −10°. Attempts to deconjugate via the dianion of the *N*-2,2,2-

[9] Salomon, M. F., Pardo, S. N., and Salomon, R. G., *J. Am. Chem. Soc.*, 1980, **102**, 2473.
[10] Davies, S. G., and Whitlam, G. H., *J. Chem. Soc., Perkin Trans. 1*, 1976, 2279.
[11] Petragnani, N., and Yonashiro, M., *Synthesis*, 1982, 521.
[12] Pfeffer, P. E., Silbert, L. S., and Kinsel, E., *Tetrahedron Lett.*, 1973, 1163.
[13] Cainelli, G., Cardillo, G., Contento, M., Grasseli, P., and Umani-Ronchi, A., *Gazz. Chim. Ital.*, 1973, **103**, 117.
[14] Herrman, J. L., Kieczykowski, G. R., and Schlessinger, R. H., *Tetrahedron Lett.*, 1973, 2433.
[15] Katzenellenbogen, J. A., and Crumrine, A. L., *J. Am. Chem. Soc.*, 1976, **98**, 4925.
[16] Albaugh-Robertson, P., and Katzenellenbogen, J. A., *Tetrahedron Lett.*, 1982, **23**, 723.
[17] Danishefsky, S., Berman, E., and Clizbe, J., *J. Am. Chem. Soc.*, 1979, **101**, 4385.
[18] Reinecke, M. G., and Daubert, R. G., *J. Org. Chem.*, 1973, **38**, 3281.
[19] Montzka, T. A., Matiskella, J. D., and Partyka, R. A., *Tetrahedron Lett.*, 1974, 1325.

trichloroethyloxycarbonyl-protected unsaturated amino acid from an intermediate in Scheme 1 gave mixtures involving reaction of this nitrogen protecting group.

(B) The free amino ester (4) similarly formed a monolithium salt (14) with lithium diisopropylamide (Scheme 3).





Reactions with the Enolate Salts

When the dilithium enolate salt (7) was quenched at low temperature with 10% HCl, methyl iodide, ethyl bromoacetate and benzyl bromide, the expected alkylation products were formed in good yields (Scheme 2). A minor product (less than 5% by ^{1}H n.m.r. spectroscopy) of these alkylations of (7) exhibited a signal at δ ($CDCl_3$) 8·2 which disappeared when the crude product was deprotected by acid hydrolysis. This product was possibly of the type (8) formed via a β'-dianion, but because of the low yield it was not further investigated. Similar β'-anions of unsaturated amides

have recently been reported.[20,21] With R = H, α-substitution was achieved with no detected γ-products. As the substituents increased in size from (9a) to (9d) the proportion of the γ-products increased as seen in Table 1. Condensation of the dianion (7) with 4-chlorobenzaldehyde at −78° yielded the α-product (11) as a 1 : 1 mixture of diastereoisomers. Deconjugation of the *N*-methyl ester (4) (Scheme 3) via the enolate salt (14) yielded (15a) almost quantitatively without any detected γ-protonation or enamine byproduct with an ^{1}H n.m.r. signal in the vicinity of δ 8.

Quenching of the dianion (7) with *N*-chlorosuccinimide yielded predominantly the γ-product (12a) (Scheme 2). This contrasted with reactions of *N*-bromosuccinimide and bromine which gave more complex mixtures. Such a chlorination at the γ-position yielding the α,β-unsaturated derivative (12a) was desirable for preparing a potential alkylating agent at the GABA transport carrier site. Further, this reaction opens a route to 5-substituted piperidine-3-carboxylic acid derivatives such as the base hydrolysis product (12b), the saturated counterpart of which has already been studied against GABA uptake processes.[5]

Table 1. Ratio of α- to γ-substitution on the lithium salts (7) and (14) by ^{1}H n.m.r. analysis

Li salt	Electrophile	Product ratio α : γ	Major product
(7)	HCl	all α	(3)
(7)	MeI	9 : 1	(10b)
(7)	$BrCH_2CO_2Et$	4 : 1	(10c)
(7)	$PhCH_2Br$	4 : 1	(10d)
(7)	4-ClC_6H_4CHO	all α	(11)
(7)	*N*-chlorosuccinimide	1 : 9	(12a)
(14)	HCl	all α	(15a)

Hydrolysis and Deprotection of the N-*t-Butyloxycarbonyl Derivatives*

The ethyl ester (9c) and the methyl ester (15a) were hydrolysed with 2 M HCl under reflux for 2 h to yield the amino acids (10c) and (15b) without detectable lactonization or isomerization. Under reflux with 6 M HCl for 18 h (3) was 70% isomerized to the conjugated (2).

The *N*-t-butyloxycarbonyl products (9a,b,d), (11) and (12b) were deprotected with HBr (48% aqueous) : AcOH (1 : 5) at 80° for 15 min to yield the corresponding hydrobromide salts. From the mixture of diastereoisomers of (11), recrystallization of the deprotected salt yielded one crystalline amino acid (10e). The *N*-t-butyloxycarbonyl chloro derivative (12a) gave a more unstable product and was deprotected with 1 M HCl (1·5 equiv.) in ethyl acetate isolated as the hydrochloride salt since its hydrobromide salt was hygroscopic.

Experimental

General

^{1}H n.m.r. spectra were measured at 60 MHz on a Varian EM-360A spectrometer in either $CDCl_3$ or D_2O with tetramethylsilane as internal or external standard respectively. Infrared spectra were recorded neat or from Nujol mulls (unless otherwise indicated) on a Perkin–Elmer 177 spectro-

[20] Kempf, D. J., Willson, K. D., and Beak, P., *J. Org. Chem.*, 1982, **47**, 1610.
[21] Beak, P., and Kempf, D. J., *J. Am. Chem. Soc.*, 1980, **102**, 4550.

photometer. Melting points (uncorrected) were measured on a Reichert hot-stage apparatus. Microanalyses were carried out by the Australian Microanalytical Service, Melbourne. Thin-layer chromatography (t.l.c.) on Merck Kieselgel 60 precoated t.l.c. plates in butan-1-ol/acetic acid/water (4 : 1 : 1) gave the reported R_F values after visualization with ninhydrin (strong heating required with the *N*-t-butyloxycarbonyl derivatives).

Preparation of the Lithium Salts

N-t-Butyloxycarbonyl-1,2,5,6-tetrahydropyridine-3-carboxylic Acid (6)

A solution of the hydrochloride of (4) (35 g, 0·18 mol) in water (100 ml) was saturated with K_2CO_3 (30 g, 0·22 mol), and the free amine was extracted into ether (300 ml). The yellow oil (4) (28 g) obtained after drying and solvent evaporation was added to 2,2,2-trichloroethyl chloroformate (56 g, 0·27 mol) and K_2CO_3 (6 g) in benzene (100 ml). The suspension was heated under reflux for 16 h, filtered, and the filtrate washed with 5 M NaOH (60 ml), 6 M HCl (50 ml), dried, and the solvent removed to yield methyl *N*-2,2,2-trichloroethyloxycarbonyl-1,2,5,6-tetrahydropyridine-3-carboxylate (47 g, 83%). To a stirred, ice-cooled solution of this product (45 g, 0·14 mol) in glacial acetic acid (50 ml), zinc dust (19 g, 0·29 mol) was added portionwise to maintain the temperature at 25–30°. After 2 h the residue was filtered and washed with acetic acid (30 ml), and the filtrate heated under reflux with 48% HBr (160 ml) for 3 h. All solvents were removed under vacuum to yield guvacine hydrobromide (5) (27 g, 91%) which could be recrystallized from acetic acid, m.p. 275–280° (dec.) (lit.[4] 280° (dec.)). ^{1}H n.m.r. δ (D_2O) 7·85, m, CH=; 4·55, q, 2H; 4·03, t, 2H; 3·33, m, 2H. ν_{max} 3160, 1710 cm^{-1}.

To guvacine hydrobromide (26 g, 0·12 mol) in 4 M NaOH (0·6 mol, 150 ml) and t-butyl alcohol (120 ml) was added di-t-butyl dicarbonate (34 g, 0·16 mol). The mixture was vigorously stirred and warmed to 45–50° for 2 h. The product was washed with hexane (2 × 80 ml), acidified with 6 M HCl and extracted into ethyl acetate (2 × 80 ml). The ethyl acetate was dried and removed to yield the crude product (18 g) which was recrystallized from ethyl acetate (30 ml) giving the *N-t-butyloxycarbonyl unsaturated acid* (6) (17 g, 60%), m.p. 153–154° (Found: C, 58·0; H, 7·3; N, 6·2. $C_{11}H_{17}NO_4$ requires C, 58·1; H, 7·5; N, 6·2%). ^{1}H n.m.r. δ ($CDCl_3$) 7·22, m, CH=; 4·15, q, CH_2; 3·50, t, CH_2; 2·45, m, CH_2; 1·49, s, $C(CH_3)_3$. ν_{max} 1716, 1676 cm^{-1}.

The Dilithium Salt (7)

Lithium diisopropylamide (2 mmol) was generated *in situ* under dry nitrogen by the addition of butyllithium in hexane (1 ml of 2 M, 2 mmol) to a solution of diisopropylamine (0·28 ml, 2 mmol) in anhydrous tetrahydrofuran (2 ml) at −78° and maintained at −10° for 15 min. A solution of (6) (216 mg, 1 mmol) in anhydrous tetrahydrofuran (2 ml) was added to the base at −78°. The temperature was allowed to rise to −10° within 20 min to complete the generation of the lithium dienolate (7) and cooled to −78° before quenching (except for protonation and halogenation which were quenched at 0° or −10°).

The Lithium Salt (14)

Likewise, to a solution of (4) (155 mg, 1 mmol) in anhydrous tetrahydrofuran (2 ml) was added to lithium diisopropylamide (1 mmol) in anhydrous tetrahydrofuran (2 ml) at −78° and stirred at −10° for 20 min to generate the lithium enolate (14).

Quenching with Electrophiles: (i) Protonation

N-t-Butyloxycarbonyl-1,2,3,6-tetrahydropyridine-3-carboxylic Acid (9a)

The dienolate (7) (30 mmol) was quenched with 10% HCl (40 ml) with ice cooling. The product was extracted with ethyl acetate (2 × 100 ml) and the solvent dried and removed to give a crude product (6·6 g, 97%). The *N-t-butyloxycarbonyl acid* (9a) was recrystallized from ethyl acetate (3·5 g, 52%), m.p. 142–144° (Found: C, 57·9; H, 7·3; N, 5·9. $C_{11}H_{17}NO_4$ requires C, 58·1; H, 7·5; N, 6·2%). ^{1}H n.m.r. δ ($CDCl_3$) 5·90, m, CH=CH; 4·2–3·1, complex, 5H; 1·49, s, $C(CH_3)_3$. ν_{max} 1735, 1680 cm^{-1}.

Methyl N-*Methyl-1,2,3,6-tetrahydropyridine-3-carboxylate* (*15a*)

The enolate (14) (14 mmol) was quenched with 10% HCl (10 ml) with ice cooling. The aqueous layer was saturated with K_2CO_3 and the product was extracted into ether (2 × 40 ml). The combined extracts were dried and the solvent removed to yield an orange oil (15a) (2 g, 96%). ^{1}H n.m.r. δ ($CDCl_3$) 5·87, m, CH=CH; 3·70, s, CO_2CH_3; 3·4–2·5, complex, 5H; 2·38, s, NCH_3. ν_{max} 1735 cm^{-1}.

Quenching with Electrophiles: (ii) Alkylation

N-*t-Butyloxycarbonyl-3-methyl-1,2,3,6-tetrahydropyridine-3-carboxylic Acid* (*9b*)

The dienolate (7) (10 mmol) was quenched with methyl iodide (13 mmol) in anhydrous tetrahydrofuran (1 ml) and stirred for 10 min at −78°, then 10% HCl (10 ml) was added at 0°. The usual workup plus additional washing with sodium thiosulfate (20 ml) and H_2O (20 ml) yielded a yellow oil (9b) (2·31 g, 96%) containing 10% of the γ-alkylation product by ^{1}H n.m.r. (δ 7·2). ^{1}H n.m.r. δ ($CDCl_3$) 5·85, m, CH=CH; 3·95, m, NCH_2; 3·80, 1H, d, J 13 Hz, NCH_2CCH_3; 3·40, 1H, d, J 13 Hz, NCH_2CCH_3; 1·49, $C(CH_3)_3$; 1·32, s, CH_3. ν_{max} 1695 (br) cm^{-1}.

Ethyl N-*t-Butyloxycarbonyl-3-(ethoxycarbonylmethyl)-1,2,3,6-tetrahydropyridine-3-carboxylic Acid* (*9c*)

The dienolate (7) (4 mmol) was quenched with ethyl bromoacetate (6 mmol) for 10 min at −78°, then 10% HCl (5 ml) was added at −10°. The product and excess reagents were extracted into ethyl acetate (2 × 40 ml) and the product was basified with K_2CO_3 and extracted into the aqueous layer (2 × 40 ml), then reacidified with 6 M HCl dropwise and extracted into ethyl acetate (2 × 40 ml). The combined extracts were dried and the solvent removed to yield a yellow oil (9c) (1·1 g, 90%) containing 20% γ-products according to ^{1}H n.m.r. spectroscopy (δ 7·2). ^{1}H n.m.r. δ ($CDCl_3$) 5·94, m, CH=CH; 4·4–3·4, 6H, complex, CH_2NCH_2, OCH_2; 2·75, 2H, s, CH_2CO_2Et; 1·5, $C(CH_3)_3$; 1·30, t, CH_3CH_2O. ν_{max} 1705(br) cm^{-1}.

*3-Benzyl-*N-*t-butyloxycarbonyl-1,2,3,6-tetrahydropyridine-3-carboxylic Acid* (*9d*)

The dienolate (7) (10 mmol) was quenched with benzyl bromide (13 mmol) for 10 min at −78°, then 10% HCl (20 ml) was added at 0°. The workup was the same as for (9c) to yield a yellow oil (9d) (2·24 g, 71%) containing 20% γ-products (δ 7·1, CH=; 2·7, CH_2Ar) by ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. δ ($CDCl_3$) 7·25, m, ArH; 5·85, m, CH=CH; 4·3–3·4, 4H, complex, CH_2NCH_2; 3·00, s, CH_2Ar; 1·50, $C(CH_3)_3$. ν_{max} 1675 (br) cm^{-1}.

Quenching with Electrophiles: (iii) Condensation

N-*t-Butyloxycarbonyl-3-*[(*4-chlorophenyl*)*hydroxymethyl*]-*1,2,3,6-tetrahydropyridine-3-carboxylic Acid* (*11*)

The dienolate (7) (2 mmol) was quenched with 4-chlorobenzaldehyde (2·4 mmol) for 10 min at −78°, then 10% HCl (5 ml) was added at 0°. The usual workup gave a yellow oil (11) (703 mg, 96%). ^{1}H n.m.r. δ ($CDCl_3$) 7·30, m, ArH; 5·9, m, CH=CH; 5·1 and 4·85, 1H, s, CH(OH)Ar; 4·3–3·3, m, CH_2NCH_2; 1·50, $C(CH_3)_3$. ν_{max} 3400 (br), 1690 (br) cm^{-1}.

Quenching with Electrophiles: (iv) Halogenation

N-*t-Butyloxycarbonyl-5-chloro-1,2,5,6-tetrahydropyridine-3-carboxylic Acid* (*12a*)

The dienolate (7) (2 mmol) was quenched with *N*-chlorosuccinimide (3 mmol) in anhydrous tetrahydrofuran (6 ml) at −10°, then after 10 min 10% HCl (5 ml) was added. The usual workup gave a yellow oil (12a) (450 mg, 86%) containing 10% α-substituted product by ^{1}H n.m.r. spectroscopy (δ 5·95). ^{1}H n.m.r. δ ($CDCl_3$) 7·1, m, CH=; 4·65, m, CHCl; 4·4–3·1, complex, CH_2NCH_2; 1·50, $C(CH_3)_3$. ν_{max} 3400 (br), 1710 (br), 1655 cm^{-1}.

N-*t-Butyloxycarbonyl-5-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic Acid* (*12b*)

The compound (12a) was added to 1 M NaOH (35 ml) and refluxed for 2·5 h. The solvent was removed and the product acidified with 1 M HCl and extracted into ethyl acetate (3 × 40 ml).

The organic layer was washed with water (30 ml) and dried to yield a yellow gum (12b) (310 mg, 65%). ^{1}H n.m.r. δ ($CDCl_3$) 7·15, m, CH=; 4·4, m, CHOH; 4·2–3·2, complex, CH_2NCH_2; 1·50, $C(CH_3)_3$. ν_{max} ($CHCl_3$) 1710 cm^{-1}.

Deprotection

Procedures

(i) (9a,b,d), (11) and (12) were heated under reflux in 48% HBr/AcOH (1 : 5) for 15 min. All solvents were removed under vacuum and the products crystallized as the corresponding hydrobromide salts (3,10b,d,e) and (13b) from AcOH. The hydrobromide salts of (3) and (10d) were adsorbed on a column of Dowex 50W(H^+) and eluted with 1 M pyridine to yield the free amino acid.

(ii) The esters (9c) and (15a) were hydrolysed with 1 M HCl for 2 h to yield the hydrochloride salts (10c) and (15b) respectively from acetic acid.

(iii) (12a) was deprotected at room temperature with 1·5 equiv. 1 M HCl in ethyl acetate to yield the hydrochloride salt (13a).

1,2,3,6-Tetrahydropyridine-3-carboxylic Acid Hydrobromide (3)

M.p. 210° (Found: C, 35·0; H, 4·9; N, 6·7. $C_6H_{10}BrNO_2$ requires C, 34·6; H, 4·8; N, 6·7%). ^{1}H n.m.r. δ (D_2O) 6·58, m, CH=CH; 4·25, 2H, m, NCH_2CH=; 4·1, 3H, m, NCH_2CHCO_2H. ν_{max} 1730 cm^{-1}. R_F 0·21. The salt was purified on Dowex 50W(H^+) and removed with 1 M pyridine to give the free *amino acid* (3), m.p. 286–289° (dec.) (Found: C, 53·2; H, 7·2; N, 10·2. $C_6H_9NO_2$,0·5H_2O requires 52·9; H, 7·4; N, 10·3%). ^{1}H n.m.r. δ (D_2O) 6·52, m, CH=CH; 4·25, m, NCH_2CH=; 3·5–4·0, 3H, m, NCH_2CHCO_2H. ν_{max} 3400, 3100, 1590 cm^{-1}.

3-Methyl-1,2,3,6-tetrahydropyridine-3-carboxylic Acid Hydrobromide (10b)

M.p. 195–196° (Found: C, 38·0; H, 5·4; N, 6·3. $C_7H_{12}BrNO_2$ requires C, 37·9; H, 5·4; N, 6·3%). ^{1}H n.m.r. δ (D_2O) 6·52, m, CH=CH; 4·4, 1H, d, J 13 Hz, NCH_2CCH_3; 4·3, m, NCH_2C=; 3·6, 1H, d, J 13 Hz, NCH_2CCH_3. ν_{max} 1750, 1595w cm^{-1}. R_F 0·30.

3-Carboxymethyl-1,2,3,6-tetrahydropyridine-3-carboxylic Acid Hydrobromide (10c)

The hydrochloride salt obtained by the HCl hydrolysis of the ester was not crystalline and thus was neutralized by passing down Dowex 50W(H^+) ion exchange resin and removed with 1 M pyridine. The *hydrobromide salt* was formed with 48% HBr and crystallized from acetic acid, m.p. 202–205° (dec.) (Found: C, 35·2; H, 4·7; N, 5·3. $C_8H_{12}BrNO_4$,0·5H_2O requires C, 34·9; H, 4·8; N, 5·1%). ^{1}H n.m.r. δ (D_2O) 6·50, m, CH=CH; 4·6, 1H, d, J 13 Hz, NCH_2CO_2H; 4·6–4·1, 2H, m, NCH_2CH=; 3·7, 1H, d, J 13 Hz, NCH_2CO_2H; 3·7, 1H, d, J 17 Hz, CH_2CO_2H; 3·2, 1H, d, J 17 Hz, CH_2CO_2H. ν_{max} 3450, 1720, 1590 cm^{-1}. R_F 0·18.

3-Benzyl-1,2,3,6-tetrahydropyridine-3-carboxylic Acid Hydrobromide (10d)

M.p. 219–220° (Found: C, 52·5; H, 5·5; N, 4·7. $C_{13}H_{10}BrNO_2$ requires C, 52·4; H, 5·4; N, 4·7%). ^{1}H n.m.r. δ (D_2O) 7·85, m, ArH; 6·5, m, CH=CH; 4·1, 1H, d, J 13 Hz, NCH_2CCO_2H; 4·1, m, NCH_2CH=; 3·7, 1H, d, J 15 Hz, CH_2Ar; 3·6 (obscured), 1H, d, J 13 Hz, NCH_2CCO_2H; 3·4, 1H, d, J 15 Hz, CH_2Ar. ν_{max} 3150, 1710, 1560 cm^{-1}. R_F 0·47 (0·55 for γ-product).

3-[(4-Chlorophenyl)hydroxymethyl]-1,2,3,6-tetrahydropyridine-3-carboxylic Acid Hydrobromide (10e)

M.p. 280–285° (dec.) (Found: C, 44·9; H, 4·5; N, 3·8. $C_{13}H_{15}BrClNO_3$ requires C, 44·8; H, 4·3; N, 4·0%). ^{1}H n.m.r. δ (D_2O) 7·90, s, ArH; 6·55, m, CH=CH; 5·8, s, ArCHOH; 4·3, 1H, d, J 13 Hz, NCH_2CCO_2H; 4·0, m, NCH_2CH=; 3·6, 1H, d, J 13 Hz, NCH_2CCO_2H. ν_{max} 3330, 1740 cm^{-1}. R_F 0·46.

5-Chloro-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Hydrochloride (13a)

M.p. 225–230° (dec.) (Found: C, 36·5; H, 4·4; N, 7·2. $C_6H_9Cl_2NO_2$ requires C, 36·4; H, 4·6; N, 7·1%). ^{1}H n.m.r. δ (D_2O) 7·7, m, CH=; 4·50, m, NCH_2C=; 4·25, m, $NCH_2CH(Cl)$; 3·90, m, CHCl. ν_{max} 1710, 1660, 1600 cm^{-1}. R_F 0·35.

5-Hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Hydrobromide (*13b*)

M.p. 236–238° (dec.) (Found: C, 32·1; H, 4·3; N, 6·4. $C_6H_{10}BrNO_3$ requires C, 32·2; H, 4·5; N, 6·3%). ^{1}H n.m.r. δ (D_2O) 7·85, m, CH=; 4·62, m, NCH_2C=; 4·10, m, NCH_2CHOH; 3·37, m, CHOH. ν_{max} 3440, 1720, 1670w, 1560 cm^{-1}. R_F 0·23.

N-*Methyl-1,2,3,6-tetrahydropyridine-3-carboxylic Acid Hydrochloride* (*15b*)

M.p. 245–250° (dec.) (Found: C, 47·3; H, 6·7; N, 8·1. $C_7H_{12}ClNO_2$ requires C, 47·3; H, 6·8; N, 7·9%). ^{1}H n.m.r. δ (D_2O) 6·55, m, CH=CH; 4·4–3·8, 5H, m, $CH_2NCH_2CHCO_2H$; 3·5, s, NCH_3. ν_{max} 2660 (br), 1725 cm^{-1}. R_F 0·17.

Acknowledgments

We are grateful to the University of Sydney for the award of a Research Scholarship (to J.F.) and to the National Health and Medical Research Council for the ^{1}H n.m.r. equipment.

Manuscript received 18 November 1982