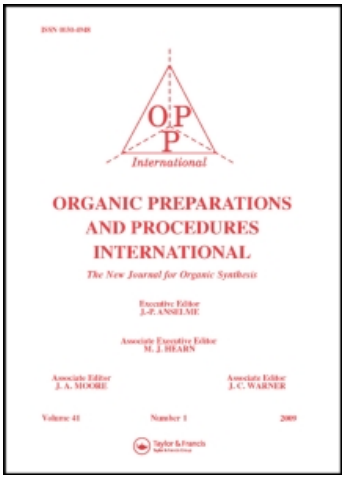

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SYNTHESIS OF 3-SUBSTITUTED 1,4-BENZODIAZEPINE-2-ONES

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SYNTHESIS OF 3-SUBSTITUTED 1,4-BENZODIAZEPINE-2-ONES†

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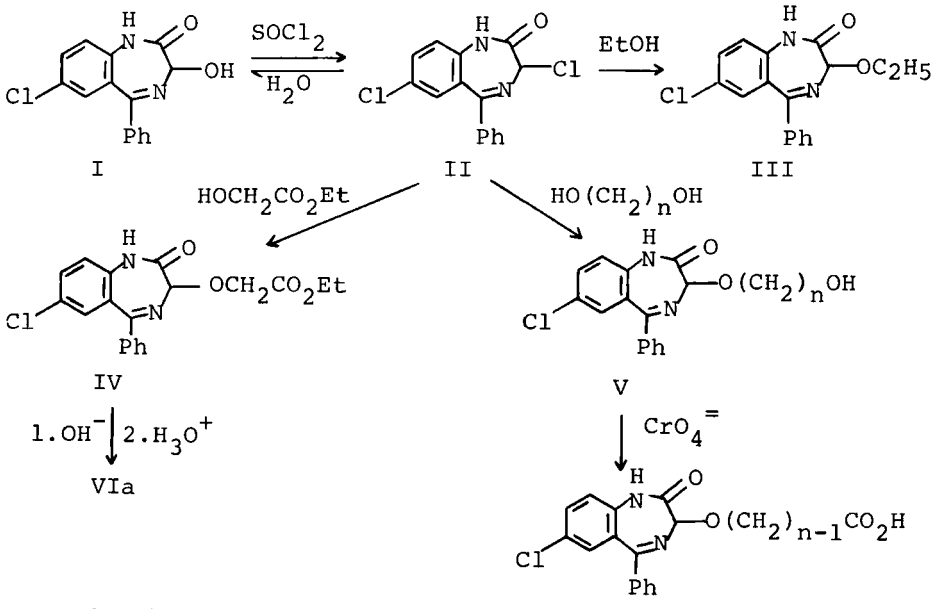
Since the discovery of 1-methyl-7-chloro-2,3-dihydro-5-phenyl-1,4-benzodiazepine-2-one (diazepam) by Sternbach as a potent antianxiety agent and anticonvulsant a considerable number of 1,4-benzodiazepine derivatives have been reported in the literature.[1] During the course of some other studies, we



needed 3-O-(carboxymethyl) derivative VIa of 7-chloro-3-hydroxy-2,3-dihydro-5-phenyl-1,4-benzodiazepine-2-one (oxazepam, I). Preparation of this compound from I in an overall

yield of 17% has been reported by Bell and coworkers.[1c] Their method involved the reaction of 3,7-dichloro-2,3-dihydro-5-phenyl-1,4-benzodiazepine-2-one (II) with ethyl glycolate followed by saponification of the product to VIa. In our hands the method, however, afforded only traces of the required product. We have developed a convenient and general method for preparation of acid VIa and its analogs in high yield and would like to report our findings.

Reaction of oxazepam I with thionyl chloride gave quantitatively the 3-chloro compound II as a pale yellow solid, mp. 139-140° (dec.), lit.[2,3] mp. 151-153° (dec.) and 120-121° (dec.) which slowly hydrolyzed back to I with moisture and gave ethoxy compound III with ethanol.[2] The chloro compound II was added slowly to an excess of vigorously stirred ethylene glycol at room temperature. The reaction mixture was diluted with water and extracted with organic solvents to afford exclusively the 1:1 product Va in 97% yield. In contrast, treatment of II with ethyl glycolate afforded only traces of IV. This is presumably due to the poor nucleophilicity of the hydroxyl group of ethyl glycolate as compared to that of the hydroxyl groups of ethylene glycol. Oxidation of Va with Jones reagent furnished the target acid VIa mp. 218-220° (dec.), lit.[1c] mp. 205-207°. It showed the expected IR and NMR data (Table 1) and was further characterized as its benzamide derivative. The overall yield of pure VIa from I was 70%. The generality of the reaction was demonstrated by high yield conversions of II to alcohols Vb and Vc and to acid VIb and VIc (Table 1) with 1,3-propanediol and 1,4-butanediol. Alcohol Va could also be

oxidized, albeit in poor yield, to its corresponding aldehyde.

TABLE 1.

PHYSICAL DATA OF ALCOHOLS V AND ACIDS VI

Product	Yield[a] (%)	Mp.[b] (dec.)	IR(KBr) (cm^{-1})	NMR,[c] δ	Anal., % Found (Calcd)
Va	97	210-212°	3450 1685	3.6-3.9(m,4H) 4.85(s,1H) 7.2-7.9(m,8H)	C,61.52(61.72) H,4.57(4.52) N,8.47(8.47) Cl, 10.56(10.74)
Vb	60	190-191°	3500 1690	1.6-2.0(m,2H) 3.4-4.0(m,4H) 4.75(s,1H) 7.2-7.8(m,8H)	C,62.72(62.69) H,4.97(4.96) N,7.98(8.12) Cl,10.03(10.29)
Vc	60	169-170°	3425 1680	1.4-1.8(m,4H) 3.2-3.9(m,4H) 4.77(s,1H) 7.2-7.8(m,8H) 10.8(br s,1H)	C,63.49(63.62) H,5.33(5.29) N,7.86(7.80) Cl, 9.89(9.89)
VIa	65	218-220°	3600-2500[d] 1730 1685	4.43(s,2H) 5.0(s,1H) 7.0-7.8(m,8H) 10.57(br s,1H)	C,59.08(59.21) H,3.90(3.77) N,8.23(8.12) Cl,10.41(10.30)
VIb	77	240-241°	3600-2500[d] 1720[e] 1690	3.7-4.2(m,4H) 4.80(s,1H) 7.2-7.8(m,8H) 10.55(br s,1H)	C,60.41(60.25) H,4.24(4.21) N,7.87(7.81) Cl,10.00(9.89)
VIc	70	226-227°	3600-2500[d] 1710[e] 1680	1.70-2.3(m,4H) 4.45(t,J=7Hz,2H) 4.72(s,1H) 7.2-8.2(m,8H)	C,60.88(61.23) H,4.62(4.56) N,7.61(7.51) Cl,9.55(9.52)

a) Isolated yields of pure material. b) Crystallized from acetonitrile. c) In DMSO-d_6 using TMS as an internal standard. d) Broad absorption band. e) Shoulder.

EXPERIMENTAL

Melting points were determined in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Solutions in organic solvents were dried over anhydrous magnesium sulfate. IR spectra were run on a Perkin-Elmer spectrophotometer. The NMR spectra were recorded on a Varian T-60 machine and the values are given in δ parts per million downfield from tetramethylsilane as an internal standard. A general method of preparation for benzodiazepine derivatives V and VI is given below.

3,7-Dichloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine (II). - To a stirred solution of freshly distilled thionyl chloride (1.6 g) and N,N-dimethylformamide (0.05 ml) at 0° was added in small portions oxazepam I (1.0 g) under nitrogen. A bright yellow solid precipitated. The reaction mixture was stirred for 1 hr. at 0°, then for 24 hr. at 4°. Excess thionyl chloride was removed under reduced pressure on a rotary evaporator. The last traces of thionyl chloride were removed by treating the yellow solid repeatedly with dry benzene and evaporating the solvent. The yellow solid was triturated with dry benzene and filtered with suction. The product was dried under vacuum to afford the chloro compound II (1.0 g, 95%) as a bright yellow solid, mp. 139-140° (dec.), lit.[2,3] mp. 120-121° (dec.) and 151-153° (dec.); NMR δ (DMSO-d_6) 6.1 (S, 1H), 7.2-7.9 (m, 8H), 9.7 (1H, concentration dependent) and 11.3 ppm.[4]

The yellow compound II reacted with water at room temperature to give oxazepam I as a colorless solid and with ethanol to give 7-chloro-2,3-dihydro-3-ethoxy-2-oxo-5-phenyl-1H-1,4-benzodiazepine (III), mp. 220°, lit.[2] mp. 225-227°.

Reaction of Chloro Compound II with Ethylene Glycol. Formation of 7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-

yloxy Ethanol (Va). - To vigorously stirred dry ethylene glycol (60 ml) under nitrogen was added in small portions the chloro compound II. After 4 hrs.,[5] the reaction mixture was diluted with excess water (200 ml) and extracted with chloroform. Evaporation of the dried organic extract afforded TLC pure hydroxy compound Va as a colorless solid (1.05 g, 97%) which when recrystallized from acetone melted at 216-217°. IR (KBr) 3450 (OH), 3100 (NH), 1685 (C=O)cm^{-1}, NMR (DMSO-d_6) δ 3.6-3.9 (m, 4H, -OCH_2-CH_2-), 4.85 (s, 1H, C-3 methine), 7.2-7.9 (m, 8H, aromatic protons).

Anal. Calcd for $C_{17}H_{15}ClN_2O_3$: C, 61.72; H, 4.54; N, 8.47; Cl, 10.74. Found: C, 61.52; H, 4.57; N, 8.47; Cl, 10.56.

The alcohols Vb and Vc were obtained by the above method using a slightly modified work up procedure. Thus, after the chloro compound II had reacted with 1,3 propanediol or 1,4-butanediol the product was isolated with chloroform. The solvent was removed and the residue triturated with a small amount of ether. The solid was recrystallized from acetonitrile to afford the pure products Vb and Vc.

Oxidation of Alcohol Va with Jones Reagent. Preparation of 7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yloxy Acetic Acid (VIa). - To an ice-cold solution of alcohol Va (0.5 g) in acetone (125 ml, distilled over $KMnO_4$) was added excess Jones reagent.[6] The reaction mixture was stirred at 0° for 1 hr. After an additional stirring for 60 min. at room temperature the reaction mixture was poured into 500 ml of ice-cold water and the product was extracted with ethyl acetate. The organic layer was extracted with 5% aqueous

sodium bicarbonate solution. The bicarbonate solution was cooled to 0°, acidified to pH 3 with dil. hydrochloric acid and was thoroughly extracted with ethyl acetate. Removal of the organic solvent from the dried extract gave the acid VIa (330 mg, 65%, mp. 205-207°). Recrystallization from acetonitrile afforded analytically pure VIa, mp. 218-220° (dec.) lit.[1c] mp. 205-207°. IR (KBr) : 2500-3650 (OH and NH), 1730 (-$\underline{C}$-OH), 1685 (-$\underline{C}$-NH); NMR (DMSO-d_6) δ 4.43 (s, 2H, -O$\underline{CH_2}$-), 5.0 (s, 1H, C-3 methine), 7.2-7.9 (m, 8H, aromatic protons), 10.6 (br s, 1H, COO$\underline{H}$).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_4$: C, 59.21; H, 3.77; N, 8.12; Cl, 10.30. Found: C, 59.08; H, 3.90; N, 8.23; Cl, 10.41

The acid VIa was further characterized as its benzamide derivative,[7] mp. 187-188°; NMR ($CDCl_3$) δ 4.5 (s, O$\underline{CH_2}$), 4.6 (d, J = 5 Hz, -NH$\underline{CH_2}$) [total 4H], 4.88 (s, 1H, C-3 methine), 7.2-7.8 (m, 8H aromatic protons), 10.0 (br s, N$\underline{H}$).

Anal. Calcd. for $C_{24}H_{20}ClN_3O_3$: C, 66.43; H, 4.61; N, 9.68; Cl, 8.19. Found: C, 66.01; H, 4.75; N, 9.63; Cl, 8.23.

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† Syva Contribution #70.

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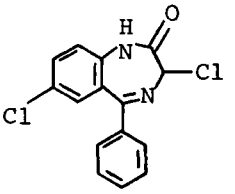
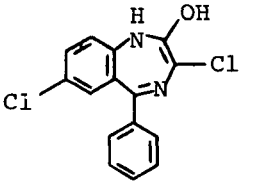
4. A low field signal at δ 11.3 ppm in NMR spectrum of II and its yellow color strongly indicates its existence in equilibrium with enol IIa.



II



IIa

5. The reaction was found, by silica tlc, to be essentially complete within few minutes.

6. L. F. Fieser and M. Fieser "Reagents for Organic Synthesis", Vol. 1, John Wiley, New York, N.Y., 1967, p. 142.

7. Prepared by treating the acid with isobutyl chloroformate in the presence of triethylamine followed by treatment of the mixed anhydride with benzylamine.

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