A New Ring Closure Synthesis of 1,4-Benzodiazepines. II.

N. Blaževič (1) and F. Kajfež (2)

Compagnia di Ricerca Chimica, S.A. Chiasso, Switzerland

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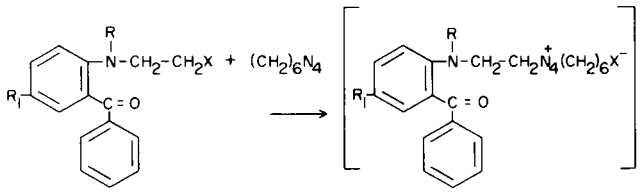
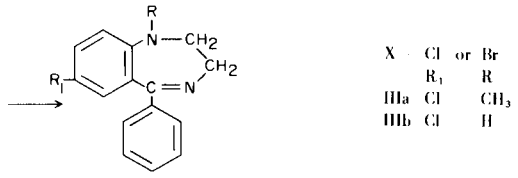
In our preceding paper (3) a new method for the ring closure of hexammonium derivatives of 2-(2-haloacylamido)benzophenones to give 1,4-benzodiazepin-2-ones was described. We now report that the same procedure can be applied to the synthesis of 1,2-dihydro-3*H*-1,4-benzodiazepines, particularly 7-chloro-5-phenyl-1-methyl-1,2-dihydro-3*H*-1,4-benzodiazepine (IIIa) (Medazepam), a very potent psychopharmacological agent (4). These compounds have been previously prepared by various procedures; reduction of some 1,4-benzodiazepin-2-ones (5) from 2-halo derivatives of benzophenone and ethylenediamine (6), and from *p*-chloroaniline *via* benzamide derivatives followed by ring closure using the Bischler-Napieralsky reaction (7). However, all of these methods proved to be rather inconvenient giving impure products in relatively low yields. Using our method recently described (3) pure 1,2-dihydro-3*H*-1,4-benzodiazepines were obtained in 70-90% yields according to the following scheme.



I II



III

	X	Cl or Br
	R_1	R
IIIa	Cl	CH_3
IIIb	Cl	H

Compounds of general formula I were prepared starting from 2-amino-5-chlorobenzophenone which was tosylated to give the 2-tosylamido derivative. Alkylation of the sodium salt of the 2-tosylamido derivative gave 5-chloro-2-[*N*-(2-haloethyl)tosylamido]benzophenone, which was detosylated yielding 2-(2-haloethylamino)-5-chlorobenzophenone. Since methylation of the amino group by known methods (8) gives low yields, methyl iodide with barium oxide was used as the alkylating agent (9) to give the methyl derivative in 85% yield.

When the cyclization reaction shown in the scheme was performed in absolute ethanol, compound III was formed immediately. However, when the reaction solvent used was chloroform, compound II was successfully isolated but could not be purified for microanalysis due to its instability and gradual transformation into compound III. Refluxing of compound II in absolute ethanol gave III in almost 100% yield. Compound I was also cyclized into III using alcoholic ammonia, but the yield was low and the product impure.

No attempt is being made at this time to account for the mechanism of this reaction. However, the results support the hypothesis that this cyclization as opposed to that described earlier (3), does not go *via* the intermediary "amino compound", 2-(2-aminoethylamino)-5-chlorobenzophenone.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 137 Spectrophotometer in potassium bromide pellets. Elemental analyses were performed by the Microanalytical Laboratory, Department of Organic Chemistry, Faculty of Pharmacy and Biochemistry, Zagreb.

5-Chloro-2-(2-bromoethylamino)benzophenone (Ia).

The sodium salt of 2-tosylamido-5-chlorobenzophenone (8c) (10.3 g., 0.023 mole) and 10.6 ml. (22.4 g., 0.115 mole) of ethylene bromide in 60 ml. of DMF was stirred and heated at 60° for 18 hours. The solvent was evaporated *in vacuo* and the residual oil was partitioned between water and chloroform. After repeated extraction of the water phase, the organic extracts were collected, dried (sodium sulfate) and evaporated. The residual tarry mass crystallized upon addition of ether and chilling to give 8.3 g. (73%) of crude 5-chloro-2[*N*-(2-bromoethyl)tosylamido]-benzophenone which melted at 107-113°. Recrystallization from absolute ether gave colorless crystals which melted at 113-115°.

5-Chloro-2-[*N*-(2-bromoethyl)tosylamido]benzophenone (23.7 g., 0.0485 mole) in 475 ml. of 75% sulfuric acid was stirred and heated on an oil bath at 120° for 30 minutes during which time all starting material dissolved. The dark-red solution was cooled and poured on crushed ice. The green-yellow viscous mass which separated was collected and recrystallized from ethanol, yield 16 g. (98%), m.p. 89-91°. An analytically pure sample melted at 91-92°, ir (potassium bromide) 3343 (N-H), 1630 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{13}BrClNO$: C, 53.26; H, 3.87; N, 4.14. Found: C, 53.20; H, 3.62; N, 4.21.

5-Chloro-2-(2-chloroethylamino)benzophenone (Ib).

This compound was obtained by the same procedure using 1-bromo-2-chloroethane as alkylating agent. Yield was 95%, m.p. 88-90°.

Anal. Calcd. for $C_{15}H_{13}Cl_2NO$: C, 61.28; H, 4.46; N, 4.76. Found: C, 60.98; H, 4.72; N, 4.85.

5-Chloro-2-(2-bromoethylmethylamino)benzophenone (Ic).

Compound Ia (4 g., 0.0118 mole), 10 ml. of methyl iodide and 10 g. of barium oxide was stirred in 100 ml. of DMF and 0.4 ml. of water at room temperature for 18 hours under a nitrogen atmosphere. The inorganic residue was removed when the reaction was complete and the organic phase was evaporated and partitioned between water and chloroform. The aqueous layer was extracted repeatedly with chloroform and the organic layers were collected, dried (sodium sulfate) and evaporated. The residual red oil had b.p. 205-210° at 0.6 mm Hg, yield 3.5 g. (85%).

Anal. Calcd. for $C_{16}H_{15}BrClNO$: C, 54.49; H, 4.29; N, 3.97. Found: C, 54.63; H, 4.16; N, 3.69.

5-Chloro-2-(2-chloroethylmethylamino)benzophenone (Id).

This compound was obtained by the same procedure in 83% yield, b.p. 180-185° at 0.3 mm Hg.

Anal. Calcd. for $C_{16}H_{15}Cl_2NO$: C, 62.40; H, 4.91; N, 4.55. Found: C, 62.22; H, 5.03; N, 4.40.

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

Method A.

Compound Ic (1.5 g., 0.004 mole) and 10 ml. of methanolic ammonia solution (saturated at 0°) was placed in a thick-walled glass tube and heated at 120-130° for 5 hours. After evaporation *in vacuo* the crude hydrobromide of IIIa crystallized on addition of ether to the residual tarry mass, m.p. 240-245°. The free base was obtained upon addition of 15% sodium hydroxide and subsequent extraction with ether. Evaporation of the dried ether phase gave 0.4 g. (37%) of crude base, m.p. 94-96°.

Method B.

Compound Ic (1.5 g., 0.004 mole) and 1.5 g. (0.107 mole) of hexamine in 20 ml. of absolute ethanol was heated under reflux for 10 hours. The solvent was evaporated *in vacuo* and the residue was distributed between water and chloroform. The aqueous layer was made alkaline (*p*H 9) separated from the organic phase and extracted twice. The dried organic phase was evaporated to dryness and the residual red oil was crystallized in ether, yield 0.95 g. (88%), m.p. 96-98°. A pure sample, recrystallized from ether, melted at 100-101°. (Lit. (7) m.p., 102-103°). A mixed m.p. with an authentic sample exhibited no depression and the infrared spectra were indistinguishable.

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

Method A.

Compound Ia when reacted with alcoholic ammonia by the same procedure gave 51% of IIIb, m.p. 168-170°.

Method B.

Compound Ia when allowed to react with hexamine gave 75% of IIIb, m.p. 172-174°. (Lit. (6) m.p. 170-171°). Mixed melting point of the compound IIIb with an authentic sample exhibited no depression; the ir spectrum was identical to that of the known substance.

REFERENCES

(1) Faculty of Pharmacy and Biochemistry, University of Zagreb.

(2) To whom correspondence should be addressed, Compagnia di Richerca Chimica SA, Chiasso, Via Motta 18, Switzerland.

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

(4) L. O. Randall, W. Schallek, C. Scheckell, R. Banzinger, and R. A. Moe, *Arzneim. Forsch.*, **18**, 1542 (1968).

(5) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **28**, 2150 (1963); (b) L. H. Sternbach, E. Reeder and G. A. Archer, *ibid.*, **28**, 2456 (1963).

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

(7) H. H. Kaegi (Hoffmann La Roche) French patent 1,524,631; *Chem. Abstr.*, **72**, 12778 (1970).

(8a) M. E. Derieg, R. M. Schweininger and R. I. Fryer, *J. Org. Chem.*, **34**, 179 (1969). (b) S. C. Bell, T. S. Sulkowski, C. Gochman and S. J. Childress, *ibid.*, **27**, 562 (1962); (c) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach and A. Stempel, *ibid.*, **27**, 3781 (1962).

(9) R. Kuhn and H. Trischmann, *Chem. Ber.*, **94**, 2258 (1961).