was worked up, giving compound **15**: 423 mg (98%); mp 180–190 °C (crude product); IR 3400, 1710 cm^{-1}; NMR δ 0.7 (s, 3 H, C-18), 1.02 (s, 3 H, C-19), 3.5 (m, 2 H, THP), 3.9 (m, 1 H, C-3), 4.52 (AB q, 2 H, C-21, J = 20 Hz), 4.8 (br s, 1 H, THP), 5.4 (br s, 1 H, C-6); MS m/e 432.

3β,17α,21-Trihydroxy-5-pregnen-20-one (17). The deprotection of 3β-OH group in compound **15** was carried out in methanol–water solution (95:5) with few drops of perchloric acid to yield known compound **17** (98%); mp 211–212 °C (lit.[8] mp 208.5–211 °C); IR 3400, 1710 cm^{-1}; NMR δ (C_5D_5N), 0.7 (s, 3 H, C-18), 0.95 (s, 3 H, C-19), 3.85 (m, 1 H, C-3), 5.0 (AB q, 2 H, C-21, J = 17.5 Hz), 5.4 (br s, 1 H, C-6); MS m/e 348.

17α-Hydroxy-3β,21-diacetoxy-5-pregnen-20-one (18). The acetylation of **17** was carried out in pyridine with acetic anhydride at room temperature. The standard workup gave known compound **18** which was checked by comparison with authentic sample:[4] mp 193–195 °C (lit.[9] mp 192, 190–193 °C); IR 3650, 1740, 1730, 1720 cm^{-1}; NMR δ 0.7 (s, 3 H, C-18), 1.05 (s, 3 H, C-19), 2.05 (s, 3 H, CH_3COO), 2.2 (s, 3 H, CH_3COO), 4.65 (m, 1 H, C-3), 4.98 (AB q, 2 H, C-21, J = 1 7.5 Hz), 5.4 (br s, 1 H, C-6); MS m/e 432. Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 68.95; H, 8.57.

Ethyl 6β-Methoxy-20ζ-chloro-17(20)-i-pregnen-21-oate (4). The chloro ester **4** was obtained by starting from 6β-methoxy-i-androstan-17-one (**2**) in the same manner as was described previously for chloro ester **3**: yield 87%; mp 114.5–116 °C; UV max (EtOH) 240 nm (ε 4800); IR 1720 cm^{-1}; NMR δ 1.05 (s, 3 H, C-18), 1.1 (s, 3 H, C-19), 1.35 (t, 3 H, OEt, J = 7.5 Hz), 3.4 (s, 3 H, OCH_3), 4.3 (q, 2 H, OEt, J = 7.5 Hz); MS m/e 406. Anal. Calcd for $C_{24}H_{35}O_3Cl$: C, 70.93; H, 8.60; Cl, 8.6. Found: C, 70.66; H, 8.74; Cl, 8.94.

Methyl 6β,20ζ-Dimethoxy-17(20)-i-pregnen-21-oate (10). To the solution of sodium (2.3 g, 0.1 mol) in anhydrous methanol (150 mL) was added the compound **4** (4.06 g, 0.01 mol), and the mixture was refluxed under argon for 24 h. After cooling, the reaction mixture was neutralized with acetic acid (5.4 g), and half of the solvent was evaporated on a rotary evaporator. To the residue was added water (200 mL), and the mixture was extracted with chloroform (3 × 100 mL). The extracts after drying and evaporation were purified by short column chromatography with hexane–ethyl acetate (9:1) mixture as an eluent. The compound **10** was obtained as an oil: yield 3.29 g (85%); IR (film) 1720 cm^{-1}; NMR δ 1.05 (s, 3 H, C-18), 1.12 (s, 3 H, C-19), 2.82 (m, 1 H, C-6), 3.43 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3); MS m/e 388.

6β,20ζ-Dimethoxy-17(20)-i-pregnen-21-ol (12). The reduction of compound **10** with DIBAL-H was carried out in toluene solution solution at −20 °C for 5 min. A standard workup gave compound **12** (95%) as an oil which was chromatographically pure (TLC, hexane–ethyl acetate, 3:2): IR 3250 cm^{-1}; NMR δ 1.0 (s, 3 H, C-18), 1.10 (s, 3 H, C-19), 2.84 (br s, 1 H, C-6), 3.4 (s, 3 H, OCH_3), 3.6 (s, 3 H, CH_3O), 4.2 (s, 2 H, C-21); MS m/e 360.

3β,21-Dihydroxy-5-pregnen-20-one (13) and Its Diacetyl Derivative (14). Compound **12**, dissolved in a dioxane–water (95:5) mixture with a few drops of perchloric acid, was left at room temperature for 1 h. Neutralization with aqueous sodium bicarbonate followed by a standard workup gave known compound **13** which after acetalization gave compound **14** which was characterized before.

17α,21-Dihydroxy-6β-methoxy-i-pregnan-20-one (16). The oxidation of compound **12** with 10% excess of MCPBA in methanol solution at room temperature gave compound **16**: 95% yield; mp (from ether) 194–199 °C; IR 3450, 1700 cm^{-1}; NMR δ 0.8 (s, 3 H, C-18), 1.12 (s, 3 H, C-19), 2.87 (br s, 1 H, C-6), 3.42 (s, 3 H, OCH_3), 4.52 (AB q, 2 H, C-21, J = 20 Hz); MS m/e 362. Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.77; H, 9.62.

3β,17α,21-Trihydroxy-5-pregnen-20-one (17) and Its Diacetyl Derivative 18. Acidic hydrolysis of **16** in dioxane–water solution with perchloric acid gave quantitatively compound **17**, which upon acetalization afforded compound **18**.

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Registry No. **1**, 19637-35-5; **2**, 14425-92-4; **3**, 81477-79-4; **4**, 81477-80-7; **5**, 81477-81-8; **6**, 81477-82-9; **7**, 81477-83-0; **8**, 81477-84-1; **9**, 81477-85-2; **10**, 81477-86-3; **11**, 81477-87-4; **12**, 81477-88-5; **13**, 1164-98-3; **14**, 1693-63-6; **15**, 81477-89-6; **16**, 81477-90-9; **17**, 1167-48-2; **18**, 3517-42-8; ethyl trichloroacetate, 515-84-4.

Palladium-Catalyzed Conjugate Addition Type Reaction of (2-Hydroxyaryl)mercury Chlorides with α,β-Unsaturated Ketones in a Two-Phase System. A New Synthesis of 2-Chromanols and 2-Chromenes

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Received November 19, 1981

In previous papers,[1,2] we have reported that arylmercury compounds containing a wide variety of substituents in the aromatic moiety (for example Me, Cl, CHO, COMe, COOMe, OH, OMe, NHCOMe, and NO_2) react at room temperature with unhindered α,β-unsaturated ketones in an acidic two-phase system, in the presence of catalytic amounts of Pd(II), to give products that can be regarded as derived from a conjugate addition reaction (Scheme I).

The reaction proceeds smoothly with good yields and allows an efficient and specific synthesis of β-aryl ketones.

As part of an overall program directed toward the search of these palladium-catalyzed conjugate addition type reactions, we report here that the reaction of α,β-enones with arylmercury compounds containing a 2-hydroxy group gives rise to the formation of 2-chromanols (**4**) and 2-chromenes (**5**) through a one-pot addition–cyclization–dehydration reaction according to Scheme II.

The general reaction conditions are as follows. The starting α,β-enone (3.4–8.0 mmol) and the (2-hydroxyaryl)mercury chloride (50 mol % excess) were added to a dichloromethane aqueous 3 N HCl (ca. 1.6:1 v/v) two-phase system containing $PdCl_2$ (5 mol %) and TBA^+Cl^- (10 mol %). The mixture was stirred at room temperature for an appropriate period (4–8 h) and worked up. Pure products were obtained through open-column chromatography.

As expected, the reaction mixture composition is controlled by the nature of R_1 and R_2 in the α,β-enonic system and by the substituents in the aromatic moiety of the arylmercury compound.

The results are summarized in the Table I.

Generalization from the limited number of examples available is probably of doubtful value, but nevertheless by examination of the Table I, and according to the literature,[3,4] it appears that formation of 2-chromanols (**4**) is favored when R_1 is other than hydrogen, when R_2 is bonded to the carbonyl group through an sp^3 carbon atom, and when no strongly electron-withdrawing groups are present on the aromatic ring of the mercurials (cf. entries a–e, Table I).

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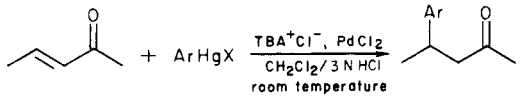
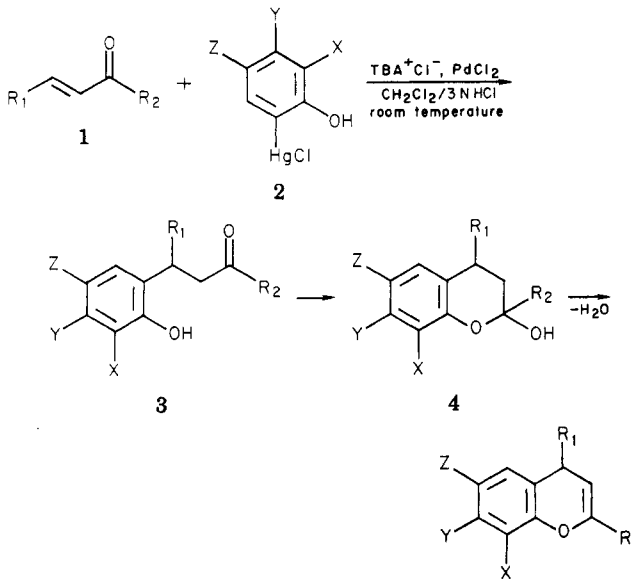
Scheme I[a]

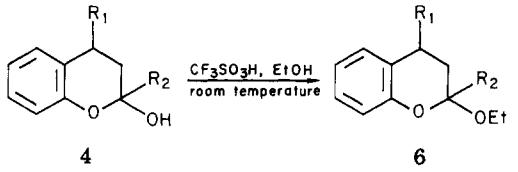


[a] X = Cl, OAc.

Scheme II



Scheme III[a]



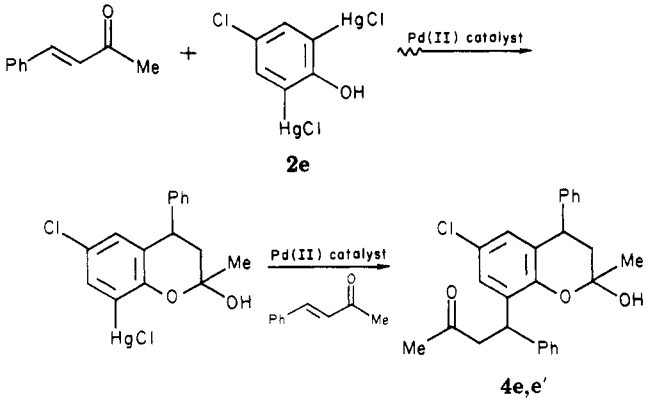
[a] a, R_1 = Ph, R_2 = Me; b, R_1R_2 = $(CH_2)_3$; c, R_1 = Ph, R_2 = $PhCH_2$.

As a chemical confirmation of the proposed structures, the obtained 2-chromanols **4a–c** were converted into the corresponding 2-ethoxychromans through the acid-catalyzed ethanolysis of the carbon–hydroxide bond (Scheme III).

Due to the lower nucleophilicity and basicity of phenolic oxygen, treatment of benzalacetone with (2-hydroxyaryl)mercury compounds containing strongly electron-withdrawing groups such as NO_2 and CHO gave only the corresponding keto–phenol forms[2] (cf. entries f and g, Table I).

From the reaction of (2-hydroxyphenyl)mercury chloride with butenone (R_1 = H; R_2 = Me) an oil was isolated which was proved to be an equilibrium mixture of the keto–phenol form and of the 2-chromanol form (cf. entry h, Table I).[5]

Scheme IV



Under our standard conditions, dehydration to 2-chromenes (**5**) was observed only when the substituent R_2 can provide assistance to the carbon–oxygen bond cleavage through π-orbital participation (cf. entries i and l, Table I). With chalcone (R_1 = R_2 = Ph, entry i, Table I) as the starting material, a mixture of **3i** and **5i** was isolated, but no 2-chromanol derivative was detected in the reaction mixture. This observation is in agreement with the described[7] greater stability of the keto–phenol form when cyclization would involve a resonance-stabilized carbonyl system.

Finally, it may be noted that the presence of two chloromercury groups in the aromatic ring allows an easy synthesis of very complex 2-chromanol derivatives (cf. entries d and e, Table I) according to Scheme IV, reported for the reaction of [2-hydroxy-3-(chloromercurio)-5-chlorophenyl]mercury chloride (**2e**) with benzalacetone.

In summary, the palladium-catalyzed addition of (2-hydroxyaryl)mercury compounds to α,β-unsaturated ketones may provide an excellent new method for the preparation of 2-chromanols and 2-chromenes. More interestingly, depending from the nature of substituents in the aromatic moiety of the organomercury compound, the reported results established that intramolecular reactions may follow the palladium-catalyzed conjugate addition type reaction of mercurials with an α,β-enone. Further studies related to this attractive observation are now in progress.

Experimental Section

Melting points are uncorrected and were determined with a Büchi apparatus. Benzalacetone, cyclohex-2-en-1-one, and butenone are commercially available and were used without further purification. Ketones **1c,i,l**, (2-hydroxyphenyl)mercury chloride, and arylmercury chlorides **2d–g** were prepared according to the cited references. Tetrabutylammonium chloride and $PdCl_2$ were purchased from Fluka and used as received. Reactions were carried out on 0.5–0.6 M dichloromethane solutions of the α,β-enones. The products were purified on silica gel open columns

(5) HPLC analysis (column prepacked with LiChrosorb-Si 60, 25 × 0.45 cm, *n*-hexane/ethyl acetate (85/15), 2 mL min^{-1}) revealed the presence of only one, narrow peak with K' = 3.1. However, ^1H NMR analysis revealed the presence of two isomeric compounds, the keto–phenol form (**3h**) and the 2-chromanol form (**4h**), with the isomeric ratio **3h/4h** varying with the solvent used: typically 72/28 (MeOD), 75/25 ($CDCl_3$), and 63/37 (CCl_4). The keto–phenol/2-chromanol isomeric ratio was determined through careful integration of Me and OH signals. Thus, we concluded that from the reaction of (2-hydroxyphenyl)mercury chloride with butenone a quick equilibrating mixture of **3h** and **4h** is obtained.[6]

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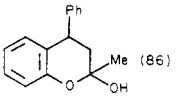
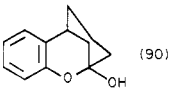
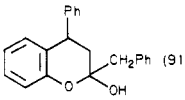
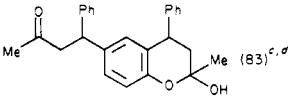
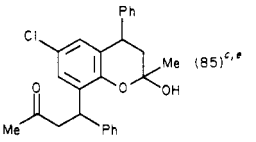
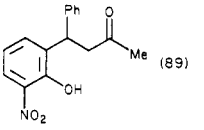
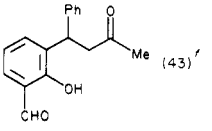
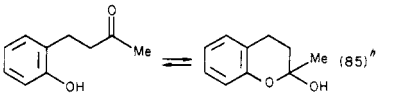
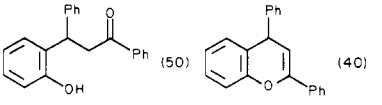
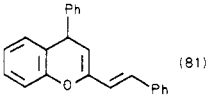
Table I. Compounds Obtained through the Palladium-Catalyzed Addition of (2-Hydroxyaryl)mercury Chlorides to α,β-Unsaturated Ketones[a]

entry	α,β-enone 1		arylmercury compd 2[i]		reaction time, h	product (yield,[b] %)
	R_1	R_2	X	Z		
a	Ph	Me	H	H	4	 (86)
b		$(CH_2)_3$	H	H	4	 (90)
c	Ph	CH_2Ph[8]	H	H	2	 (91)
d	Ph	Me	H	$HgCl$[9]	5	 (83)[c,d]
e	Ph	Me	HgCl	Cl[10]	6	 (85)[c,e]
f[2]	Ph	Me	NO_2	H[11]	8	 (89)
g[2]	Ph	Me	CHO	H[12]	8	 (43)[f]
h	H	Me	H	H	4[g]	 (85)[h]
i	Ph	Ph[13]	H	H	4	 (50) (40)
l	Ph	PhCH=CH[14]	H	H	3	 (81)

[a] Unless otherwise noted, reactions were carried out on 0.5–0.6 M dichloromethane solutions of the starting α,β-enones under the following conditions: room temperature, 3.5–8.0 mmol of 1, 5 mol % of $PdCl_2$, 10 mol % of TBA^+Cl^-, 50 mol % excess of 2, dichloromethane/aqueous 3 N HCl (ca. 1.6:1 v/v). [b] Yields are not optimized, are calculated on the starting α,β-enone, and are given for pure, isolated products. [c] Reaction was carried out by using a 2:1 1/2 molar ratio. [d] Overall yield. HPLC analysis (column prepacked with LiChrosorb Si-60, 25 × 0.45 cm, *n*-hexane/ethyl acetate (75/25), 2 mL min^{-1}) revealed the presence of two diastereoisomeric compounds with $K' = 3.73$ (76%) and $K' = 4.33$ (24%) which were not separated on a preparative scale. [e] Overall yield. Two diastereoisomeric compounds (4e and 4e′) were isolated in about a 60:40 molar ratio. [f] Reaction was carried out with a nearly 1:1 mixture of 2g with the isomeric (3-formyl,4-hydroxyphenyl)mercury chloride by using a 10 mol % excess of benzalacetone. The yield is based on the organomercury compound. The addition product derived from the 4-hydroxy isomer was isolated in 46% yield. [g] Reaction was carried out at 0 °C. [h] Overall yield.[5] [i] Y = H for all cases.

(SiO_2-60, 70–230 mesh, Merck) by eluting with *n*-hexane/AcOEt mixtures.

HPLC analyses were performed by using a Waters ALC/GPC-202 chromatograph equipped with a U6-K injector, a Model M6000 solvent-delivery system, a differential UV detector (254 nm), a Model 401 refractive index detector, and a Waters data module. ^1H NMR spectra (measured in $CDCl_3$ with Me_4Si as an internal standard) and mass spectra were recorded with a Varian EM390 spectrometer and a Hewlett-Packard HP 5980 A spectrometer equipped with a Hewlett-Packard Data System 5934 A.

General Procedure of Reaction of (2-Hydroxyaryl)mercury Chlorides with α,β-Enones. This is exemplified by the reaction of (2-hydroxyphenyl)mercury chloride with benzalacetone (entry a, table I). To a stirred solution of benzalacetone (0.5 g, 3.42 mmol) in dichloromethane (6.5 mL) were added 3 N HCl (4.0 mL), TBA^+Cl^- (0.095 g, 0.34 mmol), $PdCl_2$ (0.030 g, 0.17 mmol), and (2-hydroxyphenyl)mercury chloride (1.69 g, 5.14 mmol). The mixture was stirred for 4 h at room temperature, and the organic layer was separated, washed with a 10% thiosulfate solution and water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 75/25 *n*-hexane/ethyl acetate gave 4-phenyl-2-methylchroman-2-ol (0.71 g).

Preparation of 2-Ethoxychromans. General Procedure. Trifluoromethanesulfonic acid (0.5 mL) was slowly added to a

Table II. Characterization of Compounds 3h,i, 4a-e,e',h, and 5i,l

compd[a]	mp, °C (lit. mp)	IR,[b] cm^{-1}	^1H NMR[c]	MS, *m/e* (rel intens)
4a	119-120 (116)[7]	3240, 1220, 760, 700	7.40-6.70 (m, 9 H), 4.33 (dd, J = 6.0, 12.7, 1 H), 2.90 (d, J = 2.2, 1 H, exchange with D_2O), 2.30 (dd, J = 6.0, 12.7, 1 H), 1.98 (qd, J = 12.7, 12.7, 2.2, 1 H), 1.62 (s, 3 H)	240 (28.8), 183 (100)
4b	86-87	3250, 1125	7.50-6.50 (m, 4 H), 4.20 (br s, 1 H, exchange with D_2O), 3.05 (m, $W_{1/2}$ = 8.25, 1 H), 2.70-1.00 (m, 8 H)	147 (100)
4c	106-107	3500, 1230, 755, 700	7.45-6.60 (m, 14 H), 4.33 (dd, J = 13.5, 6.0, 1 H), 3.08 (AB q, J_{AB} = 13.9, $\Delta\nu$ = 9.24 Hz, 2 H), 2.83 (d, J = 2.2, 1 H, exchange with D_2O), 2.23 (dd, J = 13.5, 6.0, 1 H), 1.93 (qd, J = 13.5, 13.5, 2.2, 1 H)	316 (3.8), 183 (100)
4d[d]	oil	3400, 1710, 700[e]	7.53-6.40 (m, 13 H), 4.3 (m, 2 H), 3.25 (br s, 1 H, exchange with D_2O), 2.95 (m, 2 H), 2.27 (dd, J = 13.5, 6.0, 1 H), 2.13-1.73 (m, 1 H), 1.93 (s, 3 H), 1.59 (s, 3 H)	386 (29.2), 285 (100)
4e	101-102	3380, 1710, 1195, 700	7.25 (m, 10 H), 6.98 (d, J = 2.5, 1 H), 6.63 (d, J = 2.5, 1 H), 4.85 (t, J = 7.5, 1 H), 4.20 (dd, J = 13.5, 6.0, 1 H), 3.13 (d, J = 7.5, 2 H), 2.60 (br s, 1 H, exchange with D_2O), 2.30 (dd, J = 13.5, 6.0, 1 H), 2.07 (s, 3 H), 1.93 (br dd, J = 13.5, 13.5, 1 H), 1.63 (s, 3 H)	420 (12.8), 422 (4.7), 359 (100)
4e'	72-73	3390, 1705, 1200, 700	7.28 (m, 10 H), 6.95 (d, J = 2.5, 1 H), 6.60 (d, J = 2.5, 1 H), 5.00 (t, J = 7.5, 1 H), 4.28 (dd, J = 13.5, 6.0, 1 H), 3.60 (br s, 1 H, exchange with D_2O), 3.15 (d, J = 7.5, 2 H), 2.28 (dd, J = 13.5, 6.0, 1 H), 2.07 (s, 3 H), 1.93 (br dd, J = 13.5, 13.5, 1 H), 1.63 (s, 3 H)	420 (12.1), 422 (4.0), 359 (100)
3h, 4h[f]	oil[g]	3360, 1700, 1230, 755[e]	7.72 (s, 0.75 H, exchange with D_2O), 7.20-6.70 (m, 4 H), 3.93 (br s, 0.25 H, exchange with D_2O), 2.78 (m, 4 H), 2.05 (s, 2.25 H), 1.58 (s, 0.75 H)	164 (45.5), 107 (100)
3i	165-166 (167-167.5)[15]	3360, 1665, 1230	9.47 (s, 1 H), 8.20-6.40 (m, 14 H), 5.10 (t, J = 7.5, 1 H), 3.83 (d, J = 7.5, 2 H)[h]	302 (1.3), 211 (100)
5i	109-110 (110)[16]	1230, 750, 700	7.80-6.80 (m, 14 H), 5.56 (d, J = 4.2, 1 H), 4.80 (d, J = 4.2, 1 H)	284 (1.8), 211 (100)
5l	148-149	1220, 750, 700	7.55-6.75 (m, 15 H), 6.50 (B part of an AB system, J = 16.5, 1 H), 4.92 (AB q, J_{AB} = 4.5, $\Delta\nu$ = 35.72 Hz, 2 H)	310 (47.3), 256 (100)

[a] All products gave satisfactory microanalyses (C, ±0.35%; H, ±0.22%). [b] Unless otherwise noted, IR spectra were recorded in Nujol. [c] Given as δ values; J values are in hertz. Unless otherwise noted, ^1H NMR spectra were recorded in $CDCl_3$. [d] IR, ^1H NMR, and mass spectra were recorded on the diastereoisomeric mixture which was not further purified. [e] Liquid film. [f] IR, ^1H NMR, and mass spectra were recorded on the 3h/4h equilibrating mixture. [g] Treatment of oil with (2,4-dinitrophenyl)hydrazine gave a product with a melting point of 153-154 °C. [h] Me_2SO-d_6.

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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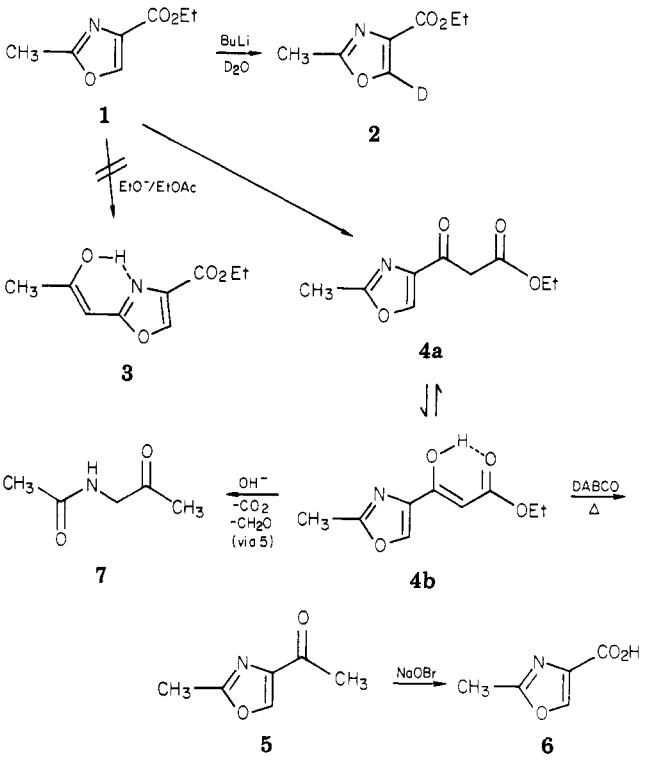
Received February 5, 1982

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]

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