A New Ring Closure of 1,4-Benzodiazepine

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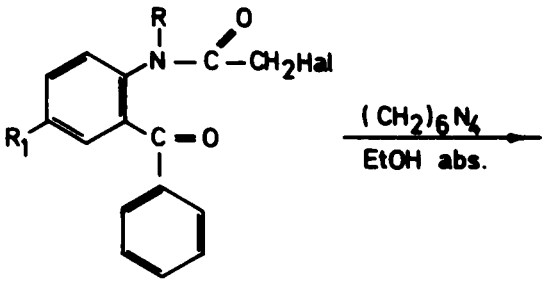
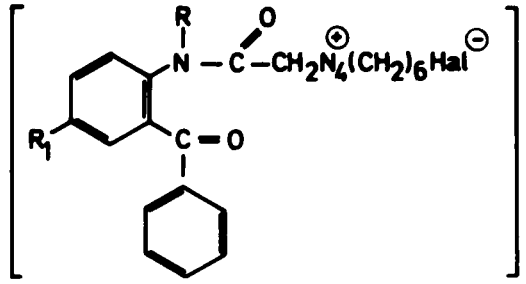
It is known that the 1,4-benzodiazepine ring can be obtained by several procedures (2-5). All of these methods give relatively low yields of 1,4-benzodiazepines and the crude products must be refined by using special patented methods (6).

Our method for the 1,4-benzodiazepine ring closure is based upon the reaction between 2-(2-haloacylamido)-benzophenone and hexamethylenetetramine. It is well known that hexamethylenetetramine reacts with alkyl or aryl-alkyl halides giving complex salts as intermediates. These complex salts were especially studied in connection with haloacetic acid and their derivatives (7-9). These complex salts react further giving aldehydes or amine hydrochlorides depending on the reaction conditions (10-11).

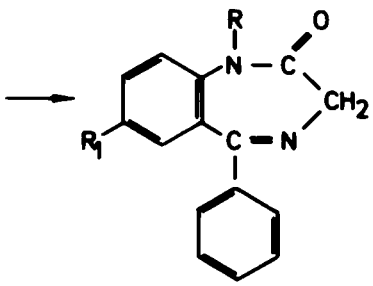
In our work the complex salts of some 2-(haloacyl-amido)benzophenones were successfully cyclized to the corresponding 1,4-benzodiazepin-2-ones. The reaction can be represented by the following scheme:



I



II



III

Hal = Cl or Br

	R	R_1
IIIa	CH_3	Cl
IIIb	H	Cl
IIIc	H	NO_2

When the reaction shown by the above scheme was performed in absolute ethanol, compound III was immediately formed. The mechanism apparently involves the formation of the intermediate complex compound II which we attempted to isolate, as the pure complex.

Compound II was found to be highly unstable gradually transforming into III. By replacing the reaction solvent, absolute ethanol with chloroform, compound II was successfully isolated. The crude product contained about 80-90% of compound II and 10-20% of compound III. However compound II was not successfully purified even by repeated recrystallization from various solvents due to its instability and gradual transformation into compound III. Although refluxing of compound II in absolute ethanol gave III in 95% yield, it is reasonable to assume that the cyclization proceeds through the complex intermediate.

The main advantage of our procedure shown in the scheme for obtaining the 1,4-benzodiazepine ring over the

method (4) which uses liquid or alcoholic ammonia is in the simplicity of the procedure, the shorter reaction time and, most important of all, in the purity of the final product which, after one recrystallization from ether, shows on thin layer chromatography only one spot (Rf = 0.3 for the solvent mixture, benzene-ethanol = 48:2).

EXPERIMENTAL

Complex Salt (IIa).

One gram (0.0031 mole) of 2-(2-chloro-*N*-methylacetamido)-5-chlorobenzophenone and 1 g. (0.007 mole) of hexamethylenetetramine, 0.5 g. of potassium iodide in 20 ml. of chloroform were refluxed for 10 hours. After this time the chloroform was evaporated *in vacuo* and the residue was recrystallized from ethanol to give 1.25 g. of the complex salt, m.p. 202-206° dec.

7-Chloro-1-methyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine-2-one (IIIa).

A mixture of 1 g. (0.0031 mole) of 2-(2-chloro-*N*-methylacetamido)-5-chlorobenzophenone, 1 g. (0.007 mole) of hexamethylenetetramine in 15 ml. of absolute ethanol was refluxed for 10 hours. The solution thus obtained was evaporated to dryness under reduced pressure and the residue was dissolved in a mixture of 10 ml. of water and 10 ml. of benzene. The benzene layer was separated and the aqueous layer was extracted with 2 x 10 ml. of benzene. The pooled benzene layers were collected, washed (water) and dried (sodium sulfate). The benzene was evaporated under reduced pressure and the residue was dissolved in ether. Chilling produced crystals which were collected and washed with ether. Partial evaporation of the mother liquor gave a second crop of crystals. Total yield, approximately 80%, m.p. 128-130° (lit. m.p. 130-131.5°; mixed m.p. 129-131°).

Similarly 2-(2-bromo-*N*-methylacetamido)-5-chlorobenzophenone yielded 85-90% of compound IIIa. Also prepared by this procedure were compounds IIIb and IIIc starting from 2-(2-chloro(or bromo)acetamido)-5-chlorobenzophenone and 2-(2-chloro(or bromo)acetamido)-5-nitrobenzophenone, respectively. The yields were 70-80%. Mixed melting points of the compounds IIIa-IIIc with authentic samples exhibited no depression; ir spectra of compounds IIIa-IIIc were identical to those of the known substances.

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