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Short Communication

Benzofuro[2,3-b]benzofurans and benzofuro[3,2-b] benzofurans from 2-hydroxyacetophenones†

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Abstract

Yamamura's modification of the Clemmensen reduction provided a one-step route to symmetrical benzofuro[2, 3-b]benzofurans and benzofuro[3,2-b]benzofurans from 2-hydroxyacetophenones.

Keywords: Acetophenones, benzofurans

Yamamura's modification[1] of the Clemmensen reduction, when applied to 2-hydroxyacetophenones (**1a–e**)[2], gave little or no Clemmensen products, but instead gave symmetrical benzofuro[3,2-b]benzofurans (**2a, b**) and benzofuro[2,3-b]benzofurans (**3b-e**) (Table I). Although yields were not optimized for compounds **2** and **3**, they were the major products identified in each case, and this is probably the best way to make them.

Products **2** and **3** resulted from pinacol reduction followed by acid-catalyzed dehydrations to **2** and rearrangement to **3**. All three of these steps are known separately in related systems: 1) Yamamura's conditions were used to convert a *cage* diketone to the corresponding pinacol through an intramolecular pinacol reduction in 74% yield;[3] 2) Certain pinacols have been previously converted under acidic conditions to benzofuro[3,2-b]benzofurans (**2**);[4] 3) Acid-catalyzed rearrangements of benzofuro[3,2-b]benzofurans (**2**) to benzofuro[2,3-b]benzofurans (**3**) have been reported.[5]

In the **1a–b** cases, with no R″ substituent *meta* to the hydroxyl group, significant amounts of the simple pinacol dehydration products (**2a–b**) were found. However, with **1c-e**, with alkyl or methoxyl R″ substituents *meta* to the hydroxyl groups, rearrangement products **3c-e** predominated, presumably because the R″ group provided stabilization to the rate-determining transition state adjacent to rearrangement intermediates (**4**).

In the case of **1e**, with R = Ph, a third type of product, **5**, isomeric with **2** and **3**, formed, presumably via the hydride shift shown in **6**. The structure of **5** was deduced from NMR and

†Dedicated to Prof. S. C. Bhattacharyya.
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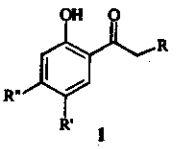
	R	R'	R''
a	H	H	H
b	H	Me	H
c	H	Me	Me
d	H	H	OMe
e	Ph	Me	Me



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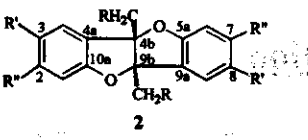

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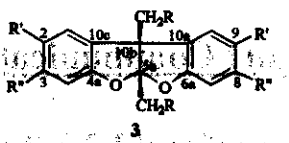

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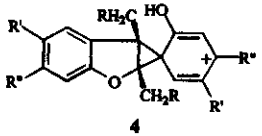

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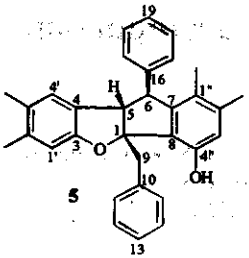

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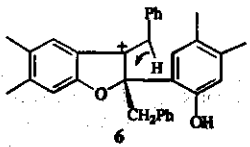

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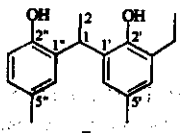

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mass spectra: the lack of coupling between H-5 and H-6 is consistent with the 90° dihedral angle between them with the 6-phenyl group *exo*, and this stereochemistry is strongly supported by the downfield shifts for 1″-C, 1″-H, and 5-H. In the case of **1b**, the normal Clemmensen product (2-ethyl-4-methylphenol) and **7**, presumably formed by a Friedel–Crafts reaction between the Clemmensen product and the alcohol from simple reduction of the ketone (**1b**), were also observed.

Under the same conditions, two compounds related to **1a-e** also gave some pinacol-derived products: 1) benzyl phenyl ketone, lacking an *ortho* hydroxyl group, still gave the pinacols[6] (*meso*, 11%; dl, 2%), along with the Clemmensen product (bibenzyl, 16%) and an alcohol dehydration product (*E*-stilbene, 5%); 2) Salicylaldehyde gave pinacol-dehydration product 2-(2-hydroxyphenyl)-benzofuran[7] (18%), isomeric with benzofurobenzofurans **2** and **3**.

Experimental

Reactions of 2-hydroxyacetophenones with Zn-HCl-ether: General procedure

Dry ether (25 ml) in a 100 ml round-bottomed flask equipped with a $CaCl_2$ drying tube was saturated with dry HCl gas at 0°C. Ketone (4 mmol) was added and dissolved by stirring. Activated zinc powder[1] (20 mmol) was added in several portions over a period of 1 h. Stirring was continued for 1 h each at 0°C and at 25°C. The mixture was poured on to crushed ice, made

Table I
Isolated yields from the zinc/HCl reduction of 2-hydroxyacetophenones

Reactant	Products (% yield)
1a	**2a** (50)
1b	**2b** (15), **3b** (21), **7** (9), 2-ethyl-4-methylphenol (4)[4]
1c	**3c** (16)
1d	**3d** (15)
1e[2]	**3e** (25), **5** (14)
$PhCOCH_2Ph$	Meso-pinacol (11), d,l-pinacol (2), *E*-stilbene (5), bibenzyl (16)
Salicylaldehyde	2-(2-Hydroxyphenyl)-benzofuran (18)

alkaline with solid Na_2CO_3 (4 g), and extracted with ether (4 × 15 ml). The combined ether solutions were washed with water (2 × 10 ml), dried, and evaporated, and the residue was chromatographed on silica gel.

*4b,9b-Dimethylbenzofuro[3, 2-b]benzofuran (**2a**)*

The general method applied to 2-hydroxyacetophenone gave an yellowish solid, eluted with petroleum ether–ether (99:1), which on recrystallization from aqueous ethanol gave **2a**: m. p. 123°C (lit.[8] 129°C). IR (Nujol) 3049, 2975, 1594, 1479, 1461, 1267, 1239, 1086, 998, 752, 745 cm^{-1}. ^1H NMR: δ 7.43 (dd, 7.5 and 1.3 Hz, 2 H, H-4), 7.23 (m, 2 H, H-2), 6.95 (dd, 7.5 and 0.9 Hz, 2 H, H-3), 6.79 (d, 8.1 Hz, 2 H, H-1), 1.77 (s, 6 H, Me). ^{13}C NMR: δ 158.4 (C-10a), 130.8 (C-4), 128.7 (C-4a), 124.5 (C-2), 120.9 (C-3), 110.7 (C-1), 96.0 (C-4b), 20.3 (Me).

*2,5a,9,10b-Tetramethylbenzofuro[2,3-b]benzofuran (**3b**)*

The general method applied to 2-hydroxy-5-methylacetophenone gave an yellowish solid which on recrystallization from aqueous ethanol gave **3b**: m. p. 204°C. IR (Nujol) 3300, 2980, 2950, 2930, 1600, 1580, 1260, 1080, 900, 800 cm^{-1}. ^1H NMR: δ 7.09 (s, 2 H, H-1), 6.93 (m, 2 H, H-3), 6.73 (d, 8.5 Hz, 2 H, H-4), 2.31 (s, 6H, 2-Me), 1.76 (s, 3 H, 5a-Me), 1.67 (s, 3 H, 10b-Me). ^{13}C NMR: δ 154.3 (C-4a), 132.6 (C-2), 130.9 (C-10a), 128.8 (C-3), 124.7 (C-5a), 123.1 (C-1), 109.5 (C-4), 56.6 (C-10b), 21.0 (2-Me, 5a-Me), 20.3 (10b-Me).

*3,4b,8,9b-Tetramethylbenzofuro[3,2-b]benzofuran (**2b**)*

Elution of the nonpolar material with petroleum ether–ether (96:4 and 95:5) gave crystalline fractions which proved to be 1:1 and 3:2 mixtures of **3b** and **2b**,[4] identified by comparison of its NMR parameters with those of **2a**. **2b**: ^1H NMR: δ 7.22 (d, 1.5 Hz, 2 H, H-4), 7.02 (dd, 8.0 and 1.5 Hz, 2 H, H-2), 6.68 (d, 8.0 Hz, 2 H, H-1), 2.31 (s, 6 H, 3-Me), 1.74 (s, 6 H, 4b-Me). ^{13}C NMR: δ153.0 (C-10a), 131.4 (C-4), 130.3 (C-3), 128.6 (C-4a), 124.6 (C-2), 110.2 (C-1), 96.1 (C-4b), 20.7 (Me).

*2,3,5a,8,9,10b-Hexamethylbenzofuro[2,3-b]benzofuran (**3c**)*

The general method applied to 2-hydroxy-4,5-dimethylacetophenone gave **3c** as a petroleum ether–insoluble solid which was recrystallized from aqueous ethanol. **3c**: m. p. 234°C. IR (Nujol) 3000–2860, 1660, 1610, 1510, 1290, 1250, 1085, 1030, 915, 850, 775 cm^{-1}. ^1H NMR: δ 7.00 (s, 2 H, H-1), 6.62 (s, 2 H, H-4), 2.18 (s, 6 H, 3-Me), 2.15 (s, 6 H, 2-Me), 1.72 (s, 3 H, 5a-Me), 1.62 (s, 3 H, 10b-Me). ^{13}C NMR: δ 154.7 (C-4a), 136.9 (C-3), 130.2 (C-10a), 129.5 (C-2), 124.7 (C-5a), 123.4 (C-1), 111.1 (C-4), 56.4 (C-10b), 21.0 (2-Me, 5a-Me), 20.2 (10b-Me), 20.1 (3-Me).

*3,8-Dimethoxy-5a,10b-dimethylbenzofuro[2,3-b]benzofuran (**3d**)*

The general method applied to 2-hydroxy-4-methoxyacetophenone followed by recrystallization from ethanol of the fraction eluted with petroleum ether–benzene (95:5) gave **3d**: m. p. 147°C. IR (KBr) 2921, 2852, 1622, 1604, 1501, 1445, 1292, 1196, 1160, 1076, 1059,

949 cm^{-1}. ^1H NMR: as reported.[5] ^{13}C NMR: δ 160.4 (C-3), 157.5 (C-4a), 127.7 (C-1), 125.8 (C-5a), 125.3 (C-10a), 107.6 (C-2), 96.5 (C-4), 55.6 (C-10b), 55.5 (OMe), 21.1 (5a-Me), 20.3 (10b-Me).

*5a,10b-Dibenzyl-2,3,8,9-tetramethylbenzofuro[2,3-b]benzofuran (**3e**)*

The general method applied to 2-phenacetyl-4,5-dimethylphenol gave, as a petroleum ether–insoluble solid, **3e**: m. p. 234°C. IR (KBr) 3040, 3020, 2920, 1620, 1600, 1480, 1450, 1270, 1180, 860, 720, 700 cm^{-1}. ^1H NMR: δ 7.0–7.4 (m, 10 H, phenyls), 6.93 (s, 2 H, H-1), 6.73 (s, 2 H, H-4), 3.56 (s, 2 H, 5a-CH_2), 3.32 (s, 2 H,10b-CH_2), 2.24 (s, 6 H, 3-Me), 2.23 (s, 6 H, 2-Me). ^{13}C NMR: δ 155.3 (C-4a), 137.5 (C-3), 136.6 and 134.9 (Ph-*ipso*), 130.9 and 130.8 (Ph-*m*), 129.3 (C-2), 129.0 (C-10a), 127.8 and 127.7 (Ph-*o*), 126.6 and 126.5 (Ph-*p*), 124.8 (C-1), 124.1 (C-5a), 111.3 (C-4), 60.5 (C-10b), 40.3 and 40.1 (CH_2), 20.5 and 19.8 (2-Me, 3-Me). Mass (*m/z*): 446 (M, 100%), 355, 264.

Compound 5

Chromatography of the petroleum ether–soluble products of the above reaction with petroleum ether–ethyl acetate (95:5) gave a white solid which was recrystallized from ethanol to give crystals of **5**: m. p. 196°C. IR (KBr) 3320, 2950, 1600, 1300, 1270, 1110, 1000, 850, 700 cm^{-1}. ^1H NMR: δ 6.85-7.35 (m, 10 H, phenyls), 7.08 (s, 1 H, H-4′), 6.65 (s, 1 H, H-1′), 6.60 (s, 1 H, H-3″), 5.50 (s, 1 H, OH), 4.58 (s, 1 H, H-5), 3.75 (s, 1 H, H-6), 3.56 and 3.16(d, 14.2 Hz, 1 H, H-9), 2 × 2.16 and 2.14 (s, 3 H, 2′-Me, 3′-Me, 2″-Me), 1.76 (s, 3H, 1″-Me). ^{13}C NMR: δ 156.3 (C-3), 151.9 and 151.8 (C-8, C-4″), 143.3 and 142.6 (C-16, C-7), 139.7 (C-2″), 136.8 (C-2′), 136.4 (C-10), 130.4 (C-18), 128.7 (C-3′), 128.1 (C-17), 127.9 (C-4), 126.5 (C-19), 126.3 (C-13), 125.6 (C-1″), 125.4 (C-4′), 118.0 (C-3″), 111.5 (C-1′), 101.2 (C-1), 60.0 (C-5), 57.2 (C-6), 43.8 (C-9), 20.1 and 20.0 and 19.8 (C-2′, C-3′, C2″), 15.9 (C-1″). Satisfactory elemental analysis. Mass (*m/z*): 446 (M), 355 (100%), 325, 281, 267, 221, 207, 191, 147.

Compound 7

Elution of the nonpolar material from the **1b** reaction above with petroleum ether–ether (94:6) gave 1-(3-ethyl-2-hydroxy-5-methylphenyl)-1-(2-hydroxy-5-methylphenyl)-ethane (**7**): m. p. 125°C. IR (Nujol) 3193, 3026, 2981, 2929, 1505, 1462, 1213, 812 cm^{-1}. ^1H NMR: δ 7.10 (br s, 1H, H-6″), 7.07 (brs, 1 H, H-6′), 6.83 (dd, 8.1 and 1.8 Hz, 1 H, H-4″), 6.81 (brs, 1 H, H-4′), 6.64 (d, 8.1 Hz, 1 H, H-3″), 5.87 (brs, 1 H, OH), 5.77 (brs, 1 H, OH), 4.56 (q, 7.1 Hz, 1 H, H-1), 2.57 and 2.55 (m, 2 H, CH_2), 2.27 and 2.26 (s, 3 H, H-5′, H-5″), 1.63 (d, 7.1 Hz, 3 H, H-2), 1.19 (t, 7.5 Hz, 3 H, 3′-Me). ^{13}C NMR: δ 149.9 (C-2′), 148.3 (C-2″), 131.1 (C-3′), 130.7 (C-1′ and C-1″), 130.1 (C-5′ and C-5″), 127.9 (C-6″), 127.7 (C-6′ and C-4″), 124.9 (C-4′), 115.6 (C-3″), 30.3 (C-1), 23.2 (CH_2), 20.9 (5″-Me), 20.8 (5′-Me), 19.9 (C-2), 13.9 (3′-Me).

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