A Convenient Synthesis of the Neuroexcitatory Amino Acid Quisqualic Acid and Its Analogues

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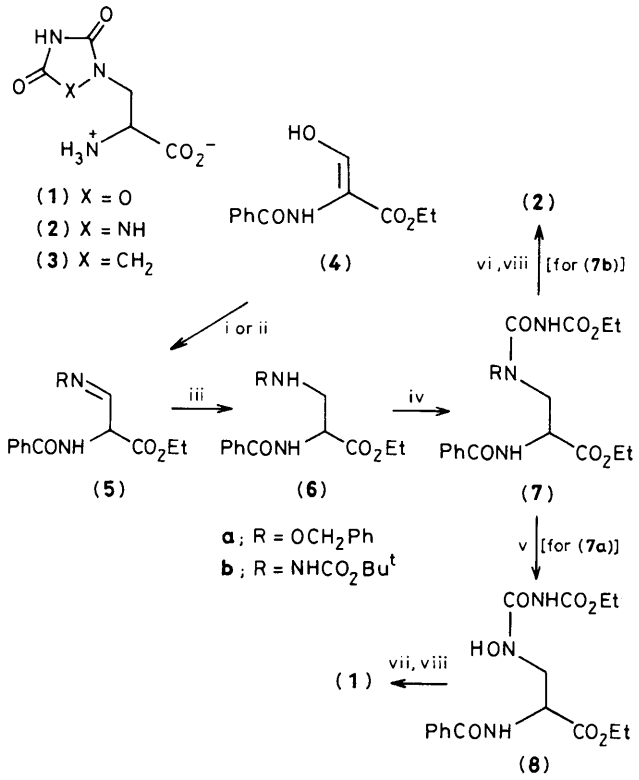
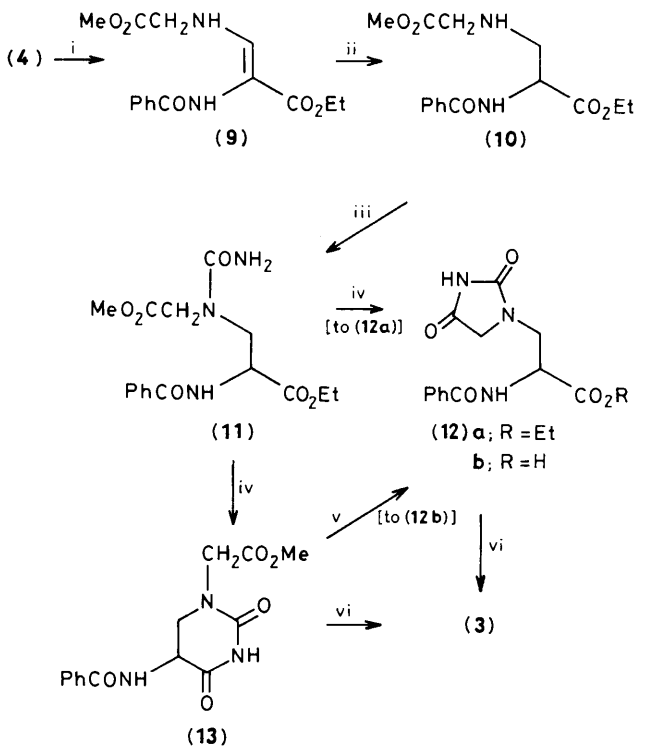
Reaction of the enol (**4**) with hydroxylamines, hydrazines, and glycine esters provides convenient intermediates for the synthesis of quisqualic acid (**1**) and its analogues (**2**) and (**3**).

L-Quisqualic acid (**1**) isolated from the seeds of the plant *Quisqualis indica* is one of the most potent agonists of the neurotransmitter amino acid L-glutamate in both the central and peripheral nervous systems of vertebrates and invertebrates.[1] Although the structure was established some years ago,[2—4] the relative inaccessibility of (**1**) from the natural source, or by a convenient synthesis, has limited detailed evaluation of the molecular pharmacology.

As part of our general interest in amino acid synthesis,[5] we now report an efficient synthetic route to (**1**) as well as to its analogues (**2**) and (**3**). The enol (**4**) which was readily prepared from ethyl hippurate and ethyl formate[6] is a



Reagents and conditions: i, $PhCH_2ONH_2$; ii, $NH_2NHCO_2Bu^t$; iii, $NaBH_3CN$, pH 2—3; iv, EtO_2CNCO; v, Pd/C–H_2; vi, CF_3CO_2H, 20 °C; vii, 1 M-NaOH, 20 °C; viii, 6 M-HCl.



Reagents and conditions: i, $MeO_2CCH_2NH_2$; ii, $NaBH_3CN$, pH 2—3; iii, KCNO, HCl; iv, H_2O, 100 °C; v, 1 M-NaOH, 20 °C; vi, 6 M-HCl.

convenient synthon for the construction of α-amino acids.[7]†

Condensation of (**4**) with *O*-benzylhydroxylamine or t-butoxycarbonylhydrazine afforded (**5a**), m.p. 88—89 °C, or (**5b**), m.p. 155 °C, both of which were identified by the AB pattern in their ^1H n.m.r. spectra as being in their imine form, whereas methyl glycinate gave the (*Z*)-enamine (**9**), showing just a vinyl proton singlet at δ_H 7.13. Sodium cyanoborohydride readily reduced both types of system to the corresponding diaminopropionic acid derivatives (**6**) and (**10**), each of which possesses an appropriate side chain for the construction of the required heterocyclic systems.

For the synthesis of (**1**), the reaction of (**6a**) with ethoxycarbonyl isocyanate gave the intermediate (**7a**), m.p. 98—100 °C, which upon hydrogenolysis afforded the *N*-hydroxyureide (**8**). Ring closure to the oxadiazolidinedione and deprotection, effected with aqueous sodium hydroxide and 6 M-hydrochloric acid, respectively, afforded (*RS*)-quisqualic acid (**1**), m.p. 190—191 °C, in an overall yield of 20% from (**4**). Enzymic resolution of the *N*-acyl derivatives of (**1**) using either hog renal or *E. coli* acylases lead to the L-(*S*)-isomer identical with the natural material.

A similar series of reactions was employed for the triazolidinedione analogue (**2**), the ring structure being formed spontaneously on deprotection of the hydrazine derivative (**7b**) with trifluoroacetic acid. Removal of the ester and acyl groups by acid hydrolysis gave the racemic amino acid (**2**), m.p. 247—250 °C, in an overall yield of 50% from the enol (**4**).

† Alternative protection for the amino and carboxy groups can be employed for the synthesis of sensitive α-amino acid systems.

The ureide (**11**), formed by treatment of the reduced methyl glycinate condensation product (**10**) with potassium cyanate, cyclised in boiling water to a mixture of the hydantoin (**12a**), m.p. 222—224 °C, and the dihydrouracil (**13**), m.p. 263—265 °C. The latter underwent ester hydrolysis and rearrangement to the imidazolidinedione (**12b**) in sodium hydroxide. Acid hydrolysis of (**12**) and (**13**) afforded the racemic amino acid (**3**), m.p. 280—282 °C, the structure of which was confirmed by *X*-ray crystallographic analysis and showed, as expected, that the ring-junction nitrogen atom had trigonal geometry, contrasting with the tetrahedral arrangement for this nitrogen atom in quisqualic acid.[4]

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