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Studies on Tetrahydroisoquinolines. XXIV.¹⁾ A Synthesis of
Dibenzo[*c,f*]-1-azabicyclo[3.3.1]nonanes and
Dibenzo[*d,g*]-1-azabicyclo[4.3.1]decane²⁾

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Treatment of the *N*-benzyl *p*-quinol acetates **2a** and **2b** with trifluoroacetic acid gave dibenzo[*c,f*]-1-azabicyclo[3.3.1]nonanes (**3a** and **3b**) in good yields. The homologs **3c**, **3d**, and **3e** were similarly prepared from the *N*-phenethyl *p*-quinol acetates **2c**, **2d**, and **2e**, respectively. On the other hand, the *o*-quinol acetate (**17**), obtained from the tetrahydroisoquinolin-6-ol (**9**) by lead tetraacetate oxidation, was rearranged to the 4-acetoxy derivative (**18**). Acid treatment of **18** induced cyclization to construct the same skeleton as that of **3a**.

Keywords—lead tetraacetate oxidation; *p*-quinol acetate; *o*-quinol acetate; trifluoroacetic acid; dibenzo[*c,f*]-1-azabicyclo[3.3.1]nonane; dibenzo[*d,g*]-1-azabicyclo[4.3.1]decane; cyclization

Up to the present, nucleophilic substitution of the so-called *p*-quinol acetates (**1**) at the 8-, 4-, or 4a-position has been reported.³⁾ As a part of our program of studies on the nucleophilic reactions of **1**, we investigated the acid treatment of *N*-benzyl (**2a, b**) and *N*-phenethyl (**2c—e**) *p*-quinol acetates. In general, ease of ring formation among 6- to 8-membered rings is considered to decrease with increase of ring size, *i.e.* preference in the formation of 6-, 7-, and 8-membered rings would be in the order of 6 > 7 > 8. Therefore, the title bicyclic heterocycles (**3**) were anticipated to be obtainable from *N*-benzyl (**2a, b**) and *N*-phenethyl (**2c—e**) *p*-quinol acetates. In other words, nucleophilic attack would occur mostly at the 4-position rather than at the 4a- or 8-position because of the intervention of the *p*-quinone methides (**4**).

The starting phenols (**5a, b**) were prepared by the known method⁴⁾ as follows. Namely, Schiff bases (**6a, b**) prepared from aryl aldehydes (**7a, b**) and phenethylamine (**8**) were subjected to a sequence of reactions (NaBH₄ reduction, Pictet–Spengler reaction, and debenzylation), giving **5a** and **5b**. Through the same route, the 6-hydroxy congener (**9**) was prepared from **7a** and **10**. On the other hand, the tetrahydroisoquinoline (**11**) was converted to phenylacetamides (**12**), which were reduced with LiAlH₄ followed by debenzylation to give the *N*-phenethyl derivatives (**5c—e**).

The *p*-quinol acetate (**2a**) (see Table I), which was obtained quantitatively by Pb(OAc)₄ oxidation of **5a**, was treated with trifluoroacetic acid (TFA) in CH₂Cl₂³⁾ to give **3a**, as expected, in 38% yield. In spite of numerous attempts under a variety of conditions (Lewis acids, solvents, and/or various reaction temperatures), no heterocycles incorporating a 7-membered ring were detected.

The structure of **3a** was supported by both infrared (IR) and nuclear magnetic resonance (NMR) spectral data [IR: 3530 cm⁻¹ and NMR (δ): 6.39, 6.41, 6.56, 6.58 (each 1H, s)] and conversion of **3a** to the known tetramethyl ether (**13a**).⁵⁾ Since we have already prepared isopavine (**14**) by acid treatment of the 4-acetoxy derivative (**15**), which was readily obtainable from the 6-phenolic tetrahydroisoquinoline (**16**),⁶⁾ we applied the same methodology to obtain an authentic sample of **13a**. Thus, the *o*-quinol acetate (**17**)¹⁾ obtained from **9**

Fig. 1

Fig. 2

TABLE I. IR and NMR Spectral Data for the Quinol Acetates

Compound	IR (cm ⁻¹)				NMR (δ)			
	OAc	Dienone			OAc	OMe	OCH ₂ O	Olefinic H
2a	1735	1670	1650	1625	2.03	3.86 (9H)	—	5.81, 6.06
2b	1745	1680	1655	1630	2.02	3.60	5.82	5.75, 6.01
2c	1740	1675	1645	1625	2.05	3.65, 3.80 (6H)	—	5.80, 6.13
2d	1750	1685	1660	1635	2.00	3.60	5.78	5.73, 6.05
2e	1750	1680	1660	1635	2.02	3.60, 3.73, 3.76 (6H)	—	5.75, 6.05
17	1740	1685			2.03	3.36, 3.77 (6H)	—	5.73, 5.79

quantitatively gave the 4-acetoxy derivative (**18**),¹⁾ treatment of which with TFA gave the cyclized product (**19**) in 80% yield. The methyl ether of **19** was identical with **13a**. Similarly, **3b** was prepared from **5b** via **2b** in 50% yield. The methyl ether of **3b**, i.e. **13b** was shown to be identical with an authentic sample⁷⁾ by mixed melting point determination.

By a simple analogy, the *N*-phenethyl *p*-quinol acetate (**2c**) was expected to be cyclized at the 4-position, giving a dibenzo[*d,g*]-1-azabicyclo[4.3.1]decane (**3c**) which incorporated a 7-membered ring. However, another possible mode of cyclization leading to the 10-hydroxytetrahydropyprotoberberine (**20**) seemed to intervene via the intermediacy of the 1,2-dihydroisoquinoline (**21**). Eventually, treatment of **2c** with TFA in CH₂Cl₂ gave the dibenzoazabicyclodecane (**3c**) in 48% yield; this product was different (mp, NMR, and thin-layer chromatography (TLC) behavior) from an authentic sample of **20**,⁸⁾ confirming that no formation of the latter has occurred. Accordingly, the structure of **3c** was unequivocally determined as 3-hydroxy-2,10,11-trimethoxydibenzo[*d,g*]-1-azabicyclo[4.3.1]decane. In addition, the methyl ether of **3c**, i.e. **13c** [mp 152–153 °C (lit.⁹⁾ 154–155 °C)] was not identical with **22**.¹⁰⁾ Thus, it was realized that the *p*-quinone methide (**4**) was reactive enough to be attacked preferentially and the isomerization of **4** to **21** was a time-consuming process, at least under the reaction conditions employed.

Similarly, *p*-quinol acetates (**2d**, **e**) gave dibenzoazabicyclodecanes (**3d**, **e**) in 43% and 49% yields, respectively. Their methyl ethers (**13d**, **e**) were also prepared readily.

Thus, we have developed a new route to dibenzo[*c,f*]-1-azabicyclo[3.3.1]nonanes and -[*d,g*]-1-azabicyclo[4.3.1]decanes by use of the so-called *p*-quinol acetates.

TABLE II. Microanalytical or High-Resolution Mass Spectral Data for New Compounds

Compound	Formula	Molecular weight	Analysis (%)		
			Calcd (Found)		
			C	H	N
3a	C ₁₉ H ₂₁ NO ₄	327.37	69.70 (69.53)	6.47 6.45	4.28 4.42)
3b	C ₁₈ H ₁₇ NO ₄ · 1/4 H ₂ O	315.824	68.44 (68.54)	5.58 5.58	4.44 4.33)
3c	C ₂₀ H ₂₃ NO ₄	341.39	70.36 (70.27)	6.79 6.86	4.10 4.29)
3d	C ₁₉ H ₁₉ NO ₄ · 1/3 C ₆ H ₆	377.422	73.18 (73.24)	6.14 6.44	3.71 3.86)
3e	C ₂₁ H ₂₅ NO ₅	371.422	67.90 (67.93)	6.78 6.84	3.77 3.89)
5a	C ₁₉ H ₂₃ NO ₄	329.38	69.28 (68.91)	7.04 7.05	4.25 4.39)
5b	C ₁₈ H ₁₉ NO ₄	313.34	68.99 (69.02)	6.11 6.11	4.47 4.27)
5c	C ₂₀ H ₂₅ NO ₄	343.41	69.95 (69.96)	7.33 7.28	4.08 3.95)
5d	C ₁₉ H ₂₁ NO ₄ · 1/6 C ₆ H ₆	340.388	70.56 (70.42)	6.51 6.53	4.12 4.07)
5e	C ₂₁ H ₂₇ NO ₅	373.43	67.54 (67.73)	7.29 7.28	3.75 3.74)
6a	C ₂₅ H ₂₇ NO ₄	405.47	74.05 (74.12)	6.71 6.74	3.45 3.60)
6b	C ₂₄ H ₂₃ NO ₄	389.43	74.02 (74.03)	5.95 5.93	3.60 3.44)
9	C ₁₉ H ₂₃ NO ₄	329.38	69.28 (69.09)	7.04 7.19	4.25 4.30)
13c	C ₂₁ H ₂₅ NO ₄	355.1781	(355.1780 ^{a)})		
13d	C ₂₀ H ₂₁ NO ₄	339.1468	(339.1464 ^{a)})		
13e	C ₂₂ H ₂₇ NO ₅	385.1888	(385.1893 ^{a)})		
19 ^{b)}	C ₁₉ H ₂₂ ClNO ₄	363.835	62.72 (62.34)	6.10 5.98	3.85 3.83)
23a	C ₂₅ H ₂₉ NO ₄	407.49	73.68 (73.63)	7.17 7.17	3.44 3.57)
24a	C ₂₆ H ₂₉ NO ₄	419.50	74.44 (74.41)	6.97 6.98	3.34 3.50)
24b	C ₂₅ H ₂₅ NO ₄	403.46	74.42 (74.22)	6.25 6.24	3.47 3.22)
24c	C ₂₇ H ₃₁ NO ₄	433.53	74.80 (74.78)	7.21 7.24	3.23 3.42)
25a	C ₂₆ H ₃₁ NO ₄	421.52	74.08 (74.07)	7.41 7.43	3.32 3.47)
25b	C ₂₅ H ₂₇ NO ₄	405.47	74.05 (73.84)	6.71 6.68	3.45 3.12)
27	C ₂₆ H ₂₉ NO ₄	419.50	74.44 (74.22)	6.97 6.99	3.34 3.45)

a) High-resolution mass spectral data. b) Hydrochloride.

Experimental

All melting points were measured on a Büchi melting point apparatus, and are uncorrected. NMR spectra were taken with a JEOL model JNM-FX100 (100 MHz) or a Hitachi model R-24 (60 MHz) instrument in CDCl₃ solution

TABLE III. NMR Spectral Data for the Dibenzoazabicyclo Derivatives and Tetrahydroprotoberberines

Compound	Chemical shift (δ)		
	OMe	OCH ₂ O	ArH
3a	3.73, 3.81 (6H)	—	6.39, 6.41, 6.56, 6.58
3b	3.82	5.73 (m ^a)	6.33, 6.41, 6.54, 6.58
3c	3.73, 3.80, 3.93	—	6.38, 6.46, 6.56, 6.78
3d^b	3.75	5.88	6.38, 6.42, 6.56, 6.75
3e	3.72, 3.79, 3.89, 3.96	—	6.27, 6.42, 6.53
13a	3.76 (6H), 3.85 (6H)	—	6.44 (2H), 6.66 (2H)
13b	3.78, 3.86	5.81 (m ^a)	6.40, 6.44, 6.63, 6.66
13c	3.73, 3.80, 3.84, 3.93	—	6.40, 6.45, 6.50, 6.78
13d	3.75, 3.84	5.88	6.41, 6.42, 6.49, 6.76
13e	3.72, 3.78, 3.84, 3.88, 3.96	—	6.26, 6.44, 6.48
14	3.77, 3.79, 3.86	—	6.43 (2H), 6.64, 6.74
20	3.77, 3.83, 3.86	—	6.54, 6.60 (2H), 6.73
22	3.86, 3.87, 3.88, 3.89	—	6.56, 6.58, 6.63, 6.70

^a) Multiplet. ^b) The signal due to protons (2H) of benzene incorporated into the crystals appeared at δ 7.32.

TABLE IV. NMR Spectral Data for Other New Compounds

Compound	Chemical shift (δ)				
	OMe	OCH ₂ O	NCH ₂ Ar	OCH ₂ Ph	Others
5a	3.78, 3.82 (6H)	—	3.47, 3.57	—	
5b	3.77	5.75	3.45, 3.52	—	
5c	3.84, 3.86, 3.88	—	3.60	—	
5d	3.84	5.90	3.59	—	7.32 (1H) ^a)
5e	3.82, 3.85 (9H)	—	3.60	—	
6a	3.74, 3.84, 3.89	—	—	5.04	7.94 (CH=N)
6b	3.74	5.86	—	5.01	7.82 (CH=N)
9	3.71, 3.80 (6H)	—	3.45, 3.53	—	
23a	3.83 (9H)	—	3.63	5.03	
23b	3.78	5.77	3.61	5.00	
24a	3.78, 3.82 (6H)	—	3.43, 3.52	4.98	
24b	3.79	5.83	3.42, 3.50	4.99	
25a	3.78 (9H)	—	3.47	5.00	2.25 (NMe)
25b	3.80	5.82	3.39	5.03	2.22 (NMe)
26	3.75 (9H)	—	3.60	4.98	
27	3.70, 3.77 (6H)	—	3.43, 3.50	4.95	

^a) The signal of protons (2H) of benzene incorporated into the crystals.

with Me₄Si as an internal standard. IR spectra were run on a Hitachi model 215 spectrometer in CHCl₃ solution. Preparative TLC was performed on Silica gel HF₂₅₄ (Merck). Microanalytical data for all new, crystalline compounds are listed in Table II. EtOH denotes 99% aq. EtOH.

1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4-dimethoxybenzyl)- (5a), 1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4-methylenedioxybenzyl)- (5b), and 1,2,3,4-Tetrahydro-6-hydroxy-7-methoxy-2-(3,4-dimethoxybenzyl)isoquinoline (9): Typical Procedure—A stirred solution of **8** (6.7 g) and **7b** (3.91 g) in benzene (200 ml) was refluxed for 2.5 h. Evaporation of the solvent under reduced pressure gave the Schiff base **6b** (7.4 g; 70%), mp 80–82 °C (EtOH). NaBH₄ (1.31 g) was added portionwise to a solution of **6b** (7 g) in MeOH (100 ml) and the whole was stirred for 30 min at room temperature. Usual work-up of the reaction mixture gave oily **23b** (7.05 g; 100%). A mixture of **23b** (7 g), 87% formic acid (10 ml), and 37% formalin (10 ml) was heated on a boiling water bath for 3 h.

After condensation followed by basification (sat. aq. NaHCO_3 solution) of the reaction mixture, the product was extracted with CH_2Cl_2 . Usual work-up of the extract and subsequent chromatographic purification on silica gel gave the 1,2,3,4-tetrahydroisoquinoline (**24b**) (4.29 g; 59%), mp 99–100 °C (EtOH) and the *N*-methylamine (**25b**) (2.26 g; 31%), mp 80.5–81.5 °C (iso-PrOH). A solution of **24b** (2 g) in a mixture of EtOH (20 ml) and conc. HCl (20 ml) was refluxed for 3 h. The reaction mixture was diluted with water and the whole was washed with ether. After basification of the aqueous layer with sat. aq. NaHCO_3 solution, the product was extracted with CHCl_3 . Usual work-up of the extract gave the phenolic base (**5b**) (1.5 g; 96%), mp 166–167 °C (MeOH). **6a**: 80.5%, mp 103–104 °C (iso-PrOH). **23a**: 85.9%, mp 52–54 °C (ether). **26**: 98%, oil. **25a**: 10.6%, mp 58–60 °C (ether). **24a**: 66.5%, mp 106–107 °C (EtOH). **5a**: 50.8%, mp 169–171 °C (EtOH).

The Pictet–Spengler reaction of **26** gave none of the *N*-methylamine. Thus, treatment of **26** (140 mg) with 37% formalin (0.5 ml) in MeOH (5 ml) for 30 min at room temperature and subsequent treatment with conc. HCl (0.5 ml) for 2 h at room temperature gave exclusively the 1,2,3,4-tetrahydroisoquinoline (**27**) (141 mg; 98%), mp 108.5–109.5 °C (EtOH). **9**: 100%, mp 149–150 °C (MeOH).

1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4-dimethoxyphenethyl)- (5c), 1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4-methylenedioxyphenethyl)- (5d), and 1,2,3,4-Tetrahydro-7-hydroxy-6-methoxy-2-(3,4,5-trimethoxyphenethyl)isoquinoline (5e): Typical Procedure—Heating of a mixture of **11**⁴⁾ and 3,4-dimethoxyphenylacetic acid (19.3 g) at 160 °C (bath temperature) for 4 h gave the amide (**12c**) (11.8 g; 96%) as a pale yellow oil. LiAlH_4 reduction of **12c** (200 mg) in a mixture of tetrahydrofuran (THF) and ether gave the 2-phenethyl-1,2,3,4-tetrahydroisoquinoline (**24c**) (176 mg; 91%), colorless needles, mp 102–103 °C (benzene–*n*-hexane). Hydrogenolysis of **24c** (4.7 g) with 13.7% Pd–C (1.74 g) for 2 h and usual work-up of the reaction mixture gave the phenolic 1,2,3,4-tetrahydroisoquinoline (**5c**) (3.52 g; 94.6%), colorless needles, mp 145–147 °C (CHCl_3). **12d**: 84.7%, oil. **12e**: 90.2%, oil. **24d**: 100%, oil. **24e**: 100%, oil. **5d**: 57.9%, colorless needles, mp 168–169 °C (benzene–*n*-hexane). **5e**: 62.1%, colorless needles, mp 157–158 °C (benzene–*n*-hexane).

3-Hydroxy-2,9,10-trimethoxy- (3a) and 3-Hydroxy-2-methoxy-9,10-methylenedioxydibenzoazabicyclononane (3b) and 3-Hydroxy-2,10,11-trimethoxy- (3c), 3-Hydroxy-2-methoxy-10,11-methylenedioxy- (3d), and (±)-3-Hydroxy-2,10,11,12-tetramethoxydibenzoazabicyclodecane (3e): Typical Procedure—A solution of **5c** (100 mg) in AcOH (1 ml) was oxidized as usual³⁾ to give the *p*-quinol acetate (116.6 mg), which was treated with $\text{CF}_3\text{CO}_2\text{H}$ (1 ml) in CH_2Cl_2 (10 ml) for 1 h at room temperature to give **3c** (47.8 mg; 48%), mp 211–212 °C (dec.) (benzene–*n*-hexane). Non-identity of **3c** with 10-hydroxy-2,3,11-trimethoxytetrahydropyrotuberberine (**20**), mp 201–204 °C¹⁰⁾ (acetone) was confirmed by comparison of their IR and NMR spectrum. **3a**: 24.9%, mp 213–215 °C (EtOH). **3b**: 50%, mp 203.5–205.5 °C (dec.) (EtOH). **3d**: 43%, mp 198–199 °C (benzene–*n*-hexane). **3e**: 49%, mp 222–225 °C (dec.) (benzene–*n*-hexane).

2-Hydroxy-3,9,10-trimethoxydibenzoazabicyclononane (19)—A solution of **9** (50 mg) in CH_2Cl_2 (10 ml) was oxidized as usual¹⁾ to give the *o*-quinol acetate (**17**); on standing at room temperature for 15 h, this product gave the 4-acetoxy compound (**18**). Treatment of **18** with $\text{CF}_3\text{CO}_2\text{H}$ as above followed by purification by preparative TLC (CHCl_3 : MeOH = 10:1) gave an amorphous mass of **19** (40 mg; 80%). Hydrochloride: mp 238–240 °C (MeOH).

2,3,9,10-Tetramethoxy- (13a) and 2,3-Dimethoxy-9,10-methylenedioxydibenzoazabicyclononane (13b) and 2,3,10,11-Tetramethoxy- (13c), 2,3-Dimethoxy-10,11-methylenedioxy- (13d), and 2,3,10,11,12-Pentamethoxydibenzoazabicyclodecane (13e)—A solution of the starting phenolic base in MeOH was methylated with diazomethane by a conventional procedure. **13a**: 47% from **3a**, 59% from **19**; hydrochloride, mp 278–279 °C (EtOH) (lit.⁵⁾ 280–282 °C). **13b**: 47%; hydrochloride, 268–270 °C (dec.) (MeOH). **13c**: 46%, mp 152–153 °C (EtOH) (lit.⁹⁾ 154–155 °C). **13d**: 57%, mp 219–220 °C (EtOH–ether). **13e**: 62%, mp 145–146 °C (EtOH–ether).

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