Perhydroindan Derivatives. XV. The Synthesis of a Tetracyclic Precursor to Epiallogibberic Acid[1]

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The tetrahydrofluorene derivative **5** has been transformed in a series of steps (Schemes I–IV) into the tetracyclic intermediate **30** that has the appropriate functionality and stereochemistry to serve as a precursor for epiallogibberic acid. A key step in the sequence is the intramolecular aldol condensation **10a** ⇄ **19** that is unfavorable in polar, protic solvents but can be forced to completion by forming a covalent magnesium alkoxide **18** in a nonpolar, aprotic medium.

In our earlier investigation of possible precursors for epiallogibberic acid (**1**), the two tetrahydrofluorene derivatives **2**[3] and **5**[4] were prepared. Since utilization of the precursor **2** and various of its derivatives was severely hampered by lack of reactivity at the C-9 keto function,[3] we concentrated our efforts on the precursor **5** obtained by addition of butadiene to the indene diester **6**. Several improvements (see Experimental Section) in the synthesis of the diester **6** from intermediates **3** and **4** and in the use of **6** as a dienophile provided an adequate supply of the intermediate **5**. The further transformation of intermediate **5** to the diketo sulfone **10**, summarized in Scheme I, is analogous to results obtained in earlier studies with model compounds.[5] The diketo sulfone acid **10a** existed primarily in the form of its lactol tautomer **11**, a result consistent with the assigned cis stereochemistry for substituents at C-9 and C-1a.

Other transformations of the intermediate lactone **8** are summarized in Scheme II. Of particular interest was the selective reaction of the lactone acid **8a** with 2 equiv of methylmagnesium chloride to form, after oxidation, the diketo acid derivatives **15**. However, a variety of attempts to effect an intramolecular aldol condensation with these diketone derivatives **15** to yield the tetracyclic intermediate **24** were not successful. Comparable results had been obtained previously with the model diketone **17**.[5]

An intramolecular aldol condensation to produce tetracyclic intermediates was accomplished by reaction of the diketo sulfone acid **10a** (or **11**) with 2 equiv of *tert*-butylmagnesium chloride in a nonpolar reaction

SCHEME I

(1) This research has been supported by Public Health Service Grant RO1-CA-12634 from the National Cancer Institute.

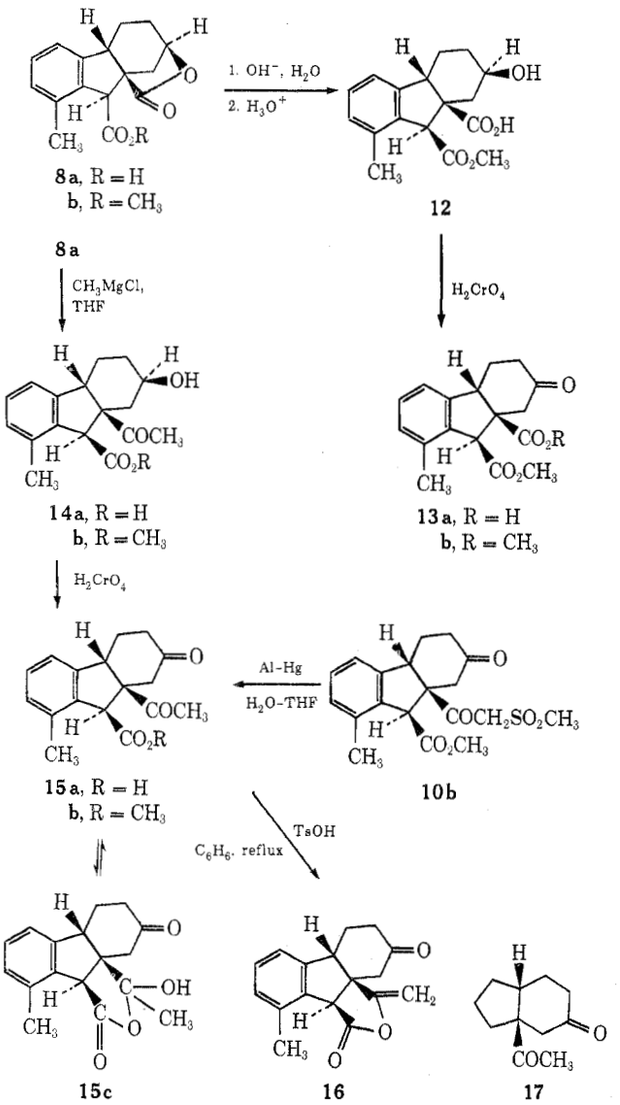
(2) National Science Foundation Predoctoral Fellow, 1965–1969. A portion of this work was taken from the Ph.D. dissertation of Frederick J. Sauter, Massachusetts Institute of Technology, 1969.

(3) H. O. House and R. Darms, *J. Org. Chem.*, **30**, 2528 (1965), and references cited therein.

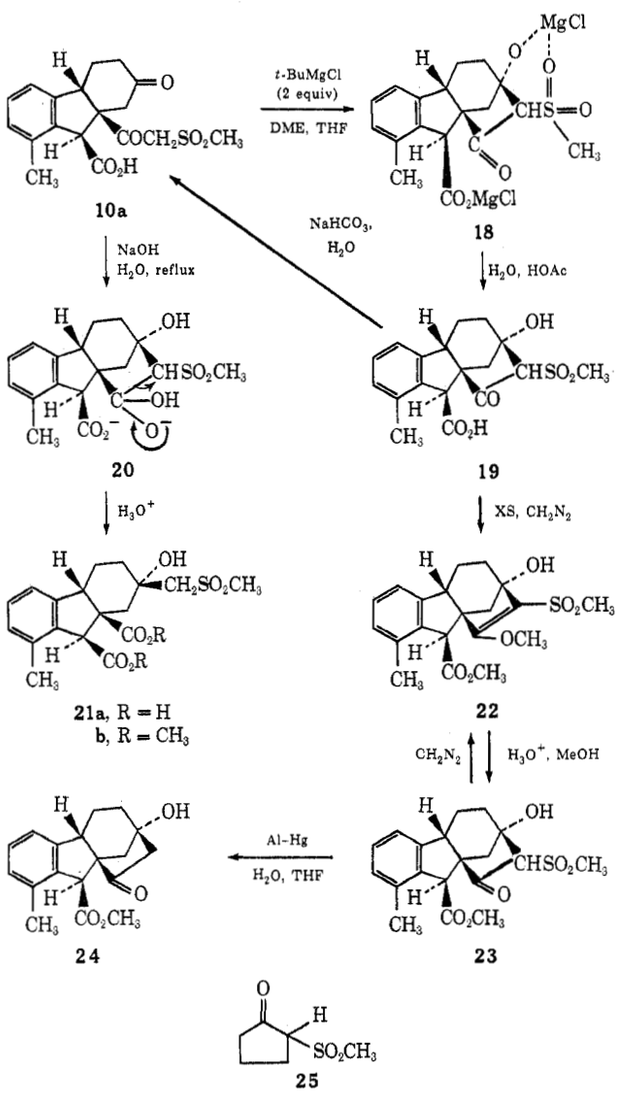
(4) H. O. House, F. J. Sauter, W. G. Kenyon, and J. J. Riehl, *ibid.*, **33**, 957 (1968).

(5) (a) H. O. House, S. G. Boots, and V. K. Jones, *ibid.*, **30**, 2519 (1965); (b) H. O. House and J. K. Larson, *ibid.*, **33**, 61 (1968); (c) L. J. Dolby, S. Esfandiari, C. A. Elliger, and K. S. Marshall, *ibid.*, **36**, 1277 (1971); (d) H. O. House, R. G. Carlson, and H. Babad, *ibid.*, **28**, 3359 (1963), and references cited therein.

SCHEME II



SCHEME III



medium (DME + THF, Scheme III). We attribute the success of this aldol condensation and other examples to be discussed elsewhere[6] to the formation of a covalent metal alkoxide such as the metal chelate **18** that is stable in the absence of polar solvents which could compete as ligands for the metal ion. An indication of the value of this procedure for effecting aldol condensation is provided by the ready reversal of the reaction when the aldol product **19** was treated with even very weak bases such as aqueous sodium bicarbonate. Reaction of the diketone **10a** with refluxing aqueous sodium hydroxide evidently produces a small equilibrium concentration of the aldol product **19** which is cleaved (see structure **20**) on prolonged reaction to form the diacid **21a**.

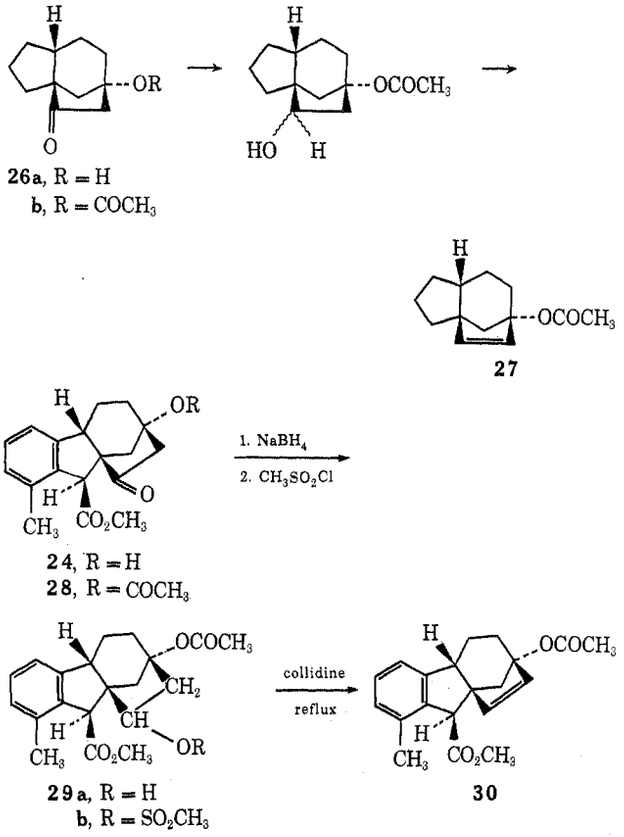
Reaction of the aldol product **19** with diazomethane posed an unexpected difficulty in that the initially formed keto ester **23** reacted relatively rapidly with additional diazomethane to form an enol ether **22**. Since we found no evidence for the presence of a significant quantity of the enol tautomer of the keto ester **23** and the model β-keto sulfone **25** did not react readily with diazomethane, the reason for the ready formation of the enol ether **22** from the ketone **23** remains unclear. It might also be noted that the *O*-acetyl derivative of a structure analogous to acid **19** was converted with diazomethane to a methyl ester without apparent problem from enol ether formation.[5c] This difficulty was best overcome in the synthetic scheme by reaction of the aldol product **19** with excess diazomethane to form the dimethoxy derivative **22**. Subsequent acid-catalyzed hydrolysis afforded the desired keto ester **23**, which was reductively cleaved with aluminum amalgam to form the hydroxy ketone **24**.

Conversion of the hydroxy ketone **24** to the acetoxy olefin **30** (Scheme IV) followed a sequence devised by Nagata and coworkers[7] and explored previously[5b] in the model systems **26** → **27**. The further transformation of the tetracyclic acetoxy olefin **30** to degradation products of gibberellic acid will be described in a subsequent publication.

(6) H. O. House, D. S. Crumrine, H. D. Olmstead, and A. Y. Teranishi, to be published.

(7) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **89**, 1483 (1967); W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *ibid.*, **89**, 1499 (1967).

SCHEME IV



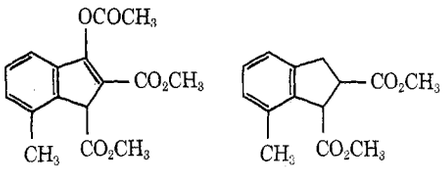
Experimental Section[8]

o-**Tolylsuccinic Anhydride** (**3**).—Tetracarboethoxyethylene, mp 52.5–54° (li.[9a] mp 52.5–53.5°), was obtained by previously described methods.[9] A 1.00 *M* solution of *o*-tolylmagnesium chloride was prepared by reaction of 52.39 g (0.41 mol) of *o*-chlorotoluene with 10.75 g (0.46 g-atom) of triply sublimed Mg[10] in 250 ml of tetrahydrofuran. To 326 ml of this cold (0°) solution (containing 326 mmol of the Grignard reagent) was added a solution of 103.3 g (327 mmol) of the tetracarboethoxyethylene. The resulting mixture was stirred for 16 hr at 25° and then partitioned between Et_2O and aqueous NH_4Cl. The organic layer was dried and concentrated to leave 175.4 g of crude 1-(*o*-tolyl)-1,1,2,2-tetracarboethoxyethane as a viscous liquid which partially crystallized on standing. A solution of this crude product in 135 ml of concentrated aqueous HCl and 225 ml of HOAc was refluxed for 68 hr, during which time 300 ml of liquid was allowed to distil from the mixture. After the reaction mixture had been further concentrated and then diluted with toluene, 33.3 g of crude *o*-tolylsuccinic acid separated and was collected. The mother liquors were subjected to the hydrolysis and decarboxylation procedure again to form an additional 30.7 g (total yield 65 g) of crude *o*-tolylsuccinic acid. A solution of the crude acid in 170 g of Ac_2O was refluxed for 1.5 hr and then distilled to separate 44.7 g (72% overall) of the anhydride **3** as a viscous yellow liquid, bp 119–128° (0.13 mm) [lit.[11] bp 174–176° (5 mm)]. Repitition of this same procedure on a larger scale produced the same anhydride **3** in a yield of 76% overall. In accord with previous observations,[4] repetition of this same reaction sequence starting with 120.2 g (380 mmol) of tetracarboethoxyethylene and 380 mmol of *o*-tolylmagnesium chloride prepared from ordinary Grignard-grade magnesium (Eastman Organic Chemicals) produced a series of very impure reaction intermediates. At the end of the sequence distillation separated 32.3 g (45% overall) of the desired anhydride **3**, bp 120–136° (0.2–0.3 mm), accompanied by 7.0 g (26%) of crude succinic anhydride, mp 117–119°, which sublimed during the early part of the distillation. This by-product was identified with an authentic sample by a mixture melting point determination and comparison of ir spectra.

A 1.5-g (72 mmol) sample of *o*-tolylsuccinic acid was esterified with excess ethereal CH_2N_2 to form the dimethyl ester, obtained as 1.5 g (88%) of colorless liquid after distillation in a short-path still (0.2 mm and 140° bath): ir (CCl_4) 1740 cm^{-1} (ester C=O); uv max (95% EtOH) 265 mμ (ε 574) and 272 (597); nmr (CCl_4) δ 6.9–7.1 (4 H, m, aryl CH) with singlets at 3.52 (6 H, OCH_3) and 2.37 (3 H, aryl CH_3) superimposed on a multiplet in the region 2.4–4.4 (3 H, aliphatic CH); mass spectrum *m/e* (rel intensity) 236 (33, M^+), 205 (20), 204 (50), 177 (21), 176 (21), 172 (20), 144 (42), 143 (40), 135 (100), 117 (43), 116 (23), 115 (27), and 91 (27).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.90; H, 6.87.

1,2-Dicarbomethoxy-7-methylindene (**6**).—The previously described[4] procedures were used to convert the *o*-tolylsuccinic anhydride to the indene diester **6**, mp 79–80.5° (lit.[4] mp 79.9–81°). In exploring various methods to hydrogenate the intermediate enol acetate **31** to the indan triester, a 3.04-g (10 mmol) sample of **31** in 50 ml of HOAc was hydrogenated at 1 atm and 27° over 0.3 g of a 10% Pd/C catalyst. When the H_2 uptake (500 ml or 2 equiv) ceased, the product (a liquid) was chromatographed on silica gel to separate 1.3 g (42%) of one stereoisomer of the indan diester **32**, mp 65–70°, in fractions eluted with



Et_2O–hexane mixtures. Recrystallization from hexane separated one pure stereoisomer of the indan **32** as white prisms: mp 76–77°; ir (CCl_4) 1745 cm^{-1} (ester C=O); uv (95% EtOH) series of weak maxima (ε 244–296) in the region 250–280 mμ; nmr (CCl_4) δ 6.8–7.2 (3 H, m, aryl CH), 2.8–4.4 (3 H, m, aliphatic CH), 3.65 (3 H, s, OCH_3), 3.52 (3 H, s, OCH_3), and 2.30 (3 H, s, aryl CH_3).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.47; H, 6.46.

To explore an alternative synthesis of the indene **6**, β-(*o*-tolyl)propionic acid was esterified with MeOH and H_2SO_4 to form methyl β-(*o*-tolyl)propionate (92% yield) as a colorless liquid: bp 70–74.3° (0.2–0.3 mm); $n^{26.8}D$ 1.4998–1.500; ir (CCl_4) 1750 cm^{-1} (ester C=O); uv (95% EtOH) series of weak maxima (ε 200–258) in the region 250–280 mμ; nmr (CCl_4) δ 6.8–7.4 (4 H, m, aryl CH), 3.56 (3 H, s, OCH_3), 2.3–3.1 (4 H, m, aliphatic CH), and 2.28 (3, H, s, aryl CH_3); mass spectrum *m/e* (rel intensity) 178 (32, M^+), 119 (36), 118 (100), and 105 (56).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.86; H, 7.95.

To a refluxing solution of 7.2 g (300 mmol) of NaH and 13.02 g (110 mmol) of $(CO_2CH_3)_2$ in 100 ml of PhH was added, dropwise over 1 hr, a solution of 17.82 g (100 mmol) of methyl β-(*o*-tolyl)propionate in 150 ml of PhH. After the reaction mixture had been refluxed for an additional 1 hr, it was acidified with 26.2 ml of HOAc and then partitioned between PhH and H_2O. The crude keto diester **33** (25.2 g) recovered from the organic layer was added to 20 g (100 mmol) of $Cu(OAc)_2$ in 200 ml of

(8) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

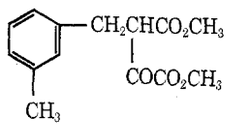
(9) (a) B. B. Corson and W. L. Benson, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 273; (b) C. S. Palmer and P. W. McWherter, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1964, p 245.

(10) This purified magnesium metal was obtained through the kindness of Dr. Francis Johnson of the Dow Chemical Co.

(11) K. Mori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem.* (*Tokyo*), **27**, 27 (1963).

warm (60°) H_2O. The resulting mixture was extracted with PhH and the organic extract was concentrated. Crystallization of the residue from a PhH–hexane mixture separated 11.16 g (43.5%) of the copper complex of the β-keto ester **33** as green needles: mp 158–163° dec; ir (CCl_4) 1745 (ester C=O) and 1605 cm^{-1} (β-keto ester enolate); uv max (95% EtOH) 284.5 mμ (ε 18,200).

Anal. Calcd for $C_{28}H_{30}CuO_{10}$: C, 56.99; H, 5.12; Cu, 10.77. Found: C, 56.70; H, 4.91; Cu, 10.51.



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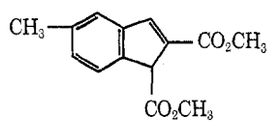

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After 1.00 g of this copper complex had been shaken with 100 ml of aqueous 0.5 *M* H_2SO_4 and 25 ml of Et_2O, the Et_2O layer was separated, washed with H_2O, dried, concentrated, and distilled in a short-path still (0.15 mm, 130–160° bath). The partially enolic keto diester **33** was collected as a colorless liquid: $n^{21.9}D$ 1.5060; ir (CCl_4) 1760, 1740 (ester C=O), 1665 (weak), and 1610 cm^{-1} (weak) (partially enolic keto ester); uv max (95% EtOH) 217 mμ (ε 5000), 260 (1800), and 272.5 (shoulder, 1660); nmr (CCl_4) δ 6.7–7.1 (4 H, m, aryl CH), 2.27 (3 H, s, aryl CH_3), and a multiplet in the region 2.9–4.5 (9 H, OCH_3 singlets and aliphatic CH); mass spectrum *m/e* (rel intensity), 264 (9, M^+), 173 (51), 145 (55), and 105 (100).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.54; H, 6.15.

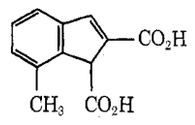
A 4.40-g (16.6 mmol) sample of the keto diester **33** was added dropwise and with stirring over 30 min to 50 g of warm (103–105°) polyphosphoric acid. The resulting mixture was stirred for an additional 30 min and then treated with ice and extracted with Et_2O. The ethereal extract was washed successively with aqueous $NaHCO_3$ and aqueous NaCl, and then dried and concentrated. Successive crystallization of the residual liquid (3.40 g) from Et_2O and from MeOH separated 1.12 g of tan prisms, mp 50–74°, with nmr absorption consistent with the presence of a mixture of comparable amounts of esters **6** and **34** and their double bond isomers. A solution of 670 mg of this material was equilibrated[12] in 15 ml of boiling MeOH containing 20 mg of TsOH. The recovered material was fractionally crystallized from Et_2O–hexane and from hexane to separate 70.5 mg of the indene diester **34** as white prisms: mp 82.5–84°; ir (CCl_4) 1745 (ester C=O) and 1720 cm^{-1} (conjugated ester C=O); uv max (95% EtOH) 232.5 mμ (ε 18,400), 238.5 (19,000), and 292 (14,800); nmr ($CDCl_3$) δ 7.74 (1 H, d, J = 1.8 Hz, vinyl CH), 7.0–7.6 (3 H, m, aryl CH), 4.63 (1 H, m, benzylic CH), 3.84 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), and 2.37 (3 H, s, aryl CH_3); mass spectrum *m/e* (rel intensity) 246 (100, M^+), 214 (36), 187 (52), 157 (78), 156 (42), 143 (61), 129 (33), 128 (78), 127 (36), and 59 (31).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.42; H, 5.73.

Since we were unable to find a practical method for separating the indene diesters **6** and **34**, this synthetic scheme was not explored further.

A solution of 2.26 g (9.2 mmol) of the diester **6** in a mixture of 75 ml of aqueous 12 *M* HCl and 75 ml of HOAc was heated to 90° for 2.5 hr and then concentrated under reduced pressure. The residual yellow solid (2.04 g) was triturated with $CHCl_3$ (to remove the soluble monoacids **36a**) to leave 1.65 g (82%) of the insoluble diacid **35** as a white solid, mp 171–180° dec. Samples of this diacid **35**, which were purified by solution in boiling $CHCl_3$ followed by concentration, were obtained as white solids melting with decomposition within the range 183–193°. Samples of **35** which had been decomposed solidified and remelted at 203–207° corresponding to the subsequently described monoacid **36a**; the ir spectra of these samples also indicated them to be the monoacid. The samples of the diacid **35** had ir absorption (KBr pellet) at 1705 and 1665 cm^{-1} (unconjugated and conjugated carboxyl C=O); titration (aqueous NaOH) indicated an equivalent weight of 114 (calcd 109). Esterification of 101 mg of this diacid **35** with excess ethereal CH_2N_2 yielded 118 mg

(12) H. O. House, J. K. Larson, and H. C. Muller, *J. Org. Chem.*, **33**, 961 (1968).



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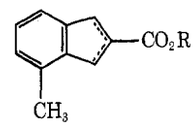
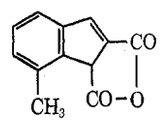


36a, R = H
b, R = CH_3



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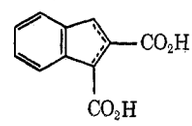

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of the crude diester **6**, mp 70–75°, which was identified with an authentic sample by comparison of nmr spectra.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 66.05; H, 4.62. Found: C, 66.14; H, 4.78.

A variety of attempts to convert the diacid **35** to the anhydride **37**, including methods which had been successful for the conversion of the diacids **38** to the corresponding anhydrides,[12] resulted either in recovery of the starting diacid or in the formation of other products which appeared to be derived from the monoacid **36a**.

The Diels–Alder Reaction with the Indene 6.—A mixture of 11.61 g (47.2 mmol) of the diester **6**, 955 mg of phenothiazine (a free-radical inhibitor), 50 ml of liquid butadiene, and 70 ml of PhH was heated to 180–192° in an autoclave for 24 hr. The mixture was cooled, 50 ml of liquid butadiene was added, and heating to 170° was continued for an additional 24 hr. Then an additional 30-ml portion of liquid butadiene was added and heating at 170° was continued for an additional 48 hr. The resulting reaction mixture was concentrated and then extracted with four 150-ml portions of boiling MeOH. The combined MeOH extracts were concentrated, diluted with Et_2O, and cooled to separate 973 mg (8.5%) of the starting diester **6**. The mother liquors were concentrated, mixed with 100 ml of aqueous 10% NaOH, and refluxed for 13 hr. After the resulting mixture had been extracted with Et_2O, the aqueous phase was acidified (HCl) and extracted with Et_2O. The acidic Et_2O solution was dried and concentrated slowly. The initial material, which separated as light, fluffy needles, was the crude monoacid **36a**. After this material had been removed, further concentration of the Et_2O solution resulted in the crystallization of 5.98 g (37%) of the ether solvate of the diacid **5** as dense prisms, mp 74° dec (lit.[4] mp 75° dec).

Recrystallization of the crude monoacid **36a** from $CHCl_3$ afforded the pure acids (presumably a mixture of double-bond isomers) as white needles: mp 214° dec; ir (KBr pellet) 3000 (broad, associated OH) and 1660 cm^{-1} (broad, carboxyl C=O); uv max (MeOH) 227 mμ (ε 10,800), 234.5 (9500), and 285 (16,800); nmr (DMSO-d_6) δ 7.6–7.8 (1 H, m, vinyl CH), 7.0–7.5 (3 H, m, aryl CH), 3.4–3.7 (2 H, m, benzylic CH_2), 2.42 and 2.33 (two singlets, total 3 H, aryl CH_3 groups of double bond isomers).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.60; H, 5.74.

An 851-mg sample of the acids **36a** was esterified with excess ethereal CH_2N_2 to yield 800 mg of the esters **36b** as tan needles: mp 43–45°; ir (CCl_4) 1715 cm^{-1} (conjugated ester C=O); uv max (95% EtOH) 231 mμ (ε 10,100), 237 (9000), and 292 (18,100); nmr (CCl_4) δ 7.5–7.8 (1 H, m, vinyl CH), 6.9–7.4 (3 H, m, aryl CH), 3.77 (3 H, s, OCH_3), 3.4–3.7 (2 H, m, benzylic CH_2), 2.46 and 2.35 (two singlets, total 3 H, aryl CH_3 of double bond isomers); mass spectrum *m/e* (rel intensity) 188 (78, M^+), 157 (25), 129 (100), and 128 (44).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.75; H, 6.54.

The Iodolactones 7.—The ether solvate of the diacid **5** (6.12 g, 17.7 mmol) was dissolved in a mixture of 240 ml of saturated aqueous $NaHCO_3$, 19.2 g (75.5 mmol) of I_2, 42 g (246 mmol) of KI, and 180 ml of H_2O and allowed to stand at 25° for 48 hr. After the reaction mixture had been acidified (HCl), it was extracted with $CHCl_3$ and the organic extract was washed with aqueous $Na_2S_2O_3$ and then dried and concentrated. Recrystallization of the residue (6.04 g) from EtOAc separated 5.37 g (75%) of the iodolactone **7a** as colorless prisms: mp 214° dec; ir ($CHCl_3$) 1790 (γ-lactone C=O) and 1720 cm^{-1} (broad, car-

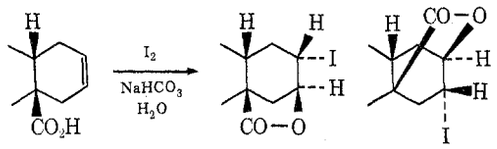
boxyl C=O); uv max (CH_3CN) 262 mμ (ε 877); nmr (pyridine-d_5) δ 11.4 (1 H, broad, OH), 6.8–7.7 (3 H, m, aryl CH), 5.10 (1 H, m, OCH), 4.2–4.6 (1 H, m, CHI), 4.30 (1 H, s, benzylic CHCO), 3.7–4.2 (1 H, m, benzylic CH), 1.8–3.4 (4 H, m, aliphatic CH), and 2.36 (3 H, s, aryl CH_3).

Anal. Calcd for $C_{16}H_{15}IO_4$: C, 48.26; H, 3.79; I, 31.86. Found: C, 48.29; H, 3.91; I, 31.76.

Esterification of 800 mg of the iodolactone acid **7a** with excess ethereal CH_2N_2 yielded 519 mg (63%) of the ester **7b** as colorless prisms from Et_2O–CH_2Cl_2: mp 210 dec; ir ($CHCl_3$) 1790 (γ-lactone C=O) and 1740 cm^{-1} (ester C=O); uv max (95% EtOH) 263 mμ (ε 912) and 270 (shoulder, 715); nmr ($CDCl_3$) δ 7.0–7.5 (3 H, m, aryl CH), 5.0–5.4 (1 H, m, CHO), 4.2–4.7 (1 H, m, CHI), 4.00 (1 H, s, benzylic CHCO), 3.5–4.0 (1 H, m, benzylic CH), 3.69 (3 H, s, OCH_3), 2.1–3.5 (4 H, m, aliphatic CH), and 2.24 (3 H, s, aryl CH_3).

Anal. Calcd for $C_{17}H_{17}IO_4$: C, 49.53; H, 4.16; I, 30.78. Found: C, 49.47; H, 4.36; I, 30.85.

The ir absorption of these iodolactones **7** and the related deiodinated lactones **8** at 1790 cm^{-1} establishes that these products are γ-lactones **39** and not δ-lactones **40**. Comparable iodolactonization studies of an analogous acid **41** in a model



41 **39** **40**

series[5a] as well as earlier studies[5d] have demonstrated that the formation of γ- rather than δ-lactones is the preferred course of this reaction.

The Lactones 8.—To a solution of 2.00 g (5.02 mmol) of the iodolactone acid **7a** in 30 ml of 1,2-dimethoxyethane was added, portionwise and with stirring over 15 min, 4.38 g (15.0 mmol) of $(n\text{-}Bu)_3SnH$.[13] The resulting mixture was stirred for 4 hr and then extracted with saturated aqueous $NaHCO_3$. The aqueous solution was acidified to precipitate 1.08 g (79%) of the lactone acid **8a**, mp 268° dec. Recrystallization from EtOAc afforded the pure acid **8a** as white prisms: mp 270° dec; ir (KBr pellet) 3400, 2940 (broad, associated OH), 1790 (γ-lactone C=O), and 1705 cm^{-1} (carboxyl C=O); uv max (CH_3CN) 263 mμ (ε 250) and 272 (187); nmr (pyridine-d_5) δ 11.4 (1 H, OH), 6.8–7.5 (3 H, m, aryl CH), 4.62 (1 H, broad, CHO), 4.16 (1 H, s, benzylic CHCO), 3.4–4.1 (1 H, m, benzylic CH), 2.26 (3 H, s, aryl CH_3), and 1.3–2.3 (6 H, m, aliphatic CH).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.33; H, 5.78.

In an alternative procedure, after reaction of 4.00 g (10.0 mmol) of the crude iodolactone **7a** with 8.9 g (31 mmol) of $(n\text{-}Bu)_3SnH$ in 55 ml of 1,2-dimethoxyethane at 25° for 4 hr, the reaction mixture was filtered and the residue was washed with Et_2O. The residual lactone acid **8a** amounted to 2.32 g (85%) of white solid, mp 280–286° dec, which was sufficiently pure for use in further synthetic transformations.

Esterification of the acid **8a** with excess ethereal CH_2N_2 afforded the lactone ester **8b** as colorless prisms from MeOH: mp 187–188°; ir ($CHCl_3$) 1780 (γ-lactone C=O) and 1735 cm^{-1} (ester C=O); uv max (95% EtOH) 260 mμ (shoulder, ε 220), 263.5 (253), and 272 (176); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 4.82 (1 H, m, CHO), 3.94 (1 H, s, benzylic CHCO), 3.72 (3 H, s, OCH_3), 3.4–4.0 (1 H, m, benzylic CH), 2.24 (3 H, s, aryl CH_3), and 1.5–2.6 (6 H, m, aliphatic CH).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.06; H, 6.38.

The Keto Sulfones 10.—To a suspension of the lithio derivative prepared from 3.4 g (36 mmol) of $CH_3SO_2CH_3$ and 33 mmol of CH_3Li in 300 ml of 1,2-dimethoxyethane was added 3.00 g (11 mmol) of the lactone acid **8a**. The resulting solution was refluxed for 15 hr and then cooled, neutralized (4 ml of HOAc), acidified (100 ml of aqueous 1.2 *M* HCl), concentrated, and extracted with $CHCl_3$. The crude alcohol **9** (5.4 g of yellow liquid) obtained from the $CHCl_3$ extract was dissolved in 250 ml of cold (5°) acetone and oxidized with excess aqueous 8 *N* H_2CrO_4 (Jones reagent).[14] After following the usual isolation procedure,[14] the crude product (3.7 g) was recrystallized from CH_2Cl_2–Et_2O to separate 2.35 g (59%) of the keto sulfone **10a** as white prisms, mp 161° dec. This product **10a**, which exists in solution primarily as the tautomeric lactol **11**, was recrystallized to raise the decomposition point to 160–165°: ir ($CHCl_3$) 3420 (broad, OH), 1795 (γ-lactol C=O), 1720 (C=O), 1330, 1320, and 1120 cm^{-1} (sulfone S=O); uv max (CH_3CN) 256 mμ (shoulder, ε 247), 263 (shoulder, 320), 267 (380), 276 (330), and 293 (31); nmr (pyridine-d_5) δ 11.0 (1 H, broad, OH), 7.0–7.7 (3 H, m, aryl CH), 5.22 (1 H, broad, $COCH_2SO_2$), 4.4–4.8 (2 H, m, benzylic CH), 3.35 (3 H, s, SO_2CH_3), 2.0–3.2 (9 H, m, aliphatic CH and aryl CH_3 at δ 2.57).

Anal. Calcd for $C_{18}H_{20}O_6S$: C, 59.33; H, 5.53; S, 8.80. Found: C, 59.06; H, 5.64; S, 8.75.

A 166-mg sample of this lactol **11** (or **10a**) was esterified with excess ethereal CH_2N_2 to yield 97 mg (57%) of the ester **10b** as white prisms from Et_2O–CH_2Cl_2: mp 152–154° (recrystallization raised the melting point to 154.5–156°); ir ($CHCl_3$) 1725 (broad, ester and ketone C=O) and 1320 cm^{-1} (SO_2); uv max (CH_3CN) 266 mμ (ε 318), 271 (shoulder, 264), 275 (228), and 290 (75); nmr ($CDCl_3$) δ 6.8–7.5 (3 H, m, aryl CH), 3.9–4.5 (4 H, m, including singlets at 4.30 and 4.07, $COCH_2SO_2$ and benzylic CH and CHCO), 3.65 (3 H, s, OCH_3), 3.14 (3 H, s, SO_2CH_3), and 2.0–3.4 (9 H, m, including a singlet at δ 2.32, aryl CH_3 and aliphatic CH); mass spectrum *m/e* (rel intensity) 378 (9, M^+), 299 (60), 239 (50), 198 (27), 197 (100), 169 (40), 155 (37), 141 (27), and 79 (26).

Anal. Calcd for $C_{19}H_{22}O_6S$: C, 60.30; H, 5.86; S, 8.47. Found: C, 60.44; H, 6.28; S, 8.63.

Preparation of the Diketo Ester 15b. A. From the Sulfone 10b.—To a solution of 110 mg (0.29 mmol) of the sulfone **10b** in 10 ml of a 1:10 (v/v) H_2O–tetrahydrofuran mixture was added the Al amalgam prepared[15] from 78 mg (2.9 mg-atoms) of Al foil. The mixture was heated to 65° with stirring for 75 min and then cooled, filtered, concentrated, and partitioned between CH_2Cl_2 and aqueous 2 *M* HCl. Concentration of the organic phase left 89 mg of crude product which was chromatographed on 4.5 g of silica gel. The fractions (47 mg) eluted with Et_2O–hexane mixtures were recrystallized from Et_2O–hexane to separate 42 mg (47%) of the diketone **15b** as white needles: mp 91.5–93°; ir ($CHCl_3$) 1720 cm^{-1} (broad, ester and ketone C=O); uv max (95% EtOH) 265 mμ (ε 301), 269 (shoulder, 260), and 273 (225); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 4.1–4.4 (1 H, m, benzylic CH), 3.94 (1 H, s, benzylic CHCO), 3.56 (3 H, s, OCH_3), and 2.0–2.9 (12 H, m, including singlets at δ 2.21 and 2.33, aliphatic CH, $COCH_3$, and aryl CH_3); mass spectrum *m/e* (rel intensity) 300 (3, M^+), 105 (30), 86 (38), 84 (56), 77 (26), 55 (25), 49 (100), 43 (32), and 41 (44).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.19; H, 6.57.

B. From the Lactone 8a.—To a cold (0°) suspension of 495 mg (1.82 mmol) of the acid lactone **8a** in 30 ml of tetrahydrofuran was added, dropwise and with stirring, 2.38 ml of an Et_2O solution containing 3.71 mmol of MeMgCl. A solution was obtained after approximately one-half of the MeMgCl had been added. The resulting solution was stirred at 0–25° for 1 hr and then acidified (1 ml of HOAc) and partitioned between EtOAc and aqueous 0.5 *M* HCl. The organic layer was washed with H_2O, dried, and concentrated to leave 515 mg of white solid which was recrystallized from EtOAc. The crude keto acid **14a** separated as 411 mg of white prisms, mp 215–225° dec. A solution of 246 mg of the crude keto acid **14a** in EtOAc was esterified with excess ethereal CH_2N_2. The resulting solution was washed successively with aqueous $NaHCO_3$ and with H_2O and then dried and concentrated. The residual crude keto ester **14b** (243 mg) was recrystallized from a hexane–Et_2O mixture to separate 158 mg (68%) of the ester **14b** as white prisms, mp 145.5–148°. Recrystallization afforded the pure keto ester **14b** as white needles: mp 151–152°; ir ($CHCl_3$) 3620, 3480 (unassociated and associated OH), 1730 (ester C=O), and 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.41; H, 7.25.

A solution of 406 mg (1.41 mmol) of the crude product **14a** in 50 ml of cold 0° acetone was oxided with excess 8 *N* H_2CrO_4[14] for 3 min and then the excess oxidant was destroyed with *i*-

(13) G. J. M. Van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem.*, **7**, 366 (1957).

(14) E. J. Eisenbraun, *Org. Syn.*, **45**, 28 (1965).

(15) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

PrOH and the solution was concentrated. The reaction mixture was partitioned between $CHCl_3$ and H_2O and the organic layer was washed with H_2O, dried, and concentrated to leave 420 mg of the diketo acid **15a** as a colorless semisolid. Recrystallization from a hexane–Et_2O mixture afforded 353 mg (88%) of the crude lactol **15c** (from diketo acid **15a**), as white prisms: mp 101–215° dec; ir ($CHCl_3$) 1775 (lactol C=O) and 1715 cm^{-1} (C=O). A 45-mg (0.16 mmol) aliquot of the crude lactol **15c** (from the diketo acid **15a**) was esterified with excess ethereal CH_2N_2 and the crude neutral product (40 mg) was isolated in the usual way. Crystallization from hexane–Et_2O separated 30 mg (63%) of the diketo ester **15b** as white needles, mp 92–93.5°, identified with the previously described sample by a mixture melting point determination.

A solution of 279 mg (0.97 mmol) of the crude diketo acid **15a** and 109 mg (0.57 mmol) of *p*-TsOH·H_2O in 40 ml of PhH was refluxed for 6 hr and then 15 ml of solvent was allowed to distil from the mixture. The residual solution was washed with aqueous $NaHCO_3$ and concentrated. Sublimation (0.04 mm, 61°) of a portion of the residue (223 mg of yellow liquid) separated the enol lactone **16** as a white solid, mp 121.5–123°. Recrystallization from an Et_2O–hexane mixture afforded the pure enol lactone **16** as white prisms: mp 122–123°; ir ($CHCl_3$) 1805 (γ-lactone C=O), 1720 (C=O), and 1670 cm^{-1} (enol C=C); uv max (CH_3CN) 265.5 mμ (ϵ 321) and 274 (255); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 4.75 (1 H, d, J = 2 Hz, vinyl CH), 4.34 (1 H, d, J = 2 Hz, vinyl CH), 3.90 (1 H, s, benzylic CHCO), 3.35 (1 H, m, benzylic CH), 2.80 (1 H, d, J = 15 Hz, CH_2CO), 2.51 (1 H, d, J = 15 Hz, CH_2CO), 2.40 (3 H, s, aryl CH_3), and 1.6–2.4 (4 H, m, aliphatic CH_2); mass spectrum *m/e* (rel intensity) 268 (49, M^-), 198 (90), 170 (20), 156 (100), 155 (20), 142 (35), 141 (43), and 115 (22).

Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.22; H, 5.98.

Preparation of the Diacid Derivatives 12 and 13.—A mixture of 720 mg (2.52 mmol) of the lactone **8b**, 60 ml of MeOH, and 60 ml of aqueous 10% NaOH was stirred at 25° for 2.5 hr and then acidified (HCl), concentrated, and partitioned between EtOAc and aqueous $NaHCO_3$. The aqueous layer was acidfied (HCl) and extracted with EtOAc. After the organic extract had been washed with H_2O, dried, and concentrated, the residual crude product (829 mg, mp 171–174° dec) was recrystallized from EtOAc–hexane to separate 507 mg (66%) of the pure hydroxy acid **12** as white prisms: mp 174–182° dec; ir ($CHCl_3$) 3300 (broad, associated OH) and 1735 cm^{-1} (broad, ester and carboxyl C=O); uv max (95% EtOH) 263 mμ (ϵ 266) and 273 (shoulder, 209); nmr (pyridine-d_5) δ 8.67 (1 H, s, OH), 6.9–7.7 (3 H, m, aryl CH), 3.9–4.9 (3 H, m, CHO and benzylic CH), 3.52 (3 H, s, OCH_3), 1.0–3.2 (6 H, m, aliphatic CH), 2.38 (3 H, s, aryl CH_3), and 1.98 (1 H, s, OH); mass spectrum *m/e* (rel intensity) 304 (1, M^+), 226 (40), 200 (40), 183 (41), 182 (100), 181 (34), 167 (33), 156 (43), 155 (39), 143 (23), 142 (31), 141 (47), 128 (27), and 115 (30). Concentration of the mother liquors separated an additional 162 mg of the crude acid **12**, mp 167.5–175° dec.

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.90; H, 6.67.

A solution of 650 mg (2.14 mmol) of the hydroxy acid **12** in 50 ml of cold (0°) acetone was oxidized with excess aqueous 8 *N* H_2CrO_4[14] for 3 min and then the excess oxidant was destroyed with *i*-PrOH and the reaction mixture was concentrated and partitioned between H_2O and $CHCl_3$. The organic phase was washed with H_2O, dried, and concentrated. Recrystallization of the crude residue (690 mg) from Et_2O–hexane afforded 548 mg (85%) of the crude keto acid **13a** as white prisms, which melted with decomposition over the range 111–125°: ir ($CHCl_3$) 2970 (broad, associated OH) and 1730 cm^{-1} (broad, C=O); uv max (95% EtOH) 264.5 mμ (ϵ 242), 270 (199), and 274 (shoulder, 156); nmr ($CDCl_3$) δ 6.7–7.4 (4 H, m, aryl CH and OH), 4.2–4.5 (1 H, m, benzylic CH), 3.93 (1 H, s, benzylic CHCO), 3.61 (3 H, s, OCH_3), and 2.0–3.3 (9 H, m, including a singlet at δ 2.33, aryl CH_3 and aliphatic CH).

A 201-mg (0.67 mmol) sample of the crude keto acid **13a** was esterified with excess ethereal CH_2N_2 and the crude neutral product (205 mg, mp 102–115°) was isolated in the usual way. Recrystallization from hexane–Et_2O separated 177 mg (88%) of the diester **13b** as white prisms, mp 111.5–113°. After an additional recrystallization the keto diester **13b** melted at 112–113°: ir ($CHCl_3$) 1740 (ester C=O) and 1720 cm^{-1} (shoulder, C=O); uv (95% EtOH) series of weak maxima (ϵ 163–252) in the region 250–275 mμ; nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 4.1–4.4 (1 H, m, benzylic CH), 3.93 (1 H, s, benzylic CHCO), 3.75 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), and 1.6–2.9 (9 H, m, including a singlet at δ 2.37, aryl CH_3 and aliphatic CH); mass spectrum *m/e* (rel intensity) 316 (8, M^+), 256 (100), 197 (37), 169 (39), 155 (44), and 141 (23).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.45; H, 6.29.

Reactions of the Diketo Sulfone 10a (or 11). A. With Aqueous NaOH.—When an aqueous solution of the sulfone **10a** and 1.5 equiv of LiOH was stirred at 25° for 4 hr and then acidified and extracted with CH_2Cl_2, the diketo sulfone **10a** was recovered with no evidence (ir spectrum, absorption at 1750 cm^{-1}) for the presence of the aldol product **19**. When an aqueous solution of 364 mg (1.0 mmol) of the sulfone **10a** and 1.46 mmol of NaOH was heated to 95° for 17 hr and then acidified, 155 mg of the crude acid **21a** (mp 130–160° dec) precipitated. Esterification with excess ethereal CH_2N_2 followed by recrystallization from a CH_2Cl_2–Et_2O mixture yielded 100 mg of the diester **21b** as white prisms, mp 172.5–175°. Recrystallization afforded the pure diester **21b**: mp 174–176°; ir ($CHCl_3$) 3490 (broad, associated OH), 1735 (ester C=O), and 1310 cm^{-1} (SO_2); uv (CH_3CN) series of weak maxima (ϵ 148–240) in the region 250–275 mμ; nmr ($CDCl_3$) δ 6.9–7.5 (3 H, m, aryl CH), 4.0–4.3 (1 H, m, benzylic CH), 3.90 (1 H, s, benzylic CHCO), 3.82 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 3.1–3.5 (3 H, m, CH_2SO_2 and OH, 1 H exchanged with D_2O), 2.95 (3 H, s, SO_2-CH_3), and 1.0–2.8 (9 H, m, including a singlet at δ 2.33, aliphatic CH and aryl CH_3); mass spectrum *m/e* (rel intensity) 379 (2, $M^+ - OCH_3$), 253 (37), 193 (20), and 40 (100).

Anal. Calcd for $C_{20}H_{26}O_7S$: C, 58.52; H, 6.38; S, 7.81. Found: C, 58.25; H, 5.37; S, 7.99.

B. With Derivatives of Na, K, and Li.—A series of small-scale reactions were performed in which the sulfone **10a** was treated with NaH, MeLi, *t*-BuOK, $(i\text{-Pr})_2NLi$, or sodium *tert*-amylate in dimethyl sulfoxide, dimethyl sulfoxide–tetrahydrofuran mixtures, or 1,2-dimethoxyethane. The reaction mixtures were acidified (HOAc) and partitioned between aqueous 1 *M* HCl and either CH_2Cl_2 or EtOAc. The organic extracts were washed with H_2O, dried, and concentrated. Examination of the ir spectrum (Nujol mull) of the residue indicated whether or not any aldol product **19** was present by ir absorption at 1750 cm^{-1}. In all of these cases only weak absorption was observed at 1750 cm^{-1} with the most promising results being obtained from reaction with NaH in a 20:1 (v/v) mixture of tetrahydrofuran and dimethyl sulfoxide.

C. With Magnesium Derivatives.—To a cold (0°) solution of 206 mg (0.57 mmol) of the sulfone **10a** in 15 ml of tetrahydrofuran was added, with stirring, 0.39 ml of a tetrahydrofuran solution containing 1.13 mmol of MeMgCl. The resulting suspension was refluxed with stirring for 33 hr and then quenched by adding 0.15 ml of HOAc. The resulting mixture was concentrated and then partitioned between EtOAc and H_2O (pH 4). The organic layer was washed with H_2O (pH 4), dried, and concentrated. Crystallization of the residual yellow liquid (310 mg) from $CHCl_3$ afforded 64 mg (31%) of the keto sulfone acid **19** as a white solid, mp 211–219° dec.

In a second experiment, the mixture from 1.00 g (2.75 mmol) of **10a** in 65 ml of 1,2-dimethoxyethane and 1.93 ml of a tetrahydrofuran solution containing 5.60 mmol of MeMgCl was refluxed for 24 hr and then poured into a solution of 5 ml of HOAc in 50 ml of $CHCl_3$. The resulting mixture was concentrated and then partitioned between $CHCl_3$ and aqueous 0.1 *M* HCl. The organic layer was washed with H_2O, dried, and concentrated and the residue (1.038 g) was crystallized from $CHCl_3$ to separate 450 mg (45%) of the keto sulfone acid **19**, mp 214–220° dec. The same procedure was followed starting with 254 mg (0.70 mmol) of **10a** in 18 ml of dioxane and 1.39 mmol of MeMgCl in 0.48 ml of tetrahydrofuran. The yield of the crude product **19** was 78 mg (31%), mp 213–220° dec. Similarly, a solution of 440 mg (1.21 mmol) of **10a** and 446 mg (2.42 mmol) of $MgBr_2$ in 15 ml of cold (0°) tetrahydrofuran was treated with 15 ml of a tetrahydrofuran solution of $(i\text{-Pr})_2NLi$, prepared from 244 mg (2.42 mmol) of $(i\text{-Pr})_2NH$ and 2.46 mmol of MeLi. The resulting suspension was refluxed for 25 hr and subjected to the same isolation procedure to separate 140 mg (33%) of the product **19**, mp 214–219° dec.

The use of a hindered Grignard reagent to impede competing addition to the carbonyl functions was the most satisfactory procedure. To a cold (0°) solution of 4.73 g (13 mmol) of the

sulfone **10a** (as the lactol **11**) in 380 ml of 1,2-dimethoxyethane was added, dropwise and with stirring, 20.0 ml of tetrahydrofuran solution containing 29 mmol of *t*-BuMgCl. The resulting white suspension was stirred at 0° for 20 min and at reflux for 51 hr and then partitioned between $CHCl_3$ and aqueous HOAc. The $CHCl_3$ solution was concentrated and the residual yellow oil was partitioned between aqueous 0.5 *M* HCl and EtOAc. The EtOAc solution was dried and concentrated to leave 5.42 g of white solid. Recrystallization from $CHCl_3$ afforded 1.100 g of the hydroxy ketone **19** as a white solid, mp 223–229° dec. The material (4.33 g containing unchanged **10a**) recovered from the mother liquors was again treated with 22 mmol of *t*-BuMgCl in 300 ml of 1,2-dimethoxyethane and 15 ml of tetrahydrofuran. After a reflux period of 46 hr, use of the same isolation procedure separated an additional 3.455 g (total yield 4.555 g or 96%) of the aldol product **19**, mp 224–229° dec.

When a sample of the crude keto sulfone acid **19** was dissolved in aqueous $NaHCO_3$ and the solution was acidified (HCl) after 10 min at 25°, the ir spectrum of the crude recovered solid indicated it to be the lactol **11** from the diketo sulfone acid **10a**. Thus, the product **19** had undergone a reverse aldol condensation under these conditions. The crude keto sulfone acid **19** (presumably a mixture of stereoisomers) was soluble in MeOH and EtOAc and relatively insoluble in CH_2Cl_2 and $CHCl_3$. The material had the following spectral properties: ir (Nujol mull, KBr pellet) 3540, 3420 (associated OH), 1750 (cyclopentanone C=O), 1705 (carboxyl C=O), and 1315 cm^{-1} (SO_2).

A solution of 264 mg (0.72 mmol) of the acid **19** in cold (0°) tetrahydrofuran was esterified with a slight excess of ethereal CH_2N_2. The crude neutral product (283 mg), isolated in the usual manner, was recrystallized from Et_2O–CH_2Cl_2 to separate 159 mg (58%) of one crude epimer of the ester **23** as white needles: mp 148.5–150° (recrystallization raised the melting point to 151–152.5°; however, the sample of the ester **23** was still contaminated with a small amount of the subsequently described enol ether **22**); ir ($CHCl_3$) 1755 (cyclopentanone C=O), 1735 (ester C=O), and 1325 cm^{-1} (SO_2); uv (95% EtOH), intense end absorption (ϵ 21,000 at 201 mμ) with weak absorption (shoulders) at 263 (364) and 271 (268); nmr (CD_3COCD_3) δ 7.0–7.5 (3 H, m, aryl CH), 3.7–4.5 (3 H, m, benzylic CH and $COCHSO_2$), 3.63 (3 H, s, OCH_3), 3.20 (3 H, s, CH_3SO_2), and 1.2–3.0 (9 H, m, aliphatic CH and aryl CH_3); mass spectrum *m/e* (rel intensity) 392 (6, M^+ for **22**), 378 (6, M^+ for **23**), 299 (38), 239 (55), 211 (39), 197 (100), 169 (57), 156 (38), 155 (61), 142 (33), 141 (54), 79 (32), and 55 (35).

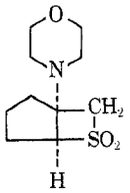
In a subsequent experiment a solution of 4.30 g (11.8 mmol) of the keto acid **19** in tetrahydrofuran was treated with a substantial excess of ethereal CH_2N_2 for 40 min at 0–25°. After concentration, the residue was recrystallized (CH_2Cl_2–Et_2O) to separate 3.506 g (76%) of the enol ether **22** as white plates: mp 174–175.5°; ir ($CHCl_3$) 3650 (associated OH), 1730 (ester C=O), and 1590 cm^{-1} (intense, conjugated C=C); uv (95% EtOH) intense end absorption (ϵ 26,400 at 202 mμ); nmr ($CDCl_3$) δ 6.8–7.3 (3 H, m, aryl CH), 4.16 (3 H, s, OCH_3), 3.4–3.8 (5 H, m, OCH_3 and benzylic CH), 3.24 (1 H, s, OH, exchanged with D_2O), 3.12 (3 H, s, CH_3SO_2), and 1.4–2.4 (9 H, m, aryl CH_3 and aliphatic CH); mass spectrum *m/e* (rel intensity) 392 (50, M^+), 363 (27), 334 (22), 333 (100), 303 (40), 273 (22), 225 (25), 191 (29), 169 (25), 166 (24), 165 (26), 155 (24), 153 (29), 152 (26), 143 (29), 141 (31), 128 (22), and 115 (21).

Anal. Calcd for $C_{20}H_{24}O_6S$: C, 61.20; H, 6.18; S, 8.17. Found: C, 61.21; H, 6.08; S, 8.07.

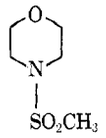
A 27-mg sample of the previously described crude keto ester **23** in tetrahydrofuran was also treated with excess ethereal CH_2N_2 to yield 21 mg (75%) of the crude enol ether **22**, mp 159–163°. Recrystallization from Et_2O afforded the enol ether **22** as white plates, mp 170–172°, which was identified with the previously described sample by a mixture melting point determination and by comparison of ir spectra.

A solution of 3.45 g (8.8 mmol) of the enol ether **22** and 110 ml of aqueous 2 *M* HCl in 110 ml of MeOH was refluxed for 1.5 hr and then concentrated. The residual white solid was recrystallized from an ether–CH_2Cl_2 mixture to separate 3.29 g (99%) of the crude keto ester **23** as white needles, mp 149–152°. This product was identified with the previously described sample by a mixture melting point determination and comparison of ir spectra. The purified product, mp 151–152.5°, existed as a hemihydrate.

Anal. Calcd for $(C_{19}H_{22}O_6S)_2H_2O$: C, 58.89; H, 5.95; S, 8.27. Found: C, 58.84; H, 6.07; S, 8.28.



42



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To examine the behavior of a simpler model system, 12.07 g (52 mmol) of the previously described[16] cycloadduct **42**, mp 115.5–118° (lit.[16] mp 117–120°), was heated to 135° in a N_2 atmosphere for 20 hr and then cooled and stirred with 40 ml of EtOH and 10 ml aqueous 1 *M* HCl for 1 hr. The solution was concentrated and the residual oil was partitioned between $CHCl_3$ and aqueous 1 *M* HCl. The organic solution was dried and concentrated to leave 7.36 g of residual brown liquid. Distillation separated 4.88 g (58%) of the crude keto sulfone **25** as a pale yellow liquid, bp 112–120° (0.5 mm). Redistillation gave the crude keto sulfone **25** as a colorless liquid: bp 108–110° (0.45 mm); $n^{25}D$ 1.4939 [lit.[17] bp 115–135° (0.6–1.0 mm)]; ir ($CHCl_3$) 1745 (cyclopentanone C=O) and 1315 cm^{-1} (SO_2); uv max (95% EtOH) 210 mμ (ϵ 216) and 271 (136). The nmr spectrum ($CDCl_3$) of this crude keto sulfone exhibits a multiplet in the range δ 1.9–4.0 (aliphatic CH) with a singlet at δ 3.08 (CH_3SO_2) as well as a weak singlet at 2.80 attributable to the methyl group of the sulfonamide **43** present as an impurity. On standing, some of this impurity **43** crystallized from the reaction mixture as white plates, mp 91–93°, and was identified with an authentic sample (mp 92.5–94°[18]) by a mixture melting point determination. Neither this model system **25** nor the keto sulfones **19** and **23** gave a color with $FeCl_3$. Reaction of a sample of the crude keto sulfone **25** with excess ethereal CH_2N_2 for 60 min at 0–25° resulted in recovery of the unchanged starting material **25** (ir analysis).

Reductive Cleavage of the Keto Sulfone 23.—To a solution of 3.288 g (8.7 mmol) of the keto sulfone **23** in 400 ml of 1:9 (v/v) H_2O–tetrahydrofuran was added freshly prepared aluminum amalgam[15] from 2.6 g (96 mg-atoms) of Al foil. The mixture was heated to 65°, with stirring, for 70 min and then concentrated and partitioned between $CHCl_3$ and H_2O. The organic solution was washed with H_2O, dried, and concentrated. The residual semisolid (2.81 g) was recrystallized from hexane–Et_2O to separate 2.029 g (78%) of the hydroxy ketone **24** as white needles, mp 139–141°. Sublimation (0.04 mm and 100°) followed by recrystallization from Et_2O–hexane separated the pure hydroxy ketone **24** as white needles: mp 142–143°; ir ($CHCl_3$) 3610, 3480 (unassociated and associated OH) and 1740 cm^{-1} (broad, ester and cyclopentanone C=O); uv max (95% EtOH) 263 mμ (ϵ 264) and 270 (210); nmr ($CDCl_3$) δ 6.8–7.4 (3 H, m, aryl CH), 3.72 (3 H, s, OCH_3), 3.5–3.7 (1 H, benzylic CH), and 1.6–2.6 (13 H, m, aryl CH_3, OH, and aliphatic CH); mass spectrum *m/e* (rel intensity) 300 (15, M^+), 241 (29), 240 (72), 199 (24), 198 (52), 181 (40), 180 (100), 169 (23), 156 (22), 155 (45), 132 (21), 131 (35), 128 (22), and 115 (22).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.99; H, 6.70.

Preparation of the Acetoxy Ketone 28.—A solution of 1.889 g (6.29 mmol) of the hydroxy ketone **24** and 40 ml of Ac_2O in 60 ml of pyridine was stirred at 25° for 41 hr and then partitioned between $CHCl_3$ and aqueous 2 *M* HCl. After the organic solution had been dried and concentrated, recrystallization of the residue (2.2 g of white solid) from Et_2O–hexane afforded 1.981 g (92%) of the acetoxy ketone **28** as white needles: mp 154.5–157° (recrystallization sharpened the melting point of **28** to 155.5–157°); ir ($CHCl_3$) 1740 cm^{-1} (ester and cyclopentanone C=O); uv max (95% EtOH) 262 mμ (ϵ 198) and 270 (156); nmr ($CDCl_3$) δ 7.0–7.5 (3 H, m, aryl CH), 3.3–4.0 [5 H, m, benzylic CH with a singlet at 3.73 (OCH_3)], 1.7–3.1 [14 H, m, including singlets at 2.28 and 2.02 (aryl CH_3 and $COCH_3$)]; mass spectrum *m/e* (rel intensity) 342 (23, M^+), 283 (23), 282 (100), 240 (19), 223 (25), and 180 (21).

Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.95; H, 6.52.

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(17) W. E. Truce and R. H. Knospe, *ibid.*, **77**, 5063 (1955).

(18) This sulfonamide **43** is reported to melt at 90–91°: A. G. Kostsova, E. I. Kozachenko, O. M. Osina, V. P. Volokhova, and L. D. Maslova, *Zh. Org. Khim.*, **1**, 728 (1965); *Chem. Abstr.*, **63**, 5637 (1965).

Preparation of the Hydroxy Acetate 29a.—A solution of 1.98 g (5.8 mmol) of the ketone **28** and 500 mg (13.2 mmol) of $NaBH_4$ in 75 ml of tetrahydrofuran and 110 ml of MeOH was stirred at 0° for 2.5 hr and at 25° for 1 hr. After 2 ml of HOAc had been added to consume the excess hydride, the solution was concentrated under reduced pressure and the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic phase was washed with H_2O, dried, and concentrated to leave 2.20 g of residual liquid. Crystallization from Et_2O–hexane afforded 1.883 g (95%) of the alcohol **29a** as white prisms: mp 169–171°; ir ($CHCl_3$) 3480 (associated OH) and 1725 cm^{-1} (ester C=O); uv max (95% EtOH) 264 mμ (ε 315) and 272 (258); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH) 4.53 (1 H, d of d, J = 6 and 10 Hz, >CHO), 3.6–4.0 (5 H, m, including a singlet at 3.71, benzylic CH and CH_3O), and 1.5–3.5 [15 H, m including singlets at 2.28 and 1.94 (aryl CH_3 and CH_3CO)]; mass spectrum m/e (rel intensity) 344 (13, M^+), 267 (21), 266 (100), 224 (17), 207 (44), and 43 (19).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.73; H, 6.93.

Preparation of the Olefin 30.—To a cold (0°) solution of 1.87 g (5.43 mmol) of the alcohol **29a** in 40 ml of pyridine was added, dropwise and with stirring, 4.2 ml of CH_3SO_2Cl. The resulting solution was allowed to stand at 5° for 26 hr and then partitioned between $CHCl_3$ and aqueous 1 M HCl. After the organic solution had been washed successively with aqueous HCl, aqueous $NaHCO_3$, and H_2O, it was dried and concentrated to leave 2.33 g of white solid. Recrystallization from Et_2O separated 2.204 g (97%) of the methanesulfonate **29b** as white prisms: mp 148.5–150°; ir ($CHCl_3$) 1730 (ester C=O), 1340, and 1365 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 5.33 (1 H, d of d, J = 6 and 9 Hz, >CHO), 3.6–4.1 (5 H, m including a singlet at 3.69, CH_3O and benzylic CH), 3.03 (3 H, s, CH_3SO_2), and 1.6–2.9 [14 H, m, including singlets at 2.18 and 1.97 (aryl CH_3 and CH_3CO)].

A solution of 309 mg (0.733 mmol) of the methanesulfonate **29b** in 9.0 ml of γ-collidine was refluxed for 30 hr and then cooled and partitioned between $CHCl_3$ and dilute aqueous HCl. The organic layer was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. The residual semisolid (249 mg) was chromatographed on 11 g of silica gel and the fractions eluted with 16% Et_2O in hexane were recrystallized from hexane to separate 166 mg (70%) of the acetoxy olefin **30** as white needles: mp 100–101°; ir ($CHCl_3$) 1730 cm^{-1} (ester C=O); uv max (95% EtOH) 265 mμ (ε 334) with intense end absorption (ε 19,800 at 206 mμ); nmr ($CDCl_3$) δ 6.8–7.3 (3 H, m, aryl CH), 6.38 (1 H, d, J = 6 Hz, vinyl CH), 6.08 (1 H, d, J = 6 Hz, vinyl CH), 3.83 (1 H, s, benzylic CH), 3.68 (3 H, s, OCH_3), 3.1–3.5 (1 H, m, benzylic CH), and 1.5–2.6 [12 H, m including singlets at 2.25 and 1.97 (aryl CH_3 and CH_3CO)]; mass spectrum m/e (rel intensity) 326 (4, M^+), 267 (26), 266 (100), 255 (21), 227 (61), 225 (85), 207 (45), 196 (32), 195 (45), and 155 (20).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.87; H, 6.66.

Registry No.—**5**, 15448-20-1; **6**, 15448-23-4; **7a**, 37741-20-1; **7b**, 37741-21-2; **8a**, 37741-22-3; **8b**, 37741-23-4; **9**, 37741-24-5; **10a**, 37741-25-6; **10b**, 37741-26-7; **11**, 37741-27-8; **12**, 37741-28-9; **13a**, 37741-29-0; **13b**, 37741-30-3; **14a**, 37741-31-4; **14b**, 37741-32-5; **15a**, 37741-33-6; **15b**, 37741-34-7; **15c**, 37741-35-8; **16**, 37741-36-9; **19**, 37741-37-0; **21a**, 37741-38-1; **21b**, 37741-39-2; **22**, 37741-40-5; **23**, 37741-41-6; **24**, 37741-42-7; **28**, 37741-43-8; **29a**, 37805-64-4; **29b**, 37741-44-9; **30**, 37741-45-0; **31**, 15448-25-6; **32**, 37741-47-2; **33**, 37805-65-5; **33** copper complex, 37818-71-6; **34**, 37741-48-3; **35**, 37741-49-4; **36a**, 37741-50-7; **36b**, 37741-51-8; **42**, 37741-52-9; β-(*o*-tolyl)propionic acid, 22084-89-5; methyl β-(*o*-tolyl)propionate, 37741-54-1; *o*-tolylsuccinic acid dimethyl ester, 37741-55-2; epiallogibberic acid, 13613-87-1.

A Study of Mechanism for the Formolysis of a 20α-Tosyloxy Steroid[1]

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The mechanism of the formolysis of 3β-acetoxy-5α-pregnan-20α-yl *p*-toluenesulfonate (**1b**) was studied with preparations containing deuterium or tritium in the 17α position. The isotopic atom was retained in the formation of 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**2b**). Neither of the two geometric isomers of the 5α-pregn-17-en-3β-yl acetate (**7b**, **8b**), therefore, is an intermediate in this reaction, although both are readily converted to this product (**2b**). The rate ratios, k_H/k_T, for the disappearance of the tosylate ester **1b** and for the formation of its major formolysis products were determined. The isotope effect on the rate of formolysis was higher than expected for the formation of a C-20 cation. This could be due to an accompanying 17-hydrogen-assisted formolysis yielding at least some of **2b** or due to a high rate of return from the ion pair. The latter explanation seems less likely. The unexpected formation of a uranediol derivative (**4b**) in this and a similar reaction which tentatively had been attributed by us and others to a two-step mechanism that included a methyl shift does not take this course because the deuterium that was located at C-17 in the starting compound was found at C-17a in the product **4b**. A different mechanism, analogous to a postulate made by Eschenmoser, *et al.*, for the biosynthesis of various steroids, is considered.

In a recent investigation[2] of the formolysis of 3β-acetoxy-5α-pregnan-20α-yl tosylate (**1b**) five compounds (**2**–**6**) were identified, which are listed in Table I. Questions arose about the mode of formation of the two rearrangement products, compounds **2b** and **4b**. Of these, the Δ^{13} olefin **2b** could arise by dehydration to a Δ^{17} olefin (**7**, **8**) which after protonation at C-20 would rearrange to the isolated product. Such a mechanism was first proposed by Leboeuf, *et al.*,[3] to explain the formation of a Δ^{13} olefin (**2c**) from a 20β-tosylate on prolonged boiling in benzene and was adopted by Aoyama, *et al.*,[4] to account for the formation of **2b** from a 20α-acetate on exposure to boron trifluoride etherate for several days. The following observations are consistent with such a scheme. Treatment of a 20α-tosylate (*e.g.*, **1b**, **1c**) with basic solvents

(1) Supported by U. S. Public Health Service Grants AM-9105 and K6-AM-14367.

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(3) M. Leboeuf, A. Cavé, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1624, 1628 (1969).

(4) S. Aoyama, K. Kamata, and T. Komeno, *Chem. Pharm. Bull.*, **19**, 1329 (1971).