A NOVEL SYNTHESIS OF DIBENZO[c,f]-1-AZABICYCLO[3.3.1]NONANES

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Abstract—Treatment of the N-benzylated p-quinol acetates (1a and 1b) with trifluoroacetic acid gave (2)-3-hydroxydibenzoazabicyclononanes (5a and 5b) in good yields. On the other hand, lead tetraacetate oxidation of 2-benzyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (2) gave the o-quinol acetate (6), which rearranged into the 4-acetoxy-6-hydroxy derivative (4a) at room temperature. Acid treatment of the 4-acetate (4a) afforded a cyclization product (5e) having the same skeleton as that of 5a.

The p-quinol acetate (1), easily prepared from 7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (2) by lead tetraacetate (LTA) oxidation, is a key compound for the synthesis of isoquinoline alkaloids1', aporphine2), homoaporphine, homoproaporphine, and homomorphinandione.3) On the other hand, LTA oxidation of 6-hydroxy-7-methoxy congener (3) gives the corresponding 4-acetoxy derivative (4)4), which undergoes acid-catalysed cyclization to isopavine alkaloids.5) Now we wish to report the synthesis of dibenzo[c,f]-1-azabicyclo[3.3.1]nonanes, through two routes via the N-benzylated p-quinol acetate (1) and 4-acetoxy derivative (4).

1a; 2a; 3a; 4a: R1=H, R2=CH3
1b; 2b: R1=H, R2=CH2

† Dedicated to Prof. T. Kametani on the occasion of his retirement.
The starting phenols (2a,b and 3a) were prepared from benzaldehyde and 8-phenethyl-
amines according to Kametani's method6) (condensation, reduction, Mannich's re-
action, and debenzylation) as shown in Scheme I.

LTA (1.2 eq.) oxidation of 2a (100 mg) in acetic acid (AcOH) (1 ml) gave the p-qui-
nol acetate (1a) [IR (cm⁻¹): 1735 (OAc), 1670, 1650, 1625 (dienone)] quantitatively,
which was treated with trifluoroacetic acid (CF₃COOH) (1 ml) in methylene chloride
(CH₂Cl₂) (10 ml) at room temperature for 1 hr to give (2)-3-hydroxy-2,9,10-trimeth-
oxydibenzo[c,f]-1-azabicyclo[3.3.1]nonane (5a)7), m.p. 213-215°, in 38% yield,
which showed four singlets due to aromatic protons (6 6.39, 6.41, 6.56, 6.58)
on its nuclear magnetic resonance (NMR) spectrum and was methylated with diazo-
methane to give a tetramethyl ether (5b). NMR spectra of both tetramethyl ether
(5b) and the authentic sample8) were completely superimposable.

Similarly, oxidation and the subsequent acid treatment of 2b afforded (2)-3-hy-
droxy-2-methoxy-9,10-methylenedioxydibenzoazabicyclononane (5c), m.p. 203.5-205.5°
(dec.), in 50% yield, the structure of which was confirmed by its conversion to
the known methyl ether (5d).9)

Oxidation [LTA (1.2 eq.)] of 3a in CH₂Cl₂ and careful work-up10) gave the oily p-
quinol acetate (6) [IR (cm⁻¹): 1740 (OAc), 1685 (C=O); NMR (δ): 2.03 (OCOMe), 3.36
(aliph. OMe), 3.77 (2 x arom. OMe), 5.73, 5.79 (each 1H, olefin. H)], which was
allowed to stand overnight to give a diastereomeric mixture of the 4-acetoxy de-
rivatives (4a)10) [IR (cm⁻¹): 3550 (OH), 1720 (OAc); NMR (δ): 1.95, 2.02 (3H, each
s, OCOMe (1 : 1.3)) as an oil. Without purification, the 4-acetoxy derivatives
(4a) were treated with CF₃COOH at room temperature for 1 hr to afford an amorphous
(2)-2-hydroxy-3,9,10-trimethoxydibenzoazabicyclononane (5e) (HCl salt: m.p. 238-
240°) in 80% yield from 3a. The structure of 5e was verified by comparison of its
methyl ether with the authentic sample (5b)8) in all respects.

Thus a novel synthesis of (2)-dibenzo[c,f]-1-azabicyclo[3.3.1]nonanes (5) was ac-
complished from either 7- or 6-hydroxy-N-benzyltetrahydroisoquinoline (2a,b or 3a)
via the intermediacy of either the p-quinol acetate (1a,b) or the 4-acetoxy der-
ivatives (4a) presumably by the following reaction pathway; deacetoxylation of
the former (1a,b) or the latter (4a) with acid would generate Michael-type acceptor,
a p-quinone methide (7) or a cation (8), which would then immediately react to-
gether in a manner of intramolecular conjugate addition to form the products.
**Scheme I**

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**REFERENCES**

7. All new compounds gave satisfactory analytical data. NMR and IR spectra were taken in CDCl₃ and CHCl₃ solution, respectively. Preparative t.l.c. was run on silica gel HF₂₅₄ (Merck).

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