Tetrahedron Letters,Vol.23,No.12,pp 1297-1298,1982 0040-4039/82/121297-02$03.00/0
Printed in Great Britain

FUNCTIONALIZED 2-AZABICYCLO[3.3.1]NONANES. III.[1] REDUCTIVE REARRANGEMENT OF AN HEXAHYDRO-2-OXOPYRANO[3,2-b]PYRIDINE

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Reduction of 5-benzoyl-8-methyl-2-oxo-3,4,4a,5,6,7-hexahydro-2*H*-pyrano[3,2-b] pyridine (1) with lithium aluminium hydride afforded (1R*,5S*,6R*,9S*)-2-benzyl-5-methyl-2-azabicyclo[3.3.1]nonane-6,9-diol (2).

The main interest in the synthesis of functionalized 2-azabicyclo[3.3.1]nonanes,[2] a structural moiety present in the *Strychnos* alkaloids as well as in morphine and in most morphine-like analgesics, lies in their usefulness as intermediates in the preparation of more complex polycyclic structures.[1b]

In this communication we report the first synthesis of a 2-azabicyclo[3.3.1]nonane simultaneously functionalized at the 6 and 9 positions through reductive rearrangement of an appropriate enol lactone 1.[3] This synthesis implies the formation of the C_5-C_6 bond in the last synthetic step and constitutes the first approach to the 2-azabicyclo[3.3.1]nonane framework by disconnection of this bond.[4] Furthermore, although the reductive rearrangement of exocyclic enol lactones is a useful approach to bridged systems, only a limited number of synthetic applications have been developed[5] and there are no precedents of its extension to the preparation of azaderivatives.

Lithium aluminium hydride was selected as the reducing agent in order to achieve simultaneously the reduction of the N-benzoyl substituent to the easily removable benzyl group. Thus, when exocyclic enol lactone 1[3] was treated with 1.5 equiv. of $LiAlH_4$ in anhydrous THF (-70°C to r.t., 4 hr) and the reaction mixture was quenched with aqueous hydrochloric acid, azabicyclo 2[6] was obtained in 35% yield. Hemiacetal 3[7] was isolated as by-product in 25% yield (Figure I).

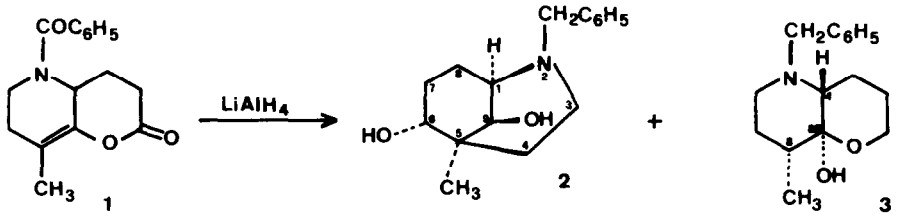

Figure I

The stereochemical assignment of diol 2 was inferred from (a) the absence of intramolecular hydrogen bonding in the infrared spectrum, (b) the reluctance to form a cyclic sulfite ester under normal conditions, and (c) mechanistic considerations (Figure II). Thus, the axial position of the C-6 hydroxyl group is a consequence of the steric arrangement of the side chain in the intermediate 4, in which the aldehyde group is coordinated to the aluminium atom attached to the enolate

oxygen.[5c,d] On the other hand, the intramolecular transfer of an hydride ion to the ketone carbonyl group in the intermediate 5 determines the C-9 stereochemistry and, therefore, the *trans* relationship between the two hydroxyl groups.

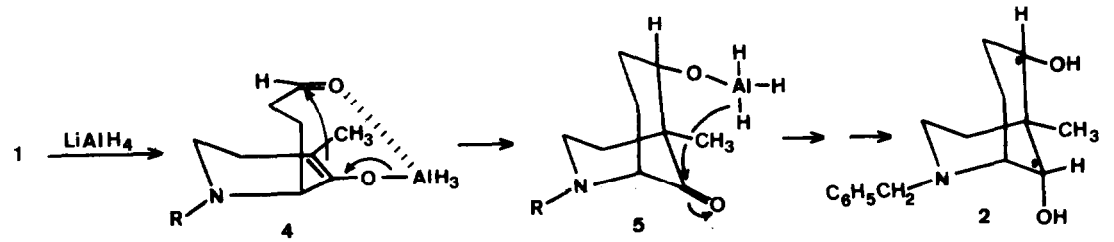

Figure II

Finally, the relative configuration of hemiacetal 3, formed by reduction of the intermediate aldehyde 4 in a competing process, was established by means of its nmr spectrum together with thermodynamic considerations taking into account the anomeric character of the chiral center at C_{8a}.

The functionalization and the N-benzyl substituent of azabicyclo 2 renders this compound a valuable intermediate for later transformations in more complex structures containing the 2-azabicyclo[3.3.1]nonane moiety.

ACKNOWLEDGMENT. We are grateful to Ms. Gemma Fabriás for experimental contributions.

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6. Nmr ($CDCl_3$/220 MHz), δ1.20 (s,3H,CH_3), 1.3-2.2 (m,6H), 2.70 (m,1H,C_3-H_{eq}), 2.75 (m,1H,C_3-H_{ax}), 2.90 (m,1H,C_1-H), 3.60-3.72 (m,2H,C_6-H and C_9-H), 3.71 and 3.79 (2d,1H each, J=13 Hz, NCH_2Ar), 7.20-7.40 (m,5H,ArH); ir (CCl_4), 3620, 3350 cm^{-1}. Picrate, m.p. 162-164°C (ethanol). Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 53.87; H, 5.30; N, 11.40. Found: C, 53.84; H, 5.37; N, 11.21.
7. Nmr ($CDCl_3$/60 MHz), δ0.95 (d,3H,CH_3), 1.2-2.3 (m,9H), 2.5-2.8 (m,1H), 3.0 and 4.0 (2d, 1H each, J=13 Hz), NCH_2Ar), 3.65 (m,3H,OH and OCH_2), 7.2 (s,5H,ArH); ir ($CHCl_3$), 3490 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.22; H, 8.96; N, 5.41.

(Received in UK 22 January 1982)