Gibbane Synthons *via* Hexahydrofluorenones.[1] An Intramolecular Reformatsky Reaction

FREDERICK E. ZIEGLER* AND MICHAEL E. CONDON[2]

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06520

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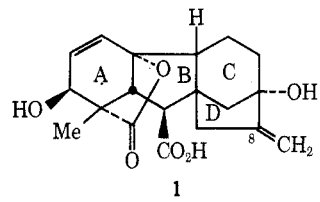
An efficient synthesis of hexahydrofluorene-2,9-dione and 7-methoxyhexahydrofluorene-2,9-dione from the appropriate phenylpyruvic acids is described. Their conversion to α-bromo esters and amides as well as the intramolecular Reformatsky reaction of these substances to provide gibbane synthons is detailed.

Synthetic efforts directed toward the gibberellins [gibberellic acid (**1**)] have led to known gibberellins,[3] degradation products thereof,[4] and gibbane synthons.[5] Our interest in this problem lay in devising an efficient synthetic route to hexahydrofluorenones **7a** and **7b**, which could in turn lead to tetracyclic gibbane synthons.

Although *trans*-2-phenyl-5-oxo-1-cyclohexanecarboxylic acid (**4**) had previously been cyclized to dione **7a**, no yields were specified and, moreover, the acid was obtained as the minor product from the Diels–Alder reaction of 2-ethoxybutadiene and *trans*-cinnamic acid.[6] It seemed reasonable that the corresponding cis acid **5a** would be more amenable to cyclization than its trans counterpart. In addition, the fact that the dissolving metal reduction of 3,4-diphenylcyclohex-2-en-1-one (**3a**) affords *cis*-3,4-diphenylcyclohexanone[7] augured well for a method of preparing the requisite cis acid, since the carboxylate anion of acid **3b** should play a similar role to that of the 3-phenyl substituent in ketone **3a**.

To this end, the condensation between *p*-methoxyphenylpyruvic acid and methyl vinyl ketone was achieved in aqueous methanolic sodium hydroxide, yielding 1-hydroxy-2-(*p*-methoxyphenyl)-5-oxo-1-cyclohexanecarboxylic acid (**2c**) as a single diastereomer in high yield. Several analogous annelations have been reported between phenylpyruvic acid and benzalacetone,[8,9] *p*-methoxybenzylidene acetone,[9] and ethyl styryl ketone.[10] The observation that recrystallization of the acid tended to lower its melting point suggested that thermal dehydration might be occurring. Thus, when the acid **2c** was heated at 180–190°, liquification occurred with concomitant loss of water, providing unsaturated acid **3c** whose nuclear magnetic resonance spectrum exhibited a one-proton doublet at δ 6.84 (J = 1.5 Hz) indicating the presence of a vinyl hydrogen, ruling out the alternative cinnamic acid formulation. Reduction of unsaturated acid **3c** with lithium–ammonia–tetrahydrofuran, as anticipated, gave rise to the cis keto acid **5c** in 54% yield. Alternatively, the use of zinc in refluxing acetic acid produced the desired material in 91% yield.

Catalytic hydrogenation of **3c** over palladized charcoal provided a mixture of the cis keto acid and unsaturated acid **6a**. The stereochemistry of the latter acid was shown to be cis on the basis of the nuclear magnetic resonance spectrum[11] of its methyl ester **6b**. Oxidation of acid **6a** with manganese dioxide[12] in chloroform pro-



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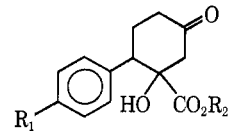
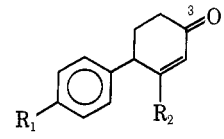
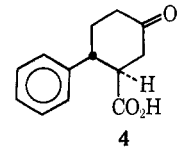


2a, $R_1 = R_2 = H$
b, $R_1 = OMe$; $R_2 = Me$
c, $R_1 = OMe$; $R_2 = H$



3a, $R_1 = H$; $R_2 = Ph$
b, $R_1 = H$; $R_2 = CO_2H$
c, $R_1 = OMe$; $R_2 = CO_2H$



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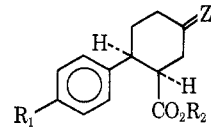
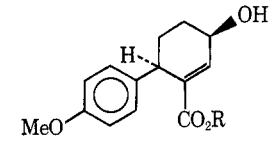


5a, $R_1 = R_2 = H$; $Z = O$
b, $R_1 = H$; $R_2 = Me$; $Z = O$
c, $R_1 = OMe$; $R_2 = H$; $Z = O$
d, $R_1 = OMe$; $R_2 = Me$; $Z = O$
e, $R_1 = R_2 = H$; $Z = (SCH_2)_2$
f, $R_1 = H$; $R_2 = Me$; $Z = (SCH_2)_2$
g, $R_1 = R_2 = H$; $Z = H_2$



6a, R = H
b, R = Me

(1) Taken in part from the Ph.D. thesis of M. E. C., Yale University, 1970; F. E. Ziegler and M. E. Condon, *Tetrahedron Lett.*, 2315 (1969).

(2) National Institutes of Health Postdoctoral Fellow, 1967–1970.

(3) K. Mori, M. Shiozaki, N. Itaya, M. Matsui, and Y. Sumiki, *Tetrahedron*, **25**, 1293 (1969); W. Nagata, T. Wakabayashi, Y. Hayase, M. Narisade, and S. Kamata, *J. Amer. Chem. Soc.*, **92**, 3202 (1970).

(4) Y. Kos and H. J. E. Lowenthal, *J. Chem. Soc.*, 605 (1963); H. J. E. Lowenthal and S. K. Malhotra, *ibid.*, 990 (1965); K. Mori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem. (Tokyo)*, **25**, 907 (1961); **27**, 527 (1963); **28**, 72 (1964); K. Mori, M. Matsui, and Y. Sumiki, *Tetrahedron Lett.*, 429 (1970).

(5) (a) H. O. House and C. B. Hudson, *J. Org. Chem.*, **35**, 647 (1970), and earlier papers in this series; (b) H. J. E. Lowenthal and H. Rosenthal, *Tetrahedron Lett.*, 3693 (1968); (c) T. Hori and K. Nakanishi, *Chem. Commun.*, 528 (1969); (d) N. N. Gerber, *J. Amer. Chem. Soc.*, **82**, 5216 (1960); (e) V. R. Ghatak, J. Chakravarty, and A. K. Banerjee, *Tetrahedron*, **24**, 1577 (1968); (f) A. Tahara and O. Hoshino, *Tetrahedron Lett.*, 5031 (1966); (g) R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.*, 1565 (1965); (h) K. Shudo, M. Natsume, and T. Okamoto, *Chem. Pharm. Bull.*, **14**, 311 (1966); (i) T. Ogawa, K. Mori, M. Matsui, and Y. Sumiki, *Tetrahedron Lett.*, 2551 (1968); (j) *ibid.*, 4483 (1968); (k) L. J. Dolby and R. J. Mulligan, *J. Amer. Chem. Soc.*, **88**, 4536 (1966); (l) M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzily, and H. J. E. Lowenthal, *J. Org. Chem.*, **34**, 126 (1969); (m) S. K. Dasgupta, R. Dasgupta, S. R. Ghosh, and U. R. Ghatak, *Chem. Commun.*, 1253 (1969); (n) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, **87**, 1148 (1965); (o) H. W. Thompson, *J. Org. Chem.*, **32**, 3712 (1967); (p) E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *J. Amer. Chem. Soc.*, **92**, 396 (1970); (q) F. E. Ziegler and J. A. Kloek, *Tetrahedron Lett.*, in press.

(6) H. O. House, W. F. Gannon, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1463 (1960).

(7) S. K. Malhotra, D. F. Moakley, and F. Johnson, *Tetrahedron Lett.*, 1089 (1967).

(8) P. Cordier and H. Maximos, *C. R. Acad. Sci.*, **227**, 347 (1948).

(9) M. Kristensen-Reh, *Bull. Soc. Chim. Fr.*, 882 (1956).

(10) M. Kristensen-Reh and P. Cordier, *C. R. Acad. Sci.*, **247**, 2150 (1958).

(11) E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 4249 (1962).

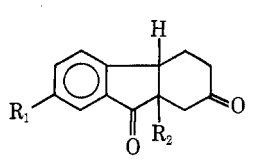
(12) O. Mancera, J. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

duced the unsaturated acid **3c**. On the other hand, pure acid **6a** could be obtained by sodium borohydride reduction of the unsaturated acid **3c**.

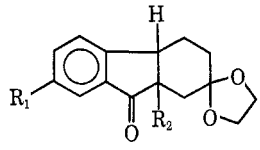
Keto acid **5a** was transformed into its ethylene thioketal **5e**, which, in turn, was converted to its methyl ester **5f** with ethereal diazomethane. Desulfurization with Raney nickel W-2 in refluxing ethanol produced an oil, homogeneous upon thin layer chromatography, whose infrared spectrum exhibited typical ester absorption and whose nuclear magnetic resonance spectrum was devoid of the characteristic thioketal singlet. Saponification of the ester with aqueous methanolic sodium carbonate provided *cis*-2-phenylcyclohexanecarboxylic acid (**5g**), mp 76–77° (lit.[13] mp 77°), thus confirming the stereochemistry of acids **5a** and **5c**.

When the polyphosphoric acid catalyzed cyclization was performed on **5c** at 80–85° at a dilution of 50:1, the yield of ketone **7b** was optimized (55–60%) after 10 min, whereas keto acid **5a** provided diketone **7a** (90%) after 45 min. The lower yield of diketone **7b** compared with **7a** reflects the known difficulties of cyclizing 3-(*p*-methoxyphenyl)propionic acid derivatives.[14]

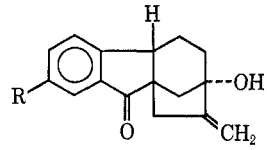
With a viable route for preparing diketones **7a** and **7b**, several investigations were initiated to devise means for constructing ring D. The first approach to the solution of this problem lay in preparing the vinyl bromide **7c**, which, it was anticipated, could undergo reductive cyclization to form tetracyclic **9b**.[15] To this



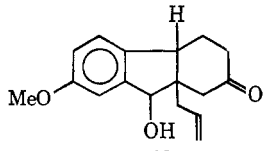
7a, $R_1 = R_2 = H$
b, $R_1 = OMe$; $R_2 = H$
c, $R_1 = OMe$; $R_2 = CH_2CBr{=}CH_2$
d, $R_1 = H$; $R_2 = CH_2CBr{=}CH_2$
e, $R_1 = OMe$; $R_2 = CH_2CH{=}CH_2$



8a, $R_1 = R_2 = H$
b, $R_1 = OMe$; $R_2 = H$
c, $R_1 = OMe$; $R_2 = CH_2CBr{=}CH_2$
d, $R_1 = H$; $R_2 = CH_2CBr{=}CH_2$



9a, R = H
b, R = OMe



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end, selective ketalization of the more reactive aliphatic carbonyl function in diketone **7b** with ethylene glycol produced the monoketal **8b**. Subsequent alkylation with 2,3-dibromopropene–potassium *tert*-butoxide in 1,2-dimethoxyethane provided the crystalline alkylated ketal **8c**. Removal of the protecting group was achieved under dilute mineral acid conditions to give rise to the desired vinyl bromide **7c**. A similar series of experiments could be executed in the sequence **7a** → **8a** → **8d**[5p] → **7d**.[5p] The cis stereochemical assignment finds ample precedent in other alkylated systems of this type.[16]

In an attempt to effect an intramolecular Grignard addition of the vinyl bromide moiety to the aliphatic ketone in **7c**, the diketone was refluxed in tetrahydrofuran solution for 5 hr in the presence of magnesium affording a mixture of allyl diketone **7e** and the corresponding alcohol **10** in a 4:1 ratio, respectively. Longer reaction times gave more of the latter material at the expense of the former. Oxidation of the alcohol yielded the allyl diketone, which was independently prepared *via* the alkylation sequence from ketal **8b**. The fact that the allyl diketone was isolated indicated that the desired Grignard reagent was being formed, but did not explain its failure to undergo cyclization. The possibility that the Grignard was being protonated upon workup of the reaction mixture was ruled out when it was quenched with deuterium oxide. The nuclear magnetic resonance spectrum of the resultant allyl diketone revealed that the three vinyl hydrogens in the allyl pattern were still intact. Thus, the Grignard was being internally protonated in the reaction medium, presumably by enolization of the aliphatic carbonyl or from degradation of the solvent.

Michael addition of ketal **8b** to methyl α-bromoacrylate in the presence of potassium *tert*-butoxide–*tert*-butyl alcohol–tetrahydrofuran provided bromo ester **11a**, which upon deketalization yielded bromo ester **12a**. The cis bromo ester was obtained as a mixture of diastereomers about the carbon bearing the ester group, as witnessed by the presence of two methyl ester singlets in the nuclear magnetic resonance spectrum. Employing freshly prepared bromo ester **12a**, the Reformatsky reaction[17] was conducted in refluxing benzene in the presence of activated zinc dust followed by quenching of the reaction mixture with acetic anhydride. A mixture of two diastereomeric acetoxy esters, **13a** and **13b**, was formed, with the former predominating over the latter. In a similar fashion, quenching of the reaction mixture with benzoyl chloride provided the corresponding benzoates, **13c** and **13d**. In each case, the major diastereomers (**13a** and **13c**) were reduced with lithium aluminum hydride to a single triol **14a**, while the minor diastereomers provided the triol **14b**.

When the cyclization was conducted in tetrahydrofuran followed by quenching of the reaction mixture with acetic anhydride, the β-hydroxy ester **13e** was isolated with no trace of acetylated products,[18] the stereochemistry of which was determined in the prescribed fashion by conversion to the triol **14a**. No attempt was made to isolate the epimer of the hydroxy ester.

The stereochemistry of the epimeric pairs of diastereomers from the cyclization was determined by an epimeri-

(13) K. Alder, H. Vagt, and W. Vogt, *Justus Liebigs Ann. Chem.*, **565**, 135 (1949).

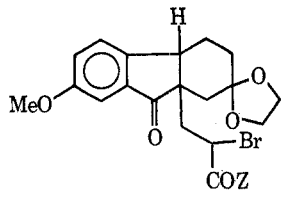
(14) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 448 (1968), and references cited therein.

(15) After our investigations on the vinyl bromide **7c** had been completed, the successful cyclization of **7d** to **9a** was accomplished in elegant fashion[5p] by the use of di-*n*-butylcopperlithium.

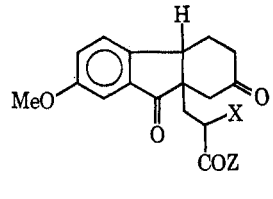
(16) H. O. House and R. G. Carlson, *J. Org. Chem.*, **29**, 74 (1964).

(17) The synthesis of mevalonic acid lactone by an intramolecular Reformatsky reaction has been described: F. H. Hulcher and T. A. Hosick, U. S. Patent 3,119,842 (1964); *Chem. Abstr.*, **60**, 10554*g* (1964).

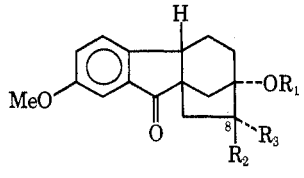
(18) The cleavage of tetrahydrofuran in Reformatsky-like reactions has been reported; *cf.* V. A. Barkhash, G. P. Smirnova, and I. V. Machinskaya, *Zh. Obshch. Khim.*, **33**, 2570 (1963).



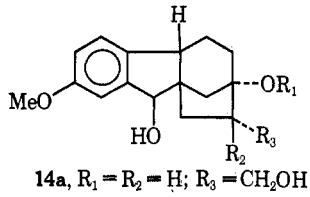
11a, Z = OMe
b, Z = O-*tert*-Bu
c, Z = NMe_2



12a, X = Br; Z = OMe
b, X = Br; Z = O-*tert*-Bu
c, X = Br; Z = NMe_2

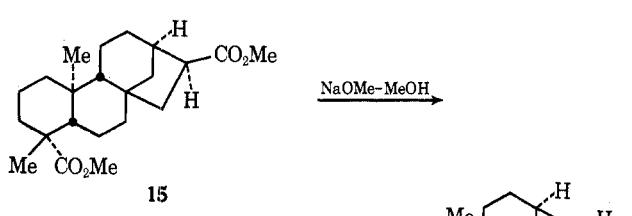


13a, R_1 = Ac; R_2 = H; R_3 = CO_2Me
b, R_1 = Ac; R_2 = CO_2Me; R_3 = H
c, R_1 = Bz; R_2 = H; R_3 = CO_2Me
d, R_1 = Bz; R_2 = CO_2Me; R_3 = H
e, R_1 = R_2 = H; R_3 = CO_2Me
f, R_1 = Ac; R_2 = H; R_3 = CO_2-*tert*-Bu
g, R_1 = Ac; R_2 = CO_2-*tert*-Bu; R_3 = H
h, R_1 = Ac; R_2 = H; R_3 = $CONMe_3$



14a, R_1 = R_2 = H; R_3 = CH_2OH
b, R_1 = R_3 = H; R_2 = CH_2OH

zation study conducted on the pair of benzoates, **13c** and **13d**. Treatment of the minor benzoate **13d** with potassium *tert*-butoxide–*tert*-butyl alcohol–tetrahydrofuran effected epimerization to the major benzoate **13c**. Under the same conditions, the major epimer was recovered unchanged. The stereochemical assignment is consonant with the known epimerization, **15** (endo) → **16** (exo).[19]



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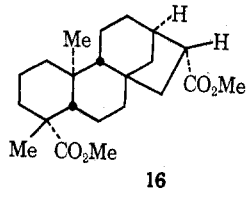

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Two other Reformatsky reactions were investigated, namely those of the α-bromo ester **12b** and α-bromo amide **12c**. Although the mixture of diastereomeric *tert*-butyl esters **13f** and **13g** could be formed in good yield, they were particularly resistant to separation. On the other hand, amide **13h** was obtained with ease, although no attempt was made to seek its epimer.

Clearly, the internal Reformatsky reaction is of particularly synthetic utility, particularly in systems where dehydration to α,β-unsaturated esters can occur.[20]

(19) C. A. Hendricks and P. R. Jefferies, *Aust. J. Chem.*, **17**, 915 (1964).

Experimental Section

General.—Melting points were obtained on a Fisher–Johns apparatus and are corrected.

Microanalyses were performed by Galbraith Laboratories and Bernhardt Microanalytische Laboratorium.

Infrared (ir) spectra were determined on a Perkin-Elmer Model 421 or 237B spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained with Varian Model A-60, A-60A, or HA-100 spectrometers. Chemical shifts are reported in δ units using tetramethylsilane as internal reference. Ultraviolet spectra were taken on a Bausch and Lomb Spectronic 505 recording spectrometer. Absorptions are reported as λ_{max} (ε) in nanometer units. Mass spectra were obtained in part by Professor McMurray of the Yale Medical School using an A.E.I. MS-9 spectrometer and in part on a Hitachi RMU-6 spectrometer. The data are reported as *m/e* (relative intensity).

Except where noted, solvents were reagent grade and were used as received. Thin layer chromatograms (silica gel G) were run using 30% ethyl acetate–benzene as the moving phase unless otherwise noted.

In all work-up procedures the drying process involved swirling over anhydrous magnesium sulfate and filtering prior to evaporation.

2-Methyl-4-(*p*-methoxybenzylidene)oxazol-5-one.—This compound was initially prepared by the method of Niederl and Ziering[21] in 30–35% yield. It was subsequently observed that the use of potassium bicarbonate[22] instead of sodium acetate afforded better yields.

In a 2-l., three-neck flask fitted with a nitrogen inlet, mechanical stirrer, thermometer, and condenser were placed 544 g (4 mol) of *p*-anisaldehyde, 640 ml of acetic anhydride, 200 g (4 mol) of potassium bicarbonate, and 214 g (2 mol) of acetylglycine.[23] On heating the reaction mixture to 70° followed by removal of the external heat, vigorous evolution of carbon dioxide occurred. The reaction temperature then rapidly reached 105° as the reaction mixture became homogeneous. After the evolution of carbon dioxide had subsided, the solution was heated to 135–140° and stirred at this temperature for 1 hr under nitrogen, the temperature being maintained by occasionally applying external heat. After cooling the solution to 80° and pouring it onto 1 kg of crushed ice, 300 ml of methanol was added, and the crude azlactone was filtered and washed with two 200-ml portions of methanol. Upon drying the azlactone to constant weight in a vacuum desiccator, a yield of 300 g (70%, mp 107–111°) was obtained: mp 111–112° (ethyl acetate–hexane) (lit.[21] mp 114°, uncorrected); ir ($CHCl_3$) 1802, 1775, 1662, and 1613 cm^{-1}; nmr ($CDCl_3$) δ 2.35 (3 H, s), 3.84 (3 H, s), 7.05 (1 H, s), and 6.75–8.20 (4 H, m, A_2B_2).

α-Acetamino-*p*-methoxycinnamic Acid.—The "Organic Syntheses"[24] procedure for the preparation of α-acetaminocinnamic acid was adapted, and afforded the acid, mp 227–229° (lit.[21] mp 216°, uncorrected), in 85–90% yield from the above azlactone.

***p*-Methoxyphenylpyruvic Acid.**—The "Organic Syntheses"[25] procedure for the preparation of phenylpyruvic acid was employed, affording the acid, mp 184° dec (depends upon the rate of heating) (lit.[21] mp 184° dec, uncorrected), in 90–95% yield from the above cinnamic acid.

1-Hydroxy-2-(*p*-methoxyphenyl)-5-oxocyclohexanecarboxylic Acid (2c) and Its Methyl Ester 2b.—To a suspension of 132.00 g (0.68 mol) of freshly prepared *p*-methoxyphenylpyruvic acid in 1 l. of methanol maintained under a nitrogen atmosphere was added a solution of 57.12 g (0.82 mol) of methyl vinyl ketone in 100 ml of methanol. The reaction mixture was cooled to 0–5° in an ice bath, and a solution of 32.64 g (0.82 mol) of sodium hydroxide in 300 ml of water (precooled to 5°) was added dropwise at such a rate that the temperature of the reaction mixture was maintained below 15°. The *p*-methoxyphenylpyruvic acid,

(20) K. H. Fung, K. J. Schmalzl, and R. N. Mirrington, *Tetrahedron Lett.*, 5017 (1969).
(21) J. B. Niederl and A. Ziering, *J. Amer. Chem. Soc.*, **64**, 885 (1942).
(22) A. Galat, *ibid.*, **72**, 4436 (1950).
(23) A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1957, p 11.
(24) Reference 23, p 1.
(25) Reference 23, p 519.

which is relatively insoluble in cold methanol, gradually dissolved on addition of the aqueous base. The reaction vessel was then removed from the ice bath, and the clear solution was stirred at room temperature under nitrogen for 10 hr, during which time the sodium salt of the product partially precipitated from solution.

The reaction mixture was then diluted with 300 ml of water and acidified with concentrated hydrochloric acid, and the resulting clear solution cooled for several hours. The product, which precipitated during this time, was filtered and dried in a vacuum desiccator, affording 153.00 g (86%) of acid: mp 175–177° (ethyl acetate, dehydrates upon melting); ir (KBr) 3500, 3100–2800, 1730, and 1675 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.53; H, 6.35.

Treatment of the above acid with excess ethereal diazomethane afforded the methyl ester **2b** as colorless crystals: mp 122–124° [benzene–petroleum ether (bp 30–60°), dehydrates upon melting]; ir ($CHCl_3$) 3540, 1738, and 1728 cm^{-1} (sh); nmr ($CDCl_3$) δ 1.75–2.65 (4 H, m), 2.88 (1 H, s), 3.10–3.50 (3 H, m), 3.60 (3 H, s), 3.72 (3 H, s), and 6.60–7.25 (4 H, m, A_2B_2).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.70; H, 6.70.

1-Hydroxy-2-phenyl-5-oxocyclohexanecarboxylic Acid (2a).—In the manner described (*vide supra*), 72.96 g (0.44 mol) of phenylpyruvic acid[25] in 500 ml of methanol, 27.45 g (0.54 mol) of methyl vinyl ketone in 100 ml of methanol, and 21.40 g (0.54 mol) of sodium hydroxide in 150 ml of water afforded, upon stirring at room temperature under nitrogen for 3 hr, 93.00 g (90%) of acid **2a**: mp 180–182° (ethyl acetate, dehydrates upon melting); ir (KBr) 3455, 3100–2700, 1727, and 1685 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.47; H, 6.18.

3-Oxo-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (3c).—In a flask fitted with a nitrogen inlet was placed 20.00 g (0.076 mol) of hydroxy acid **2c** and the flask was heated at 180–190° in an oil bath until all of the acid had melted (5–10 min). The reaction flask was removed from the oil bath and cooled for several minutes with constant stirring under nitrogen. To the warm yellow, viscous liquid was added 10 ml of benzene and 1 ml of methanol. The product, which crystallized upon cooling to room temperature, was filtered and dried in a vacuum desiccator, yielding 15.88 g of acid: mp 138.5–139.5° (benzene–methanol); ir (KBr) 3200–2800, 1730, 1712, and 1660 cm^{-1}; nmr (CD_3OD) δ 1.84–2.58 (4 H, m), 3.74 (3 H, m), 4.17 (1 H, poorly resolved triplet, $W_{1/2}$ = 5 Hz), 6.84 (1 H, d, J = 1.3 Hz), and 6.70–7.25 (4 H, m, A_2B_2).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.28; H, 5.82.

3-Oxo-6-phenyl-1-cyclohexenecarboxylic Acid (3b).—In the manner described (*vide supra*), dehydration of 13.68 g (0.058 mol) of hydroxy acid **2a** at 190–200° afforded 11.36 g (90%) of acid **3b**: mp 170–171° (benzene–methanol); ir (KBr) 3300–2900, 1730, 1712, and 1650 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.23; H, 5.60.

Catalytic Reduction of 3-Oxo-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (3c). Acids 5c and 6a and Their Respective Methyl Esters, 5d and 6b.—A solution of 5.24 g (0.021 mol) of acid **3c** in 250 ml of absolute ethanol was hydrogenated with 0.250 g of 10% palladized carbon in a Paar shaker. During the hydrogenation, the product partially precipitated from solution, and uptake of hydrogen stopped after consumption of 1 equiv of hydrogen. The reaction mixture was then warmed on a steam bath to effect solution of precipitated materials and filtered through Celite. The ethanol was removed *in vacuo*, and the crystalline mixture of acids was subjected to a series of fractional crystallizations.

Recrystallization from ethanol afforded 2.14 g (40.3%) of relatively pure *cis*-2-(*p*-methoxyphenyl)-5-oxo-1-cyclohexanecarboxylic acid (**5c**), mp 185–189°. An additional fraction (0.225 g) of less pure acid was obtained upon concentrating the mother liquors. Several recrystallizations from ethanol afforded an analytical sample of **5c**: mp 188–190°; ir (KBr) 3200–2800, 1725, and 1695 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 248 (48), 178 (14), 148 (36), 147 (100), 134 (97), 121 (23), and 91 (15).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.82; H, 6.74.

The ethanol was removed from the above mother liquors, and, upon recrystallization from benzene, 1.56 g (29.5%) of *cis*-3-hydroxy-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic acid (**6a**) containing a small amount of keto acid **5c** was obtained. Several recrystallizations from benzene afforded an analytical sample of **6a**: mp 195–196.5°; ir (KBr) 3375, 3100–2700, 1695, 1660, and 1605 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 249 (16), 248 (99), 231 (12), 230 (71), 202 (15), 186 (15), 185 (26), 174 (15), 160 (17), 159 (38), 158 (26), 148 (11), 147 (30), 141 (13), 140 (100), 135 (10), 134 (52), 121 (22), 115 (17), 108 (64), 95 (21), and 91 (16).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.95; H, 6.79.

Upon removal of the benzene from the above mother liquors, 1.10 g of a mixture of both acids was obtained.

Treatment of keto acid **5c** with excess ethereal diazomethane afforded keto ester **5d**: mp 100–101° (benzene–petroleum ether); ir ($CHCl_3$) 1725 cm^{-1} (broad); nmr ($CDCl_3$) δ 1.90–2.80 (6 H, m), 3.40 (2 H, m), 3.48 (3 H, s), 3.82 (3 H, s), and 6.80–7.30 (4 H, m, A_2B_2).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.71; H, 6.91.

Treatment of acid **6a** with excess ethereal diazomethane afforded the methyl ester **6b**: mp 84–85° (diisopropyl ether); ir ($CHCl_3$) 3550–3300, 1715, and 1605 cm^{-1}; nmr ($CDCl_3$) δ 1.35–2.13 (4 H, m), 3.43 (1 H, s, concentration dependent), 3.57 (3 H, s), 3.73 (3 H, s), 3.86 (1 H, $W_{1/2}$ = 8 Hz), 4.37 (1 H, $W_{1/2}$ = 16 Hz, poorly resolved triplet), 6.65–7.32 (4 H, m, A_2B_2), and 6.84 (1 H, s).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.68; H, 6.91.

Manganese Dioxide Oxidation of 3-Hydroxy-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (6a).—A solution of 0.496 g (0.002 mol) of acid **6a** in 50 ml of chloroform was refluxed under nitrogen for 3 hr with 2.50 g of manganese dioxide.[12] The manganese dioxide was removed by filtration, boiled with chloroform for 10 min, and refiltered. The combined filtrates were dried and concentrated *in vacuo*. The crude red-brown oil obtained crystallized on trituration with ether to give 0.210 g (35%) of a solid, mp 138–139° (benzene–methanol), which showed no melting point depression upon admixture with an analytical sample of acid **3c**.

Sodium Borohydride Reduction of 3-Oxo-6-(*p*-methoxyphenyl)-cyclohexenecarboxylic Acid (3c).—To a solution of 496 mg (2 mmol) of acid **3c** in 50 ml of 50% aqueous methanol 0–5°, containing a small amount of potassium carbonate, was added 76 mg (2 mmol) of sodium borohydride. After stirring the reaction mixture for 1 hr, the methanol was removed *in vacuo*, and the reaction mixture was diluted with water, acidified with dilute hydrochloric acid, and thoroughly extracted with ethyl acetate. The combined extracts were dried, concentrated *in vacuo*, and triturated with ether giving 441 mg (90%) of acid **6a**, mp 195–196° (benzene), which showed no melting point depression upon admixture with an analytical sample of acid **6a**.

Lithium–Ammonia Reduction of 3-Oxo-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (3c).—To 300 ml of ammonia (from sodium) was slowly added 0.680 g (0.098 g-atom) of lithium, followed by the addition of 4.03 g (0.016 mol) of acid **3c** in 100 ml of dry tetrahydrofuran. After stirring for 2 hr, a few crystals of ferric chloride were added, and the reaction mixture was stirred until discharge of the blue color was complete. After addition of 1 ml of *tert*-butyl alcohol and further stirring for 5 min, solid ammonium chloride was added, and the resulting mixture was left to evaporate overnight.

The residue was taken up in 300 ml of water and acidified with dilute hydrochloric acid, and the solution was saturated with salt and thoroughly extracted with ethyl acetate. The combined extracts were dried and concentrated *in vacuo*. Trituration of the crude residue with ether gave 2.19 g (54%) of acid **5c**, mp 188–189° (ethanol), which showed no melting point depression upon admixture with an analytical sample of acid **5c**. Treatment of a small amount of the acid with excess ethereal diazomethane gave a methyl ester which was homogeneous by analytical thin layer chromatography and identical with an authentic sample of ester **5d**.

Zinc–Aqueous Acetic Acid Reduction of 3-Oxo-6-(*p*-methoxyphenyl)-1-cyclohexenecarboxylic Acid (3c).—A mixture of 37.00 g (0.150 mol) of acid **3c**, 500 ml of glacial acetic acid, 50 ml of water, and 120 g of zinc dust was refluxed under nitrogen for 30 hr. The reaction mixture was cooled to room temperature, the

zinc removed by filtration and washed with glacial acetic acid, and the filtrate evaporated to dryness. The residual solid mixture of product and zinc acetate was partitioned between warm water–ethyl acetate, and the layers were separated. The aqueous layer was cooled to room temperature, salted, and thoroughly extracted with ethyl acetate. The combined extracts, upon drying and concentration, gave 34.00 g (91%) of acid **5c**, mp 188–189° (ethanol), exhibiting no melting point depression upon admixture with an analytical sample of acid **5c**.

***cis*-2-Phenyl-5-oxocyclohexanecarboxylic Acid (5a) and Its Methyl Ester 5b.**—In the manner described (*vide supra*), refluxing a solution of 34.27 g (0.159 mol) of acid **3b** in a mixture of 500 ml of glacial acetic acid, 50 ml of water, and 120 g of zinc dust afforded 32.50 g (94%) of crude acid **5a**: mp 201–202° (ethanol); ir (KBr) 3225 (broad), 1726, and 1695 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.45; H, 6.52.

Treatment of the above acid with excess ethereal diazomethane gave the methyl ester **5b**: mp 114.5–115.5° (methanol); ir ($CHCl_3$) 1725 cm^{-1} (broad); nmr ($CDCl_3$) δ 1.85–2.90 (6 H, m), 3.40 (3 H, s), 3.10–3.55 (2 H, m), and 7.00–8.40 (5 H, m).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.29; H, 7.11.

Ethylene Thioketal of *cis*-2-Phenyl-5-oxocyclohexanecarboxylic Acid (5e) and Its Methyl Ester 5f.—To a solution of 6.00 g (0.028 mol) of acid **5a** in 60 ml of hot glacial acetic acid were added 5 ml of boron trifluoride etherate and 5 ml of ethanedithiol.[26] The resulting solution was cooled to room temperature and stored in a refrigerator overnight. The crystalline thioketal was filtered and air-dried: mp 159–160° (ethyl acetate); ir (KBr) 3200–2800 and 1685 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 296 (10), 295 (16), 294 (90), 234 (11), 233 (22), 201 (10), 200 (23), 176 (18), 155 (36), 149 (15), 133 (15), 132 (15), 131 (100), 129 (11), 115 (14), 104 (25), 91 (31), 86 (11), 77 (12), and 61 (17).

Anal. Calcd for $C_{15}H_{18}O_2S_2$: C, 61.21; H, 6.17. Found: C, 61.10; H, 6.11.

Treatment of the above acid with excess ethereal diazomethane gave the methyl ester **5f**: mp 72.5–73.5° (methanol); ir ($CHCl_3$) 1735 cm^{-1}; nmr ($CDCl_3$) δ 1.95–2.32 (4 H, m), 2.42–2.60 (2 H, m), 2.87–3.38 (2 H, m), 3.25 (2 H, m), 3.42 (3 H, s), and 7.00–7.37 (5 H, m).

Anal. Calcd for $C_{16}H_{20}O_2S_2$: C, 62.32; H, 6.54. Found: C, 62.19; H, 6.51.

***cis*-2-Phenylcyclohexanecarboxylic Acid (5g).**—A mixture of 308 mg (1 mmol) of thioketal **5f**, 6.00 g of Raney nickel W-2, and 25 ml of absolute ethanol was refluxed under nitrogen for 17 hr. The reaction mixture was filtered through Celite, and the Raney nickel was washed thoroughly with ethanol. Concentration of the filtrate *in vacuo* yielded 196 mg (90%) of desulfurized product (homogeneous by analytical thin layer chromatography) exhibiting ester absorption at 1725 cm^{-1} in its infrared spectrum, and no thioketal singlet in its nmr spectrum.

The above desulfurized product was hydrolyzed by refluxing it in a mixture of 10 ml of methanol, 10 ml of water, and 212 mg (2 mmol) of sodium carbonate for 18 hr. The solution was cooled to room temperature, saturated with salt, and thoroughly extracted with ether. The combined ether extracts, upon drying and concentration *in vacuo*, yielded 35 mg (17%) of unhydrolyzed ester.

The basic aqueous layer was acidified with dilute hydrochloric acid and thoroughly extracted with ether. Upon drying the combined ether extracts and concentrating *in vacuo*, 105 mg of oil was obtained. The oil completely crystallized on standing to give acid **5g**: mp 76–77° (petroleum ether) (lit.[13] mp 77°); ir (KBr) 3200–2800 and 1700 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 204 (54), 186 (21), 158 (37), 144 (21), 131 (10), 130 (16), 129 (15), 118 (30), 117 (97), 115 (19), 113 (21), 104 (49), 92 (40), 91 (100), 78 (14), and 77 (14).

7-Methoxy-*cis*-1,2,3,4,4a,9a-hexahydrofluorene-2,9-dione (7b).—To 500 g of polyphosphoric acid heated to 80–85° in an oil bath, 10.00 g (0.0404 mol) of finely powdered keto acid **5c** was added in one portion, and the resulting solution was stirred for 10 min. The yellow-brown solution was poured into 1.5 l. of ice-cold water, stirred until decomposition of the polyphosphoric acid was complete, saturated with salt, and extracted with three portions of chloroform (250, 250, and 100 ml). The combined chloroform extracts, after washing with two 100-ml portions of 8% aqueous solium hydroxide, drying, and concentrating *in vacuo*, afforded 7.80 g (84%) of semicrystalline solid. Trituration with ether gave 5.60 g (60%) of crude solid, mp 94–98°, which provided diketone **7b**: mp 103–103.5° (ethanol); ir ($CHCl_3$) 1713 cm^{-1}; uv λ_{max} (EtOH) 322 nm (ϵ 4940) and 251 (11,800); nmr ($CDCl_3$) δ 1.65–2.60 (4 H, m), 2.70 (1 H, m), 2.80 (1 H, s), 3.10 and 3.20 (1 H, m), 3.50–3.80 (1 H, m), 3.85 (3 H, s), and 7.20–7.70 (3 H, m).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.90; H, 6.21.

***cis*-1,2,3,4,4a,9a-Hexahydrofluorene-2,9-dione (7a).**—Following the above procedure, 10.00 g (0.046 mol) of keto acid **5a** (reaction time 45 min) afforded 8.30 g (90%) of neutral oil, which on trituration with ether gave 7.28 g (80%) of **7a**, mp 106–107° (ethyl acetate–hexane) (lit.[6] mp 106–107°).

Monoketal 8b.—A solution of 5.44 g (23.6 mmol) of diketone **7b**, 2.80 g (34.4 mmol) of ethylene glycol, and 0.450 g (2.36 mmol) of *p*-toluenesulfonic acid monohydrate in 50 ml of benzene was refluxed under nitrogen for 3 hr with constant separation of water (Dean–Stark trap). The solution was cooled to room temperature, washed with dilute aqueous sodium hydroxide, and dried. Upon concentration *in vacuo*, 4.51 g (70%) of solid, mp 119–121°, was obtained: mp 122–123° (ethanol); ir ($CHCl_3$) 1706 cm^{-1}; uv λ_{max} (EtOH) 320 (ϵ 4360) and 249 (10,000); nmr ($CDCl_3$) δ 1.30–2.40 (6 H, m), 2.70–3.11 (1 H, m), 3.25–3.60 (1 H, m), 3.80 (3 H, m), 3.86–4.04 (4 H, m), and 7.00–7.45 (3 H, m).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.93; H, 6.51.

Monoketal 8a.—Reaction of 5.14 g (25.7 mmol) of diketone **7a** with 2.42 g (38.6 mmol) of ethylene glycol and 0.490 g (2.57 mmol) of *p*-toluenesulfonic acid monohydrate in 50 ml of benzene as described above afforded 2.58 g (41%) of crude ketal **8a**, mp 80–81° (diisopropyl ether) (lit.[5b] mp 80–82°). The mother liquors contained ketal **8a** and diketal which could readily be hydrolyzed (*vide infra*) and recycled.

Alkylation of Ketal 8b with 2,3-Dibromopropene.—To a suspension of 2.64 g (22.0 mmol) of freshly prepared dry potassium *tert*-butoxide in 25 ml of dry glyme was added 5.58 g (20.0 mmol) of ketal **8b** in 100 ml of glyme. After stirring the resulting solution at room temperature under nitrogen for 5 min, 4.80 g (24.0 mmol) of freshly distilled 2,3-dibromopropene[27] in 25 ml of glyme was added over a period of 15 min. Stirring under nitrogen was continued for 1 hr, during which time potassium bromide precipitated from solution. The reaction mixture was poured into 200 ml of water, saturated with salt, and extracted with four portions of chloroform (two 100-ml and two 50-ml portions). The combined extracts were dried and concentrated *in vacuo*, affording 6.15 g (77%) of alkylated ketal **8c**: mp 103–104° (ethanol); ir ($CHCl_3$) 1712, 1625, 1110, and 1094 cm^{-1}; nmr ($CDCl_3$) δ 1.15–2.40 (6 H, m), 3.12 (2 H, s), 3.59 (1 H, t, J = 5 Hz), 3.82 (3 H, s), 3.71–4.03 (4 H, m), 5.45 (1 H, d, J = 1.5 Hz), 5.60 (1 H, s, br), and 7.06–7.50 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 394 (<1), 392 (<1), 314 (11), 313 (56), 271 (27), 270 (35), 186 (22), 99 (100), 86 (11), and 54 (13).

Anal. Calcd for $C_{19}H_{21}O_4Br$: C, 58.02; H, 5.38. Found: C, 58.17; H, 5.27.

Diketone 7c from Hydrolysis of Ketal 8c.—A solution of ketal **8c** (4.44 g, 11.3 mmol) was refluxed under nitrogen in 75 ml of methanol containing 25 ml of 5% hydrochloride acid for 1 hr. The solution was poured into 200 ml of water, saturated with salt, and extracted with five portions of chloroform. The solution was dried, concentrated, and triturated with methanol to afford 3.65 g (93%) of diketone **7c**: mp 114–115° (methanol); ir ($CHCl_3$) 1713 and 1623 cm^{-1}; nmr ($CDCl_3$) δ 1.60–2.60 (4 H, m), 2.65 (2 H, s), 2.83 (2 H, s), 3.84 (3 H, s), 3.98 (1 H, m), 5.63 (2 H, m), and 7.10–7.60 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 350 (<1), 348 (<1), 270 (100), 228 (26), 186 (57), and 173 (10).

Anal. Calcd for $C_{17}H_{17}O_3Br$: C, 58.48; H, 4.88. Found: C, 58.50; H, 5.05.

Alkylation of Ketal 8a with 2,3-Dibromopropene.—Following the procedure described (*vide supra*), 6.34 g (26.0 mmol) of ketal **8a** in 50 ml of dry glyme, 3.43 g (28.6 mmol) of freshly prepared dry potassium *tert*-butoxide, and 6.18 g (31.2 mmol) of 2,3-di-

(26) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 356.

(27) H. Gilman and A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1958, p 209. The compound was freshly distilled prior to use.

bromopropene in 25 ml of glyme afforded a yellow oil, which on trituration with ether gave 7.16 g (76%) of ketal **8d**, mp 100–102° (ethanol) (lit.[5p] mp 100–102°).

Diketone 7d from Hydrolysis of Ketal 8d.—In the manner described (*vide supra*), 3.00 g (8.29 mmol) of ketal **8d** provided, upon trituration with ether, 2.18 g (83%) of the known[5p] diketone **7d**, mp 74–75°.

Allyl Diketone 7e from Ketal 8b.—To a suspension of 624 mg (5.5 mmol) of freshly prepared dry potassium *tert*-butoxide in 10 ml of dry glyme was added 1.37 g (5 mmol) of ketal **8b** in 30 ml of glyme. After stirring the resulting solution at room temperature under nitrogen for 5 min, 726 mg (6.0 mmol) of allyl bromide in 10 ml of glyme was added over a period of 15 min. Stirring under nitrogen was continued for 1 hr, during which time potassium bromide precipitated from solution. The reaction mixture was then poured into 100 ml of water, saturated with salt, and extracted with four portions of chloroform. The combined extracts were dried and concentrated *in vacuo*, yielding 1.60 g (100%) of alkylated ketal as a yellow oil: ir ($CHCl_3$) 1711, 1642, 1115, 1095, 992, and 905 cm^{-1}; nmr ($CDCl_3$) δ 1.36–2.24 (6 H, m), 2.30 (1 H, d, J_{AB} = 15 Hz), 2.55 (1 H, d, J_{AB} = 15 Hz), 3.22 (1 H, t, J = 6 Hz), 3.82 (3 H, s), 3.70–3.98 (4 H, m), and 4.83–6.00 (3 H, m).

The above ketal (1.60 g, 5 mmol) was refluxed under nitrogen with 25 ml of methanol and 10 ml of 5% hydrochloric acid for 1 hr. The solution was poured into 100 ml of water, saturated with salt, and extracted with four portions of chloroform. After washing the chloroform extracts with water and drying, the solvent was removed *in vacuo* to give 1.24 g (90%) of allyl diketone **7e** as a yellow oil: ir ($CHCl_3$) 1713, 1642, 992, and 905 cm^{-1}; nmr ($CDCl_3$) δ 1.66–2.50 (6 H, m), 3.49 (1 H, t, J = 6 Hz), 3.82 (3 H, s), 4.89–6.06 (3 H, m), and 7.10–7.56 (3 H, m).

Grignard Reaction of Diketone 7c.—To a mixture of 915 mg (37.6 mg-atoms) of 70–80 mesh magnesium, 5 ml of dry tetrahydrofuran, and a crystal of iodine was added two drops of ethylene dibromide, and the mixture was warmed briefly until the color of the iodine had disappeared. The mixture was brought to reflux as 1.13 g (3.76 mmol) of diketone **7c** in 20 ml of tetrahydrofuran was added over a period of 15 min, after which the resulting mixture was refluxed for 5 hr under nitrogen.

The reaction mixture was then cooled to room temperature, filtered through glass wool into 100 ml of saturated aqueous ammonium chloride solution, and thoroughly extracted with chloroform. Upon drying of the extracts and concentration *in vacuo*, 1.3 g of yellow oil was obtained. An analytical thin layer chromatogram indicated that the oil consisted of allyl diketone **7e** and a slower moving component, subsequently shown to be alcohol **10**, and polar material at the origin. The polar material was removed by chromatography of the oil (1.31 g) on Florisil (39 g). Elution with 2–10% ether–benzene afforded 330 mg of a mixture of **7e** and **10**. The nmr spectrum of this oil exhibited methoxyl singlets at δ 3.82 (**7e**) and 3.74 (**10**) in a ratio of 4:1. Separation of the major component was effected by preparative thin layer chromatography (employing 30% ethyl acetate–benzene as the mobile phase), 130 mg of the mixture affording 60 mg of allyl diketone **7e**. The ir and nmr spectra of this material were identical with those of an authentic allyl diketone **7e** (*vide supra*).

In another experiment, the reaction was carried out exactly as described above, except that the reaction mixture was allowed to reflux for a total of 48 hr. Work-up as described above afforded 1.08 g of oil, which, after washing through a column of Florisil (10 g) in benzene, yielded 626 mg of oil. The nmr spectrum of the oil exhibited methoxyl singlets at δ 3.82 and 3.74 in a ratio of 1:5. Separation of the major component was effected by preparative thin layer chromatography employing 30% ethyl acetate–benzene as the mobile phase and afforded 233 mg of alcohol **10** contaminated with a trace of allyl diketone **7e** (analytical thin layer chromatography). The ir spectrum of this oil exhibited broad hydroxyl absorption at 3600–3300 cm^{-1} and carbonyl absorption at 1722 cm^{-1} (alkyl ketone) and displayed a typical allyl multiplet at δ 4.70–6.00 in its nmr spectrum.

Oxidation of 80 mg of the above alcohol **10** with Sarett's reagent afforded 55 mg of oil, having an nmr spectrum identical with that of allyl diketone **7e**.

Addition of Ketal 8b to Methyl α-Bromoacrylate.—To a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (23 mg, 0.60 mmol) was added 548 mg (2.00 mmol) of ketal **8b** in 5 ml of dry tetrahydrofuran followed immediately by a solution of 363 mg (2.20 mmol) of methyl α-bromoacrylate in 5 ml of dry tetrahydrofuran. The resulting solution was diluted with water, saturated with salt, and thoroughly extracted with ether. The extracts were dried and concentrated *in vacuo*. The residue was dissolved in a mixture of 10 ml of tetrahydrofuran and 5 ml of 10% hydrochloric acid and allowed to stand at room temperature for 2 hr. The solution was poured into water, saturated with salt, and thoroughly extracted with ether. After drying and concentrating *in vacuo*, the crude product was washed through a short column of Florisil with benzene, and afforded 523 mg (67% overall) of bromo ester **12a**: ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.60–2.80 (8 H, m), 3.40–3.65 (1 H, m), 3.69 and 3.74 (3 H, s, 3:5 ratio, respectively), 3.85 (3 H, s), 4.20–4.58 (1 H, m) and 7.05–7.60 (3 H, m).

***N,N*-Dimethyl-α-bromoacrylamide.**[28]—The procedure of Drake,[29] *et al.*, for the preparation of α-halo amides was adapted. To a solution of 39.27 g (0.157 mol) of α,β-dibromopropionyl chloride[30] in 100 ml of ether cooled to 0° in an ice bath was added 21 ml (0.314 mol) of dimethylamine in 200 ml of ether (precooled to 0°) with constant stirring under nitrogen. The dimethylamine solution was added at such a rate that the temperature of the reaction mixture was maintained at 0–5°. Enough water to dissolve the precipitated dimethylamine hydrobromide was added, the layers were separated, and the aqueous layer was thoroughly extracted with ether. The combined ether extracts were dried and concentrated *in vacuo*, and the residue was stirred with 100 ml of tetrahydrofuran and 100 ml of 5% aqueous sodium hydroxide for 30 min under nitrogen. The solution was diluted with water, saturated with salt, and extracted with ether, providing 20.20 g (73% overall) of α-bromo-*N,N*-dimethylacrylamide: bp 70° (0.5 mm); nmr ($CDCl_3$) δ 3.05 (6 H, s, br), 5.87 (1 H, d, J = 3 Hz), and 6.21 (1 H, d, J = 3 Hz).

Addition of Ketal 8b to *N,N*-Dimethyl-α-bromoacrylamide.—To a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (398 mg, 10.2 mmol of potassium dissolved in 50 ml of dry *tert*-butyl alcohol) was added 9.29 g (33.9 mmol) of ketal **8b** in 80 ml of dry tetrahydrofuran, followed immediately by a solution of 6.64 g (37.3 mmol) of *N,N*-dimethyl-α-bromoacrylamide in 50 ml of tetrahydrofuran. The resulting solution was stirred at room temperature under nitrogen for 18 hr. The reaction mixture was worked up, hydrolyzed, and passed through a short column of Florisil with benzene as described for bromo ester **12a**, affording 9.19 g (67%) of bromoamide **12c** as a 1:2 mixture of diastereomers: nmr ($CDCl_3$) δ 2.80 (3 H, s), 2.84 (3 H, s), 3.85 (3 H, s), and 4.54 (1 H, dd, J_{AX} = 4, J_{BX} = 10 Hz) for the minor diastereomer and 3.02 (3 H, s), 3.85 (3 H, s), and 4.96 (1 H, dd, J_{AX} = 4, J_{BX} = 10 Hz) for the major diastereomer.

Addition of Ketal 8b to *tert*-Butyl α-Bromoacrylate.—To a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (235 mg, 6 mmol of potassium dissolved in 5 ml of dry *tert*-butyl alcohol) was added 5.48 g (20.0 mmol) of ketal **8b** in 60 ml of dry tetrahydrofuran followed immediately by a solution of 4.55 g (22.0 mmol) of *tert*-butyl α-bromoacrylate in 20 ml of tetrahydrofuran. The resulting solution was stirred at room temperature under nitrogen for 3 hr. Work-up, hydrolysis, and passage of the crude product through a short column of Florisil with benzene as described for bromo ester **12a** afforded 6.19 (71%) of bromo ester **12b** as a mixture of diastereomers: ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$ δ 1.60–2.98 (8 H, m), 1.40 and 1.46 (9 H, 2s, ratio 2:3), 3.40–3.70 (1 H, m), 3.84 (3 H, s), 4.10–4.46 (1 H, m), and 7.20–7.55 (3 H, m).

Reformatsky Reaction of Bromo Ester 12a. Benzoates 13c and 13d.—To a suspension of 19.00 g (0.29 g-atom) of activated zinc dust[31] in 50 ml of dry benzene was added a crystal of iodine. After warming the reaction flask briefly until the color of the iodine had disappeared, a solution of 4.58 g (11.6 mmol) of freshly prepared bromo ester **12a** in 50 ml of dry benzene was added, and the resulting solution was refluxed under nitrogen for 24 hr. The reaction mixture was cooled to room temperature, 10 ml of benzoyl chloride was added, and the mixture was stirred overnight under nitrogen. The excess zinc was removed by filtration and washed with benzene, and excess benzoyl chloride

(28) This compound has been reported in the literature, although no details or data were given: I. R. Knunpants, E. E. Rytslin, and N. P. Gambaryan, *J. Gen. Chem. USSR*, **32**, 1235 (1962).

(29) N. L. Drake, C. E. Baker, and W. Shenk, *J. Amer. Chem. Soc.*, **70**, 677 (1948).

(30) C. S. Marvel, J. Dec, H. G. Cooke, and J. C. Cowan, *ibid.*, **62**, 3495 (1940).

(31) The zinc was activated by washing successively with dilute hydrochloric acid, absolute ethanol, acetone, and ether, and drying *in vacuo*.

was decomposed by stirring the benzene filtrate with aqueous sodium bicarbonate at room temperature. The layers were separated and the aqueous bicarbonate solution was thoroughly extracted with benzene. Upon drying the combined benzene extracts and concentrating *in vacuo*, 3.55 g (69%) of semicrystalline solid was obtained. The thin layer chromatogram of this material indicated two components of almost identical R_f values contaminated with a small amount of polar material. Upon trituration of the residue with ether, 1.09 g (22%) of impure benzoate **13c**, mp 141–146°, was obtained, Recrystallization from methanol afforded pure benzoate **13c**, obtained at different times in two crystalline modifications: needles, mp 153–154°, and rhombs, mp 166–167°. That these two samples were the same material was indicated by their identical infrared, nmr, and mass spectra, as well as a mixture melting point, 166–167°: ir ($CHCl_3$) 1736 and 1700 cm^{-1}; uv λ_{max} (EtOH) 323 nm (ϵ 3750) and 250 (11,000); nmr ($CDCl_3$) δ 1.60–2.55 (8 H, m), 2.60–3.00 (1 H, m), 3.25–3.55 (1 H, m), 3.68 (3 H, s), 3.86 (3 H, s), and 7.15–8.10 (8 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 420 (10), 298 (11), 266 (13), and 105 (100).

Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.42; H, 5.84.

Chromatography of the above mother liquor (2.35 g) on Florisil (70 g) afforded 250 mg (5%) of benzoate **13d**, mp 159–160° (methanol), on elution with 1–5% ether–benzene: ir ($CHCl_3$) 1730 and 1710 cm^{-1}; uv λ_{max} (EtOH) 323 nm (ϵ 3330) and 250 (11,500); nmr ($CDCl_3$) δ 1.60–2.70 (8 H, m), 2.83–3.25 (1 H, m), 3.35–3.70 (1 H, m), 3.77 (3 H, s), 3.81 (3 H, s), and 7.15–8.15 (8 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 420 (4), 299 (20), 298 (100), 266 (22), 239 (49), 238 (46), 225 (12), 185 (22), 105 (64), 83 (12), 71 (19), 70 (13), 69 (17), 57 (32), 43 (19), and 41 (22).

Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.34; H, 5.94.

Elution with 10% ether–benzene ether gave 600 mg of benzoate **13c**, mp 166–167°, obtained by trituration with ether (total yield of benzoate **13c**, 1.69 g, 35%).

Lithium Aluminum Hydride Reduction of Benzoate 13c.—A mixture of 210 mg (0.5 mmol) of benzoate **13c** and 150 (4 mmol) of lithium aluminum hydride in 15 ml of dry tetrahydrofuran was refluxed under nitrogen for 1 hr. The reaction mixture was cooled for an ice bath, the excess aluminum hydride was decomposed with saturated aqueous sodium sulfate solution, and the resulting mixture was thoroughly extracted with ether, dried, and concentrated, giving 145 mg (100%) of triol **14a**: mp 178–180° (ethyl acetate); ir (KBr) 3400–3200 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 290 (35), 272 (20), 233 (15), 232 (100), 231 (19), 230 (100), 229 (17), 223 (10), 215 (12), 213 (12) 211 (11), 202 (15), 199 (18), 188 (10), 186 (38), 185 (33), 180 (10), 178 (15), 175 (12), 174 (25), 173 (40), 172 (65), 171 (30), 169 (10), 160 (12), 159 (38), 152 (10), 129 (18), 121 (18), 115 (12), 102 (60), 95 (10), 93 (18), 87 (49), 83 (98), 73 (15), 60 (65), 59 (30), and 57 (38).

Lithium Aluminum Hydride Reduction of Benzoate 13d.—A mixture of 30 mg (0.71 mmol) of benzoate **13d** and 10 mg (0.263 mmol) of lithium aluminum hydride in 5 ml of dry tetrahydrofuran was refluxed under nitrogen for 1 hr. Work-up as described (*vide supra*) afforded 18 mg (88%) of triol **14b**: mp 209–210° (acetone); ir (KBr) 3450–3200 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 290 (33), 233 (16), 232 (100), 231 (10), 230 (49), 215 (11), 214 (45), 199 (14), 187 (16), 186 (30), 185 (16), 178 (19), 175 (10), 174 (18), 173 (36), 172 (59), 171 (21), 160 (11), 159 (38), 158 (15), 115 (14), 91 (10), 57 (11), and 41 (18).

Epimerization of Benzoate 13d.—To a solution of 20 mg (0.476 mmol) of benzoate **13d** in 3 ml of dry tetrahydrofuran was added 1.5 ml of 0.046 *M* potassium *tert*-butoxide–*tert*-butyl alcohol solution, and the resulting solution was left at room temperature for 18 hr. The solution was then acidified with 0.1 *N* hydrochloric acid and evaporated to dryness *in vacuo*. The residue was taken up in water and thoroughly extracted with ether. Upon drying and concentrating 18 mg of an oil was obtained. The thin layer chromatogram of this oil indicated that the product was identical with benzoate **13c** contaminated with a small amount of polar material. No trace of starting benzoate **13d** was found.

Treatment of 15 mg (0.36 mmol) of benzoate **13d** as above gave 14 mg of recovered benzoate.

Reformatsky Reaction of Bromo Ester 12a. Acetates 13a and 13b.—In the manner described for the preparation of benzoates **13c** and **13d**, a mixture of 3.55 g (8.45 mmol) of freshly prepared bromo ester **12a** and 13.9 g (0.214 g-atom) of activated zinc dust in 100 ml of dry benzene was refluxed under nitrogen for 24 hr. The reaction mixture was cooled to room temperature, 10 ml of acetic anhydride was added, and the mixture was stirred overnight at room temperature under nitrogen. Work-up (*vide supra*) afforded 2.65 g (88%) of semicrystalline solid, the thin layer chromatogram of which indicated a mixture of two components of almost identical R_f values contaminated with a small amount of polar material. Trituration of the residue gave 1.21 g (40%) of acetate **13a**: mp 181–192° (methanol); ir ($CHCl_3$) 1745, 1738 (sh), and 1712 cm^{-1}; nmr ($CDCl_3$) δ 1.50–2.66 (8 H, m), 1.99 (3 H, s), 2.71–3.00 (1 H, m), 3.10–3.45 (1 H, m), 3.75 (3 H, s), 3.86 (3 H, s), and 7.20–7.50 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 358 (24), 298 (16), 272 (13), 266 (10), 239 (10), 238 (13), 231 (14), 230 (100), 174 (18), and 173 (13).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.26; H, 6.27.

The mother liquors (1.44 g) upon Florisil chromatography afforded 93 mg (3%) of acetate **13b**: mp 129–131° (2–5% ether–benzene eluents); ir ($CHCl_3$) 1738 (sh), 1730, and 1708 cm^{-1}; nmr ($CDCl_3$) 1.60–2.88 (8 H, m), 2.04 (3 H, s), 2.98–3.60 (2 H, m), 3.76 (3 H, s), 3.85 (3 H, s), and 7.10–7.50 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 358 (2), 299 (21), 298 (100), 267 (15), 266 (33), 240 (15), 239 (81), 238 (62), 225 (17), 224 (19), 223 (11), 173 (8), and 43 (13).

The remainder of the material in the mother liquors was eluted in the 10% ether–benzene → ether fractions, and afforded a broad melting (110–170°) mixture of the two diastereomers.

Lithium Aluminum Hydride Reduction of Acetate 13a.—A mixture of 358 mg (1 mmol) of acetate **13a** and 100 mg (2.63 mmol) of lithium aluminum hydride in 20 ml of dry tetrahydrofuran under nitrogen for 1 hr afforded, upon work-up, 248 mg (86%) of triol **14a**, mp 178–180° (ethyl acetate), which exhibited no melting point depression on admixture with a sample of triol **14a** prepared by reduction of benzoate **13c**.

Lithium Aluminum Hydride Reduction of Acetate 13b.—Refluxing a mixture of 50 mg (0.140 mmol) of acetate **13b** and 50 mg (1.3 mmol) of lithium aluminum hydride in 5 ml of dry tetrahydrofuran under nitrogen for 1 hr afforded, upon work-up, 34 mg (84%) of triol **14b**, mp 207–209°. Recrystallization from acetone afforded crystals, mp 209–210°, which gave no melting point depression on admixture with a sample of triol **14b** prepared by reduction of benzoate **13d**.

Reformatsky Reaction of Bromo Ester 12a. Alcohol 13e.—A mixture of 984 mg (2.84 mmol) of freshly prepared bromo ester **12a** and 3.26 g (0.05 g-atom) of activated zinc dust in 20 ml of dry tetrahydrofuran was refluxed under nitrogen for 24 hr. The reaction mixture was cooled to room temperature, 2 ml of acetic anhydride was added, and the reaction mixture was stirred overnight at room temperature under nitrogen. Work-up as described (*vide supra*) afforded 647 mg (82.5%) of a semicrystalline solid, the thin layer chromatogram of which indicated a mixture of two components contaminated with a small amount of polar material. Trituration of the residue afforded 347 mg (44%) of alcohol **13e**: mp 198.5–200° (ethyl acetate); ir (KBr) 3500 and 1710 cm^{-1}; nmr ($CDCl_3$) δ 1.50–3.30 (10 H, m), 3.50–3.70 (1 H, s, br), 3.76 (3 H, s), 3.86 (3 H, s), and 7.10–7.45 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 316 (31), 231 (16), 230 (100), 229 (11), 202 (15), and 175 (11).

Anal. Calcd for $C_{15}H_{20}O_6$: C, 68.34; H, 6.37. Found: C, 68.09; H, 6.25.

Lithium Aluminum Hydride Reduction of 13e.—A mixture of 50 mg (0.16 mmol) of alcohol **13e** and 50 mg (1.3 mmol) of lithium aluminum hydride in 5 ml of dry tetrahydrofuran was refluxed under nitrogen for 1 hr, affording 40 mg (99%) of triol **14a**, mp 178–180° (ethyl acetate), which exhibited no melting point depression on admixture with a sample of triol **14a** prepared by reduction of benzoate **13c**.

Reformatsky Reaction of Bromo Amide 12c. Amide 13h.—A mixture of 2.63 g (6.42 mmol) of freshly prepared bromo amide **12e** and 10.5 g (0.16 g-atom) of activated zinc in 100 ml of dry benzene was refluxed under nitrogen for 24 hr. The reaction mixture was cooled to room temperature, 5 ml of acetic anhydride was added, and the mixture was stirred overnight under nitrogen. Work-up as described for benzoates **13c** and **13d** afforded 1.96 g (82%) of a semicrystalline solid, the thin layer chromatogram (25% methanol–benzene) of which indicated two components of almost identical R_f values contaminated with a small amount of polar material. Trituration of the residue with acetone gave 1.23 g (51%) of amide **13h**: mp 194–196° (methanol); ir ($CHCl_3$) 1727, 1710, and 1644 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (3 H, s), 1.60–

2.95 (8 H, m), 3.00 (3 H, s), 3.13 (3 H, s), 2.95–3.30 (1 H, m), 3.40–3.70 (1 H, m), 3.84 (3 H, s), and 7.10–7.50 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 371 (4), 273 (11), 231 (15), 230 (100), 100 (25), 55 (20), 46 (11), and 43 (18).

No attempt was made to isolate the minor diastereomer from the mother liquors.

Reformatsky Reaction of Bromo Ester 12b. Esters 13f and 13g.—A mixture of 6.19 g (14.2 mmol) of freshly prepared bromo ester **12b** and 23.2 g (0.35 g-atom) of activated zinc dust in 150 ml of dry benzene[32] was refluxed under nitrogen for 4 hr. The reaction mixture was cooled to room temperature, 10 ml of acetic anhydride was added, and the mixture was stirred for 1 hr under nitrogen. Work-up (*vide supra*) afforded 5.14 g (90%) of a semicrystalline solid, the thin layer chromatogram of which indicated a mixture of two components of almost identical R_f contaminated with a small amount of polar material. Trituration of the residue with ether afforded 980 mg (19%) of ester **13f**: mp 153–154° (ethanol); ir ($CHCl_3$) 1732 and 1709 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (9 H, s), 2.00 (3 H, s), 1.30–2.60 (8 H, m), 2.65–3.30 (2 H, m), 3.82 (3 H, s), and 7.10–7.60 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 400 (17), 343 (17), 327 (12), 285 (17), 284 (46), 272 (27), 267 (14), 266 (10), 256 (11), 242 (13), 240 (37), 239 (12), 230 (63), 229 (23), 211 (12), 187 (12), 174 (16), 173 (11), 57 (100), 55 (21), 43 (38), and 41 (25). Chromatography of the mother liquors on Florisil afforded 170 mg (3%) of pure ester **13g**, mp 98–99° (methanol), upon elution with 1–2% ether–benzene: ir ($CHCl_3$) 1710 cm^{-1}; nmr ($CDCl_3$) δ 0.52 (9 H, s), 2.03 (3 H, s), 1.50–2.65 (8 H, m), 2.70–3.70 (2 H, m), 3.82 (3 H, s), and 7.10–7.60 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 400 (1), 343 (10), 285 (24), 284 (100), 267 (14), 266 (15), 265 (10), 240 (14), 239 (46), 238 (41), 237 (26), 211 (17), 57 (32), 55 (18), 43 (36), and 41 (19).

Lithium Aluminum Hydride Reduction of Ester 13f.—A mixture of 50 mg (0.125 mmol) of ester **13f** and 20 mg (0.53 mmol) of lithium aluminum hydride in 5 ml of tetrahydrofuran was refluxed under nitrogen for 1 hr. Work-up (*vide supra*) yielded 34 mg (94%) of triol **14a**, mp 178–180° (ethyl acetate), exhibiting no melting point depression on admixture with a sample of triol **14a** prepared by reduction of benzoate **13c**.

Lithium Aluminum Hydride Reduction of Ester 13g.—A mixture of 30 mg (0.075 mmol) of ester **13g** and 15 mg (0.39 mmol) of lithium aluminum hydride in 3 ml of tetrahydrofuran was refluxed under nitrogen for 1 hr. Work-up (*vide supra*) yielded 24 mg (92%) of triol **14b**, mp 209–210° (ethyl acetate), exhibiting no melting point depression on admixture with a sample of triol **14b** prepared by reduction of benzoate **13d**.

Registry No.—**2a**, 23673-44-1; **2b**, 31729-94-9; **2c**, 23673-45-2; **3a**, 23673-46-3; **3c**, 23673-47-4; **5a**, 23668-27-1; **5b**, 31729-99-4; **5c**, 23668-28-2; **5d**, 31730-01-5; **5e**, 31730-02-6; **5f**, 31730-03-7; **5g**, 24905-74-6; **6a**, 31730-05-9; **6b**, 31730-06-0; **7b**, 23755-91-1; **7c**, 31730-08-2; **7e**, 31730-09-3; **8b**, 31730-10-6; **8c**, 31730-11-7; **12a**, 31730-12-8; **12b**, 31790-82-6; **12c**, 31790-83-7; **12d**, 31730-13-9; **13a**, 31730-14-0; **13b**, 31730-15-1; **13c**, 31730-16-2; **13d**, 31730-17-3; **13e**, 31730-18-4; **13f**, 31730-19-5; **13g**, 31730-20-8; **13h**, 31730-21-9; **14a**, 31730-22-0; **14b**, 31730-23-1; 2-methyl-4-(*p*-methoxybenzylidene)oxazol-5-one, 31730-24-2; α-bromo-*N*,*N*-dimethylacrylamide, 31730-25-3.

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The Influence of Reaction Conditions and Stereochemistry on Some Thioacetate Displacements with Carbohydrate Sulfonates[1]

M. H. HALFORD,[2] D. H. BALL,* AND L. LONG, JR.

Pioneering Research Laboratory, U. S. Army Natick Laboratories, Natick, Massachusetts 01760

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The reaction of 1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-apio-L-furanose (**1**) with potassium thioacetate in boiling ethanol gave bis(5-deoxy-1,2-*O*-isopropylidene-α-D-apio-L-furanose-5-yl) disulfide (**2**) in high yield. Deacetylation of the intermediate thiolacetate **6** and subsequent oxidation of the thiol to **2** evidently occurred under these conditions. In aprotic solvents (DMF or acetone), both intramolecular S → O acetyl migration and S acetylation were observed in the reaction of **1** with potassium thioacetate, and a complex mixture of products was obtained. Acid-catalyzed methanolysis of the thiol obtained by reduction of **2** led to migration of the isopropylidene group and the formation of methyl 2,3-*O*-isopropylidene-4-thio-β-D-apio-D-furanoside (**8**). The reaction of methyl 2,3-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-β-D-apio-D-furanoside (**9**) with potassium thioacetate in boiling ethanol gave a mixture of disulfide **12** and monosulfide **13**. In this case, the intermediate thiol is a sufficiently powerful nucleophile to complete with thioacetate ion for **9** and, when thes ame reaction was carried out with 1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-D-xylofuranose (**14**), the monosulfide **15** was obtained in 85% yield. Displacement of the sulfonyloxy group of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-allofuranose was readily effected with potassium thioacetate in DMF to give, in high yield, 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-glucofuranose. Oxidative deacetylation of this compound gave the corresponding gluco disulfide and similar treatment of 3-*S*-acetyl-1,2:5,6-di-*O*-isopropylidene-3-thio-α-D-allofuranose gave the isomeric allo disulfide.

The use of potassium thioacetate in nucleophilic displacements of sulfonyloxy groups was reported first by Owen and coworkers in 1950.[3,4] They found that primary sulfonates reacted readily on heating with 2 equiv of potassium thioacetate in acetone or ethanol to give fairly good yields of thiolacetates. An advantage to the use of ethanol is that potassium thioacetate is very much more soluble in this solvent than it is in acetone; and the secondary mesyloxy groups of 1,4:3,6-dianhydro-2,5-di-*O*-methylsulfonyl-D-mannitol can be displaced by potassium thioacetate in ethanol at 110°[4] to give an L-iditol derivative.[5] Deacetylation was observed in this reaction and the reaction mixture was reacetylated prior to isolation of the product. In view of our results (see below), it is probable that transfer of the acetyl group from initially formed thiolacetate to solvent is a rapid reaction in boiling ethanol, catalyzed by the alkalinity of the medium.

(1) Part VI in a series of publications from this laboratory concerning the chemistry of apiose.

(2) National Academy of Sciences, National Research Council Visiting Scientist Research Associate, 1968–1970.

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