Phosphoryl Chloride Induced Ring Contraction of 1,4-Benzodiazepinones to Chloromethylquinazolines

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A ring contraction of 1,4-benzodiazepin-2-one to 2-chloromethylquinazoline in phosphoryl chloride is described. The intermediacy of an aziridinoquinazoline is proposed.

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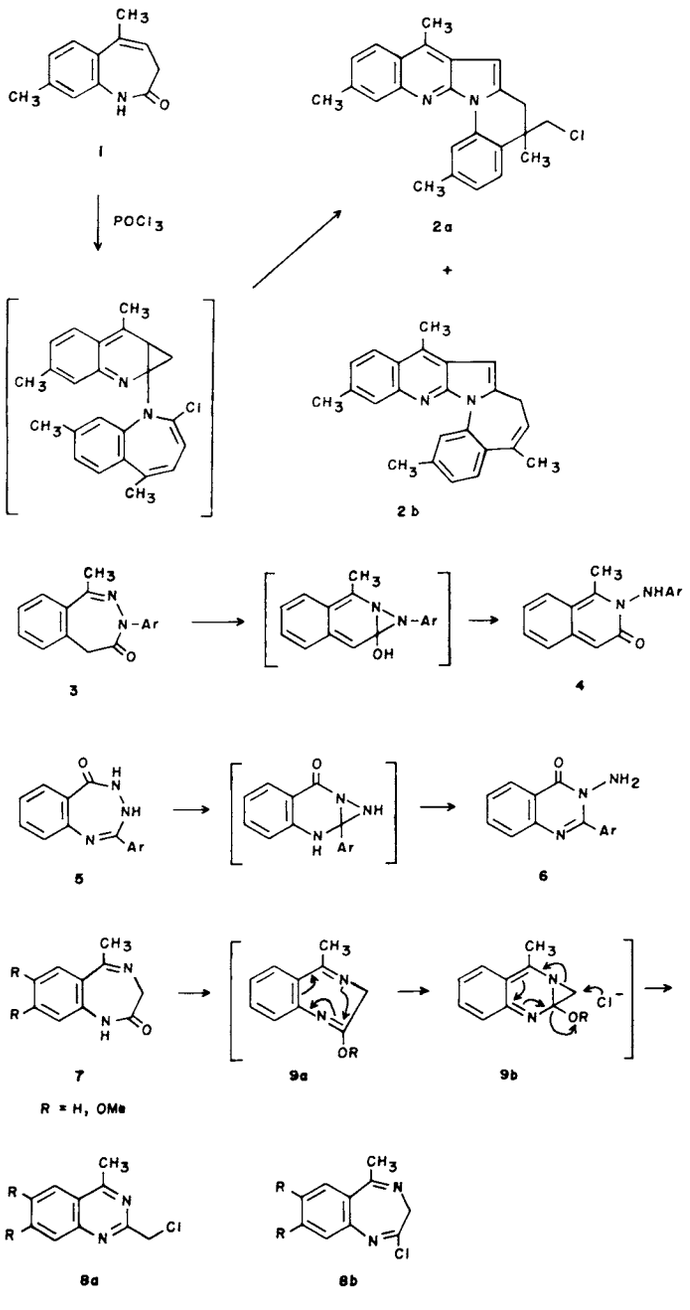
Contractions of seven-membered azaheterocycles to quinolines, isoquinolines and quinazolines have recently been reported in the literature [1-3]. All of these ring contractions are proposed to go through a three membered ring intermediate.

Bowie [1] describes a ring contraction-dimerization of 1-benzazepinones **1** to quinolines **2** using phosphoryl chloride. Flammang [2] reports the transformation of 2,3-benzodiazepines **3** to isoquinolines **4** in acid and Ratnam [3] presents a similar ring contraction of 1,3,4-[5*H*]-benzotriazepinones **5** to 3-aminoquinazolines **6** under oxidizing conditions.

We wish to report here the discovery of an analogous ring contraction which presumably passes through an intermediate similar to those described by the above workers.

In an attempt to form iminochloride **8b** as part of an ongoing synthesis program, lactam **7** (R = H) was treated with an excess of phosphoryl chloride at reflux for 30 minutes. A single product was isolated from silica gel chromatography. Spectral characterization (^1H, ^{13}C nmr) of the resultant chloride **8a** revealed that the product was in fact a chloromethylquinazoline rather than the expected iminochloride. A similar result was observed in the dimethoxy series (R = OMe).

A possible mechanism for this transformation might involve enol-lactam tautomerization to **9a** possibly driven by coordination of oxygen with the phosphorus reagent, and subsequent 4 + 2 electrocyclic reaction of **9a** to give fused aziridinoquinazoline system **9b**. Subsequent chloride ion attack with concomitant ring-opening and expulsion of hydroxide ion, which also might be facilitated by coordination with phosphorus, causes the formation of **8a**.



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. The ^1H nmr spectra were recorded in deuterochloroform at 60 MHz on a Varian T-60 instrument; ^{13}C nmr spectra were recorded in deuterochloroform at 20 MHz on a Varian FT-80A spectrometer. Microanalyses were performed on a Perkin Elmer model 240c elemental analyzer and Mass Spectra were obtained at

70 eV by direct insertion with a Finnigan 1015 c gcms instrument. The uv spectra were measured in ethanol on a Hewlett Packard model 8450A UV/VIS spectrophotometer.

1,3-Dihydro-5-methyl-2*H*-1,4-benzodiazepine-2-one (**7**, R = H) and 1,3-Dihydro-7,8-dimethoxy-5-methyl-2*H*-1,4-benzodiazepine-2-one (**7**, R = OCH_3).

These compounds were prepared by a modification of the procedure of Bell *et. al.* [4].

2-Chlorometyl-4-methylquinazoline (**8a**, R = H).

1,3-Dihydro-5-methyl-2*H*-1,4-benzodiazepine-2-one **7** (R = H) (11.0 g, 63 mmoles) and phosphorus oxychloride (50 ml, 536 mmoles) was heated to reflux with magnetic stirring for 30 minutes. The mixture was cooled and evaporated at reduced pressure leaving a residue which was taken up in ice water (100 ml) and neutralized with solid sodium bicarbonate to *p*H 7. The aqueous solution was extracted with dichloromethane (4 x 100 ml). The combined extracts were dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed on 100 g of silica gel (Mallinkrodt) eluted with diethyl ether. The fractions containing the product were evaporated giving a yellow oil which crystallized upon trituration with ether. The crystalline solid was collected by filtration and washed with hexane. Drying at 10 mm Hg for 8 hours gave 6.3 g (52%) of **8a** (R = H) mp 162-164°; ^{1}H nmr (deuteriochloroform): δ 7.9 (m, aromatic, H), 4.8 (s, CH_2, 2H), 2.9 (s, CH_3, 3H); ^{13}C nmr (deuteriochloroform): 21.7, 47.8, 122.9, 124.9, 127.9, 128.9, 133.9, 149.8, 161.0, 169.3; uv: λ max, (log ε) 242 (3.2), 272 (3.0), 308 (2.9), 318 (2.8); ms: 192 (M^+) (1 Cl).

Anal. Calcd. for $C_{10}H_9ClN_2$: C, 62.34; H, 4.70; N, 14.54. Found: C, 62.53; H, 4.97; N, 14.80.

2-Chloromethyl-6,7-dimethoxy-4-methylquinazoline (**8a**, R = OCH_3).

1,3-Dihydro-7,8-dimethoxy-5-methyl-2*H*-1,4-benzodiazepin-2-one (**7**, R = OCH_3) (1.0 g, 43 mmoles) and 5 ml of phosphoryl chloride (54 mmoles) was heated to reflux with stirring for 1 hour, cooled and poured slowly into ice water (100 ml). Solid sodium bicarbonate was added to bring the *p*H to 7 and the solution extracted with 4 x 50 ml dichloromethane. The organic extracts were combined, dried over magnesium sulfate and filtered. The filtrates were concentrated at reduced pressure giving a tan solid which afforded crystals upon trituration with 1:1 acetone:ether. The crystals were collected by filtration, washed with acetone and dried at 50° at 10 mm Hg for 16 hours, yield 0.55 g (52%), mp 154-156°; ^{1}H nmr (deuteriochloroform): δ 7.3 (s, aromatic, 1H), 7.1 (s, aromatic, 1H), 4.8 (s, CH_2Cl, 2H), 4.0 (s, OCH_3, 6H), 2.8 (s, CH_3, 3H); ^{13}C nmr (deuteriochloroform): 21.7, 47.9, 56.1, 56.4, 102.1, 107.0, 118.4, 147.8, 150.4, 155.9, 159.7, 165.6; uv: λ max (log ε) 250 (4.54), 318 (3.83), 331 (3.93); ms: 252 (M^+), (1 Cl).

Anal. Calcd. for $C_{12}H_{13}N_2O_2Cl$: C, 56.99; H, 5.18; N, 11.08. Found: C, 56.65; H, 5.18; N, 10.82.

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REFERENCES AND NOTES

[1] M. B. Stringer, V. Candeloro, J. H. Bowie, R. H. Prager, L. M. Engelhardt, and A. M. White, *J. Chem. Soc., Perkin Trans. I*, 2529 (1984).

[2] M. Flammang, *C. R. Seances Acad. Sci., Ser C*, **290**, 349 (1980).

[3] Ch. K. Reddy, P. S. N. Reddy, and C. V. Ratnam, *Indian J. Chem., Sect. B*, **24**, 695 (1985).

[4] S. C. Bell, T. S. Sulkowski, C. Gochman and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).