Excitatory Amino Acids. Improved Synthesis of Ibotenic Acid and *X*-Ray Analysis of an Unexpected Reaction Product, (*RS*)-*N*-[2-(3-benzyloxyisoxazol-5-yl)-1-phenylethyl]-3-oxobutyramide

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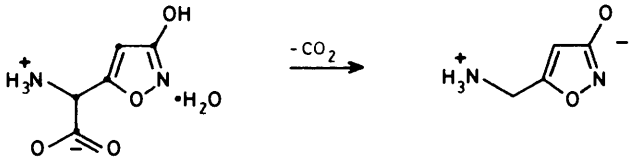
A new synthesis of the excitotoxic natural product ibotenic acid (**1**) is described. Benzylation of 3-hydroxy-5-methylisoxazole (**5**) yielded 3-benzyloxy-5-methylisoxazole (**7**) and the isomeric isoxazol-3(2*H*)-one (**6**). While metallation of compound (**7**) by lithium di-isopropylamide followed by treatment with carbon dioxide gave an easily separable mixture of the acid (**10**) and the desired intermediate (**11**), reaction of compound (**7**) with butyl-lithium yielded the unexpected products (*RS*)-*N*-(1-phenylpentyl)-3-oxobutyramide (**8**) and (*RS*)-*N*-[2-(3-benzyloxyisoxazol-5-yl)-1-phenylethyl]-3-oxobutyramide (**9**). The structure of (**9**) was confirmed by *X*-ray analysis. Benzylation of (**11**) gave (**12**) in quantitative yield when benzyl chloroformate and triethylamine were used as reagents. The oxime (**13**), prepared by nitrosation of (**12**) under basic conditions, was reduced and deprotected by catalytic hydrogenation to give ibotenic acid (**1**) in good yields and without formation of significant amounts of decarboxylated product.

Ibotenic acid [(*RS*)-α-amino-3-hydroxyisoxazol-5-ylacetic acid monohydrate] (**1**), a structural analogue of the central excitatory neurotransmitter glutamic acid (GLU), is biosynthesized by the fly agaric mushroom *Amanita muscaria*.[1] Compound (**1**) very easily undergoes decarboxylation,[2] and the dried mushroom contains varying amounts of the decarboxylation product, muscimol (**2**).[1]

The powerful neuroexcitatory effects of compound (**1**) are mediated by the (*R*)-*N*-methylaspartic acid (NMA) sub-type of GLU receptors.[3-8] Interestingly, certain analogues of (**1**), notably (*RS*)-3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-7-carboxylic acid (7-HPCA) (**3**)[9,10] and (*RS*)-α-amino-3-hydroxy-5-methylisoxazol-4-ylpropionic acid (AMPA) (**4**)[11,12] are specific agonists at another distinct sub-type of central GLU receptors, the quisqualic acid-preferring receptors.



(**1**) (**2**)

(**3**) (**4**)

The neurotoxic effects of compound (**1**), which are also probably mediated by NMA receptors, have made ibotenic acid a very useful tool in experimental neurobiology and neuroanatomy.[13-17] The distinct pattern of neurolesions induced by (**1**) and the biphasic response seen in electrophysiological experiments with (**1**) probably reflect partial decarboxylation of (**1**) to the γ-aminobutyric acid agonist, muscimol (**2**),[3,18] in brain tissues. This decomposition of (**1**) is catalyzed by GLU decarboxylase (GAD).[2]

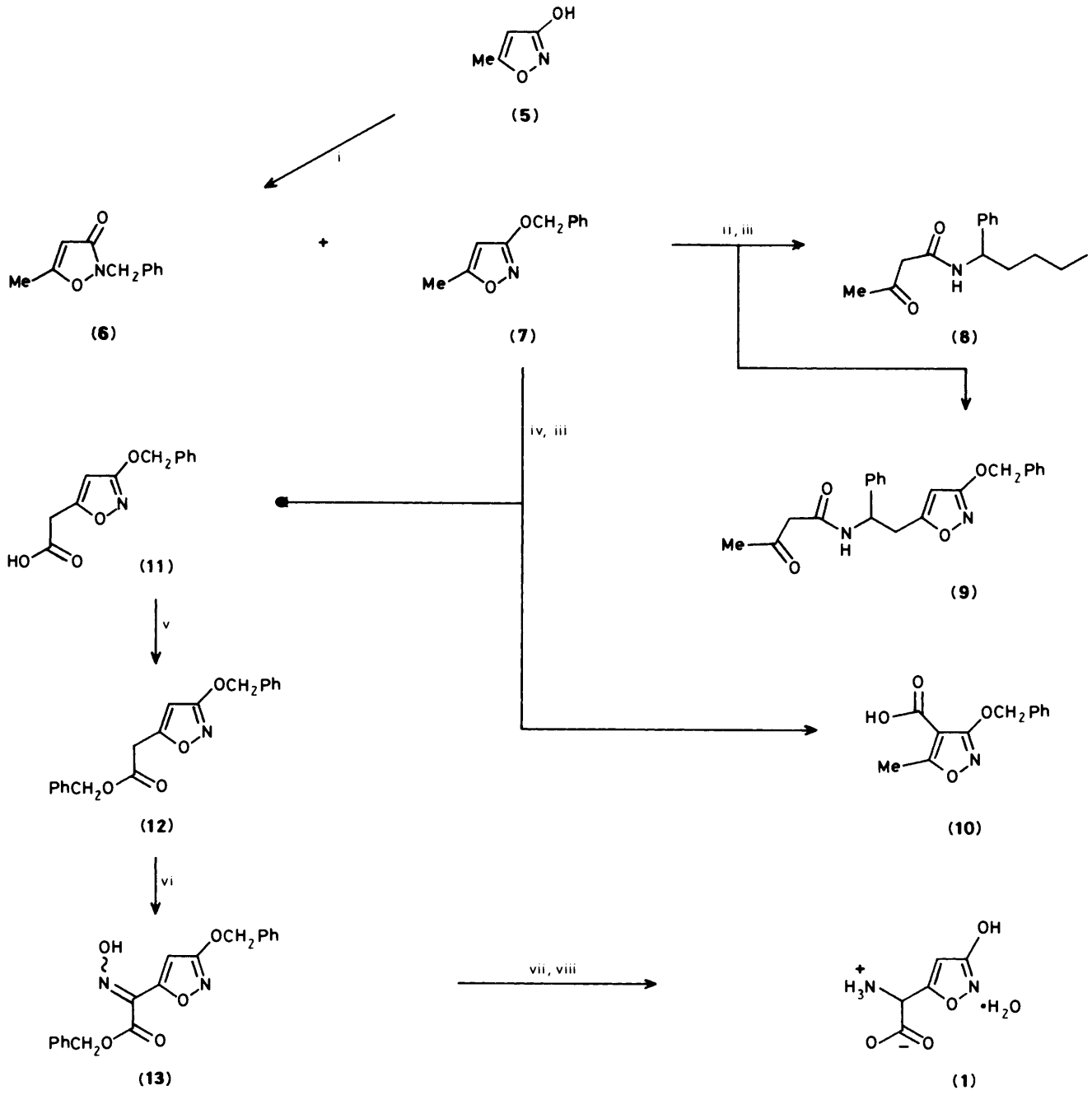
The very high selling price of compound (**1**), isolated from the fly agaric mushroom, has prompted us to develop an improved procedure for the synthesis of (**1**) which takes into account its instability. All previously reported syntheses of (**1**)[19-29] are multi-step reaction sequences giving low yields of the final product. This improved synthesis of (**1**) in five steps, four of which require chromatographic purification, gives an overall yield of 7.1%.

Results and Discussion

3-Hydroxy-5-methylisoxazole (**5**)[30] was converted into a separable mixture of compounds (**6**) and (**7**) (Scheme 1). Metallation of compound (**7**) by lithium di-isopropylamide (LDA) and subsequent carboxylation yielded the desired product (**11**) (36%) together with compound (**10**) (9%). Attempts to prepare compound (**11**) using butyl-lithium as a base instead of LDA unexpectedly led to a mixture of (*RS*)-*N*-[2-(3-benzyloxyisoxazol-5-yl)-1-phenylethyl]-3-oxobutyramide (**9**) and (*RS*)-*N*-(1-phenylpentyl)-3-oxobutyramide (**8**).

We believe that this reaction course is initiated by coordination of lithium to the nitrogen atom[31,32] of compound (**7**) (Scheme 2), favouring the generation of a carbanion at the benzyl α-carbon atom (**14**).[32,33] Migration of the benzyl group accompanied by a ring cleavage of (**14**) is then likely to proceed with transient formation of a cyclic transition state (**15**) and subsequent formation of (**16**). This key intermediate (**16**) is then assumed to be converted into compounds (**8**) and (**9**) by nucleophilic addition of the butyl carbanion or the methyl carbanion of (**7**) (not shown), respectively. The proposed four-membered ring transition state (**15**) involved in the 1,3-oxygen-to-nitrogen shift is analogous with that of the Chapman rearrangement.[34,35] Oxygen-to-nitrogen migration of the benzyl group prior to the cleavage of the N–O bond of the isoxazole ring is unlikely, since treatment of compound (**6**) with butyl-lithium under conditions similar to those under which (**7**) was converted into (**8**) and (**9**) did not give detectable amounts of (**8**). The structure of compound (**9**) has been established by *X*-ray analysis (see Experimental section). An ORTEP[36] display of compound (**9**) is shown in Figure 1.

Benzylation of the acid (**11**) (Scheme 1) under basic



Scheme 1. *Reagents:* i, K_2CO_3, $PhCH_2Br$; ii, n-BuLi; iii, CO_2; iv, LDA, v, $ClCO_2CH_2Ph$, Et_3N; vi, NaH, BuONO; vii, H_2/Pd; viii, Et_3N or IRA-400

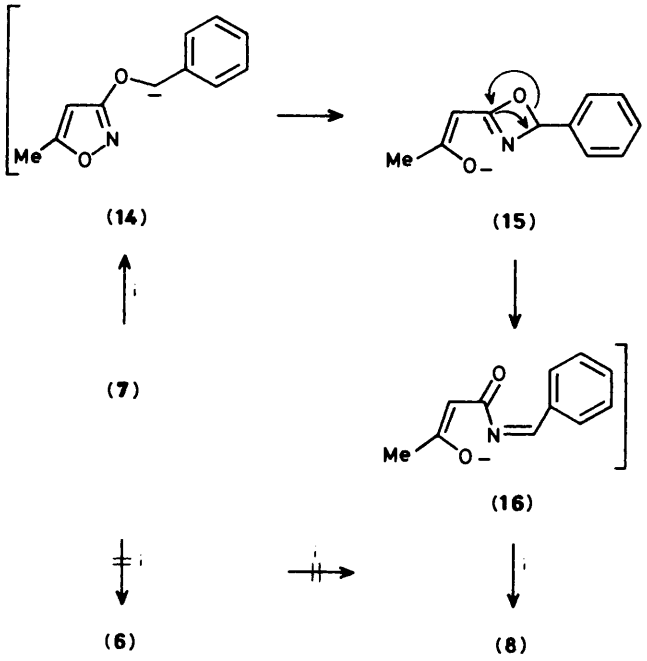
conditions as well as conventional esterification using dicyclohexyl carbodi-imide and benzyl alcohol gave only low yields of compound (**12**). However, a mixture of (**11**), benzyl chloroformate, and triethylamine dissolved in dichloromethane reacted spontaneously to give approximately 100% yield of (**12**). This mixed anhydride-type reaction has been reported to require *N*,*N*-dimethylaminopyridine as a catalyst.[37]

A mixture of the *Z*- and *E*-oximes (**13**) was synthesized by nitrosation of metallated (**12**). The course of this reaction step was strictly dependent on the nature of the metallation reagent and the reaction conditions used. Thus, treatment of compound (**12**) with butyl-lithium or LDA followed by addition of butyl nitrite under a variety of different conditions resulted in extensive decomposition of the starting material. Good yields (60—70%) of compound (**13**) were, however, obtained by using sodium amide or sodium hydride as bases and adding butyl nitrite immediately after the initiation of the metallation of compound (**12**). T.l.c. analyses of the crude reaction product revealed the presence of two components assumed to be the *E*- and *Z*-forms of (**13**). Attempts to separate these two components by recrystallization or column chromatographic separation procedures gave one product probably due to facile isomerization of one of the geometrical isomers. No attempts were made to establish the configuration of the isolated isomer of (**13**).

Reduction of the oxime group of compound (**13**) and simultaneous hydrogenolysis of the benzyloxy groups of this

Table 1. Positional parameters for the non-hydrogen atoms of compound (**9**). Estimated standard deviations are given in parentheses

Atom	*x*	*y*	*z*
O(1)	−0.032 6(3)	0.070 0(3)	0.687 8(4)
N(2)	0.085 7(4)	0.061 4(3)	0.754 8(5)
C(3)	0.149 8(5)	0.073 8(3)	0.655 2(6)
C(4)	0.081 5(5)	0.090 3(3)	0.523 6(6)
C(5)	−0.029 8(5)	0.088 2(3)	0.552 2(6)
C(2)	−0.149 2(5)	0.101 1(3)	0.469 9(6)
C(6)	−0.204 2(4)	0.169 3(3)	0.513 9(4)
N(1)	−0.132 6(3)	0.227 5(2)	0.478 2(4)
C(7)	−0.081 6(5)	0.272 3(4)	0.571 9(6)
O(3)	−0.087 4(5)	0.267 6(3)	0.697 2(4)
C(8)	−0.012 8(7)	0.330 8(5)	0.518 0(7)
C(9)	0.100 7(7)	0.335 7(6)	0.576 6(9)
O(4)	0.154 2(5)	0.362 2(4)	0.675 3(7)
C(Me)	0.180 7(9)	0.280 5(7)	0.493 4(16)
O(2)	0.268 5(3)	0.070 4(2)	0.675 3(4)
C(1)	0.318 5(5)	0.047 9(4)	0.814 5(7)
C(01)	0.451 9(5)	0.050 3(4)	0.824 4(7)
C(02)	0.512 7(6)	−0.001 3(4)	0.765 9(9)
C(03)	0.633 3(7)	−0.000 8(4)	0.779 5(10)
C(04)	0.695 8(6)	0.049 8(6)	0.852 1(10)
C(05)	0.638 6(8)	0.100 0(5)	0.912 4(8)
C(06)	0.514 5(7)	0.100 6(4)	0.898 4(7)
C(10)	−0.333 3(4)	0.175 9(3)	0.448 3(5)
C(20)	−0.364 4(5)	0.203 0(4)	0.316 2(7)
C(30)	−0.484 6(7)	0.206 8(4)	0.260 9(9)
C(40)	−0.570 1(6)	0.183 7(4)	0.338 8(10)
C(50)	−0.538 7(5)	0.156 4(5)	0.465 3(8)
C(60)	−0.421 3(5)	0.152 0(4)	0.521 8(6)



Scheme 2. *Reagent:* i, n-BuLi

intermediate were accomplished by hydrogenation at atmospheric pressure in ethanolic hydrogen chloride using a palladium catalyst. Under these conditions a mixture of compound (**1**) and its ethyl ester was formed. Attempts to avoid the formation of the latter product by using other solvent

Table 2. Interatomic distances and angles for compound (**9**). Estimated standard deviations are given in parentheses

Bond lengths (Å)

C(01)–C(02)	1.367(11)	C(10)–C(20)	1.368(8)
C(02)–C(03)	1.360(10)	C(20)–C(30)	1.402(10)
C(03)–C(04)	1.345(13)	C(30)–C(40)	1.369(12)
C(04)–C(05)	1.333(14)	C(40)–C(50)	1.323(12)
C(05)–C(06)	1.399(12)	C(50)–C(60)	1.377(8)
C(06)–C(01)	1.347(10)	C(60)–C(10)	1.369(8)
C(01)–C(1)	1.506(8)	C(10)–C(6)	1.526(6)
C(1)–O(2)	1.443(7)	C(6)–C(2)	1.532(8)
O(2)–C(3)	1.339(6)	C(6)–N(1)	1.449(7)
C(3)–C(4)	1.425(8)	N(1)–C(7)	1.320(7)
C(4)–C(5)	1.327(8)	C(7)–O(3)	1.208(7)
C(5)–O(1)	1.344(7)	C(7)–C(8)	1.496(11)
O(1)–N(2)	1.423(6)	C(8)–C(9)	1.342(11)*
N(2)–C(3)	1.290(8)	C(9)–O(4)	1.171(11)*
C(5)–C(2)	1.499(7)	C(9)–C(Me)	1.661(17)*

Valency angles (°)

C(01)–C(02)–C(03)	120.7(7)	C(10)–C(20)–C(30)	119.5(6)
C(02)–C(03)–C(04)	121.0(8)	C(20)–C(30)–C(40)	120.2(7)
C(03)–C(04)–C(05)	119.5(7)	C(30)–C(40)–C(50)	119.7(6)
C(04)–C(05)–C(06)	120.3(8)	C(40)–C(50)–C(60)	121.2(7)
C(05)–C(06)–C(01)	120.2(7)	C(50)–C(60)–C(10)	120.8(6)
C(06)–C(01)–C(02)	118.3(6)	C(60)–C(10)–C(20)	118.6(5)
C(06)–C(01)–C(1)	121.0(7)	C(60)–C(10)–C(6)	119.2(4)
C(02)–C(01)–C(1)	120.5(6)	C(20)–C(10)–C(6)	122.2(5)
C(01)–C(1)–O(2)	109.0(5)	C(10)–C(6)–C(2)	111.2(4)
C(1)–O(2)–C(3)	114.8(5)	C(10)–C(6)–N(1)	112.2(4)
O(2)–C(3)–N(2)	122.5(5)	C(2)–C(6)–N(1)	109.7(4)
O(2)–C(3)–C(4)	124.3(5)	C(6)–N(1)–C(7)	123.7(4)
N(2)–C(3)–C(4)	113.2(5)	N(1)–C(7)–C(8)	117.4(5)
C(3)–C(4)–C(5)	103.9(5)	N(1)–C(7)–O(3)	123.2(6)
C(4)–C(5)–O(1)	110.1(5)	O(3)–C(7)–C(8)	119.4(6)
C(4)–C(5)–C(2)	135.3(5)	C(7)–C(8)–C(9)	115.1(7)*
O(1)–C(5)–C(2)	114.7(5)	C(8)–C(9)–O(4)	137.7(9)*
C(5)–O(1)–N(2)	109.1(4)	C(8)–C(9)–C(Me)	108.1(8)*
O(1)–N(2)–C(3)	103.7(4)	O(4)–C(9)–C(Me)	113.7(8)*
C(5)–C(2)–C(6)	111.8(4)		

Inter molecular hydrogen bond distances (Å) and angles (°)

A–H···B	A–H	H···B	A···B	<AHB
N(1)–H···O(3^{i})	1.02 Å	1.78 Å	2.792(6) Å	171°

Symmetry code: (i) $x, \frac{1}{2} - y, z - \frac{1}{2}$

* Several atoms, especially those of the acetyl group, undergo considerable thermal motion resulting in unreliable bond lengths and angles.

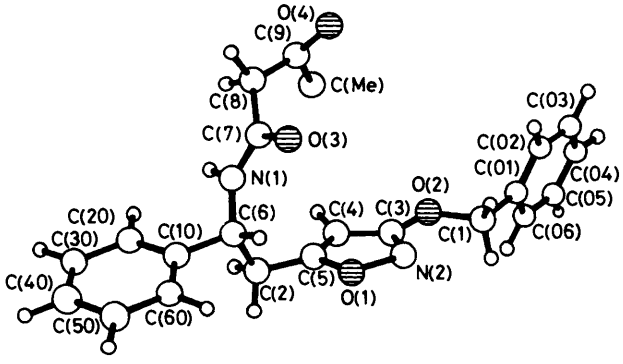


Figure 1. Perspective drawing of compound (**9**) with the crystallographic numbering system. The hydrogen atoms of the methyl group [C(Me)] have not been included in the calculations

systems such as aqueous hydrochloric acid, glacial acetic acid, or tetrahydrofuran gave multicomponent reaction mixtures containing only small amounts of compound (**1**). Two procedures were developed for the conversion of the mixture of (**1**) and its ethyl ester into pure compound (**1**) without significant decarboxylation of the product (**1**). Treatment of the mixture with an aqueous solution of triethylamine (TEA) for 45 min or with a strongly basic ion exchange resin (IRA-400) for 2 h afforded compound (**1**) in 65—75% yields.

Experimental

M.p.s were determined in capillary tubes and are corrected. Elemental analyses were performed by M. G. Cornali, Microanalytical Laboratory, Leo Pharmaceutical Products, DK-2750 Ballerup, Denmark. I.r. spectra, obtained on a Perkin-Elmer 781 Infrared Spectrophotometer, were recorded in KBr pellets or as liquid films between NaCl discs. ^{1}H N.m.r. spectra were recorded on a Varian EM360L spectrometer using TMS as an internal standard. A Waters PrepLC-system 500A instrument was used for the preparative high-pressure liquid chromatography (h.p.l.c.) using silica gel columns (PrepPAK®-500/Silica). T.l.c. and gravity column chromatography were performed on silica F_{254} plates (Merck) and silica gel (Woelm, 0.063—0.200 mm), respectively. Evaporations were performed at temperatures below 50 °C, using a vacuum rotatory evaporator connected to a water aspirator.

3-Benzyloxy-5-methylisoxazole (**7**) *and 2-Benzyl-5-methylisoxazol-3(2H)-one* (**6**).—Potassium carbonate (56 g, 0.4 mol) was added to a solution of 3-hydroxy-5-methylisoxazole[30] (20 g, 0.2 mol) in acetone (500 ml) and the mixture stirred at *ca.* 60 °C for 1 h. Benzyl bromide (36 ml, 0.3 mol) was added slowly and the suspension stirred overnight at *ca.* 60 °C. After being cooled, the suspension was filtered and evaporated, and the resulting oil was subjected to preparative h.p.l.c on a silica gel column. Elution with toluene gave the *O*-benzylated compound (**7**) (15.3 g, 40%), m.p. 36.5—37.0 °C (ethyl acetate–light petroleum); $\nu_{max.}$ 3 140m, 3 080w, 3 060m, 3 030m, 2 930m, 2 880w, 1 620s, 1 505s, and 1 455s cm^{-1}; $\delta_H(CDCl_3)$ 7.4 (5 H, s), 5.65 (1 H, s), 5.3 (2 H, s), and 2.3 (3 H, s) (Found: C, 69.75; H, 6.0; N, 7.35. $C_{11}H_{11}NO_2$ requires C, 69.82; H, 5.86; N, 7.40%). Further elution with ethyl acetate gave the *N*-benzylated compound (**6**) (19.6 g, 51%), m.p. 54—55 °C (ethyl acetate–light petroleum); $\nu_{max.}$ 3 100m, 3 050w, 3 020w, 1 665s, 1 625m, and 1 490 cm^{-1}; $\delta_H(CDCl_3)$ 7.4 (5 H, s), 5.5 (1 H, s), 5.0 (2 H, s), and 2.2 (3 H, s) (Found: C, 69.7; H, 5.9; N, 7.3. $C_{11}H_{11}NO_2$ requires C, 69.82; H, 5.86; N, 7.40%).

(RS)-N-(*1-Phenylpentyl*)-*3-oxobutyramide* (**8**) *and* (RS)-N-[*2-(3-Benzyloxyisoxazol-5-yl)-1-phenylethyl*]-*3-oxobutyramide* (**9**).—A solution of 3-benzyloxy-5-methylisoxazole (**7**) (378 mg, 2 mmol) in dry tetrahydrofuran (THF) (5 ml) was slowly added to a stirred solution of butyl-lithium (2 ml, 1.1M in hexane, *ca.* 2.2 mmol) in dry THF (8 ml), previously cooled to −78 °C and kept under a nitrogen blanket. The dark brown solution was stirred for 15 min at −78 °C, then poured into a stirred suspension of carbon dioxide (*ca.* 50 g) in ether (50 ml). The suspension was stirred for *ca.* 2 h, the carbon dioxide was evaporated off, and the solution acidified with 4M hydrochloric acid and extracted with dichloromethane (3 × 10 ml). After evaporation of the dichloromethane phase, the residue was subjected to gravity column chromatography (*ca.* 30 g of silica gel). Elution with toluene–ethyl acetate (3:1) gave compound (**8**) (90 mg, 18%) as an oil; $\nu_{max.}$ 3 280br, 3 050m, 3 020m, 2 950s, 2 920s, 2 850m, 1 710br, and 1 640br cm^{-1}; $\delta_H(CDCl_3)$ 7.25 (5 H + 1 H, s), 4.9 (1 H, q), 3.35 (2 H, s), 2.2 (3 H, s), 1.85 (2 H, m), 1.25 (4 H, m), and 0.9 (3 H, pert. t) (Found: C, 72.45; H, 8.7; N, 5.55. $C_{15}H_{21}NO_2$ requires C, 72.83; H, 8.56; N, 5.69%). Further elution gave compound (**9**) (45 mg, 12%) (ethyl acetate–light petroleum), m.p. 114.0—114.5 °C; $\nu_{max.}$ 3 270s, 3 120m, 3 080m, 3 030w, 2 960w, 2 940w, 2 880w, 1 720s, 1 640s, and 1 615s cm^{-1}; $\delta_H(CDCl_3)$ 7.6 (1 H, d), 7.4—7.2 (10 H, m), 5.6 (1 H, s), 5.4 (1 H, q), 5.2 (2 H, s), 3.4 (2 H, s), 3.2 (2 H, d), and 2.2 (3 H, s) (Found: C, 69.8; H, 6.05; N, 7.35. $C_{22}H_{22}N_2O_4$ requires C, 69.83; H, 5.86; N, 7.40%).

Following a procedure similar to that described above, but with addition of butyl-lithium to a solution of compound (**7**), compound (**9**) was isolated as the sole product.

3-Benzyloxy-5-methylisoxazol-4-ylcarboxylic Acid (**10**) *and 3-Benzyloxyisoxazol-5-ylacetic Acid* (**11**).—A 1.1M solution of butyl-lithium in hexane (80 ml, 88 mmol) was added to a stirred solution of di-isopropylamine (13.6 ml, 96 mmol) in dry THF (150 ml), previously cooled to −78 °C and kept under a nitrogen blanket. 3-Benzyloxy-5-methylisoxazole (**7**) (15.1 g, 80 mmol), in THF (50 ml) was added slowly, while the temperature was kept below −65 °C. Stirring was continued for 30 min at −78 °C after which the dark brown solution was poured into a stirred suspension of carbon dioxide (*ca.* 500 g) in dry ether (200 ml). The excess of carbon dioxide evaporated overnight, and the resulting suspension (*ca.* 200 ml) was extracted with a half saturated solution of sodium hydrogen carbonate (3 × 100 ml). The combined aqueous phases were acidified with 4M hydrochloric acid and extracted with dichloromethane (3 × 150 ml). The combined dichloromethane extracts were dried ($MgSO_4$) and evaporated, then subjected to preparative h.p.l.c. on a silica gel column. Elution with toluene–ethyl acetate (9:1) containing 1% of glacial acetic acid gave compound (**10**) (1.65 g, 9%), m.p. 183—184 °C (ethyl acetate–light petroleum); $\nu_{max.}$ 3 300—2 400w—m, 1 755s, 1 615s, 1 525s, 1 470s, and 1 450m cm^{-1}; $\delta_H(CDCl_3)$ 7.5 (5 H, s), 5.35 (2 H, s), and 2.6 (3 H, s) (Found: C, 61.75; H, 4.85; N, 6.0. $C_{12}H_{11}NO_4$ requires C, 61.80; H, 4.75; N, 6.01%) and compound (**11**) (6.75 g, 36%), m.p. 93.0—93.5 °C (ethyl acetate–light petroleum); $\nu_{max.}$ 3 300—2 400 (several bands, w—m), 1 725s, 1 705s, 1 630s, and 1 510s cm^{-1}; $\delta_H(CDCl_3)$ 10.8 (1 H, s), 7.45 (5 H, s), 6.0 (1 H, s), 5.3 (2 H, s), and 3.8 (2 H, s) (Found: C, 61.85; H, 4.85; N, 5.95. $C_{12}H_{11}NO_4$ requires C, 61.80; H, 4.75; N, 6.01%).

Benzyl 3-Benzyloxyisoxazol-5-ylacetate (**12**).—Benzyl chloroformate (3.3 ml, 90%, 21 mmol) was added at 0 °C to a stirred solution of 3-benzyloxyisoxazol-5-ylacetic acid (**11**) (4.5 g, 19.3 mmol) and triethylamine (3 ml, 21.5 mmol) in dichloromethane (80 ml). After being stirred for 5 min the reaction mixture was extracted with 0.2M hydrochloric acid (80 ml); the dichloromethane phase was dried ($MgSO_4$), evaporated, and then subjected to preparative h.p.l.c. Elution with toluene gave compound (**12**) (6.1 g, 98%) as an oil; $\nu_{max.}$ 3 060w, 3 020w, 2 940w, 2 915w, 1 740s, 1 615s, 1 500s, and 1 450s cm^{-1}; $\delta_H(CDCl_3)$ 7.25 (5 H, s), 7.15 (5 H, s), 5.8 (1 H, s), 5.15 (2 H, s), 5.05 (2 H, s), and 3.65 (2 H, s) (Found: C, 70.65; H, 5.45; N, 4.3. $C_{19}H_{17}NO_4$ requires C, 70.57; H, 5.30; N, 4.33%).

(E,Z)-*Benzyl α-Hydroxyimino-3-benzyloxyisoxazol-5-ylacetate* (**13**).—Sodium hydride (33 mg, 80% dispersion in white oil, 1.1 mmol) was added at 0 °C to a solution of benzyl 3-benzyloxyisoxazol-5-ylacetate (**12**) (323 mg, 1 mmol) in dry THF (6 ml); this was followed immediately by the addition of butyl nitrite (200 µl, *ca.* 2 mmol). After being stirred for 5 min the reaction mixture was quenched with acetic acid (50 µl), water (10 ml) was added, and the mixture extracted with ether (3 × 10 ml). The combined organic phases were dried ($MgSO_4$) and evaporated and the residue subjected to column chromatography on silica (*ca.* 30 g). Elution with toluene–ethyl acetate (10:1) gave a mixture of the *E*- and the *Z*-forms of compound

(**13**) (245 mg, 70%). After recrystallization only one stereoisomer was obtained, m.p. 127—128 °C (toluene–light petroleum); $\nu_{max.}$ 3 400—3 100m, 3 060w, 3 030w, 1 745s, 1 590s, and 1 505s cm^{-1}; $\delta_H(CDCl_3)$ 7.5—7.3 (10 H, m), 6.7 (1 H, s), 5.4 (1.4 H, s), 5.35 (2 H, s), and 4.7 (0.6 H, s) (Found: C, 64.5; H, 4.55; N, 7.9. $C_{19}H_{16}N_2O_5$ requires C, 64.77; H, 4.58; N, 7.95%).

(RS)-α-*Amino*-3-*hydroxyisoxazol*-5-*ylacetic Acid Monohydrate* (**1**) (*Ibotenic Acid*).—A stream of hydrogen was passed for 1.5 h through a solution of (*E,Z*)-benzyl α-hydroxyimino-3-benzyloxyisoxazol-5-ylacetate (**13**) (141 mg, 0.4 mmol) in a solution of hydrogen chloride in ethanol (*ca.* 1%, 10 ml) containing palladium-on-carbon (40 mg, 10%). The reaction mixture was filtered through Celite and evaporated. The conversion of the reaction product into (**1**) was accomplished following two different procedures: (*a*) The residue was dissolved in water (5 ml) containing triethylamine (0.5 ml) and left for 45 min. After evaporation, the residue was dissolved in water (*ca.* 1 ml) and the pH of the solution was adjusted to *ca.* 3.5 by addition of glacial acetic acid when product (**1**) was precipitated (51 mg, 72%). The i.r. spectrum was identical with that of an authentic sample of ibotenic acid monohydrate. (*b*) The crude reaction mixture was dissolved in water (*ca.* 1 ml) and placed on a basic ionic exchange column (IRA-400) for 2 h. Elution with 2M acetic acid gave, after recrystallization from water, ibotenic acid monohydrate (**1**) (12 mg, 68%).

X-Ray Crystallographic Analysis of (RS)-N-[2-(3-*Benzyloxyisoxazol*-5-*yl*)-1-*phenylethyl*]-3-*oxobutyramide* (**9**).—The colourless, needle shaped crystals used for the *X*-ray examination were crystallized from ethyl acetate.

Crystal Data.—$C_{22}H_{22}N_2O_4$, M = 378.43. Monoclinic, a = 11.356(3), b = 19.218(4), c = 9.534(3) Å, β = 97.21(3)°, U = 2 064 $Å^3$, space group $P2_1/c$ (no. 14), Z = 4, D_c = 1.218 g cm^{-3}, μ(Mo-K_α) = 0.79 cm^{-1}.

Data Collection and Processing.—A single crystal of the size 0.30 × 0.30 × 0.45 mm was used for the determination of the unit cell parameters and for the collection of intensity data. The measurements were performed at room temperature with an Enraf-Nonius CAD-4 diffractometer using graphite monochromated (Mo-K_α) radiation (λ = 0.710 73 Å). A total of 4 252 independent reflections with θ < 27° were measured with θ—2θ scans; of these 1 565 had net intensities greater than 3σ(I), where σ(I) is the estimated standard deviation of an intensity as calculated from counting statistics. These were regarded as observed reflections and used in the refinement procedure. No absorption corrections were made.

Structure Analysis and Refinement.—The structure was solved by direct methods with the MULTAN program.[38] The structure was refined by full-matrix least-squares methods,[39] the quantity minimized was $\Sigma w(|F_o| - k|F_c|)^2$, where the weights were initially taken as unity. All hydrogen atoms, except hydrogen atoms of the methyl group could be located on intermediate difference maps. In subsequent least-squares calculations an overall scale factor, atomic co-ordinates and anisotropic thermal parameters for the non-hydrogen atoms were refined. The hydrogen atoms of the methyl group were not included in the calculations. The remaining hydrogen atoms were fixed in calculated positions (C–H = 1.0 Å), with the exception of the hydrogen atom bonded to N(1), which was fixed at the position located in a difference map. The thermal parameters for the hydrogen atoms were fixed at isotropic values corresponding to those of the atoms to which they are bonded. The weights used in the final cycles of refinement were given by $w = x \cdot y$, $x = 1$ for sin θ ≥ 0.30, else x = sin θ/0.30, $y = 1$ for $|F_o| \leq 20.0$ else $y = 20.0/|F_o|$, except reflections for which $|F_c| < 0.33|F_o|$, which were given $w = 0$. On the last cycle of least-squares refinement the value of the maximum shift/error was 0.01. The final R and R_w values are 0.071 and 0.081, respectively. Residual electron density in final difference Fourier map within +0.37 and −0.24 e $Å^{-3}$, except for one peak 0.73 e $Å^{-3}$, 2.1 Å from C(8).

The *X*-ray atomic scattering factors were those of Cromer and Mann[40] for O, N, and C, and of Stewart, Davidson, and Simpson[41] for H.

Table 1 lists the final positional parameters of the non-hydrogen atoms. Bond lengths and angles, and dimensions of an intermolecular hydrogen bond are given in Table 2. Several atoms, especially those of the acetyl group, undergo considerable thermal motion resulting in unreliable bond lengths and angles. During the refinement procedure intermediate difference maps have been carefully inspected. In particular, atoms of the acetyl group were removed and relocated on difference maps prior to refinement, but a better model was not obtained.

Isotropic and anisotropic thermal parameters of the non-hydrogen atoms and fractional co-ordinates for the hydrogen atoms are available on request from the Cambridge Crystallographic Data Centre.*

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* For details see para. 5.6.3 in Instructions for Authors (1988), *J. Chem. Soc., Perkin Trans. 1*, 1988, Issue 1.

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