A New Method for Preparing 5-Aryl-2,3-dihydro-1*H*-1,4-benzodiazepines

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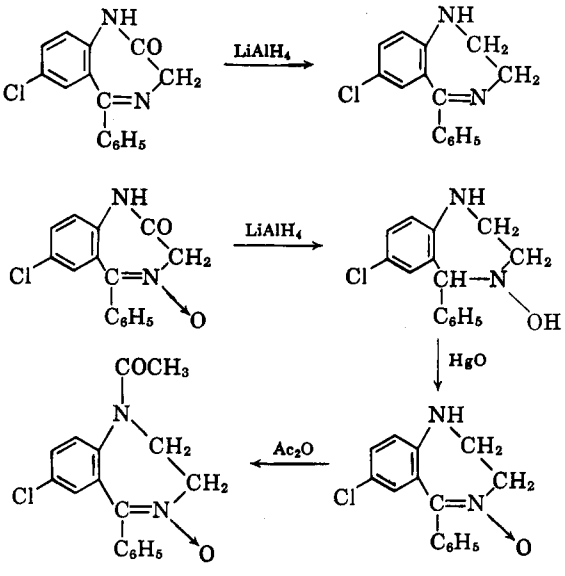
A recent publication[1] has described the preparation of 7-nitro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine from 2-chloro-5-nitrobenzophenone and ethylenediamine. We have had occasion to prepare benzodiazepines of this type, but have found this method to be of limited use. Nitro activation of the aryl chloride appears to be necessary since treatment of 2-bromo-5-chlorobenzophenone with ethylenediamine afforded no benzodiazepine. A more versatile method is the lithium aluminum hydride reduction of 5-aryl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones.



Reduction of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one with lithium aluminum hydride in ether has afforded 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine in good yield. 7-Chloro-5-phenyl-3,3-tetramethylene-2,3-dihydro-1*H*-1,4-benzodiazepine was prepared similarly.

Lithium aluminum hydride reduction of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide gave 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine which could be oxidized by mercuric oxide to afford 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxide. The 5-*o*-chlorophenyl analog was made by the same route.

Since a large variety of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones with differing substituents in positions 3,5,6,7,8, and 9 has been disclosed,[2,3] this method can afford a varied group of 2,3-dihydro-1*H*-1,4-benzodiazepines.

The 5-aryl-2,3-dihydro-1*H*-1,4-benzodiazepines were potent central nervous system depressants in animal tests.

(1) J. A. Hill, A. W. Johnson, and T. J. King, *J. Chem. Soc.*, 4430 (1961).
(2) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).
(3) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962).

Experimental[4]

7-Chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine.—7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7 g.) was added in portions to a stirred suspension of lithium aluminum hydride (1.6 g.) in anhydrous ether (200 ml.). The mixture was heated under reflux for an hour and the excess hydride was decomposed by careful addition of water. The ether layer was separated, dried over magnesium sulfate, and evaporated to dryness. Recrystallization of the residue from ethanol afforded 3.5 g. of product, m.p. 174–176°.

Anal. Calcd. for $C_{15}H_{13}ClN_2$: C, 70.17; H, 5.11; Cl, 13.81; N, 10.91. Found: C, 70.32; H, 5.07; Cl, 13.6; N, 10.98.

7-Chloro-5-phenyl-3,3-tetramethylene-2,3-dihydro-1*H*-1,4-benzodiazepine, m.p. 180–181° (from ethanol), was similarly prepared in 42% yield.

Anal. Calcd. for $C_{19}H_{19}ClN_2$: C, 73.46; H, 6.16; Cl, 11.41; N, 9.01. Found: C, 73.16; H, 5.92; Cl, 11.20; N, 8.71.

7-Chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine.—7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (10 g.) was treated with lithium aluminum hydride (2.8 g.) in anhydrous ether (250 ml.) as in the preceding example. There was obtained 7 g. of product, m.p. 170–172°.

Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; Cl, 12.90; N, 10.20. Found: C, 65.87; H, 5.26; Cl, 13.0; N, 10.32.

7-Chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide.—A suspension of the previous solid (12 g.), mercuric oxide (20 g.), acetone (250 ml.), and water (25 ml.) was stirred for 3 hr. at room temperature. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from 95% ethanol afforded 8 g. of product, m.p. 247–248°.

Anal. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.05; H, 4.81; Cl, 13.00; N, 10.27. Found: C, 66.20; H, 4.92; Cl, 13.3; N, 9.92.

7-Chloro-5-*o*-chlorophenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide, m.p. 215–217° (from ethanol), was prepared similarly (45%) from 7-chloro-5-*o*-chlorophenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide,[5] but without the isolation of the intermediate 7-chloro-5-*o*-chlorophenyl-4-hydroxy-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine.

Anal. Calcd. for $C_{15}H_{12}Cl_2N_2O$: C, 58.65; H, 3.94; Cl, 23.09; N, 9.12. Found: C, 58.94; H, 4.04; Cl, 23.50; N, 8.87.

1-Acetyl-7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide.—A solution of 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxide (4 g.) in acetic anhydride (20 ml.) was warmed on a steam bath for 0.5 hr. The solution was evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to afford 1.5 g. of product, m.p. 222–224°. The carbonyl absorption band was at 6.02 μ.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.27; N, 8.90. Found: C, 64.90; H, 4.76; Cl, 11.2; N, 9.13.

(4) Melting points are uncorrected.
(5) This compound, m.p. 249–250° dec., was prepared by C. Gochman following method A of ref. 3.

The Decomposition of Methylethylphenylbenzylphosphonium Acetate

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A few examples of thermal decomposition of phosphonium carboxylate salts have been studied.[2] These

(1) Petroleum Research Fund Scholar, 1961–1962.
(2) (a) E. A. Letts and N. Collie, *Phil. Mag.*, **22**, 183 (1886); (b) N. Collie, *J. Chem. Soc.*, **53**, 636 (1888); (c) D. B. Denney and L. C. Smith, *Chem. Ind.* (London), 290 (1961); (d) D. B. Denney and L. C. Smith, *J. Org. Chem.*, **27**, 3404 (1962).