Simple Preparation of Azetidino-[1.2-*d*]benzodiazepines

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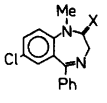
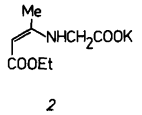
Both 1,4-benzodiazepines and condensed β-lactams are compounds of great interest. This prompted us to synthesize new derivatives having a tricyclic azetidino[1.2-*d*]benzodiazepine structure. The new heterocycle fused to the "*d*" face of the parent molecule [7] may cause an interesting influence on pharmacological activities as well as provide a new starting site for further chemical transformations.

The reaction between ketene or diketene and diazepam (*1a*) is reported to yield an oxazino-benzodiazepine adduct.[1] Several methods are known for the introduction of an amino-substituted β-lactam ring; a very useful one was discovered by Bose *et al.*[2] and Sharma *et al.*[3], namely the use of glycine Dane-salts:[4] *i.e.* on appropriate activation potassium α-methyl-β-ethoxycarbonylethenylaminoacetate (*2*) and a Schiff base give rise to the corresponding azetidinone. Phosphorus oxychloride was found useful as a reagent for activating *2*. Thus, if a mixture of diazepam and *2* was treated with $POCl_3$ in the presence of excess triethylamine, 54% of *3a* was isolated. In the case of medazepam (*1b*), the oily *3b* was obtained in about 70% yield and was converted directly to *3d*. When *4* was used as starting material, the yield of *5* was significantly lower; only some percent of the desired *5* could be isolated by thick-layer chromatography. In this case the 1-NH group presumably interfered with the active intermediates.



1a X = O
1b X = H_2



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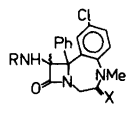
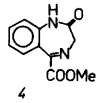


3a R =  X = O
3b R = X = H_2
3c R = TsOH·H- X = O
3d R = TsOH·H- X = H_2
3e R = $ClCH_2CO$- X = O



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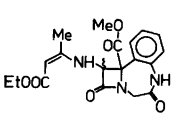

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Trifluoroacetic anhydride could also be used [5] for the activation of *2*. In this method, *3a* resulted in a yield of only 18%.

Regeneration of the amino group was performed with *p*-toluenesulfonic acid.[6] Thus, *3c* was obtained in nearly quantitative yield as its *p*-toluenesulfonate salt, and *3d* in somewhat lower yield. *3c* was converted to its *N*-chloroacetyl derivative (*3e*) by standard acylation. Compounds of type *3* exhibit spectroscopic evidence of the β-lactam ring, *i.e.* in their ^1H NMR spectra the β-lactam proton appears at 5.1 – 5.7 ppm, as a doublet coupled ($J \sim 10$ Hz) to the NH proton. In the IR spectra the carbonyl absorption appears at 1750 – 1785 cm^{-1}.

We have also tried to add *N*-chloroacetylglycine to *1a* instead of the Dane-salt *2*, using $POCl_3$ and NEt_3, but only traces of *3e* could be observed. The preparation of similar compounds using differently substituted benzodiazepine compounds is in progress.

Experimental. General. Melting points were determined on a Kofler apparatus and are uncorrected. ^1H NMR spectra were obtained on a JEOL FX60 or Bruker WP 200 SY spectrometer with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 283B spectrometer, using KBr discs. TLC were run on precoated plates (Merck Silica Gel F_{254}) with toluene-ethyl acetate 1:1.

9-Chloro-4,5,6,10b-tetrahydro-1-(α-methyl-β-ethoxycarbonylethenyl)amino-6-methyl-10b-phenylazetidino[1,2-d][1,4]benzodiazepine-2,5-dione (3a). To a mixture of *2* (2.25 g), diazepam (1.4 g) and triethylamine (2.05 g) in dry CH_2Cl_2 (30 ml), $POCl_3$ (1.54 g) in CH_2Cl_2 (12 ml) was added dropwise, while the temperature was kept at 0 °C. After the addition the suspension was stirred overnight at room temperature and was then washed with water and 5% $NaHCO_3$ solution. After removal of the solvent, the resulting oil crystallized on standing. Recrystallization from $CHCl_3$ – light petroleum led to 1.2 g (54%) of the title compound, m.p. 185 – 186 °C. IR (KBr): 1766 (s), 1721 (s), 1662 (s), 1262 (s), 1167 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.12 (3 H, t), 2.04 (3 H, s), 2.78 (3 H, s), 3.78 (H, d, J_1 14 Hz), 3.89 (2 H, q), 4.45 (H, d, J_1 14 Hz), 4.41 (H, s), 5.41 (H, d, J_2 10 Hz), 7.1 – 7.8 (8 H, m), 8.34 H, (d, J_2 10 Hz).

9-Chloro-4,5,6,10b-tetrahydro-1-(α-methyl-β-ethoxycarbonylethenyl)amino-6-methyl-10b-phenylazetidino[1,2-d][*1,4*]*benzodiazepine-2-one* (3b). Prepared as for *3a* yielding 2.2 g of thick oily crude product. Its ^1H NMR spectrum revealed two doublets, at 5.17 and 8.62 ppm (J 10.7 Hz), corre-

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sponding of the β-lactam and NH protons. The compound contained some free ethyl acetoacetate and was converted directly to *3d* without purification.

9-chloro-4,5,6,10b-tetrahydro-1-amino-6-methyl-10b-phenylazetidino[1,2-d][1,4]benzodiazepine-2,5-dione tosylate (3c). *3a* (1.02 g) and *p*-toluenesulfonic acid (0.47 g) were dissolved in acetone (20 ml) and 6 drops of water were added. The mixture was stirred overnight and next day the precipitate formed was collected and washed with CCl_4: 1.11 g (96.5 %). M.p. 238–239 °C (from MeOH – ether). Anal. $C_{25}H_{24}N_3O_5SCl$: N, Cl. IR (KBr): 1784 (br s), 1642 (s), 1484 (s), 1225 (br s), 1220 (s), 1009 (s) cm^{-1}. ^1H NMR (200 MHz, DMSO-d_b): δ 2.33 (3 H, s), 2.41 (3 H, s), 4.02, 4.16 (2 H, ABq, *J* 15 Hz), 5.55 (H, s), 7.1–8.1 (12 H, m), 8.55 (H, br s).

9-Chloro-4,5,6,10b-tetrahydro-1-amino-6-methyl-10b-phenylazetidino[1,2-d][1,4]benzodiazepine-2-one tosylate (3d). Crude *3b* (4.4 g) was dissolved in acetone (75 ml) and H_2O (0.5 ml). *p*-Toluenesulfonic acid (1.9 g) was added and the gelatinous suspension formed was briefly warmed to ~60 °C, with vigorous stirring. It was allowed to react overnight at room temperature. The precipitate was collected, washed with a little CCl_4 and recrystallized from a minimum amount of hot acetone – MeOH, giving 2.3 g of off-white product, m.p. 184–186 °C. Anal. $C_{25}H_{26}N_3O_4SCl$: N, Cl. IR (KBr): 1747 (br s), 1600 (m), 1500 (s), 1178 (s), 1008 (s) cm^{-1}. ^1H NMR (200 MHz, CD_3OD): δ 2.35 (3 H, s), 2.74 (3 H, s), 2.8–4.0 (4 H, AA'BB'), 5.15 (H, s), 7.1–7.8 (12 H, m).

9-Chloro-4,5,6,10b-tetrahydro-1-chloroacetamido-6-methyl-10b-phenylazetidino[1,2-d][1,4]benzodiazepine-2,5-dione (3e). To a mixture of *3c* (0.51 g) and triethylamine (0.33 ml) in dry CH_2Cl_2 (30 ml), chloroacetyl chloride (0.25 g) in CH_2Cl_2 (3 ml) was added dropwise, and the mixture was stirred for 1 h and washed with brine, 5 % $NaHCO_3$ solution and 5 % H_2SO_4. Evaporation and recrystallization from acetone – ether yielded 0.32 g (78 %) of white material, m.p. 221–222 °C. IR (KBr): 1776 (s), 1678 (s), 1489 (m), 1412 (m), 1205 (m) cm^{-1}. ^1H NMR (60 MHz, DMSO-d_b): δ 2.46 (3 H, s), 3.62, 3.84 (2 H, ABq, *J* 13 Hz), 3.94, 4.14 (2 H, ABq, *J* 13.3 Hz), 5.75 (H, d, *J* 8 Hz), 6.6–8.3 (8 H, m), 9.04 (H, d, *J* 8 Hz).

4,5,6,10b-Tetrahydro-1-(α-methyl-β-ethoxycarbonylethenyl)amino-10b-methoxycarbonylazetidino-[1,2-d][1,4]benzodiazepine-2,5-dione (5). This was prepared as for *3a* from 0.3 g of *4*. After work-up, the oily residue was purified by thick-layer chromatography (silica gel, twice benzene – ethyl acetate 1:1), yielding 17 mg of pure *5* (3.2 %), m.p. 177–179 °C. ^1H NMR (60 MHz, DMSO-d_6): 1.15 (3 H, t), 2.08 (3 H, s), 3.63 (3 H, s), 4.02 (2 H, q), 4.16 (2 H, br s), 4.65 (H, s), 5.81 (H, d, *J* 10.1 Hz), 6.7–7.9 (4 H, m), 9.0 (H, d, *J* 10.1 Hz), 10.05 (H, s).

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