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Synthesis of Optically Active Bis(1-mesitylethyl) Ethers

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The racemic and meso bis(1-mesitylethyl) ethers were synthesized. The optical resolution of the dicarboxylic acid derivative showed that the high-melting compounds were racemic in form and the low-melting isomers meso in form.

In a previous paper,[1] we reported that 1-(4-substituted 2,6-dimethylphenyl)-1-ethanol gave meso and racemic bis[1-(4-substituted 2,6-dimethylphenyl)ethyl] ethers in the presence of a Lewis acid such as *p*-toluenesulfonic acid.

This paper will describe a synthesis of optically active and meso bis(1-mesitylethyl) ethers from mesitylene. This experiment clarified unambiguously that the high-melting isomer, **1B** (mp 119—120 °C), was racemic and the low-melting one, **1A** (mp 98.5—99.5 °C), was meso in form.

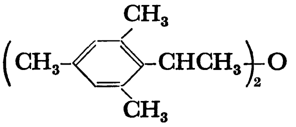
Results

Optically active bis(1-mesitylethyl) ethers (+)-**1B** and (−)-**1B** were synthesized from 2,4,6-trimethylbenzaldehyde by the following method. 2,4,6-Trimethylbenzaldehyde was treated with hydrogen cyanide in the presence of calcium oxide to give a cyanohydrin, **2**, in a 90% yield. When **2** was heated under reflux in absolute benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, a dibenzyl ether, **3**, was obtained in a 60% yield. Though, in the IR spectrum of **3**, the absorption for nitrile groups was not observed, an elemental analysis and the NMR spectrum supported the structure. The separation of meso and racemic isomers was unsuccessful (on TLC showed only a single spot), and in the NMR spectrum the presence of a hindered rotation was not observed. The treatment of **3** with hydrogen chloride in absolute ethanol gave a carboxamide, **4**. Again, the separation of isomers was unsuccessful (by either recrystallization or column chromatography). The hydrolysis of **4**, followed by methylation, gave a dimethyl ester. Careful chromatography over silica gel of the crude products and elution with acetone–$CHCl_3$ (3:97) gave the dimethyl ester samples with a mp of 114—116 °C, **6A**, and a mp of 167—168 °C, **6B**, in a ratio of 1:2. In the NMR spectra of these esters, the aromatic methyls at C_2 and C_6 appeared as singlets at 2.10 and 2.20 ppm respectively. Upon hydrolysis, dicarboxylic acids (**5A**, mp 199—199.5 °C (dec) and **5B**, mp 230—231 °C (dec) respectively) were obtained. On the other hand, the treatment of the carboxamide, **7**, which was obtained directly from the cyanohydrin, **2**, and of the methyl ester, **8**, with *p*-toluenesulfonic acid in benzene did not give the corresponding esters, **4** and **6**.

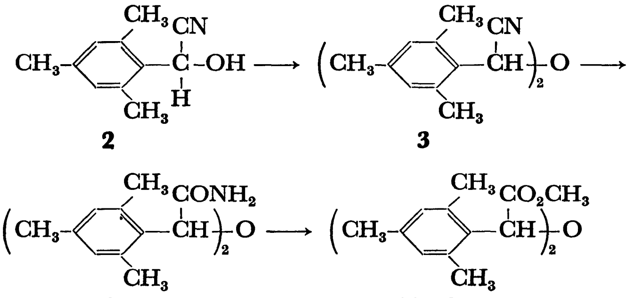
The treatment of the dicarboxylic acid **5B** with cinchonine and cinchonidine in methanol and the recrystallization of each salt gave optical active salts **I**; $[\alpha]^{20}_{D}+1°$ (c=1, MeOH) and **II**; $[\alpha]^{20}_{D}-29°$ (c=1, MeOH). The subsequent acid hydrolysis of these salts gave a (+)-dicarboxylic acid, (+)-**5B**, $[\alpha]^{20}_{D}+223.5°$ (c=1, MeOH) and a (−)-dicarboxylic acid, (−)-**5B**, $[\alpha]^{20}_{D}-235°$ (c=1, MeOH), respectively. The carboxylic acids gave the (+)-**6B** and (−)-**6B** esters. The reduction of the **6A**, (+)-**6B**, and (−)-**6B** esters with lithium aluminum hydride gave **9A**, (+)-**9B**, and (−)-**9B** respectively. The NMR spectra of these alcohols indicated the presence of a hindered rotation of the benzene rings. The meso isomer **9A** showed a broad singlet ($W_{1/2}$=12 Hz) at 2.15 ppm for two aromatic methyl resonances at C_2 and C_6 at room temperature; this singlet changed to two signals at a lower temperature, whereas the racemic **9B** showed two broad lines at 1.50 and 2.50 ppm at room temperature, while at a higher temperature, they changed to one sharp signal.

The treatment of the **9A**, (+)-**9B**, and (−)-**9B** alcohols with tosyl chloride in pyridine at room temperature gave only monotosylates, but at 80 °C it gave the **10A**, (+)-**10B**, and (−)-**10B** ditosylates respectively. The reduction of these ditosylates with lithium aluminum hydride failed to give the desired methyl derivatives, but it did give the starting alcohols. Then **10A** was converted into an iodide with sodium iodide in acetone in a sealed tube at 100 °C.[2] The iodide was treated with activated zinc in acetic acid to give 1-ethyl-2,4,6-trimethylbenzene, presumably formed by the cleavage of the ether linkage with hydrogen iodide formed *in situ*.

The conversion of the carboxyl group into the methyl one was finally achieved by the following routes. The **9A** alcohol was converted into a meso mesylate, **11A**, which was reduced by lithium aluminum hydride to give the **1A** ether (a low-melting isomer) in a 4% yield. The **1A** ether was identical with the specimen obtained by a different route[1] (IR and mixed mp). However, the corresponding optically active mesylates (+)-**11B** and (−)-**11B** gave only the starting alcohols on reduction with lithium aluminum hydride. Optically active **1B**'s were obtained from the ditosylates (+)-**10B** and (−)-**10B** by treatment with phenylmethanethiol, followed by desulfurization with Raney Ni, according to the method of Hussey *et al.*[3] (+)-**1B**; $[\alpha]^{20}_{D}+214°$ (c=0.11, MeOH), (−)-**1B**; $[\alpha]^{20}_{D}-212°$ (c=0.175, MeOH). A similar treatment of **10A** gave **1A** in an 8% yield. These isomers also indicated the presence of a hindered rotation of the benzene rings in their NMR spectra. The aromatic methyl resonances at C_2 and C_6 of **1A** and **1B** showed a singlet ($W_{1/2}$=4.4 Hz) at 2.20 ppm and a broad signal at 1.5—2.5 ppm at room temperature respectively; each of them changed to two signals at lower temperatures and to one sharp signal at higher temperatures.

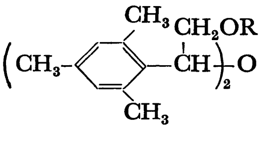


1A
1B



2 **3**

4 **6A, 6B**



R=H **9A**, (+)-**9B**, (−)-**9B**
R=Ts **10A**, (+)-**10B**, (−)-**10B**
R=Ms **11A**, (+)-**11B**, (−)-**11B**

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a Shimadzu IR-27C spectrophotometer. The NMR spectra were measured with a JEOL JNM 60 apparatus at room temperature and at different temperatures with a JEOL JNM 100 apparatus (with TMS as the internal standard). The optical rotations were measured with a Shimadzu photoelectropolarometer, TA-20.

Cyanohydrin 2 of 2,4,6-Trimethylbenzaldehyde. A mixture of 2,4,6-trimethylbenzaldehyde (2 g) and anhydrous HCN (2 ml) was kept with CaO (400 mg) in a sealed tube at 50 °C for 3 h. After the removal of the unchanged HCN and CaO, the crude product gave 2.1 g (90%) of a cyanohydrin, **2**, as plates from petroleum ether; mp 112 °C. Found: C, 75.64; H, 7.50; N, 7.96%. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%. NMR ($CDCl_3$): δ 2.33 (3H, s, Ar-C$\underline{H}_3$), 2.41 (6H, s, Ar-C$\underline{H}_3$), 3.12 (1H, d, J=4 Hz, -O$\underline{H}$), 5.80 (1H, d, J=4 Hz, -C$\underline{H}$-OH), 6.84 (2H, s, Ar-$\underline{H}$) ppm.

Bis(α-cyano-2,4,6-trimethylbenzyl) Ether, 3. The cyanohydrin, **2**, (3 g) was refluxed with a catalytic amount of TsOH in dry benzene for 6 h. The crude product gave 1.7 g (61%) of **3** as prisms from EtOH; mp 150—151 °C. Found: C, 79.64; H, 7.32; N, 8.33%. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43%. NMR ($CDCl_3$): δ 2.28 (6H, s, Ar-C$\underline{H}_3$), 2.48 (12H, s, Ar-C$\underline{H}_3$), 5.82 (2H, s, Ar-C$\underline{H}$-O), 6.94 (4H, s, Ar-$\underline{H}$) ppm.

Bis(α-carbamoyl-2,4,6-trimethylbenzyl) Ether, 4. Into a solution of the ether **3** (250 mg) in abs EtOH, dry HCl gas was passed for 5 h at 45—50 °C. The subsequent crystallization of the crude product from acetone gave 237 mg (85%) of **4**; mp 261—295 °C. Found: C, 71.85; H, 7.77; N, 7.48%. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.60; N, 7.60%.

Bis(α-carboxy-2,4,6-trimethylbenzyl) Ether, 5. The **4** ether (300 mg) was hydrolyzed with 30% aq KOH in ethylene glycol to give 227 mg(75%) of **5** as prisms from ether-petroleum ether. Found: C, 70.84; H, 7.14%. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08%.

Bis(α-methoxycarbonyl-2,4,6-trimethylbenzyl) Ethers, 6A and 6B. The **5** acid was methylated with diazomethane, and the crude product was chromatographed over silica gel. Elution with $CHCl_3$ containing acetone (3% v/v) gave **6A** (32%) as needles from EtOH; mp 114—116 °C. Found: C, 72.44; H, 7.69%. Calcd for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59%. IR (CCl_4): 1760, 1740, 1200, 1185 (sh), 1150, 1105 cm^{-1}. NMR (CCl_4): δ 2.10 (12H, s, Ar-C$\underline{H}_3$), 2.23 (6H, s, Ar-C$\underline{H}_3$), 3.65 (6H, s, $CO_2C\underline{H}_3$), 5.35 (2H, s, Ar-C$\underline{H}$-O), 6.73 (4H, s, Ar-$\underline{H}$) ppm. Further elution with the same solvent gave the second isomer, **6B** (61%), as prisms from EtOH; mp 167—168 °C. Found: C, 72.25; H, 7.83%. IR (CCl_4): 1740, 1210, 1195, 1180 (sh), 1145, 1100 cm^{-1}. NMR (CCl_4): δ 2.20 (12H, s, Ar-C$\underline{H}_3$), 2.23 (6H, s, Ar-C$\underline{H}_3$), 3.64 (6H, s, $CO_2C\underline{H}_3$), 5.35 (2H, s, Ar-C$\underline{H}$-O), 6.77 (4H, s, Ar-$\underline{H}$) ppm.

Mesitylglycolamide, 7. In a manner similar to that described for **3**, the **2** cyanohydrin gave **7** (78%) as plates from benzene; mp 145.5—146 °C. Found: C, 68.49; H, 7.91; N, 7.29%. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%.

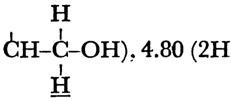
Methyl Mesitylglycolate, 8. The **7** amide was hydrolyzed with 30% aq KOH and methylated with diazomethane to give **8** (66%) as prisms from hexane-acetone; mp 149—150 °C. Found: C, 68.02; H, 7.27%. Calcd for $C_{12}H_{16}O_3$: C, 67.64; H, 7.38%.

Bis(α-carboxy-2,4,6-trimethylbenzyl) Ethers, 5A and 5B. The **6A** and **6B** esters were hydrolyzed to give **5A** (mp 199—199.5 °C (dec)) and **5B** (mp 230—231 °C (dec)) respectively.

Optical Resolution of Bis(α-carboxy-2,4,6-trimethylbenzyl) Ether, 5B. (1) The high-melting carboxylic acid **5B** (170 mg) was dissolved with cinchonidine (307 mg) in MeOH, after which the solution was allowed to stand overnight at room temperature. The residue, after removal of the MeOH, was crystallized from MeOH-AcOEt six times to give one optically active salt, **I** (110 mg) as prisms; $[\alpha]_D^{20}$ +1° (MeOH); mp 189—190 °C. Found: C, 73.41; H, 7.63; N, 5.62%. Calcd for $C_{60}H_{70}N_4O_7$+AcOEt: C, 73.39; H, 7.51; N, 5.35%. Into a solution of **I** in MeOH we stirred concd HCl to give (+)-**5B**; $[\alpha]_D^{20}$ +223.5° (MeOH); mp 219°C (dec). (2) **5B** (470 mg) was treated with cinchonine (250 mg) in MeOH, and the product was recrystallized from acetone-AcOEt five times to give another optically active salt, **II** (136 mg); $[\alpha]_D^{20}$ −29° (MeOH); mp 151—152 °C. Found: C, 70.07; H, 7.49; N, 3.71%. Calcd for $C_{41}H_{48}N_2O_6$ +2AcOEt: C, 69.97; H, 7.67; N, 3.33%. (−)-**5B** was afforded from **II**; $[\alpha]_D^{18}$ −235° (MeOH).

Optically Active Bis(α-methoxycarbonyl-2,4,6-trimethylbenzyl) Ethers, (+)-6B and (−)-6B. (+)-**5B** and (−)-**5B** were methylated with diazomethane to give (+)-**6B** ($[\alpha]_D^{20}$ +148° (MeOH); mp 157—157.5 °C) and (−)-**6B** ($[\alpha]_D^{20}$ −147° (MeOH)) respectively.

Bis[α-(hydroxymethyl)-2,4,6-trimethylbenzyl] Ethers, meso-9A, (+)-9B, and (−)-9B. The **6A**, (+)-**6B**, and (−)-**6B** esters were reduced with $LiAlH_4$ in ether to give **9A**, (+)-**9B**, and (−)-**9B** respectively as needles from acetone. **9A**; mp 147—147.5 °C. Found: C, 77.26; H, 8.83%. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83%. NMR ($CDCl_3$): δ 2.20 (18H, s, Ar-C$\underline{H}_3$), 3.15 (2H, dd, J=4.3 and 11.7 Hz, Ar-CH-$\overset{\underline{H}}{\underset{H}{C}}$-OH), 4.20 (2H, dd, J=9.0 and 11.7 Hz, Ar-CH-$\overset{H}{\underset{\underline{H}}{C}}$-OH), 5.15 (2H,dd,$J$=4.3 and 9.0 Hz, Ar-C$\underline{H}$-CH$_2$-), 6.75 (4H, s, Ar-H) ppm. (+)-**9B**; $[\alpha]_D^{23}$ +153° (MeOH); mp 172—173 °C. Found: C, 77.13; H, 8.87%. NMR ($CDCl_3$): δ 1.50 (6H, broad s, Ar-C$\underline{H}_3$), 2.20 (6H, s, Ar-C$\underline{H}_3$), 2.52 (6H, broad s, Ar-CH$_3$), 3.55 (2H, dd, J=4.5 and 10.5 Hz, Ar-CH-$\overset{\underline{H}}{\underset{H}{C}}$-OH), 4.10 (2H, dd, J=8.5 and 10.5 Hz, Ar-



$\overset{|}{\mathrm{C}}\mathrm{H}-\underset{\underline{\mathrm{H}}}{\overset{\mathrm{H}}{\mathrm{C}}}-\mathrm{OH}$), 4.80 (2H, dd, J=4.5 and 8.5 Hz, $\mathrm{Ar}-\overset{|}{\mathrm{C}}\underline{\mathrm{H}}-\mathrm{CH_2}-$), 6.8 (4H, s, Ar–$\underline{\mathrm{H}}$) ppm. (−)-**9B**; $[\alpha]_D^{22}$ −154° (MeOH).

Bis[α-(tosyloxymethyl)-2,4,6-trimethylbenzyl] Ethers, meso-***10A**, (+)-**10B**, and (−)-**10B**.* The **9A**, (+)-**9B**, and (−)-**9B** alcohols were tosylated with tosyl chloride in pyridine at 80 °C to give **10A** (78%), (+)-**10B** (73%), and (−)-**10B** (74%) respectively. **10A**; mp 163 °C. Found: C, 66.65; H, 6.62%. Calcd for $C_{36}H_{42}O_7S_2$: C, 66.45; H, 6.51%. (+)-**10B**; $[\alpha]_D^{22}$ +125° ($CHCl_3$); mp 140—141 °C. Found: C, 66.48; H, 6.63%. (−)-**10B**; $[\alpha]_D^{22}$ −125° ($CHCl_3$). Found: C, 66.52; H, 6.56%.

*Reaction of the **10A** Tosylate with Sodium Iodide.* The **10A** tosylate (250 mg) was reacted with sodium iodide (300 mg) in acetone in a sealed tube at 100 °C for 24 h. The reaction product (128 mg) was then treated with activated zinc (300 mg) in acetic acid under reflux for 3 h to give 63 mg of 1-ethyl-2,4,6-trimethylbenzene; bp 209—211 °C.

*Reactions of the **10A**, (+)-**10B**, and (−)-**10B** Tosylates with LAH.* The treatments of **10A**, (+)-**10B**, and (−)-**10B** with $LiAlH_4$ gave the **9A**, (+)-**9B**, and (−)-**9B** alcohols respectively in high yields.

Bis[α-(mesyloxymethyl)-2,4,6-trimethylbenzyl] Ethers, meso-***11A**, (+)-**11B**, and (−)-**11B**.* The mesylations of the **9A**, (+)-**9B**, and (−)-**9B** alcohols with mesyl chloride in pyridine at 80 °C for 2 h gave **11A** (63%), (+)-**11B** (72%), and (−)-**11B** (68%) respectively. **11A**; mp 127—127.5 °C. Found: C, 58.02, H, 6.95%. Calcd for $C_{24}H_{34}O_7S_2$: C, 57.81; H, 6.87%. (+)-**11B**; $[\alpha]_D^{20}$ +41° (MeOH); mp 134 °C. Found: C, 58.01; H, 6.94%. (−)-**11B**; $[\alpha]_D^{20}$ −42° (MeOH). Found: C, 57.95; H, 6.92%.

meso-*Bis(1-mesitylethyl) Ether, **1A**.* (1) The treatment of the **11A** mesylate (200 mg) with $LiAlH_4$ (531 mg) in ether under reflux for 2 h gave 6 mg (4%) of **1A** (mp 98—99 °C) as plates from EtOH. IR (CCl_4): 1615, 1160, 1095, 1075, 945, 855 cm^{-1}. (2) The **10A** tosylate (440 mg) was reacted with phenylmethanethiol (330 mg) and Na (80 mg) in diethylene glycol monoethyl ether (8 ml) under reflux for 4 h. The reaction mixture was then poured into ice water, and the unreacted thiol was removed by steam distillation after acidification with dil HCl. An ether extract of the reaction product was treated with Raney Ni(w-2) in EtOH under reflux for 8 h to give 23 mg (11%) of **1A**.

*Reaction of the (+)-**11B** Mesylate with LAH.* The treatment of (+)-**11B** with $LiAlH_4$ in ether under reflux gave the (+)-**9B** alcohol (83%).

*Optically Active Bis(1-mesitylethyl) Ethers, (+)-**1B** and (−)-**1B**.* The optically active tosylates, (+)-**10B** and (−)-**10B**, were transformed into dibenzyl sulfides in a manner similar to that described for **10A**. These crude sulfides were then treated with Raney Ni(w-2) to give (+)-**1B** (8%) and (−)-**1B** (12%) respectively. (+)-**1B**; $[\alpha]_D^{20}$ +214° (MeOH); mp 132.5—133 °C. (−)-**1B**; $[\alpha]_D^{20}$ −212° (MeOH). IR (CCl_4): 1615, 1160, 1095, 1075, 945, 885 cm^{-1}. These compounds were identical in IR spectrum with, but differ in mp from, the high-melting isomer, **1B**, obtained by another route.[1]

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