Angular Methylation

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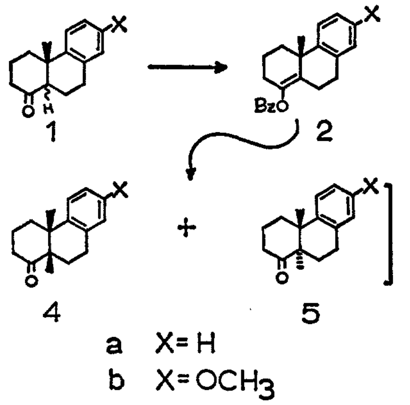
We wish to report one possibly useful solution to the general problem of angular methylation of ketones. It involves reaction between enolate ions, produced in a structurally specific manner by the procedure of House,[1] and iodomethylzinc iodide (Simmons–Smith reagent)[2] and leads directly to the α-methylated ketone.[3]

In the case at hand we were faced with the problem of angular methylation of two ketones **1a** and **1b**.[4]



Enol benzoylation of **1a** was achieved by the action of benzoic anhydride and perchloric acid to afford principally $\Delta^{4,5}$-enol benzoate **2a**. Enol acetylation afforded mainly the $\Delta^{3,4}$ isomer. Conversion of enol benzoate **2a** into lithium enolate **3a** by the procedure of House and Trost[1] followed by reaction with methyl iodide under a variety of conditions afforded in all cases an inseparable mixture of un-, mono-, di-, and trimethylated ketones. The steric situation here presumably slows methylation to such a degree that intermolecular transenolization may effectively compete with it. In marked contrast to these results addition of a solution of Simmons–Smith reagent to **3a** afforded high (65–75%) yields of a 3:1 mixture of *cis* (**4a**) and *trans* (**5a**) angularly methylated ketones without formation of any higher alkylated ketones.

In an exactly analogous manner **1b** was enol benzoylated, the enol benzoate was treated with methyllithium, and **3b** was allowed to react with an excess of Simmons–Smith reagent to afford in good yield a 7:3 mixture of **4b** and **5b**.

The actual processes involved in this methylation of **3a** and **3b** are not clear since quenching of the reaction mixture with deuterated acids afforded deuterium-free **4** and **5**. Two of the three hydrogens of the introduced methyl group are derived from the Simmons–Smith reagent since use of methylene iodide-d_2 [5] in alkylation of **3b** afforded **4b**-d_2 and **5b**-d_2 of the expected isotopic purity.

This synthetic procedure could prove of use in those cases where one wishes to introduce an alkyl group[6,7] by a process that is fast relative to any possible transenolization.[8]

Stoichiometric production of the enolate ion as above would seem to be a prerequisite of application of this synthetic method.

Experimental Section

Infrared spectra were determined in chloroform on a Model IR-5 Beckman infrared recording spectrophotometer. Ultraviolet adsorption spectra were determined in 95% ethanol on a Model 8 Cary recording spectrophotometer. Nuclear magnetic resonance (nmr) spectra were determined on a Varian Associates A-60 or A-60A recording spectrometer in deuteriochloroform, using tetramethylsilane (τ 10 ppm) as an internal reference. Melting points were determined on a calibrated Fisher-Johns melting point apparatus. The microanalyses were carried out by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

1-Benzoyloxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (2a).—A solution of 67.8 g (0.300 mol) of benzoic anhydride, 0.5 ml of 65% perchloric acid, 150 ml of methylene chloride and 30.0 g (0.143 mol) of **1a**[9] was stirred at room temperature under nitrogen for 3 hr. The solution was diluted with methylene chloride, washed successively with saturated sodium bicarbonate solution and water, and dried over magnesium sulfate. After removal of the solvent *in vacuo* the resulting brown oil was chromatographed on alumina to afford ultimately 30.6% (68% yield) of **2a**, an oil. An analytical sample was prepared by evaporative distillation at 140° (0.1 mm): infrared 5.80 μ (enol benzoate C=O); nmr τ 1.8–2.0 (2 H, multiplet, *o*-benzoyloxy aryl H), 2.3–3.0 (7 H, multiplet, aryl H), 7.0–7.5 (2 H, multiplet, benzylic CH$_2$), 8.25 (3 H, singlet, angular CH$_3$); mass spectrum (*m/e*) 318 (parent, 2%), 303 (7%), 105 (100%).

Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 82.79; H, 6.90.

cis- **(4a) and** *trans*-**4a,10a-Dimethyl-3,4,4a,9,10,10a-hexahydro1(2H)phenanthrone (5a).**—Simmons-Smith reagent[2] was prepared by refluxing for 55 min a mixture of 396 g (1.48 mol) of methylene iodide, 96 g (1.48 mol) of zinc-copper couple, 400 ml of ether, and a large crystal of iodine. While this reagent was cooling to 0°, in another flask 200 ml of 1.3 *M* ethereal methyllithium was added to a solution of 200 ml of anhydrous dimethoxyethane (DME) containing a few crystals of triphenylmethane. To the bright red methyllithium solution was added dropwise a solution of 23.0 g (0.0724 mol) of enol benzoate **2a** in 100 ml anhydrous dimethoxyethane. The Simmons-Smith reagent was filtered under a nitrogen atmosphere through a dry sintered-glass funnel, and the yellow filtrate was added slowly to the pink enolate solution. The initial reaction appeared to subside after addition of 20% of the reagent. After stirring for 30 min at room temperature, the reaction was quenched by pouring it into saturated aqueous ammonium chloride, and the ether layer was separated, washed with water, and dried over magnesium sulfate. The solvent was removed *in vacuo* to yield 20.0 g of a dark yellow oil. Chromatography of this on silica gel afforded 10.5 g (64% yield) of a 7:3 (by nmr) mixture of **4a** and **5a**. Crystallization from hexane of the early fractions afforded 5.86 g of **4a**: mp 67–68°; infrared 5.88 μ; nmr τ 2.6–2.9 (4 H, multiplet, aryl H), 6.9–7.3 (2 H, multiplet, benzylic -CH$_2$-), 8.75 (3 H, singlet, angular CH$_3$), 8.90 (3 H, singlet, angular CH$_3$); mass spectrum (*m/e*) 288 (parent, 77%), 213 (45%), 143 (100%).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.96; H, 8.75.

Crystallization of the last fraction eluted from hexane yielded 1.81 g (11%) of pure **5a**: mp 79–80°; infrared 5.88 μ (saturated

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[1] H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965), and earlier papers.

[2] H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

[3] E. Wenkert and D. A. Berges [*ibid.*, **89**, 2507 (1967)] have reported a similar reaction between enol ethers and iodomethylzinc iodide followed by hydrolysis of the alkoxycyclopropane.

[4] Details of the stereochemical assignment of ketones **4** and **5** will be reported later in a full paper.

[5] E. P. Blanchard and H. E. Simmons, *J. Amer. Chem. Soc.*, **86**, 1337 (1964).

[6] J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron Lett.*, 3353 (1966).

[7] J. Furukawa, N. Kawabata, and J. Nishimura, *ibid.*, 3495 (1968).

[8] J. A. Marshall, G. L. Bundy, and W. I. Fanta, *J. Org. Chem.*, **33**, 3913 (1968).

[9] G. Stork and A. Burgstahler, *J. Amer. Chem. Soc.*, **73**, 3544 (1951).

C=O); nmr τ 2.6–2.9 (4 H, multiplet, aryl H), 6.9–7.3 (2 H, multiplet, benzylic $-CH_2-$), 8.92 (3 H singlet, angular CH_3), 8.93 (3 H, singlet, angular CH_3); mass spectrum (*m/e*) 228 (parent, 65%), 213 (73%), 131 (100%).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.07; H, 8.75.

1-Benzoyloxy-7-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (2b).—Following a procedure similar to that for the preparation of **2a**, 5.98 g (0.025 mol) of **1b**[8] was converted into 4.81 g (66%) of **2b**: mp 84–86°; infrared 5.78 μ (enol benzoate C=O); nmr τ 1.8–2.0 (2 H, multiplet, orthobenzoloxy aryl H), 2.4–3.5 (7 H, multiplet, aryl H), 6.24 (3 H, singlet, OCH_3), 8.54 (3 H, singlet, angular CH_3); ultraviolet λ_{max} 285 mμ (log ε 3.46), 275 (3.54), 228 (4.36); mass spectrum (*m/e*) 348 (parent 0.5%), 333 (6%), 105 (100%).

Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.33; H, 7.04.

cis- **(4b) and** *trans*-**4a,10a-Dimethyl-7-methoxy-3,4,4a,9,10,10a-hexahydro-1(2H)-phenanthrone (5b).**—Following a procedure similar to that for the preparation of **4a** and **5a**, 1.00 g (2.87 mmol) of **2b** was converted into 0.533 g (72%) of a 70:30 mixture of **4b** and **5b**. Crystallization of the mixture from hexane at room temperature yielded 114 mg (16%) of pure **5b**: mp 128–129.5; infrared 5.87 μ (saturated C=O); nmr τ 2.6–2.9 (1 H, multiplet, aryl H), 3.0–3.4 (2 H, multiplet, aryl H), 6.21 (3 H, singlet, OCH_3), 8.92 (3 H, singlet, angular CH_3), 8.93 (3 H, singlet, angular CH_3); mass spectrum (*m/e*) 258 (parent 47%), 243 (100%).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.35; H, 8.32.

Upon cooling the hexane solutions to 0° **4b** slowly crystallized. After several crops there was obtained 292 mg (40%) of **4b**: mp 50.5–53.5° (after one recrystallization from hexane); infrared 5.88 μ (s, saturated C=O); nmr τ 2.7–2.9 (1 H, multiplet, aryl H), 3.1–3.5 (2 H, multiplet, aryl H), 6.24 (3 H, singlet, $-OCH_3$), 8.77 (3 H, singlet, angular CH_3), 8.90 (3 H, singlet, angular CH_3); mass spectrum (*m/e*) 258, 243 (100%).

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.14; H, 8.75.

Registry No.—**2a**, 18968-34-8; **2b**, 18936-36-2; **4a**, 18936-37-3; **4b**, 18936-38-4; **5a**, 18936-39-5; **5b**, 18936-40-8.

The Epoxidation of 3,3,6,6-Tetramethyl-1,4-cyclohexadiene[1]

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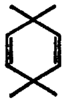
In 1965, we reported the synthesis and some reactions of 3,3,6,6-tetramethyl-1,4-cyclohexadiene (**1**).[2] Our interest in this system and the reports of the unusual reactivity of the structurally similar norbornadiene toward epoxidation[3] stimulated us to investigate the oxidation of **1** with peracetic acid. The recent publication of Berchtold's work on 1,4-cyclohexadiene[4] prompted us to report our findings.

The starting material, **1**, as obtained by the pyrolysis of the diacetate of 2,2,5,5-tetramethylcyclohexane-1,3-diol was contaminated with about 20% *p*-xylene.[2] To obviate the necessity of separating this contaminant from **1** it was determined that *p*-xylene did not react with peracetic acid under the conditions of our experiments. The epoxidation of **1** with peracetic acid in the presence of sodium carbonate[5] resulted in the formation of 2,2,5,5-tetramethyl-7-oxabicyclo[4.1.0]heptane (**2**) in 30% yield and *cis*-2,2,6,6-tetramethyl-4,8-dioxatricyclo[5.1.0.0^{3,5}]octane (**3**) in 11% yield. A gas chromatogram of the crude reaction mixture indicated that these were the only volatile products present and thus **1** upon epoxidation does not yield any products resulting from a skeletal rearrangement. The low yields of the two products were the result of their isolation by preparative gas chromatography rather than the presence of unidentified reaction products.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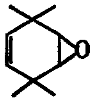
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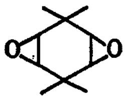
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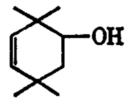

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Monoepoxide **2** was characterized by its elemental analysis, its spectral properties, and its conversion by reduction with lithium aluminum hydride into 3,3,6,6-tetramethylcyclohexen-4-ol (**4**).

In order to place the structural assignment of **2** on firm ground, but with the somewhat unusual lithium aluminum hydride reduction of *exo*-2,3-epoxynorborn-5-ene[3b] in mind, we reduced **2** with lithium aluminum hydride. As in the epoxidation reaction above there was no evidence of a sketetal rearrangement and **4** was obtained in 71% yield. This material was identified by its elemental analysis, its spectral properties, and its conversion into a 3,5-dinitrobenzoate.

Bisepoxide **3** was characterized by its elemental analysis and its infrared and nmr spectra. The *cis* stereochemistry was assigned on the basis of the nmr spectrum and the examination of a molecular model of monoepoxide **2**. The nmr spectrum of **3** (CCl_4) had a singlet at δ 1.08 (6 H), a singlet at 1.22 (6 H), and a singlet at 2.56 (4 H). This spectrum is consistent with a system with four equivalent ring junction protons and a nonequivalent pair of two equivalent methyl groups, that is, the *cis*-bisepoxide. The *trans*-bisepoxide would be expected to have an nmr spectrum that would indicate the equivalence of the 12 methyl protons and the equivalence of the four ring junction protons.

The selective epoxidation of **2** to form **3** can be understood by examination of a molecular model of **2**. The combination of the epoxide ring (with forces carbon atoms 3, 4, 5, and 6 into a plane[6]) and the carbon–carbon double bond (which forces carbon atoms 1, 2, 3, and 6 into a plane) requires that the ring assume a boat conformation. There are two boat conformations possible. In one, **5**, the "flagpole" and "bowsprit" methyl groups are *trans* to the oxide ring and, in the other, **6**, they are *cis* to the oxide ring. Inspection of models of the two conformers shows that in **6** there are two hydrogen–methyl eclipsings and two methyl–

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[1] Taken from the M.S. Thesis of J. T. S., Middlebury College, 1967.

[2] F. W. Grant, R. W. Gleason, and C. H. Bushweller, *J. Org. Chem.*, **30**, 290 (1965).

[3] (a) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Amer. Chem. Soc.*, **85**, 582 (1963); (b) J. Meinwald, S. S. Labana, L. L. Labana, and G. H. Wahl, *Tetrahedron Lett.*, No. 23, 1789 (1965).

[4] T. W. Craig, G. R. Harvey and G. A. Berchtold, *J. Org. Chem.*, **32**, 3743 (1967). The authors are indebted to Professor Berchtold for a copy of their manuscript and for the nmr spectra of the *cis*- and *trans*-bisepoxide of 1,4-cyclohexadiene and to Dr. Craig for a copy of his thesis.

[5] M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Amer. Chem. Soc.*, **82**, 4328 (1960).

[6] B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947).