

REACTION OF CYANOGEN BROMIDE WITH 1-(ω -HYDROXYALKYL)-1,3,4,6,7,11b-HEXAHYDRO-2H-BENZO[A]QUINOLIZINES AS A ROUTE TO ANNELATED BENZAZECINE DERIVATIVES

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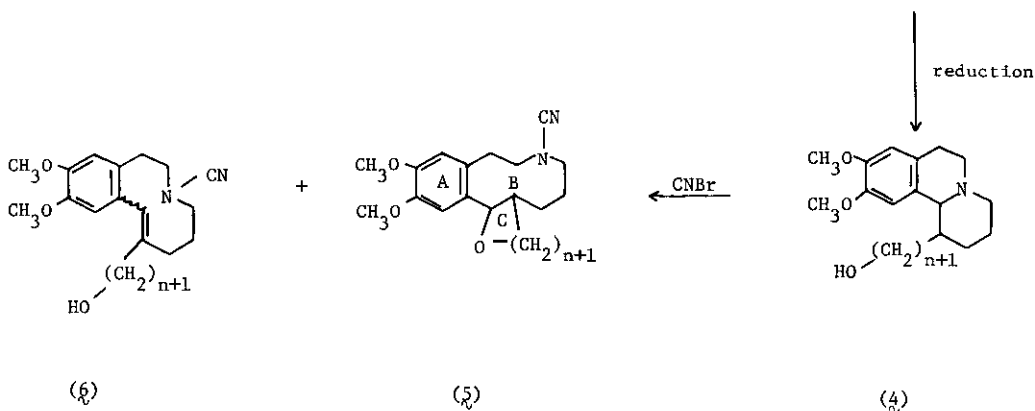
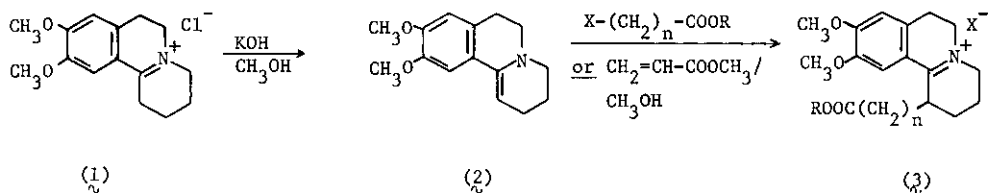
Abstract — Treatment of 1-(2-hydroxyethyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizine ($4a$) with cyanogen bromide in chloroform/potassium carbonate gave the new heterocyclic product, 11,12-dimethoxy-2,3,3a,5,6,8,9,13b-octahydro-furo[3,2-g][3]benzazecine-7(4H)-carbonitrile ($5a$) in moderate yield. The corresponding octahydro-2H-pyrano[3,2-g]- and decahydrooxepino[3,2-g]-benzazecine-carbonitrile derivatives ($5b$ and $5c$) were prepared similarly from the appropriate reduced 1-(ω -hydroxyalkyl)-2H-benzo[a]quinolizines. Elimination products were also isolated in some cases.

A number of cyanogen bromide-mediated routes to fused medium-ring heterocyclic systems have recently been described.^{1,2,3} Further extensions of this work involving the conversion of 1-(ω -hydroxyalkyl)-hexahydro-2H-benzo[a]quinolizine derivatives to some new annelated benzazecines are now reported.

The amino alcohol substrates required ($4a-c$)^{8,9}, were conveniently prepared by C-alkylation^{4,5} of the known enamine (2)⁴ from (1)⁶, followed by reduction of the resultant immonium salts (3)⁷ either with lithium tetrahydroaluminate in one step or in a two-step sequence involving initial reduction with sodium tetrahydroborate (with $3b$, R = CH₃, X = OCH₃).

Reaction (10 hr) of ($4a$) (1.72 m mole) with cyanogen bromide (3.43 m mole) in refluxing ethanol-free chloroform (100 ml) and in the presence of anhydrous potassium carbonate (8.6 m mole) gave the 2,3,3a,5,6,8,9,13b-octahydro-furo[3,2-g][3]benzazecine-7(4H)-carbonitrile ($5a$) (m.p. 204–205°C; 68% yield; M⁺ 316.1787) after preparative thin layer chromatography (silica gel impregnated with 0.5 M KOH; chloroform-5% methanol, v/v). Likewise, the reduced pyrano- and oxepino- analogues, ($5b$) (m.p. 136–137°C; 61% yield; M⁺ 330.1943) and ($5c$) (m.p. 133–134°C; 28% yield, M⁺ 344.2100) were prepared from ($4b$) and ($4c$) respectively; some of the elimination product ($6c$)^{cf. 10} [gum; 21% yield; M⁺ 344.2097; IR (liquid film) 3420 (OH), 2200 (CN) cm⁻¹; λ_{max} (CH₃OH), 287 (ϵ 3065), 241 (ϵ 6880) nm; δ (CDCl₃) 6.75, 6.70 (2 x 1H, 2s, 2 x ArH), 6.49 (1H, s, olefinic H), 3.92 (6H, s, 2 x OCH₃), 3.85–0.70 (19H, m, 9 x CH₂ and OH)] was isolated from the latter reaction. Attempts to extend the ring expansion procedure to give (5), n = 4)

were not successful, only the hexahydrobenzazecine (δ , $n = 4$) [gum; 55% yield; $M^+ 358.2255$; IR (liquid film), 3420 (OH), 2205 (CN) cm^{-1} ; λ_{max} (CH_3OH), 286 (ϵ 3906), 240 (ϵ 8625) nm; δ (CDCl_3), 6.70, 6.66 (2 x 1H, 2s, 2 x ArH), 6.35 (1H, s, olefinic H), 3.88 (6H, s, 2 x OCH_3), 3.75-1.20 (21H, m, 10 x CH_2 and OH)] being isolated.



a) $n = 1$

b) $n = 2$

c) $n = 3$

In the ^1H -n.m.r. spectra (100 MHz, CDCl_3 , TMS) of (5a,b,c), diagnostic downfield signals centred at δ 5.28 (d, J 8.75 Hz), 4.65¹¹, and 4.95 (d, J 6.25 Hz) respectively, were observed for the methine proton adjacent to oxygen and the aromatic ring. However, it was not possible to determine the stereochemistry of the B/C ring fusions in these systems from the coupling constants, although only one diastereomer appeared to be present in each case. Other signals in the n.m.r. spectra of (5a-c) were as follows: [(5a) δ 6.92 and 6.61 (2 x 1H, 2 s, 2 x ArH) 4.30-3.61 (4H, m, 2 x CH_2), 3.92 and 3.89 (2 x 3H, 2s, 2 x OCH_3), 3.40-0.79 (11H, m, 5 x CH_2 and H3a); (5b) δ 7.20 and 6.60 (2 x 1H, 2s, 2 x ArH), 4.31-2.50 (8H, m, 4 x CH_2), 3.91 and 3.88 (2 x 3H, 2s, 2 x OCH_3), 2.20-1.00 (9H, m, 4 x CH_2 and H4a); (5c); δ 7.15 and 6.67 (2 x 1H, 2s, 2 x ArH), 4.37-0.70 (19H, m, 9 x CH_2 and H5a), 3.93 and 3.90 (2 x 3H, 2s, 2 x OCH_3)]. In the infrared

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- the signal was incompletely resolved.
- Dr. A. J. Jones (The National N.M.R. Centre, Camberra) for this spectrum. At 100 MHz, This signal appeared as a doublet (\bar{J} 3.25 Hz) at 270 MHz; we are grateful to
10. P. W. Jeffs and J. D. Scharver, *J. Amer. Chem. Soc.*, 1976, **98**, 4301.
 11. This signal appeared as a doublet (\bar{J} 3.25 Hz) at 270 MHz; we are grateful to
 9. Satisfactory elemental analyses and/or mass spectral molecular compositions were obtained for all new compounds described in this paper.
 8. (δ_a), m.p. 101-102°C; (δ_b), m.p. 98-99°C; (δ_c), m.p. 91-92°C.
 7. (δ_a , R = CH₂CH₃, X = Br), m.p. 202-203°C(dec); (δ_b , R = CH₃, X = OCH₃), not isolated; (δ_c , R = CH₃, X = I), m.p. 188-189°C(dec).
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REFERENCES AND NOTES

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actively pursued.

Extensions of this work to annelated benzazoline analogues and related systems are being

chemical aspects of these reactions are still to be resolved.

of the O-alkylation product (δ_2 , n = 4) was obtained. The detailed mechanistic and stereo-

further supported by the fact that when the hydroxyalkyl chain was extended still further, none

factor presumably accounts for the considerable decrease in yield of (δ_c), and this view is

nucleophilic displacement in the intermediate N-guanammonium salts. An unfavourable entropy

Mechanistically, the ring expansion products (δ_a -c) most probably arise² from intramolecular

2195 cm⁻¹ (δ_b and δ_c) for the secocyanamide group.

spectra of these medium ring systems a strong absorption band was seen at 2200 cm⁻¹ (δ_a) or