

SYNTHESIS OF SOME HEXAHYDRO-2,7-BENZOXAZACYCLOUNDECINE-7(1H)-CARBONITRILE DERIVATIVES
FROM TETRAHYDROISOQUINOLINE PRECURSORS

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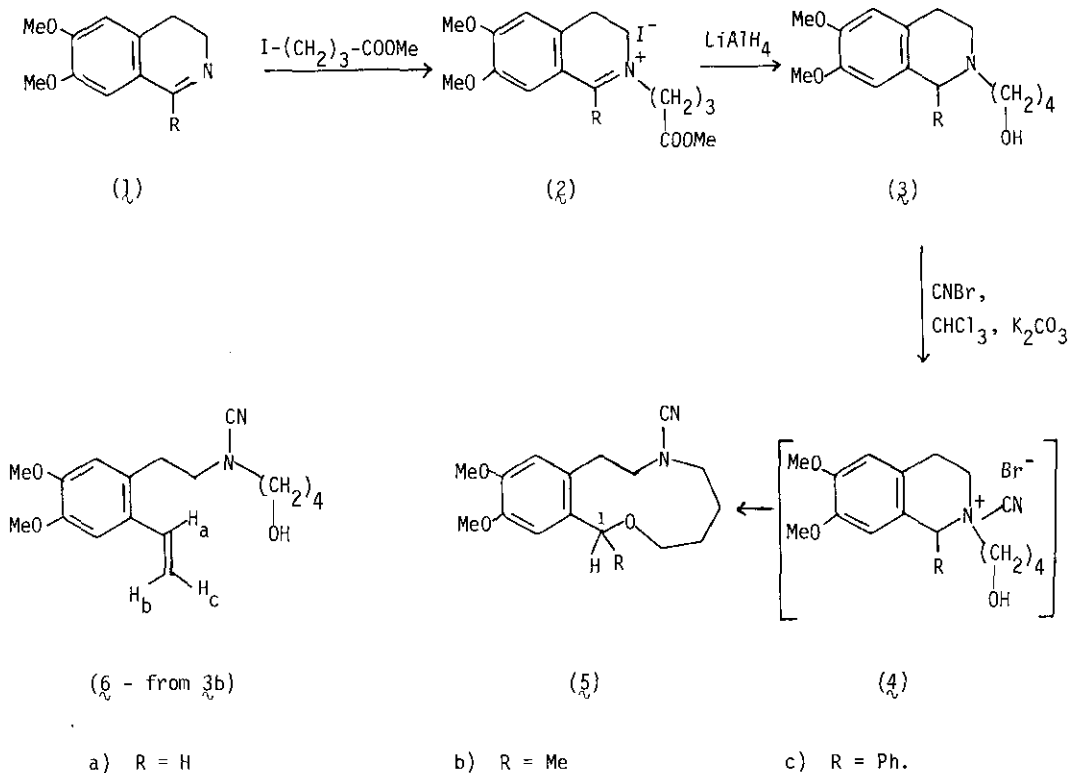
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Abstract - Treatment of 2-(4-hydroxybutyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3a**) with cyanogen bromide in chloroform/potassium carbonate gave the novel heterocyclic product, 11,12-dimethoxy-3,4,5,6,8,9-hexahydro-2,7-benzoxazacycloundecine-7(1H)-carbonitrile (**5a**) in low yield. The 1-methyl (**5b**) and 1-phenyl (**5c**) derivatives of (**5a**) were prepared in a similar fashion.

Cyanogen bromide-induced intermolecular nucleophilic substitution affords¹ a convenient route to a variety of benz-fused nine- and ten-membered heterocyclic systems. An intramolecular counterpart of this general type of reaction has now been applied to the synthesis of the reduced derivatives, (**5a-c**), of 2,7-benzoxazacycloundecine. Although yields were relatively low, these are the first representatives of this ring system.

The appropriately N-substituted tetrahydroisoquinolines (**3a-c**)⁶ required as starting materials were prepared readily by quaternization of the 3,4-dihydroisoquinolines (**1a-c**)² with methyl 4-iodobutanoate³, followed by reduction of the salts (**2a-c**)⁴ with lithium tetrahydroaluminate in tetrahydrofuran.

Reaction (10 hr) of (**3a**) (1.13 mmole) with cyanogen bromide (2.26 mmole) in refluxing chloroform (50 ml) and in the presence of anhydrous potassium carbonate (7.24 mmole) gave the 3,4,5,6,8,9-hexahydro-2,7-benzoxazacycloundecine-7(1H)-carbonitrile (**5a**) (m.p. 107-107.5°C; 15% yield; M^+ 290.1630)⁵ after preparative thin layer chromatography. Likewise, the eleven-membered ring derivatives (**5b**) (m.p. 106-107°C; 9%; M^+ 304.1733) and (**5c**) (m.p. 147-148°C; 21%; M^+ 366.1898) were prepared from (**3b**) and (**3c**) respectively under similar experimental conditions. A variety of other products were observed in all cases, and from the reaction with (**3b**) a considerable amount of the elimination product (**6**) [35% yield; IR (liquid film) 2200 (CN), 3380 (OH) cm^{-1} ; δ (CDCl₃) 7.10-6.68 (3H, m, 2ArH and H_a), 5.60 (1H, d, J_{trans} 17.5 Hz, H_b), 5.29 (1H, d, J_{cis} 10.6 Hz, H_c), 3.91 (6H, s, 2 x OCH₃), 3.80-2.80 (8H, m, 4 x CH₂), 2.52 (1H, br. s, OH), 1.90-1.30 (4H, m, 2 x CH₂)] was also isolated.



The presence of a secocyanamide moiety in each of the medium-ring derivatives (5a-c) was indicated by a strong absorption band at $2190-2200\text{ cm}^{-1}$ in the infrared spectra. In the $^1\text{H-n.m.r.}$ spectra (100 MHz, $CDCl_3$, TMS), characteristic downfield signals were observed for the benzylic protons (or proton) adjacent to oxygen; in (5a) these protons appeared as a singlet at δ 4.50, while in (5b) and (5c) the corresponding C-1 proton exhibited quartet (δ 4.44, \underline{J} 6.25 Hz) and singlet (δ 5.40) resonances respectively. A doublet (\underline{J} 6.25 Hz) centred at δ 1.48 was observed for the C-methyl group in (5b). Other signals in the n.m.r. spectra of (5a-c) were as follows: [(5a) δ 6.77 (2H, s, ArH), 3.90 (6H, s, $2 \times OCH_3$), 3.64 (2H, t, \underline{J} 4.5 Hz, 3- CH_2), 3.43 (2H, t, \underline{J} 5 Hz, 8- CH_2), 3.17 (2H, t, \underline{J} 4.5 Hz, 6- CH_2), 2.94 (2H, t, \underline{J} 5 Hz, 9- CH_2), 1.90-1.50 (4H, m, 4,5- CH_2 , shown to be coupled to H3 and H6 by double irradiation); (5b) δ 6.65 and 6.61 ($2 \times 1\text{H}$, 2s, ArH), 3.81 (6H, s, $2 \times OCH_3$), \underline{c} . 4.10-1.50 (12H, m, $6 \times CH_2$); (5c) δ 7.29 (5H, br. s, 1-Ph), 6.76 and 6.65 ($2 \times 1\text{H}$, 2s, 2ArH), 3.89 and 3.83 ($2 \times 3\text{H}$, 2s, $2 \times OCH_3$), \underline{c} . 4.30-1.50 (12H, m,

6 x CH₂).

It is probable that (5a-c) arise by attack of the hydroxyl group on the C-1 benzylic carbon in the intermediate N-cyanoammonium salts⁷ (4a-c). However, whether this attack is a concerted 7-Endo-Tet process or a stepwise one via a stabilized benzylic carbonium ion intermediate, is yet to be established. Similar cyanogen bromide-induced intramolecular O-alkylations have been observed previously with both acyclic⁸ and more constrained cyclic⁹ substrates.

The bromide ion associated with (4a-c) could also act as a competitive nucleophile and when this counter ion in (4a) was exchanged for fluoroborate, the yield of (5a) was more than doubled to 32%. The salt (4a) was first formed at -40° to -50° by reaction of (3a) with cyanogen bromide in anhydrous ether. Anion exchange was then effected⁷ in situ by the addition of silver tetrafluoroborate in acetonitrile. After removal of the silver bromide by centrifugation, more acetonitrile was added to the supernatant and the solution then refluxed over anhydrous potassium carbonate for 1 hr.

Further work is in progress to investigate the synthetic usefulness and mechanism of this reaction in other tetrahydroisoquinoline and related systems.

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