Acta Chemica Scandinavica B 30 (1976) 884—888

Synthesis of 1-Acyl-3-piperidones and Ring Expansion of Methyl 3-Oxopiperidine-1-carboxylate with Ethyl Diazoacetate

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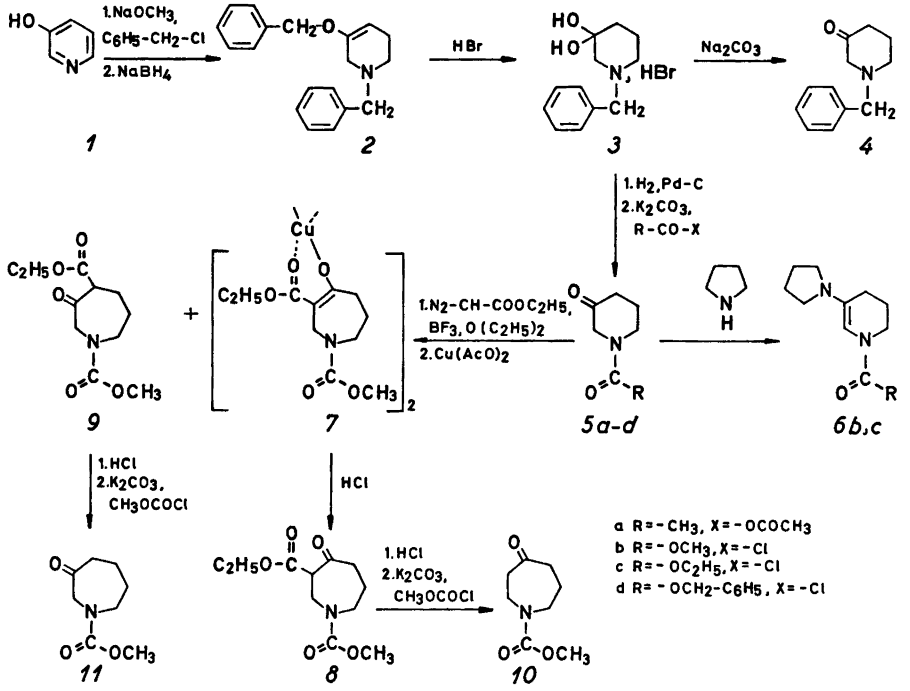
The 1-acyl-3-piperidones *5a–d* have been synthesized from pyridin-3-ol *via* a reaction sequence, which seems to be of general utility for the preparation of 1-acyl-3-piperidones. Pyridin-3-ol was converted into 1-benzyl-3-piperidone hydrobromide hydrate (*3*) *via* 1-benzyl-1,2,5,6-tetrahydro-3-pyridyl benzyl ether (*2*). Hydrogenolysis of *3* followed by treatments with the appropriate acylating agents gave *5a–d*. Compound *3* was converted into 1-benzyl-3-piperidone (*4*). The 1-acyl-3-piperidones *5b,c* were transformed into the corresponding 1-pyrrolidinyl enamines *6b,c*. The boron trifluoride catalyzed reaction of *5b* with ethyl diazoacetate gave a mixture of the two cyclic β-oxoesters ethyl 1-methoxycarbonyl-4-oxoperhydroazepine-3-carboxylate (*8*) and ethyl 1-methoxycarbonyl-3-oxoperhydroazepine-4-carboxylate (*9*), which were separated *via* selective formation of the copper(II) chelate of *8*. The structures of *8* and *9* were finally confirmed by conversion into the ketones methyl 4-oxoperhydroazepine-1-carboxylate (*10*) and methyl 3-oxoperhydroazepine-1-carboxylate (*11*), respectively. The amide rotation in the urethane groups of *5b–d*, *6b,c*, and *11* is discussed on the basis of the ^{1}H NMR spectra.

Nipecotic acid (piperidine-3-carboxylic acid)[1–3] and guvacine (1,2,5,6-tetrahydropyridine-3-carboxylic acid)[3,4] represent a new structural class of potent γ-aminobutyric acid (GABA) uptake inhibitors of neurophysiological and pharmacological interest. In our attempts to evaluate structural analogues of nipecotic acid and guvacine certain 1-acyl-3-piperidone derivatives have proved useful as synthetic intermediates.

The synthetic aspects of 3-piperidone derivatives have not been profoundly investigated. 1-Methyl-[5,6] and 1-benzyl-3-piperidone [7] have been synthesized. 1-*tert*-Butyl-3-piperidone and 1-*tert*-butyl-4-methyl-3-piperidone were formed by rearrangement of the appropriate aminomethylcyclopropylketones.[8] 1-Acetyl-3-piperidone (*5a*)[9] and the corresponding 5*S*-methyl analogue [10] were formed in very small scale by pyrolysis of 1-acetyl-2-benzoyloxypiperidin-3-ols. This paper presents a synthetic procedure, apparently of general utility, for the preparation of 1-acyl-3-piperidones as outlined in Scheme 1. In addition the syntheses of the two isomeric cyclic β-oxoesters *8* and *9* are presented using *5b* as a starting material.

The reaction sequence for the preparation of *3* as shown in Scheme 1 is analogous to that described for the corresponding 1-methyl derivative.[5] Because the parent compound 3-piperidone may be unstable like its 1-methyl [6] and 1-benzyl derivatives, [7] aqueous solutions of the crude reaction products from hydrogenolysis of *3* were treated with the appropriate acylating agents immediately after addition of base to give the 1-acyl-3-piperidones *5a–d*. Attempts to increase the yield of *5b* by addition of methyl chloroformate to the reaction mixture immediately before addition of base were unsuccessful.

Treatment of *5b* with ethyl diazoacetate and boron trifluoride etherate gave as the only products a mixture of the cyclic β-oxoesters *8* and *9*, as established by TLC. Attempts to separate *8* and *9* by distillation *in vacuo* under a variety of conditions were unsuccessful. Repeated column chromatographic treatments of an analytical sample of the concerned mixture, however, afforded *8* and *9* in a pure state. The ^{1}H NMR spectra of *8* and *9* in tetrachloromethane solutions revealed that *8* as regards



Scheme 1.

ca. 25 % is in the enol form, whereas the enol form of *9* could hardly be detected. Thus there was reason to suppose that *8* and *9* might be separated *via* selective copper(II) salt formation of *8*. After treatment of the mixture of *8* and *9* with copper(II) acetate, the copper(II) chelate *7* actually could be isolated. Subsequent treatment of *7* with hydrochloric acid gave *8* in a pure state. Repeated column chromatographic treatments of the residue, which largely contained *9*, gave this compound in a pure state.

The compounds *2*, *3*, *5b–d*, *6b,c*, and *7–11* are new and the structure determinations of all except *7* were supported by elemental analyses. The structure determinations of *2* and *3* were based on ^{1}H NMR and IR spectroscopy. Heating of *3* to 120 °C for 4 h was accompanied by the loss of one mol of water and the appearance of a carbonyl absorption band at 1725 cm^{-1}. Treatment of *3* with sodium carbonate gave *4*. The IR and ^{1}H NMR data of *4* are in agreement with the depicted structure. The 1-acetyl-3-piperidone *5a* [9] and its 5*S*-methyl analogue [10] have been shown by ^{1}H NMR spectroscopy to exist in two conformers at room temperature as a result of slow amide rotation. In the ^{1}H NMR spectra of *5b–d*, however, the signals from the C-2 protons were singlets. These findings compared with the ^{1}H NMR signals from the urethane groups of *5b–d* indicate lower barriers to amide rotation in *5b–d* than in the above-mentioned 1-acetyl-3-piperidones in agreement with the general findings for different types of amides.[11] In the ^{1}H NMR spectrum of *11* the methyl group appeared as a singlet, and the C-2 protons gave rise to a broadened signal probably indicating non-equivalence of the two protons rather than hindered amide rotation.

The enamine-enamide structure of the unstable compounds *6b,c*, as depicted in Scheme 1, was supported by UV absorptions at 250 nm. Simple enamines normally absorb at much lower wavelengths.[12] ^{1}H NMR spectroscopy confirmed the depicted positions of the double bonds in *6b*, *c* and demonstrated the existence of two conformers of both *6b* and *6c* at room temperature, in agreement with the findings for the 1-pyrrolidinyl enamine of *5a*.[9] Thus the

C-2 proton in both *6b* and *6c* gave rise to two slightly broadened singlets.

The structure of the copper(II) chelate *7* was not investigated in detail. As an indication of the purity of *7*, acid cleavage of this compound gave the β-oxoester *8* as the only organic compound. The structure determination of *8* and *9* were based on IR and ^{1}H NMR spectroscopy and finally confirmed by conversion into *10* and *11*, respectively, the structures of which were established by the same spectroscopic methods.

EXPERIMENTAL

Unless otherwise stated the determination of melting points, the recording of IR, UV, and ^{1}H NMR spectra, and the performance of microanalyses were accomplished as described in a previous paper.[13] Unless otherwise stated TLC and column chromatographic procedures were accomplished using Silica gel GF_{254} plates (Merck) and Silica gel, 0.05–0.20 mm (Merck), respectively. The ketones *4*, *5a–d*, *10*, and *11* were visualized on TLC plates by using a 2,4-dinitrophenylhydrazine (DNP) spraying reagent and the β-oxoesters *8* and *9* by using a DNP spraying reagent and subsequent treatment with iodine vapour followed by heating to 100 °C for 5 s.

1-Benzyl-1,2,5,6-tetrahydro-3-pyridyl benzyl ether (2). To a solution of sodium methoxide prepared from 160 ml of methanol and 8.6 g (0.37 mol) of sodium was added 31.0 g (0.33 mol) of pyridin-3-ol (*1*). Upon addition of 84 g (0.66 mol) of benzyl chloride the solution was refluxed for 7 h. After cooling to room temperature 25 g (0.66 mol) of sodium borohydride was added in portions. The solvent was removed *in vacuo* and the residue was stirred with water (200 ml), potassium carbonate (20 g), and ether (250 ml) for 1 h to give two homogeneous liquid phases. The ether phase was isolated, dried (K_2CO_3), and evaporated *in vacuo* to give a brown oil. To a solution of this oil in ether (9 ml) was added slowly and with vigorous stirring light petroleum (650 ml) and diatomaceous earth (11 g), and stirring was continued for an additional 30 min. After filtration and evaporation of the filtrate *in vacuo* 61.5 g (67 %) of crude *2* was obtained as a pale yellow oil, which crystallized at −20 °C. An analytical sample was recrystallized twice (ether–light petroleum) to give *2* as colourless crystals, m.p. 55.0–56.0 °C. Anal. $C_{19}H_{21}NO$: C, H, N. IR (KBr): 3025 (w), 2945–2745 (several bands, m), 1675 (s), 1500 (m), 1455 (m), 1380 (m) cm^{-1}. ^{1}H NMR (CCl_4): δ 7.17 (10 H, broad s), 4.63–4.43 (m) and 4.58 (s) (a total of 3 H), 3.47 (2 H, s), 2.92–2.70 (2 H, broad s), 2.53–2.27 (2 H, t), 2.23–1.87 (2 H, m).

1-Benzyl-3,3-dihydroxypiperidine hydrobromide (3). A solution of 34.0 g (0.12 mol) of *2* in hydrobromic acid (100 ml; 48 %) was refluxed for 3 h. After cooling to room temperature the reaction mixture was extracted with four 100 ml portions of ether. The aqueous phase was evaporated *in vacuo* to give an oil, which was crystallized (butanone) to give 25.1 g (72 %) of *3* as colourless crystals, m.p. 108.0–109.0 °C. Anal. $C_{12}H_{18}BrNO_2$: C, H, Br, N. Anal. $C_{12}H_{16}BrNO$ (after drying of *3* at 120 °C for 4 h): C, H, Br, N. IR (KBr): 3320–3260 (s), 3230–3170 (s), 2990–2860 (m), 2770–2660 (w), 1505 (w), 1442 (m), 1410 (m) cm^{-1}. IR (KBr) (after drying of *3* at 120 °C for 4 h): 3600–3150 (m), 2980–2830 (m), 2750–2480 (several bands, m), 1725 (s), 1500 (w), 1450 (m), 1422 (m), 1400 (m) cm^{-1}. ^{1}H NMR (D_2O): δ 7.58 (5 H, s), 4.78 (3 H, s), 4.37 (2 H, d), 3.8–2.7 (4 H, m), 2.2–1.7 (4 H, m).

1-Benzyl-3-piperidone (4). To a solution of 11.3 g (40 mmol) of *3* in water (15 ml) was added a solution of 5.3 g (50 mmol) of sodium carbonate in water (15 ml). The mixture was extracted with three 50 ml portions of ether. The combined ether phases were dried (K_2CO_3), filtered, and evaporated *in vacuo*. Distillation of the residue gave 6.4 g (86 %) of *4* as a colourless oil, which rapidly turned brown, b.p. 115–116 °C/20 Pa (Ref. 7, b.p. 89–91 °C/3 Pa). IR (film): 3035 (w), 2950 (m), 2800 (m), 1720 (s), 1500 (w), 1455 (w) cm^{-1}. ^{1}H NMR (CCl_4): δ 7.17 (5 H, s), 3.45 (2 H, s), 2.83 (2 H, s), 2.50 (2 H, t, *J* 6.0 Hz), 2.3–2.0 (2 H, m), 2.0–1.4 (2 H, m).

1-Acetyl-3-piperidone (5a). A solution af 14.8 g (52 mmol) of *3* in an aqueous solution of ethanol (200 ml; 25 %) was hydrogenated (304 kPa) in a PARR hydrogenation apparatus by using 3.5 g of a 5 % Pd-C catalyst. The reaction mixture was filtered and evaporated to dryness *in vacuo*. To an iced solution of the residue in water (15 ml) was added with stirring an iced solution of 17.9 g (130 mmol) of potassium carbonate in water (15 ml) immediately followed by addition of 8.1 g (79 mmol) of acetic anhydride during a period of 10 s. Stirring was continued at 0 °C for 30 min. The reaction mixture was continuously extracted with ether-dichloromethane (4:1) at room temperature for 21 h. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to give 6.6 g of crude product, distillation of which gave 5.2 g (72 %) of *5a* as a colourless oil, b.p. 106–108 °C/10 Pa (Ref. 9, 118–120 °C/30 Pa). IR and ^{1}H NMR data were in agreement with those published for *5a*.[9]

Methyl 3-oxopiperidine-1-carboxylate (5b). *5b* was prepared in analogy with the preparation of *5a* described above by using 21.7 g (75 mmol) of *3*, 4.5 g of a 5 % Pd-C catalyst, 25.6 g (185 mmol), of potassium carbonate, and 21.3 g (225 mmol) of methyl chloroformate. However, a crude product of *5b* was isolated by extraction of the reaction mixture with three 100 ml por-

tions of ether. The combined and dried (K_2CO_3) ether phases were evaporated *in vacuo* and distillation of the residue gave 7.2 g (61 %) of *5b* as a colourless liquid, b.p. 85–87 °C/20 Pa. Anal. $C_7H_{11}NO_3$: C, H, N. IR (film): 2955 (m), 2870 (w), 1722 (s), 1710 (s), 1455 (s), 1410 (m) cm^{-1}. ^1H NMR (CCl_4): δ 3.87 (2 H, s), 3.62 (s) and 3.53 (t) (a total of 5 H), 2.5–2.2 (2 H, m), 2.2–1.7 (2 H, m).

Ethyl 3-oxopiperidine-1-carboxylate (5c). *5c* was prepared as described above for *5b* by using 14.8 g (52 mmol) of *3*, 3.0 g of a 5 % Pd-C catalyst, 17.5 g (127 mmol) of potassium carbonate, and 16.9 g (156 mmol) of ethyl chloroformate. Obtained was 4.4 g (50 %) of *5c* as a colourless liquid, b.p. 100–101 °C/40 Pa. Anal. $C_8H_{13}NO_3$: C, H, N. IR (film): 2980 (m), 2875 (w), 1730 (s), 1705 (s), 1480 (m), 1435 (s), 1393 (m) cm^{-1}. ^1H NMR (CCl_4): δ 4.03 (2 H, q, J 6.5 Hz), 3.87 (2 H, s), 3.53 (2 H, t, J 5.5 Hz), 2.5–2.2 (2 H, m), 2.2–1.7 (2 H, m), 1.23 (3 H, t, J 6.5 Hz).

Benzyl 3-oxopiperidine-1-carboxylate (5d). *5d* was prepared as described above for *5c* by using 26.6 g (156 mmol) of benzyl chloroformate. Obtained was 9.5 g (79 %) of slightly impure *5d*, as established by TLC (eluent: benzene–ethyl acetate 3:2), b.p. 154–157 °C/20 Pa. The impurity could not be removed by redistillation. An analytical sample was submitted to column chromatography (eluent: dichloromethane to which increasing amounts of ethyl acetate were added). Appropriate fractions were mixed and evaporated *in vacuo*. The residue was purified by ball-tube distillation at 20 Pa (oven temperature 180 °C) to give pure *5d* as a colourless oil. Anal. $C_{13}H_{15}NO_3$: C, H, N. IR (film): 3030 (w), 2950 (m), 2870 (m), 1720 (s), 1703 (s), 1500 (m), 1420 (s) cm^{-1}. ^1H NMR (CCl_4): δ 7.22 (5 H, s), 4.97 (2 H, s), 3.82 (2 H, s), 3.47 (2 H, t, J 5.5 Hz), 2.4–2.1 (2 H, m), 2.1–1.6 (2 H, m).

Methyl 3-(1-pyrrolidinyl)-1,4,5,6-tetrahydropyridine-1-carboxylate (6b). A solution of 1.57 g (10 mmol) of *5b* and pyrrolidine (5 ml) in benzene (100 ml) was refluxed for 2 h, water being removed by azeotropization with a Dean-Stark apparatus. The reaction mixture was evaporated *in vacuo*. The oily residue was distilled to give 1.7 g (81 %) of *6b* as a colourless liquid, which rapidly turned brown, b.p. 119–121 °C/15 Pa. Anal. $C_{11}H_{18}N_2O_2$: C, H, N. IR (film): 3115 (w), 2950 (s), 2860 (m), 2800 (m), 1700 (s), 1655 (m), 1445 (s), 1395 (s) cm^{-1}. UV [methanol (log ε)]: 250 (3.96) nm. ^1H NMR (CCl_4): δ 5.80 and 5.67 (a total of 1 H, slightly broadened s), 3.62 (3 H, s), 3.6–3.3 (2 H, m), 3.1–2.6 (4 H, m), 2.3–2.0 (2 H, m), 2.0–1.6 (6 H, m).

Ethyl 3-(1-pyrrolidinyl)-1,4,5,6-tetrahydropyridine-1-carboxylate (6c). *6c* was prepared as described above for *6b* by using 1.71 g (10 mmol) of *5c* as starting material. Obtained was 1.5 g (67 %) of *6c* as a colourless liquid, which rapidly turned brown, b.p. 125–127 °C/15 Pa. Anal. $C_{12}H_{20}N_2O_2$: C, H, N. IR (film): 3120 (w), 2970 (s), 2865 (m), 2800 (m), 1695 (s), 1655 (m), 1465 (m), 1420 (s), 1385 (s) cm^{-1}. UV [methanol (log ε)]: 250 (3.99) nm. ^1H NMR (CCl_4): δ 5.75 and 5.63 (a total of 1 H, slightly broadened s), 3.98 (2 H, q, J 7.0 Hz), 3.5–3.3 (2 H, m), 3.1–2.6 (4 H, m), 2.4–2.0 (2 H, m), 2.0–1.6 (6 H, m), 1.22 (3 H, t, J 7.0 Hz).

(±)-Ethyl 1-methoxycarbonyl-4-oxoperhydroazepine-3-carboxylate (8). To a stirred solution of 7.4 g (47 mmol) of *5b* in dry ether (60 ml), maintained at −60 to −50 °C, were added simultaneously and drop by drop 6.7 g (47 mmol) of freshly distilled boron trifluoride etherate and 6.7 g (59 mmol) of ethyl diazoacetate, both of which were dissolved in dry ether (20 ml). The addition of the reagents took 20 min and 35 min, respectively. Stirring was continued at the same temperature for an additional 30 min and subsequently until the temperature of the reaction mixture reached 20 °C. The reaction mixture was shaken with an aqueous solution of potassium carbonate (60 ml; 30 %) and the ether phase was separated. The aqueous phase was extracted with two 50 ml portions of ether. The combined ether phases were dried (K_2CO_3) and evaporated *in vacuo* to give an oil, which was shown to consist of two compounds with $R_F = 0.57$ and $R_F = 0.55$ (eluent: dichloromethane–ether–ethyl acetate (16:3:1)). The oily residue was dissolved in methanol (10 ml) and to this solution was added with vigorous stirring a hot (80 °C) solution of 9.0 g of copper(II) acetate in water (85 ml). After stirring for 16 h at 20 °C the precipitate was filtered off and thoroughly treated with two 20 ml portions of water and subsequently with two 20 ml portions of ether. The precipitate was dried *in vacuo* to give 5.6 g of the copper(II) chelate *7* as a greyish blue powder. IR (KBr): 3700–3100 (m), 2930 (m), 1695 (s), 1585 (s), 1480 (s), 1440 (m), 1404 (w) cm^{-1}. The combined filtrate and wash water was extracted with two 50 ml portions of ether. The combined 2 × 20 ml and 2 × 50 ml ether phases were dried (K_2CO_3) and evaporated *in vacuo* to give 4.6 g of a yellow oil. This was examined as described under the next heading.

5.6 g of *7* was treated with iced hydrochloric acid (4 M; 40 ml) for 30 s, after which the mixture was extracted with three 30 ml portions of dichloromethane. The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil, which by ball-tube distillation at 55 Pa (oven temperature 160 °C) gave 3.9 g (34 %, calculated on the basis of *5b*) of pure *8* as a colourless oil. Anal. $C_{11}H_{17}NO_5$: C, H, N. IR (film): 2980 (m), 2955 (m), 1735 (s), 1710 (s), 1640 (m), 1480 (s), 1445 (s), 1410 (s) cm^{-1}. ^1H NMR (CCl_4): δ 13.2 (*ca.* 0.25 H, s), 4.3–3.8 (a total of 4 H, q, J 7.0 Hz, overlapped by m), 3.60 (s), 3.53 (s), and 3.8–3.3 (m) (a total of 4 H), 3.3–2.2 (4 H, m), 2.0–1.5 (2 H, m), 1.32 and 1.27 (a total of 3 H, two

overlapping t, both with J 7.0 Hz).

(±)-Ethyl 1-methoxycarbonyl-3-oxoperhydroazepine-4-carboxylate (9). The oily by-product (4.6 g), obtained in the preparation of *8*, was shown by TLC (eluent: dichloromethane – ether – ethyl acetate (16:3:1)) to consist mainly of *9*. Column chromatography [silica gel (Woelm 0.063 – 0.1 mm): 150 g; eluent; benzene to which increasing amounts of ether were added] of this product and rechromatography of appropriate fractions several times gave *9*, which by ball-tube distillation at 55 Pa (oven temperature 160 °C) gave 1.7 g (15 %, calculated on the basis of *5b*) of pure *9* as a colourless oil. Anal. $C_{11}H_{17}NO_5$: C, H, N. IR (film): 2980 (m), 2955 (m), 2870 (w), 1740 (s), 1710 (s), 1475 (s), 1470 (s), 1440 (s), 1410 (s) cm^{-1}. ^1H NMR (CCl_4): δ 13.4 (< 0.05 H, s), 4.07 (s) and 4.03 (q, J 7.0 Hz) (a total of 4 H), 3.65 (3 H, s), 3.6 – 3.0 (3 H, m), 2.1 – 1.6 (4 H, m), 1.25 (3 H, t, J 7.0 Hz).

Methyl 4-oxoperhydroazepine-1-carboxylate (10). A mixture of 400 mg (1.6 mmol) of *8* and 6 ml of hydrochloric acid (4 M) was refluxed for 1½ h. The solution formed was evaporated to dryness *in vacuo*. To an iced solution of the residue in water (1.5 ml) was added with stirring an iced solution of 1.7 g (12 mmol) of potassium carbonate in water (1.5 ml) immediately followed by addition of 450 mg (4.8 mmol) of methyl chloroformate. Stirring was continued at 0 °C for 30 min and subsequently at 25 °C for 30 min. The reaction mixture was extracted with three 10 ml portions of ether. The combined ether phases were dried (K_2CO_3) and evaporated *in vacuo* to give an oil, which by ball-tube distillation at 40 Pa (oven temperature 140 °C) gave 159 mg (56 %) of *10* as a colourless oil. Anal. $C_8H_{13}NO_3$: C, H, N. IR (film): 2950 (m), 2860 (w), 1700 (s), 1690 (s), 1535 (w), 1480 (s), 1440 (s), 1410 (s) cm^{-1}. ^1H NMR (CCl_4): δ 3.60 (s) and 3.7 – 3.4 (m) (a total of 7 H), 2.6 – 2.3 (4 H, m), 1.9 – 1.5 (2 H, m).

Methyl 3-oxoperhydroazepine-1-carboxylate (11). *11* was prepared from 400 mg (1.6 mmol) of *9* as described above for *10*. Obtained was 176 mg (63 %) of *11* as a colourless oil. Anal. $C_8H_{13}NO_3$: C, H, N. IR (film): 2950 (m), 2860 (w), 1710 (s), 1690 (s), 1485 (s), 1475 (s), 1445 (s), 1410 (s) cm^{-1}. ^1H NMR (CCl_4): δ 3.88 (2 H, slightly broadened s), 3.65 (3 H, s), 3.5 – 3.2 (2 H, m), 2.6 – 2.2 (2 H, m), 2.0 – 1.4 (4 H, m).

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. Krogsgaard-Larsen, P. and Johnston, G. A. R. *J. Neurochem. 25* (1975) 797.
2. Krogsgaard-Larsen, P., Johnston, G. A. R., Curtis, D. R., Game, C. J. A. and McCulloch, R. M. *J. Neurochem. 25* (1975) 803.
3. Johnston, G. A. R. In Roberts, E., Chase, T. N. and Tower, D. B., Eds., *GABA in Nervous System Function*, Raven, New York 1976, p. 395.
4. Johnston, G. A. R., Krogsgaard-Larsen, P. and Stephanson, A. L. *Nature (London) 252* (1975) 634.
5. Lyle, R. E., Adel, R. E. and Lyle, G. G. *J. Org. Chem. 24* (1959) 342.
6. Prill, E. A. and McElvain, S. M. *J. Am. Chem. Soc. 55* (1933) 1233.
7. Iselin, B. M. and Hoffmann, K. *Helv. Chim. Acta 37* (1954) 178.
8. Semenova, N. A., Katvalyan, G. T. and Mistryukov, E. A. *Tetrahedron Lett.* (1976) 445.
9. Masamune, T., Hayashi, H., Takasugi, M. and Fukuoka, S. *J. Org. Chem. 37* (1972) 2343.
10. Masamune, T., Takasugi, M. and Murai, A. *Tetrahedron 27* (1971) 3369.
11. Hirsch, J. A., Augustine, R. L., Koletar, G. and Wolf, H. G. *J. Org. Chem. 40* (1975) 3547.
12. Malhotra, S. K. In Cook, A. G., Ed., *Enamines: Synthesis, Structure, and Reactions*, Dekker, New York 1969, p. 41.
13. Krogsgaard-Larsen, P., Christensen, S. B. and Hjeds, H. *Acta Chem. Scand. 27* (1973) 2803.

Received May 7, 1976.