Improved Syntheses of 1,4-Benzodiazepine-2,5-diones

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Our effort to find a novel type of antihypertensive agent required 1,4-benzodiazepine-2,5-diones in large quantities. Although numerous methods on the synthesis of 1,4-benzodiazepine-2,5-dione have been described in the literature (1-6), these methods were found to be unsatisfactory for large scale preparation. The literature methods were either lengthy in operation and/or gave products in poor yields. We wish to report an improved method which is convenient and simple in practice, and gives high purity product in satisfactory yield.

Recently, Carabateas and Harris reported that the preparation of 1,4-benzodiazepine-2,5-dione by heating isatoic anhydride with ethyl glycinate in DMF (4). However, the poor yield (20%) obtained made this method less attractive than others. An equally disappointing yield (21%) was obtained when the reaction of isatoic anhydride and glycine ester was carried out in an aqueous sodium hydroxide solution as reported by Ermili and Filacchioni (6). The present method is a modification of the above methods. We learned that employment of pyridine as medium makes the reaction proceed cleanly in satisfactory yield.

Simple heating of an equimolar mixture of 5-chloroisatoic anhydride and ethyl glycinate hydrochloride in pyridine under refluxing conditions for 7 hours afforded 7-chloro-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione (IIb) of high purity in a 53% yield. Other benzodiazepine-2,5-diones prepared in this fashion are listed in Table I.

It appears that hydrogen chloride serves as a catalyst for this reaction. While 2-amino-5-chlorohippuric acid ethyl ester, a possible intermediate for this reaction failed to cyclize in boiling pyridine alone, an addition of an equimolar quantity of pyridine hydrochloride to the reaction mixture caused the cyclization reaction to occur. The

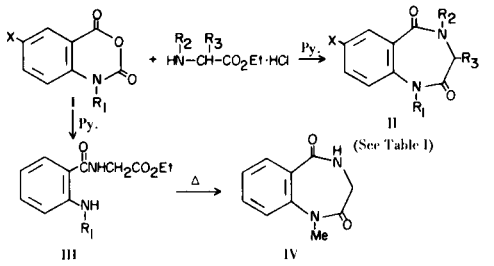
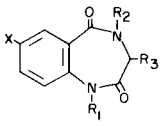


Table I

1,4-Benzodiazepine-2,5-diones



Compound	X	R_1	R_2	R_3	M.p., °C (a)	Lit. m.p. °C	Yield, %
IIa	H	H	H	H	328-330	327-327.5(2)	58
b	Cl	H	H	H	323-325	323-325(4)	53
c	H	H	Me	H	243-246	246.2-247.0(4)	52 (b)
d	H	H	H	Me	331-333 (c)	316(5)	46
e	Cl	H	Me	H	259-262 (d)		47.5
IV	H	Me	H	H	188-190	192-193(3)	52 (e)

(a) Melting points were taken on products without purification except in case of IV. (b) Commercially available sarcosine methyl ester hydrochloride was used. (c) *Anal.* Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.36; H, 5.49; N, 14.49. (d) *Anal.* Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.04; N, 12.47. Found: C, 53.68; H, 4.06; N, 12.68. (e) Yield of cyclization reaction (see Experimental).

open chain 2-amino-5-chlorohippuric acid ethyl ester was isolated from the pyridine solution after separation of IIb in the above reaction. In case of *N*-methylisatoic anhydride, direct formation of 3*H*-1-methyl-1,4-benzodiazepine-2,5-(1*H*,4*H*)dione (IV) was unsuccessful under these conditions (7). Instead, 2-methylaminohippuric acid ethyl ester (III, R_1 = Me) was obtained in 88% yield. The cyclization of the latter to IV was effected thermally by fusion without solvent.

EXPERIMENTAL

Melting points were taken in capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were obtained in potassium bromide discs using a Perkin-Elmer spectrophotometer Model 21. Nmr spectra were determined using a Varian Model A-60 spectrometer using TMS as the internal reference. Combustion elemental analyses were carried out by the Analytical Section of these laboratories using a Perkin-Elmer Model 240 elemental analyzer.

3*H*-1,4-Benzodiazepine-2,5(1*H*,4*H*)dione (IIa).

The preparation of compound IIa-e (see Table I) is exemplified by this procedure.

A mixture of isatoic anhydride (114.1 g.), glycine ethyl ester hydrochloride (105 g.), and pyridine (450 ml.) was heated under reflux for 7 hours then chilled in a refrigerator overnight. The precipitate thus separated was collected on a filter and washed with water, then with ethanol several times, giving 73 g. of the product, m.p. 328-330° dec.

7-Chloro-3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)dione (IIb).

A mixture of 5-chloroisatoic anhydride (197 g.), glycine ethyl ester hydrochloride (140 g.), and pyridine (1 l.) was heated under reflux for 7 hours. The reaction mixture was concentrated to *ca.* 250 ml. by distillation, diluted with an equal amount of ethanol, then chilled in ice. The precipitate thus separated was collected on a filter and washed repeatedly with ethanol to give 111.9 g. of the product (IIb), m.p. 323-325° dec.

The filtrate and washings were combined and concentrated by evaporation on a rotary evaporator under reduced pressure. The concentrated solution was then poured into a large amount of water. The supernatant layer was decanted and fresh water was added. Chilling and scratching of the oil thus separated caused solidification. The precipitate was collected on a filter and recrystallized from ether to give 2-amino-5-chlorohippuric acid ethyl ester, m.p. 104-106°; ir: 2.94, 3.00, 5.76 and 6.07 μ.

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3$: C, 51.47; H, 5.10; N, 10.91. Found: C, 51.57; H, 5.24; N, 10.95.

A mixture of 2.6 g. of 2-amino-5-chlorohippuric acid ethyl ester, 1.0 g. of pyridine hydrochloride and 20 ml. of pyridine was heated under reflux for 8 hours. Removal of pyridine on a rotary evaporator under reduced pressure gave a solid residue which was collected on a filter and washed with water, then with ethanol giving 0.8 g. of IIb, m.p. 321-322° dec.

2-(Methylamino)hippuric Acid Ethyl Ester (III, R_1 = Me).

A mixture of *N*-methylisatoic anhydride (52 g.), glycine ethyl ester hydrochloride (44 g.) and pyridine (200 ml.) was heated under reflux for 3.5 hours. The pyridine was removed on a rotary evaporator under reduced pressure to give an oil. Treatment of the oil with a large amount of water caused separation of solid material which was collected on a filter and washed with water several times to give 61 g. of product, m.p. 55-59°. An analytical sample which was recrystallized from ether melted at 72-74.5°; ir: 2.90, 2.98, 5.72, 6.06 μ; nmr (deuteriochloroform): δ 1.28 (3H, t), 2.85 (3H, s), and 4.20 (4H, m).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.97; H, 6.96; N, 11.82.

3*H*-1-Methyl-1,4-benzodiazepine-2,5(1*H*,4*H*)dione (IV).

Nine g. of III was fused in an Erlenmeyer flask with a gas burner for 10 minutes. After cooling to room temperature, the solid material was dissolved in 20 ml. of dichloromethane with warming on a steam bath. Addition of ether (30 ml.) to the dichloromethane solution and chilling in ice caused separation of a precipitate which was collected on a filter, and washed with ether to give 3.8 g. of product, m.p. 184-186°.

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(7) Prolonging of the reaction time up to 18 hours did not form IV but gave III.