Syntheses of (*RS*)-Homoibotenic Acid and (*RS*)-4-Bromohomoibotenic Acid. An Unusual Michael Type Reaction and Isoxazole Deprotection

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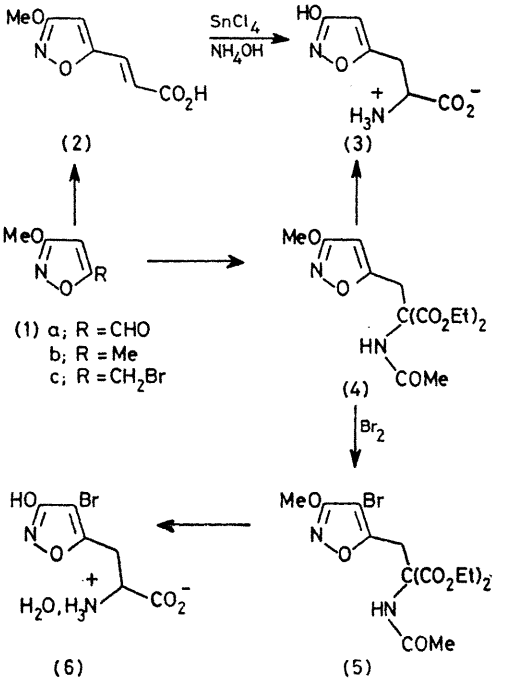
Summary Addition of ammonia to (*E*)-3-methoxyisoxazole-5-propenoic acid with concurrent Lewis acid induced deprotection yields (*RS*)-α-amino-3-hydroxyisoxazole-5-propionic acid (homoibotenic acid), which was independently synthesized by an unambiguous route also used for the preparation of (*RS*)-α-amino-3-hydroxy-4-bromoisoxazole-5-propionic acid.

Ibotenic acid [(*RS*)-α-amino-3-hydroxyisoxazole-5-acetic acid], a powerful neuronal excitant[1] isolated from *Amanita muscaria*,[2] is a semirigid analogue of the excitatory central neurotransmitter (*S*)-glutamic acid (Glu). The effects of Glu on the central nervous system are antagonized by (*R*)- and (*RS*)-α-aminoadipic acid,[3] and viewing the isoxazol-3-ol nucleus of ibotenic acid as a masked carboxy group

these findings prompted us to synthesize (*RS*)-α-amino-3-hydroxyisoxazole-5-propionic acid (homoibotenic acid) (**3**) and its 4-bromo derivative (**6**).

Homoibotenic acid (**3**) was synthesized in 25% yield, m.p. 250 °C (decomp.) (from H_2O),† by a Lewis acid catalysed nucleophilic addition of ammonia to (*E*)-3-methoxyisoxazole-5-propenoic acid (**2**) with simultaneous demethylation of the 3-methoxyisoxazole unit (Scheme).



SCHEME

The propenoic acid (**2**),‡ obtained in 55% yield, m.p. 201—202 °C (from EtOH), by a Knoevenagel condensation of (**1a**)[4] with malonic acid, was dissolved in saturated aqueous ammonia and tin(IV) chloride was added, with precipitation of tin(IV) oxide hydrate. After heating the mixture under pressure at 105 °C for *ca.* 6 days the resulting 'inverse' addition to the αβ-unsaturated acid appears to be effected with a high degree of regioselectivity. In no case was any β-amino acid isolated. The dominant influence of the 3-methoxyisoxazole nucleus on the course of the reaction is in agreement with the recent finding that a methyl group is introduced regiospecifically into the position α to the isoxazole ring by methylation of a lithiated derivative of 3-methoxyisoxazole-5-propionic acid.[5] Treatment of (**2**) with concentrated aqueous ammonia under the above-mentioned conditions, but without addition of tin(IV) chloride, yielded after work-up only *ca.* 2% of a ninhydrin-active product mixture, from which neither (**3**) nor its *O*-methylated derivative was isolated. The concurrent Lewis acid induced demethylation of the 3-methoxyisoxazole unit under mildly basic conditions is new and seems to be of general utility. For example, 3-methoxyisoxazole-5-propionic acid was demethylated by the described procedure, a reaction not effected by either concentrated aqueous ammonia or by a refluxing aqueous solution of tin(IV) chloride. Ether cleavage of 3-methoxyisoxazole derivatives is of synthetic importance and is normally accomplished under strongly acidic conditions.

The structure of (**3**) was confirmed by its unequivocal synthesis *via* cleavage of (**4**) with refluxing 48% aqueous HBr for 15—20 min (55% yield after triethylamine treatment). The intermediate (**4**) was prepared in 65% yield, m.p. 113—114 °C (from H_2O), by alkylation of diethyl acetamidomalonate by 3-methoxy-5-bromomethylisoxazole (**1c**). Compound (**1c**)[6] was obtained in 50% yield, b.p. 118—123 °C at 15 mmHg, by a convenient new procedure utilizing free-radical bromination of (**1b**).[7]

Treatment of (**4**) with bromine (neat) at 25 °C for 6 h gave (**5**) in 85% yield, m.p. 98—99 °C (from H_2O), in contrast to its lack of reaction during 24 h in refluxing Br_2–CCl_4. Conversion of (**5**) into (*RS*)-α-amino-4-bromo-3-hydroxyisoxazole-5-propionic acid monohydrate (**6**), in 45% yield, m.p. 207 °C (decomp.) (from H_2O), was accomplished under conditions similar to those applied to the conversion of (**4**) into (**3**).

Based on microelectrophoretic experiments on cat spinal interneurones, (**3**) is moderately potent and (**6**) very potent and specific as Glu-like neuronal excitants.[8]

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† The new compounds (**2**)—(**6**) gave satisfactory (within ± 0·2%) elemental analyses and i.r. and ^1H n.m.r. spectra consistent with the depicted structures.

‡ This compound was also isolated by us as a by-product from a reaction sequence stated (J. Thiele and H. Landers, *Annalen*, 1909, **369**, 300) to give 3-methoxyisoxazole-5-propionic acid as the only product.

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