Quaternization of 2-Aziridino-5-chlorobenzophenone, An Efficient Synthesis of Medazepam

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Quaternization of 2-aziridino-5-chlorobenzophenone (**1**) with methyl iodide resulted in formation of 2-(*N*-β-iodoethyl-*N*-methyl)aminobenzophenone (**2**), *via* an unstable quaternary compound. Rate constants for **1** → **2** conversion, as determined by an nmr method at 35 ± 0.1°, varied between 0.22 x 10^{-3} sec^{-1} in DMSO-d_6, and 0.95 x 10^{-6} sec^{-1} in methanol-d_4. Ammonolysis with hexamine, and subsequent cyclization afforded 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (**3**, generic name medazepam) in 92% over-all yield.

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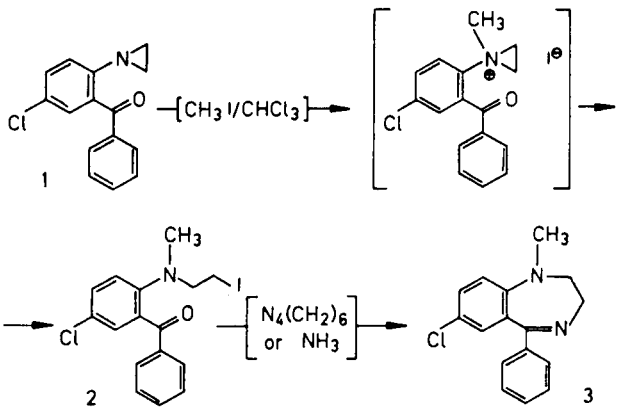
The preparations of *N*(1)-methyl-2-deoxy-1,4-benzodiazepines, among them 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (**3**), require methylation of a weakly basic secondary nitrogen atom at various stages. This step was performed either before 1,4-benzodiazepine ring closure, on the intermediate 2-*N*-acylated-2-amino-5-chlorobenzophenone (1,2), or after ring closure using different methylation agents in combination with bases as acid scavengers (3,4).

While the first approach requires a two-step preparation of a reactive intermediate and its subsequent deacylation, the second one suffers on the formation of some side products, mainly *N*-(4)quaternary derivatives, and consequently on the poor yields. The Eschweiler-Clarke method afforded in one case moderate (65%) yield of a *N*-methylated open chain derivative (5).

We have developed a simple, high-yield preparation of medazepam (**3**) based on our recent studies of the mechanism of recyclization of 2-aziridino-5-substituted benzophenones into various achiral and chiral 1,4-benzodiazepines (6,7). It was found that these compounds undergo ring-opening with weak nucleophiles like ammonia or hexamine, and subsequently recyclize into 1,4-benzodiazepines. Furthermore, the stereochemical outcome of cyclization of some chiral 2-*N*-β-bromoalkylamino-5-nitrobenzophenones into corresponding 2-(or 3)-substituted-7-nitro-1,4-benzodiazepines, revealed the intermediate formation of 2-aziridinium ions. These findings prompted us to attempt quaternization of aziridine derivative **1** with methyl iodide and its subsequent ring-opening with hexamine to medazepam (see Scheme 1).

We assumed that *N*-methylation of 2-aziridinobenzophenones should proceed much easier than previously attempted methylations of 2-aminobenzophenones, or 2-deoxy-1,4-benzodiazepines, since it is known that high electron-donating properties (basicity) of the aziridine nitrogen atom remain unaffected on *N*-arylation, or even on *N*-acylation (8). Quaternization of **1**, *i.e.*, the first step in the above Scheme, was studied by nmr in different solvents. It turned out, however, that the quaternary compound was highly unstable in the presence of strongly

SCHEME 1



nucleophilic iodide ions, and opened immediately into the β-iodoethyl derivative **2**. No signals of methylene or methyl hydrogens α- to the quaternary nitrogen could be observed in the nmr spectra, instead, new signals at 2.67 ppm (in deuteriochloroform, for N-CH_3), and at 3.00, 3.28 ppm (doublet, 4H) revealed formation of the non-symmetric **2**. Formation of **2** in different solvents was followed, and the corresponding kinetic data are given in Table I.

Table I

Rate Constants for Conversion **1** → **2** in Various Solvents at 35 ± 0.1°

Solvent	k x 10^{-3} sec^{-1}	t½[min]
DMSO-d_6	0.22 ± 0.04	5.2
DMF-d_7	4.3 ± 0.2	26.5
Deuteriochloroform	25 ± 1	460.0
Perdeuteriomethane	950 ± 20	1210.0

Significantly lower rates were observed for quaternization in methanol, which is the rate-determining step in the conversion **1** → **2**, is presumably increased by the strong hydrogen bonding, observed for various aziridines in the hydroxylic solvents. The intermediate quaternary com-

pound could not be isolated, even when silver perchlorate was added, as a scavenger for the iodide ions, according to the method of Leonard (9).

Based on these results, a simple one-pot procedure has been elaborated, whereby compound **2** has been quantitatively prepared in chloroform and without isolation cyclised, according to our earlier findings (10,11), with hexamine, into **3** in an over-all yield of 92%.

EXPERIMENTAL

Melting points were determined on a Microheating stage (Kofler). Ir spectra were obtained with Perkin Elmer M 257 instrument. The nmr spectra were run, and kinetical measurements were performed on a Varian T-60 spectrometer using TMS as the internal standard.

Kinetic Measurements.

These were performed using *ca.* 50 mg. of compound **1**, dissolved in 0.50 ml. of the particular solvent, and 0.01 ml. of methyl iodide. The reaction solution was kept at 35 ± 0.1° and progress of the reaction followed for 5-7 half-times by integration of the disappearing singlet (4H) for methylene protons in **1**. The integer for the aromatic protons (7.2-7.9 ppms, 8H) has been used for internal calibration of integration accuracy. Pseudo-first order rate constants have been calculated as cited earlier (12).

Syntheses.

Compound **1** has been prepared as described earlier (7). A quantitative yield of crude, chromatographically pure **1** was obtained, and this material was used in the next step, *i.e.*, in preparation of **2**. For kinetic measurements, crude **1** was recrystallized twice from *n*-heptane, m.p. 103-105°.

Attempted Preparation of 2-*N*-Methylaziridinium-5-chlorobenzophenone Perchlorate.

Compound **1** (52.0 mg., 0.20 mmole) was dissolved in DMF-d_7 (0.50 ml.), and silver perchlorate (45.0 mg., 0.21 mmole) was added. No change in the nmr spectrum was observed on standing for 1 hour at 35 ± 0.1°. Then, the solution was cooled to 0° and methyl iodide (0.05 ml.) was added. Precipitated silver iodide was filtered through a cotton-plug, and the clear solution checked by nmr; no signals corresponding to the aziridinium ion could be observed.

The same results were obtained when DMSO-d_6 was used as the solvent.

2-(*N*-β-Iodoethyl-*N*-methyl)amino-5-chlorobenzophenone (**2**).

Compound **1** (10.3 g., 40 mmoles) and methyl iodide (45.6 g., 320 mmoles), were dissolved in chloroform (200 ml.) and heated under reflux for 6 hours. Then excess of the methyl iodide and the solvent were evaporated leaving 16 g. of the chromatographically pure **2** (Rf = 0.75 in cyclohexane-ether-acetone = 10:10:1). Repeated column chromatography of a sample (silicagel "Merck", 0.05-0.2 mm - the above elution system) afforded pure **2**, which decomposes on an attempted distillation at 0.01 mm Hg; ir (nujol): 2960-2830, 1667, 1495, 1460, 1450, 1395, 890, 875, 720, 700 cm^{-1}; nmr (deuteriochloroform): δ ppm 2.67 (s, 3H), 3.00 and 3.28 (double t, 4H), 6.8-7.9 (m, 8H).

Anal. Calcd. for $C_{16}H_{15}ClNO$ (399.66): C, 48.08; H, 3.78; N, 3.51. Found: C, 48.23; H, 3.56; N, 3.28.

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

Compound **2** (16.0 g., 40 mmoles) from the preceeding procedure, was dissolved in the same reaction vessel on addition of ethanol (300 ml.) and hexamine (6.3 g., 45 mmoles) was added. The resulting solution was heated under reflux for 8 hours, then the solvent was evaporated, and crude product was slurried in water (700 ml.) which contains *ca.* 1 g. of sodium metabisulfite. On extraction with chloroform (3 x 100 ml.), the organic extracts were dried (sodium sulfate), evaporated and the residual oil crystallized from acetone-water, affording 8.9 g. (92%) of **3**, m.p. 99-101° (lit. (13) m.p. 102-103°).

REFERENCES AND NOTES

(1) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, and A Stempel, *J. Org. Chem.*, 27, 3788 (1962).

(2) B. Morowski, Polish Patent 56,125; *Chem. Abstr.*, 71, 3147e (1969).

(3) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).

(4) L. H. Sternbach, G. A. Archer, and E. Reeder, *ibid.*, **28**, 3013 (1963).

(5) M. E. Derieg, R. M. Schweininger, and R. I. Fryer, *ibid.*, **34**, 179 (1969).

(6) M. Mihalić, V. Šunjić, and F. Kajfež, *Tetrahedron Letters*, 1011 (1975).

(7) M. Mihalić, V. Šunjić, P. Mildner, and F. Kajfež, *Croat. Chem. Acta*, **48**, 125 (1976).

(8) R. P. Shibaeva, L. O. Atovmin, and R. G. Kostjanovskii, *Dokl. Akad. Nauk SSSR*, 175, 586 (1967).

(9) N. J. Leonard and J. V. Paukstellis, *J. Org. Chem.*, 30, 821 (1965).

(10) N. Blažević and F. Kajfež, *J. Heterocyclic Chem.*, 7, 1173 (1970).

(11) N. Blažević and F. Kajfež, *ibid.*, 8, 845 (1971).

(12) M. Štromar, V. Šunjić, T. Kovač, L. Klasinc, and F. Kajfež, *Croat. Chem. Acta*, **46**, 265 (1974).

(13) H. H. Kaegi, French Patent 1,524,631; *Chem. Abstr.*, 72, 12778 (1970).