talline oil: λ_{max} (KBr) 1730, 1658, 1592, 1580 cm^{-1}; δ ($CDCl_3$) 5.93 (s, 1 H), 5.25 (broadened S, 2 H), 4.08 (t, J = 8 Hz, 2 H), 3.48–2.85 (m, 3 H), 2.45–1.62 (m, 4 H), 0.95 (t, J = 8 Hz, 3 H). Chromatography on 12 g of silica gel eluting with chloroform afforded 0.089 g (46% based on starting **10**[16]) of **3** as a white solid, mp 145–148° (lit.[2] 149–150°).

Preparation of De-*AB*-camptothecin (4). A solution of 0.190 g (0.000815 mol) of deoxy **3** at 0.200 g (0.0018 mol) of potassium *tert*-butoxide in 40 ml of methanol was allowed to stir at room temperature for 10 min prior to the addition of 10.15 ml of a solution of 1 ml of 30% hydrogen peroxide in 20 ml of ether dried over Na_2SO_4. The resulting solution was stirred for 26 hr at room temperature. The reaction mixture was then acidified with methanolic hydrochloric acid and freed of volatiles *in vacuo*. The residue was triturated with 3 × 20 ml of methylene chloride. The combined methylene chloride extracts were dried over anhydrous magnesium sulfate and freed of solvent of afford 0.191 g of a yellow oil. Crystallization from ethanol afforded 0.126 g of a white solid which, from its nmr spectrum, was judged to contain *ca.* 80% of the desired analog **4** and 20% of the starting deoxy **3**. This material was dissolved in 20 ml of methanol and treated as described above with 0.097 g (0.000865 mol) of potassium *tert*-butoxide and 5 ml of a solution of 1 ml of 30% H_2O_2 in 20 ml of anhydrous ether dried over sodium sulfate. Upon work-up, there was obtained 0.125 g of a yellow oil whose nmr spectrum indicated it to be almost pure **4**. Chromatography on 15 g of silica gel, after chloroform elution afforded 0.088 g (43%) of analog **4** as a white solid, mp 172–182°. Two recrystallizations from ethanol afforded the analog **4** as a white solid: mp 176–179° (reported[2] mp 175–177°); λ_{max} (KBr) 3401, 1748, 1730, 1647, 1582; δ ($CDCl_3$) 6.45 (s, 1 H), 5.75–4.95 (AB quartet, 2 H), 4.25–4.03 [t + s (OH), 3 H], 3.30–3.05 (t, 2 H), 2.5–1.6 (quintet + quartet, 4 H), 1.10–0.85 (t, 2 H).

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Registry No.—**3,** 43083-10-9; **4,** 40163-27-7; **5,** 13939-73-6; **6,** 36625-47-5; **7,** 52358-42-6; **8,** 52358-43-7; **9,** 52358-44-8; **10,** 52358-45-9; **11,** 52358-46-0; paraformaldehyde, 30525-89-4.

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(12) This was assigned to the sample first submitted by Professor Rapoport.
(13) We wish to thank Dr. Robert Engle, National Cancer Institute, National Service Center, Drug Development Brand, Bethesda, Md., for expediting these studies.
(14) Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 247 spectrophotomer. Nmr spectra were measured on a Varian Associates T-60 spectrometer with tetramethylsilane as the internal standard. Combustion analysis were performed by Galbraith Laboratories, Knoxville, Tenn.
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(16) Two other runs afforded **3** in yields of 44 and 26%.

The Chemistry of 2-Alkoxy-3,4-dihydro-2*H*-pyrans. II. Addition of Dimethyl Acetylenedicarboxylate to 2-Alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans

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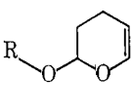
The introduction of an alkoxy group at the 2 position of 3,4-dihydro-2*H*-pyran (**1**) drastically alters the chemistry of the title compounds, 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2**), as compared to the parent compound, 3,4-dihydro-2*H*-

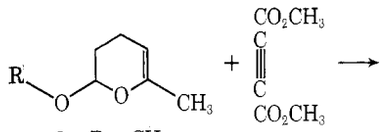
1



2

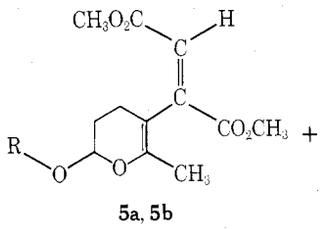
pyran (**1**). This can be most dramatically appreciated by comparing the addition of tetracyanoethylene,[1] condensation with benzenesulfonyl azide,[2] and oxidation by *m*-chloroperbenzoic acid,[3,4] with 3,4-dihydro-2*H*-pyran (**1**) and 2-alkoxy-3,4-dihydro-2H-pyrans (**2**).[5] Herein we wish to report yet another unusual reaction of the title pyrans with dimethyl acetylenedicarboxylate.

Refluxing a toluene solution of 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3a**) and dimethyl acetylenedicarboxylate (**4**) for 65 hr afforded a mixture of 2-methoxy-5-(dimethylfumaryl)-6-methyl-3,4-dihydro-2*H*-pyran (**5a**)[6] and dimethyl 2-acetyl-3-methoxycyclohex-6-ene-1,2-dicarboxylate (**6a**) in a ratio of 1:1 (glpc). Similar results were obtained with 2-ethoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3b**).

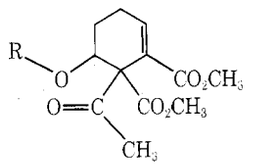


3a, R = CH_3
b, R = C_2H_5

4



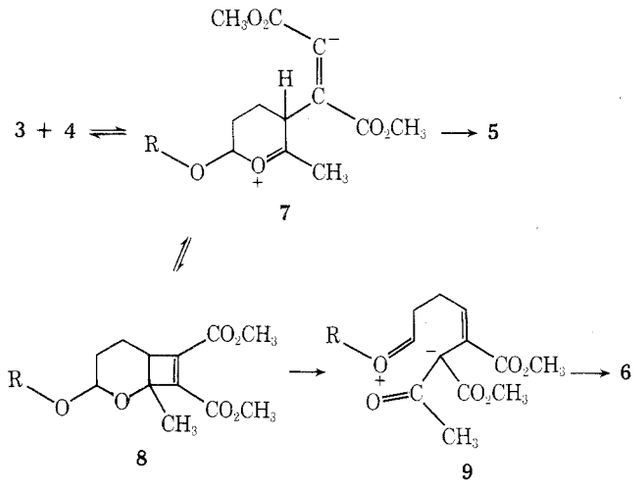
5a, 5b



6a, 6b

The assigned structures of the two products are consistent with the spectral data and composition analyses. The isolated yields are presumably low owing to the lability of 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans.[7]

The above reactions might best be described as involving the intermediacy of zwitterion **7,** analogous to intermediates invoked in enamine chemistry,[8] which can lead to product **5** by proton transfer or to the cyclobutene intermediate **8** by cyclization. The cyclobutene intermediate **8,** similar to that proposed as intermediates in reactions of ketene diethyl acetal[9] and enamines[8b,10] with acetylenic esters, can subsequently rearrange to **6.** Frequent monitoring (glpc) of the reaction indicated that no stable intermediate accumulated, and resubjecting products **5** and **6** to the conditions confirmed that each is a true end product of the reaction.



In addition, we have found in a study of related compounds that the parent 3,4-dihydro-2*H*-pyran (**1**) and the closely related 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2**) are inert to these reaction conditions, suggesting a remarkable effect of the 6-methyl group, which had been noted in the peracid studies,[4] on the reactivity of these compounds.[11]

Experimental Section[12]

The 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans (**3**) were prepared as reported.[5a,b] In all the experiments described below, the toluene was freshly distilled from CaH_2 and the reaction mixtures were degassed prior to refluxing under a static argon atmosphere. The progress of the reactions were monitored by thin layer chromatography (tlc) and by gas chromatography (glpc) on a Hewlett-Packard Model 7610A high-efficiency chromatograph (flame detector) using a 4 ft × 6 mm (all glass) 4% silicone gum rubber UCC-W-982 (methylvinyl) on 80–100 HP Chromosorb W (AW, DMCS) column and a 4 ft × 6 mm (all glass) 1% silicone gum rubber OV-1 (methyl) on 80–100 HP Chromosorb W (AW, DMCS) column. Column chromatography of the product mixtures was performed on Woelm neutral aluminum oxide (activity grade III) and eluted with petroleum ether and petroleum ether–Et_2O. Further purification, when necessary, was accomplished using a Büchi kugelrohr bulb to bulb distillation apparatus at reduced pressure. All boiling points are uncorrected.

Reaction of 2-Methoxy-6-methyl-3,4-dihydro-2*H*-pyran (3a) with Dimethyl Acetylenedicarboxylate (4). A solution of 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (1.41 g, 11 mmol) and dimethyl acetylenedicarboxylate (1.42 g, 10 mmol) in toluene (8 ml) was refluxed for 65 hr. The solvent was then removed *in vacuo* and the residue (2.65 g) after repeated chromatography yielded 450 mg (17%) of **5a** as a yellow liquid, a mixture which contained 48 mg (2%) of **5a** and 259 mg (10%) of **6a**, and 231 mg (8%) of **6a** as a pale yellow liquid (mixture of geometric isomers).

2-Methoxy-5-(dimethylfumaryl)-6-methyl-3,4-dihydro-2*H*-pyran (**5a**): bp 135–140° (0.2 mm); ir (film) 1725 cm^{-1}; uv (EtOH) λ_{max} 204 nm (ϵ 15,250), 332 (815); nmr (220 MHz, CCl_4) δ 6.71 (1 H, s), 4.89 (1 H, t, J = 3 Hz), 3.75 (3 H, s), 3.69 (3 H, s), 3.43 (3 H, s), 2.27–2.09 (1 H, m), 2.09–1.91 (1 H, m), 1.91–1.77 (2H, m), 1.56 (3 H, perturbed s); mass spectrum m/e (rel intensity) 270 (M^+, 8), 239 (8), 238 (19), 195 (23), 179 (17), 147 (21), 75 (38), 71 (31), 58 (100), 43 (96).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.79; H, 6.63.

Dimethyl 2-Acetyl-3-methoxycyclohex-6-ene-1,2-dicarboxylate (**6a**): ir (film) 1720 cm^{-1}; uv (EtOH) λ_{infl} 215 nm (ϵ 8,815); nmr (60 MHz, $CDCl_3$) δ 7.17 (1 H, t, J = 4 Hz), 4.03 (1 H, d of d, J = 5 and 4 Hz), 3.78 (3 H, s), 3.74 (3 H, s), 3.39 (3 H, s), 2.41 (3 H, s), 2.38–2.10 (2 H, m), 2.08–1.78 (2 H, m); mass spectrum m/e (rel intensity) 270 (M^+, 2), 238 (10), 196 (76), 165 (74), 164 (67), 163 (100), 137 (31), 105 (40), 77 (36), 59 (40), 43 (16).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 58.04; H, 7.00.

Reaction of 2-Ethoxy-6-methyl-3,4-dihydro-2*H*-pyran (3b) with Dimethyl Acetylenedicarboxylate (4). A solution of 2-ethoxy-6-methyl-3,4-dihydro-2*H*-pyran (1.57 g, 11 mmol) and dimethyl acetylenedicarboxylate (1.42 g, 10 mmol) in toluene (8 ml) was refluxed for 65 hr. The solvent was removed *in vacuo* and the residue (3.0 g) after repeated chromatography yielded 493 mg (17%) of **5b** as a yellow liquid, a mixture which contained 170 mg (6%) of **5b** and 177 mg (6%) of **6b**, and 520 mg (18%) of **6b** as a pale yellow liquid (mixture of geometric isomers).

2-Ethoxy-5-(dimethylfumaryl)-6-methyl-3,4-dihydro-2*H*-pyran (**5b**): bp 140–145° (0.2 mm); ir (film) 1725 cm^{-1}; uv (EtOH) λ_{max} 208 nm (ϵ 10,360), λ_{infl} 295 nm (ϵ 500); nmr (220 MHz, CCl_4) δ 6.72 (1 H, s), 4.99 (1 H, t, J = 3 Hz), 3.86 (1 H, q, J = 7 Hz), 3.76 (3 H, s), 3.70 (3 H, s), 3.57 (1 H, q, J = 7 Hz), 2.32–2.11 (1 H, m), 2.11–2.91 (1 H, m), 1.91–1.77 (2 H, m), 1.55 (3 H, perturbed s), 1.21 (3 H, t, J = 7 Hz); mass spectrum m/e (rel intensity) 284 (M^+, 4), 239 (4), 238 (8), 225 (4), 207 (11), 195 (14), 181 (17), 147 (18), 89 (24), 72 (61), 59 (16), 43 (100).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.27; H, 6.95.

Dimethyl 2-Acetyl-3-ethoxycyclohex-6-ene-1,2-dicarboxylate (**6b**): ir (film) 1720; uv (EtOH) λ_{infl} 210 nm (ϵ 14,480); nmr (100 MHz, $CDCl_3$) δ 7.16 (1 H, t, J = 4 Hz), 4.08 (1 H, d of d, J = 6, 4 Hz), singlets at 3.68 (3 H, s) and 3.66 (3 H, s) superimposed on an apparent quartet at 3.64 (1 H, q, J = 7 Hz), two overlapping quartets at 3.38 and 3.36 (1 H, d of q, J = 7 Hz), a singlet at 2.36 (3 H, s) superimposed on a multiplet at 2.42–2.16 (2 H, m), 1.92–1.68 (2 H, m), overlapping triplets at 1.18 and 1.13 (3 H, t, J = 7 Hz); mass spectrum m/e (rel intensity) 284 (M^+, 1), 253 (6), 196 (100), 165 (32), 164 (58), 163 (53), 137 (12), 105 (8), 77 (3), 59 (4), 43 (11).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.10; H, 6.98.

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Registry No.—**3a**, 28194-35-6; **3b**, 52438-71-8; **4**, 762-42-5; **5a**, 52438-72-9; **5b**, 52438-73-0; *cis*-**6a**, 52438-74-1; *trans*-**6a**, 52438-75-2; *cis*-**6b**, 52438-76-3; *trans*-**6b**, 52438-77-4.

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(6) Comparison of the δ values for the vinyl proton of methyl citraconate (5.77 ppm) and methyl mesaconate (6.68 ppm) shows the effect of a group on the malonate and fumarate system [see R. R. Fraser and D. E. McGreer, *Can. J. Chem.*, **39**, 505 (1961)] and served as a basis for the assigned trans stereochemistry.
(7) The 2-alkoxy-3,4-dihydro-2*H*-pyrans are extremely sensitive compounds and are easily hydrolyzed [W. S. Johnson, Ed., Org. Syn., **34**, 71 (1954)] and polymerized.[5a]
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(11) We have found, in a related study that will be published, the order of reactivity of these compounds to be **3** > **1** > **2** in competitive electrophilic addition reactions with *tert*-butyl hypochlorite in alcohol.
(12) The ir spectra were determined with a Perkin-Elmer Model 237B ir recording spectrophotometer and a Beckman Model IR-10 ir recording spectrophotometer. The uv spectra were determined with a Cary Model 14 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Associates Model T-60 nmr spectrometer, at 100 MHz with a Varian Associates Model HA-100 nmr spectrometer, and at 220 MHz with a Varian Associates Model HR-220 nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with a Consolidated Electronics Corporation Model 110-21B mass spectrometer and a LKB Model 9000 mass spectrometer.