Reaction of *N,N'*-Methylenedilactams from Cyclic Iminochlorides and Dimethylsulfoxide

*Dietmar Habeck and William J. Houlihan**

Sandoz Pharmaceuticals, Research and Development Division, Hanover, New Jersey 07936

Received January 20, 1976

J. Heterocyclic Chem., 13, 897 (1976).

In connection with work on the preparation of some 5-alkoxy-7-chloro-1-methyl-3*H*-1,4-benzodiazepin-2(1*H*)-ones (**3b**) the 5-chloro analog **3a** was prepared by treatment of **1** with phosgene followed by thermal decomposition of the resultant 5,5-dichloro derivative **2** in refluxing benzene (Scheme I).

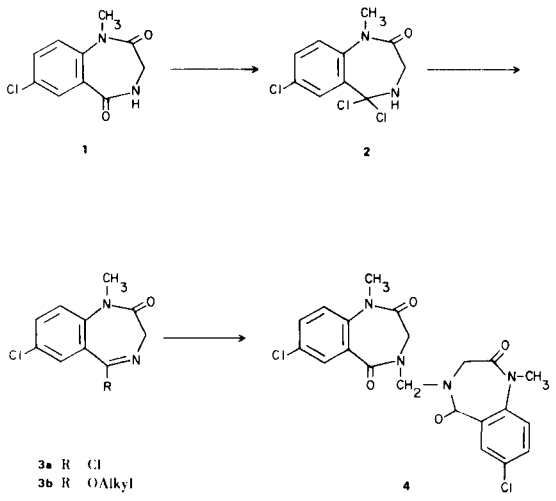
When **3a** was dissolved in anhydrous dimethylsulfoxide a slightly exothermic reaction occurred to give a solid with empirical formula $C_{21}H_{18}Cl_2N_4O_4$ (MW 461) that has been established as 4,4'-methylenedi[7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione] (**4**) on the basis of spectral data and an analogous reaction with 2-chloro-1-pyrroline (**5**) and dimethylsulfoxide.

The mass spectrum of **4** gave a parent peak at m/e 460 and a fragmentation pattern consistent with the assigned structure. The ir spectrum gave intense bands at 1650 and 1600 cm^{-1} typical of the 2,5-dione system in **4**. A 6*H* singlet at 3.40 δ, a 4*H* AB quartet centered at 4.10 δ, a 2*H* singlet at 5.10 δ and 8 aromatic H were observed in the nmr spectrum. The signals at δ 3.40 and 4.10 are characteristic of the NCH_3 and $O{=}CCH_2N$ groups found in other 3*H*-1,4-benzodiazepin-2,5(1*H*)diones prepared in this laboratory. The low field signal at δ 5.10 has been assigned to the NCH_2N grouping.

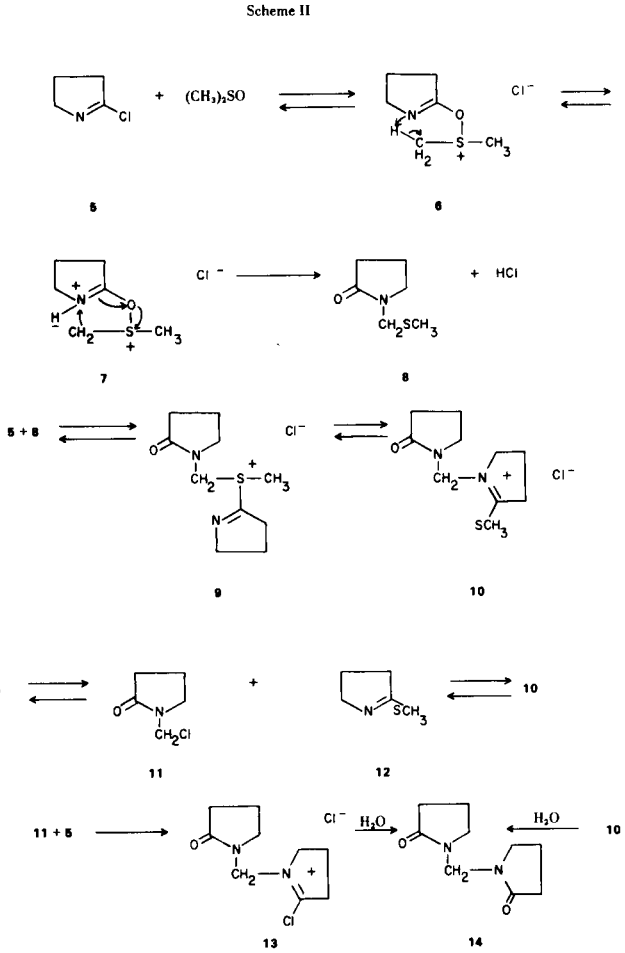
When **5** was refluxed in anhydrous dimethylsulfoxide the known (1,2) 1,1'-methylene di-2-pyrrolidinone (**14**) was isolated in 55% yield (Scheme II).

The formation of **4** and **14** from the reaction of a chloroimine and dimethylsulfoxide indicates that this method might be useful for preparing a variety of NCH_2N derivatives of cyclic amides.

Scheme I



Scheme II



A possible pathway to the formation of the methylene amides is given for **14** in Scheme II.

The first stage of the reaction possibly involves the formation of *N*-methylthiomethylpyrrolidone (**8**) from the ylid **7** and the sulfoxonium intermediate **6**. Alkylation of **8** by **5** gives the sulfide salt **9** which can undergo a C to N rearrangement to form **10** or a cleavage to give *N*-chloromethylpyrrolidone (**11**) and 2-methylthio-1-pyrroline (**10**). Compound **11** can alkylate **12** to form **10** or **5** to form the immonium chloride **13**. Hydrolysis of **10** or **13** gives 1,1′-methylenedi-2-pyrrolidinone (**14**).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or a Kofler hot-stage and have not been corrected. Ir spectra were taken on a Perkin-Elmer "Infracord" Spectrophotometer. Proton nmr were measured on a Varian Associates A-60 Spectrometer using TMS as an internal reference. The mass spectra were obtained on a LKB 900 mass spectrometer.

Elemental analysis were determined by Mr. W. Bonkoski and his associates in our laboratories.

5,7-Dichloro-1-methyl-3*H*-1,4-benzodiazepin-2(1*H*)one (**3a**).

A solution of 50.9 g. (0.225 mole) of 7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione in 250 ml. of dry chloroform was cooled in an ice-bath and treated with a stream of phosgene gas until saturation. After standing overnight at room temperature the resultant precipitate was filtered off and washed with chloroform to give 46 g. (73%) of 1-methyl-5,5,7-trichloro-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**2**), m.p. 140°, mass spectrum; molecular ion peak at m/e 278.

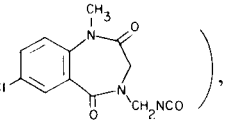
Anal. Calcd. for $C_{10}H_9Cl_3N_2O$: C, 43.0; H, 3.2; Cl, 38.0; N, 10.0. Found: C, 43.4; H, 3.5; Cl, 37.7; N, 9.7.

Compound **2** (45 g.) was added to 500 ml. of dry benzene and the mixture was refluxed until evolution of hydrogen chloride gas ceased (*ca.* 9 hours). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (500 g.) with chloroform as solvent and eluent. There was obtained 27.1 g. (70%) of **3a**, m.p. 135°; ir (potassium bromide): 1670 (C=O) and 1630 (C=N) cm^{-1}; nmr (chloroform): δ 3.4 (3H, s, CH_3), 4.4 (2H, broad singlet, CH_2); mass spectrum: molecular ion peak at m/e 242, 207 (M-Cl), 179 (m-Cl, CO).

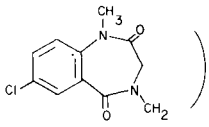
Anal. Calcd. for $C_{10}H_8Cl_2N_2O$: C, 49.4; H, 3.3; Cl, 29.2; N, 11.9. Found: C, 49.3; H, 3.6; Cl, 29.5; N, 11.9.

4,4′-Methylenedi-[7-chloro-1-methyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione] (**4**).

A solution of 5 g. of **3a** in 20 ml. of anhydrous dimethyl sulfoxide was stirred at room temperature for *ca.* 12 hours. The solvent was removed *in vacuo* and the residue treated with *ca.* 50 ml. of water and then 100 ml. of chloroform. The organic layer was separated, dried with magnesium sulfate, filtered and concentrated *in vacuo* to give 3.1 g. of **4**, m.p. 288-289° (acetone); ir (potassium bromide): 1660 and 1650 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 3.40 (6H, s, CH_3), 4.10 (4H, broad doublet, CH_2), 5.10 (2H, s, NCH_2N); mass spectrum: molecular ion peak at m/e 460,



403 (M-CH_3NCO), 279 ($C_{12}H_{10}ClN_3O_3$;



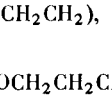
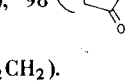
251 (279-CO or CH_2N), 237 ($C_{11}H_{10}ClN_2O_2$;

, 209 (237-CO or CH_2N), 195 (237-CON or $COCH_2$).

Anal. Calcd. for $C_{21}H_{18}Cl_2N_4O_4$: C, 53.9; H, 3.9; Cl, 15.2; N, 12.2. Found: C, 53.7; H, 3.8; Cl, 15.0; N, 12.1.

1,1′-Methylenedi-2-pyrrolidinone (**14**).

A solution of 25 g. of pyrrolidone in 150 ml. of chloroform-pyridine (4:1) was cooled in an ice-bath and treated with a stream of phosgene gas until saturation. The mixture was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was dissolved in 100 ml. of anhydrous dimethyl sulfoxide and refluxed for *ca.* 70 hours and worked-up as in **4**. Distillation gave 15 g. (55%) of **14**, b.p. 90° (0.05 mm) that crystallized on standing, m.p. 74° (lit. m.p. 72-73°, 73-74°); ir (potassium bromide): 1680 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 3.30 (8H, m, $2CH_2CH_2N$), 3.45 (4H, m, $2CH_2CO$), 4.80 (2H, s, NCH_2N); mass spectrum: molecular ion peak at m/e 182, 154 (M-CO), 126

(M-$COCH_2CH_2$), 98  , 70  ,

70 ($COCH_2CH_2CH_2$).

Acknowledgment.

We gratefully acknowledge the efforts of Dr. Sandor Barcza and his associates in obtaining the instrumental data used in this work.

REFERENCES

(1) Chemische Werke Hüls A. G., German Patent 1,074,045; *Chem. Abstr.*, 55, 13454 (1961).

(2) J. W. Breitenbach and E. Wolf, *Monatsh. Chem.*, 87, 367 (1956).