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

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Abstract — Treatment of 1-(2-hydr0xyethyl)-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-2H-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. 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), were conveniently prepared by C-alkylation of the known enamine (2) from (1), followed by reduction of the resultant immonium salts (3) 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 (5c) was isolated from the latter reaction. Attempts to extend the ring expansion procedure to give (5, n = 4)
were not successful, only the hexahydrobenzaecine (5, \( n = 4 \)) [gum; 55% yield; \( M^+ 358.2255 \); IR (liquid film), 3420 (OH), 2205 (CN) cm\(^{-1}\); \( \lambda_{\max} \) (CH\(_3\)OH), 286 (c 3906), 240 (c 8625) nm; \( \delta \) (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.

\[
\text{CH}_3O-\begin{array}{c}
\begin{array}{c}
\text{CH}_3
\end{array}
\end{array}\begin{array}{c}
\begin{array}{c}
\text{Cl}^-
\end{array}
\end{array}\xrightarrow{\text{KOH}} \text{CH}_3O-\begin{array}{c}
\begin{array}{c}
\text{CH}_3
\end{array}
\end{array}\begin{array}{c}
\begin{array}{c}
\text{N}
\end{array}
\end{array}\xrightarrow{\text{CH}_3OH}
\]
(1)

\[
\text{CH}_3O-\begin{array}{c}
\begin{array}{c}
\text{CH}_3
\end{array}
\end{array}\begin{array}{c}
\begin{array}{c}
\text{N}
\end{array}
\end{array}\xrightarrow{\text{X-(CH\(_2\))\_n-COOR}} \text{CH}_3O-\begin{array}{c}
\begin{array}{c}
\text{CH}_3
\end{array}
\end{array}\begin{array}{c}
\begin{array}{c}
\text{N}
\end{array}
\end{array}\xrightarrow{\text{ROOC(CH\(_2\))\_n}}
\]
(2) or \( \text{CH}_2=\text{CH-COOCH}_3/-\text{2CH}_3OH \)

In the \( ^1\text{H-n.m.r.} \) spectra (100 MHz, CDCl\(_3\), TMS) of (\( \xi a-c \)), diagnostic downfield signals centred at 85.28 (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 (\( \xi a-c \)) were as follows: \((\xi a) \) 66.92 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); \((\xi b) \) 67.20 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); \((\xi c) \) 67.15 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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