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A New Synthesis of 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide

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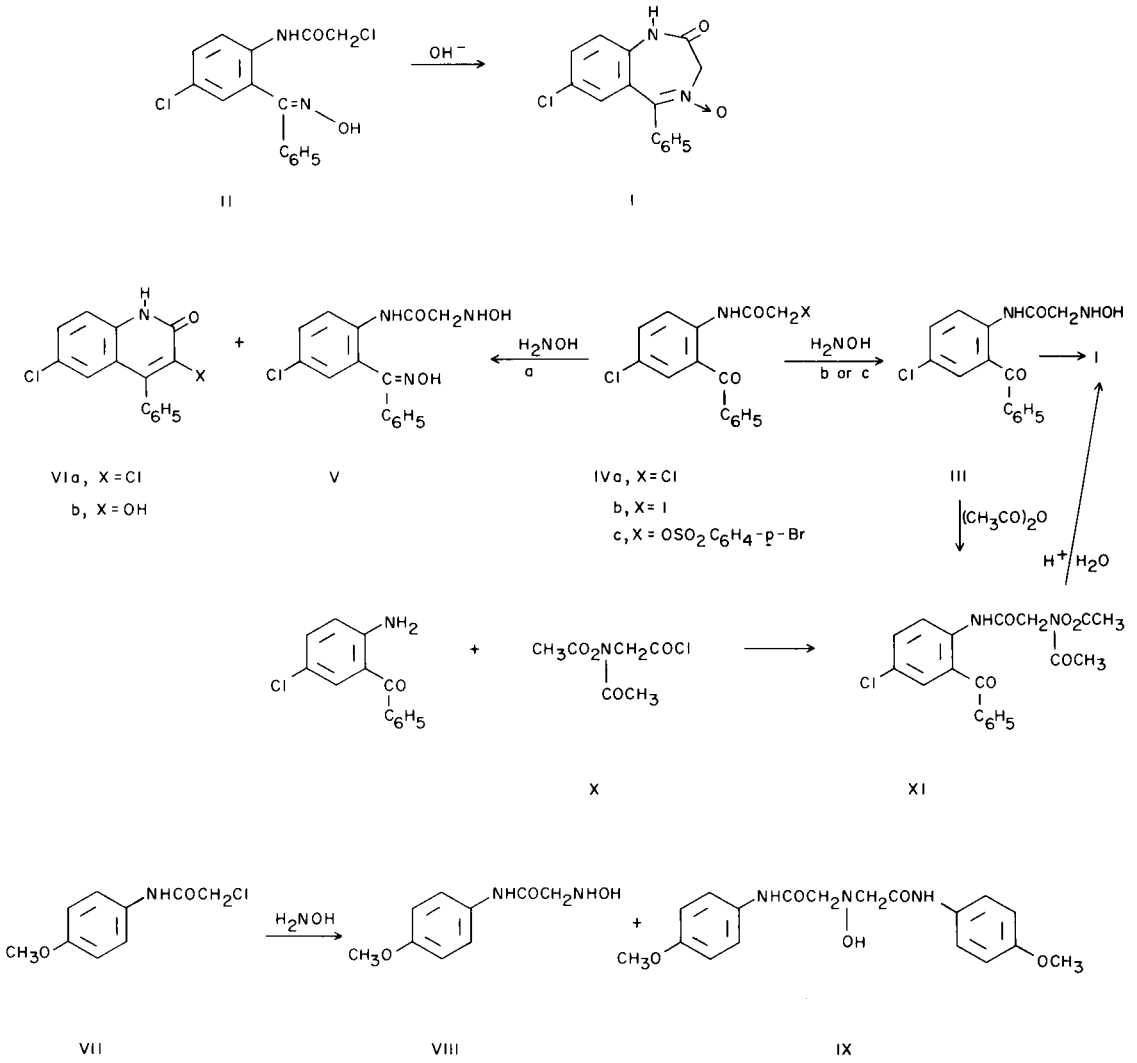
7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (I) is of considerable importance in the psychopharmacological field. Not only is I the principal metabolite of chlordiazepoxide in the human, it can also serve as a chemical intermediate in the production of both diazepam and oxazepam (1). Several methods already exist for the synthesis of this key compound and we should like to report on a new route that we have developed.

Sternbach and Reeder (2) have described a method for the preparation of I from 2-chloroacetamido-5-chlorobenzophenone, β-oxime (II) by treatment with base. A drawback to the use of this method lies in the difficulty of obtaining the necessary β-oxime since the predominant form resulting from oximation and acylation of the corresponding aminoketone is the α-oxime. A two-step conversion of the α-oxime into the β-oxime has been



described (2).

The formation of nitrones by *N*-alkylation of oximes in the fashion detailed by Sternbach and Reeder is well-known (3). The formation of nitrones from unhindered carbonyl compounds and *N*-monoalkylated hydroxylamines is also known but difficulty has been encountered with benzophenones requiring the use of the corresponding ketals. Certain cyclic nitrones have been prepared by reductive generation of the hydroxylamine function *in situ* (4). We sought to use this cyclization method in the synthesis of I without preliminary ketal formation. The necessary intermediate was thus 2-hydroxyaminoacetamido-5-chlorobenzophenone (III).

A possible access to III was through alkylation of hydroxylamine with the requisite haloacetamido compound. The preparation of *N*-monoalkylhydroxylamines in this way had, however, been unsuccessful in the past. Indeed, a recent review (5) of hydroxylamine preparation does not even mention alkylation as a possible route. Nevertheless, we have found that 2-iodoacetamido-5-chlorobenzophenone (IVb) reacts with a considerable excess of hydroxylamine to afford III in good yield. Satisfactory yields were obtained with 2-*p*-bromophenylsulfonoxyacetamido-5-chlorobenzophenone (IVc) as well, but with 2-chloroacetamido-5-chlorobenzophenone (IVa) a mixture resulted, the exact composition of which was not determined. By varying reaction conditions the oxime (V) of III was isolated, as was 3,6-dichloro-4-phenylcarbostyril (VIa) and 6-chloro-3-hydroxy-4-phenylcarbostyril (VIb). The presence of III in the mixture seems likely, as does the presence of the dialkylated hydroxylamine, since in a related reaction using 4'-methoxy-2-chloroacetanilide (VII) both mono- (VIII) and dialkylated (IX) products were obtained.

Compound III cyclized readily in the presence of acid to afford I in almost quantitative yield. The success of this method led us to seek a more direct preparation of the intermediate since the alkylation method requires excess reagent and very precise experimental control in order to obtain the best results. Accordingly, *N*-acetoxyacetamidoacetic acid (6) was prepared by acetylation of hydroxyaminoacetic acid and was converted into its acid chloride (X) with thionyl chloride. Direct acylation of 2-amino-5-chlorobenzophenone led to XI, identical with material obtained by acetylation of III. Mild acid hydrolysis of XI did not give III, but afforded I directly in a yield almost comparable to that obtained in the direct cyclization of III.

EXPERIMENTAL (7)

5-Chloro-2-iodoacetamidobenzophenone (IVb).

A mixture of 7.0 g. of IVa, (8) 7.0 g. of sodium iodide and 100 ml. of acetone was heated under reflux for 2 hours. The reaction mixture was cooled, filtered from sodium chloride and diluted with 100 ml. of water. Compound IVb, 8.5 g., m.p. 125-127°, was collected.

Anal. Calcd. for $C_{15}H_{11}ClINO_2$: C, 45.08; H, 2.78; N, 3.51. Found: C, 45.31; H, 2.89; N, 3.08.

2-Acetoxyacetamido-5-chlorobenzophenone.

To a solution of 40 g. of 2-amino-5-chlorobenzophenone in 150 ml. of chloroform was added a solution of 26 g. of acetoxyacetyl chloride (9) in 60 ml. of chloroform. The solution became warm and after the addition was completed the reaction mixture was heated on the steam bath for 15 minutes. The solvent was removed *in vacuo* and the residue was recrystallized from ethanol to give 50 g. (87%) of product, m.p. 121-123°.

Anal. Calcd. for $C_{17}H_{14}ClNO_4$: C, 61.55; H, 4.25; Cl, 10.69; N, 4.22. Found: C, 61.48; H, 4.30; Cl, 10.90; N, 4.03.

5-Chloro-2-hydroxyacetamidobenzophenone.

To a suspension of 66.6 g. of 2-acetoxyacetamido-5-chlorobenzophenone in 550 ml. of ethanol was added with stirring a solution of 8 g. of sodium hydroxide in 60 ml. of water. The mixture became clear and the product was precipitated by the addition of 750 ml. of water. Recrystallization from ethanol gave 55 g. (94%) of 5-chloro-2-hydroxyacetamidobenzophenone, m.p. 151-153°.

Anal. Calcd. for $C_{15}H_{12}ClNO_3$: C, 62.18; H, 4.18; Cl, 12.24; N, 4.84. Found: C, 62.29; H, 4.15; Cl, 12.30; N, 4.72.

2-*p*-Bromophenylsulfonoxyacetamido-5-chlorobenzophenone (IVc).

To a solution of 15.0 g. of 5-chloro-2-hydroxyacetamidobenzophenone and 200 ml. of triethylamine was added 28 g. of *p*-bromobenzenesulfonyl chloride. After heating on the steam bath for 0.5 hours the reaction mixture was cooled, diluted with water and the product was collected and recrystallized from acetonitrile. There was obtained 17 g. (60%) of IVc, m.p. 153-155°.

Anal. Calcd. for $C_{21}H_{15}BrClNO_5S$: C, 49.58; H, 2.97; N, 2.75; S, 6.30. Found: C, 49.94; H, 2.84; N, 2.93; S, 6.30.

Compound IVc can also be prepared by treating 2-amino-5-chlorobenzophenone with *p*-bromophenylsulfonoxyacetyl chloride (10) in the manner used above with acetoxyacetyl chloride.

5-Chloro-2-(2-hydroxyaminoacetamido)benzophenone (III).

Method A.

To a mixture of 70 g. of 75% hydroxylamine sulfate and 21 g. of sodium hydroxide in 200 ml. of ethanol and 120 ml. of water at 75° was added with stirring 32 g. of IVb. The reaction mixture was kept for 15 minutes at 75° and diluted with a large volume of water. There was obtained 22 g. of crude product, m.p. 115-120°. Recrystallization from benzene gave pure III, m.p. 129-131°.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; N, 9.20; Cl, 11.63. Found: C, 59.38; H, 4.16; N, 9.00; Cl, 11.64.

Method B.

To a mixture of 5.1 g. of 2-*p*-bromophenylsulfonoxyacetamido-5-chlorobenzophenone (IVc) in 100 ml. of methoxyethanol at 85° was added a solution of 10.0 g. of hydroxylamine hydrochloride and 5.0 g. of sodium hydroxide in 20 ml. of water. After 15 minutes at 85°, the reaction mixture was cooled, diluted with water and the precipitate was collected and recrystallized from benzene to obtain 1.2 g. of III, m.p. 129-131°.

2-[2-(*N*-Acetoxyacetamido)acetamido]-5-chlorobenzophenone (XI).

Method A.

A mixture of 21 ml. of acetic anhydride and 9.1 g. of hydroxyaminoacetic acid was kept at 65° with stirring for 15 minutes and

cooled to room temperature. The resultant clear solution was diluted with 50 ml. of methylene chloride and 33 ml. of thionyl chloride was carefully added. After refluxing for 15 minutes the the solvent and the excess reagents were removed *in vacuo*. The residue (X) was dissolved in 100 ml. of benzene and added to a solution of 20 g. of 2-amino-5-chlorobenzophenone dissolved in 100 ml. of benzene. After standing for 1 hour the benzene was removed *in vacuo* and the residue was recrystallized from ethanol. There was obtained 22 g. of XI, m.p. 150-152°. Recrystallization from ethanol gave an analytical sample m.p. 153.5-155°.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_5$: C, 58.69; H, 4.41; N, 7.21; Cl, 9.12. Found: C, 58.68; H, 4.42; N, 7.11; Cl, 9.11.

Method B.

A mixture of 7.0 g. of III and 25 ml. of acetic anhydride was heated on the steam bath for 45 minutes. The reaction mixture was chilled and the resultant solid was filtered and washed with ethanol to give 6.6 g. (74%) of XI, m.p. 150-152°.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (I).

To a mixture of 5.0 g. of III, 40 ml. of alcohol and 110 ml. of water was added 10 ml. of 6 *N* hydrochloric acid and the reaction mixture was heated on the steam bath for 10 minutes. The solution was diluted with 100 ml. of water, seeded and cooled. There was obtained 4.5 g. of product (95%), m.p. 231-233°.

In the alternative preparation, 5.0 g. of XI in 100 ml. of alcohol and 10 ml. of 6 *N* hydrochloric acid was heated under reflux for 10 minutes. Upon cooling, 1.6 g. of I, m.p. 232-233°, was obtained. The filtrate was concentrated to dryness *in vacuo* and the residue was recrystallized from 40 ml. of alcohol to afford an additional 1.3 g. of I, m.p. 227-229°. The total yield was 79%.

6-Chloro-3-hydroxy-4-phenylcarbostyril (VIb) and 3,6-Dichloro-4-phenylcarbostyril (VIa).

To a solution of 14 g. of hydroxylamine hydrochloride, 160 ml. of 2 *N* sodium hydroxide and 200 ml. of ethanol was added 12.4 g. of IVa. After stirring for 1 hour the solution was acidified with with acetic acid, filtered and the collected solid was recrystallized from ethanol. There was obtained 2.5 g. of VIb, m.p. 242-244°. Two more recrystallizations from ethanol raised the m.p. to 253-255°. The ultraviolet absorption spectrum of VIb [λ max (EtOH), 232 (ε, 45,000), 287 (ε, 7,900), 312 (ε, 6,700), 326 (ε, 9,250) and 338 mμ (ε, 8,250)] was consistent with that of 6-dechloro-VIb (11).

Anal. Calcd. for $C_{15}H_{10}ClNO_2$: C, 66.30; H, 3.71; N, 5.15; Cl, 13.05. Found: C, 66.14; H, 3.62; N, 5.33; Cl, 13.10.

The filtrate from the above reaction mixture was partially concentrated *in vacuo* precipitating out 0.5 g. of VIa, m.p. 279-282°. Several recrystallizations from ethanol raised the melting point to 299-301°. For comparison, VIa was prepared more conveniently by heating under reflux for 10 minutes a mixture of 30 g. of IVa, 180 ml. of water, 300 ml. of ethanol and 120 ml. of 2 *N* sodium hydroxide. Acidification of the solution with hydrochloric acid gave 5.6 g. of solid, m.p. 280-289°. Several recrystallizations from ethanol gave the product, m.p. 299-301°, λ max (EtOH), 237 (ε, 41,500), 276 (ε, 7,300), 286s (ε, 6,700), 329s (ε, 5,600) and 342 mμ (ε, 7,300).

Anal. Calcd. for $C_{15}H_9Cl_2NO$: C, 62.09; H, 3.12; N, 4.82; Cl, 24.44. Found: C, 61.70; H, 3.12; N, 4.77; Cl, 24.15.

5-Chloro-2-(2-hydroxyaminoacetamido)benzophenone Oxime (V).

A solution of 28 g. of hydroxylamine hydrochloride, 40 ml. of 4 *N* sodium hydroxide in 100 ml. of water and 400 ml. of ethanol was treated with 24.8 g. of IVa and the reaction mixture was heated under reflux for 24 hours. The solvent was removed *in vacuo* and the residue was dissolved in ether and washed with water. After removal of the ether, the solid was recrystallized from acetonitrile. There was obtained 9.6 g. of V, m.p. 224-226°.

Anal. Calcd. for $C_{15}H_{14}ClN_3O_3$: C, 56.34; H, 4.41; N, 13.14; Cl, 11.09. Found: C, 56.49; H, 4.56; N, 13.34; Cl, 11.00.

2-Hydroxyamino-4′-methoxyacetanilide (VIII) and 2,2′-Hydroxyimino-bis(4′-methoxyacetanilide) (IX).

Eight grams of 2-chloro-4′-methoxyacetanilide (VII) was added to a solution of 14 g. of hydroxylamine hydrochloride in 200 ml. of ethanol and 80 ml. of 2 *N* sodium hydroxide and the mixture was heated under reflux overnight. The solution was concentrated *in vacuo* to 140 ml. and diluted with 140 ml. of water. The solid (1.7 g.) that formed was collected and washed with 1 *N* hydrochloric acid and water. Recrystallization from aqueous dimethylformamide afforded IX, m.p. 196-197°.

Anal. Calcd. for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.06; H, 5.93; N, 11.83.

Further dilution of the filtrate gave an additional 2.7 g. of IX. Concentration of the filtrate after removal of IX gave 0.5 g. of a crude mixture, m.p. 160-165°. The new filtrate was chilled to yield 0.1 g. of VIII which was recrystallized from ethanol. Compound VIII had m.p. 137-138°.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.19; H, 5.84; H, 13.87.

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