Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.45; H, 10.76.

epi-β-Santalene (VIII).—The ketone VII (0.7 g., 0.0034 mole) dissolved in 10 ml. of anhydrous ether was treated with 21.25 ml. (0.034 mole) of 1.6 *N* methyllithium solution in ether at reflux under nitrogen for 5 days. This was cooled in an ice-bath, hydrolyzed with ice-water and worked up in the usual way to give 0.69 g. (91.5%) of the desired hydroxy compound as a pale yellow liquid, showing infrared absorption at 2.71(w), 7.28(m) and 11.25(m) μ. A portion of this product (0.223 g.) dissolved in 5 ml. of anhydrous pyridine and 1 ml. of dry methylene chloride was cooled in an ice–salt-bath below 0°, and treated with a cooled solution of 1 ml. of pyridine and 1 ml. of thionyl chloride. At the end of the addition the brown mixture was kept at 0° for 10 minutes and then diluted with 10 ml. of pentane followed by 27 ml. of 3 *N* HCl (efficient cooling). The product was extracted with pentane, filtered through a column of alumina using pentane and distilled to give 0.14 g. (69%) of *epi-β*-santalene (VIII) as a colorless liquid. The compound showed infrared absorption (in carbon tetrachloride) at 3.2(w), 6.02(m) 7.26(m) and 11.3(s) μ and on vapor phase chromatography on a 10-ft. tricyanoethoxypropane column (25% on Chromasorb) at 135° with a helium flow rate of 33 ml./min. gave a retention time of 37 min. 20 sec. A mixture of the synthetic and the natural (isolated from natural *β*-santalene sample) *epi-β*-santalenes gave a single peak with the same retention time under the above conditions while pure *β*-santalene (both synthetic and natural) gave the retention time of 38 min. 55 sec. In the n.m.r. spectrum (in carbon tetrachloride) the *exo*-methyl proton appeared as a sharp single peak at 9 τ, the methyl proton of the side chain showed up as a single peak at 8.38 τ and the three olefinic protons showed up at 4.92 (side chain), 5.38 (terminal methylene) and 5.61 τ (terminal ethylene), respectively. In an n.m.r. spectrum of the mixture of pure *β*-santalene and the epimer VIII the protons due to *endo* (of *β*-santalene) and the *exo* (of epi-*β*-santalene) methyl groups appeared at 8.97 and at 9.00 τ, respectively, with a separation of 0.034 p.p.m. Furthermore, the absence of bands characteristic of *β*-santalene (V) in the n.m.r. spectrum of the product from the above reaction confirmed the vapor phase chromatographic analysis and supports the conclusion that the reactions leading to VII are stereo-specific.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

Synthesis of *cis*- and *trans*-Derivatives of 1a-Carboxymethyl-8-methylhexahydrofluorenone[1a]

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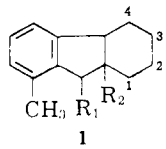
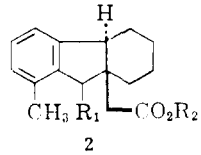
The previously described unsaturated acid **6** has been converted to the keto lactone 11, a possible intermediate for the synthesis of allogibberic acid. Suitable transformations have transformed the keto acid **18a** to the unsaturated lactone **20** which yields both *cis*- (22) and *trans*- (21) hexahydrofluorenone derivatives on hydrogenation.

In continuing our studies[2] of synthetic approaches to the gibberellins[3] and their degradation products, we desired synthetic routes to hexahydrofluorenones **1** containing an oxygen function at C_2 and to 1a-substituted hexahydrofluorenones (*e.g.*, **2**) having a *trans* fusion of the alicyclic rings. This paper describes solutions to these objectives as well as improved synthesis of several previously described[2c,d] intermediates. The previously described[2c] intermediates **3** and **4** were transformed to the diketo lactone **11** as indicated in Chart I.



1



2

The conversion of the unsaturated acid **6** to the iodo-*cis*-*γ*-lactone **9** is the result which would be predicted on steric grounds assuming a transition state involving *trans* copolanar addition to the carbon–carbon double bond.[4,5] The further transformation of the iodo lactone **9** to the epoxy ester **8** permits the assignment of the indicated configuration to the epoxy ester.[6] The fact that reaction of the epoxy ester **8** with aqueous acid produced two isomeric hydroxy lactones **10**, each of which produced the same diketo lactone **11** on oxidation, indicates either that the hydroxy lactones **10** differ in stereochemistry only at C2 or that one of the two diketo lactones **11** initially formed was epimerized under the mild oxidizing conditions[7] employed. The latter explanation is more probable if the usual[5] *trans* diaxial opening of the epoxide ring occurred prior to the formation of the hydroxy lactones **10** and both chair conformations of the epoxy ester **8** are of comparable energy. Although the abnormally high cyclohexanone carbonyl stretching frequency (1735 cm.$^{-1}$) in the infrared indicates that the preferred conformation of the diketo lactone **11** places the ethereal lactone oxygen atom on a equatorial bond, our data do not permit an unambiguous stereochemical assignment at C2 of the diketo lactone **11** to be made. However, the n.m.r. spectrum of (see Experimental) of this lactone **11** does exclude the alternative formulation **12** for this product

Reaction of keto acid **6** with sodium borohydride produced the *trans* hydroxy acid **13a** which was

(1) (a) This research has been supported by National Science Foundation Grant No. G-9486; (b) National Institutes of Health Predoctoral Fellow, 1960–1962; (c) National Research Council Postdoctoral Fellow, 1960–1961.

(2) (a) H. O. House, V. Paragamian, R. S. Ro and D. J. Wluka, *J. Am. Chem. Soc.*, **82**, 1452, 1457 (1960); (b) H. O. House, W. F. Gannon, R. S. Ro and D. J. Wluka, *ibid.*, **82**, 1463 (1960); (c) H. O. House, V. Paragamian and D. J. Wluka, *ibid.*, **82**, 2561 (1960); (d) **83**, 2714 (1961).

(3) For a recent review, see J. F. Grove, *Quart. Revs.*, **15**, 56 (1961).

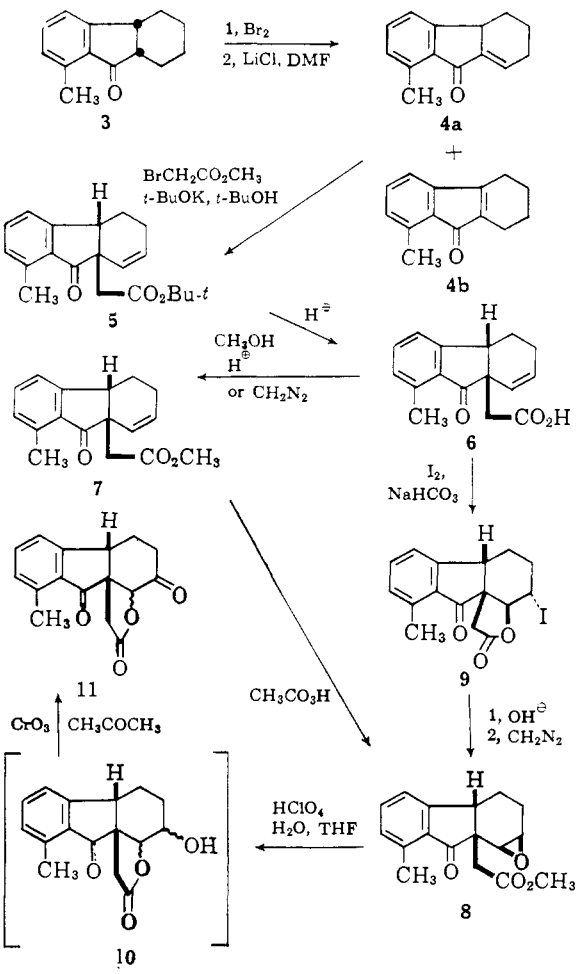
(4) For discussion of an analogous iodolactonization, see A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, **83**, 198 (1961).

(5) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

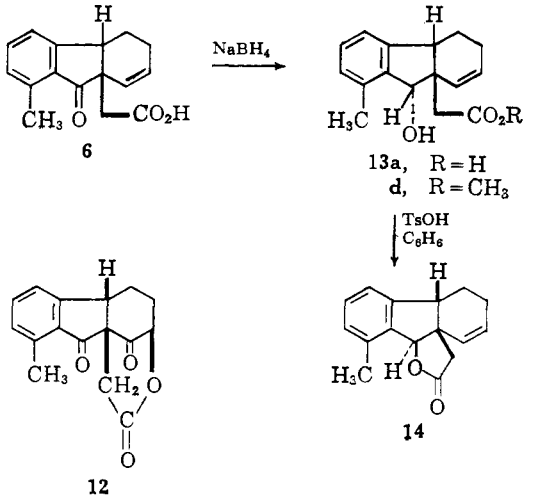
(6) The formation of only the same epoxy ester **8** by direct reaction of the unsaturated ester **7** with peracetic acid appears to be another example of an addition reaction stereodirected by a nearby functional group. For discussion and leading references see H. B. Henbest and B. Nicholls, *Proc. Chem. Soc.*, 225 (1958).

(7) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lewis. *J. Chem. Soc.*, 2548 (1953).

CHART I.



converted to the lactone **14** by a boiling benzene solution of *p*-toluenesulfonic acid. Saponification of the lactone **14** followed by cautious acidification resulted in immediate regeneration of the lactone[2c] permitting the stereochemical assignments **13** and **14** to be made. An analogous situation was previously found[2d] in the hydrogenation of the corresponding saturated ester.



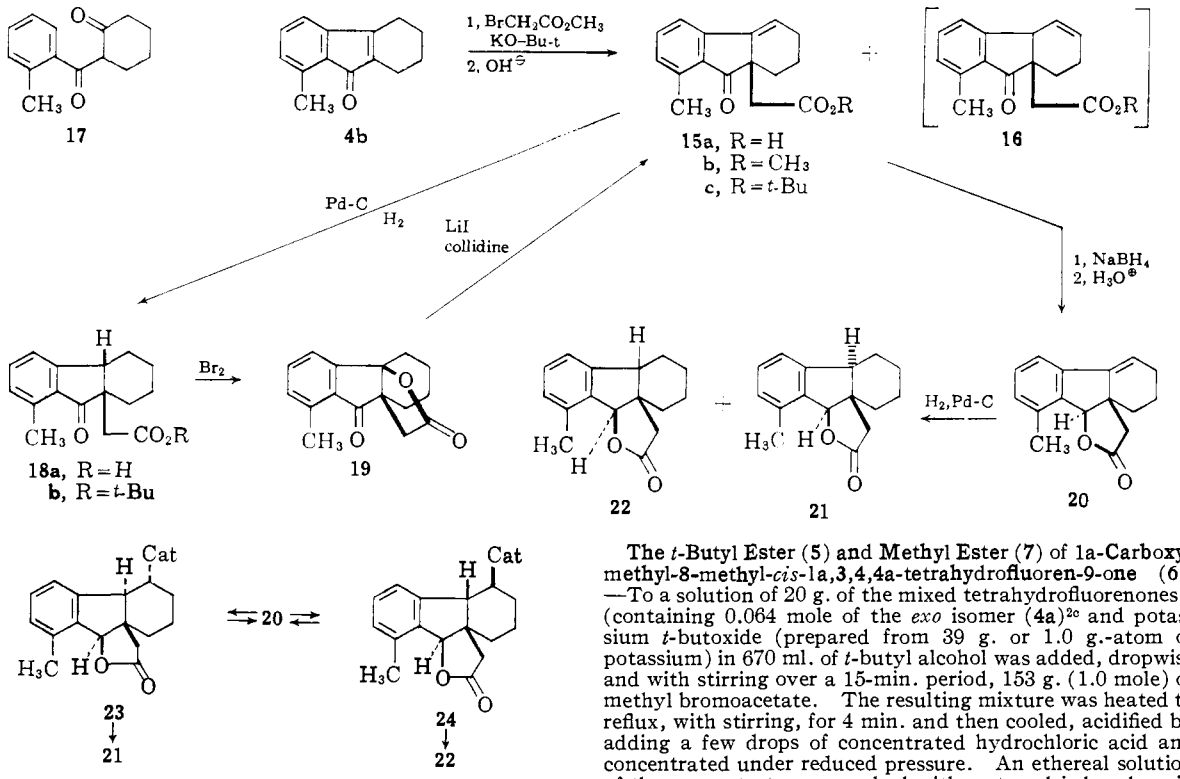
Since the most direct route to the *trans*-hexahydrofluorenone series **2** appeared to be the catalytic reduction of a suitable derivative of the unsaturated acid **15a**, we turned our attention to the preparation of this substance. The direct alkylation of the tetrahydrofluorenone **4b** was found to yield a difficultly separable mixture of the keto acid **15a** and a second partially characterized substance, possibly the double bond isomer **16**. Because use of this alkylation procedure, unlike the preparation of the ester **5**, was clearly impractical starting with a mixture of tetrahydrofluorenones **4** and the separation of these isomers was tedious,[2a] we explored other possible synthesis of the tetrahydrofluorenone **4b**. However, these efforts, including the acid-catalyzed cyclization of the diketone **17**, were unrewarding.

At this point, we discovered that the direct reaction of the saturated keto acid **18a** with bromine afforded the lactone **19** in high yield. Subsequent reaction of this lactone **19** with lithium iodide in collidine[8] constituted a very efficient route to the unsaturated acid **15a**. Catalytic hydrogenation of either the acid **15a** or the *t*-butyl ester **15c** afforded only the *cis*-keto acid derivatives **18**. Successive reaction of the unsaturated acid **15a** with sodium borohydride and aqueous acid yielded the unsaturated lactone **20**. Catalytic hydrogenation of the lactone **20**, a compound in which the side chain is held rigidly above the plane of the molecule, produced an approximately equal mixture of the saturated lactones **21** and **22**[2a] which was readily separated by chromatography. The stereochemistry assigned the unsaturated lactone **20** follows from the conversion of **20** in part to the previously described[2c] lactone **22**.

An interesting observation made in the course of hydrogenation of the lactone **20** was the fact that the expected stereospecificity of the reduction (to form **21**) increased as the ratio weight of reactant/weight of catalyst increased. The obvious explanation that compound **21** was being isomerized to compound **22** by the hydrogenation catalyst (and became more important with larger amounts of catalyst) was excluded by demonstrating that *trans*-lactone **21** was not altered by the hydrogenation conditions. However, a possible explanation for this observation may be found in a two-stage hydrogenation mechanism[9] in which the first stage is reversible as exemplified in the accompanying equation where structures **23** and **24** are arbitrary representations of the half-hydrogenated state.[9] In the presence of large amounts of catalyst where the hydrogenation is relatively rapid, we suggest that the hydrogen concentration on the catalyst surface becomes depleted (the rate being controlled by diffusion of the hydrogen to the catalyst surface) permitting substantial reversal of the first stage and permitting the equilibration **23** $\rightleftarrows$ **20** $\rightleftarrows$ **24** to become important as is observed for hydrogena-

(8) F. Elsinger, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960). We are indebted to Professor Eschenmoser for informing us of the effectiveness of these conditions for promoting an elimination reaction with tertiary esters. In the case reported here, the lactone was not affected by boiling collidine alone.

(9) For a recent discussion with leading references, particularly to the work of R. L. Burwell, Jr., and S. Siegel, see J. F. Sauvage, R. H. Baker and A. S. Hussey, *J. Am. Chem. Soc.*, **83**, 3874 (1961).



tions at low hydrogen pressure.[9] This circumstance would diminish the importance of the kinetically favored approach of the catalyst surface to the olefin **20** from the less hindered, bottom side of the molecule (to form **23**) and would, consequently, decrease the stereospecificity of the hydrogenation.

Experimental[10]

1-Cyclohexenyl *o*-Tolyl Ketone.—After a solution of *o*-tolylmagnesium chloride, prepared from 53 g. (0.417 mole) of *o*-chlorotoluene and 10 g. (0.417 g.-atom) on magnesium, in 100 ml. of tetrahydrofuran had been concentrated to one-half its volume and then diluted with 200 ml. of ether, 25.5 g. (0.239 mole) of 1-cyanocyclohexene was added, dropwise and with stirring, and the mixture was refluxed overnight with stirring.[11] The reaction mixture was poured into dilute, aqueous hydrochloric acid and, after separation of the ether layer, the aqueous phase was heated on a steam-bath, with stirring, for 16 hr. and then cooled and extracted with ether. After the combined ether solutions had been washed with aqueous sodium bicarbonate, dried and concentrated, distillation afforded 33.6 g. (70%) of the ketone, b.p. 98–115° (0.05 mm.), $n^{25}D$ 1.5552 [lit.[2c] b.p. 140–141° (0.55 mm.), $n^{28.5}D$ 1.5550].

(10) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, model B, or a Perkin–Elmer, model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. Unless otherwise stated, magnesium sulfate was employed as a drying agent.

(11) When the precaution of lowering the reaction temperature by replacing half of the tetrahydrofuran with ether was not taken, the yield of the ketone was drastically lowered and substantial amounts of high-boiling material were produced. That this result was attributable to the instability of the Grignard adduct and not the Grignard reagent was demonstrated by carbonating portions of a tetrahydrofuran solution of *o*-tolylmagnesium chloride before and after a 14-hr. reflux period. The yield (73%) of *o*-toluic acid after heating was not decreased.

The *t*-Butyl Ester (5) and Methyl Ester (7) of 1a-Carboxymethyl-8-methyl-*cis*-1a,3,4,4a-tetrahydrofluoren-9-one (6).—To a solution of 20 g. of the mixed tetrahydrofluorenones **4** (containing 0.064 mole of the *exo* isomer (**4a**)[2c] and potassium *t*-butoxide (prepared from 39 g. or 1.0 g.-atom of potassium) in 670 ml. of *t*-butyl alcohol was added, dropwise and with stirring over a 15-min. period, 153 g. (1.0 mole) of methyl bromoacetate. The resulting mixture was heated to reflux, with stirring, for 4 min. and then cooled, acidified by adding a few drops of concentrated hydrochloric acid and concentrated under reduced pressure. An ethereal solution of the concentrate was washed with water, dried and again concentrated under reduced pressure to remove the low-boiling products derived from methyl bromoacetate. A solution of the residue in aqueous methanol containing 17.0 g. (0.303 mole) of potassium hydroxide was refluxed overnight and then cooled and extracted with ether. After the aqueous layer had been acidified and extracted with ether, the ethereal extract was dried and concentrated to leave 17.5 g. of a dark viscous oil from which 2.0 g. (14%) of the keto acid **6**, m.p. 138–141° (lit.[2c] 141–142.5°), could be separated by fractional crystallization from a petroleum ether–ether mixture.[12] The ethereal extract containing the neutral products was dried and concentrated to leave 13.4 g. of residual yellow solid which was recrystallized from aqueous methanol. The *t*-butyl ester **5**, m.p. 93–95°, yield 6.6 g. (22%),[13] which separated was recrystallized to afford the pure ester as white prisms, m.p. 99–100°, with infrared absorption[14] at 1730 cm.$^{-1}$ (ester C=O) and 1712 cm.$^{-1}$ (conj. C=O in a 5-membered ring) and ultraviolet maxima[15] at 250 mμ (ε 12,000) and 298 mμ (ε 2,400).

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.83; H, 7.46.

Because of the difficulty[12] in isolating the free keto acid **6**, in subsequent preparations the reaction time for saponification was shortened to permit isolation of the bulk of the alkylation product as the *t*-butyl ester **5**. Thus the crude product (34 g.) from the alkylation of 16.0 g. of the tetrahydrofluorenones **4** (containing 0.048 mole of **4a**) with 123 g. (0.81 mole) of methyl bromoacetate in the presence of potassium *t*-butoxide (from 31.0 g. or 0.81 g.-atom of potassium) and 610 ml. of *t*-butyl alcohol was dissolved in aqueous methanol containing 10 g. (0.178 mole) of potassium hy-

(12) This fractional crystallization to separate the acid **6**, which was employed in our previously described procedure (ref. 2c) is particularly tedious on a large scale since the majority of the by-products from the reaction are in this easily saponified fraction. An appreciable amount of the *t*-butyl ester **5** remains in the unsaponified fraction from which it is easily isolated as subsequently described. Our efforts to isolate the keto acids **15** and **16** from the crude acidic fraction were fruitless.

(13) The isolation of the material, which is sufficiently pure for conversion to the acid **6**, was described previously (ref. 2c) but the product was not characterized.

(14) Determined in carbon tetrachloride solution.

(15) Determined in ethanol solution.

droxide. After the solution had been refluxed for 1.5 hr., application of the previously described isolation procedures separated 7.8 g. (52%) of the *t*-butyl ester **5**, m.p. 96–98°.

After a solution of 1.0 g. (3.2 mmoles) of the *t*-butyl ester **5** and 20 mg. of *p*-toluenesulfonic acid in 20 ml. of benzene had been refluxed for 4 hr., the mixture was diluted with ether and extracted with aqueous sodium bicarbonate. After the aqueous extract had acidified and was extracted with ether, the ethereal extract was dried and concentrated to leave 0.65 g. (79%) of the keto acid **6**, m.p. 141–143°. Reaction of a 7.5-g. (0.029 mole) sample of the keto acid **6** with excess ethereal diazomethane followed by removal of the solvent and recrystallization from methanol yielded 6.4 g. (81%) of the methyl ester **7**. An additional crystallization afforded the pure ester as white prisms, m.p. 70.1–71°, with infrared absorption[14] at 1740 (ester C=O) and 1710 cm.$^{-1}$ (conj. C=O in a 5-membered ring) and ultraviolet maxima[15] at 252 mμ (ε 13,000) and 301 mμ (ε 2,300).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.40; H, 6.71.

The same methyl ester **7**, m.p. 69.5–71°, was obtained in 80% yield by refluxing a solution of 2.50 g. (9.76 mmoles) of the keto acid **6** and 4 drops of sulfuric acid in 40 ml. of methanol for 3 hr. followed by the usual isolation procedure.

1a-Carboxymethyl-8-methyl-*cis*-1a,3,4,4a-tetrahydrofluoren-9-ol (13a).—A solution of 1.00 g. (3.90 mmoles) of the keto acid **6** in 16 ml. of water containing 3.90 mmoles of sodium hydroxide was added to a solution of 75 mg. (1.97 mmoles) of sodium borohydride in 1 ml. of aqueous 0.2 *N* sodium hydroxide. After the mixture had been stirred overnight, it was acidified and extracted with ether. The ethereal solution was extracted with aqueous sodium bicarbonate and the bicarbonate extract was acidified and extracted with ether. After this ethereal solution of the acidic products had been dried and concentrated, crystallization of the residue from aqueous methanol separated 0.65 g. (65%) of the hydroxy acid, m.p. 175–177°. An additional crystallization afforded the pure hydroxy acid **13a** as white prisms, m.p. 177–178°, with infrared absorption[16] at 3400 cm.$^{-1}$ (broad, assoc. O—H) and 1695 cm.$^{-1}$ (carboxyl C=O) and a series of low intensity (ε 280–340) ultraviolet maxima[15] in the region 260–280 mμ.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.20; H, 7.02.

Reaction of a 1.00-g. (3.88 mmoles) sample of the hydroxy acid **13a** with an excess of diazomethane in ether solution followed by the usual isolation procedure yielded 0.78 g. (78%) of the methyl ester **13b** as white prisms, m.p. 76–78°, from methanol. An additional crystallization afforded the pure methyl ester, m.p. 78.5–79.5°, with infrared absorption[14] at 3520 cm.$^{-1}$ (assoc. O—H) and 1735 and 1720 cm.$^{-1}$ (ester C=O with partial intramolecular hydrogen bonding) and ultraviolet maxima[15] at 265 mμ (ε 345) and 274 mμ (ε 292).

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.03; H, 7.37.

A solution of 800 mg. (3.10 mmoles) of the hydroxy acid **13a** and 30 mg. of *p*-toluenesulfonic acid in 150 ml. of benzene was refluxed overnight with continuous separation of the water produced. The resulting solution was concentrated to one-third its original volume, washed with aqueous sodium bicarbonate, dried and concentrated to dryness. Recrystallization of the residual solid from aqueous methanol separated 617 mg. (81.9%) of the lactone **14** as white needles, m.p. 147–149°, whose melting point was raised to 149–150° by recrystallization. The product has infrared absorption[17] at 1765 cm.$^{-1}$ (γ-lactone C=O) with ultraviolet maxima[15] at 266 mμ (ε 398) and 275 mμ (ε 394). After saponification of the lactone **14** with aqueous potassium hydroxide, acidification of the alkaline solution at room temperature with dilute aqueous hydrochloric acid regenerated the starting lactone, m.p. 149.5–151°, (80% recovery).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.83; H, 6.70.

The Lactone 9 of 1a-Carboxymethyl-2-hydroxy-3-iodo-8-methyl-*cis*-1,1a,2,3,4,4a-Hexahydrofluoren-9-one.—To a solution of 2.50 g. of (9.75 mmoles) of the keto acid **6** in 60 ml. of aqueous 0.5 *N* sodium bicarbonate was added a solution of 5.08 g. (20 mmoles) of iodine and 10.0 g. (60.2 m-moles) of potassium iodide in 30 ml. of water. After the mixture had been allowed to stand for 48 hr., with occasional shaking, the solid which separated was collected, washed with water and dissolved in methylene chloride. The aqueous filtrate was extracted with methylene chloride and the combined organic solutions were washed successively with aqueous sodium thiosulfate, aqueous sodium bicarbonate and water. After the methylene chloride solution had been dried and concentrated, recrystallization of the residue from a methanol–methylene chloride mixture separated 3.08 g. (82.6%) of the iodo lactone **9** as white prisms, m.p. 200–202° dec., with infrared absorption[16] at 1775 cm.$^{-1}$ (γ-lactone C=O) and 1705 cm.$^{-1}$ (conj. C=O in a 5-membered ring) and ultraviolet maxima[15] at 252 mμ (ε 14,000) and 299 mμ (ε 2,520).

Anal. Calcd. for $C_{16}H_{15}O_3I$: C, 50.28; H, 3.96; I, 33.20. Found: C, 50.06; H, 3.88; I, 33.56.

1a-Carbomethoxymethyl-1,2-epoxy-8-methyl-*cis*-1,1a,-2,3,4,4a-hexahydrofluoren-9-one (8). A. From the Iodo Lactone 9.—A suspension of 300 mg. (0.789 mmole) of the iodolactone in 25 ml. of aqueous methanol containing 690 mg. (17 mmoles) of sodium hydroxide was stirred at room temperature until solution was complete (about 6 hr.) The resulting aqueous solution was extracted with ether, cooled in an ice-bath, acidified by the dropwise addition of hydrochloric acid and again extracted with ether. After this ethereal extract had been dried and concentrated, the crude epoxy acid (206 mg. melting at 208–210°) was esterified by reaction with excess diazomethane in ether solution. The resulting ethereal solution was washed with aqueous sodium bicarbonate, dried and concentrated to leave 194 mg. of the crude methyl ester, m.p. 96–99°. Recrystallization from methanol afforded 124 mg. (55%) of the pure epoxy ester **8** as white prisms, m.p. 101.5–102.5°, identified with the subsequently described sample by a mixed melting-point determination and comparison of infrared spectra.

B. From the Unsaturated Ester 7.—A mixture of 1.41 g. (5.2 mmoles) of the unsaturated ester **7**, 3.2 g. (17 mmoles) of 40% peracetic acid in acetic acid, 52 mg. of sodium acetate and 7 ml. of chloroform was stirred at room temperature for 15 hr. and then diluted with 35 ml. of chloroform and washed successively with aqueous sodium bisulfite and aqueous sodium bicarbonate. After the organic layer had been dried and concentrated, crystallization of the residue from methanol separated 1.12 g. (77.2%) of the epoxy ester **8** as white prisms, m.p. 102–103°. Recrystallization raised the melting point to 102.7–103.7°. The product has infrared absorption[17] at 1730 cm.$^{-1}$ (ester C=O) and 1705 cm.$^{-1}$ (conj. C=O in a 5-membered ring) with ultraviolet maxima[15] at 252 mμ (ε 13,000) and 301 mμ (ε 2,330).

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.30; H, 6.30.

The Lactone 11 of 1a-Carboxymethyl-1-hydroxy-8-methyl-*cis*-1,1a,2,3,4,4a-hexahydrofluorene-2,9-dione.—A solution of 388 mg. (1.35 mmoles) o the epoxy ester **8** and four drops of 70% perchloric acid in 25 ml. of a 2:1 (by volume) tetrahydrofuran–water mixture was refluxed under a nitrogen atmosphere for 27 hr. and then diluted with 100 ml. of water, saturated with sodium chloride and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate, dried and concentrated to leave 412 mg. of a mixture of the crude hydroxy lactones **10**, m.p. 174–194°, with infrared absorption[18] at 3550 (O—H), 1790 (γ-lactone C=O) and 1710 cm.$^{-1}$ (conj. C=O in a 5-membered ring). The thin-layer chromatogram (silica gel coating) of the crude mixture indicated the presence of small quantities of the starting material and two major components in approximately equal amounts. To a solution of 890 mg. (3.26 mmoles) of the mixture of hydroxy lactones **10** in 25 ml. of acetone was added 1 ml. (2.67 mmoles) of a 2.67 *M* solution of chromium trioxide in aqueous sulfuric acid.[7] After the mixture had been stirred at room temperature for 45 min., an additional 1 ml. of the chromium trioxide solution was added and stirring was continued for 45 min. Several drops of methanol was added and the mixture was diluted with 100 ml. of water, saturated with sodium chloride and extracted with ether. After the ethereal solution had been washed with aqueous sodium bicarbonate, dried and concentrated, recrystallization of the residue from ethyl acetate afforded 560 mg. (63% based on

(16) Determined as a suspension in a potassium bromide pellet.

(17) Determined as a chloroform solution.

(18) Determined as Nujol mull.

the crude mixture of hydroxy lactones) of the diketo lactone **11** as white needles, m.p. 165–168°. The product, whose melting point was raised to 168.5–170° by recrystallization, exhibits infrared absorption[16,18] at 1780 (γ-lactone C=O), 1735 (cyclohexanone C=O with an adjacent equatorial electronegative substituent) and 1705 cm.$^{-1}$ (conj. C=O in a 5-membered ring) with ultraviolet maxima[16] at 252 mμ (ϵ 11,100) and 300 mμ (ϵ 2,100). The n.m.r. spectrum (60 mc., as a solution in perdeuteriodimethylformamide) exhibits a multiplet in the region of 2.4 τ (3 protons, aromatic CH), a singlet at 4.67 τ (1 proton, >CH–O), a set of three peaks at 6.87, 7.17 and 7.23 τ presumably representing three of the four peaks of a quadruplet (J = 18 c.p.s., 2 protons, $-CH_2-CO-$ of lactone ring) and a singlet at 7.39 τ (3 protons, aryl–CH_3). The presence of an unsplit peak at 4.67 τ confirms the formulation of this product as the γ-lactone 11 and not the isomeric ζ-lactone **12**.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.92; H, 5.53.

The Lactone 19 of 1a-Carboxymethyl-4a-hydroxy-8-methyl-*cis*-1,1a,2,3,4,4a-hexahydrofluoren-9-one.—A solution of 10.0 g. (38.8 mmoles) of the keto acid **18a** and 3 ml. (58 mmoles) of bromine in 100 ml. of carbon tetrachloride was refluxed for 1 hr. and then concentrated under reduced pressure. After a solution of the residue in chloroform had been washed with aqueous sodium bicarbonate, dried and concentrated, crystallization of the residue (9.3 g.) from an acetone–methanol mixture afforded 7.0 g. (70%) of the lactone as white prisms, m.p. 165–166°. The product has infrared absorption[17] at 1775 (γ-lactone C=O) and 1712 cm.$^{-1}$ (conj. C=O in a 5-membered ring) with ultraviolet maxima[15] at 250.5 mμ (ϵ 11,800) and 294 mμ (ϵ 2,010).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.97; H, 6.19.

1a-Carboxymethyl-8-methyl-1,1a,2,3-tetrahydrofluoren-9-one (15a) and Its Derivatives. A. From the Lactone 19.—After a solution of 3.2 g. (12 mmoles) of the lactone 19 and 16.1 g. (120 mmoles) of lithium iodide in 16 ml. of γ-collidine had been refluxed for 96 hr., the mixture was poured into cold, dilute hydrochloric acid and extracted with ether. The ethereal extract was extracted with aqueous sodium bicarbonate and the aqueous extract was acidified and extracted with ether. After this ether solution had been dried and concentrated, recrystallization of the residue (2.84 g. or 89%, m.p. 115–125°) from a ligroin–ethyl acetate mixture separated 2.4 g. (75%) of the pure unsaturated acid **15a** as white prisms, m.p. 129–130°, with infrared absorption[17] at 3000 (broad, assoc. O—H) and 1710 cm.$^{-1}$ (carboxyl C=O and conj. C=O in a 5-membered ring) and with ultraviolet maxima[15] at 237.5 mμ (ϵ 27.500), 262 mμ (shoulder, ϵ 11,900) and 327 mμ (ϵ 1900).[19]

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.74; H, 6.20.

Reaction of a 395-mg. (1.45 mmoles) sample of the unsaturated acid **15a** with excess diazomethane in ether solution, followed by the usual isolation procedure, yielded 415 mg. of the crude **methyl ester 15b**, m.p. 69–74°, which crystallized from hexane as white prisms, m.p. 77–78°, yield 380 mg. (91%). This ester **15b**, which underwent change when exposed to air but was stable when stored under nitrogen, has infrared absorption[14] at 1737 (ester C=O), 1715 (conj. C=O in a 5-membered ring) and 1667 cm.$^{-1}$ (C=C exocyclic to a 5-membered ring with ultraviolet maxima[15] at 238 mμ (ϵ 28,500), 250 mμ (shoulder, ϵ 17,000), 264 mμ (shoulder, ϵ 12,200) and 328 mμ (ϵ 2,000).[19] The n.m.r. spectrum (60 mc., in deuteriochloroform) has a multiplet in the region of 2.70 τ (aromatic C—H) a triplet. (J = 3.5 c.p.s.) centered at 3.82 τ (vinyl C—H of >C=CH—CH_2—), a singlet at 6.64 τ (O—CH_3) and two partially resolved peaks at 7.33 τ (CH_2CO) and 7.37 τ (aryl—CH_3).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.41; H, 6.57.

After a solution of 1.024 g. (4 mmoles) of the keto acid **15a** and 1.53 g. of *p*-toluenesulfonyl chloride in 10 ml. of pyridine[20] had been heated on a steam-bath for 30 min., 4 ml. of *t*-butyl alcohol was added and the resulting mixture was heated on a steam-bath for 15 hr. and then poured onto an ice–water mixture and extracted with ether. After the ethereal solution had been washed successively with cold, dilute hydrochloric acid and aqueous sodium bicarbonate, dried and concentrated, a 480-mg. portion of the residual crude ester (1.18 g. or 94%, m.p. 95–105°) was sublimed at 115° and 0.05 mm. to separate 415 mg. (81%) of the ***t*-butyl ester 15c**, m.p. 105–106°. Recrystallization of a 300-mg. sample of this material from an ether–petroleum ether mixture afforded 220 mg. of the pure ester **15c** as white prisms, m.p. 109–109.5°. The material has infrared absorption[14] at 1715 (broad, ester C=O and conj. C=O in a 5-membered ring) and 1665 cm.$^{-1}$ (C=C exocyclic to a 5-membered ring) with ultraviolet maxima[15] at 239 mμ (ϵ 26,000) 251 mμ (shoulder, ϵ 16,700), 264 mμ (shoulder, ϵ 12,500) and 329 mμ (ϵ 2,100).[19]

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.91; H, 7.79.

B. From Alkylation of the Tetrahydrofluorenone 4b.—To a solution of 3.15 g. (15.9 mmoles) of the tetrahydrofluorenone **4b** and potassium *t*-butoxide (prepared from 9.30 g. or 0.238 g.-atom of potassium) in 183 ml. of *t*-butyl alcohol was added 33.2 g. (0.199 mole) of ethyl bromoacetate. After the mixture had been refluxed for 5 min. and then neutralized, the isolation procedure described earlier in this paper was applied to the reaction mixture, the saponification being effected by refluxing the crude product with a solution of 5 g. of potassium hydroxide in 10 ml. of water and 10 ml. of methanol for 3.5 hr. Since we were able to isolate no single product from either the neutral or acidic fractions after this saponification, the crude acidic product (2.541 g.) was methylated with excess diazomethane in ether to yield 2.413 g. of a crude mixture of methyl esters as an oil. The gas chromatogram (a column packed with Dow Silicone Fluid No. 710 on ground firebrick) has two peaks, the second of which constituted the major component of the mixture and was shown both by comparison of retention times and infrared spectra to be the unsaturated ester **15b**. By employing similar criteria the first peak was shown not to be either the methyl ester of the saturated acid **18a** or the unsaturated ester **7**.

After a rather involved series of chromatographic separations and fractional crystallizations, it was possible to isolate small amounts of the unsaturated ester **15b**, m.p. 78.7–80°, identified by its infrared and ultraviolet spectra, and a partially purified sample of material, m.p. 87.7–89.2°, corresponding to the first peak in the gas chromatogram of the mixture of methyl esters. The material had infrared absorption at 1738 (ester C=O) and 1710 cm.$^{-1}$ (conj. C=O in a 5-membered ring) with ultraviolet maxima at 249 mμ (ϵ 11,800) and 299 mμ (ϵ 3,460). We were unable to obtain a sufficient quantity of the material to effect further purification and characterization. In view of the previously noted instability of the unsaturated ester **15b**, it seems likely that our efforts to purify the products of this alkylation were complicated by the continuous alteration of this component during our efforts to separate the mixture.

1a-Carbo-*t*-butoxymethyl-*cis*-1,1a,2,3,4,4a-hexahydrofluoren-9-one (18b).—A mixture of 512 mg. (2 mmoles) of the keto acid **18a**, 764 mg. (4 mmoles) of *p*-toluenesulfonyl chloride, 1.9 ml. of *t*-butyl alcohol and 5 ml. of pyridine was allowed to stand at room temperature for 20 hr. and then heated on a steam-bath for 3 hr. After following the previously described isolation procedure, distillation of the crude ester in a short-path still (130–140° at 0.05 mm.) separated 500 mg. (79.5%) of the pure *t*-butyl ester **18b** as a colorless liquid, n^{25}D 1.5299, which crystallized, m.p. 53–55°, on standing. The product has infrared absorption[14] at 1728 (ester C=O) and 1710 cm.$^{-1}$ (conj. C=O in a 5-membered ring) with ultraviolet maxima[15] at 249.5 mμ (ϵ 12,600) and 298 mμ (ϵ 2,330).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.37; H, 8.36.

A solution of 312 mg. (1 mmole) of the unsaturated ester **15c** in 25 ml. of ethanol was hydrogenated over 31 mg. of a 30% palladium-on-carbon catalyst at 29° and 761 mm.

(19) *o*-Butyroylstyrene has a similar ultraviolet pattern with maxima at 225 mμ (ϵ 17,500), 252 mμ (ϵ 10,300) and 297 mμ (ϵ 1400). We are indebted to Professor Wesley J. Dale, University of Missouri, who supplied us with generous samples of this and other *o*-acylstyrenes.

(20) The esterification procedure of J. H. Brewster and C. J. Cotti, Jr. [*J. Am. Chem. Soc.*, **77**, 6214 (1955)]. A longer reaction time at elevated temperatures was found necessary in this case.

After 20 min., the hydrogen uptake (25 ml. or 1.01 equiv.) ceased and the solution was filtered and concentrated under reduced pressure. Distillation of the residue in a short-path still (135° at 0.01 mm.) separated 210 mg. (67%) of the *t*-butyl ester **18b** as a colorless liquid, $n^{25}D$ 1.5302, which crystallized, m.p. 52–55°, when seeded. The product was identified with the previously described sample by a mixed melting-point determination and by comparison of the infrared and ultraviolet spectra of the two samples.

A solution of 175 mg. (0.55 mmole) of the *t*-butyl ester **18b** (from hydrogenation of **15c**) and 3 mg. of *p*-toluenesulfonic acid in 3 ml. of benzene was refluxed for 4 hr. and then diluted with ether and extracted with aqueous sodium bicarbonate. After the bicarbonate extract had been acidified and extracted with ether, the ethereal extract was dried and concentrated to leave 100 mg. (70%) of the crude keto acid **18a**, m.p. 135–138°. Recrystallization from ethyl acetate afforded 75 mg. (53%) of the pure keto acid **18a**, m.p. 141–142°, which was identified by a mixed melting point determination and by comparison of infrared and ultraviolet spectra.

A solution of 512 mg. (2 mmoles) of the unsaturated acid **15a** in ethanol was hydrogenated at 26° and 760 mm. over 50 mg. of a 10% palladium-on-carbon catalyst until the hydrogen uptake ceased. After the mixture had been filtered and concentrated, a solution of the residue in ether was extracted with aqueous sodium bicarbonate. The aqueous extract was acidified and extracted with ether. After the ethereal extract had been dried and concentrated, recrystallization of the residue (474 mg., m.p. 125–135°) from ethyl acetate afforded 412 mg. (80%) of the keto acid **18a**, m.p. 141–141.5°, identified as in the previous experiment.

The Lactone 20 of 1a-Carboxymethyl-9-hydroxy-8-methyl-1,1a,2,3-tetrahydrofluoren-9-ol.—To a solution of the sodium salt obtained from 4.50 g. (17.5 mmoles) of the keto acid **15a** in 60 ml. of water was added 330 mg. (8.75 mmoles) of sodium borohydride. After the solution had been stirred at room temperature for 48 hr., 20 ml. of concentrated hydrochloric acid was added and the resulting mixture was allowed to stand at room temperature for 20 hr.[21] After the reaction mixture had been extracted with ether, the organic phase was washed with aqueous sodium bicarbonate, dried and concentrated to leave 3.22 g. (76%) of the crude lactone, m.p. 120–124°. Sublimation (120° at 0.01 mm.) afforded the pure lactone **20** as white prisms, m.p. 123–124° (sinters at 121°), yield 2.83 g. (67%), with infrared absorption[17] at 1765 cm.$^{-1}$ (γ-lactone C=O) and with ultraviolet maxima[16] at 216 mμ (ε 17,200), 254 mμ (ε 12,200) and 263 mμ (shoulder, ε 10,400).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.69; H, 6.63.

Hydrogenation of the Unsaturated Lactone 20.—A solution of 2.00 g. (8.3 mmoles) of the unsaturated lactone **20** in 150 ml. of ethanol was hydrogenated over 50 mg. of a 30% palladium-on-carbon catalyst at 27° and 760 mm. After 45 min. the hydrogen uptake (206 ml. or 1.01 equiv.) ceased and the mixture was filtered and the filtrate concentrated. The residue, which contained both lactones **21** and **22**,[22] was combined with 280 mg. of the lactone mixture from a comparable hydrogenation and subjected to a series of fractional crystallizations from an ether–petroleum ether mixture to separate 400 mg. of the lactone **21** as white prisms, m.p. 133–134°. The material has infrared absorption[17] at 1770 cm.$^{-1}$ (γ-lactone C=O), with ultraviolet maxima[15] at 266 mμ (ε 435) and 275 mμ (ε 435). The n.m.r. spectrum (60 mc., determined in deuteriochloroform) has a multiplet in the region of 2.9 τ (3 protons, aromatic C–H), a singlet at 4.57 τ (1 proton, >CH–O) and a singlet at 7.65 τ (3 protons, aryl–CH_3).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.11; H, 7.39.

(21) In other experiments where the reaction mixture was acidified cautiously, all of the initial reduction products did not lactonize immediately suggesting that both possible diastereoisomeric hydroxy acids were formed in this reduction. However, we were unable to isolate a pure hydroxy acid from this reaction and, therefore, used the described acid treatment to convert both hydroxy acids to the *cis*-lactone **20**.

(22) Thin-layer chromatography employing plates coated with Silica Gel was used to analyze qualitatively the various fractions from these reactions.

The combined mother liquors from the above crystallizations were concentrated and the residue (1.836 g.) was chromatographed on 150 g. of silica gel, the fractions being eluted with a 20% ether–80% petroleum ether mixture. Fractions 1–31 contained 785 mg. of the *trans* isomer **21**[22] which afforded 620 mg. of the lactone **21**, m.p. 133–134°, after recrystallization. The total yield of the recrystallized lactone was, therefore, 1.020 g. (45%; yield before recrystallization 1.185 g. or 52%).

Fractions 33–39 contained 186.7 mg. of a mixture of the lactones[22] and fractions 40–46 (the last two fractions were eluted with ether) contained 675 mg. (31%) of the *cis* isomer **22**.[22] Recrystallization afforded 475 mg. (21%) of the pure *cis*-lactone **22** as white needles, m.p. 111.5–112° (lit.[2d] 111–112°), identified with the previously described sample by a mixed melting-point determination and comparison of infrared spectra. The n.m.r. spectrum (60 mc., determined in deuteriochloroform) of the *cis*-lactone **22** has a multiplet in the region of 2.9 τ (3 protons, aromatic C–H), a singlet at 4.62 τ (1 proton, >CH–O), a triplet (J = 6 c.p.s.) centered at 6.93 τ (1 proton, >*CH*–CH_2–), a quadruplet (J = 17 c.p.s.) at 7.10, 7.39, 7.49 and 7.79 τ (2 protons, CH_2CO of lactone) and a singlet at 7.61 τ (3 protons, aryl–CH_3).

Table I summarizes the results of a number of hydrogenations with differing weights of catalyst for a given weight of the unsaturated lactone. The yields listed are derived from the weights of chromatographic fractions containing[22] only one isomer. A solution of 25 mg. of the *trans*-lactone **21** in 2.5 ml. of ethanol was stirred under a hydrogen atmosphere and over 10 mg. of a 30% palladium-on-carbon catalyst at 26° and 760 mm. for 1 hr. The crude *trans*-lactone **21** recovered from this experiment contained[22] none of the *cis* isomer **22**.

TABLE I

HYDROGENATION OF THE UNSATURATED LACTONE 20

$\frac{\text{Wt. cat.} \times 100}{\text{Wt. lactone 20}}$	Reaction time, min.	Lactone 21, %	Lactone 22, %
2.5	45	52	31
10	17	40	28
20	10	19.5	55.5

2-(*o*-Toluyl)-cyclohexanone (17).—To a cold (10°) solution of 44.8 g. (0.296 mole) of the freshly distilled pyrrollidine enamine of cyclohexanone, b.p. 76° (0.6 mm.),[23] in 125 ml. of chloroform was added, dropwise and with stirring over 35 min., a solution of 18.32 g. (0.119 mole) of *o*-toluyl chloride in 50 ml. of chloroform. After the resulting solution had been allowed to stand for 17 hr., it was heated to reflux for 15 min. and treated with 100 ml. of 6 *N* hydrochloric acid. The resulting mixture was refluxed, with stirring, for 2 hr. and then cooled and the layers separated. The aqueous layer was extracted with ether and the combined organic layers were washed with aqueous sodium bicarbonate, dried and concentrated. A solution of the residue in 25 ml. of ethanol was added to a warm solution of 30 g. (0.15 mole) of cupric acetate monohydrate in 400 ml. of water. The mixture was allowed to cool and the solid, which separated, was washed with a small volume of ether. A mixture of this crude copper complex (25.67 g. or 77.6%) with 3 *N* hydrochloric acid and ether was shaken to regenerate the diketone which was extracted into the ether phase. After the ethereal solution had been dried and concentrated, crystallization of the residue from ethanol separated 17.2 g. (67%) of the enolic diketone **17**, m.p. 62.5–65°, whose melting point was raised to 62.7–64.7° (lit.[24] 64–65°) by recrystallization.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.81; H, 7.56.

Methyl 2-Ketocyclohexylacetate.—To a solution of 42.0 g. (0.278 mole) of the pyrrolidine enamine of cyclohexanone in 150 ml. of refluxing benzene was added, dropwise and with stirring, 46.0 g. (0.300 mole) of methyl bromoacetate. After the resulting mixture had been refluxed for 1.5 hr.

(23) M. E. Kuehne [*J. Am. Chem. Soc.*, **81**, 5400 (1959)] gives b.p. 92–93° at 5 mm.

(24) R. D. Campbell and H. M. Gilow, *ibid.*, **82**, 2389 (1960). We believe our preparation to be more convenient than the one described by these authors.

and concentrated, the viscous residue was mixed with 100 ml. of methanol and 20 ml. of water and then refluxed for 2 hr. and concentrated. The residual mixture was extracted with ether and the ethereal solution was washed successively with dilute, aqueous hydrochloric acid and aqueous sodium bicarbonate and then dried and concentrated. Distillation of the residue separated 26.0 g. (55%) of the keto ester as a colorless liquid, b.p. 72–74° (0.2 mm.), $n^{25}D$ 1.4590, with infrared absorption[14] at 1740 (ester C=O) and 1710 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.46; H, 8.57.

Saponification of a 2.00-g. (11.8 mmoles) sample of the keto ester with 1.4 g. (25 mmoles) of potassium hydroxide in refluxing aqueous methanol for 12 hr. followed by the usual isolation procedure afforded 1.27 g. (81.5%) of 2-ketocyclohexaneacetic acid as white prisms, m.p. 74–76° (lit.[25] 73°), from an ethyl acetate–hexane mixture.

o-Tolylacetic Acid.—A mixture of 10.0 g. (0.0746 mole) of *o*-methylacetophenone,[26] 3.56 g. (0.111 g.-atom) of sulfur and 9.84 g. (*0.112* mole) of morpholine was heated to reflux for 16 hr. and then cooled and poured into 40 ml. of ethanol. The product separated as light yellow crystals, m.p. 85–87°, yield 8.81 g. (50.5%). The pure thiomorpholide of *o*-tolylacetic acid crystallized as white prisms, m.p. 86–87.5°, with no infrared absorption[14] in the 3 and 6 μ region attributable to an O—H, N—H or C=O function and an ultraviolet maximum[15] at 281 mμ (ϵ 15,900).

Anal. Calcd. for $C_{13}H_{17}NOS$: C, 66.36; H, 7.28; N, 5.95; S, 13.60. Found: C, 66.33; H, 7.25; N, 5.96; S, 13.90.

A solution of 2.08 g. (8.85 mmoles) of the thiomorpholide in 90 ml. of constant-boiling hydrobromic acid was refluxed for 23 hr. and then cooled, diluted with water and extracted with ether. The acidic product, separated from the ether solution by extraction with aqueous sodium bicarbonate, was isolated in the usual way. Recrystallization of the crude acid from water afforded 0.90 g. (67%) of the *o*-tolylacetic acid as white needles, m.p. 88–89° (lit.[27] 88–89°). The same acid was obtained from α-bromo-*o*-xylene in an over-all yield of 63% by way of the intermediate *o*-tolyl[8] acetonitrile, b.p. 67–69° (0.36 mm.), $n^{25}D$ 1.5259 [lit.[2] b.p. 125° (14 mm.)].

1-Methylfluoren-9-one.—After chromatography of samples of the crude tetrahydrofluorenones **4**, the disproportionation product, 1-methylfluoren-9-one, was isolated as yellow needles, m.p. 97.5–99° (lit.[29] 97.5–98.5°), from methanol. The product has infrared absorption[14] at 1705 cm.$^{-1}$ (conj. C=O in a 5-membered ring), with ultraviolet maxima[15] at 251 mμ (ϵ 59,600), 258 mμ (ϵ 93,200) 288 mμ (shoulder, ϵ 2,530), 297 mμ (ϵ 3,140), 317 mμ (ϵ 2,440), 322 mμ (ϵ 2,410) and 329 mμ (ϵ 2,270).

(25) W. Cocker and S. Hoinsby, *J. Chem. Soc.*, 1157 (1947).

(26) This ketone, b.p. 104–106°, $n^{26}D$ 1.5290, was prepared in 71% yield by the procedure of M. S. Newman and W. T. Booth, *J. Am. Chem. Soc.*, **67**, 154 (1945).

(27) P. Schorigin, *Ber.*, **43**, 1938 (1910).

(28) M. S. Newman, *J. Am. Chem. Soc.*, **62**, 2295 (1940).

(29) T. P. C. Mulholland and G. Ward, *J. Chem. Soc.*, 4676 (1954).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY, LEXINGTON, KY.]

Evidence for a Delocalized Intermediate in the Favorskii Rearrangement. 2,6-Lutidine-promoted Methanolysis of α-Chlorodibenzyl Ketone[1]

BY ARTHUR W. FORT

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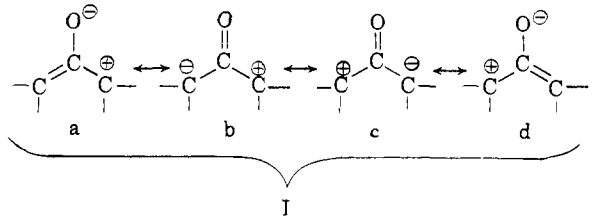
α-Chlorodibenzyl ketone undergoes rapid methanolysis in the presence of 2,6-lutidine to give α-methoxydibenzyl ketone. The reaction is first order in chloroketone, first order in lutidine, and almost independent of the lutidinium ion produced. Chloroacetone and desyl chloride are unreactive in methanolysis reactions in the presence of 2,6-lutidine. An elimination–addition mechanism, involving a delocalized intermediate, is proposed for the methanolysis of α-chlorodibenzyl ketone. This interpretation receives strong support from the finding that α,α'-dibromodibenzyl ketone is dehalogenated by sodium iodide in methanol to give α-methoxydibenzyl ketone. The possible significance of these results for the Favorskii rearrangement is discussed.

Several aspects of the Favorskii rearrangement of α-haloketones[2] have led to proposals that the reaction sometimes proceeds through a delocalized intermediate[3] (Ia–d). The present work examines the possibility that the proposed delocalized intermediate may be stabilized by conjugation of the delocalized system with aryl groups. Such stabilization, if it occurs, might be reflected in increased ease of dehydrohalogenation of the parent α-haloketone.



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In the absence of strong, nucleophilic base, the reaction course taken by the key intermediate of the Favorskii rearrangement might furnish additional evidence as to the structure of this intermediate (see below). The possibility that a change in the character of the base employed would lead to changes in the structures of the products provided another motive for undertaking the present work.[4]

A serious objection to the proposed intermediate (Ia–d)[3] arises from the fact that the only forms shown contributing to the hybrid molecule are forms involving separation of charges. Resonance stabilization for such a molecule could not be very large, and the proposed delocalized intermediate could not be expected to be stable relative to a classical cyclopropanone structure with all bonds essentially localized. This objection to a delocalized

(1) Presented at the Organic Division, A.C.S. Meeting, New York, N. Y., September, 1960; abstracts, p. 45-P.

(2) Reviewed by A. S. Kende, *Org. Reactions*, **11**, 261 (1960).

(3) (a) J. G. Aston and J. D. Newkirk, *J. Am. Chem. Soc.*, **73**, 3900 (1951); (b) J. G. Burr, Jr., and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954); (c) H. O. House and W. F. Gilmore, *J. Am. Chem. Soc.*, **83**, 3972, 3980 (1961).

(4) Another possible way of preventing the Favorskii intermediate from reacting with strong, nucleophilic base is simply to keep the concentration of base very low. The effect of low base concentration, achieved by slow addition of alkoxide, is described in another paper, *ibid.*, **84**, 2625 (1962).