

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

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Abstract - The new heterocyclic derivatives, 1,9,10-trimethoxy-3,4,6,7-tetrahydro-1H-1,5-methano-2,5-benzoxazone (ζ_a) and 9,10-dimethoxy-3,4,6,7-tetrahydro-1H-1,5-methano-2,5-benzoxazone-1-carbonitrile (ζ_b), 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 (λ_b) with cyanogen bromide in the presence of methanol and potassium carbonate. Acid hydrolysis of (ζ_a), followed by reduction with lithium tetrahydroaluminate, afforded 3-(2-hydroxy)ethyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepin-1-ol (μ) in good yield. A mechanism of formation of (ζ_a) and (ζ_b) is outlined.

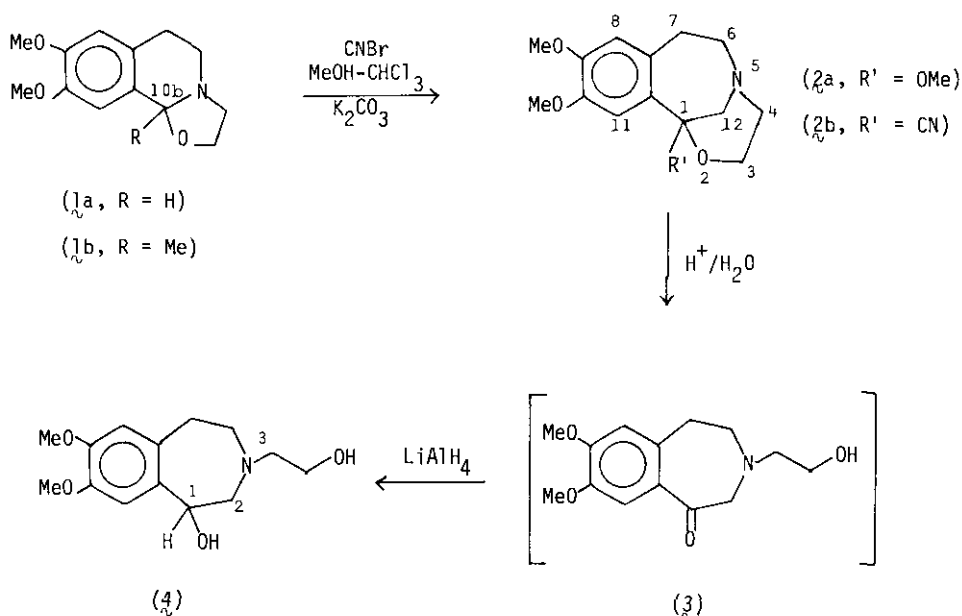
As part of a project on the synthesis of new fused nine- and ten-membered heterocycles, the preparation of a 2,5-benzoxazone-5(1H)-carbonitrile derivative from the cyanogen bromide-induced solvolysis of the 5H-oxazolo[2,3-a]isoquinoline (λ_a) was recently described.¹

In an extension of this work we now wish to report that the substituted analogue (λ_b) 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 (λ_b)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-benzoxazone derivative (ζ_a) (gum, 76% yield; methiodide⁴ m.p. 241-242° dec.) (Scheme 1) as the major product [M^+ 279.1427; δ ¹H (100 MHz, CDCl₃, 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 OCH₃); 3.41 (3H, s, C-1-OCH₃); 2.52-2.20 (1H, m, one H-7). δ ¹³C (67.89 MHz, CDCl₃, 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-OCH₃ and C-10-OCH₃)⁵; 57.0 (t, C-3); 50.9 (q, C-1-OCH₃); 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 (ζ_b) (4% yield, m.p. 141-142°) was obtained as a minor product

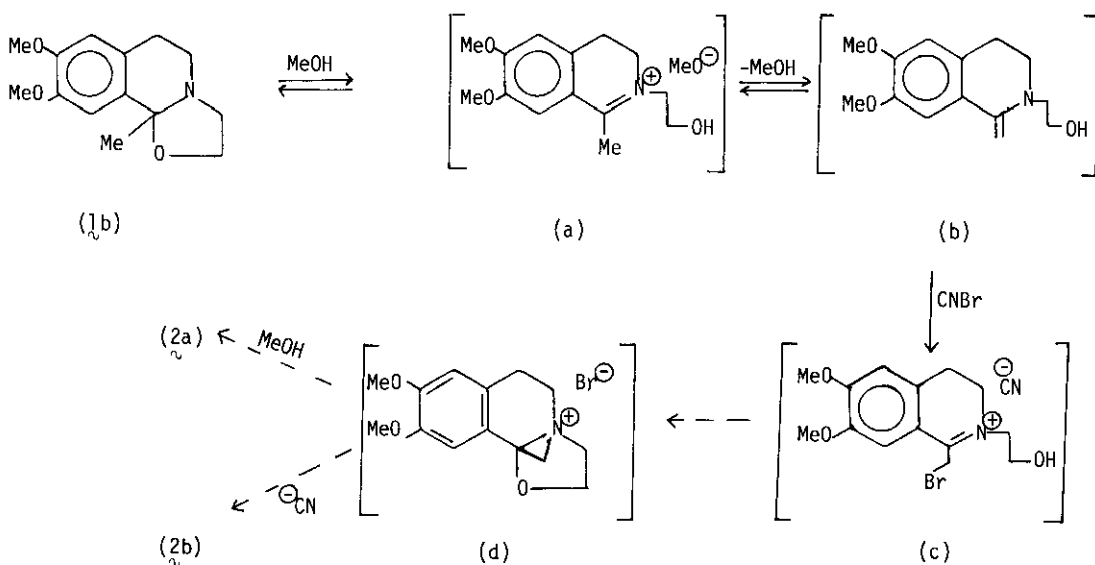
from this reaction [M^+ 274.1280; δ ($CDCl_3$) 7.18, 6.65 (2 x 1H, 2s, H-8 and H-11); 3.94, 3.91 (2 x 3H, 2s, 2 x OCH_3); 4.00-2.60 (8H, m, H-3, H-4, H-6 and H-7); 3.62 (2H, s, H-12)]. The $C\equiv N$ stretching vibration could not be discerned in the infrared spectrum of (2b) (chloroform solution); however it is known⁶ 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), formed³ from the reversible fission of the C-10b-O bond of (1b) (Scheme 2). Reaction of (b) with cyanogen bromide should afford⁷ the immonium salt (c), and there is evidence^{7,8} to suggest that (2a) may be derived from (c), possibly via an aziridinium bromide salt⁷ 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-d₁-methanol-d₄ (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.

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