SYNTHESIS OF THE 3,4,6,7-TETRAHYDRO-1H-1,5-METHANO-2,5-BENZOXAZONINE RING SYSTEM BY CYANOGEN BROMIDE-MEDIATED REARRANGEMENT OF A 10b-METHYL-5H-OXAZOLO[2,3-a] ISOQUINOLINE DERIVATIVE

John B. Bremner* and Kevin N. Winzenberg

Department of Chemistry, University of Tasmania, G.P.O. Box 252C, Hobart, Tasmania, Australia 7001.

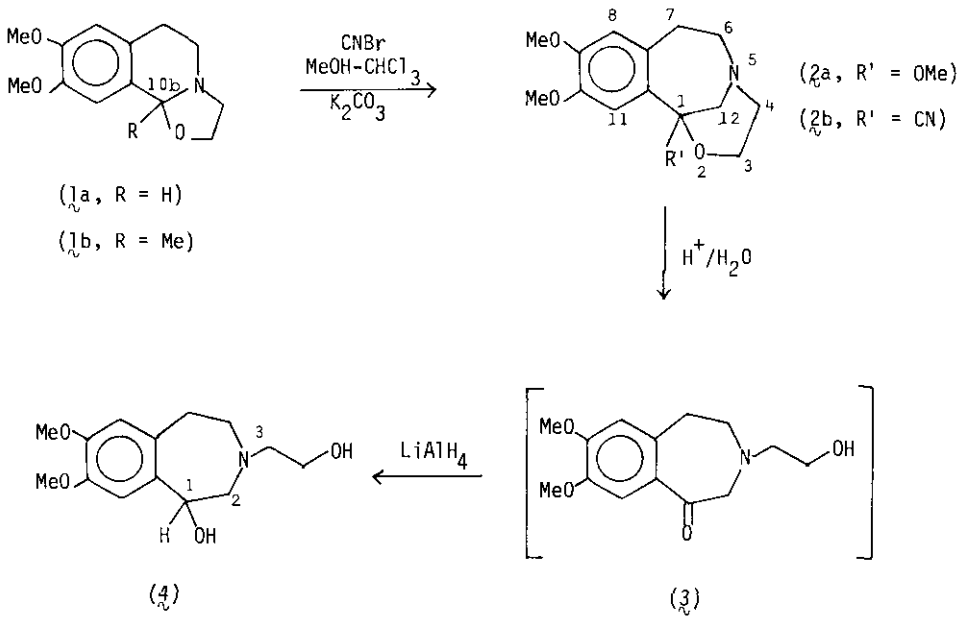
Abstract - The new heterocyclic derivatives, 1,9,10-trimethoxy-3,4,6,7-tetrahydro-1H-1,5-methano-2,5-benzoxazonine (2a) and 9,10-dimethoxy-3,4,6,7-tetrahydro-1H-1,5-methano-2,5-benzoxazonine-1-carbonitrile (2b), were prepared in 76% and 4% yield respectively by the reaction of 8,9-dimethoxy-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[2,3-a]isoquinoline (1b) with cyanogen bromide in the presence of methanol and potassium carbonate. Acid hydrolysis of (2a), followed by reduction with lithium tetrahydroaluminate, afforded 3-(2-hydroxy)ethyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepin-1-ol (4) in good yield. A mechanism of formation of (2a) and (2b) is outlined.

As part of a project on the synthesis of new fused nine- and ten-membered heterocycles, the preparation of a 2,5-benzoxazonine-5(1H)-carbonitrile derivative from the cyanogen bromide-induced solvolysis of the 5H-oxazolo[2,3-a]isoquinoline (1a) was recently described.[1] In an extension of this work we now wish to report that the substituted analogue (1b) also undergoes a reaction on treatment with cyanogen bromide in the presence of methanol, but, unexpectedly, methano-bridged medium-ring heterocycles were obtained.[2]

Reaction (20h at ambient temperature) of compound (1b)[3] (1.604 mmol) with cyanogen bromide (2.125 mmol) in methanol-chloroform (1:2 v/v; 30 ml) in the presence of anhydrous potassium carbonate gave, after p.l.c., the 1H-1,5-methano-2,5-benzoxazonine derivative (2a) (gum, 76% yield; methiodide[4] m.p. 241-242° dec.) (Scheme 1) as the major product [M^+ 279.1427; δ ^{1}H (100 MHz, $CDCl_3$, TMS) 6.93, 6.68 (2 x 1H, 2s, H-8 and H-11); 4.00-2.80 (9H, m, H-3, H-4, H-6, H-12 and one H-7); 3.88 (6H, s, 2 x OCH_3); 3.41 (3H, s, C-1-OCH_3); 2.52-2.20 (1H, m, one H-7). δ ^{13}C (67.89 MHz, $CDCl_3$, TMS) 148.0, 147.1 (2s, C-9 and C-10)[5]; 134.0, 133.3 (2s, C-7a and C-11a)[5]; 114.8 (d, C-8); 110.0 (d, C-11); 100.3 (s, C-1); 56.2, 56.1 (2q, C-9-$O\underline{C}H_3$ and C-10-$O\underline{C}H_3$)[5]; 57.0 (t, C-3); 50.9 (q, C-1-$O\underline{C}H_3$); 56.7, 54.6, 48.4 (3t, C-4, C-6 and C-12)[5]; 35.0 (t, C-7)]. The methano-bridged 1-carbonitrile (2b) (4% yield, m.p. 141-142°) was obtained as a minor product

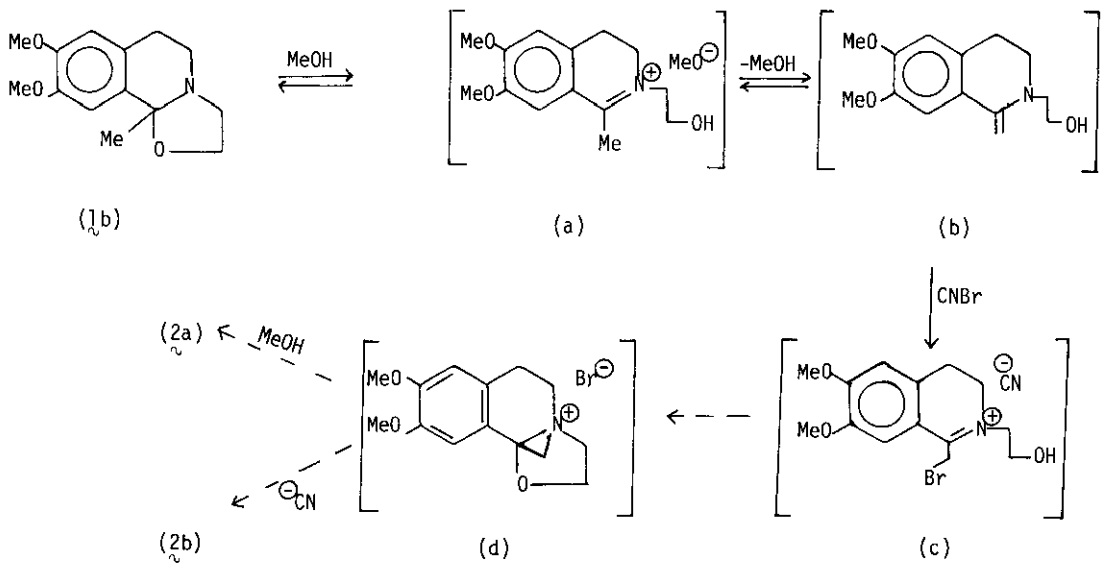
from this reaction [M^+ 274.1280; δ ($CDCl_3$) 7.18, 6.65 (2 x 1H, 2s, H-8 and H-11); 3.94, 3.91 (2 x 3H, 2s, 2 x OCH_3); 4.00-2.60 (8H, m, H-3, H-4, H-6 and H-7); 3.62 (2H, s, H-12)]. The C≡N stretching vibration could not be discerned in the infrared spectrum of (2b) (chloroform solution); however it is known[6] that, occasionally, this absorption band may be very weak or absent.

Some chemical transformations further support the structural assignment of (2a). Treatment of this compound with 2.4 M hydrochloric acid at ambient temperature for 1 h afforded crude 3-(2-hydroxyethyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-3-benzazepin-1-one (3) as a gum [M^+ 265.1314; ν_{max} (thin film) 3420 (OH), 1665 (C=O) cm^{-1}; δ ($CDCl_3$) 7.33 (1H, s, H-9); 6.72 (1H, s, H-6); 3.94, 3.90 (2 x 3H, 2s, 2 x OCH_3); 3.85-3.75 (1H, broad s, exchanged with D_2O, OH); 3.52 (2H, s, H-2); 3.62-3.48 (2H, m, CH_2OH); 2.98 (4H, broad s, H-4 and H-5); 2.85-2.65 (2H, m, CH_2CH_2OH)]. While this amino-ketone decomposed on storage and on attempted purification by p.l.c., reduction of a freshly-prepared sample with lithium tetrahydroaluminate afforded, after p.l.c., the more stable 1H-3-benzazepin-1-ol (4) (oil, 83% yield; methiodide m.p. 149.5-150.5°) [M^+ 267; ν_{max} (thin film) 3460 (OH) cm^{-1}; δ ($CDCl_3$) 6.88, 6.69 (2 x 1H, 2s, H-6 and H-9); 5.00-4.20 (2H, broad s, exchanged with D_2O, 2 x OH); 4.80-4.60 (1H, m, H-1); 3.75 (2 x 3H, s, 2 x OCH_3); 3.70-3.50 (2H, m, CH_2OH); 3.15-2.45 (8H, m, H-2, H-4, H-5 and CH_2CH_2OH)].



Scheme 1

The rearrangement is thought to proceed via the enamine (b) which may arise from the immonium salt (a), formed[3] from the reversible fission of the C-10b-O bond of (1b) (Scheme 2). Reaction of (b) with cyanogen bromide should afford[7] the immonium salt (c), and there is evidence[7,8] to suggest that (2a) may be derived from (c), possibly via an aziridinium bromide salt[7] such as (d); (2b) could also arise from (d).[9] In support of the intermediacy of the enamine (b), 85% exchange of the protons of the C-10b methyl substituent of (1b) for deuterium was observed, from P.M.R. spectroscopic analysis, when this compound was stirred with chloroform-d_1-methanol-d_4 (2:1 v/v) for 24 h at ambient temperature in the presence of anhydrous potassium carbonate.



Scheme 2

Some aspects of the synthetic scope of this rearrangement, together with further evidence for the proposed reaction mechanism, will be published later.

Acknowledgements

The award of a Commonwealth Postgraduate Research Award (to K.N.W.) is gratefully acknowledged. We are also very grateful to Dr. A.J. Jones (The National N.M.R. Centre, Canberra) for the ^{13}C N.M.R. spectrum, and to Dr. M.J. Lacey (C.S.I.R.O. Division of Entomology, Canberra), Mr. J.C. Bignall and Mr. M. Power (Central Science Laboratory, University of Tasmania) for the measurement of the mass spectra.

REFERENCES AND NOTES

1. J.B. Bremner and K.N. Winzenberg, Chem. Ind. (London), 1979, 319.
2. Presented, in part, at the 5th National Conference of the Division of Organic Chemistry of The Royal Australian Chemical Institute, Hobart, January 14-18, 1979, Abstract WEA-P13.
3. W. Schneider and E. Kämmerer, Arch Pharm. (Weinheim), 1966, 299, 817.
4. Satisfactory elemental analyses were obtained for all the methiodide salts described in this paper and for the crystalline base (2b).
5. The chemical shifts of these atoms may be reversed.
6. D.H. Williams and I. Fleming. 'Spectroscopic Methods in Organic Chemistry', 2nd Edn., McGraw-Hill, London, 1973, p. 53.
7. G. Costa, C. Riche and H.-P. Husson, Tetrahedron, 1977, 33, 315.
8. A. Buzas, C. Retourné, J.-P. Jacquet and G. Lavielle, Heterocycles, 1977, 6, 1307.
9. Other pathways for the formation of (2a) and (2b) via aziridinium salts are also possible and cannot be excluded at this stage.

Received, 6th May, 1980