Bromination Products of 2,4-Dimethyl-1,5-benzodiazepine

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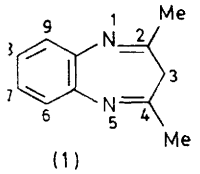
Bromination of the title diazepine (1) in chloroform gives 2-bromomethyl-4-methyl-1,5-benzodiazepinium bromide (5), whereas bromination in glacial acetic acid gives 2,4-bis(dibromomethyl)-1,5-benzodiazepinium bromide (6) and 3,7,8-tribromo-2,4-bis(tribromomethyl)-1,5-benzodiazepine (12).

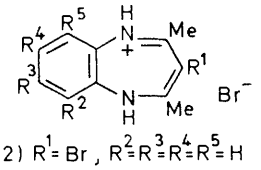
EARLIER reports on the bromination of 2,4-dimethyl-1,5-benzodiazepine suggest that the base (1) with 1 equiv. of bromine [1] gives the 3-bromodiazepinium salt (2), and that the salt (3) with an excess of bromine [2] in glacial acetic acid gives the 6,7,8,9-tetrabromo-derivative (4). As a part of a more extensive study of the chemistry of 1,5-benzodiazepines these reactions have

[1] R. Lund, Ph.D. Thesis, University of Washington, 1959.
[2] D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc.*, 1965, 3785.

recently been re-examined and the results cast doubt on the above assignments.



(1)



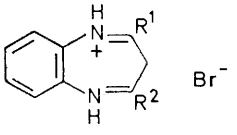
(2) R^1 = Br, R^2 = R^3 = R^4 = R^5 = H

(3) R^1 = R^2 = R^3 = R^4 = R^5 = H

(4) R^1 = H, R^2 = R^3 = R^4 = R^5 = Br

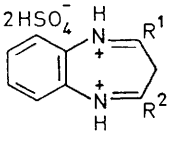
The earlier identification of the monobromo-derivative (2) was not supported by any spectral data, and was based primarily on the observation that acidic hydrolysis gave 2-methylbenzimidazole and bromoacetone.[1] Similar hydrolysis products could be anticipated, however, from 2-bromomethyl-4-methyl-1,5-benzodiazepinium bromide (5), and this latter structure is in agreement with the n.m.r. spectrum of this product, which shows a sharp singlet at δ 3.9 (CH_2) and a broader peak at 4.4 (H-3).

The reported synthesis of the tetrabromide (4) consisted of treatment of the perchlorate salt of (3) with 6 equiv. of bromine in a large volume of glacial acetic acid; however, we find that the same tetrabromide can be prepared by treatment of the monobromide (5) with 4 equiv. of bromine. This suggests that the earlier assignment of structure (4) is incorrect, and that the compound is best represented as 2,4-bis(dibromomethyl)-1,5-benzodiazepinium bromide (6). This reassignment



(5) R^1 = CH_2Br, R^2 = Me

(6) R^1 = R^2 = $CHBr_2$

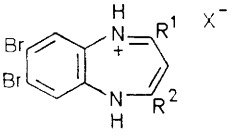


(7) R^1 = R^2 = $CHBr_2$

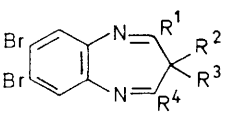
(8) R^1 = R^2 = Me

is further supported by the n.m.r. spectrum of (6) in sulphuric acid, which clearly demonstrates the presence of aromatic protons and the lack of methyl absorption from the colourless dication (7) arising in concentrated sulphuric acid. The position of the aromatic peak for (6) is in good agreement with that reported[3] in an earlier analysis of the dication (8) arising from the diazepine (1) in concentrated sulphuric acid.

Bromination of either (5) or (6) with a large excess of bromine in glacial acetic acid has now yielded a new, yellow crystalline material, $C_{11}H_{13}Br_9N_2$ (*m/e* 488). The i.r. spectrum suggests the absence of NH groups, and the n.m.r. spectrum consists simply of two singlets at δ 7.3 (2 H) and 7.8 (1 H). In an effort to establish the position of the bromine atoms in this new compound, 7,8-dibromo-2,4-dimethyl-1,5-benzodiazepinium hydrogen sulphate (9) was synthesized from 4,5-dibromo-1,2-phenylenediamine[4] and acetylacetone. No diazepine was formed from 3,6-dibromo-1,2-phenylenediamine[5] under the same conditions. The n.m.r. spectrum of the corresponding base (10) showed a singlet associated with the two aromatic protons at C-6 and C-9 in reasonably good agreement with the two-proton peak observed for the new polybromo-system arising from (5) or (6). Bromination of (9) with 6-equiv. of bromine produced the corresponding 2,4-bis(dibromomethyl) system (11), which when treated with an excess of bromine in glacial acetic acid gave the same $C_{11}H_{13}Br_9N_2$ species as arose from (5) or (6). On this base we believe that this polybromo-product is 3,7,8-tribromo-2,4-bis(tribromomethyl)-1,5-benzodiazepine (12).



(9) R^1 = R^2 = Me, X = HSO_4



(10) R^1 = R^4 = Me, R^2 = R^3 = H

(11) R^1 = R^2 = $CHBr_2$, X = Br

(12) R^1 = R^4 = CBr_3, R^2 = H, R^3 = Br

Although the 1,5-benzodiazepine system has been shown to be susceptible to ring contraction in acidic media,[2] a similar ring contraction was not anticipated during the formation of compound (12), in view of the relative mildness of the reaction conditions. This argument is supported by the observation that (12) can be converted back into the diazepinium hydrobromide (11) (48%) by catalytic reduction over platinum–carbon.

The lack of diazepinium salt formation in the case of (12) can be attributed to steric crowding resulting from the disposition of the two tribromomethyl groups at C-2 and C-4 and the bromine atom at C-3, preventing the molecule from achieving the planar configuration characteristic of 1,5-benzodiazepinium salts.

EXPERIMENTAL

M.p.s were determined with either a Thomas–Hoover or a Mel-Temp apparatus. I.r. absorption spectra were recorded with a Perkin-Elmer 137 or 521 spectrophotometer. Analyses were performed by M-H-W Laboratories, Garden City, Michigan.

2,4-Dimethyl-1,5-benzodiazepine (1).—This was prepared as described[6] and had m.p. 130° (lit.,[6] 132°); $\nu_{max.}$ (KBr) 1 625 cm^{-1}; δ($CDCl_3$) 2.25 (6 H, s, 2 Me), 2.72 (2 H, s, CH_2), and 7.25 (4 H, m, ArH). The hydrogen sulphate salt of (1), prepared as described,[7] had m.p. of 230° (lit.,[7] 226°); $\nu_{max.}$ (KBr) 1 640 cm^{-1}; δ[$(CD_3)_2SO$] 1.8 (6 H, s, 2 Me), 4.2 (1 H, s, CH), 6.8 (4 H, m, ArH), and 7.3 (2 H, s, 2NH).

2-Bromomethyl-4-methyl-1,5-benzodiazepinium Bromide (5).[1] —A solution of the diazepine (1) (5 g) in chloroform (200 ml) was treated with a solution of bromine (5 g, 1 equiv.) in chloroform (150 ml). The mixture was stirred overnight at room temperature. Addition of cold ether caused precipitation of the salt (5), which yielded purple

[3] H. Staab and F. Vögtle, *Chem. Ber.*, 1965, **98**, 2701.
[4] M. Schiff, *Monatsh.*, 1890, **11**, 338.
[5] J. Calhane, *J. Amer. Chem. Soc.*, 1889, **22**, 452.
[6] J. Thiele and G. Steimmig, *Ber.*, 1907, **40**, 955.
[7] J. Barltrop, C. Richards, D. Russel, and G. Ryback, *J. Chem. Soc.*, 1959, 1132.

needles, m.p. 201° (from methanol) (lit.,[1] 184—185°); $\nu_{max.}$ (KBr) 3 400 and 1 640 cm^{-1}, δ[$(CD_3)_2SO$] 1.9 (3 H, s, Me), 3.9 (2 H, s, CH_2) 4.4 (1 H, s, CH), and 6.8 (4 H, m, ArH) (Found: C, 38.35; H, 3.35; N, 8.45. $C_{11}H_{12}Br_2N_2$ requires C, 39.8; H, 3.65; N, 8.45%).

2,4-*Bis*(*dibromomethyl*)-1,5-*benzodiazepinium Bromide* (6) [2].—A stirred suspension of the hydrogen sulphate salt of (1) (10 g) in glacial acetic acid (1 600 ml) was treated with bromine (12 ml). When the mixture was left overnight at room temperature the tetrabromo-derivative crystallized as black *prisms*, which were washed repeatedly with methanol; yield 14.5 g (71%); m.p. 400° (lit., 360°); $\nu_{max.}$ (KBr) 3 400 cm^{-1}; δ(H_2SO_4) 5.0 (2 H, s, CH_2), 7.0 (2 H, s, $CHBr_2$), and 8.2 (4 H, s, ArH) (Found: C, 24.6; H, 2.0; Br, 70.2; N, 5.4. $C_{11}H_8Br_5N_2$ requires C, 23.2; H, 1.6; Br, 70.3; N, 4.9%). Satisfactory carbon analyses for this compound, as well as for (5), were difficult to obtain; earlier workers [3] had a similar problem.

7,8-*Dibromo*-2,4-*dimethyl*-1,5-*benzodiazepinium Hydrogen Sulphate* (9).—A solution of 4,5-dibromo-1,2-phenylenediamine (2.7 g) in ethanol (20 ml) and glacial acetic acid (10 ml) was treated with acetylacetone (2 ml). The purple solution was then treated with concentrated sulphuric acid (5 ml) and subsequently with ether to induce crystallization of the *diazepinium salt* (9) (62%), m.p. 220—221° (from methanol–ether); $\nu_{max.}$ (KBr) 3 400 and 1 650 cm^{-1}, δ [$(CD_3)_2SO$] 1.75 (6 H, s, 2 Me), 4.2 (1 H, s, CH), 6.8 (2 H, s, ArH), and 9.1 1 H, (s, NH) (Found: C, 30.8; H, 2.35; N, 6.55. $C_{11}H_{12}Br_2N_2O_4S$ requires C, 30.85; H, 2.8; N, 6.55%). Dissolution in methanol and treatment with aqueous base gave the *free base* (10), m.p. 130—132°; $\nu_{max.}$ (KBr) 1 625 cm^{-1}; δ($CDCl_3$) 2.3 (6 H, s, 2 Me), 2.8 (2 H, s, H_2), and 7.65 (2 H, s, ArH) (Found: C, 39.7; H, 3.45; N, 8.55. $C_{11}H_{10}Br_2N_2$ requires C, 40.0; H, 3.05; N, 8.5%).

7,8-*Dibromo*-2,4-*bis*(*dibromomethyl*)-1,5-*benzodiazepinium Bromide* (11).—A solution of the dibromodiazepine (10) (4.28 g) in glacial acetic acid (25 ml) was treated with a solution of bromine (9.6 g, 6 equiv.) in glacial acetic acid. The mixture was stirred overnight and the crude *product* filtered off and washed repeatedly with methanol; m.p. 285°; $\nu_{max.}$ (KBr) 1 625 cm^{-1} (Found: C, 18.3; H, 0.85; N, 3.6. $C_{11}H_7Br_7N_2$ requires C, 18.15; H, 0.95; N, 3.85%).

2,4-*Bis*(*tribromomethyl*)-3,7,8-*tribromo*-1,5-*benzodiazepine* (12).—(i) A stirred suspension of compound (6) (0.6 g) in glacial acetic acid (80 ml) was treated with bromine (2.06 ml) at room temperature. When the mixture was set aside overnight, pale yellow needles of (12) precipitated; m.p. 195—196° (from tetrahydrofuran) (yield 68%); $\nu_{max.}$ (KBr) 1 440, 1 320, and 700 cm^{-1}; δ(C_6D_6) 7.3 (2 H, s, ArH) and 7.8 (1 H, s, CH) (Found: C, 14.75; H, 0.65; N, 3.0. $C_{11}H_3Br_9N_2$ requires C, 14.95; H, 0.35; N, 3.15%).

(ii) A stirred suspension of the benzodiazepinium bromide (11) (7.27 g) in glacial acetic acid (25 ml) was treated with bromine (6 g) in glacial acetic acid (25 ml). The suspension was stirred overnight and filtered to give pale yellow needles of (12), identical (i.r.) with that arising from the bromination of (6).

Reduction of the Nonabromo-derivative (12).—A solution of compound (12) (0.1 g) in tetrahydrofuran (40 ml) was purged with nitrogen for ½ h and then treated with platinum–carbon (0.1 g). The mixture was then shaken for 2 h in hydrogen at 45 lb in^{-2}. The suspension was filtered to give a purple crystalline solid (0.055 g), identical (i.r.) with the benzodiazepinium salt (11).

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