solution of the appropriate 2-chromanol (1.25 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 24 h, shaken with sodium bicarbonate solution, and extracted with dichloromethane. The dichloromethane fraction was dried (Na_2SO_4), filtered, and evaporated to give a residue from which pure 2-ethoxy derivatives were obtained through open-column chromatography by eluting with *n*-hexane/ethyl acetate mixtures.

2-Ethoxy-2-methyl-4-phenylchroman (6a). 4-Phenyl-2-methylchroman-2-ol (**4a**) gave **6a**: 98% yield; mp 72–73 °C; IR (Nujol) 1230, 1060, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–6.67 (m, 9 H), 4.37 (X part of an ABX system, dd, J_{BX} = 12.75 Hz, J_{AX} = 6.3 Hz, 1 H), 3.63 (q, J = 7.5 Hz, 2 H), 2.30 (A part of an ABX system, dd, J_{AB} = 13.5 Hz, J_{AX} = 6.3 Hz, 1 H), 1.98 (B part of an ABX system, dd, J_{BX} = 12.75 Hz, J_{AB} = 13.5 Hz, 1 H), 1.53 (s, 3 H), 1.03 (t, J = 7.5 Hz, 3 H); MS (70 eV) m/e (relative intensity) 268 (10.5), 181 (100).

1-Ethoxy-3,4-benzo-2-oxabicyclo[3.3.1]nonane (6b). 1-Hydroxy-3,4-benzo-2-oxabicyclo[3.3.1]nonane (**4b**) gave **6b**: 50% yield (the starting material was recovered in about 45% yield); mp 54–55 °C; ^1H NMR ($CDCl_3$) δ 7.25–6.66 (m, 4 H), 3.68 (q, J = 7.0 Hz, 2 H), 3.11 (m, $W_{1/2}$ = 8.0 Hz, 1 H), 2.3–1.00 (m, 8 H), 1.20 (t, J = 7.0 Hz, 3 H); MS (70 eV), m/e (relative intensity) 218 (47.5), 175 (100).

2-Ethoxy-2-benzyl-4-phenylchroman (6c). 4-Phenyl-2-methylchroman-2-ol (**4c**) gave **6c**: 98% yield; mp 100–101 °C; IR (Nujol) 1240, 1120, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–6.60 (m, 14 H), 4.29 (X part of an ABX system, dd, J_{BX} = 12.75 Hz, J_{AX} = 6.0 Hz, 1 H), 3.75 (m, 2 H), 3.17 (s, 2 H), 2.13 (A part of an ABX system, dd, J_{AB} = 13.5 Hz, J_{AX} = 6.0 Hz, 1 H), 1.80 (B part of an ABX system, dd, J_{AB} = 13.5 Hz, J_{BX} = 12.75 Hz, 1 H), 1.05 (t, J = 7.1 Hz, 3 H); MS (70 eV), m/e (relative intensity) 299 (4.1), 253 (100).

All 2-ethoxychromans gave satisfactory microanalyses (C, ±0.32%; H, ±0.24%).

Acknowledgment. We thank Dr. G. Cancelliere for her helpful technical assistance.

Registry No. **1a**, 122-57-6; **1b**, 930-68-7; **1c**, 5409-59-6; **1h**, 78-94-4; **1i**, 94-41-7; **1l**, 538-58-9; **2a**, 90-03-9; **2d**, 81603-15-8; **2e**, 81603-16-9; **2f**, 33631-70-8; **2g**, 80331-23-3; **3f**, 80331-32-4; **3g**, 80331-34-6; **3h**, 61844-32-4; **3h** 2,4-DNP, 81603-17-0; **3i**, 4376-83-4; **4a**, 81603-18-1; **4b**, 81603-19-2; **4c**, 81603-20-5; **4d**, 81603-21-6; **4e/4e'**, 81603-22-7; **4h**, 61844-27-7; **5i**, 53209-37-3; **5l**, 81603-23-8; **6a**, 81603-24-9; **6b**, 81603-25-0; **6c**, 81603-26-1; $PdCl_2$, 7647-10-1; (3-formyl-4-hydroxyphenyl)mercury chloride, 80331-22-2; 4-[(5-formyl-2-hydroxy)phenyl]-4-phenyl-2-butanone, 81603-27-2.

A Reinvestigation of the Condensation of 2-Methyl-4-(carboxyethyl)oxazole with Ethyl Acetate

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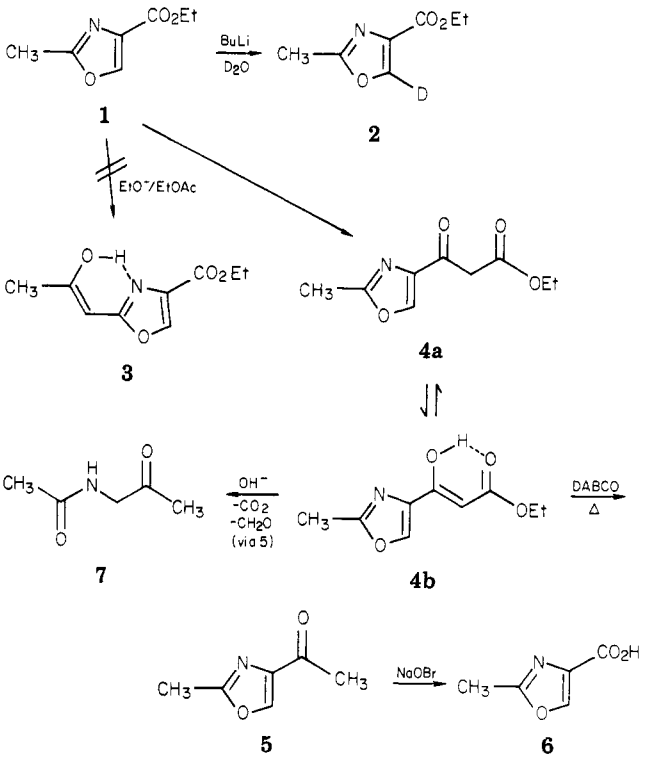
We recently described the metalation behavior of certain 2-methyl-1,3-oxazoles[1] which indicated the total inertness of the 2-methyl group in **1** toward deprotonation. Instead the only proton to show acidity (kinetic or thermodynamic) was the 5-H, which furnished **2** after D_2O quench. It was, therefore, concluded that elaboration of the 2-methyloxazole **1** would require a different strategy.

In 1966, Todd and co-workers[2] described the elaboration of **1** to the 2-acetonyl derivative **3** by use of ethoxide and ethyl acetate. Since this result was contradictory to our own findings (**1** → **2**), we repeated the work of the British group and found that **3** was not the product claimed but, as one would have expected, the ketoester **4** was formed as a result of a typical Claisen condensation (Scheme I). The product isolated in our hands possessed consistent IR, NMR, and UV spectra with those reported by Todd and co-workers. However, the 60-MHz ^1H NMR spectrum in $CDCl_3$ showed that the product **4** was a 4:1 mixture of tautomers **4a** and **4b**. In CCl_4 solvent, the ratio was reversed to 1:2 in favor of **4b**, consistent with the fact that chelation is more important in nonpolar solvents. Surprisingly, no mention of the tautomeric behavior was made in the earlier report on this reaction, only that **3** corresponded to the enolic form.

Scheme I



Further proof that **4** was the correct product was obtained by deuterium exchange studies, which, as observed earlier in our laboratory,[1] did not affect the 2-methyl group and gave 75% incorporation at the methylene of the β-ketoester. The methyl singlet at δ 2.48 was unchanged after treatment with D_2O. Finally, we converted **4** into the 4-acetyl derivative **5** by heating a xylene solution in the presence of DABCO.[3] Since **5** was not reported previously, it was transformed into the known 2-methyl-4-carboxyoxazole[4] (**6**) using sodium hypobromite.[5] The formation of **6**, coupled with the physical data and the D-exchange study, provide overwhelming evidence that the product of **1** with ethyl acetate under basic conditions is **4** and not **3** as previously reported.

When the decarboxylation of **4** was carried out in aqueous base, none of the ketone **5** was isolated, only the acetyl derivative of α-aminoacetone, **7**.[6] The inability to isolate **5** is due to the known lability of 4-acyloxazoles toward base, causing **5** to ring open and eliminate formaldehyde.[7]

(1) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163.
(2) Delpierre, G. R.; Eastwood, F. W.; Gream, G. E.; Kingston, D. G. I.; Sarin, P. S.; Lord Todd; Williams, D. H. *J. Chem. Soc. C* **1966**, 1653.
(3) Huang, B. S.; Parish, E. J.; Miles, D. H. *J. Org. Chem.* **1974**, *39*, 2647.
(4) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1947**, 96.
(5) Allan, A. W.; Walter, B. H. *J. Chem. Soc. C* **1968**, 1397.
(6) Wiley, R. H.; Borum, O. H. *J. Am. Chem. Soc.* **1948**, *70*, 2005.

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In summary, the earlier report on elaboration of the 2-methyloxazole, **1**, must be considered incorrect, and the surprising resistance of the 2-methyl group toward carbanion formation still stands.

Experimental Section

Reaction of 2-Methyl-4-carbethoxy-1,3-oxazole (1) with Ethyl Acetate. A flame-dried flask under a blanket of dry argon was charged with 318 mg (6.9 mmol, 1.7 equiv) of sodium hydride (50% oil dispersion) and 2 mL of dry ether (from benzophenone ketyl). A total of 0.64 mL (6.5 mmol, 1.6 equiv) of ethyl acetate (distilled) was added, followed by one drop of absolute ethanol (noted vigorous evolution of gas). Within 1 min, a solution of 650 mg (4.1 mmol) of oxazole ester **1** in 10 mL of dry ether was added dropwise with efficient stirring. After the addition was complete, a total of 9 mL of dry 1,4-dioxane (from benzophenone ketyl) was introduced into the reaction. The resulting dark solution was gently heated under reflux for 1 h. After this time, the dark solution was cooled to ambient temperature, and absolute ethanol was added (ca. 1 mL). The pH of the reaction was adjusted to 7 by addition of 30% glacial acetic acid in water (v/v). To the resulting suspension was added 10 mL of saturated aqueous sodium sulfate solution, and the solution was extracted with ether (5 × 20 mL). The combined ethereal extracts were washed with pH 7 buffered water (1 × 10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under aspirator pressure to afford 478 mg (59%) of crude product. Preparative TLC using 30% acetone in hexanes as developing solvent gave 208 mg (26%) of a colorless solid. The 60-MHz NMR spectrum ($CDCl_3$) showed it to be a mixture of β-ketoester **4a** and enol **4b**, in the ratio 4:1, based on comparative integration of the oxazole C_5 hydrogen resonances. Recrystallization of the solid from hexanes (3 times) yielded a colorless, crystalline solid: mp 79–81 °C; R_f 0.49 (silica gel, 30% acetone in hexanes); IR (KBr) 3420, 1727 (CO_2Et), 1642 (C=O), 1585, 1545 cm^{-1}; NMR ($CDCl_3$) for **4a** δ 1.25 (t, J = 7 Hz, 3 H, OCH_2CH_3), 2.48 (s, 3 H), 3.85 (s, 2 H, $COCH_2CO_2Et$), 4.13 (q, J = 7 Hz, 2 H, OCH_2CH_3), 8.11 (s, 1 H, oxazole C_5 H); for **4b** δ 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3), 2.48 (s, 3 H), 4.18 (q, J = 7 Hz, 2 H, OCH_2CH_3), 5.71 (s, 1 H, C(OH)=$CHCO_2Et$], 7.85 (s, 1 H, oxazole C_5 H), 11.98 (br, s, 1 H, OH); in CCl_4, the ratio of **4a** to **4b** was 1:2; UV (95% ethanol) λ_{max} 253 nm (log ϵ 3.74), λ_{infl} 265 nm (log ϵ 3.73); UV (0.1 N ethanolic sodium hydroxide) λ_{max} 303 nm (log ϵ 4.10).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 55.06; H, 5.62; N, 7.38.

Deuterium Exchange on 4a,b. A solution of 8 mg (0.04 mmol) of oxazoles **4** in 5 mL of D_2O/1 mL of Et_2O was stirred at ambient temperature for 72 h, after which time the ether was removed by concentration under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The 60-MHz NMR spectrum of this material in $CDCl_3$ showed deuterium incorporation in the following positions: δ 3.85 (**4a**, $COCH_2CO_2Et$), 5.71 [**4b**, C(OH)=$CHCO_2Et$], 11.98 (**4b**, OH). Integration of the spectrum showed deuterium exchange to be ca. 75% complete with no exchange of hydrogen for deuterium at δ 2.48 (2-Me).

2-Methyl-4-acetyloxazole (5). A flask under a blanket of dry argon was charged with 50 mg (0.25 mmol) of **4**, 284 mg (2.54 mmol, 10.0 equiv) of 1,4-diazabicyclo[2.2.2]octane, and 0.5 mL of xylenes. The resulting solution was gently heated under reflux by placing the flask into an oil bath maintained at 140 °C. The progress of the reaction was closely monitored by TLC (silica gel, 30% acetone in hexanes; R_f 0.49 for **4**; R_f 0.41 for **5**). After 45 min, the reaction was cooled to room temperature. The resulting semisolid was flash chromatographed using 30% acetone in hexanes as eluent to yield 20 mg (63%) of **5** as a colorless solid, which readily sublimed: mp 64–65 °C; R_f 0.41 (silica, 30% acetone–hexane); IR (KBr) 1685, 1598, 1548 cm^{-1}; NMR ($CDCl_3$) δ 2.49 (s, 6 H), 8.03 (s, 1 H); MS (70 eV), m/e 125 (M^+). This material was used directly in the next step.

2-Methyl-4-carboxyoxazole (6). The procedure of Allan and Walter[5] was employed using sodium hypobromite. The acid **6** was obtained in 59% yield, mp 182–183 °C dec (acetone), lit.[4] mp 183–184 °C dec.

Hydrolysis of 4 to 7. A total of 60 mg (0.30 mmol) of the mixture of **4a,b** and 0.5 mL (0.61 mmol, 2.0 equiv) of 5% aqueous sodium hydroxide solution were placed in a flask and stirred at ambient temperature. The progress of the reaction was monitored by TLC (30% acetone in hexanes; **4a,b** R_f 0.49). After 46 h, TLC showed no starting material. The dark solution was acidified to pH 4 by addition of 0.35 mL of 1 N sulfuric acid. The resulting solution was gently heated under reflux for 90 min. After this time, the solution was cooled to room temperature. The aqueous solution was extracted with dichloromethane (3 × 25 mL), and the combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 14 mg (40%) of *N*-acetonylacetamide (**7**): NMR ($CDCl_3$) δ 2.03 (s, 3 H), 2.20 (s, 3 H), 4.15 (d, J = 5 Hz, 2 H, CH_2COCH_3), 6.33 (br, 1 H, exchanged with D_2O, NH) [reported for *N*-acetonylacetamide:[8] NMR ($CDCl_3$) δ 2.05 (s, 3 H, CH_2COCH_3), 2.22 (s, 3 H, $NHCOCH_3$), 4.18 (d, J = 5 Hz, 2 H, CH_2COCH_3), 6.48 (br, 1 H, NH)].

Acknowledgment. The authors are grateful to the National Institutes of Health for support of this work.

Registry No. 1, 10200-43-8; **4a**, 81725-19-1; **4b**, 81725-20-4; **5**, 81740-16-1; **6**, 23012-17-1; **7**, 7737-16-8; ethyl acetate, 141-78-6.

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Reaction of Dimethyl Diazomalonate and Ethyl 2-Diazoacetoacetate with *N*-Methylpyrrole

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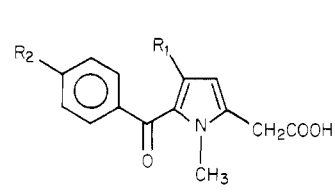
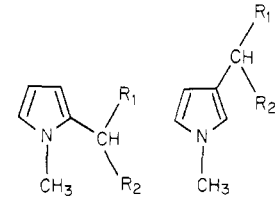
A study of the reaction of ethyl diazoacetate (EDA) with *N*-methylpyrrole and other pyrrole derivatives was conducted in our laboratory[1] as part of research directed toward improved synthetic processes for tolmetin (**1**) and zomepirac (**2**).[2] In that work we found some copper-



1, R_1 = H; R_2 = CH_3
2, R_1 = CH_3; R_2 = Cl



3 **4**

a, R_1 = H; R_2 = $CO_2C_2H_5$
b, R_1 = R_2 = CO_2CH_3
c, R_1 = H; R_2 = CO_2CH_3
d, R_1 = $C(O)CH_3$; R_2 = $CO_2C_2H_5$

(1) (a) Maryanoff, B. E. *J. Org. Chem.* **1979**, *44*, 4410; Maryanoff, B. E. *J. Heterocycl. Chem.* **1977**, *14*, 177. (b) We wish to correct two errors in the *J. Org. Chem.* paper: on p 4417, dimethyl sulfate should read diethyl sulfate; on p 4416, the EM-360 NMR instrument should be attributed to Varian (not Perkin-Elmer).

(2) Tolmetin is an important nonsteroidal antiinflammatory agent for the treatment of arthritis, and its sodium salt is sold by McNeil Pharmaceutical under the registered tradename Tolectin. Zomepirac is a potent nonnarcotic analgesic, and its sodium salt is sold by McNeil Pharmaceutical under the registered tradename Zomax.

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