# A Selective and Efficient Synthesis of Quisqualamine, a Novel GABA-Related Depressant Amino Acid

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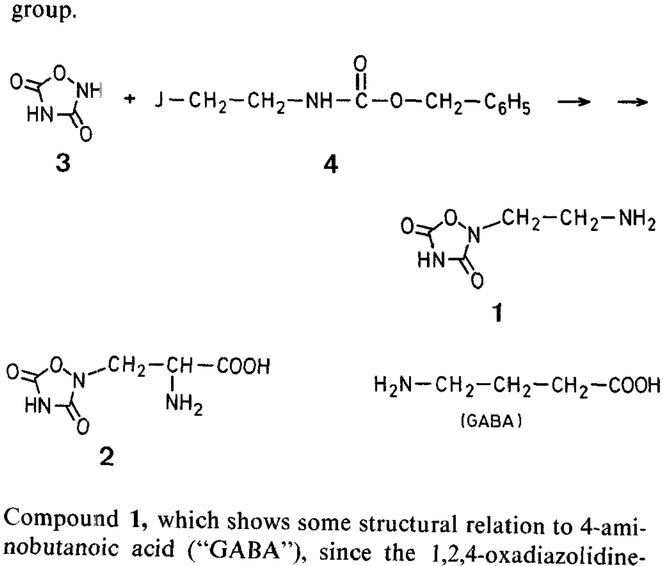
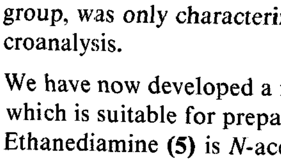
Quisqualamine (**1**), the decarboxylated derivative of quisqualic acid (**2**) isolated[1] from the chinese plant *Quisqualis Indica*, has been synthesized[2] in 10% yield by the reaction of 1,2,4-oxadiazolidine-3,5-dione[3] (**3**) with *N*-benzyloxycarbonyliodoethanamine and subsequent deprotection of the amino group.

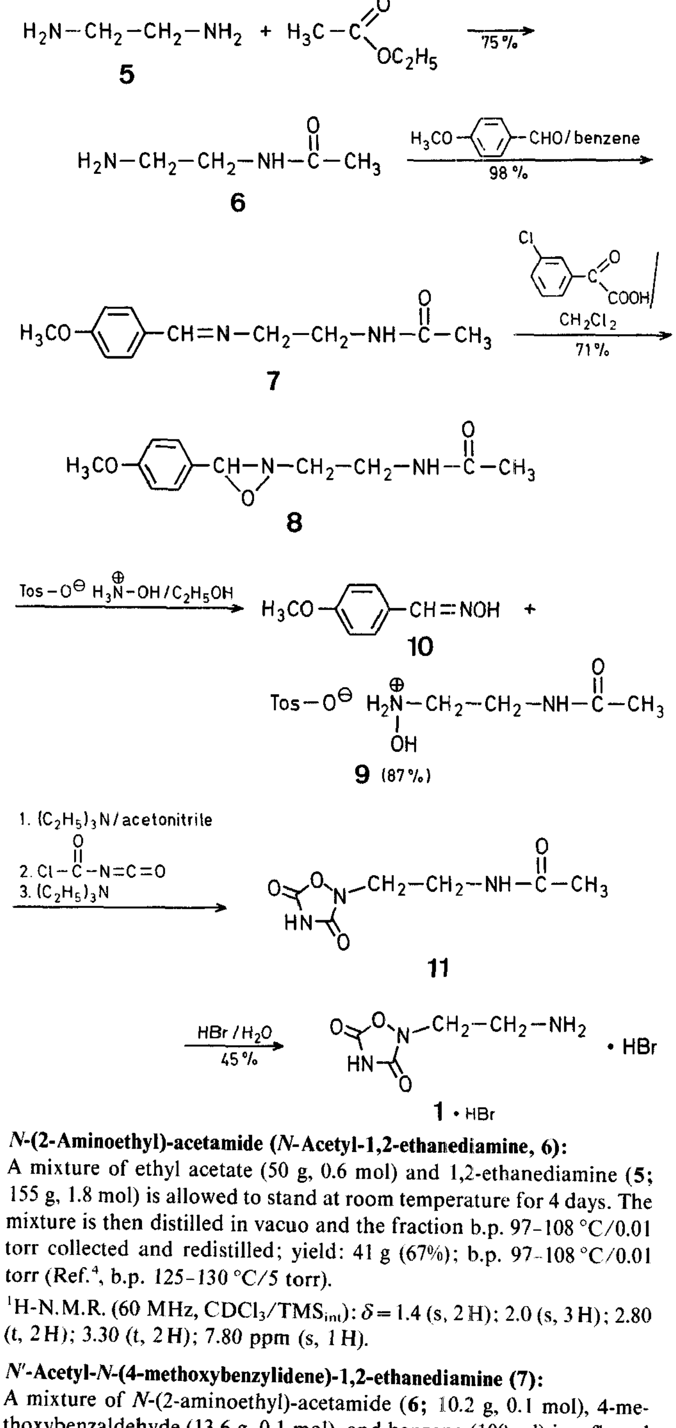



**2**

$H_2N-CH_2-CH_2-CH_2-COOH$
(GABA)

Compound **1**, which shows some structural relation to 4-aminobutanoic acid ("GABA"), since the 1,2,4-oxadiazolidine-3,5-dione nucleus can be regarded[9] as a masked carboxyl group, was only characterized by its melting point and by microanalysis.

We have now developed a new synthesis of quisqualamine (**1**) which is suitable for preparations on a larger, 10 g, scale. 1,2-Ethanediamine (**5**) is *N*-acetylated with ethyl acetate[4] and the resultant monoacetyl derivative **6** condensed with 4-methoxybenzaldehyde to give the *N*′-protected aldimine **7**. Oxidation[5,6] of **7** with 3-chlorobenzoperoxoic acid affords the oxaziridine derivative **8** which is cleaved with hydroxylammonium tosylate[7] to give the aldoxime **10** and the *N*′-protected 2-aminoethylhydroxylamine salt **9**. Neutralization of **9** with triethylamine followed by reaction with chlorocarbonyl isocyanate[8] affords *N*-acetylquisqualamine (**11**) which can be cleaved with 1.3 normal hydrobromic acid to give quisqualamine hydrobromide (**1** · HBr). Free quisqualamine (**1**) is obtained in 14% overall yield (based on **5**) by treatment of **1** · HBr with KOH and a H$^{\oplus}$ resin (Dowex 50 WX 8, 50-100 mesh).



**N-(2-Aminoethyl)-acetamide (N-Acetyl-1,2-ethanediamine, 6):**
A mixture of ethyl acetate (50 g, 0.6 mol) and 1,2-ethanediamine (**5**; 155 g, 1.8 mol) is allowed to stand at room temperature for 4 days. The mixture is then distilled in vacuo and the fraction b.p. 97-108 °C/0.01 torr collected and redistilled; yield: 41 g (67%); b.p. 97-108 °C/0.01 torr (Ref.[4], b.p. 125-130 °C/5 torr).

$^1$H-N.M.R. (60 MHz, $CDCl_3/TMS_{int}$): $\delta = 1.4$ (s, 2H); 2.0 (s, 3H); 2.80 (t, 2H); 3.30 (t, 2H); 7.80 ppm (s, 1H).

**N′-Acetyl-N-(4-methoxybenzylidene)-1,2-ethanediamine (7):**
A mixture of *N*-(2-aminoethyl)-acetamide (**6**; 10.2 g, 0.1 mol), 4-methoxybenzaldehyde (13.6 g, 0.1 mol), and benzene (100 ml) is refluxed for 3 h with azeotropic removal of water. Then, the solvent is removed using a rotary evaporator and the residual crude product allowed to crystallize; yield: 22 g (>98%); m.p. 63 °C. For purification, the product may be recrystallized from ligroin; m.p. 64 °C.

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|---|---|---|---|---|
| $C_{12}H_{16}N_2O_2$ | calc. | C 65.46 | H 7.27 | N 12.73 |
| (220.3) | found | 65.64 | 7.31 | 12.54 |

$^1$H-N.M.R. (60 MHz, $CDCl_3/TMS_{int}$): $\delta = 1.95$ (s, 3H); 3.6 (m, 4H); 3.75 (s, 3H); 6.25 (s, 1H); 7.25 (AB pattern, 4H); 8.15 ppm (s, 1H).

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**2-(2-Acetylaminoethyl)-3-(4-methoxyphenyl)-oxaziridine (8):**

A solution of imine **7** (53.4 g, 0.24 mol) in dichloromethane (180 ml) is added, over 1 h, to a stirred suspension of 85% 3-chlorobenzoperoxoic acid (50 g, 0.24 mol) in dichloromethane (250 ml) at 0–3 °C. After the end of the addition, the mixture is kept 48 h at 5 °C and then is filtered from the precipitated 3-chlorobenzoic acid. The solvent is removed on a rotary evaporator at 20 °C and the residue is redissolved in the minimum amount of dichloromethane (25 ml). Ether (100 ml) is added a few minutes later whereupon product **8** precipitates as a white solid. The product is isolated by suction, washed with ether, and dried in vacuo; yield: 40.2 g (71%); m.p. 95 °C.

| | | | | |
|---|---|---|---|---|
| $C_{12}H_{16}N_2O_3$ | calc. | C 61.02 | H 6.78 | N 11.86 |
| (236.3) | found | 61.37 | 6.80 | 11.53 |

$^1$H-N.M.R. (100 MHz, $CDCl_3/TMS_{int}$): $\delta = 2.01$ (s, 3 H); 2.4–2.7, 3.2–3.45 (2 m, 2 H); 3.55 (m, 2 H); 3.67 (s, 3 H); 4.52 (s, 1 H); 6.55 (s, 1 H); 7.08 ppm (AB pattern, 4 H).

$^{13}$C-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 23.08$ ($CO—\underline{C}H_3$); 38.37 ($\underline{C}H_2—NH$); 55.19 ($H_3\underline{C}O$); 60.73 ($N—\underline{C}H_2—CH_2—NH$); 79.82 ($C_6H_4—\underline{C}H$); 170.24 ($\underline{C}O—CH_3$); 113.84, 125.97, 128.83, 160.98 ppm ($\underline{C}_6H_4$).

***N*-Hydroxy-2-acetylaminoethanaminium Tosylate (9):**

A mixture of the oxaziridine **8** (28.1 g, 0.12 mol), hydroxylamine *p*-toluenesulfonate (24.1 g, 0.12 mol), and ethanol (90 ml) is stirred at room temperature overnight. The resultant white precipitate is isolated by suction; yield: 30.0 g (87%): m.p. 154 °C. For purification, the product may be recrystallized from ethanol; m.p. 154 °C.

| | | | | |
|---|---|---|---|---|
| $C_{11}H_{18}N_2O_5S$ | calc. | C 45.67 | H 6.23 | N 9.69 |
| (289.3) | found | 45.46 | 6.30 | 9.51 |

$^1$H-N.M.R. (100 MHz, $D_2O/TMS_{ext}$): $\delta = 1.96$ (s, 3 H); 2.30 (s, 3 H); 3.4 (m, 4 H); 7.50 ppm (AB, pattern, 4 H).

$^{13}$C-N.M.R. ($D_2O/TMS_{ext}$): $\delta = 23.51$ ($CO—\underline{C}H_3$); 24.79 ($H_3\underline{C}—C_6H_4$); 36.6 ($CH_2—\underline{C}H_2—NH—CO$); 53.30 ($\underline{C}H_2—CH_2—NH—CO$); 178.2 ($\underline{C}O—CH_3$); 128.28, 132.36, 142.4, 145.3 ppm ($\underline{C}_6H_4$).

***N*-Acetylquisqualamine (11):**

A solution of *N*-hydroxy-2-acetylaminoethylethanaminium tosylate (**9**; 20 g, 0.069 mol) in acetonitrile (60 ml) is neutralized by the addition of a solution of triethylamine (7.0 g, 0.07 mol) in acetonitrile (15 ml). The mixture is then cooled to −10 °C and a solution of chlorocarbonyl isocyanate (7.28 g, 0.069 mol) in acetonitrile (15 ml) is added, followed at 0 °C by triethylamine (7.0 g, 0.07 mol). The mixture is allowed to stand at room temperature for 2 h, and the solvent then removed in vacuo. To the residue, a solution of potassium hydroxide (15.5 g, 0.28 mol) in methanol (70 ml) is added and the mixture is kept at −15 °C overnight. The precipitated salts (potassium chloride and tosylate) are filtered off, the solvent and free triethylamine are removed in vacuo, the basic residue is dissolved in methanol (100 ml), and gaseous hydrogen chloride is passed through this solution until pH 1 is reached. The potassium chloride is filtered off and the filtrate is evaporated to give crude **11** as a viscous oil; yield: 13 g (98%).

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|---|---|---|---|---|
| $C_6H_9N_3O_4$ | calc. | C 38.50 | H 4.81 | N 22.45 |
| (187.2) | found | 38.42 | 4.76 | 22.40 |

$^1$H-N.M.R. (100 MHz, $D_2O/TMS_{ext}$): $\delta = 2.00$ (s, 3 H); 3.5 (m, 2 H); 3.83 ppm (m, 2 H).

$^{13}$C-N.M.R. ($D_2O/TMS_{ext}$): $\delta = 24.3$ ($CO—\underline{C}H_3$); 39.1 ($CH_2—\underline{C}H_2—NH$); 51.6 ($\underline{C}H_2—CH_2—NH$); 155.4, 159.8 ($2CO_{ring}$); 176.8 ($\underline{C}O—CH_3$).

**Quisqualamine Hydrobromide (1 · HBr):**

The crude *N*-acetylquisqualamine (**11**; 13 g, 0.07 mol) is stirred with 1.3 normal hydrobromic acid (300 ml) for 10 h at 70 °C. Water is then removed in vacuo at 50 °C, the residue is washed with acetone (2 × 20 ml), and recrystallized from methanol to give **1** · HBr as a grey powder; yield: 7.1 g (45%); m.p. 215 °C.

I.R. (1% in KBr): $\nu = 1755$; 1795 cm$^{-1}$.

$^1$H-N.M.R. (100 MHz, $D_2O/TMS_{ext}$): $\delta = 3.45$ (t, 2 H); 4.10 ppm (t, 2 H, $J = 6$ Hz),

$^{13}$C-N.M.R. ($D_2O/TMS_{ext}$): $\delta = 40.1$ ($CH_2—\underline{C}H_2—NH_3$); 49.80 ($\underline{C}H_2—CH_2—NH_3$); 145.42, 161.25 ppm ($2\underline{C}O_{ring}$).

**Quisqualamine (1, Zwitterionic Form):**

Quisqualamine hydrobromide (**1** · HBr; 1.5 g, 0.0066 mol) and potassium hydroxide (2 g, 0,036 mol) are mixed in water (10 ml). This solution is poured on 25 g of Dowex 50 WX 8, 50–100 mesh and the resin is gently stirred for 30 min. The resin is then filtered, washed with water (200 ml) and pure quisqualamine is eluted using triethylamine/methanol/water (5/4/16) as eluent; yield: 0.75 g (78% from **1** · HBr, 14% overall from **5**); m.p. 194 °C (Ref.[2], m.p. 188°–190 °C).

| | | | | |
|---|---|---|---|---|
| $C_4H_7N_3O_3$ | calc. | C 33.10 | H 4.83 | N 28.97 |
| (145.1) | found | 33.10 | 4.73 | 29.84 |

$^1$H-N.M.R. (100 MHz, $D_2O/TMS_{ext}$): $\delta = 3.20$ (t, 2 H); 3.70 ppm (t, 2 H, $J = 6$ Hz),

$^{13}$C-N.M.R. (s, $D_2O/TMS_{ext}$): $\delta = 40.7$ ($CH_2—\underline{C}H_2—NH_3$); 50.5 ($\underline{C}H_2—CH_2—NH_3$); 170.9, 177.1 ppm ($2\underline{C}O_{ring}$).

Received: November 6, 1981
(Revised form: January 28, 1982)

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