Rearrangement of 1,4-Benzodiazepin-2,4-diones to 3,1-Benzoxazin-4-ones by Acetic Anhydride

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Treatment of 7-chloro-3,4-dihydro-1*H*-1,4-benzodiazepin-2,5-dione (Ia) with refluxing acetic anhydride in the presence of pyridine afforded 6-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (IIa). A plausible reaction path for this novel rearrangement reaction is described: Ia → 4-acetyl-7-chloro-3,4-dihydro-1*H*-1,4-benzodiazepin-2,5-dione → 7-chloro-1,4-diacetyl-3,4-dihydro-1*H*-1,4-benzodiazepin-2,4-dione → IIa. When 7-chloro-3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepin-2,5-dione (Ib), 3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepin-2,5-dione (Id) and 3,4-dihydro-1-methyl-1*H*-1,4-benzodiazepin-2,5-dione (Ie) were allowed to react with acetic anhydride under conditions similar to those used for the rearrangement reaction, only acetylation occurred.

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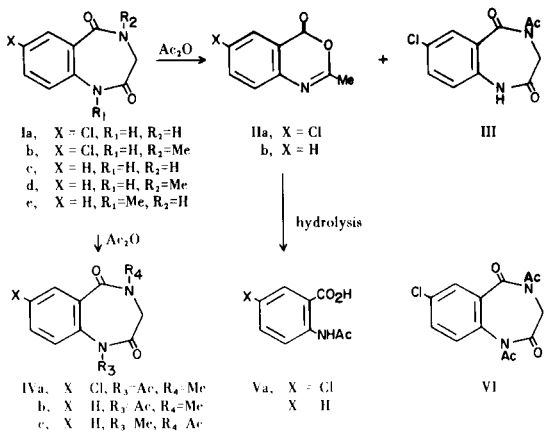
Numerous rearrangement reactions of 1,4-benzodiazepines have been reported (1). Most of the reported rearrangements involve a ring contraction leading to a variety of heterocyclic systems (1). We wish to report still another type of ring contraction reaction observed with 1,4-benzodiazepin-2,4-diones resulting in the formation of 2-methyl-4*H*-3,1-benzoxazin-4-ones.

Treatment of 7-chloro-3,4-dihydro-1*H*-1,4-benzodiazepin-2,5-dione (Ia) for 1.5 hours with a large excess of boiling acetic anhydride in the presence of pyridine gave two products. The crystalline product which was separated first on chilling of the reaction mixture was found to be 6-chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (IIa). The nmr spectrum (deuteriochloroform) of this product showed one methyl proton signal at δ 2.47 apart from those of the aromatic protons. An absorption band at 5.70 μ appeared in the ir spectrum. The structure IIa was proven by an independent synthesis described by Tomisek and Christensen (2). The second product, which was isolated by concentration of the mother liquor and subsequent chilling, was assigned the 4-acetylbenzodiazepine structure III. In consonance with this structure, the nmr spectrum in DMSO-d_6 showed the methylene (C_3) proton signal at δ 4.40 as a singlet and the N_1 proton at δ 10.77 also as a singlet. The protons of the acetyl group appeared at δ 2.50. In comparison, the methylene (C_3) protons of Ia appeared at δ 3.63 as a doublet and the N_4 proton at δ 8,62 as a triplet. The proton at the N_1 position of Ia resonated at δ 10.30 ppm.

When Ic was treated similarly with acetic anhydride in the presence of pyridine, acetylanthranilic acid (Vb) was isolated instead. This acid is believed to have formed from the rearrangement product, IIb during the work up; the latter is known to be extremely unstable and rapidly hydrolyzes to Vb (3). 6-Chloroacetylanthranilic acid (Va) was fromed when IIa was treated with dilute aqueous sodium hydroxide solution, and then acidified.

Scheme I



It is not unreasonable to consider the 4-acetylbenzodiazepinedione III as a likely intial intermediate for the rearrangement reaction. Since primary amines are known to give diacetylated products under forcing conditions (4), the formation of III as the initial product would be expected. Nevertheless, to establish this intermediacy, III was treated with acetic anhydride under the reaction conditions. Two products were isolated from this reaction, namely the rearrangement product IIa and the

diacetylated benzodiazepinedione VI, in yields of 16% and 25%, respectively. Furthermore, when the reaction of Ia with acetic anhydride was terminated in 15 minutes, as expected there was obtained only III and VI in yields of 35% and 47%, respectively. Incidentally, it is interesting to note that in the nmr spectrum of VI (DMSO-d_6) the methylene (C_3) proton signals no longer appeared as a singlet, but rather as two doublets, at δ 4.12 (J = 15 Hz) and 4.93 (J = 15 Hz).

Now then a possibility of VI as being the second intermediate for the rearrangement reaction becomes an apparent question. In order to answer the question, VI was refluxed for 1.5 hours with an excess of acetic anhydride in the presence of pyridine and two equivalent amounts of acetic acid. The addition of two equivalents of acetic acid was based on the stoichiometric consideration of the preceding acetylation reactions with acetic anhydride to form III and subsequently VI, with concomitant generation of acetic acid in each step. From this reaction, the rearrangement product IIa was isolated in 19% yield. When the reaction was repeated with the exclusion of acetic acid, no rearrangement product was obtained; instead VI was recovered intact. With one equivalent amount of acetic acid present, VI afforded IIa in 5% yield.

The foregoing experimental results strongly indicate the involvement of VI as a second intermediate for the rearrangement reaction and suggest that the acetate ion is involved as a nucleophile, effecting the cleavage of the diazepine ring to give an open chain intermediate such as VII (Scheme II). Cyclization of the latter would then give the isolated product IIa.

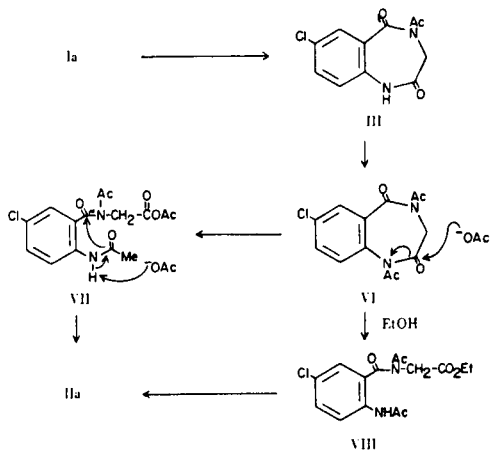
A plausible reaction pathway for the ring contraction-rearrangement reaction Ia → IIa may be formulated in the following (Scheme II). In support of the last step of the proposed mechanism, IIa was obtained in 59% yield when VIII was treated for 1.5 hours with excess boiling acetic anhydride in the presence of pyridine and acetic acid. Compound VIII was formed in an attempted recrystal- of VI from ethanol.

Only acetylation occurred when compounds Ib, Id, and Ie, in which one of two nitrogens of the diazepine ring is substituted, were allowed to react with acetic anhydride under conditions similar to those used for the conversion of Ia into IIa, giving IVa-c, respectively. Interestingly, Ib failed to undergo the rearrangement reaction even under 3 hours refluxing conditions, giving only IVa in a 86.5% yield.

Pyridine has been commonly employed as a catalyst for the acetylation reaciton of amine and alcohol with acetic anhydride. As expected, when the reaction of Ia with boiling acetic anhydride was carried out in the absence of pyridine catalyst, the yield of IIa was decreased to *ca.* 9% even after 3 hours of reflux. Compound III was isolated in a 14% yield. Apparently, the effect of the pyridine in this reaction is twofold: it catalyzes the acetylation to form III and VI at the initial stage of the reaction, and then serves as a base to form the acetate ion with the acetic acid generated. The acetate ion thus formed is the effective nucleophile responsible for the cleavage of the diazepine ring, as demonstrated in the following experiment. Thus, when VI was heated for 1.5 hours with an excess of acetic anhydride in the presence of two equimolar amounts of acetic acid, but without pyridine, no rearrangement product was obtained. Instead, a small amount of deacetylated product III was isolated along with the unreacted VI.

was improved from 22% to 46.5% by extending the reaction period from 1.5 hours to 3 hours. No significant increase in the yield was observed, however, by further extension of the reaction period to a total of 6 hours.

Scheme II



EXPERIMENTAL

Melting points were determined in a capillary tube 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 with a Varian Model A-60 spectrometer using TMS as the internal standard. Combustion elemental analyses were carried out by the Analytical Section of these laboratories using a Perkin-Elmer Model 240 elemental analyzer. Tlc was performed on Alumina GF precoated plate (Uniplate from Analtech Inc.) using a mixture of benzene (5), dichloromethane (4). and triethylamine (1) as the eluent.

6-Chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (IIa) and 4-Acetyl-7-chloro-3,4-dihydro-1*H*-1,4-benzodiazepin-2,5-dione (III).

A mixture of 7-chloro-3,4-dihydro-1*H*-1,4-benzodiazepin-2,5-dione (Ia) (5.0 g.), acetic anhydride (25 ml.), and pyridine (1 ml.) was heated under reflux for 1.5 hours, then chilled in ice. The precipitate thus separated was collected on a filter and washed with acetic anhydride to give IIa, m.p. 124-126°. A mixture m.p.

with IIa prepared from 5-chloroanthranilic acid and acetic anhydride by the literature method (3) was not depressed, yield, 1.45 g. (22%).

The acetic anhydride mother liquor was concentrated on a rotary evaporator under reduced pressure to *ca.* 10 ml., then allowed to set at room temperature overnight, whereby a precipitate deposited. The precipitate was collected on a filter, washed with acetic anhydride, then recrystallized from ethanol to give 0.75 g. (13%) of III, m.p. 201-203°; ir: μ 3.13, 5.88.

Anal. Calcd. for $C_{11}H_9ClN_2O_3$: C, 52.29; H, 3.59; N, 11.09. Found: C, 52.27; H, 3.76; N, 11.06.

Reaction of 3,4-Dihydro-1*H*-1,4-benzodiazepin-2,4-dione (Ic).

A mixture of Ic (15 g.), acetic anhydride (70 ml.) and pyridine (1.5 ml.) was heated under reflux for 2 hours. Removal of the excess acetic anhydride on the rotary evaporator under reduced pressure gave an oil. The oil was extracted with ether. The combined ether extract was washed with water, then dried over anhydrous mangesium sulfate. Evaporation of ether under reduced pressure gave an oily residue. Treatment of the oil with a small anount of ether caused separation of a precipitate which was collected on a filter, and recrystallized from ether, giving 2.5 g. (16%) of *N*-acetylanthranilic acid (Vb), m.p. 185-187°, lit. m.p. (5) 184-186°.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.45; H, 5.17; N, 7.91.

Reaction of 4-Acetyl-7-chloro-3,4-dihydro-1*H*-1,4-benzodiazepin-2,5-dione (III) with Acetic Anhydride.

A mixture of III (2.5 g.), acetic anhydride (12 ml.) and pyridine (0.5 ml.) was heated under reflux for 1.5 hours, then chilled in ice. The precipitate thus separated was collected on a filter and washed with acetic anhydride to give 0.1 g. of IIa. An additional amount (0.2 g.) was isolated from the mother liquor by allowing to set at room temperature after being concentrated to approximately 4 ml. under reduced pressure and recrystallization from acetic anhydride, m.p. 124-126°. When the filtrate was allowed to set at room temperature, another crop of precipitate was separated. The precipitate was collected on a filter and washed with ethanol, then with ether, giving 0.7 g. of VI, m.p. 129-131°; ir spectrum identical to that of VI prepared from Ia.

4-Acetyl-7-chloro-3,4-dihydro-1*H*-1,4-benzodiazepin-2,5-dione (III) and 7-Chloro-1,4-diacetyl-3,4-dihydro-1*H*-1,4-benzodiazepin-2,5-dione (VI).

A mixture of Ia (10 g.), acetic anhydride (50 ml.) and pyridine (1 ml.) was allowed to stir at room temperature for 1 hour, then heated to reflux and kept at reflux for 15 minutes. In *ca.* 10 minutes, the reaction mixture became a clear solution. The reaction mixture was chilled in a freezer overnight. The precipitate thus separated was collected on a filter and washed with acetic anhydride, giving 4.2 g. (35%) of III (m.p. 201-203°) which is identical to III obtained in the preceding experiment.

The combined mother liquor and washings were evaporated on a rotary evaporator under reduced pressure to an oil which solidified on chilling and scratching. The solid mass thus obtained was recrystallized from THF and ether to give 4.6 g. of VI, m.p. 138-140°; ir: μ 5,74, 5.82, and 5.90. An additional amount (1.95 g.) was isolated from the mother liquor to give a total of 6.55 g. (47%) of VI.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_4$: C, 52.98; H, 3.76; N, 9.51. Found: C, 52.92; H, 3.72; N, 9.54.

Attempted recrystallization of VI from ethanol resulted in cleavage of the diazepine ring to give *N*-acetyl-2-acetylamino-5-chlorohippuric acid ethyl ester (VIII), m.p. 134-136°; mass spectrum: 340 m/e (M^+); ir: μ 3.01 and 5.80-5.96; nmr (DMSO-d_6): δ 1.20 (t, 3H, CH_2CH_3), 2.01 (s, 3H, CCH_3), 2.22 (d, 3H, CCH_3), 4.12 (q, 2H, CH_2CH_3), 4.43 (s, 2H, CH_2), 7.32-7.82 (m, 3H, aromatic) and 10.10 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{17}ClN_3O_5$: C, 52.87; H, 5.03; N, 8.22. Found: C, 52.96; H, 5.14; N, 8.27.

4-Acetyl-3,4-dihydro-1-methyl-1*H*-1,4-benzodiazepin-2,5-dione (IVc).

A mixture of 3,4-dihydro-1-methyl-1*H*-1,4-benzodiazepin-2,5-dione (Ie) (2.5 g.), acetic anhydride (30 ml.), and pyridine (5 drops) was heated under reflux for 1.5 hours, then chilled in ice to cause separation of a precipitate. The precipitate was collected on a filter and washed with ethanol to give 2.5 g. (81.5%) of the product, m.p. 206-209°. Recrystallization from ethanol afforded an analytical sample, m.p. 205-207°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.36; H, 5.19; N, 11.97.

1-Acetyl-3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepin-2,4-dione (IVb).

A mixture of 3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepin-2,5-dione (Id) (1.0 g.), acetic anhydride (15 ml.), and pyridine (5 drops) was heated under reflux for 3.5 hours. The excess acetic anhydride was removed on a rotary evaporator under reduced pressure to give an oil which solidified on standing. Recrystallization of the solid residue from ethanol with charcoal treatment afforded 0.35 g. (28%) of the product, m.p. 160-161°.

Anal. Calcd. for $C_{12}H_{11}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.65; H, 5.36; N, 11.82.

1-Acetyl-7-chloro-3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepin-2,5-dione (IVa).

A mixture of 7-chloro-3,4-dihydro-4-methyl-1*H*-1,4-benzodiazepin-2,5-dione (Ib) (2,2 g.), acetic anhydride (11 ml.), and pyridine (0.8 g.) was heated under reflux for 3 hours, then evaporated on a rotary evaporator under reduced pressure to give an oil. The oil was solidified on chilling. The solid mass was collected on a suction filter with pressing to give 2.3 g. (86.5%) of product, m.p. 149-151°. Analytical sample which was obtained by recrystallization from ethanol melted at 155-157°.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_3$: C, 54.03; H, 4.16; N, 10.51. Found: C, 53.86; H, 3.91; N, 10.67.

6-Chloro-2-methyl-4*H*-3,1-benzoxazin-4-one (IIa) from *N*-Acetyl-2-acetylamino-5-chlorohippuric Acid Ethyl Ester (VIII).

A mixture of VIII (1.9 g.), acetic anhydride (5.5 ml.), glacial acetic acid (0.67 g.), and pyridine (0.44 g.) was heated under reflux for 1.5 hour, then chilled in ice. The precipitate thus separated was collected on a filter and washed with acetic anhydride giving 0.65 g. (59%) of IIa (m.p. 125-127°) which is identical to IIa prepared from Ia.

N-Acetyl-5-chloroanthranilic Acid (Va).

A mixture of IIa (1.0 g.), 15% aqueous sodium hydroxide solution (10 ml.) and water (25 ml.) was stirred at room temperature overnight. The reaction mixture was filtered and the filtrate was acidified with dilute hydrochloric acid. The precipitate thus separated was collected on a filter, washed with water, and recrystallized from ethanol, giving 0.6 g. of product, m.p.

203-205°, lit. m.p. 204° (3); ir: μ 4.05 (borad, CO_2H), 5.85 ($-CO_2H$), and 6.05 ($NHCOCH_3$).

Anal. Calcd. for $C_9H_8ClNO_3$: C, 50.60; H, 3.77; N, 6.56. Found: C, 50.27; H, 3.70; N, 6.49.

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