Influence of Alkoxyalkyl Substituents in the Regioselective Lithiation of the Benzene Ring

Elio Napolitano,* Enrico Giannone, Rita Fiaschi, and Antonio Marsili

Istituto di Chimica Organica della Facoltà di Farmacia, 56100 Pisa, Italy

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The concomitant presence of an alkoxyalkyl group (α-alkoxyalkyl, α- or β-dialkoxyalkyl) and of an alkoxy group in the relative positions 1 and 3 in a benzene ring generally permits an easy lithiation of position 2 by proton–metal exchange with *n*-butyllithium; the only aromatic compound tested, bearing a β-alkoxyalkyl group, gave, however, extensive decomposition in the metalation step. Reaction of the metalated species with an electrophile (such as carbon dioxide or ethyl chloroformate) leads to the corresponding substituted products in good to excellent yields. The following transformations are described: 3,4-dimethoxybenzyl α-ethoxyethyl ether (**1**) into 6,7-dimethoxyphthalide (**15**); 3,4-(methylenedioxy)benzyl α-ethoxyethyl ether (**2**) into 6,7-(methylenedioxy)phthalide (**16**); 3,4-dimethoxybenzyl methyl ether (**3**) into ethyl 2-(methoxymethyl)-5,6-dimethoxybenzoate (**18**) and into ethyl 2-(chloromethyl)-5,6-dimethoxybenzoate (**20**); 3,4-(methylenedioxy)benzyl methyl ether (**4**) into ethyl 2-(methoxymethyl)-5,6-(methylenedioxy)benzoate (**19**) and into ethyl 2-(chloromethyl)-5,6-(methylenedioxy)benzoate (**21**); 3,4-dimethoxybenzaldehyde dimethyl acetal (**5**) into 5,6-dimethoxyphthalaldehydic acid (**22**); 3,4-(methylenedioxy)benzaldehyde dimethyl acetal (**6**) into 5,6-(methylenedioxy)phthalaldehydic acid (**23**); (3,4-dimethoxyphenyl)acetaldehyde dimethyl acetal (**7**) into ethyl 2-(2,2-dimethoxyethyl)-5,6-dimethoxybenzoate (**25**); 3,4,4′-trimethoxydeoxybenzoin ethylene acetal (**10**) into 2-(ethoxycarbonyl)-3,4,4′-trimethoxydeoxybenzoin (**26**); 4,3′,4′-trimethoxydeoxybenzoin ethylene acetal (**11**) into 2′-(ethoxycarbonyl)-4,3′,4′-trimethoxydeoxybenzoin (**27**); 3,4,3′,4′-tetramethoxydeoxybenzoin ethylene acetal (**12**) into a mixture of 3-(3,4-dimethoxybenzylidene)-6,7-dimethoxyphthalide (**28**) and 3-(3,4-dimethoxyphenyl)-7,8-dimethoxyisocoumarin (**29**). The dioxole ring of methylenedioxy-substituted benzenes is sometimes unstable under these metalation conditions, and partial decomposition usually causes the yields to be lower than those in the case of the corresponding methoxy-substituted benzenes. Many of the products listed above, which have been already prepared by other methods, are more conveniently obtained by the present approach.

It is well-known that certain substituents containing heteroatoms are able to promote the lithiation of an aromatic ring at the ortho position (ortholithiation) by proton–metal exchange with an alkyl lithium reagent.[1] The effect of the heteroatom has been explained in terms both of increased intrinsic acidity of the ortho proton and of coordination of the metalating agent with consequent enhancement of its ability to abstract the ortho proton.

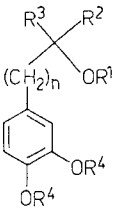
Because of its high degree of regioselectivity and the ease of transformation of the carbon–metal bond, ortholithiation has become an important tool in the synthesis of substituted benzenes, and particularly of those bearing contiguous substituents, which are generally difficult to obtain by sequences involving the classical electrophilic aromatic substitution.

Among the substituents which can lead to metalation through coordination of the metalating agent, alkoxyalkyl groups are usually regarded as poor ones. Although such groups have found extensive use in providing regioselectivity in the metalation of π-excessive five-membered heterocycles, which are by themselves easily metalable substrates, very scarce attention has been devoted to them as activating groups in the metalation of fully carbocyclic aromatic systems: this could be possibly due in part to the known tendency of benzyl ethers to undergo benzylic deprotonation and subsequent Wittig rearrangement by action of organometallic reagents.[1a] To our best knowledge, only one short report has appeared in the literature concerning the successful ortholithiation of dimethyl acetals of alkoxy-substituted benzaldehydes.[2] Our need of benzene rings bearing contiguous and functionalized substituents, to be used as starting materials for a new synthesis of protoberberine-like compounds,[3] led us to explore the title argument in a more systematic way.

We have now found that when an alkoxy group is present in the meta position, many alkoxyalkyl groups can effectively cooperate in promoting the metalation of a benzene ring, thus providing a short, efficient, and completely regiocontrolled route to many interesting and valuable compounds.

Results and Discussion

3,4-Dimethoxybenzyl alcohol was protected by acetalization to 3,4-dimethoxybenzyl α-ethoxyethyl ether (**1**).



1 n = 0; R^1 = $CH(CH_3)OC_2H_5$; R^2 = R^3 = H; R^4 = CH_3
2 n = 0; R^1 = $CH(CH_3)OC_2H_5$; R^2 = R^3 = H; R^4 = CH_2
3 n = 0; R^1 = CH_3; R^2 = R^3 = H; R^4 = CH_3
4 n = 0; R^1 = CH_3; R^2 = R^3 = H; R^4 = CH_2
5 n = 0; R^1 = CH_3; R^2 = OCH_3; R^3 = H; R^4 = CH_3
6 n = 0; R^1 = CH_3; R^2 = OCH_3; R^3 = H; R^4 = CH_2
7 n = 1; R^1 = CH_3; R^2 = OCH_3; R^3 = H; R^4 = CH_3
8 n = 1; R^1 = CH_3; R^2 = OCH_3; R^3 = H; R^4 = CH_2
9 n = 1 R^1 = $CH(CH_3)OC_2H_5$; R^2 = R^3 = H; R^4 = CH_3
10 n = 0; R^1 + R^2 = CH_2CH_2O; R^3 = 4-methoxybenzyl; R^4 = CH_3
11 n = 1; R^1 + R^2 = CH_2CH_2O; R^3 = 4-methoxyphenyl; R^4 = CH_3
12 n = 0; R^1 + R^2 = CH_2CH_2O; R^3 = 3,4-dimethoxybenzyl; R^4 = CH_3

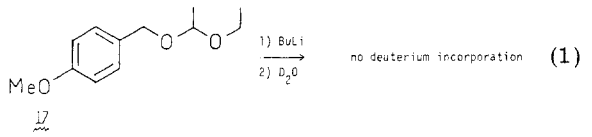
(1) (a) Gschwend, H. G.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) For recent developments in this field, see: Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101 and references cited therein.

(2) Paulmann, H. P.; Keay, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, 4921.

(3) Barili, P. L.; Fiaschi, R.; Napolitano, E.; Pistelli, L.; Scartoni, V.; Marsili, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1654. Napolitano, E.; Fiaschi, R.; Scartoni, V.; Marsili, A. "Abstracts of Papers", 3rd Convegno Nazionale della Divisione di Chimica Farmaceutica della Società Chimica Italiana, 1982, p 38.

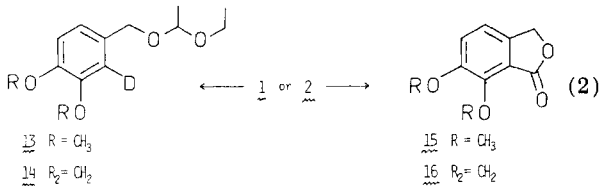
0022-3263/83/1948-3653$01.50/0

This compound was smoothly lithiated at position 2 by treatment with 1.1 equiv of *n*-butyllithium in ether–hexane solution at 0 °C for 1 h, as deduced after quenching with deuterium oxide and NMR analysis of the recovered product. 4-Methoxybenzyl α-ethoxyethyl ether (**17**), on the contrary, did not undergo any detectable metalation (eq 1) either under similar conditions or after 8 h at 20 °C:



17 (1)

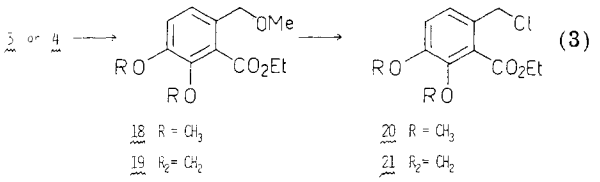
this shows that the alkoxyalkyl group, when located in the appropriate (meta) position, really enhances the known tendency of the position ortho to an alkoxy group to undergo proton–metal exchange. Upon treatment of lithiated **1** with carbon dioxide and subsequent hydrolysis of the carbonated material with hot dilute hydrochloric acid, 6,7-dimethoxyphthalide (**15**) was obtained in excellent yields (eq 2). Analogous results were obtained from



(2)

3,4-(methylenedioxy)benzyl α-ethoxyethyl ether (**2**). Although 7-methoxy-substituted phthalides may be also obtained directly from the appropriate benzyl alcohols, the use of the latter compounds requires 2 mol of metalating agent, and incomplete conversion into products is sometimes observed.[4] The use of protected alcohols therefore appears to be more suitable for large-scale preparations.

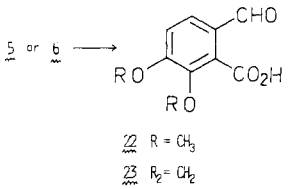
Metalation of 3,4-dimethoxybenzyl methyl ether (**3**) closely parallels metalation of compound **1**. Reaction of lithiated **3** with ethyl chloroformate afforded ester **18** in high yields (eq 3). Analogous results were obtained from



(3)

3,4-(methylenedioxy)benzyl methyl ether (**4**), although the yields of compound **19** were slightly lower, owing possibly to formation of phenolic compounds derived from decomposition of the dioxole ring.[5] Compounds **18** and **19** were converted in quantitative yields to the important chloro esters **20** and **21**, respectively, by short treatment with an excess of acetyl chloride in ether solution in the presence of a catalytic amount of anhydrous zinc chloride. Compounds **20** and **21** have been already described; they have been obtained by sequences involving ortholithiation of (3,4-dimethoxybenzyl)dimethylamine[6] and of either [3,4-(methylenedioxy)benzyl]dimethylamine or 3,4-(methylenedioxy)benzaldehyde cyclohexylimine,[7] respectively. However, if one considers that 3,4-dimethoxybenzaldehyde and 3,4-(methylenedioxy)benzaldehyde are in any case the respective starting materials, the present approach constitutes a better synthetic method since it gives consistently higher overall yields.

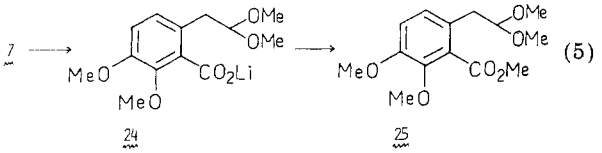
Our observations concerning the metalation of 3,4-dimethoxybenzaldehyde dimethyl acetal (**5**) and its subsequent transformation into the phthalaldehydic acid derivative **22** (eq 4) are in complete agreement with those of



(4)

the previously cited authors.[2] Minor differences were found in the behavior of 3,4-(methylenedioxy)benzaldehyde dimethyl acetal (**6**) which, in our hands, gave the phthalaldehydic acid derivative **23** in consistently lower yields, owing possibly to an extensive decomposition of the dioxole ring in the metalation step. Furthermore, when 3,4-(methylenedioxy)benzaldehyde ethylene acetal was used as the starting material in the place of **5**, the yields of **23** dropped to 10%. The use of an excess of *n*-butyllithium did not lead to better yields in either cases. Indeed, the starting material recovered after lithiation and quenching with deuterium oxide exhibited in both cases incomplete deuterium incorporation.

The regioselective metalation of the benzene ring does not strictly require an etheral oxygen bound to a benzylic carbon atom; also β-alkoxyalkyl groups may be suitable functions. For instance, (3,4-dimethoxyphenyl)acetaldehyde dimethyl acetal (**7**) was converted into the lithium salt **24** (eq 5) by lithiation–carbonation and finally into



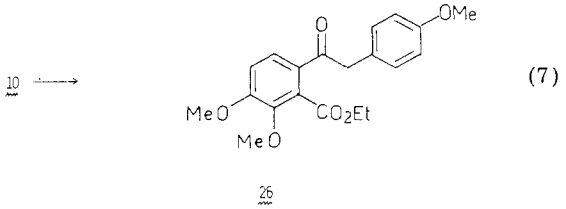
(5)

the ester **25** in good overall yields. Compound **8**, however, underwent extensive decomposition (eq 6) in the metalation step, as observed for compound **4**.

$$\textbf{8 or 9} \xrightarrow[\text{2. } D_2O]{\text{1. BuLi}} \text{extensive decomposition} \qquad (6)$$

Decomposition was also observed with compound **9**: attempted metalation and deuterium incorporation led to only traces of recovered starting material exhibiting incomplete deuterium incorporation. Most of the reaction product was a polymer-like material, insoluble both in ether and in water.

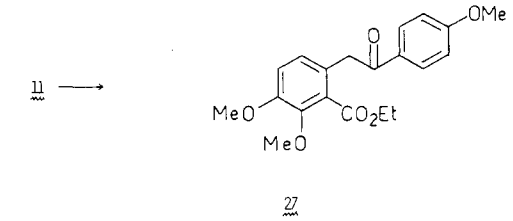
Good results were finally obtained in the lithiation of the ethylene acetals of some deoxybenzoins bearing methoxy substituents at position 3 or 3′, the metalation occurring exclusively at positions 2 or 2′, respectively, i.e., at the position which is ortho with respect to both the methoxy and the alkoxyalkyl group (the aliphatic portion of the molecule). Thus, compound **10** gave ester **26** (eq 7) upon lithiation in toluene–hexane solution followed by



(7)

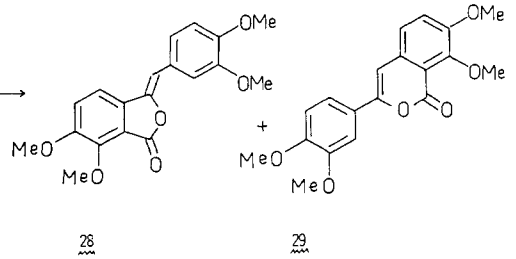
(4) Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835.
(5) Renade, A. C.; Mali, R. S.; Bhide, S. R.; Mehta, S. R. *Synthesis* **1976**, 123 and references cited therein.
(6) Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2115.
(7) Cushman, M.; Chong, T. C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067.

treatment with ethyl chloroformate and by hydrolysis of the acetal group with moist acetic acid. By an analogous sequence, compound **11** gave exclusively **27** (eq 8). The structures of compounds **26** and **27** were deduced mainly by NMR spectroscopy (see Experimental Section).



(8)

In order to evaluate the relative effectiveness of an α- and β-alkoxyalkyl group in promoting the metalation of the benzene ring, deoxybenzoin ethylene acetal **12**, containing two methoxy groups at the 3- and 3′-positions, was lithiated under conditions analogous to those used for compounds **10** and **11**. In this case lithiation occurred either at position 2 or at position 2′, with a slight preference for the former. In fact, after reaction of metalated **12** with carbon dioxide followed by hydrolysis–dehydration of the acid reaction products by means of 100% phosphoric acid, a mixture was obtained containing the benzylidenephthalide **28** and the isocoumarin **29** (eq 9) in an ap-



(9)

proximate ratio of 7:3, the overall yields from **12** being good. The structures of the two isomeric lactones **28** and **29** were mainly deduced on the basis of their spectral characteristics. In addition, compound **28** gave the known 3-(3,4-dimethoxyphenyl)-6,7-dimethoxyindan-1,3-dione on treatment with sodium methoxide.[8]

Experimental Section

Melting points were determined with a Kofler hot stage and are uncorrected; IR spectra were recorded for Nujol mulls or neat liquids on a Perkin-Elmer 197 spectrophotometer, and the most intense and/or representative bands are given; NMR spectra were registered in $CDCl_3$ solution with a Varian EM360A spectrometer, and signals are quoted in parts per million from Me_4Si as an internal standard; $MgSO_4$ was used to dry solutions, unless otherwise stated; evaporation of solvents was made with a rotary evaporator under diminished pressure; dry ether was obtained by distillation from sodium benzophenone ketyl; all reactions involving *n*-butyllithium were performed in a nitrogen atmosphere.

Starting Materials. Compounds **1**, **2**, **9**, and **17** were obtained in almost quantitative yields by mixing at room temperature the appropriate alcohol with an excess of ethyl vinyl ether in the presence of a catalytic amount of trifluoroacetic acid; after 5 h the reaction mixture was diluted with ether and washed with 10% NaOH, and the reaction product was obtained by evaporation of the dried (K_2CO_3) organic solution and distillation of the residue over a little of K_2CO_3. Methyl ethers **3** and **4** were obtained by reaction of the appropriate alcohol with NaH and CH_3I in THF or with $(CH_3)_2SO_4$ and 50% NaOH(aq) in the presence of tetrabutylammonium iodide.[9] Acetals **5–8** were prepared by heating at reflux in methanol for 1 h the appropriate aldehyde with a slight excess of methyl orthoformate in the presence of *p*-toluenesulfonic acid as a catalyst; the reaction mixture was made basic by addition of methanolic sodium methoxide, diluted with water, and extracted with ether, and finally the reaction product was purified by distillation over a little K_2CO_3. Compounds **10–12** were obtained in two steps: (a) intermolecular condensation of the appropriate phenylacetic acid with an alkoxybenzene by means of polyphosphoric acid and (b) acetalization by standard methods of the deoxybenzoin thus formed. This two-step process is exemplified below for compound **10**.

3,4-Dimethoxybenzyl α-ethoxyethyl ether (1): from 3,4-dimethoxybenzyl alcohol; colorless liquid; bp 120 °C (0.1 mmHg); IR 1260, 1140, 1010 cm^{-1}; NMR δ 1.21 (t, J = 7 Hz, 3, CH_2CH_3), 1.35 (d, J = 5.3 Hz, 3, $CHCH_3$), 3.30–3.80 (m, 2, CH_2CH_3), 3.83, 3.85 (2 s, 2 × 3, OCH_3), 4.28, 4.48, 4.51 (part of an AB q, 2, $ArCH_2$), 4.76 (q, J = 5.3 Hz, 1, $CHCH_3$), 6.88 (s, 3, aromatic). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.85; H, 8.32.

3,4-(Methylenedioxy)benzyl α-ethoxyethyl ether (2): from 3,4-(methylenedioxy)benzyl alcohol; colorless liquid; bp 142 °C (0.5 mmHg); IR 1240, 1120, 1090, 1030, 920, 800 cm^{-1}; NMR δ 1.21 (t, J = 7 Hz, 3, CH_2CH_3), 1.33 (d, J = 5.3 Hz, 3, $CHCH_3$), 3.21–3.93 (m, 2, CH_2CH_3), 4.25, 4.45, 4.48, 4.68 (AB q, 2, $ArCH_2$), 4.76 (q, J = 5.3 Hz, $CHCH_3$), 5.88 (s, 2, OCH_2O), 6.82, 6.92 (2 s, 3, aromatic). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.85; H, 7.15.

4-Methoxybenzyl α-ethoxyethyl ether (17): from 4-methoxybenzyl alcohol; colorless liquid; bp 84 °C (0.05 mmHg); IR 1600, 1240, 1120, 1020, 820 cm^{-1}; NMR δ 1.20 (t, J = 7 Hz, 3, CH_2CH_3), 1.33 (d, J = 5.3 Hz, 3, $CHCH_3$), 3.21–3.93 (m, 2, CH_2CH_3), 3.72 (s, 3, OCH_3), 4.37, 4.48, 4.51 (part of an AB q, 2, $ArCH_2$), 4.75 (q, J = 5.5 Hz, 3, $CHCH_3$), 6.77, 6.93, 7.20, 7.35 (AA′BB′ q, 4, aromatic). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.35; H, 8.50.

3,4-Dimethoxybenzyl methyl ether (3): from 3,4-dimethoxybenzyl alcohol; colorless liquid; bp 84 °C (0.05 mmHg); IR 1600, 1580, 1500, 1260, 1160, 1020 cm^{-1}; NMR δ 3.35, 3.85, 3.88 (3, s, 3 × 3, OCH_3), 4.55 (s, 2, OCH_2), 6.83–6.96 (m, 3, aromatic). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.85; H, 7.69.

3,4-(Methylenedioxy)benzyl methyl ether (4): from 3,4-(methylenedioxy)benzyl alcohol; colorless liquid; bp 75 °C (0.02 mmHg); IR 1620, 1600, 1440, 1240, 1110, 1040 cm^{-1}; NMR δ 3.33 (s, 3 OCH_3), 4.33 (s, 2, $ArCH_2$), 5.88 (s, 2, OCH_2O), 6.71–6.97 (m, 3, aromatic). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.21; H, 6.11.

3,4-Dimethoxybenzaldehyde dimethyl acetal (5): from 3,4-dimethoxybenzaldehyde; colorless liquid; bp 94 °C (0.05 mmHg); IR 1600, 1580, 1260, 1180, 1160, 1100, 1050 cm^{-1}; NMR δ 3.33 (s, 6, $CH(OCH_3)_2$), 3.89 (s, 6, $ArOCH_3$), 5.33 (s, 1, ArCH), 6.77–7.08 (m, 3, aromatic). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 61.85; H, 7.49.

3,4-(Methylenedioxy)benzaldehyde dimethyl acetal (6): from 3,4-(methylenedioxy)benzaldehyde; colorless liquid; bp 84 °C (0.05 mmHg); IR 1250, 1040, 800 cm^{-1}; NMR δ 3.33 (s, 6, $CH(OCH_3)_2$), 5.31 (s, 1, ArCH), 5.95 (s, 2, OCH_2O), 6.70–7.10 (m, 3, aromatic). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.12. Found: C, 60.91; H, 6.15.

(3,4-Dimethoxyphenyl)acetaldehyde dimethyl acetal (7): from (3,4-dimethoxyphenyl)acetaldehyde;[10] colorless liquid; bp 115 °C (0.03 mmHg); IR 1580, 1260, 1230, 1120, 1020, 800 cm^{-1}; NMR δ 2.83 (d, J = 5.5 Hz, 2, $CHCH_2$), 3.33 (s, 6, $CH(OCH_3)_2$), 3.83, 3.87 (2 s, 2 × 3, $ArOCH_3$), 4.45 (t, J = 5.5 Hz, 1, $CHCH_2$), 6.80 (s, 3, aromatic). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.71; H, 7.96. Found: C, 63.50; H, 7.84.

[3,4-(Methylenedioxy)phenyl]acetaldehyde dimethyl acetal (8): from [3,4-(methylenedioxy)phenyl]acetaldehyde;[10] bp 110 °C (0.05 mmHg); IR 1240, 1120, 1040, 800 cm^{-1}; NMR δ 2.81 (d, J = 5.5 Hz, 2, CH_2CH), 3.33 (s, 6, $CH(OCH_3)_2$), 4.50 (t, J = 5.5 Hz, 1, $CHCH_2$), 5.93 (s, 2, OCH_2O), 6.73 (br, 3, aromatic). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.58; H, 6.65.

2-(3,4-Dimethoxyphenyl)ethyl α-ethoxyethyl ether (9): from 2-(3,4-dimethoxyphenyl)ethyl alcohol; colorless liquid; bp 120 °C (0.05 mmHg); IR 1600, 1580, 1500, 1260, 1130, 1020 cm^{-1};

(8) Smula, V.; Coundasawmy, N. E.; Holland, H. *Can. J. Chem.* **1973**, *51*, 3287.
(9) Merz, A. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 896.
(10) Ban, Y.; Oishi, T. *Chem. Pharm. Bull.* **1958**, *6*, 574.

NMR δ 1.15 (t, J = 7 Hz, 3, CH_2CH_3), 1.28 (d, J = 5.5 Hz, 3, $CHCH_3$), 2.82 (t, J = 7 Hz, 2, OCH_2CH_2), 3.20–3.87 (m, 4, $CH_2OCH(CH_3)OCH_2$), 3.87 (s, 6, OCH_3), 4.68 (q, J = 5.5 Hz, 1, $CHCH_3$), 6.80 (s, 3, aromatic). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 65.97; H, 8.60.

3,4,4′-Trimethoxydeoxybenzoin Ethylene Acetal (10). A mixture of (4-methoxyphenyl)acetic acid (8.3 g, 50 mmol), 1,2-dimethoxybenzene (13.8 g, 100 mmol), and polyphosphoric acid (250 g) was mechanically stirred in an oil bath at 75 °C for 4 h. The resulting deep red solution was poured into ice–water to decompose the excess of polyphosphoric acid, the yellow solid was collected and dissolved in $CHCl_3$, and the organic solution was washed with water and diluted NaOH, dried, and evaporated. The residue was recrystallized from EtOH to afford **3,4,4′-trimethoxydeoxybenzoin**: 10.6 g (76%); mp 115 °C (lit.[11] mp 118 °C); IR 1660, 1260, 1240, 1140, 1010, 780 cm^{-1}; NMR δ 3.77, 3.93 (2 s, 9, OCH_3), 4.18 (s, 2, CH_2), 6.80, 6.95, 7.17, 7.43, 7.60, 7.73, 7.78 (m, 7, aromatic). A mixture containing the above compound in toluene (250 mL), ethylene glycol (15 mL), and p-toluenesulfonic acid (0.5 g) was refluxed for 10 h with continuous azeotropic removal of water. The reaction mixture was then allowed to cool to room temperature, treated with a diluted solution of sodium methoxide in order to eliminate acidity, and washed with water, and the organic layer was dried over K_2CO_3 and evaporated. The residue was recrystallized from methanol to afford **10**: 11 g (88%); mp 125–126 °C; IR 1600, 1580, 1500, 1260, 1130, 1010 cm^{-1}; NMR δ 3.10 (s, 2, $ArCH_2$), 3.70–4.00 (m, 13, OCH_3 and OCH_2), 6.63–7.33 (m, 7, aromatic). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.09; H, 6.66. Found: C, 68.96; H, 6.77.

4,3′,4′-Trimethoxydeoxybenzoin ethylene acetal (11): 70% overall yield from (3,4-dimethoxyphenyl)acetic acid and methoxybenzene; mp 97–98 °C; IR 1600, 1580, 1500, 1240, 1140, 1020, 820 cm^{-1}; NMR δ 3.11 (s, 2, $ArCH_2$), 3.66–4.00 (m, 13, OCH_3 and OCH_2), 6.63, 6.76, 6.93, 7.27, 7.40 (m, 7, aromatic). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.09; H, 6.66. Found: C, 69.36; H, 6.81. Intermediate **3,3′,4′-trimethoxydeoxybenzoin**: mp 139 °C (lit.[11] mp 138 °C); IR 1670, 1600, 1260, 1020, 780 cm^{-1}; NMR δ 3.83 (superimposed s, 9, OCH_3), 4.17 (s, 2, $ArCH_2$), 6.83, 7.02, 7.96, 8.11 (m, 7, aromatic).

3,4,3′,4′-Tetramethoxydeoxybenzoin ethylene acetal (12): 65% overall yield from (3,4-dimethoxyphenyl)acetic acid and 1,2-dimethoxybenzene; mp 95 °C; IR 1600, 1580, 1510, 1460, 1260, 1140, 1020, 850, 760 cm^{-1}; NMR δ 3.07 (s, 2, $ArCH_2$), 3.53–4.00 (m, 13, OCH_3 and OCH_2), 6.43–6.90 (m, 6, aromatic). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.66; H, 6.66. Found: C, 66.38; H, 6.81. Intermediate **3,4,3′,4′-tetramethoxydeoxybenzoin**: mp 107 °C (lit.[12] mp 107 °C); IR 1670, 1260, 1230, 1140, 1010, 770 cm^{-1}; NMR δ 3.90, 3.96 (superimposed s, 12, OCH_3), 4.23 (s, 2, $ArCH_2$), 6.86, 7.00, 7.33, 7.65, 7.80 (m, 6, aromatic).

General Procedure for Lithiation and Reaction with Electrophiles. To a solution (0.1–0.5 M, ether or toluene) of the compound to be metalated was added 1.15 equiv of n-butyllithium as a 2 M solution in hexane dropwise under stirring and cooling with ice–water. A precipitate was usually formed at this stage. Stirring was continued for 1 h, the ice bath was replaced with a dry ice–acetone bath, and the appropriate electrophile (D_2O, solid CO_2 or ethyl chloroformate) was added. After the addition, the cooling bath was removed, and the reaction mixture was allowed to return to room temperature. Water was added until two homogeneous phases were obtained, and the reaction product was isolated from the appropriate phase.

6,7-Dimethoxyphthalide (15). Compound 1 (24 g, 100 mmol) in ether (300 mL) was metalated according to the general procedure and quenched with an excess of CO_2. The aqueous phase obtained from hydrolysis was further washed with ether, made acidic by adding concentrated HCl, and gently heated on a steam bath. A solid separated which was recrystallized from CH_2Cl_2/ether to afford **15**: 17.5 g (91%); mp 103 °C (lit.[13] mp 102–103 °C); IR 1750, 1260, 1100, 1030, 1000 cm^{-1}; NMR δ 3.90, 4.07 (2 s, 2 × 3, OCH_3), 5.18 (s, 2, CH_2), 7.00, 7.13, 7.20, 7.35 (AB q, 2, aromatic).

6,7-(Methylenedioxy)phthalide (16) was prepared by the same procedure in 89% yield from compound **2** and recrystallized from acetic acid: mp 236 °C (lit.[14] mp 233–234 °C); IR 1740, 1240, 1020, 950 cm^{-1}.

Ethyl 2-(Methoxymethyl)-5,6-dimethoxybenzoate (18). Compound **3** (23 g, 126 mmol) in ether (300 mL) was lithiated according to the general procedure with ethyl chloroformate as the quenching agent. The etheral phase obtained from hydrolysis was dried (Na_2SO_4) and evaporated, and the residual oil was slowly distilled, collecting **18** as the fraction with a boiling point of 120 °C (0.05 mmHg): 26 g (81%); IR 1720, 1260, 1060 cm^{-1}; NMR δ 1.38 (t, J = 7 Hz, 3, CH_2CH_3), 3.33, 3.88 (2 s, 3 + 6, OCH_3), 4.42 (q, J = 7 Hz, 2, CH_2CH_3), 4.45 (s, 2, $ArCH_2$), 6.66, 7.00, 7.05, 7.18 (AB q, 2, aromatic). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.42; H, 7.09. Found: C, 61.70; H, 6.95. The fractions boiling below 100 °C (0.05 mmHg) contained mainly unreacted starting material.

Ethyl 2-(methoxymethyl)-5,6-(methylenedioxy)benzoate (19) was obtained from compound **4** by the same procedure: 75% yield; bp 117 °C (0.02 mmHg); IR 1710, 1440, 1260, 1040 cm^{-1}; NMR δ 1.38 (t, J = 7 Hz, 3, CH_2CH_3), 3.36 (s, 3 OCH_3), 4.41 (q, J = 7 Hz, 2, CH_2CH_3), 4.63 (s, 2, $ArCH_2$), 6.05 (s, 2, OCH_2O), 6.77, 6.90, 6.93, 7.07 (AB q, 2, aromatic). Anal. Calcd $C_{12}H_{14}O_5$: C, 60.50; H, 5.88. Found: C, 60.45; H, 5.80.

Ethyl 2-(Chloromethyl)-5,6-dimethoxybenzoate (20). To a solution containing compound **18** (5 g, 19.7 mmol) and anhydrous $ZnCl_2$ (0.1 g) in dry ether (50 mL) was added acetyl chloride (5 mL) dropwise under stirring and cooling in an ice bath. After 0.5 h Al_2O_3 (5 g) was added and the mixture filtered on a short pad of Al_2O_3. The eluate was evaporated and the residue distilled to affort **20** in about quantitative yield as a colorless liquid, bp 140 °C (0.05 mmHg). The spectral data were identical with those reported for the same compound.[6]

Ethyl 2-(Chloromethyl)-5,6-(methylenedioxy)benzoate (21) was obtained from compound **19** in about quantitative yield by using the same procedure; bp 160 °C (0.05 mmHg). The spectral data were identical with those reported for the same compound.[7]

5,6-Dimethoxyphthalaldehydic Acid (22). Compound **5** (21 g, 100 mmol) in ether (500 mL) was metalated according to the general procedure and quenched with an excess of solid CO_2. The water phase from the hydrolyzed reaction mixture was further washed with ether, made acidic with concentrated HCl, and gently heated on a steam bath. When the mixture cooled, **22** separated as a white solid (20 g, 95%). An analytical sample was recrystallized from water; mp 146–148 °C (lit.[15] mp 146 °C).

5,6-(Methylenedioxy)phthalaldehydic acid (23) was obtained in 51% yield from compound **6** by using the same procedure; mp 165–166 °C (lit.[16] mp 164.5–165.5 °C).

Ethyl 2-(2,2-Dimethoxyethyl)-5,6-dimethoxybenzoate (25). Compound **7** (3 g, 13 mmol) in ether (20 mL) was metalated according to the general procedure and quenched with an excess of solid CO_2. The solid lithium carboxylate **24** thus formed was collected, dried (2.5 g, 68%), and sealed in a tube with dimethylformamide (6 mL) and methyl iodide (2 mL), and the mixture was heated on a steam bath for 8 h. The reaction mixture was then partitioned between ether and water, and the organic phase was thoroughly washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by bulb to bulb distillation to afford **25** as a colorless oil: 2,3 g (60.5% overall); bp 170 °C (0.05 mmHg); IR 1720, 1480, 1270, 1060 cm^{-1}; NMR δ 2.83 (d, J = 5.5 Hz, 2, CH_2CH), 3.33 (s, 6, $CH(OCH_3)_2$), 3.87 (s, 6, $ArOCH_3$), 3.93 (s, 3, CO_2CH_3), 4.48 (t, J = 5.5 Hz, 1, $CHCH_2$), 6.83, 6.96, 7.00, 7.12 (AB q, 2, aromatic). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.04. Found: C, 58.96; H, 7.12.

2-(Ethoxycarbonyl)-3,4,4′-trimethoxydeoxybenzoin (26). Compound **10** (3.3 g, 10 mmol) in toluene (50 mL) was metalated according to the general procedure and quenched with ethyl chloroformate (1 mL). The organic phase from hydrolysis of the reaction mixture was washed with water, dried, and evaporated. The oily residue was dissolved in acetic acid (30 mL) containing few drops of concentrated HCl and heated on a steam bath for 1 h. The solution was then partitioned between water and CH_2Cl_2,

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and the organic phase was washed with water, dried, and evaporated to leave solid **26** which was recrystallized from $CHCl_3$/MeOH to give 2.8 g (62%) of pure **26**: mp 91–92 °C; IR 1670, 1240, 1040 cm^{-1}; NMR δ 1.33 (t, J = 7 Hz, 3, CH_2CH_3), 3.77, 3.87, 3.90 (3 s, 3 × 3, OCH_3), 4.13 (s, 2, $ArCH_2$), 4.43 (q, J = 7 Hz, 2, CH_2CH_3), 6.85, 7.00, 7.62, 7.77 (AB q, 2, 5-H and 6-H), 6.77, 6.92, 7.10, 7.25 (AA'BB' q, 4, 2'-H, 3'-H, 5'-H, and 6'-H). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.14. Found: C, 67.27; H, 6.30.

2'-(Ethoxycarbonyl)-4,3',4'-trimethoxydeoxybenzoin (27) was obtained in 57% yield from **11** by the same procedure: mp 81–82 °C; IR 1720, 1670, 1260, 830 cm^{-1}; NMR δ 1.26 (t, J = 7 Hz, 3, CH_2CH_3), 3.87, 3.90 (superimposed s, 9, OCH_3), 4.23 (s, 2, $ArCH_2$), 4.28 (q, J = 7 Hz, 2, CH_2CH_3), 6.87, 7.02, 7.96, 8.11 (AA'BB' q, 4, 2-H, 3-H, 5-H, and 6-H, 6.95 (s, 2, 5'-H and 6'-H). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.14. Found: C, 66.98; H, 6.31.

3-(3,4-Dimethoxybenzylidene)-6,7-dimethoxyphthalide (28) and 3-(3,4-Dimethoxyphenyl)-7,8-dimethoxyisocoumarin (29). Compound **12** (19 g, 52.7 mmol) was lithiated according to the general procedure except that the ice bath was removed after the addition of *n*-butyllitium; solid CO_2 was used as the electrophile. The aqueous phase from the hydrolyzed reaction mixture was washed with ether, made acidic by adding concentrated HCl, and extracted with CH_2Cl_2. The organic extract was dried and evaporated. The residue was suspended in 100% H_3PO_4 (150 mL) and the mixture heated on a steam bath for 1 h. The resulting solution was poured into water, the oil which separated was taken up in $CHCl_3$, and the organic solution was washed with diluted NaOH, dried, and evaporated to give a thick oil which solidified by trituration with EtOH. This material (13.5 g, 74.9%) turned out to be a mixture of **28** and **29** in the approximate ratio of 7:3. Compound **28** was obtained in a pure form by crystallization of the mixture from $CHCl_3$/EtOH: mp 170–172 °C; IR 1770 (five-membered lactone), 1500, 1260, 1010, 800 cm^{-1}; NMR δ 3.88, 3.90, 3.92, 4.15 (4 s, 4 × 3, OCH_3), 6.15 (s, 1, vinylic), 6.75, 6.88, 7.03–7.37 (m, 5, aromatic). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.30; H, 5.30. By refluxing **28** with an excess of sodium methoxide in MeOH, a deep red solution was obtained, from which 2-(3,4-dimethoxyphenyl)-6,7-dimethoxyindan-1,3-dione separated as a solid [mp 189–191 °C (lit.[8] mp 190–191 °C)] on treatment with diluted HCl. The isocoumarin **29** was obtained in a pure form by chromatography (silica gel, eluant $CHCl_3$) and recrystallization from $CHCl_3$/MeOH: mp 160 °C; IR 1720 (six-membered lactone), 1270, 1250, 1010, 800 cm^{-1}; NMR δ 3.90, 3.93, 3.96 (partially superimposed s, 12, OCH_3), 6.70 (s, 1, vinylic), 6.83–7.53 (m, 5, aromatic). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.35; H, 5.46.

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Registry No. 1, 2878-54-8; **2**, 2878-55-9; **3**, 3840-28-6; **4**, 86633-25-2; **5**, 59276-33-4; **6**, 59259-90-4; **7**, 85452-72-8; **8**, 86633-26-3; **9**, 86633-27-4; **10**, 86633-28-5; **11**, 86633-29-6; **12**, 86633-30-9; **15**, 569-31-3; **16**, 4741-65-5; **17**, 86633-31-0; **18**, 86633-32-1; **19**, 86633-33-2; **20**, 65495-31-0; **21**, 75267-19-5; **22**, 519-05-1; **23**, 58343-48-9; **24**, 86633-34-3; **25**, 86633-35-4; **26**, 86633-36-5; **27**, 86633-37-6; **28**, 86633-38-7; **29**, 86633-39-8; ethyl vinyl ether, 109-92-2; 3,4-dimethoxybenzyl alcohol, 93-03-8; 3,4-(methylenedioxy)benzyl alcohol, 495-76-1; 4-methoxybenzyl alcohol, 105-13-5; 3,4-dimethoxybenzaldehyde, 120-14-9; 3,4-(methylenedioxy)benzaldehyde, 120-57-0; (3,4-dimethoxyphenyl)acetaldehyde, 5703-21-9; [3,4-(methylenedioxy)phenyl]-acetaldehyde, 6543-34-6; 2-(3,4-dimethoxyphenyl)ethyl alcohol, 7417-21-2; (4-methoxyphenyl)acetic acid, 104-01-8; 1,2-dimethoxybenzene, 91-16-7; 3,4,4'-trimethoxydeoxybenzoin, 4927-54-2; ethylene glycol, 107-21-1; (3,4-dimethoxyphenyl)acetic acid, 93-40-3; methoxybenzene, 100-66-3; 3,3',4'-trimethoxydeoxybenzoin, 4927-53-1; 3,4,3',4'-tetramethoxydeoxybenzoin, 4927-55-3; 2-(3,4-dimethoxyphenyl)-6,7-dimethoxyindan-1,3-dione, 1641-12-9.

Studies in the 2,4-Disubstituted Adamantanes. Preparation and Reactivity of Pure Epimeric 4-Hydroxy- and 4-Methoxyadamantan-2-ones[1]

James G. Henkel* and Joni H. Spector

Section of Medicinal Chemistry and Pharmacognosy, School of Pharmacy, U-92, The University of Connecticut, Storrs, Connecticut 06268

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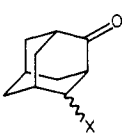
Facile syntheses of the epimerically pure 4(e)- and 4(a)-hydroxyadamantan-2-ones (**7** and **8**), as well as the corresponding 4(e)- and 4(a)-methoxyadamantan-2-ones (**9** and **10**), are reported. Although **7** and **8** are both acid and base labile, the corresponding ethylene ketals are stable to base and serve as useful intermediates for both syntheses. The acid-catalyzed epimerization of **7** and **8** was studied and found to occur under relatively mild conditions, while the corresponding methoxy derivatives were found to be inert to the same acidic conditions. This approach offers a convenient route to protected 4-substituted adamantan-2-ones that are configurationally stable to further synthetic transformations.

The chemistry of bridge-substituted adamantanes has stimulated considerable investigative effort in recent years.[2-4] One family within this series that has been particularly rich in its yield of chemical insight is the 4-substituted adamantan-2-one system, **1**. The defined geometry of this series is ideally suited for studies of a variety of intramolecular mechanistic processes[5,6] as well



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as biological[7] interactions. Of particular interest is the strong influence of the stereochemistry of the 4-substituent on chemical reactivity. When X is equatorial to the cyclohexanone ring portion of the molecule, π-route-related fragmentation reactions are often observed. Cogent ex-

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