

A New Method of Synthesis of 1,2,3,4-Tetrahydro-5H-5-oxo-1,4-benzodiazepines (1)

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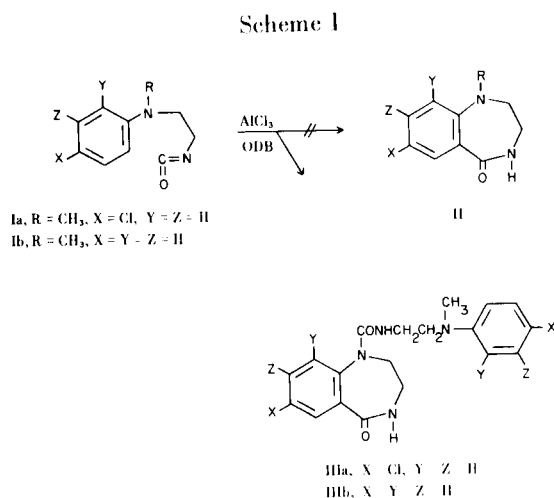
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A new one-step facile method for the synthesis of 1,2,3,4-tetrahydro-5H-5-oxo-1,4-benzodiazepines is described. The method involves the addition of methyl anthranilates to ethyl-imine followed by intramolecular cyclization of the resulting intermediate compounds. Another attempted method starting from β -anilinoethylisocyanates is also described.

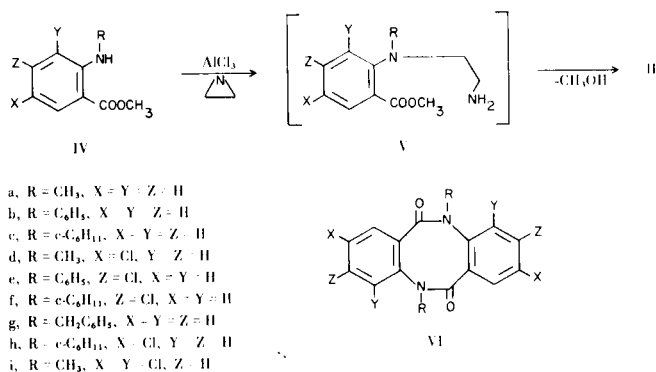
J. Heterocyclic Chem., 14, 99 (1977).

Although three methods (3,4,5) have been devised already for the synthesis of some of the title compounds, none of them appeared to be of practical application.

Our interest in 5H-1,4-benzodiazepine-5-ones II prompted us to try two new possible methods for their synthesis. In the first method (Scheme 1), the catalytic intramolecular cyclization of the isocyanates I was attempted. However, when compounds Ia or Ib were refluxed for one hour in *o*-dichlorobenzene in the presence of aluminum chloride, instead of the corresponding derivatives II, only the compounds IIIa and IIIb were isolated, as shown by the analytical data and ir and nmr spectra. Therefore cyclization was accomplished, but it seemed to be followed by *N*-demethylation and reaction of the formed NH group with another molecule of the starting isocyanate I.



Scheme 2



In the second method (Scheme 2), a methyl anthranilate IV should react in the presence of aluminum chloride with aziridine to yield compound V which should cyclize to the desired 5H-5-oxo-1,4-benzodiazepine II.

Coleman and Callen (6) allowed the adduct of *N*-methylaniline and aluminum chloride to react in benzene at 90° with vaporized aziridine to obtain *N*-methyl-*N*-(β -aminoethyl)aniline in more than 80% yield.

When this procedure was applied to methyl *N*-methylanthranilate (IVa), compound IIa was isolated, after work up, in 70% yield. However, when compounds IVb and IVc were used no corresponding compound II was obtained. The products of reaction were shown to be VIb and VIc, respectively.

This fact led us to change the initial experimental conditions in order to avoid formation of compounds VI.

Thus, when to a stirred suspension of the adduct of IV and aluminum chloride in benzene at room temperature, was added liquid aziridine and the mixture was heated at 90° for 45 minutes, compounds II were obtained in all cases studied in acceptable yields without detecting the formation of any compounds VI.

The availability of the starting materials and the simplicity of this procedure provided an easy route to 1,2,3,4-tetrahydro-5*H*-5-oxo-1,4-benzodiazepine derivatives having been prepared earlier by other cumbersome multiple step reactions.

EXPERIMENTAL

All melting points (uncorrected) were determined using a Gallenkamp capillary apparatus. The ir spectra were recorded with a Perkin Elmer Model 257 instrument. Pmr spectra were obtained with a Perkin-Elmer R-12 spectrophotometer using TMS as an internal reference.

Starting Materials and Reference Compounds.

Methyl *N*-phenylanthranilate (IVb) (7), methyl *N*-cyclohexylanthranilate (IVc) (8,11), methyl 5-chloro-*N*-methylanthranilate (IVd) (9,10), methyl 4-chloro-*N*-phenylanthranilate (IVe) (8), methyl 4-chloro-*N*-cyclohexylanthranilate (IVf) (8) and methyl *N*-benzylanthranilate (IVg) (12) were prepared by reported methods.

Methyl 5-Chloro-*N*-cyclohexylanthranilate (IVh).

5-Chloro-*N*-cyclohexylanthranilic acid (39.5 g., 0.156 mole) was dissolved in 500 ml. of absolute methyl alcohol. The red solution was saturated with dry hydrogen chloride and refluxed for 12 hours. The solvent was evaporated under reduced pressure and the residue treated with 10% sodium hydroxide solution and extracted with benzene. The washed (water) and dried (magnesium sulfate) organic solution was evaporated, yielding 17 g. (41%) of the crude ester which had m.p. 71-72° after recrystallization from benzene. From the alkaline layer by precipitation with hydrochloric acid, 9 g. of the starting acid were recovered.

Anal. Calcd. for C₁₄H₁₈ClNO₂: C, 62.80; H, 6.72; N, 5.23. Found: C, 63.02; H, 6.69; N, 5.32.

5-Chloro-*N*-cyclohexylanthranilic Acid.

This compound was prepared by the Legrand and Lozách technique (13) from the potassium salt of 2,5-dichlorobenzoic acid, cyclohexylamine and copper powder in *N,N*-dimethylformamide (63%), m.p. 146-147° (from benzene).

Anal. Calcd. for C₁₃H₁₆ClNO₂: C, 61.53; H, 6.31; N, 5.52. Found: C, 61.72; H, 6.28; N, 5.34.

Methyl 3,5-Dichloro-*N*-methylanthranilate (IVi).

Sulphuryl chloride (32.5 ml., 0.4 mole) was added dropwise to a stirred solution of 33 g. (0.2 mole) of methyl *N*-methylanthranilate in 100 ml. of anhydrous benzene. After addition was complete, the mixture was refluxed until evolution of hydrogen chloride and sulfur dioxide ceased. The resulting solid was removed by filtration giving 45.5 g. of the hydrochloride, m.p. 178-180°, which was treated with water and extracted with ether. The organic layer was washed with water, dried (magnesium sulfate), and concentrated. The residue was fractionated under reduced pressure, b.p. 95-96° (0.1 mm) (36 g., 77%).

Anal. Calcd. for C₉H₉Cl₂NO₂: C, 46.15; H, 3.84; N, 5.98. Found: C, 46.34; H, 3.98; N, 6.23.

1,2,3,4-Tetrahydro-5*H*-5-oxo-1,4-benzodiazepines (II).

General Procedure.

A solution of 0.1 mole of the corresponding *N*-alkyl- or *N*-aryl-substituted methyl anthranilate in a minimum quantity of benzene was added dropwise to a stirred mixture of 0.075 mole of anhydrous aluminum chloride and 10 ml. of dry benzene. When the addition was complete, a solution of 3.2 g. (0.075 mole) of aziridine in 4 ml. of dry benzene was added cautiously. The mixture was heated at 90° in an oil-bath for 45 minutes. It was then cooled by immersion in an ice-bath and 55 g. of ice and water was added slowly. The resulting solids were separated by filtration, washed several times with water and purified by crystallization. The benzene layer was separated and the aqueous layer extracted with benzene. The combined benzene layers were washed with water, dried (magnesium sulfate) and concentrated *in vacuo*, giving the unreacted starting methyl anthranilate. By this method the following compounds were prepared:

1-Methyl-1,2,3,4-tetrahydro-5*H*-5-oxo-1,4-benzodiazepine (IIa).

This compound was obtained in 68% yield, m.p. 176°, from benzene; literature (3) m.p. 167-168°; (4) m.p. 169-170°.

1-Phenyl-1,2,3,4-tetrahydro-5*H*-5-oxo-1,4-benzodiazepine (IIb).

This compound was obtained in 50% yield, m.p. 227°, from ethanol; literature (4) m.p. 226-228°.

1-Cyclohexyl-1,2,3,4-tetrahydro-5*H*-5-oxo-1,4-benzodiazepine (IIc).

This compound was obtained in 35% yield, m.p. 110°, from benzene-petroleum ether; ir (Nujol): 3180 (NH), 1650 cm⁻¹ (C=O); nmr (deuteriochloroform): δ 8.25 (s, 1H, NH), δ 7.8-6.8 (m, 4H, phenyl hydrogens), δ 3.4 (s, 4H, CH₂-CH₂), δ 1.9-1.1 (m, 11 H, cyclohexyl hydrogens).

Anal. Calcd. for C₁₅H₂₀N₂O: C, 73.73; H, 8.25; N, 11.46. Found: C, 73.46; H, 8.34; N, 11.58.

7-Chloro-1-methyl-1,2,3,4-tetrahydro-5*H*-5-oxo-1,4-benzodiazepine (IId).

This compound was obtained in 42% yield, m.p. 188-190°, from ethanol-tetrahydrofuran; literature (4) m.p. 186-188°; (15) m.p. 183-185°.

8-Chloro-1-phenyl-1,2,3,4-tetrahydro-5*H*-5-oxo-1,4-benzodiazepine (IIe).

This compound was obtained in 20% yield, m.p. 182°, from benzene; literature (5) m.p. 179-181°.

8-Chloro-1-cyclohexyl-1,2,3,4-tetrahydro-5*H*-5-oxo-1,4-benzodiazepine (IIf).

This compound was obtained in 41% yield, m.p. 184-185°, from benzene; ir (Nujol): 3190 (NH), 1660 cm⁻¹ (C=O); nmr (deuteriochloroform): δ 8.1 (s, 1H, NH), δ 7.9-6.8 (m, 3H, phenyl hydrogens), δ 3.43 (d, 4H, CH₂-CH₂), δ 2.3-1.3 (m, 11H, cyclohexyl hydrogens).

Anal. Calcd. for C₁₅H₁₉ClN₂O: C, 64.65; H, 6.82; N, 10.05; Cl, 12.71. Found: C, 64.47; H, 6.72; N, 9.99; Cl, 12.71.

1-Benzyl-1,2,3,4-tetrahydro-5*H*-5-oxo-1,4-benzodiazepine (IIg).

This compound was obtained in 50% yield, m.p. 141-142°, from benzene-petroleum ether; literature (3) m.p. 140-142°.

7-Chloro-1-cyclohexyl-1,2,3,4-tetrahydro-5H-5-oxo-1,4-benzodiazepine (IIh).

This compound was obtained in 41% yield, m.p. 167-168°, from methanol; ir (Nujol): 3190 (NH), 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.0 (broad s, 1H, NH), δ 8.0-6.8 (m, 3H, phenyl hydrogens), δ 3.4 (d, 4H, CH_2CH_2), δ 2.3-1.3 (m, 11H, cyclohexyl hydrogens).

Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{ClN}_2\text{O}$: C, 64.65; H, 6.82; N, 10.05; Cl, 12.71. Found: C, 64.43; H, 6.54; N, 9.82; Cl, 12.45.

7,9-Dichloro-1-methyl-1,2,3,4-tetrahydro-5H-5-oxo-1,4-benzodiazepine (IIi).

This compound was obtained in 37% yield, m.p. 97-99°, from ethanol-water; ir (Nujol): 3230 (NH), 1665 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.7-7.2 (m, 3H, NH and phenyl hydrogens), δ 3.35 (d, 4H, CH_2CH_2), δ 3.0 (s, 3H, CH_3).

6,12-Diphenyl-5-dioxo[b,f][1,5]dibenzodiazocine (VIb).

This compound was isolated in 30% yield from the reaction of IVb, aziridine and aluminum chloride using the experimental conditions of Coleman and Callen (6), m.p. 345° dec. (from DMF); ir (Nujol): 1640-1600 cm^{-1} (C=O); nmr (trifluoroacetic acid): δ 8.2-7.0 (m, phenyl hydrogens).

Anal. Calcd. for $\text{C}_{26}\text{H}_{18}\text{N}_2\text{O}_2$: C, 80.00; H, 4.61; N, 7.17. Found: C, 79.76; H, 4.48; N, 7.17.

2,8-Dichloro-6,12-diphenyl-5,11-dioxo[b,f][1,5]dibenzodiazocine (VIe).

This compound was also isolated in 28% yield from IVe, aziridine and aluminum chloride as described (6), m.p. 350°, from DMF-water; literature (8), m.p. 350°.

Synthesis of 2-Anilinoethylisocyanates (I).

3-(N-Methyl-p-chloroanilino)propionitrile.

A mixture of 56 g. (0.39 mole) of *N*-methyl-*p*-chloroaniline, 21 g. (0.39 mole) of acrylonitrile and 2.4 g. of cupric acetate monohydrate was stirred and heated for 4 hours, then the reaction mixture was fractionated under reduced pressure. The nitrile was collected at 129-132°/0.3 mm, yield 40 g. (53%).

3-(N-Methyl-p-chloroanilino)propionic Acid.

To a solution of 11.5 g. (0.205 mole) of potassium hydroxide in 125 ml. of water, 36.3 g. (0.186 mole) of 3-(*N*-methyl-*p*-chloroanilino)propionitrile was added and the mixture was refluxed with stirring for 15 hours. The mixture was cooled and extracted with ether. The aqueous layer was acidified with 16.5 ml. of concentrated hydrochloric acid diluted with water and the resulting oil was extracted with ether. Evaporation of the ether extracts yielded a white solid (31.7 g., 80%), m.p. 67-68° (from petroleum ether); ir (Nujol): 3200 (OH), 1700 cm^{-1} (C=O).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{ClNO}_2$: C, 56.23; H, 5.62; N, 6.56. Found: C, 56.48; H, 5.66; N, 6.66.

This acid could also be prepared in 94% yield by the addition of the *N*-methyl-*p*-chloroaniline to propiolactone according to the literature directions (14).

2-(N-Methyl-p-chloroanilino)ethylisocyanate (Ia).

To a stirred mixture of 21.3 g. (0.1 mole) of 3-(*N*-methyl-*p*-chloroanilino)propionic acid and 75 ml. of acetone was added 11.1 g. (0.11 mole) of triethylamine over 5 minutes. The solution was chilled to -5 to 0° in an ice-salt bath, and 12 g. (0.11 mole) of ethyl chlorocarbonate in 25 ml. of acetone was slowly added. After the addition was complete, the cold mixture was stirred for an addi-

tional 15 minutes. A solution of 13 g. (0.2 mole) of sodium azide in 37 ml. of water was then added while the temperature was kept at -5 to 0°. The mixture was stirred for an additional 30 minutes, poured into 375 ml. of ice water and extracted with toluene. The extracts were dried (magnesium sulfate), refluxed on a steam bath for 1 hour and concentrated. The resulting oil was fractionated under reduced pressure yielding 7.1 g. (34%) of a yellow oil, b.p. 134-137° (0.5 mm). From the aqueous layer by acidification with hydrochloric acid, 6 g. of the starting acid was recovered; ir (liquid film): 2280-2270 cm^{-1} (N=C=O).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{ClN}_2\text{O}$: C, 68.57; H, 6.28; N, 16.00. Found: C, 68.31; H, 6.21; N, 15.86.

2-(N-Methylanilino)ethylisocyanate (Ib).

This compound was obtained in the same manner from 3-(*N*-methylanilino)propionic acid (14) in 61% yield as a yellow oil, b.p. 95-98° (0.1 mm); ir (liquid film): 2280 cm^{-1} (N=C=O).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}$: C, 68.18; H, 6.81; N, 15.90. Found: C, 68.10; H, 6.90; N, 16.08.

7-Chloro-1-[β -(*N*-methyl-*p*-chloroanilino)ethyl] carbamoyl-1,2,3,4-tetrahydro-5H-5-oxo-1,4-benzodiazepine (IIIa).

To a mixture of 3.1 g. (0.023 mole) of aluminum chloride and 30 ml. of *o*-dichlorobenzene heated at 90-100° was slowly added a solution of 4.2 g. (0.02 mole) of Ia in 20 ml. of *o*-dichlorobenzene. The mixture was then heated at 150° for 1 hour and poured on ice. The solvent was removed by steam distillation and the residue solidified to a white solid on standing at room temperature, m.p. 179-180°, from methanol, yield 2.5 g. (31%); ir (Nujol): 3380-3340 (NH), 1720-1700 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.3 (m, 1H, NH), δ 7.6-6.6 (m, 8H, NH and phenyl hydrogens), δ 3.9 (m, 4H, $\text{CH}_2\text{-CH}_2$), δ 3.5 (m, 4H, cyclic $\text{CH}_2\text{-CH}_2$), δ 3.0 (s, 3H, CH_3).

1-[β -(*N*-Methylanilino)ethyl] carbamoyl-1,2,3,4-tetrahydro-5H-5-oxo-1,4-benzodiazepine (IIIb).

This compound was obtained from Ib by the procedure described above in 30% yield as a white solid, m.p. 135-136°, from methanol; ir (Nujol): 3350-3340 (NH), 1720-1700 and 1675 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.3 (m, 1H, NH), δ 7.6-6.6 (m, 10H, NH and phenyl hydrogens), δ 3.85 (m, 4H, $\text{CH}_2\text{-CH}_2$), δ 3.5 (m, 4H, cyclic CH_2CH_2), δ 3.0 (s, 3H, CH_3).

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