Effect of Substituents on the Reactivity of Various Alkyl- and Phenyl-Substituted 3,4-Dihydro-2*H*-pyrans with *tert*-Butyl Hypochlorite[1]

Giuseppe F. Weber[2] and Stan S. Hall*

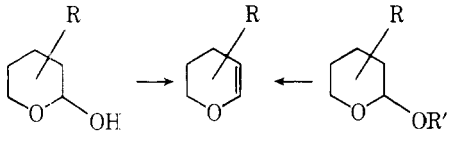
Olson Chemistry Laboratories, Rutgers University, Newark, New Jersey 07102

Received June 13, 1978

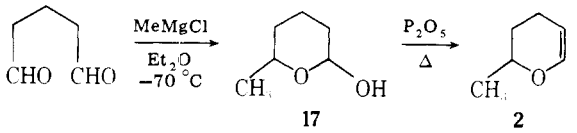
A series of alkyl- and phenyl-substituted 3,4-dihydro-2*H*-pyrans were synthesized: 2-methyl- (**2**), 4-methyl- (**3**), 5-methyl- (**4**), 6-methyl- (**5**), 6-phenyl- (**6**), and 2,2,6-trimethyl-3,4-dihydro-2*H*-pyran (**7**). The effect of substituents on the reactivity of the 3,4-dihydro-2*H*-pyran ring was determined using *tert*-butyl hypochlorite in competitive experiments with 3,4-dihydro-2*H*-pyran (**1**). The relative reactivities are **7** > **6** > **5** > **4** > **3** > **2** ≈ **1** with the phenyl and methyl substituents at the C-6 position having the most pronounced rate enhancement effect. The products of the addition of *tert*-butyl hypochlorite to the 3,4-dihydro-2*H*-pyrans **1–7** are cis/trans mixtures of the corresponding 1,2-addition products 3-chloro-2-methoxytetrahydropyrans **9–15**.

In our ongoing studies of the chemistry of 2-alkoxy-3,4-dihydro-2*H*-pyrans we recently observed significant rate enhancements attributable to alkyl substituents on the 2-alkoxy-3,4-dihydro-2*H*-pyran ring system, particularly at position C-6.[1] And since it was also determined in the same study that the 2-alkoxy substituents, which are predominantly axial, have a deactivating effect on the ring system, it was of interest to examine the sole effect of the alkyl and phenyl substituents on the reactivity of the 3,4-dihydro-2*H*-pyran ring. This information may prove especially useful because of the importance of 3,4-dihydro-2*H*-pyrans and other vinyl ethers as hydroxyl protecting groups in synthesis.[3]

Synthesis. Various methyl- and phenyl-substituted 3,4-dihydro-2*H*-pyrans **2–7** used in this study were generally prepared by dehydration or elimination of alcohol from the appropriately substituted 2-hydroxy- or 2-alkoxytetrahydropyrans.



2-Methyl-3,4-dihydro-2*H*-pyran (**2**), for example, was obtained by the phosphorus pentoxide dehydration of 2-hydroxy-6-methyltetrahydropyran (**17**) that had been prepared[4]

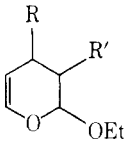


17 **2**

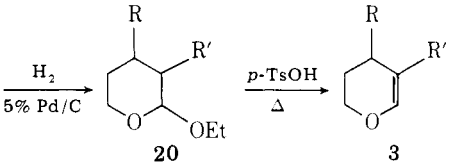
by the addition of 1 equiv of methylmagnesium chloride in ether to a cold (−70 °C) ethereal solution of glutaraldehyde. The coupling constants of the NMR signal centered at δ 3.95 (four overlapping quartets, J_{aa} = 12 Hz, J_{ae} = 2.9 Hz, J_{vic} = 6.6 Hz) for the proton at C-2 indicated the predominate conformer of **2** to be with the C-2 methyl substituent equatorial.

4-Methyl- (**3**) and 5-methyl-3,4-dihydro-2*H*-pyran (**4**) were prepared by a general approach previously described[5] that involves the hydrogenation of 4-methyl- (**18**) and 3-methyl-2-ethoxy-3,4-dihydro-2*H*-pyran (**19**), each prepared by cycloaddition reactions.[1,6] The 4-methyl- (**20**) and 3-methyl-2-ethoxytetrahydropyran (**21**) were subsequently converted to **3** and **4**, respectively, by the elimination of ethanol during distillation from a catalytic amount of *p*-toluenesulfonic acid.

Alternatively, 5-methyl-3,4-dihydro-2*H*-pyran (**4**) was also prepared by hydrolysis and dehydration of 5-acetoxy-2-methyl-1-pentenyl methyl ether (**23**) that was prepared from 4-pentanon-1-ol acetate (**22**) using a Wittig reaction with triphenylphosphonium methoxymethylide.

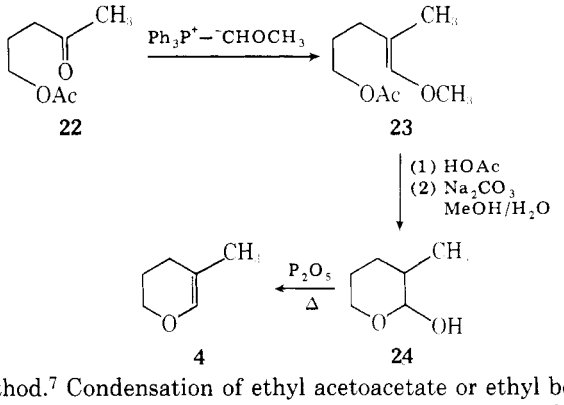


18 (R = CH_3, R′ = H)
19 (R = H, R′ = CH_3)



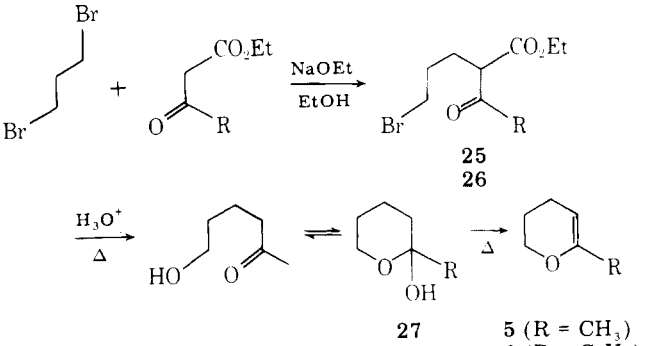
20 **3**
21 **4**

6-Methyl- (**5**) and 6-phenyl-3,4-dihydro-2*H*-pyran (**6**) were both prepared by improvements of a previously described



22 **23** **4** **24**

method.[7] Condensation of ethyl acetoacetate or ethyl benzoylacetate with 1,3-dibromopropane in the presence of sodium ethoxide in ethanol yielded the corresponding condensed product **25** or **26**. Subsequent hydrolysis with aqueous hydrochloric acid resulted in the formation of the hydroxy ketone **27** or **28**, which was a mixture of the cyclic and acyclic material. Dehydration by heating **27** in the presence of aluminum oxide or by distilling **28** yielded the corresponding



25 **26**
27 **28** **5** (R = CH_3) **6** (R = C_6H_5)

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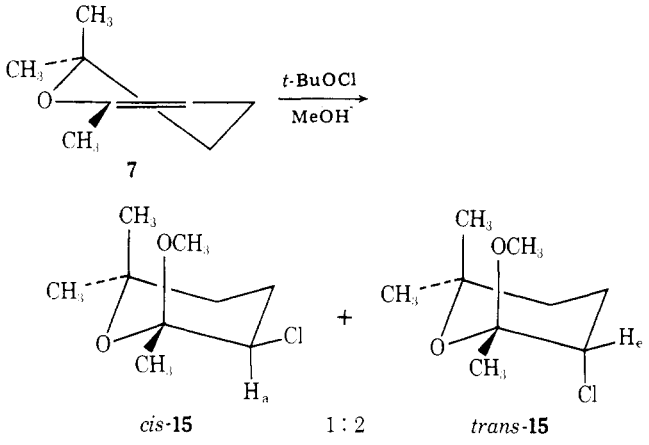
6-methyl- (**5**) or 6-phenyl-3,4-dihydro-2*H*-pyran (**6**).

2,2,6-Trimethyl-3,4-dihydro-2*H*-pyran (**7**) was prepared by a previously described thermally promoted cyclization of methyl vinyl ketone and isobutylene.[8]

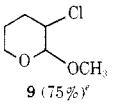
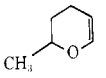
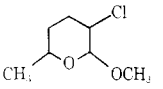
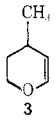
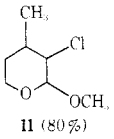
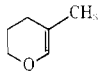
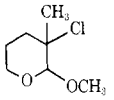
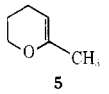
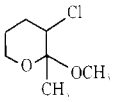
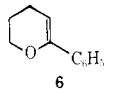
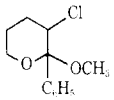
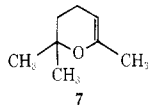
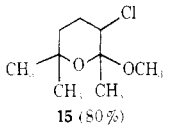
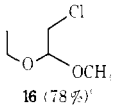
Reaction and Products. The choice of *tert*-butyl hypochlorite as the electrophile for this study and previous studies was made because of its reactivity, convenience in preparation, and handling, and so that it would be possible to compare directly these results with a similar study with the substituted 2-alkoxy-3,4-dihydro-2*H*-pyrans.[1] Table I is a listing of the products of the reaction of *tert*-butyl hypochlorite in methanol at 0 °C with each of the substituted 3,4-dihydro-2*H*-pyrans **2–7**, as well as 3,4-dihydro-2*H*-pyran (**1**) and ethyl vinyl ether (**8**). Addition of *tert*-butyl hypochlorite to these unsaturated compounds yielded the corresponding 1,2-addition products.[9] With the 3,4-dihydro-2*H*-pyrans, the 1,2-addition products are diastereomeric mixtures that resulted from both cis and trans addition to the olefin.[10] For example, addition of *tert*-butyl hypochlorite to 2,2,6-trimethyl-3,4-dihydro-2*H*-pyran (**7**) in methanol at 0 °C resulted in a 1:2 diastereomeric cis/trans mixture of 3-chloro-2-methoxy-2,6,6-trimethyltetrahydropyran (**15**). Assuming the methoxy



group at the newly developed anomeric center (C-2) is axial in both isomers as is predicted by the anomeric effect,[11] then the cis and trans product **15** are distinguishable and assignable by NMR. The minor component is the cis addition product **15**, where the proton at C-3 is axial since the NMR signal centered at δ 3.75 for this proton is an ABX doublet of doublets pattern (J_{aa} = 12.5 Hz, J_{ae} = 4.4 Hz). The major component can be assigned the trans addition configuration, where the proton at C-3 is clearly equatorial since the NMR signal centered at δ 3.91 is a superficial triplet ($J_{ea} \approx J_{ee} = \sim$ 3 Hz).

Relative Rate Studies. Relative rate studies between each of the substituted 3,4-dihydro-2*H*-pyrans **2–7** and 3,4-dihydro-2*H*-pyran (**1**) were performed to measure the effect of the alkyl and phenyl substituents at various positions on the reactivity of the 3,4-dihydro-2*H*-pyran ring system. Equimolar mixtures of each substituted 3,4-dihydro-2*H*-pyran **2–7** and 3,4-dihydro-2*H*-pyran (**1**) were allowed to compete for an equivalent of *tert*-butyl hypochlorite. The relative ratio (GLC analyses) of the product material from the substituted 3,4-dihydro-2*H*-pyran (**2–7**) and 3,4-dihydro-2*H*-pyran (**1**) was then used to determine the reactivity of the substituted 3,4-dihydro-2*H*-pyran relative to the unsubstituted pyran **1**. These results are summarized in Table I. There is a substantial difference in the relative rates of the variously substituted 3,4-dihydro-2*H*-pyrans that is directly attributable to the substituent(s). The most significant seems to be the activating effect of the methyl group at C-5 (rate enhanced by a factor of ~2) and both the methyl and phenyl group at C-6 (rate enhanced by a factor of ~4) toward electrophilic reagents. In these cases, the substituent is directly attached to the unsaturation and because the field effects for these groups are electron-donating would be expected to have some activating effect. Had the reactions in this relative rate study been allowed to go only 10% to completion rather than to 50%, these relative rates would have been slightly higher. For example, when an equimolar mixture of 2,2,6-trimethyl-3,4-dihydro-2*H*-pyran (**7**), the most reactive in this series, and 3,4-dihydro-2*H*-pyran (**1**) competed for only 0.2 equiv of *tert*-butyl hypochlorite, the relative rate for the substituted dihydropyran **7** was ~6 rather than ~5. Also included in Table I is the acyclic example ethyl vinyl ether that has about half the reactivity of 3,4-dihydro-2*H*-pyran toward electrophiles.

Table I. *tert*-Butyl Hypochlorite Addition to Substituted 3,4-Dihydro-2*H*-pyrans[a] and Relative Reactivity[b]

dihydropyran[c]	relative rate to pyran 1[b]	product[c] (yield)[d]
 1	1.00	 9 (75%)[e]
 2	1.16 ± 0.11[f]	 10 (81%)
 3	1.29 ± 0.04	 11 (80%)
 4	1.90 ± 0.13	 12 (72%)
 5	3.75 ± 1.27	 13 (78%)
 6	4.12 ± 0.67	 14 (47%)[g]
 7	4.75 ± 0.84[h]	 15 (80%)
 8	0.45 ± 0.02	 16 (78%)[f]

[a] Reaction conditions are described in the Experimental Section for the addition of *tert*-butyl hypochlorite to 2-methyl-3,4-dihydro-2*H*-pyran (**2**). [b] Relative rate study conditions are those described in the Experimental Section for 2-methyl-3,4-dihydro-2*H*-pyran (**2**) vs. 3,4-dihydro-2*H*-pyran (**1**). [c] Composition analyses for all new 3,4-dihydro-2*H*-pyrans (±0.4% for C, H) and all new 1,2-addition products (±0.4% for C, H, Cl) were submitted to the Editor. [d] Isolated by column chromatography unless stated otherwise. [e] Isolated by distillation. [f] Standard deviation using experiments performed in triplicate. The error is large in some cases where the product mixtures were not completely resolved by GLC. [g] Isolated after recrystallization. [h] When the reaction was allowed to go only 10% to completion (1 mmol each of **7** and **1** and only 0.2 mmol of *tert*-butyl hypochlorite) rather than 50% to completion, the relative rate was 6.12 ± 0.49.

Experimental Section[12]

General Comments. The syntheses of the substituted 3,4-dihydro-2*H*-pyrans **2–6** are described in detail in this section. 3,4-Dihydro-2*H*-pyran (**1**) and ethyl vinyl ether (**8**) are available from Aldrich Chemical Co. The *tert*-butyl hypochlorite was prepared,[13] dried, and stored over $CaCl_2$ in the dark below 0 °C. For best results, it is recommended to use rather freshly prepared *t*-BuOCl. For the reactions involving *t*-BuOCl, the methanol was reagent grade and the reactions were performed in oven-dried glassware under a static argon atmosphere. Gas chromatographic analyses (GLC) were performed on 200 × 0.3 cm (i.d.) glass columns packed with 3.8% silicon gum rubber SE-30 (methyl) or 10% silicon gum rubber XE-60 (25% cyanoethyl, methyl) supported on 60–80 mesh Chromosorb W (AW, DMCS) or on a 150 × 0.3 cm (i.d.) glass column packed with 20% Carbowax 20M supported on 80–100 mesh Chromosorb W (AW, DMCS). Column chromatography was performed on 60–100 mesh Floridin magnesium silicate (Florisil), 70–230 mesh silica gel 60 (Merck), or aluminum oxide (W200, neutral, activity grade Super III) columns by eluting with pentane–Et_2O. Distillations were accomplished with a short-path or Kugelrohr apparatus; all boiling points are uncorrected. The assigned structure of each product (or mixture) was consistent with the spectral data. Composition analyses (±0.4% for C, H or C, H, Cl) for all the new substituted 3,4-dihydro-2*H*-pyrans **2–6**, 1,2-addition products **10–16**, and synthetic intermediates **17**, **20–24**, and **27** were submitted to the editor. Significant data on all new compounds are included in the Experimental Section. A representative experiment for the addition of *t*-BuOCl to a substituted 3,4-dihydro-2*H*-pyran (**2**) and a relative rate study experiment between **2** and **1** are described to illustrate these procedures, and then the total syntheses of the substituted 3,4-dihydro-2*H*-pyrans **2–6** are described.

Reaction of 2-Methyl-3,4-dihydro-2*H*-pyran (2) with *tert*-Butyl Hypochlorite. To a stirred solution (0–5 °C) of 980 mg (10.0 mmol) of 2-methyl-3,4-dihydro-2*H*-pyran (**2**) in 10 mL of methanol was slowly added 1.20 g (11 mmol) of *tert*-butyl hypochlorite in 2 mL of methanol. After 10 min the reaction mixture was partitioned between brine and petroleum ether. The organic layer was separated, washed with water, and dried ($MgSO_4$). Removal of solvent in vacuo afforded 880 mg of an oil that on analysis (GLC and NMR) indicated a 75:17:8 diastereomeric 1,2-addition mixture of **10**. Chromatography (Florisil, 1:1 pentane–Et_2O) afforded three fractions, each enriched in one of the diastereomers (81% total isolated yield).

3-Chloro-2-methoxy-6-methyltetrahydropyran (10). Major diastereomer: bp 60 °C (12 torr); NMR (100 MHz, $CDCl_3$) δ 4.67 (1 H, superficial d, J_{ee} = ~1 Hz, equatorial anomeric proton at C-2, a trans isomer), 4.05–3.90 (1 H, m), 3.90–3.65 (1 H, m), 3.37 (3 H, s), 2.65–1.25 (4 H, complex m), 1.18 (3 H, d, J = 6.2 Hz); MS *m/e* (rel intensity) 166 (M^+, 1), 164 (M^+, 3), 135 (6), 133 (18), 106 (7), 104 (22), 97 (6), 94 (11), 92 (31), 88 (16), 67 (11), 61 (100), 55 (23). NMR of a minor (17%) diastereomer (100 MHz, $CDCl_3$): δ 4.24 (1 H, d, J_{aa} = 8 Hz, axial anomeric proton at C-2, a trans isomer), 3.45 (3 H, s) superimposed on 4.0–3.34 (2 H, m), 2.56–1.36 (4 H, complex m), 1.23 (3 H, d, J = 6 Hz).

3-Chloro-2-methoxy-4-methyltetrahydropyran (11). The bp 80–85 °C (12 torr) fraction was a 50:35:15 diastereomeric mixture: NMR (100 MHz, $CDCl_3$) δ 4.70 (0.5 H, superficial d, J = ~1 Hz) superimposed on 4.84–4.62 (0.15 H, m), 4.19 (0.35 H, d, J = 8 Hz), 4.09–3.11 (3 H, complex m) on which is superimposed three singlets at 3.50 (1.05 H), 3.42 (0.45 H), and 3.36 (1.5 H), 2.52–2.05 (1 H, m), 2.05–1.0 (2 H, complex m) on which is partially superimposed three doublets at 1.13 (1.05 H, d, J = 6.2 Hz), 0.99 (1.5 H, d, J = 6.6 Hz), and 0.87 (0.45 H, d, J = 6.4 Hz); MS *m/e* (rel intensity) 166 (M^+, 1.5), 164 (M^+, 4.5), 138 (2), 136 (6), 135 (5), 133 (15), 106 (5), 104 (14), 78 (21), 76 (67), 69 (55), 61 (100), 41 (100).

3-Chloro-2-methoxy-3-methyltetrahydropyran (12). Chromatography (Florisil, 4:1 pentane–Et_2O) afforded two diastereomers. Major diastereomer: bp 80 °C (16 torr); NMR (100 MHz, $CDCl_3$) δ 4.42 (1 H, s), 3.93–3.45 (2 H, m), 3.40 (3 H, s), 2.2–1.75 (3 H, m), 1.75–1.33 (1 H, m) on which is superimposed 1.52 (3 H, s); MS *m/e* (rel intensity) 166 (M^+, 1.2), 164 (M^+, 3.6), 138 (3), 136 (11), 135 (7), 133 (24), 106 (17), 104 (37), 78 (38), 76 (100), 61 (93), 41 (59). Minor diastereomer: NMR (100 MHz, $CDCl_3$) δ 4.16 (1 H, s), 4.06–3.80 (1 H, m), 3.63–3.30 (1 H, m) on which is superimposed 3.48 (3 H, s), 2.35–2.00 (1 H, m), 1.95–1.50 (3 H, m) on which is superimposed 1.61 (3 H, s).

3-Chloro-2-methoxy-2-methyltetrahydropyran (13). Chromatography (silica gel, 9:1 pentane–Et_2O) afforded a 1:1 diastereomeric mixture: NMR (100 MHz, $CDCl_3$) δ 3.97–3.43 (3 H, complex m), 3.27 (1.5 H, s), 3.25 (1.5 H, s), 2.6–1.0 (4 H, complex m), 1.40 (1.5 H, s), 1.37 (1.5 H, s); MS *m/e* (rel intensity) 151 (1), 149 (3), 135 (11), 133 (34), 129 (24), 101 (24), 75 (98), 62 (30), 55 (41), 43 (100).

3-Chloro-2-methoxy-2-phenyltetrahydropyran (14). Chromatography and recrystallization afford a pure diastereomer: mp 76–78 °C; NMR (100 MHz, $CDCl_3$) δ 7.55–7.20 (5 H, m), 4.17 (1 H, t, J = ~3 Hz, equatorial proton at C-3), 3.95–3.85 (1 H, m), 3.85–3.75 (1 H, m), 2.93 (3 H, s), 2.79–1.82 (3 H, complex m), 1.58–1.22 (1 H, m); MS *m/e* (rel intensity) 228 (M^+, 10), 226 (M^+, 27), 197 (7), 195 (21), 137 (24), 136 (43), 105 (100), 77 (31), 55 (11), 51 (9).

3-Chloro-2-methoxy-2,6,6-trimethyltetrahydropyran (15). The bp 52 °C (0.5 torr) fraction was 2:1 diastereomeric mixture: NMR (100 MHz, $CDCl_3$) δ 3.91 (0.67 H, t, J = ~3 Hz, equatorial proton at C-3), 3.75 (0.33 H, d of d, J = 12.5, 4.3 Hz, axial proton at C-3), 3.26 (1 H, s), 3.21 (2 H, s), 2.70–1.50 (4 H, complex m), two sets of methyl singlets at 1.36 (2 H), 1.29 (2 H), 1.21 (2 H), and 1.37 (1 H), 1.34 (1 H), 1.16 (1 H); MS *m/e* (rel intensity) 179 (1), 177 (5), 163 (1), 161 (5), 121 (4), 119 (13), 108 (5), 106 (17), 75 (100), 69 (25), 56 (55), 43 (39).

α-Chloroacetaldehyde Ethyl Methyl Acetal (16): bp 58 °C (20 torr); NMR (60 MHz, $CDCl_3$) δ 4.62 (1 H, t, J = 6 Hz), 3.43 (3 H, s) and 3.53 (2 H, q, J = 7 Hz) superimposed on 4.08–3.23 (2 H, m), 1.25 (3 H, t, J = 7 Hz); MS *m/e* (rel intensity) 109 (10), 107 (26), 95 (19), 93 (59), 89 (56), 81 (12), 79 (44), 61 (100), 43 (47).

Relative Rate Study Using Competitive Conditions. 2-Methyl-3,4-dihydro-2*H*-pyran (2) vs. 3,4-Dihydro-2*H*-pyran (1). To a stirred solution (0–5 °C) of 96 mg (1 mmol) of 2-methyl-3,4-dihydro-2*H*-pyran (**2**) and 84 mg (1 mmol) of 3,4-dihydro-2*H*-pyran (**1**) in 2 mL of methanol was added 108 mg (1 mmol) of *tert*-butyl hypochlorite in 0.2 mL of methanol. After 3 min the reaction mixture was worked up as described above for the reaction with **2** and afforded an oil that was analyzed by GLC. The relative ratio of product material from **2** vs. **1** was calculated by measuring the relative areas of all product peaks and then correcting these areas using predetermined response factors. These response factors[14] were determined under the analysis conditions by the use of standard solutions of known concentrations of each product or product mixture from each dihydropyran.

2-Methyl-3,4-dihydro-2*H*-pyran (2). Using a previously described procedure,[4] 2-hydroxy-6-methyltetrahydropyran (**17**) was prepared as a colorless oil after distillation (55%): bp 110 °C (15 torr); IR ($CHCl_3$) 3600, 3390 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 5.28 (0.33 H, superficial t, J = ~3 Hz), 4.73 (0.67 H, q, J = ~14, 6 Hz) on which is superimposed 4.83 (0.67 H, br s, exchangeable in D_2O), 4.35 (0.33 H, br s, exchangeable in D_2O) that is superimposed on 4.47–3.87 (0.33 H, m), 3.87–3.30 (0.67 H, m), 2.77–2.10 (1 H, m), 2.10–0.90 (5 H, m) on which is superimposed two doublets at 1.20 (2 H, d, J = 6 Hz) and 1.10 (1 H, d, J = 6 Hz); MS *m/e* (rel intensity) 116 (M^+, 8), 98 (32), 88 (28), 83 (21), 70 (30), 57 (30), 55 (37), 43 (100).

Heating (oil bath from 130 to 200 °C) a mixture of 3.8 g (32.8 mmol) of δ-lactol **17** and 38 mg of phosphorus pentoxide in a short-path distillation apparatus afforded 2.22 g of distillate that was dried (K_2CO_3) and redistilled (58–62 °C, 150 torr), yielding 1.35 g (42%) of 2-methyl-3,4-dihydro-2*H*-pyran (**2**): bp 62 °C (150 torr); IR (film) 1650 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 6.37 (1 H, d of t, J = 6.4, ~2 Hz), 4.77–4.58 (1 H, complex m), 3.95 (1 H, four overlapping q, J = 12, 6.6, 2.9 Hz, proton at C-2), 2.19–1.90 (2 H, m), 1.90–1.35 (2 H, m), 1.25 (3 H, d, J = 6.6 Hz); MS *m/e* (rel intensity) 98 (M^+, 80), 83 (40), 79 (12), 69 (30), 57 (100), 55 (30).

4-Methyl-3,4-dihydro-2*H*-pyran (3).[5] A mixture of 14.4 g (0.1 mol) of 2-ethoxy-4-methyl-3,4-dihydro-2*H*-pyran (**18**)[1,6] and 1.4 g of 5% Pd on C in 150 mL of ethyl acetate absorbed ~2.45 L of H_2 in ~8 h at 24 °C and 751 torr. The catalyst was removed by filtration (Celite), the solvent was evaporated in vacuo, and the residue was distilled, yielding 10.2 g (71%) of 2-ethoxy-4-methyltetrahydropyran (**20**) as a colorless liquid: bp 64 °C (21 torr); NMR (100 MHz, $CDCl_3$) δ 4.80 (0.33 H, superficial t, J = ~3 Hz, equatorial anomeric proton), 4.33 (0.67 H, d of d, J = 10, 2.5 Hz, axial anomeric proton), 4.13–3.26 (4 H, complex m), 2.10–0.82 (5 H, m) on which is superimposed 1.20 (3 H, t, J = 7 Hz), 0.94 (2 H, d, J = 6 Hz), and 0.87 (1 H, d, J = 6 Hz); MS *m/e* (rel intensity) 144 (M^+, 3), 143 (27), 99 (100), 75 (82), 70 (39), 55 (76), 47 (53), 42 (63).

Distillation of a mixture of 6.0 g (41.5 mmol) of 2-ethoxy-4-methyltetrahydropyran (**20**), 30 mg of *p*-toluenesulfonic acid, and a trace (0.11 mL) of toluene afforded a fraction (145 °C, 760 torr) that was washed twice with water, dried (K_2CO_3), and redistilled, yielding 3.2 g (78%) of 4-methyl-3,4-dihydro-2*H*-pyran (**3**): bp 58 °C (170 torr); IR (film) 1640 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 6.28 (1 H, d of d, J = 6.3, 1.9 Hz), 4.56 (1 H, d of d with further fine splitting, J = 6.3, 2.9 Hz), 4.13–3.75 (2 H, complex m), 2.45–2.08 (1 H, m), 2.08–1.74 (1 H, m), 1.67–1.10 (1 H, m), 0.98 (3 H, d, J = 6.9 Hz); MS *m/e* (rel intensity) 98 (M^+, 40), 83 (100), 69 (37), 55 (50), 41 (45).

5-Methyl-3,4-dihydro-2*H*-pyran (4).[5] Catalytic hydrogenation of 2-ethoxy-3-methyl-3,4-dihydro-2*H*-pyran (**19**)[1] as described above for **18** afforded 2-ethoxy-3-methyltetrahydropyran (**21**) as a colorless

oil (75%): bp 58 °C (22 torr); NMR (100 MHz, $CDCl_3$) δ 4.51 (0.6 H, d, J_{ee} = 3 Hz, equatorial anomeric proton, trans isomer), 4.02 (0.4 H, d, J_{ea} = 6.5 Hz, equatorial anomeric proton, cis isomer) overlapping 4.02–3.22 (4 H, complex m), 2.0–1.3 (5 H, m), overlapping triplets at 1.19 (1.2 H, t, J = 7 Hz) and 1.17 (1.8 H, t, J = 7 Hz), overlapping doublets at 0.93 (1.2 H, d, J = 7 Hz) and 0.85 (1.8 H, d, J = 7 Hz); MS *m/e* (rel intensity) 144 (M^+, 4), 143 (7), 99 (46), 75 (100), 70 (39), 57 (37), 55 (46), 47 (73), 42 (63).

Distillation of 2-ethoxy-3-methyltetrahydropyran (**21**) from *p*-toluenesulfonic acid as described above for **20** afforded 5-methyl-3,4-dihydro-2*H*-pyran (**4**) as a colorless oil (67%): bp 60–70 °C (160 torr); IR ($CDCl_3$) 1676 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 6.15 (1 H, superficial s with fine splitting), 3.81 (2 H, superficial t, J = ~5 Hz), 2.06–1.62 (4 H, m), 1.49 (3 H, s with fine splitting); MS *m/e* (rel intensity) 98 (M^+, 25), 83 (26), 69 (30), 55 (22), 42 (100).

Dihydropyran **4** was also prepared as follows. To a cooled (2–5 °C), stirred suspension of 41 g (0.12 mol) of methoxymethyltriphenylphosphonium chloride in 300 mL of THF under an argon atmosphere was added 78 mL (0.12 mol, 1.5 M) of *n*-butyllithium in benzene. After 20 min, a solution of 10.4 g (72 mmol) of 4-pentanon-1-ol acetate (**22**)[15] in 80 mL of THF was added slowly and the reaction mixture was maintained at 2–5 °C for 2 h and then at ambient temperature overnight. A saturated NH_4Cl solution (80 mL) was added, followed by 500 mL of petroleum ether. After partitioning, the organic phase was separated, filtered to remove the precipitate, and reduced to two-thirds of its volume in vacuo. The newly formed precipitate was removed by filtration, and the supernate was dried ($MgSO_4$) and concentrated in vacuo. Distillation (Kugelrohr) of the residue afforded 7.4 g (59%) of 5-acetoxy-2-methyl-1-pentenyl methyl ether (**23**): bp 65 °C (0.5 torr); IR (film) 1738, 1685 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 5.90 (1 H, br s with fine splitting), two overlapping triplets at 4.13 (0.4 H, t, J = 7 Hz) and 4.10 (1.6 H, t, J = 7 Hz), 3.60 (2.4 H, s), 3.55 (0.6 H, s), 2.18 (0.6 H, s), and 2.07 (2.4 H, s), as well as two overlapping doublets at 1.58 (0.6 H, d, J = 1.6 Hz) and 1.53 (2.4 H, d, J = 1.6 Hz) superimposed on 2.35–1.45 (4 H, m); MS *m/e* (rel intensity) 172 (M^+, 10), 112 (18), 111 (15), 97 (45), 85 (50), 55 (45), 43 (100).

Enol ether **23** (3.8 g, 11 mmol) was refluxed in 20 mL of an 80% HOAc solution for 45 min. After extracting the reaction mixture with CH_2Cl_2, the organic phase was washed twice with brine, saturated $NaHCO_3$, and brine and then dried ($MgSO_4$), and the solvent was removed in vacuo, affording 3.2 g (91%) of crude 5-acetoxy-2-methylpentanal. A mixture of this aldehyde, 8 mL of methanol, and 2 mL of saturated Na_2CO_3 was stirred for 17 h at ambient temperature. After extraction with Et_2O, the organic layer was washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo, yielding 2.3 g (98%) of crude 2-hydroxy-3-methyltetrahydropyran (**24**): bp 58 °C (0.5 torr); IR (film) 3400 br cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 4.98 (0.3 H, br s that sharpens and resolves to a doublet with D_2O, J = 2 Hz, equatorial anomeric proton), 4.35 (0.7 H, br s that sharpens and resolves to a doublet with D_2O, J = 7 Hz, axial anomeric proton), 4.12–3.76 (1 H, m), 3.72–3.32 (1 H, m) on which is superimposed a broad singlet at 3.54 (0.7 H, s) that exchanges with D_2O, 3.07 (0.3 H, br s, exchanges with D_2O), 2.1–1.0 (5 H, complex m), 0.97 (2.1 H, d, J = 7 Hz), 0.91 (0.9 H, d, J = 7 Hz); MS *m/e* (rel intensity) 116 (M^+, 10), 99 (4), 83 (7), 70 (50), 55 (65), 41 (100).

Dehydration of δ-lactol **24** with PO_5 using the method described above for δ-lactol **17** afforded 5-methyl-3,4-dihydro-2*H*-pyran (40% yield).

6-Methyl-3,4-dihydro-2*H*-pyran (5).[7] To a cooled (ice bath) ethanolic solution of sodium ethoxide, prepared by adding 12 g (0.52 g-atom) of sodium metal to 150 mL of absolute ethanol, was slowly added 65 g (0.50 mol) of ethyl acetoacetate. After 15 min, 100 g (0.50 mol) of 1,3-dibromopropane was added, causing the reaction mixture to turn cloudy and become exothermic. The temperature of the suspension was allowed to rise to ~60 °C, and the mixture was stirred at this temperature for 1 h. Upon cooling, the total volume of the reaction mixture was reduced in vacuo by two-thirds and then diluted with Et_2O. After washing with 5% KOH and then water and then drying ($MgSO_4$), the solvent was removed in vacuo and the residue was refluxed for 3 h in 130 mL of a 4.2 N HCl solution. After cooling, the aqueous layer was separated and reduced to a volume of ~100 mL with a rotary evaporator. The aqueous phase was then saturated with NaCl and extracted with CH_2Cl_2. After washing the organic phase twice with brine, $NaHCO_3$, and brine again and then drying ($MgSO_4$), the solvent was removed in vacuo. Distillation (Kugelrohr) afforded 29 g (50%) of a cyclic and acyclic (1:1) mixture of 6-hydroxy-2-hexanone (**27**): bp 67 °C (20 torr); IR ($CHCl_3$) 3622, 3460, 1712 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 3.57 (1 H, t, J = 6 Hz) superimposed on 3.55 (1 H, br s, exchanges with D_2O), 3.38 (1 H, t, J = 6 Hz), 2.46 (1 H, t, J = 7 Hz), 2.10 (1.5 H, s), 2.02–1.06 (5 H, m) on which is superimposed 1.24 (1.5 H, s); MS *m/e* (rel intensity) 98 (27), 97 (11), 83 (12), 55 (28), 43 (100).

A mixture of 4.70 g (40.5 mmol) of 6-hydroxy-2-hexanone (**27**) and 0.94 g of aluminum oxide (neutral, grade I) was heated in a short-path distillation apparatus from 150 to 240 °C (oil bath temperature). The distillate was dried (K_2CO_3) and redistilled, affording 2.78 g (70%) of 6-methyl-3,4-dihydro-2*H*-pyran (**5**): bp 94 °C (760 torr); IR ($CHCl_3$) 1683 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 4.45 (1 H, superficial t, J = ~4 Hz, with further fine splitting), 3.97 (2 H, superficial t, J = 5.5 Hz, with further fine splitting), 2.06–1.82 (2 H, complex m), 1.74 (2 H, apparent quintet, J = 5.5 Hz) on which is superimposed a singlet with fine splitting of 1.68 (3 H); MS *m/e* (rel intensity) 98 (M^+, 47), 97 (25), 83 (22), 55 (61), 43 (100).

6-Phenyl-3,4-dihydro-2*H*-pyran (6).[7] To a cooled (ice bath) ethanolic solution of sodium ethoxide, prepared by adding 12 g (0.52 g-atom) of sodium metal to 150 mL of absolute ethanol, was added 96 g (0.50 mol) of ethyl benzoylacetate. After stirring for 30 min at ambient temperature, 100 g (0.50 mol) of 1,3-dibromopropane was added and the mixture heated at 60 °C (water bath) for 2 h. After cooling and then reducing the total volume by two-thirds in vacuo, the residual mixture was diluted with Et_2O and washed with 5% KOH and then brine. After the solvent was removed in vacuo, the residue was refluxed for 3 h in 130 mL of a 4.2 N HCl solution. After cooling, the product was extracted with ether, and the combined ether extracts were washed with brine, saturated $NaHCO_3$, and brine, and then dried ($MgSO_4$). Removal of solvent in vacuo and distillation (fractions 95–100 °C, 1 torr) afforded 32 g (26%) of 6-phenyl-3,4-dihydro-2*H*-pyran (**6**) as a viscous colorless oil: bp 100 °C (1 torr); IR ($CHCl_3$) 1685, 1655 cm^{-1}; UV_{max} (isopropyl alcohol) 216, 260 nm (ϵ 8070, 6225); NMR (100 MHz, $CDCl_3$) δ 7.64–7.37 (2 H, m), 7.37–7.12 (3 H, m), 5.28 (1 H, t, J = 4.1 Hz), 4.08 (2 H, superficial t, J = 5 Hz), 2.14 (2 H, superficial q, J = ~6 Hz), 1.82 (2 H, superficial quintet, J = ~6 Hz); MS *m/e* (rel intensity) 160 (M^+, 30), 159 (15), 131 (6), 123 (13), 105 (100), 77 (36).

Acknowledgments. The authors are grateful to Drs. W. Benz, F. Scheidl, and T. Williams, all of Hoffmann-La Roche Inc., Nutley, N.J., for the MS, microanalyses, and NMR spectra and to the Research Council (Rutgers University), the Charles and Johanna Busch Memorial Fund, and NIH (Biomedical Sciences Support Grant) for supporting grants.

Registry No.—**1,** 110-87-2; **2,** 13039-50-4; **3,** 2270-61-3; **4,** 15990-73-5; **5,** 16015-11-5; **6,** 13544-26-8; **7,** 37642-94-7; **8,** 109-92-2; *cis*-**9,** 6559-29-1; *trans*-**9,** 6559-30-4; **10,** 68258-37-7; **11,** 68258-38-8; *cis*-**12,** 68258-42-4; *trans*-**12,** 68258-43-5; *cis*-**13,** 30652-10-9; *trans*-**13,** 30652-09-6; **14,** 68258-39-9; *cis*-**15,** 68258-44-6; *trans*-**15,** 68258-45-7; **16,** 64362-62-5; **17,** 18545-19-2; **18,** 10138-44-0; **19,** 2397-95-7; *cis*-**20,** 17230-25-0; *trans*-**20,** 17322-78-0; *cis*-**21,** 31357-89-8; *trans*-**21,** 31357-88-7; **22,** 5185-97-7; **23,** 68258-40-2; **24,** 68258-41-3; **27,** 34884-60-1; *tert*-butyl hypochlorite, 507-40-4; methoxymethyltriphenylphosphonium chloride, 4009-98-7; ethyl acetoacetate, 141-97-9; 1,3-dibromopropane, 109-64-8; 6-hydroxy-2-hexanone, 21856-89-3; ethyl benzoylacetate, 94-02-0.

References and Notes

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(15) Prepared (84%) by the acetylation (1:1 Ac_2O–pyridine) of 5-hydroxy-2-pentanone: bp 100 °C (14 torr); IR (film) 1740, 1716 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 4.13 (2 H, t, J = 7 Hz), 2.60 (2 H, t, J = 7 Hz), singlets at 2.20 (3 H, s) and 2.07 (3 H, s) that are superimposed on 1.93 (2 H, quintet, J = 7 Hz); MS *m/e* (rel intensity) 144 (M^+, 4), 101 (17), 87 (18), 84 (16), 58 (20), 43 (100).

Endoperoxides of Naphthalenes. Synthesis and Reactions of Substituted 2,3-Epoxynaphthalene 1,4-Endoperoxides

Michio Sasaoka and Harold Hart*

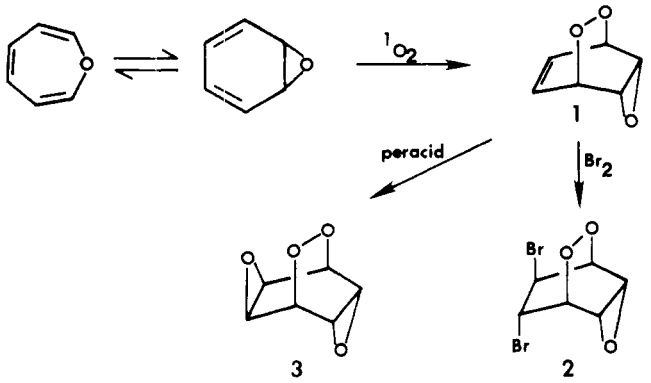
Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Received July 18, 1978

Oxidation of the 1,4-endoperoxides of 1,2,3,4-tetramethyl- or octamethylnaphthalene with *m*-chloroperbenzoic acid gave the stable, crystalline epoxy endoperoxides **8** and **9**. Epoxidation occurred predominantly syn to the peroxide bridge. The *syn*-epoxy peroxides underwent acid-catalyzed solvolytic rearrangement to the stable peroxy acetals **14** and **24**, respectively, but the *anti*-epoxy endoperoxide **8a** was recovered under similar conditions. The rearrangement involves a 1,2-aryl migration. Catalytic hydrogenolysis of **14** gave *cis*-1-acetyl-1,2,3-trimethylindan-2,3-diol (**16**), which was obtained independently from the acid-catalyzed methanolysis of the *syn*-epoxide of 1,2,3,4-tetramethylnaphthalene 1,4-endoxide (**19**). Deuterium labeling studies support the proposed mechanism for these rearrangements (Scheme II). Thermolysis of the epoxy endoperoxide **8s** occurs with O–O bond cleavage, as established by trapping the intermediate diradical with good hydrogen donors (diglyme, benzhydrol) to give the epoxydiol **10s**, synthesized independently by hydrogenolysis of **8s**. In the absence of trapping agent, thermolysis of **8s** occurs with loss of a methyl group to give the ketone **33**.

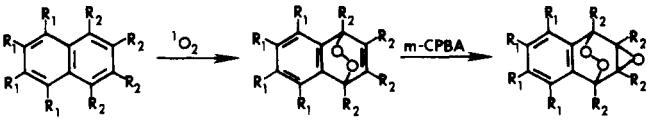
Endoperoxides of polycyclic aromatic compounds have been the subject of many investigations owing to their synthetic usefulness[1] and their biological importance.[2] Anthracenes and higher polyarenes are well known to give endoperoxides with singlet oxygen,[3] but only a few naphthalene endoperoxides have been similarly prepared.[4-6] Electron-donating groups on the 1 and 4 positions are necessary for the reaction of naphthalenes with singlet oxygen.[7]

Naphthalene endoperoxides have an isolated 2,3 double



bond which could be used for further functionalization of the molecule, and it was our purpose in this work to explore that possibility. Indeed, a similar double bond in oxepin endoperoxide **1** was found to undergo epoxidation and bromine addition.[8] More recently, the reduction of such strained double bonds by diimide without reducing the peroxide bond has been described.[9]

We were able to epoxidize the 1,4-endoperoxides of 1,2,3,4-tetramethylnaphthalene[5] and octamethylnaphthalene[6] to give extremely stable[10] epoxy peroxides **8** and **9**. We wish to report here on the synthesis and chemistry of these compounds, and in particular on their acid-catalyzed solvolysis



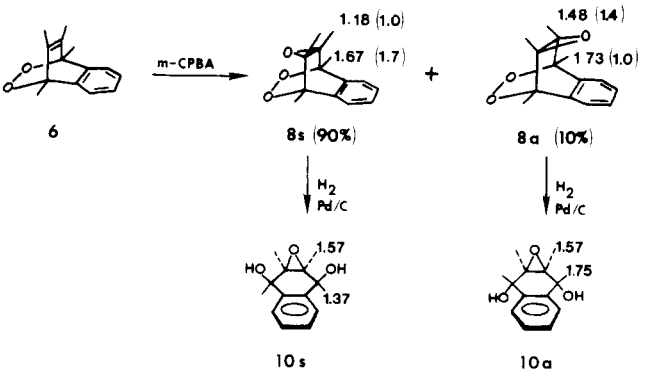
4; R_1 = H, R_2 = CH_3 **6**; R_1 = H, R_2 = CH_3 **8**; R_1 = H, R_2 = CH_3

5; R_1 = R_2 = CH_3 **7**; R_1 = R_2 = CH_3 **9**; R_1 = R_2 = CH_3

to give another class of surprisingly stable bicyclic peroxides.

Results and Discussion

Epoxy Endoperoxide of 1,2,3,4-Tetramethylnaphthalene. Oxidation of endoperoxide **6**[5] with *m*-chloroperbenzoic acid (*m*-CPBA) gave two isomeric epoxy endoperoxides in a 9:1 ratio.[1] These isomers were separated after recrystallization from ether. The major isomer formed colorless rods, and the minor isomer formed colorless cloudy plates which could be separated mechanically (tweezers). Catalytic hydrogenolysis of each isomer gave an epoxydiol. The NMR spectra of the epoxy endoperoxides and diols were consistent with the symmetry of their structures.[12] The peak assignments for the



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