Oxidation of 2,4-Benzodiazepin-3-ones

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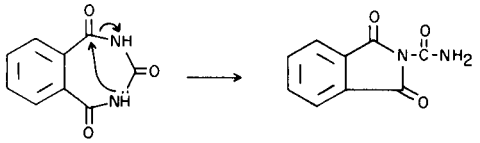
Although there are several reports in the literature which describe the preparation of the benzodiazepin-1,3,5-trione I (Ia-c), more recent work has shown that these compounds have, in fact, structure II (2a-c).

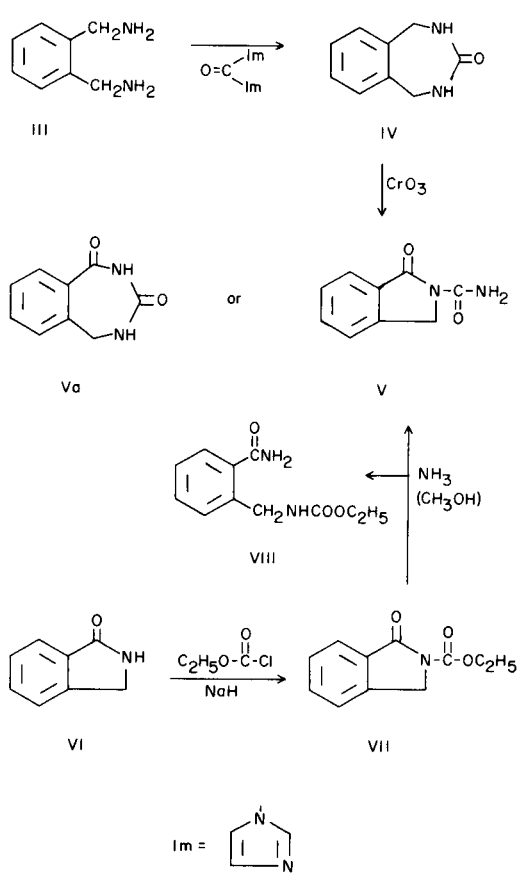


I II

All of the reported syntheses of I involved a cyclization as the last step. One can envision the rearrangement of any benzodiazepin-1,3,5-trione that may have formed to the phthalimide derivative II. In an attempt to prepare an authentic sample of the trione I, we chose to synthesize the cyclic system first and to introduce the amide functions by oxidation in the last step.

Using α,α′-dibromo-*o*-xylene as the starting material, the 7-membered heterocycle IV, was synthesized as shown in Scheme I. The first step involved the conversion of α,α′-dibromo-*o*-xylene to α,α′-diamino-*o*-xylene (III) by the method developed by Carpino (3). This diamine was than cyclized to 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepin-3-one (IV) by treatment with carbonyldiimidazole. Oxidation of IV with chromic acid afforded a dicarbonyl compound whose physical properties were compatible with either structure V or Va. The reported synthesis of an authentic sample of Va by the carbonylation of benzaldehydeazine had been published by Rosenthal and Millward (4) and although the melting points are different (lit. (4) 255-256° as compared with 216.5-219.5°), the reported infrared and n.m.r. spectra for Va are essentially identical with those obtained for our product. However, since these authors did not consider the alternative structure V and were also unable to substantiate their proposed structure by an unequivocal syntheses, we undertook the independent synthesis of V for purposes of comparison.

Scheme I

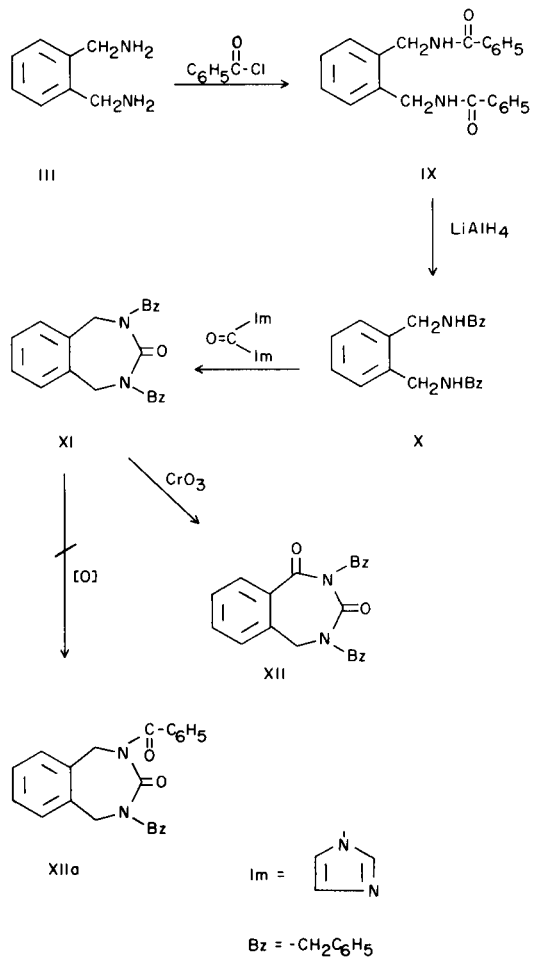


Treatment of phthalimidine (5) (VI), with sodium hydride and ethyl chloroformate afforded 1-oxo-2-isoindolinecarboxylic acid ethyl ester (VII) in high yield. Subsequent amination of VII with methanolic ammonia gave a mixture of the desired 1-oxo-2-isoindoline-carboxamide compound V together with an equal amount of the carbamate VIII. A comparison of a sample of authentic V with the product obtained from the oxidation of IV showed, by the usual criteria, that the two compounds were identical in all respects. The structure of VIII was assigned on the basis of compatible infrared, n.m.r. and mass spectra.

It therefore seems reasonable that the formation of V from IV proceeds via the oxidation product Va which then undergoes rearrangement with ring contraction to give the 5-membered system in a manner completely analogous to the rearrangement of I to II. Attempts to isolate Va by the use of other oxidizing agents (6a-d) were unsuccessful. We found that in all cases, the oxidation was accompanied by a ring contraction. We therefore feel that the compound Va reported by Rosenthal and Millward may in reality be the isomeric phthalimidine derivative, compound V.

In a series of experiments designed to eliminate the possibility for ring contraction to the isoindoline system, we chose to oxidize 2,4-dibenzyl-1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepin-3-one, (XI). This protected 7-membered heterocycle was synthesized from α,α′-diamino-*o*-xylene (III) as shown in Scheme II.

Scheme II



Oxidation of XI with chromic acid afforded 2,4-dibenzyl-4,5-dihydro-1*H*-2,4-benzodiazepine-1,3-(2*H*)-dione (XII). The assignment of structure XII was based on compatible infrared and n.m.r. spectra. The isomer, XIIa was excluded on the basis of the observed molecular and fragment ions from the low resolution mass spectra. Thus fragments corresponding to the loss of (C_6H_5-CH=NH) and ($C_6H_5CH_2$-N=C=O) were observed but no fragments from (C_6H_5-C≡O) or (C_6H_5-CO-N=C=O) which would be expected for structure XIIa were noted. The presence of a molecular ion corresponding to (*o*-$CH_3C_6H_4$C≡O) added further support to structure XII.

EXPERIMENTAL

All melting points were determined microscopically on a hot stage and are corrected. The infrared spectra were determined on a Beckman IR-9 spectrophotometer. The n.m.r. spectra were determined with a Varian A-60 instrument. Thin and preparative layer chromatography were done on plates prepared with silica gel G. Mass spectra were determined with a (CEC) 21-110 spectrometer. The α,α′-dibromo-*o*-xylene (Eastman Organic Chemicals, Rochester, N. Y.) and carbonyldiimidazole (Aldrich Chemical Co., Milwaukee, Wis.) were used without further purification. In experiments where dried solvents are indicated, that solvent was dried over Woelm Grade I neutral alumina.

α,α′-Diamino-*o*-xylene (III).

A suspension of 10.9 g. (0.05 mole) of α,α′-diamino-*o*-xylene hydrochloride [prepared in 69% yield by the method of Carpino (3)] in 200 ml. of methanol was treated with 46.2 ml. of a 2.165 *M* solution of sodium methoxide in methanol. The mixture was stirred for 1 hour at 25°, evaporated to dryness, taken up in ether and filtered. The filtrate was concentrated and the product was purified by vacuum distillation to give 5.5 g. (81%) of III as a colorless liquid, b.p. 106-106.5° (0.025 mm.).

1,2,4,5-Tetrahydro-3*H*-2,4-benzodiazepin-3-one (IV).

A solution of 13.7 g. (0.084 mole) of carbonyldiimidazole in 200 ml. of dry tetrahydrofuran was added dropwise with stirring at 25° to a solution of 9.4 g. (0.069 mole) of α,α′-diamino-*o*-xylene in 100 ml. of dry tetrahydrofuran. After the addition was complete the reaction mixture was stirred for 48 hours and was then filtered. The precipitate was washed with tetrahydrofuran and dried to give 10.6 g. (92.2%) of IV as white rods, m.p. 240-244°. An analytical sample was obtained by recrystallization from a mixture of chloroform and ethanol (m.p. 256-260°).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 67.01; H, 6.30; N, 17.55.

Ethyl 1-Oxo-2-isoindolinecarboxylate (VII).

A solution of 6.0 g. (0.05 mole) of phthalimidine in 200 ml. of dry tetrahydrofuran was treated with 2.0 g. (0.05 mole) of a 60% dispersion of sodium hydride in mineral oil. Stirring was continued for 1 hour at 25° when a solution of 5.5 g. (0.05 mole) of ethylchloroformate in 25 ml. of dry tetrahydrofuran was added dropwise. The mixture was stirred for 3 hours at 25°, evaporated to dryness, taken up in water and set aside at 0° for crystallization. Filtration afforded 9.0 g. of VII as tan needles, m.p. 131-133°.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.48; H, 5.41; N, 6.76.

1-Oxo-2-Isoindolinecarboxamide (V).

Method A. Oxidation of 1,2,4,5-tetrahydrofuran-3*H*-2,4-benzodiazepin-3-one (IV).

A solution of 487 mg. (3.0 mmole) of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepin-3-one (IV) in 10 ml. of glacial acetic acid was treated with 3.36 ml. (9.0 mmole) of a freshly prepared 2.672 *M* solution of chromic acid (8) and the reaction mixture was stirred at 25° for 12 hours. The brown solution was poured into 500 ml. of water and brought to *p*H 8-9 with concentrated ammonium hydroxide. The mixture was extracted with methylene chloride and the organic layer was dried over magnesium sulfate and evaporated. The residue was recrystallized from a mixture of chloroform and hexane to give 43 mg. (8.1%) of V as white rods, m.p. 216.5-219.5°.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.22; H, 4.40; N, 15.66.

Method B: Amination of ethyl 1-oxo-2-isoindolinecarboxylate (VII).

A saturated solution of ammonia in 75 ml. of methanol was treated with 2.6 g. (0.013 mole) of ethyl 1-oxo-2-isoindolinecarboxylate (VII). The solution was stirred at 25° for 12 hours, and evaporated to dryness. The residue was recrystallized from water to give 0.8 g. of yellow crystals. Thin layer chromatography revealed this to be a 2 component mixture (Rf = 0.63 and 0.83; 10% methanol in chloroform) and the mixture was separated by thick layer chromatography using 10% methanol in chloroform as the eluant. The fast moving fraction was finally crystallized from a mixture of ethanol and water to give 0.3 g. (7.5%) of V as white rods, m.p. and m.m.p. 218-220.5°.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 60.86; H, 4.64; N, 15.44.

Ethyl 2-Carbamoylbenzylcarbamate (VIII).

The slow moving fraction from the thick layer chromatogram was crystallized from water. There was obtained 0.3 g. (7%) of VIII as white needles, m.p. 194.5-195.0°; n.m.r. peaks (DMSO D_6) at δ 1.15 (3H triplet, CH_3-) at δ 3.98 (2H quartet, O-CH_2-) at δ 4.32 (2H doublet, J = 6 cps; collapses to singlet on exchange with D_2O; -NH-CH_2-) at 7.38 (7H multiplet, NH; NH_2; 4H aromatic).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.43; H, 6.43; N, 12.58.

N,N'-Dibenzyl-*o*-xylylenediamine (X).

A solution of 7.6 g. (0.19 mole) of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran was heated to reflux and treated with a solution of 26.5 g. (0.0622 mole) of *N,N'*-dibenzoyl-*o*-xylylenediamine (IX) (9) in 1 l. of dry tetrahydrofuran. The reaction mixture was heated under reflux for 2 hours, cooled in an ice-bath and water was carefully added to decompose the excess lithium aluminum hydride. Solvent was removed at reduced pressure and a mixture of 500 ml. of ether and 800 ml. of a 20% aqueous solution of potassium sodium tartrate was added. The mixture was filtered over celite and the layers were separated. The aqueous layer was washed several times with ether. The combined ether layers were dried (magnesium sulfate) and evaporated. The product (12.5 g., 51%) was obtained as a yellow oil, b.p. 250° (0.75 mm.).

Anal. Calcd. for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85. Found: C, 83.28; H, 7.75; H, 8.58.

A portion of the base was converted to the dihydrochloride by treatment with ethereal hydrogen chloride. The salt was recrystallized from a mixture of methanol and tetrahydrofuran to give the analytically pure sample as white rods, m.p. 260-268° dec.

Anal. Calcd. for $C_{22}H_{24}N_2 \cdot 2HCl$: C, 67.86; H, 6.73; N, 7.20. Found: C, 67.86; H, 6.86; N, 7.04.

2,4-Dibenzyl-1,2,4,5-tetrahydrofuran-3*H*-2,4-benzodiazepin-3-one (XI).

A solution of 1.65 g. (5.20 mmole) of *N,N'*-dibenzyl-*o*-xylylenediamine (X) in 50 ml. of toluene was treated with 1.05 g. (6.5 mmole) of carbonyldiimidazole. The solution was heated under reflux for 4 hours, and evaporated to dryness. Carbon tetrachloride was added to the residue and cooled to 0°. The solution was filtered to remove imidazole and the filtrate was evaporated to dryness to give 1.65 g. (92%) of XI as a pale yellow oil. Thin layer chromatography showed 1 spot (Rf = 0.79; 6% methanol in chloroform). The low resolution mass spectrum of XI showed a molecular ion peak at m/e 342. Major fragment ions were observed at m/e 251, 238 209, 194, 146, 132, 118, 104 and 91.

2,4-Dibenzyl-4,5-dihydro-1*H*-2,4-benzodiazepine-1,3-(2*H*)-dione (XII).

A solution of 685 mg. (2.0 mmole) of 2,4-dibenzyl-1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepin-3-one in 10 ml. of glacial acetic acid was treated with 3.36 ml. (9.0 mmole) of a freshly prepared 2.672 *M* solution of chromic acid (8). The resulting solution was stirred at 25° for 12 hours, and then was poured into 500 ml. of water. The *p*H was adjusted to 8-9 with concentrated ammonium hydroxide and the reaction mixture was extracted with methylene chloride. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness. The residue was purified by thick layer chromatography using 5% methanol in chloroform as the eluant. Crystallization from carbon tetrachloride-hexane afforded 190 mg. (26.5%) of XII as white prisms, m.p. 114.5-115.5°. Thin layer chromatography showed 1 spot with Rf = 0.35 (chloroform).

Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.56; H, 5.71; N, 7.77.

The low resolution spectrum of XII showed a molecular ion peak at m/e 356. Major fragment ions were observed at m/e 265, 252, 223, 222, 160, 132, 119 and 91.

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