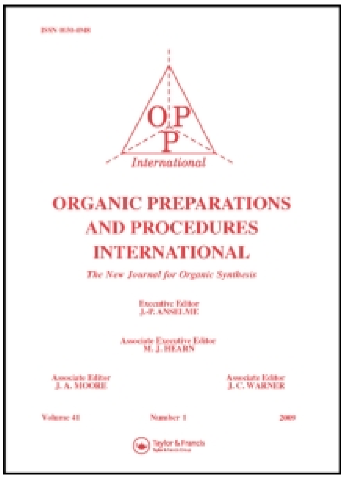

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SYNTHESIS OF TWO METHYLBENZOSUBERONES AND A DIMETHYLBENZOCYCLOHEPTENE

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SYNTHESIS OF TWO METHYLBENZOSUBERONES AND A DIMETHYLBENZOCYCLOHEPTENE

Submitted by (04/13/92)

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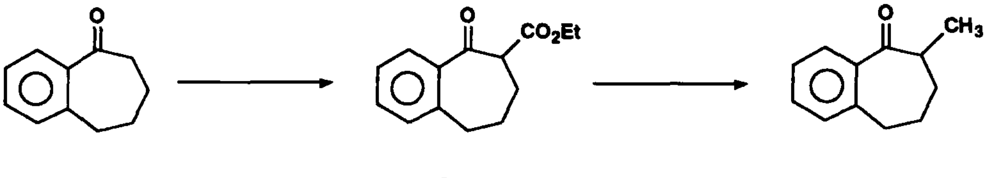
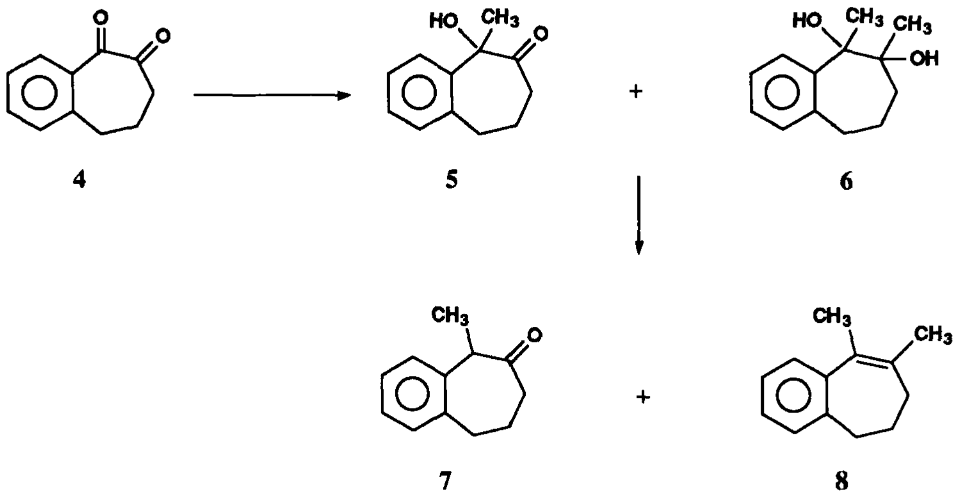
In connection with the exploration of routes to benzazaazulenes,[1] two methylbenzosuberones, **3** (6-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one) and **7** (5-methyl-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one) were required. A by-product of the preparation of **7** was 5,6-dimethyl-8,9-dihydro-7*H*-benzocycloheptene (**8**).

Benzosuberone (6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-one) (**1**) was prepared and converted to **2** as previously described.[2] Treatment of **2** sequentially with NaH, MeI, and methanolic $Ba(OH)_2 \cdot 8H_2O$ gave **3** in 59% yield from **1** and 53% yield from phenylpentanoic acid. A synthesis of **3** in 37% yield from phenylpropanol has been reported.[3]



1 **2** **3**



For the synthesis of **7** (5-methyl-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-5-one), **1** was oxidized with SeO_2 to **4** (75%) and the latter treated with MeMgI to give a mixture presumed to be **5** and **6**. Reaction of the mixture of products with Zn, conc. hydrochloric acid, and CH_3CO_2H formed **7** (ca. 58% from **4**, 46% from **1**) and **8** (ca. 29% from **4**, 22% from **1**). Compound **8** (5,6-dimethyl-8,9-dihydro-7*H*-benzocycloheptene) was postulated to be formed from **6** by hydrogenolysis of the benzylic hydroxyl followed by acid-catalyzed dehydration. The preparation of **7** from 1-oxo-1,2,3,4-tetrahydronaphthalene by a Wittig reaction, Prevost oxidation, and rearrangement has been reported.[4]

EXPERIMENTAL SECTION

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Spectra were recorded on a Cary Model 115 (UV-vis), and Perkin-Elmer Model 21 (IR) spectrophotometers. Elemental analyses were performed by B. Nist and C. H. Ludwig of this Department.

6-Methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (3).- A solution of 3.25 g (14 mmol) of **2** in 20 ml of purified dioxane[5] was added dropwise (1 hr) with stirring to a gently refluxing mixture of 0.34 g (14 mmol) of sodium hydride in 10 mL of dioxane. After an additional 30 min, a solution of 2 g (14 mmol) of methyl iodide in 10 mL of dioxane was added dropwise. The mixture was refluxed with stirring overnight, cooled, and filtered. To the filtrate residue after solvent removal (steam bath), was added a solution of 19.5 g of barium hydroxide octahydrate in 65 mL of water and 32 mL of methanol. The mixture was refluxed vigorously for 20 hrs. Water (300 mL) was then added and the solution was extracted with three 50-mL portions of ether. The combined extracts were washed with water (25 mL), and dried ($MgSO_4$) and concentrated. Distillation of the residue gave 2 g (82%) of **3**, bp 111-112°/1.5 mm, $n_D^{25°}$ 1.5496. UV (EtOH): λ_{max} (D_{max}) at 245 (1.93) and 286 (0.28) nm; lit[3] λ_{max} at 245 and 284 nm. IR: 971, 1220, 1449, 1599, 1681 (C=O), 2857 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.93; H, 8.24

8,9-Dihydro-5*H*,7*H*-benzocyclohepta-5,6-dione (4).- In the manner described by Cook *et al.*,[6] from the oxidation of 25.7 g (161 mmol) of **1** with 18.2 g (164 mmol) of freshly sublimed SeO_2 was obtained 20.9 g (75%) of **4** as a yellow oil, bp 128-132°/0.4 mm, lit[6] bp 128-132°/0.4 mm. UV (C_2H_5OH): λ_{max} (D_{max}) at 252 (1.63) and 292 (0.76) nm. IR: 1176, 1250, 1292, 1399, 1449, 1600, 1681, 3390, 3279 cm^{-1}.

5-Methyl-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-5-one (7) and 5,6-Dimethyl-8,9-dihydro-7*H*-benzocycloheptene (8).- A solution of 21.3 g (150 mmol) of methyl iodide in 50 mL of sodium-dried ether was added dropwise to 3.6 g (0.15 g-atm) of magnesium ribbon in 50 mL of dry ether. The mixture was refluxed for 1 hr and then cooled. A solution of 10 g (575 mmol) of **4** in 25 mL of dry ether was added dropwise with stirring. Stirring was continued for 15 hrs, 100 mL of saturated NH_4Cl solution was added, and the ether layer was separated. The aqueous layer was extracted with ether (2 × 25 mL) and the combined ethereal solutions were dried ($MgSO_4$). Removal of the solvent and distillation of the residue gave a first fraction of 0.45 g, bp 77-106°, followed by 7.65 g (ca. 70%), bp 106-138°/3 mm, presumed to be a mixture of 5-hydroxy-5-methyl-5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one (**5**) and 5,6-dihydroxy-5,6-dimethyl-5,7,8,9-tetrahydro-7*H*-benzocycloheptene (**6**).

To the above mixture (8 g) was added 17.4 g of Zn, 17 mL of acetic acid, and 9.9 mL of conc. hydrochloric acid and the mixture was heated (steam cone) with stirring. Two further 9.9 mL portions of hydrochloric acid were added at 30 min intervals. After another 30 min, the mixture was cooled and filtered. Water (30 mL) was added to the filtrate and the whole extracted twice with ether (ca. 30 mL). The combined extracts were washed with 10% $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated to afford an oil which was fractionally distilled at 2.5 mm to give 1.67 g (ca. 29%), of **8**, bp 70-72°, $n_D^{25°}$ 1.5445. UV (C_2H_5OH): λ_{max} (D_{max}) at 245 (2.04) nm. IR: 1369, 1449, 1481, 2857 cm^{-1}. The compound readily reduced potassium permanganate.

Anal. Calcd. for $C_{13}H_{16}$: C, 90.64; H, 9.46. Found: C, 90.23; H, 9.46

A 3.48 g (ca. 58%) fraction of **7**, bp 104-106°, $n_D^{25°}$ 1.5425, was collected. UV (C_2H_5OH): λ_{max} (D_{max}) at 267 and 274 (1.61 and 1.55, split peak), 282 (0.86 shoulder), and 292 (0.67 shoulder) nm. IR: 1360, 1449, 1481, 1695 (C=O), 2857 cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.37; H, 8.11

A middle fraction of 1.32 g, bp 72-98°, was indicated to be a mixture of **7** and **8** by its UV and IR spectra.

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SYNTHESIS OF ESTRIOL 16α-4',5'-DEHYDROGLUCURONIDE

Submitted by (4/29/92)

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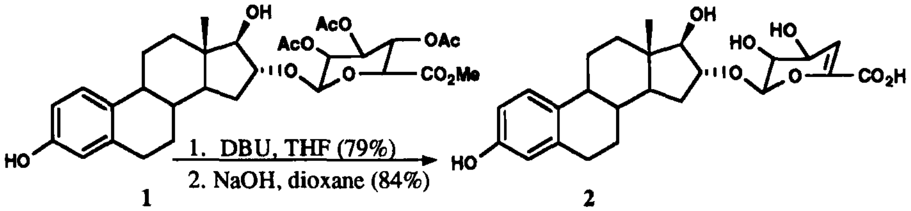
Glucuronides of biologically active compounds are essential as reference standards for analytical procedures and in basic research. For a total estriol immunoassay, we needed analytically-pure estriol 16α-glucuronide; HPLC analysis of commercial as well as our own synthetic estriol 16α-glucuronide[1] revealed that the material contained two components. The unknown material was tentatively identified as estriol-16α-4',5'-dehydroglucuronide **2**. We undertook the synthesis of **2** to confirm the structure of the unknown material and evaluate its cross-reactivity in our immunoassay. As shown below, elimination of acetic acid from glucuronate **1**[2] gave an intermediate α,β-unsaturated glucuronate which was hydrolyzed to the desired estriol 16α-4',5'-dehydroglucuronide **2** in 66% overall yield. The purity of other glucuronides has recently come under scrutiny[3] and this procedure should facilitate the identification of 4',5'-dehydroglucuronide "impurities" present in either synthetic or commercial preparations.



EXPERIMENTAL SECTION

Proton (500 MHz) and carbon (125 MHz) spectra were recorded on a GE-500 NMR spectrometer and mass spectra (FAB) were recorded on a Nermag 3010 spectrometer. Melting points were determined in open capillaries in a Thomas melting point apparatus and are uncorrected. All solvents were HPLC grade and used as is except for tetrahydrofuran (THF) which was distilled from sodium benzophenone ketyl immediately prior to use. Silica gel (EM grade 60) was purchased from Aldrich.