Structural Analogues of GABA. A New Convenient Synthesis of Muscimol

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Muscimol (5-aminomethyl-3-isoxazolol) (8), a centrally active constituent of Amanita muscaria, is a semirigid analogue of γ -aminobutyric acid (GABA) 1 of considerable pharmacological and neurochemical interest. Various widely different routes for the synthesis of muscimol (8) have been published. $^{2-5}$ This paper presents a new and more convenient synthesis of δ .

Attempts to convert 2, prepared from 1, into 3-methoxy-5-aminomethylisoxazole hydrochloride (6) via reduction with lithium aluminium hydride gave 6 in very low yields. Attempts to convert 1 into 4 by treatment with lithium tri-t-butoxyaluminium hydride according to a general procedure 6 were unsuccessful. Finally the acid chloride 1 was transformed into muscimol hydrobromide (7) (Scheme 1) without purification of intermediate products. A crude product of the unstable 1-acylaziridine 3 was treated with lithium aluminium hydride, followed by hydrolysis, to give 3-methoxy-5isoxazolecarboxaldehyde (4) in a good yield. However, contrary to previous findings from analogous reactions,^{5,7,8} satisfactory yields of 4 could only be obtained by using equimolar amounts of 3 and the reagent. Kishida et al. have reported a synthesis of 4 based on 3,3-diethoxypropyn through several steps. The mixture of isomeric oximes 5 was reduced by aluminium amalgam, and 3-methoxy-5-aminomethylisoxazole was isolated as the hydrochloride 6, which was transformed into 7. The total yield of 7 from 1 was 35 %.

The structure determinations of 3, 5, and 7, which are new compounds, are based on spectro-

scopic methods. The IR, UV, and ¹H NMR data of 2 and 6, which have not previously been reported, are described. The product 5 consists of a mixture of the Z- and E-forms of the aldoxime as established by TLC and ¹H NMR spectroscopy in agreement with the findings for a series of similarly prepared ketoximes. ^{10,11} The structure of 7 was determined by conversion of the compound into muscimol (8), the identity of which was established.

Experimental. The determination of melting points, the recording of IR, UV, and ¹H NMR spectra, and the performance of microanalyses were accomplished as described in a previous paper. ¹² Mass spectra were measured on a Finnigan 3500D mass spectrometer at 70 eV. TLC was carried out using silica gel GF₂₈₄ plates (Merck).

3-Methoxy-5-isoxazolecarboxamide (2). 3-Methoxy-5-isoxazolecarbonylchloride (1) 10 (970 mg; 6 mmol) was added drop by drop to aqueous ammonia (2 ml; ϱ 0.88) at 0 °C. Upon standing at 0 °C for 15 min the mixture was evaporated in vacuo. Recrystallization (water) afforded 700 mg (82 %) of 2, m.p. 175.0 – 176.0 °C (Ref. 3, m.p. 174 – 175 °C). $\lambda_{\rm max}$ 221 nm (CH₃OH) (ε = 1.25 × 10⁴). IR data (KBr) cm⁻¹: 3360 (m), 3195 (m), 3150 (m), 1680 (s), 1625 (m), 1610 (m), 1530 – 1515 (s). ¹H NMR data (DMSO – $d_{\rm g}$): δ 8.4 – 7.7 (two broad s, 2 H); 6.75 (s, 1 H); 3.91 (s, 3 H).

N,N-Ethylene-3-methoxy-5-isoxazolecarbox-amide (3). To a solution of aziridine (900 mg; 21 mmol) and triethylamine (2.4 g; 24 mmol) in ether (120 ml) was slowly added at 0 °C a solution of 1 (3.4 g; 21 mmol) in ether (80 ml). After stirring for 10 min at 0 °C the mixture was filtered to give an ether solution of 3, an analytical sample of which was evaporated in vacuo. Recrystallization (benzene-petroleum ether) gave 3, m.p. 56.0-57.0 °C (decomp.). $\lambda_{\rm max}$ 231 nm (CH₃OH) (ε =1.14×10⁴). IR data (KBr) cm⁻¹: 3130 (m), 3010 (w), 2950 (w), 1675 (s), 1610 (m), 1530 (m), 1515 (s). ¹H NMR

Scheme 1.

data (CDCl₃): δ 6.47 (s, 1 H); 3.97 (s, 3 H);

2.50 (s, 4 H).

3-Methoxy-5-isoxazolecarboxaldehyde (4). To the above ether solution of crude 3 was added at 0 °C lithium aluminium hydride (722 mg; 21 mmol). After stirring the mixture at 0 °C for 2 h an aqueous solution of sulfuric acid (40 ml; 20 %) was added. The organic phase was isolated and the aqueous phase extracted with three 40 ml portions of ether. The combined ether phases were dried and concentrated in vacuo to give 2.1 g of crude 4. An analytical sample was distilled in vacuo in a "kugelrohr" to give 4, the IR and ¹H NMR data of which were consistent with those published for 4.º

3-Methoxy-5-hydroxyiminomethylisoxazole (5). A solution of crude 4 (2.1 g; ca. 17 mmol), sodium acetate trihydrate (2.5 g; 18 mmol), and hydroxylammonium chloride (1.3 g; 18 mmol) in aqueous ethanol (50 ml; 50 %) was refluxed for 30 min. The solution was evaporated in vacuo and upon addition of water (10 ml) the mixture was extracted with three 20 ml portions of ether. The combined ether phases were dried and evaporated in vacuo to give 1.8 g of crude 5, which was shown by TLC to consist of two compounds with $R_F = 0.05$ and $R_F = 0.03$ (eluent: methylene chloride). ¹H NMR data of crude δ (DMSO- $d_{\rm e}$), which are consistent with a mixture (ca. 2:3) of the isomeric oximes: δ 12.5 and 12.0 (two broad signals, 0.4 H and 0.6 H, respectively); 8.08 and 7.60 (two s, 0.6 H and 0.4 H, respectively); 6.72 and 6.38 (two s, 0.4 H and 0.6 H, respectively); 3.93 and 3.91 (two s, a total of 3 H).

3-Methoxy-5-aminomethylisoxazole hydrochloride (6). To a solution of crude 5 (1.8 g; ca. 13 mmol) in aqueous methanol (80 ml; 50 %) was added aluminium amalgam, prepared by treatment of aluminium strips (3.9 g; 144 mmol) with an aqueous solution of mercuric chloride (200 ml; 5 %) for 30 s followed by washing with ethanol. After stirring for 4 h at 25 °C the mixture was filtered. Upon addition of hydrochloric acid (4 ml; 4 N) the filtrate was evaporated in vacuo to give 2.5 g of crude 6. Recrystallization (2-propanol) of an analytical sample afforded 6, m.p. 176-177 °C (decomp.) (Ref. 3, m.p. 175-177 °C). λ_{max} < 210 nm (CH₂OH). IR data (KBr) cm⁻¹: 3500-3350 (m), 3130 (m), 3050-2400 (s), 1625 (s), 1580 (w), 1510 (s). ¹H NMR data (DMSO-d_e): δ 9.6-8.4 (broad s, 3 H); 6.45 (s, 1 H); 4.17 (broad s, 2 H); 3.94 (s, 3 H).

5-Aminomethyl-3-isoxazolol hydrobromide (7). A solution of crude 6 (2.5 g; ca. 15 mmol) in glacial acetic acid (30 ml) containing 43 % of hydrogen bromide was refluxed for 10 min. The solution was evaporated in vacuo. Recrystallization (methanol-ether) afforded 1.49 g of 7, m.p. 179-181 °C (decomp.). Anal. C₄H₇BrN₂O₂: C, H, N, Br. $\lambda_{\text{max}} < 210$ nm (CH₃OH). IR data (KBr) cm⁻¹: 3530-3300 (m), 3200-2300 (s), 1635 (s), 1595 (m), 1580 (m), 1545 (s), 1505 (s). ¹H NMR data (DMSO- d_{θ}):

 δ 10.3 – 9.0 (broad s, 4 H); 6.25 (s, 1 H); 4.15 (s. 2 H).

5-Aminomethyl-3-isoxazolol (Muscimol) (8). An analytical sample of 7 was passed through a column containing ion exchange resin [Amberlite IRA 400, (OH), 5 ml] using acetic acid (1 M) as an eluent. The fractions containing 8 were concentrated in vacuo, and recrystallization (water-ethanol) of the residue gave muscimol (8), m.p. 171-172 °C (decomp.) [Ref. 3, m.p. 172-174 °C (decomp.)]. The IR and mass spectra of 8 were identical with those of an authentic sample.

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