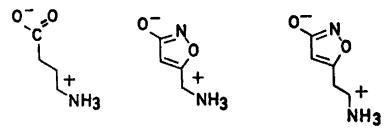
Acta Chemica Scandinavica B 31 (1977) 577—583

Muscimol Analogues. I. Syntheses of 4- and 8-Aminocyclohepteno[1,2-*d*]isoxazol-3-ols and 4-(3-Aminopropyl)-5-methyl-3-isoxazolol

POVL KROGSGAARD-LARSEN, LILIANA NATOVA * and SØREN BRØGGER CHRISTENSEN

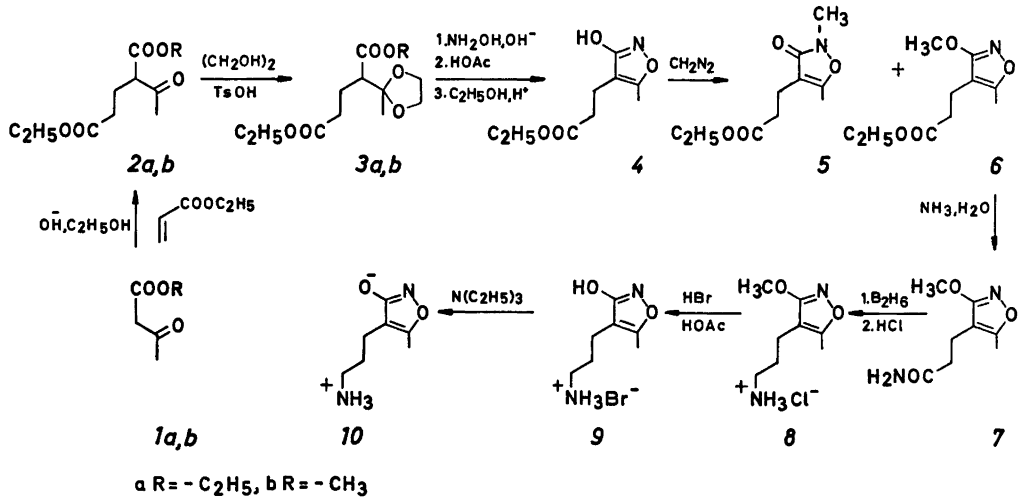
Royal Danish School of Pharmacy, Department of Chemistry BC, DK-2100 Copenhagen Ø, Denmark

The syntheses of the zwitterions 4-(3-aminopropyl)-5-methyl-3-isoxazolol (*10*) and 4- and 8-aminocyclohepteno[1,2-*d*]isoxazol-3-ols (*23*) and (*19*), which are structural analogues of muscimol (5-aminomethyl-3-isoxazolol) and γ-aminobutyric acid (GABA), are described. The 3-isoxazolol zwitterion *10* was synthesized *via* ethyl 3-(3-hydroxy-5-methylisoxazol-4-yl)-propionate (*4*) by using 1-methyl 5-ethyl 2-acetylglutarate (*2b*) as a starting compound. The zwitterions *19* and *23* were prepared *via* 3-methoxycyclohepteno[1,2-*d*]isoxazol-8-one (*15*) and 3-methoxycyclohepteno[1,2-*d*]isoxazol-4-one (*16*), respectively. *15* and *16* were prepared by chromic acid oxidation of 3-methoxycyclohepteno[1,2-*d*]isoxazole (*13*). The pK_A values of *10*, *19*, and *23* have been determined.



Scheme 1.

Muscimol [1,2] and related 5-aminoalkyl-3-isoxazolol zwitterions, including homomuscimol (Scheme 1), are potent γ-aminobutyric acid (GABA) agonists.[3] The development of conformationally restrained GABA analogues related to muscimol is part of an investigation of the relationship between structure, molecular



a R = - C_2H_5, b R = - CH_3

Scheme 2.

* Present address: University of Sofia, Bulgaria.

flexibility, and biological activity of GABA agonists. This paper presents the synthesis of *10*, *19*, and *23*.

The key step in the reaction sequence for the preparation of *10* is formation of the 3-isoxazolol derivative *4* from *3a,b* (Scheme 2). A crude product formed by reaction of *3a* [4] with hydroxylamine, was treated with an ethanolic solution of hydrogen chloride to give *4* in a low yield. Moderate yields of *4* were obtained by using *3b* instead of *3a* as starting material. Treatment of *4* with diazomethane gave almost equal amounts of the *N*- and *O*-methylated products *5* and *6* in agreement with general findings.[5] The primary amine obtained by diborane reduction of *7*, prepared from *6*, was isolated as the hydrochloride *8* and deprotected by hydrogen bromide in glacial acetic acid.

The structure determinations of the new compounds *2b*, *3b*, and *4*–*10* are based mainly on ^{1}H NMR and IR spectroscopic methods and elemental analyses. For the compounds *4*–*10* this was supported by UV spectroscopy. The ^{1}H NMR and IR data obtained from the 4,5-disubstituted 3-oxygenated isoxazole moieties of *4* and *6*–*9* and from the 3-isoxazolone moiety of *5* are in accordance with general findings.[5] The spectroscopic data and protolytic properties of *10* are in agreement with those published for other 3-isoxazolol zwitterions.[6–10]

The reaction sequences for the preparations of *19* and *23* are outlined in Scheme 3. Cyclohepteno[1,2-*d*]isoxazol-3-ol (*11*) was prepared according to a described method,[11] but a considerably higher yield was obtained by using a different isolation procedure.

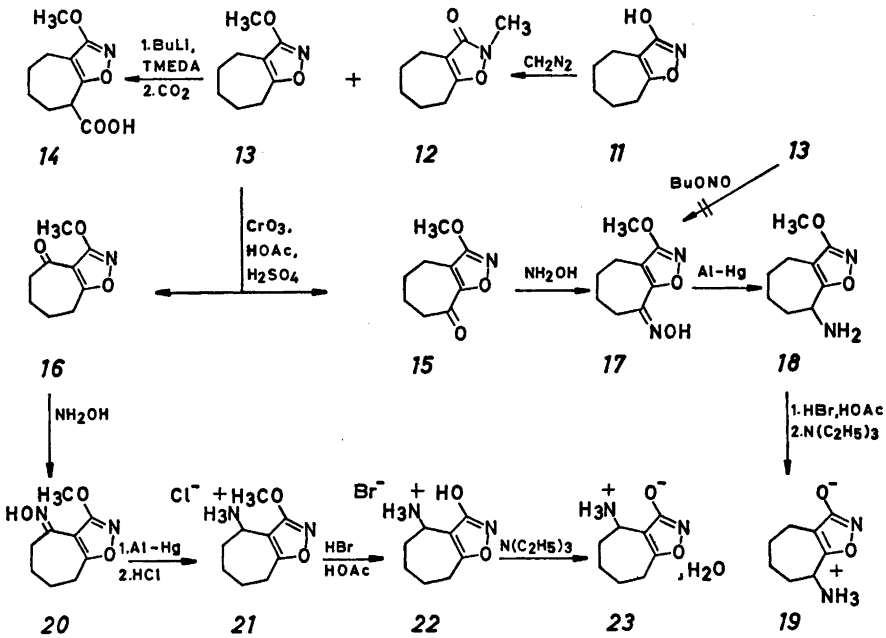
Attempts were made to synthesize *19* *via* the carboxylic acid *14*. Compound *13* was treated with butyllithium and carbon dioxide in analogy with the preparation of 3-methoxy-4-methylisoxazol-5-ylacetic acid from 3-methoxy-4,5-dimethylisoxazole.[12] Only the starting material (*13*) could be isolated from the reaction mixture. Lithiation of *13* in the presence of 1,2-bis(dimethylamino)ethane (TMEDA) and subsequent carboxylation gave *14* in a very low yield, and the planned reaction sequence from *14* to *19* involving a Curtius rearrangement was considered inapplicable.

Chromic acid oxidation of *13* gave the ketones *15* and *16* in yields of 15 and 44 %, respectively. Despite the consumption of excess of chromic acid during the oxidation process, starting material was always isolated from the reaction mixtures indicating that further oxidation of one or both of the ketones *15* and *16* must take place.

An attempt to synthesize *17* directly from *13* by oximation with butyl nitrite using a method analogous to that earlier described [13,14] was unsuccessful. The primary amine *18*, prepared by aluminium amalgam reduction of *17*, was demethylated, and the crude reaction product was treated with triethylamine to give the zwitterion *19*. A similar reaction sequence was utilized for the synthesis of *23* from the oxime *20*.

The structures of the new compounds *12*–*23* were established spectroscopically and by elemental analyses. The identities of the 3-isoxazolone moiety of *12* and the 3-oxygenated isoxazole moieties of *13*–*18* and *20*–*22* were established as mentioned above for *4*–*9*. By comparing the ^{1}H NMR spectra of *11*, which has not been described in connection with the previous preparations of this compound,[11,15] and *13* with the published ^{1}H NMR data of 4,5-dimethyl-3-isoxazolol [5] the signals at δ *ca.* 2.3 in the spectra of *11* and *13* are assigned to the protons in the positions 4 and the signals at δ *ca.* 2.7 to the protons attached to C-8. Based on these assignments the ^{1}H NMR data of *14* confirm the position of the carboxyl group as depicted in Scheme 3.

The structure determinations of the ketones *15* and *16* and the oximes *17* and *20* are based mainly on ^{1}H NMR and UV spectroscopy. In the ^{1}H NMR spectrum of *16* the absence of a signal at δ 2.3 indicates that no protons are attached to C-4. Correspondingly the ^{1}H NMR spectrum of *15* indicates that no protons are attached to C-8 in this compound. The relative positions of the UV absorption maxima of *15* and *16* are in agreement with those of the related monocyclic compounds 3-methoxy-5-acetylisoxazole (at 238 nm) [9] and 3-methoxy-4-acetyl-5-methylisoxazole [12] (at 233 nm). The ^{1}H NMR data of the oximes *17* and *20* are similar to those of the parent ketones *15* and *16*, respectively. The considerable difference between the wavelengths of the UV absorption maxima of *17* and *20* is similar to the difference between those of the related mono-



Scheme 3.

cyclic oximes 3-methoxy-5-(1-hydroxyiminoethyl)isoxazole (248 and 250 nm for the *Z*- and *E*-forms)[16] and 3-methoxy-4-(1-hydroxyiminoethyl)-5-methylisoxazole[12] (214 nm). The structures of the zwitterions *19* and *23* were established by spectroscopic methods as mentioned above for *10*.

The pK_A values of *10* (5.32 ± 0.01 and 10.6 ± 0.1) are significantly different from those of its structural analogue homomuscimol (5.12 ± 0.03 and 9.46 ± 0.02).[7] The pK_A values of *19* (4.51 ± 0.06 and 8.30 ± 0.05) are comparable with those of the structurally related compound muscimol (4.78 and 8.43).[17]

EXPERIMENTAL

Unless otherwise stated 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.[18] Unless otherwise stated thin layer chromatography (TLC) and CC was accomplished by using silica gel F_{254} plates (Merck) and silica gel, 0.05 – 0.200 mm (Merck), respectively, and columns were developed by stepwise gradient elution. Compounds containing a 3-isoxazolol nucleus were visualized on TLC plates by using an iron(III) chloride spraying reagent (yellow colour) and ammonium derivatives and the amine *18* by using a ninhydrin spraying reagent. The pK_A values were determined as described in a previous paper.[7]

1-Methyl 5-ethyl 2-acetylglutarate (2b). *2b* was synthesized from 50.0 g (0.43 mol) of *1b* and 43.0 g (0.43 mol) of ethyl acrylate by using a method analogous to that described[19] for the preparation of *2a*. *2b* (60.2 g; 65 %) was obtained as a colourless oil, b.p. 127.0 – 127.5 °C/0.50 kPa. Anal. $C_{10}H_{16}O_5$: C, H. IR (film): 2980 (m), 2955 (m), 1730 (s), 1645 (w) cm^{-1}. ^1H NMR (CCl_4): δ 4.03 (2 H, q, J 7 Hz), 3.7 – 3.3 (m) and 3.68 (s) (a total of 4 H), 2.5 – 1.7 (m) and 2.18 (s) (a total of 7 H), 1.23 (3 H, t, J 7 Hz).

1-Methyl 5-ethyl 2-acetylglutarate ethylene acetal (3b). A mixture of 130 g (0.6 mol) of *2b*, 75 g (1.2 mol) of ethylene glycol, 1 g of 4-toluenesulfonic acid, and 1000 ml of benzene was refluxed for 6 h by using a Dean-Stark water separator. The solution was washed with two 200 ml portions of aqueous sodium carbonate (1 M) and two 200 ml portions of water, dried (K_2CO_3), and distilled to give *3b* (120 g; 77 %) as a colourless oil, b.p. 126 – 132 °C/53 Pa. Anal. $C_{12}H_{20}O_6$: C, H. IR (film): 2990 (m), 2955 (m), 2895 (m), 1735 (s) cm^{-1}. ^1H NMR (CCl_4): δ 4.02 (q, J 7 Hz) and 3.87 (s) (a total of 6 H), 3.63 (3 H, s), 2.7 – 2.3 (m) and 2.3 – 1.5 (m) (a total of 5 H), 1.33 (s) and 1.23 (t, J 7 Hz) (a total of 6 H).

Ethyl 3-(3-hydroxy-5-methylisoxazol-4-yl)propionate (4). To a stirred solution of 33.7 g (*ca.* 0.60 mol) of potassium hydroxide in methanol (80 ml) was added a solution of 31.3 g (0.45 mol) of hydroxylamine hydrochloride in methanol (300 ml). After stirring for further 90 min and subsequent cooling of the mixture to 0 °C a solution of 78.0 g (0.30 mol) of *3b* in methanol (50 ml) was added, and the mixture was allowed to stand at 8 °C for 5 d. Upon addition of glacial acetic acid (70 ml) the mixture was filtered. The filtrate was evaporated *in vacuo* and the residue submitted to CC [silica gel: 900 g; eluents: ethyl acetate containing methanol (8–22 %) and formic acid (1 %)]. 35.4 g of an oily product was obtained, which was almost homogenous on TLC plates [R_F: 0.40; eluent: ethyl acetate-methanol-formic acid (90:9:1); visualization with an iron(III) chloride spraying reagent (purple colour)]. The intermediate product (35.4 g) was dissolved in an ethanolic solution of hydrogen chloride (300 ml; 5 %), and the solution was refluxed for 7 h. Evaporation *in vacuo* gave 25.9 g (43 %, calculated on the basis of *3b*) of crude *4*. An analytical sample was purified by sublimation *in vacuo* (60 Pa) at 80 °C to give *4* as colourless crystals, m.p. 65.5–66.5 °C. Anal. $C_6H_{13}NO_4$: C, H, N. IR (KBr): 3600–2300 (m), 2990 (m), 1730 (s), 1665 (m), 1545 (m), 1530 (m) cm^{-1}. UV (methanol (log ε)]: 214 (3.71) nm. ^1H NMR ($CDCl_3$): δ 11.4 (1 H, s), 4.07 (2 H, q, J 7 Hz), 2.58 (4 H, s), 2.27 (3 H, s), 1.23 (3 H, t, J 7 Hz).

Ethyl 3-(3-methoxy-5-methylisoxazol-4-yl)propionate (6) and ethyl 3-(2-methyl-3-oxo-5-methylisoxazolin-4-yl)propionate (5). To a solution of 5.0 g (*ca.* 25 mmol) of crude *4* in ether (150 ml) was added with stirring a solution of *ca.* 1.4 g (32 mmol) of diazomethane [prepared from 9.8 g (45 mmol) of *N*-methyl-*N*-nitroso-4-toluenesulfonamide] in ether (100 ml). Stirring was continued for 4 h and unreacted diazomethane was destroyed by addition of formic acid (0.5 ml). The ether solution was evaporated *in vacuo* and the oily residue was submitted to CC [silica gel (Woelm 0.063–0.1 mm): 150 g; eluents: methylene chloride containing ethyl acetate (10–60 %)]. *6* (1.9 g; 36 %) was obtained as a colourless oil after ball-tube distillation at 35 Pa (oven temperature 130 °C). Anal. $C_{10}H_{15}NO_4$: C, H, N. IR (film): 3000–2800 (several bands, m), 1730 (s), 1650 (m), 1525 (s) cm^{-1}. UV [methanol (log ε)]: 214 (3.79) nm. ^1H NMR (CCl_4): δ 3.97 (q, J 7 Hz) and 3.83 (s) (a total of 5 H), 2.40 (4 H, s), 2.22 (3 H, s), 1.18 (3 H, t, J 7 Hz). *5* (1.4 g; 26 %) was obtained as a colourles oil after ball-tube distillation at 65 Pa (oven temperature 160 °C). Anal. $C_{10}H_{15}NO_4$: C, H, N. IR (film): 3000–2850 (several bands, w), 1730 (s), 1660 (s), 1420 (m) cm^{-1}. UV [methanol (log ε)]: 233 (3.97) nm. ^1H NMR ($CDCl_3$): δ 4.07 (3 H, q, J 7 Hz), 3.43 (3 H, s), 2.57 (4 H, s), 2.20 (3 H, s), 1.23 (3 H, t, J 7 Hz).

3-(3-Methoxy-5-methylisoxazol-4-yl)propionamide (7). A mixture of 1.78 g (8.4 mmol) of *6* and aqueous ammonia (100 ml; ϱ 0.87) was stirred at 25 °C for 19 h. The clear solution was evaporated *in vacuo* to give 1.67 g of crystalline product. Recrystallization (benzene) gave *7* (1.27 g; 83 %) as colourless crystals, m.p. 141.5–142.5 °C. Anal. $C_8H_{12}N_2O_3$: C, H, N. IR (KBr): 3385 (s), 3185 (s), 3010–2860 (several bands, w), 1655 (s), 1645 (s), 1520 (s), 1475 (s) cm^{-1}. UV [methanol (log ε)]: 213 (3.87) nm. ^1H NMR [$CDCl_3$–DMSO-d_6 (5:1)]: δ 7.0–6.5 and 6.3–5.8 (two broad signals, a total of 2 H), 3.87 (3 H, s), 2.7–2.3 (4 H, m), 2.23 (3 H, s).

3-(3-Methoxy-5-methylisoxazol-4-yl)propylammonium chloride (8). A solution of 1.11 g (6 mmol) of *7* in tetrahydrofuran (100 ml) containing diborane, externally generated[20] from 0.82 g (22 mmol) of sodium borohydride in diglyme (25 ml) and 4.8 g (34 mmol) of boron trifluoride etherate in diglyme (10 ml) was refluxed for 16 h. After cooling to 25 °C followed by careful addition of hydrochloric acid (10 ml; 5 M) the solution was evaporated to dryness *in vacuo*. Upon addition of water (1 ml) and aqueous potassium hydroxide (10 ml; 50 %) the mixture was extracted with two 10 ml portions of ether. The combined ether phases were dried (K_2CO_3) and evaporated *in vacuo* to give 0.95 g of an oil. The oily product was dissolved in an ethanolic solution of hydrogen chloride (5 ml; 5 %) and upon addition of ether (2 ml) *8* (0.88 g; 71 %) was obtained as colourless crystals, m.p. 153.0–154.0 °C. Anal. $C_8H_{15}ClN_2O_3$: C, H, Cl, N. IR (KBr): 3700–2500 (several bands, s), 2050 (w), 1655 (m), 1630 (w), 1525 (s), 1475 (s) cm^{-1}. UV [methanol (log ε)]: 213 (3.89) nm. ^1H NMR [D_2O (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard)]: δ 4.77 (*ca.* 3.5 H, s), 3.93 (3 H, s), 3.2–2.8 (2 H, t), 2.6–2.2 (m) and 2.28 (s) (a total of 5 H), 2.2–1.6 (2 H, m).

3-(3-Hydroxy-5-methylisoxazol-4-yl)propylammonium bromide (9). To a solution of hydrogen bromide in glacial acetic acid (3 ml; 43 %) was added *8* (362 mg; 1.8 mmol), and the solution was refluxed for 15 min. Upon evaporation to dryness *in vacuo* the residue was treated as described above for further 15 min. Evaporation of the reaction mixture to dryness *in vacuo* followed by recrystallization (methanol-ether) of the residue gave *9* (315 mg; 76 %) as colourless crystals, m.p. 218–219 °C (decomp.). Anal. $C_7H_{13}BrN_2O_3$: C, H, Br, N. IR (KBr): 3700–2300 (several bands, s), 1660 (m), 1625 (w), 1605 (w), 1525 (s), 1455 (m) cm^{-1}. UV (methanol): < 210 nm. ^1H NMR [D_2O (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard)]: δ 4.73 (*ca.* 5 H, s), 3.2–2.8 (2 H, t), 2.6–2.2 (m) and 2.27 (s) (a total of 5 H), 2.2–1.6 (2 H, m).

4-(3-Aminopropyl)-5-methyl-3-isoxazolol zwitterion (10). To a solution of 82 mg (0.35 mmol) of *9* in water (0.2 ml) was added a solution

of 36 mg (0.36 mmol) of triethylamine in ethanol (0.8 ml). Upon standing at 5 °C for several days *10* (30 mg; 56 %) was obtained as colourless crystals, m.p. 202 – 203 °C (decomp.). Anal. $C_7H_{12}N_2O_2$: C, H, N. IR (KBr): 3700 – 2350 (several bands, s), 2255 (m), 1665 – 1645 (several bands, m), 1505 (s), 1495 (s) cm^{-1}. UV [methanol (log ε)]: 213 (3.71) nm. pK_A values (H_2O, 26 °C): 5.32 ± 0.01, 10.6 ± 0.1.

*Cyclohepteno[1,2-*d*]isoxazol-3-ol (11).* 32.0 g (0.17 mol) of ethyl 2-oxocycloheptane-1-carboxylate [21] was treated with hydroxylamine under basic conditions as earlier described.[11] After standing at 5 °C for 18 h the reaction mixture was acidified with concentrated hydrochloric acid (22 ml) and extracted with three 200 ml portions of ether. The combined ether phases were dried (Na_2SO_4) and evaporated *in vacuo*. The oily residue was submitted to CC [silica gel: 300 g; eluents: benzene containing ethyl acetate (30 – 50 %) and formic acid (1 %)]. Appropriate fractions were mixed and evaporated *in vacuo* to give *11* (9.6 g; 36 %). Sublimation of an analytical sample *in vacuo*, (20 Pa) at 90 °C gave *11* as colourless crystals, m.p. 118.0 – 119.0 °C (Ref. 11, 120 °C; Ref. 15, 119 – 120 °C). ^{1}H NMR [CCl_4 – $CDCl_3$ (4:1)]: δ 12.5 (1 H, s), 2.8 – 2.6 (2 H, m), 2.4 – 2.2 (2 H, m), 1.9 – 1.5 (6 H, m). IR and UV data were in agreement with those published.[15]

*3-Methoxycyclohepteno[1,2-*d*]isoxazole (13) and 2-methylcyclohepteno[1,2-*d*]isoxazolin-3-one (12).* To a solution of 9.2 g (60 mmol) of *11* in ether (120 ml) was added with stirring a solution of *ca.* 3 g (75 mmol) of diazomethane [prepared from 21.5 g (100 mmol) of *N*-methyl-*N*-nitroso-4-toluenesulfonamide] in ether (200 ml). Stirring was continued for 18 h and the remaining diazomethane was destroyed by addition of glacial acetic acid (1 ml). The ether solution was evaporated *in vacuo* and the oily residue (11 g) submitted to CC [silica gel: 250 g; eluents: benzene containing ethyl acetate (40 – 60 %) and formic acid (1 %)]. *13* (4.7 g; 47 %) was obtained as a colourless oil, b.p. 123 – 125 °C/1.6 kPa. Anal. $C_9H_{13}O_2N$: C, H, N. IR (film): 2930 (s), 2855 (m), 1655 (m), 1520 (s), 1480 (s) cm^{-1}. UV [cyclohexane (log ε)]: 217 (3.73) nm. ^{1}H NMR (CCl_4): δ 3.88 (3 H, s), 2.8 – 2.6 (2 H, m), 2.4 – 2.2 (2 H, m), 1.9 – 1.5 (6 H, m). *12* (5.3 g; 53 %) was obtained as a colourless oil, b.p. 150 – 153 °C/1.7 kPa. Anal. $C_9H_{13}O_2N$: C, H, N. IR (film): 2935 (s) 2850 (m), 1675 (s), 1655 (s), 1440 (m) cm^{-1}. UV [cyclohexane (log ε)]: 244 (3.76) nm. ^{1}H NMR (CCl_4): δ 3.39 (3 H, s), 2.7 – 2.4 (2 H, m), 2.4 – 2.1(2 H, m), 1.9 – 1.5 (6 H, m).

*3-Methoxycyclohepteno[1,2-*d*]isoxazole-8-carboxylic acid (14).* To a solution of 334 mg (2 mmol) of *13* in tetrahydrofuran (7 ml) kept under nitrogen at – 70 °C was added 229 mg (2.5 mmol) of TMEDA and a solution of butyllithium in hexane (1.25 ml; 2 M). Upon standing at – 70 °C for 20 min the reaction mixture was added to a suspension of 1 g of freshly prepared carbon dioxide in ether (5 ml). The mixture was left for 30 min and after extraction with aqueous sodium hydroxide (5 ml; 2 M) the ether phase was dried (K_2CO_3) and evaporated *in vacuo* to give unreacted *13* (311 mg; 93 %), identified by IR spectroscopy. The aqueous phase was acidified with hydrochloric acid (5 ml; 4 M) and extracted with ether (10 ml). The ether phase was dried (Na_2SO_4) and evaporated *in vacuo* to give *14* (25 mg; 6 %), m.p. 164.0 – 165.5 °C (2-propanol – benzene – light petroleum). Anal. $C_{10}H_{13}O_4N$: C, H, N. IR (KBr): 3700 – 2400 (several bands, m), 1730 (s), 1660 (m), 1530 (s), 1480 (m) cm^{-1}. UV [methanol (log ε)]: 214 (3.80) nm. ^{1}H NMR [$CDCl_3$ – DMSO-d_6 (2:1)]: δ 9.72 (1 H, s), 4.0 – 3.8 (m) and 3.92 (s) (a total of 4 H), 2.4 – 2.2 (2 H, m), 2.2 – 1.3 (6 H, m).

*3-Methoxycyclohepteno[1,2-*d*]isoxazol-8-one (15) and 3-methoxycyclohepteno[1,2-*d*]isoxazol-4-one (16).* To a solution of 751 mg (4.5 mmol) of *13* in glacial acetic acid (20 ml) containing concentrated sulfuric acid (0.5 ml) and kept at 25 – 30 °C was added dropwise and with stirring a solution of 940 mg (3.2 mmol) of sodium dichromate dihydrate in glacial acetic acid (10 ml). To the green reaction mixture was added a suspension of sodium hydrogen carbonate (42 g) in water (100 ml). Extraction of the mixture with four 50 ml portions of ether, and evaporation *in vacuo* of the combined and dried (K_2CO_3) ether phases gave 720 mg of an oily product. CC [silica gel (Woelm 0.063 – 0.1 mm): 50 g; eluents: benzene containing ethyl acetate (15 – 31 %)] gave unreacted *13* (200 mg; 27 %) identified by IR spectroscopy. The yield of *15* was 120 mg (15 %), m.p. 88.0 – 89.0 °C (cyclohexane). Anal. $C_9H_{11}O_3N$: C, H, N. IR (KBr): 2945 (m), 2880 (w), 1670 (s), 1615 (w), 1530 (s) cm^{-1}. UV [methanol (log ε)]: 249 (3.94) nm. ^{1}H NMR (CCl_4): δ 3.80 (3 H, s), 2.7 – 2.3 (4 H, m), 2.1 – 1.7 (4 H, m). The yield of *16* was 360 mg (44 %), m.p. 76.0 – 77.0 °C (cyclohexane). Anal. $C_9H_{11}O_3N$: C, H, N. IR (KBr): 2950 (m), 2880 (w), 1670 (s), 1605 (s), 1525 (s), 1465 (s) cm^{-1}. UV [methanol (log ε)]: 232 (3.97) nm. ^{1}H NMR (CCl_4): δ 3.85 (3 H, s), 3.0 – 2.8 (2 H, m), 2.6 – 2.4 (2 H, m), 2.1 – 1.7 (4 H, m).

*3-Methoxycyclohepteno[1,2-*d*]isoxazol-8-one oxime (17).* A solution of 372 mg (2.1 mmol) of *15*, 174 mg (2.5 mmol) of hydroxylammonium chloride, and 340 mg (2.5 mmol) of sodium acetate trihydrate in ethanol-water (2:1) (5 ml) was refluxed for 45 min. Evaporation of the solution to *ca.* 1 ml followed by filtration and washing of the crystals with water (5 ml) afforded 282 mg (70 %) of crude *17* as colourless and TLC-pure crystals [R_F: 0.41; eluent: benzene-ethyl acetate (2:1)]. An analytical sample was recrystallized (ethanol-water) to give pure *17*, m.p. 177.0 – 178.0 °C. Anal. $C_9H_{12}O_3N_2$: C, H, N. IR (KBr): 3600 – 3000 (m), 2940 (m), 2860 (w), 1650 (m), 1615 (w), 1535 (s), 1475 (s) cm^{-1}. UV [methanol (log ε)]: 252

(4.04) nm. ^{1}H NMR ($CDCl_3$): δ 10.1 (1 H, s), 3.97 (3 H, s), 3.0–2.7 (2 H, m), 2.6–2.3 (2 H, m), 2.0–1.6 (4 H, m).

(±)-3-Methoxy-8-aminocyclohepteno[1,2-d]-isoxazole (18). To a solution of 343 mg (1.8 mmol) of *17* in methanol–water (6:1) (15 ml) was added aluminium amalgam. [The latter was prepared by treatment of 567 mg (21 mmol) of aluminium strips with an aqueous mercury-(II) chloride solution (18 ml; 5 %) for 30 s followed by washing with ethanol]. After stirring for 4 h at 25 °C the mixture was filtered and concentrated *in vacuo* to give an oil. Ball-tube distillation at 120 Pa (oven temperature 150 °C) gave *18* (245 mg; 77 %) as a colourless oil. Found: C 58.90; H 7.61; N 14.97. Calc. for $C_9H_{14}O_2N_2$: C 59.32; H 7.74; N 15.37. IR (film): 3380 (m), 3300 (m), 2935 (s), 2850 (m), 1655–1640 (three bands, m), 1520 (s) cm^{-1}. UV [methanol (log ε)]: 216 (3.84) nm. ^{1}H NMR (CCl_4): δ 4.0–3.7 (m) and 3.83 (s) (a total of 4 H), 2.3–2.1 (2 H, m), 2.0–1.4 (m) and 1.50 (s) (a total of 8 H).

(±)-8-Aminocyclohepteno[1,2-d]isoxazol-3-ol zwitterion (19). *18* (245 mg; 1.35 mmol) was demethylated as described above for the preparation of *9* by treatment with two 2 ml portions of the reagent. The evaporated reaction mixture was kept at 1.8 kPa over potassium hydroxide for 2 d. To a solution of the glassy residue in water (6 ml) was added a solution of 157 mg (1.55 mmol) of triethylamine in ethanol (1.5 ml). Upon standing at 5 °C for 10 d *19* (143 mg; 63 %) was isolated as colourless crystals, m.p. 206–207 °C (decomp.). Anal. $C_8H_{12}O_2N_2$: C, H, N. IR (KBr): 3700–3200 (m), 3200–2000 (several bands, s), 1665 (m), 1630 (m), 1565 (m), 1495 (s), 1485 (s) cm^{-1}. UV [methanol-water (99:1)]: < 210 nm. pK_A values (H_2O, 25 °C): 4.51 ± 0.06, 8.30 ± 0.05.

3-Methoxycyclohepteno[1,2-d]isoxazol-4-one oxime (20). *20* was synthesized as described for *17* by using 1.08 g (6.0 mmol) of *16*, 0.45 g (6.5 mmol) of hydroxylammonium chloride, and 0.89 g (6.5 mmol) of sodium acetate trihydrate as starting materials and 15 ml of solvent. Crude *20* (0.99 g; 85 %) was obtained as colourless and TLC-pure crystals [R_F: 0.32; eluent: benzene–ethyl acetate (2:1)]. An analytical sample was recrystallized (ethanol) to give pure *17*, m.p. 175.0–175.5 °C. Anal. $C_9H_{12}N_2O_3$: C, H, N. IR (KBr): 3600–3100 (s), 2940 (m), 2865(w), 1630 (s), 1525 (s) cm^{-1}. UV [methanol (log ε)]: 226 (4.02) nm. ^{1}H NMR ($CDCl_3$): δ 10.6–9.6 (*ca.* 1 H, broad s), 3.97 (3 H, s), 3.0–2.7 (4 H, m), 2.0–1.6 (4 H, m).

(±)-3-Methoxy-4-aminocyclohepteno[1,2-d] isoxazole hydrochloride (21). A solution of 0.98 g (5.0 mmol) of *20* in methanol–water (7:1) (80 ml) was treated with aluminium amalgam, prepared from 2.0 g (74 mmol) of aluminium, as described above for *18*. After stirring for 60 h at 25 °C the mixture was filtered and evaporated *in vacuo*. The oily residue was mixed with hydrochloric acid (30 ml; 1 M). Upon extraction with four 10 ml portions of ether the aqueous phase was evaporated to dryness *in vacuo*. Recrystallization of the residue (ethanol–ether) gave *21* (0.88 g; 81 %) of *21* as colourless crystals, m.p. 217–218 °C (decomp.). Anal. $C_9H_{15}ClN_2O_2$: C, H, Cl, N. IR (KBr): 3700–3200 (m), 3200–2700 (s), 2615 (w), 1640 (m), 1590 (m), 1530 (s) cm^{-1}. UV (methanol): < 210 nm. ^{1}H NMR [D_2O (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard)]: δ 4.75 (*ca.* 4 H, s), 4.5–4.2 (1 H, m), 3.97 (3 H, s), 3.0–2.7 (2 H, m), 2.2–1.7 (6 H, m).

(±)-4-Aminocyclohepteno[1,2-d]isoxazol-3-ol hydrobromide (22). *22* was synthesized as described for *9* by using 730 mg (3.3 mmol) of *21* as a starting material and two 6 ml portions of the reagent. *22* (675 mg; 82 %) was obtained as colourless crystals, m.p. 195.0–197.0 °C (methanol–ether). Anal. $C_8H_{13}BrN_2O_2$: C, H, Br, N. IR (KBr): 3700–3300 (m), 3200–2200 (several bands, s), 1650 (s), 1595 (m), 1545 (s), 1525 (m), 1505 (s) cm^{-1}. UV (methanol): < 210 nm. ^{1}H NMR [D_2O (sodium 3-(trimethylsilyl)propanesulfonate was used as an internal standard)]: δ 4.77 (*ca.* 5 H, s), 4.5–4.2 (1 H, m), 3.0–2.7 (2 H, m), 2.2–1.6 (6 H, m).

(±)-4-Aminocyclohepteno[1,2-d]isoxazol-3-ol zwitterion hydrate (23). To a solution of 142 mg (0.57 mmol) of *22* in water (0.5 ml) was added a solution of 65 mg (0.64 mmol) of triethylamine in ethanol (0.5 ml). Upon standing at 25 °C for 5 min *23* (90 mg; 85 %) was obtained as colourless crystals, m.p. 191–194 °C (decomp.). Anal. $C_8H_{12}N_2O_2.H_2O$: C, H, N. IR (KBr): 3700–2300 (several bands, s), 2100 (w), 1650 (s), 1535 (s), 1505 (s) cm^{-1}. UV (methanol): < 210 nm. pK_A values (H_2O, 26 °C): 4.63 ± 0.01, 9.89 ± 0.02.

Acknowledgements. This work was supported by the Danish Medical Research Council. The authors express their gratitude to Mrs. U. Geneser for skilful technical assistance.

REFERENCES

1. Johnston, G. A. R., Curtis, D. R., de Groat, W. D. and Duggan, A. W. *Biochem. Pharmacol. 17* (1968) 2488.
2. Curtis, D. R., Duggan, A. W., Felix, D. and Johnston, G. A. R. *Brain Res. 32* (1971) 69.
3. Krogsgaard-Larsen, P., Johnston, G. A. R., Curtis, D. R., Game, C. J. A. and McCulloch, R. M. *J. Neurochem. 25* (1975) 803.
4. Kühn, M. *J. Prakt. Chem. 156* (1940) 103.
5. Jacquier, R., Petrus, C., Petrus, F. and Verducci, J. *Bull. Soc. Chim. Fr.* (1970) 1978.
6. Krogsgaard-Larsen, P. and Hjeds, H. *Acta Chem. Scand. B 28* (1974) 533.

7. Brehm, L., Krogsgaard-Larsen, P. and Hjeds, H. *Acta Chem. Scand. B 28* (1974) 308.
8. Brehm, L. and Krogsgaard-Larsen, P. *Acta Chem. Scand. B 28* (1974) 625.
9. Krogsgaard-Larsen, P. and Christensen, S. B. *Acta Chem. Scand. B 28* (1974) 636.
10. Hjeds, H. and Krogsgaard-Larsen, P. *Acta Chem. Scand. B 30* (1976) 567.
11. Jacquier, R., Petrus, C., Petrus, F. and Verducci, J. *Bull. Chim. Soc. Fr.* (1970) 2685.
12. Bowden, K., Crank, G. and Ross, W. J. *J. Chem. Soc. C* (1968) 172.
13. Kato, T. and Goto, Y. *J. Pharm. Soc. Jpn. 85* (1965) 451; *Chem. Abstr. 63* (1965) 5596f.
14. Kato, T., Goto, Y. and Chiba, T. *J. Pharm. Soc. Jpn. 87* (1967) 689; *Chem. Abstr. 67* (1967) 99968q.
15. Boulton, A. J., Katritzky, A. R., Hamid, A. M. and Øksne, S. *Tetrahedron 20* (1964) 2835.
16. Christensen, S. B. and Krogsgaard-Larsen, P. *Acta Chem. Scand. B 29* (1975) 65.
17. Eugster, C. H. *Fortschr. Chem. Org. Naturst. 27* (1969) 261.
18. Krogsgaard-Larsen, P., Christensen, S. B. and Hjeds, H. *Acta Chem. Scand. 27* (1973) 2802.
19. Henecka, H. *Chem. Ber. 81* (1948) 197.
20. Zweifel, G. and Brown, H. C. *Org. React. 13* (1963) 1.
21. Jacob, T. M., Vatakencherry, P. A. and Dev, S. *Tetrahedron 20* (1964) 2815.

Received January 14, 1977.