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

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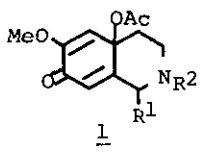
Abstract——Treatment of the N-benzylated p-quinol acetates (1a and 1b) with trifluoroacetic acid gave (±)-3-hydroxydibenzoazabicyclononanes (5a and 5c) in good yields. On the other hand, lead tetraacetate oxidation of 2-benzyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (3a) gave the o-quinol acetate (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 alkaloids[1], aporphine[2], homoaporphine, homoproaporphine, and homomorphinandienone.[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).



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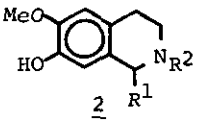

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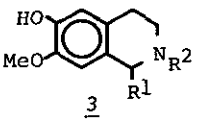

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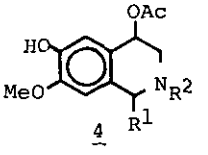

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1a; 2a; 3a; 4a: R^1=H, R^2=-CH_2-(3,4-dimethoxyphenyl)

1b; 2b: R^1=H, R^2=-CH_2-(3,4-methylenedioxyphenyl)

† Dedicated to Prof. T. Kametani on the occasion of his retirement.

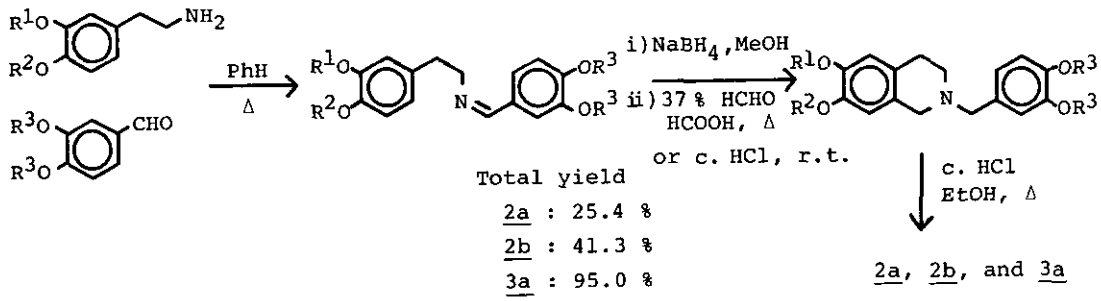
The starting phenols (2a,b and 3a) were prepared from benzaldehyde and β-phenethylamines according to Kametani's method[6] (condensation, reduction, Mannich's reaction, and debenzylation) as shown in Scheme I.

LTA (1.2 eq.) oxidation of 2a (100 mg) in acetic acid (AcOH) (1 ml) gave the p-quinol acetate (1a) [IR (cm^{-1}): 1735 (OAc), 1670, 1650, 1625 (dienone)] quantitaively, which was treated with trifluoroacetic acid (CF_3COOH) (1 ml) in methylene chloride (CH_2Cl_2) (10 ml) at room temperature for 1 hr to give (±)-3-hydroxy-2,9,10-trimethoxydibenzo[*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 (δ 6.39, 6.41, 6.56, 6.58) on its nuclear magnetic resonance (NMR) spectrum and was methylated with diazomethane to give a tetramethyl ether (5b). NMR spectra of both tetramethyl ether (5b) and the authentic sample[8] were completely superimposable.

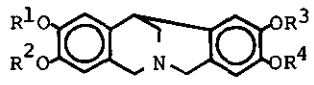
Similarly, oxidation and the subsequent acid treatment of 2b afforded (±)-3-hydroxy-2-methoxy-9,10-methylenedioxydibenzoazabicyclononane (5c), m.p. 203.5-205.5° (dec.), in 50% yield, the structure of which was confirmed by its conversion to the known methyl ether (5d).[9]

Oxidation [LTA (1.2 eq.)] of 3a in CH_2Cl_2 and careful work-up[10] gave the oily o-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 derivatives (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 CF_3COOH at room temperature for 1 hr to afford an amorphous (±)-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 (±)-dibenzo[*c*,*f*]-1-azabicyclo[3.3.1]nonanes (5) was accomplished 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 derivatives (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 together in a manner of intramolecular conjugate addition to form the products.



Scheme I



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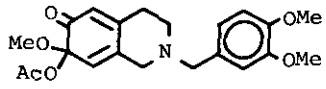
	R^1	R^2	R^3	R^4
5a :	Me	H	Me	Me
5b :	Me	Me	Me	Me
5c :	Me	H	$-CH_2-$	
5d :	Me	Me	$-CH_2-$	
5e :	H	Me	Me	Me



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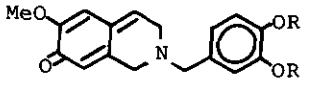

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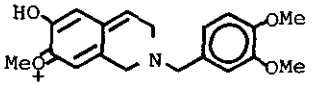

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7. All new compounds gave satisfactory analytical data. NMR and IR spectra were taken in $CDCl_3$ and $CHCl_3$ solution, respectively. Preparative t.l.c. was run on silica gel HF_{254} (Merck).

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