

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

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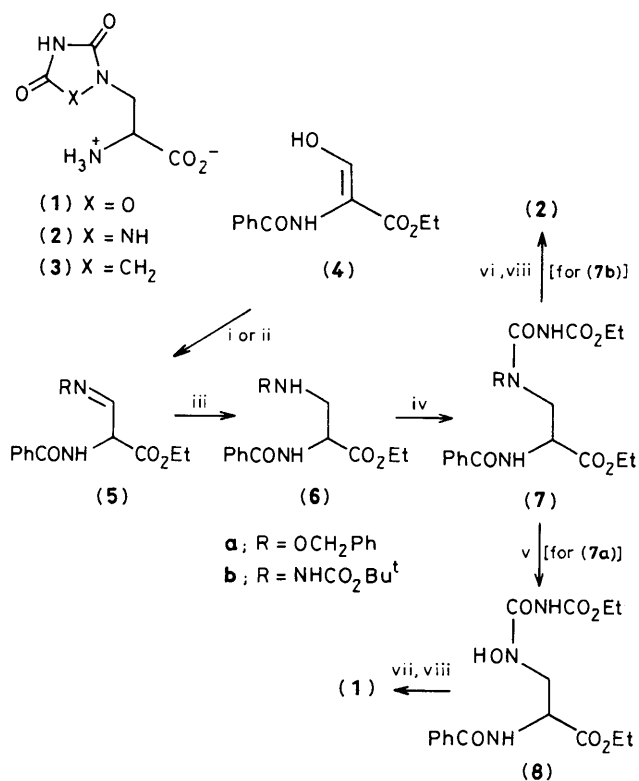
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Reaction of the enol (**4**) with hydroxylamines, hydrazines, and glycine esters provides convenient intermediates for the synthesis of quisqualic acid (**1**) and its analogues (**2**) and (**3**).

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 formate⁶ is a



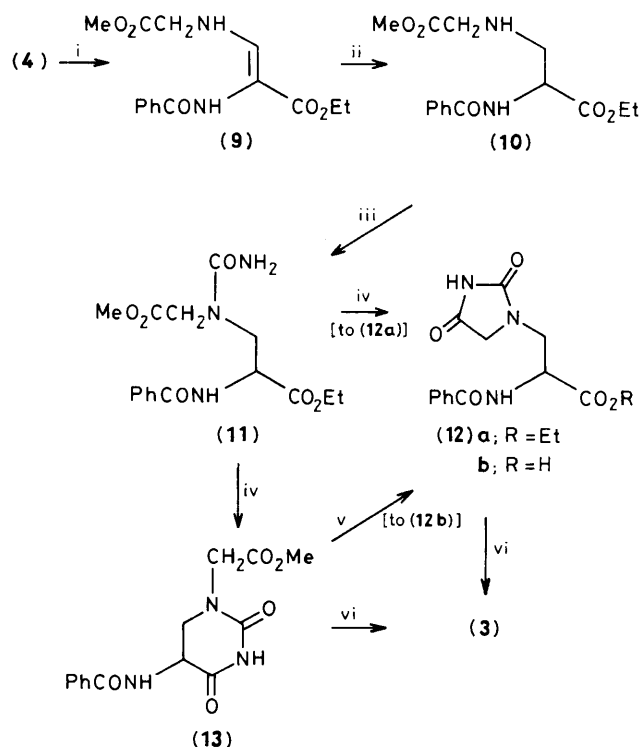
Reagents and conditions: i, PhCH₂ONH₂; ii, NH₂NHCO₂Bu^t; iii, NaBH₃CN, pH 2–3; iv, EtO₂CNCO; v, Pd/C–H₂; vi, CF₃CO₂H, 20 °C; vii, 1 M-NaOH, 20 °C; viii, 6 M-HCl.

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 triazolinedione 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).



Reagents and conditions: i, MeO₂CCH₂NH₂; ii, NaBH₃CN, pH 2–3; iii, KCN, HCl; iv, H₂O, 100 °C; v, 1 M-NaOH, 20 °C; vi, 6 M-HCl.

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