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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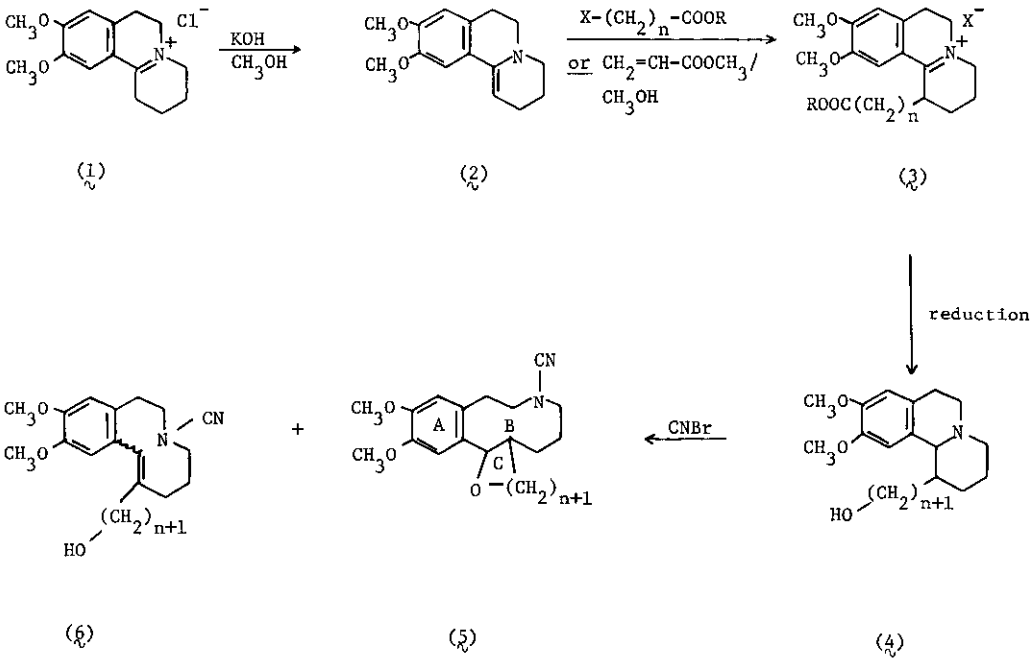
Abstract — Treatment of 1-(2-hydroxyethyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizine (4a) with cyanogen bromide in chloroform/potassium carbonate gave the new heterocyclic product, 11,12-dimethoxy-2,3,3a,5,6,8,9,13b-octahydro-furo[3,2-g][3]benzazecine-7(4H)-carbonitrile (5a) in moderate 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 = CH_3, X = OCH_3).

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} (CH_3OH), 287 (ε 3065), 241 (ε 6880) nm; δ ($CDCl_3$) 6.75, 6.70 (2 x 1H, 2s, 2 x ArH), 6.49 (1H, s, olefinic H), 3.92 (6H, s, 2 x OCH_3), 3.85-0.70 (19H, m, 9 x CH_2 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 (6, 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.



(1) (2) (3) (4) (5) (6)

a) n = 1 b) n = 2 c) n = 3

In the ^{1}H-n.m.r. spectra (100 MHz, $CDCl_3$, TMS) of (5a,b,c), diagnostic downfield signals centred at δ5.28 (d, J 8.75 Hz), 4.65[11], 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) δ6.92 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) δ7.20 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); δ7.15 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

spectra of these medium ring systems a strong absorption band was seen at 2200 cm^{-1} (5a) or 2195 cm^{-1} (5b and 5c) for the secocyanamide group.

Mechanistically, the ring expansion products (5a-c) most probably arise[2] from intramolecular nucleophilic displacement in the intermediate N-cyanoammonium salts. An unfavourable entropy factor presumably accounts for the considerable decrease in yield of (5c), and this view is further supported by the fact that when the hydroxyalkyl chain was extended still further, none of the O-alkylation product (5, n = 4) was obtained. The detailed mechanistic and stereochemical aspects of these reactions are still to be resolved.

Extensions of this work to annelated benzazonine analogues and related systems are being actively pursued.

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7. (3a, R = CH_2CH_3, X = Br), m.p. 202-203°C(dec); (3b, R = CH_3, X = OCH_3), not isolated; (3c, R = CH_3, X = I), m.p. 188-189°C(dec).
8. (4a), m.p. 101-102°C; (4b), m.p. 98-99°C; (4c), m.p. 91-92°C.
9. Satisfactory elemental analyses and/or mass spectral molecular compositions were obtained for all new compounds described in this paper.
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11. This signal appeared as a doublet (J 3.25 Hz) at 270 MHz; we are grateful to Dr. A.J. Jones (The National N.M.R. Centre, Canberra) for this spectrum. At 100 MHz, the signal was incompletely resolved.

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