69-8605

MARTIN, Ronald Allen, 1942-

I. SYNTHESIS OF [4.2.2] , [4.2.1] , AND [3.3.1] PROPELLANES. II. SOLVENT EFFECTS IN THE REACTION OF DIETHYLMALONATE ANION WITH STYRENE OXIDE. III. SYNTHESIS OF FIVE- AND SIX-MEMBERED OXYGEN AND SULFUR HETEROCYCLES VIA CONCOMITANT MICHAEL AND DIECKMANN CONDENSATIONS.

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THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

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A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

BY

RONALD ALLEN MARTIN

Norman, Oklahoma

1969

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DISSERTATION COMMITTEE

ACKNOWLEDGEMENTS

The author expresses his appreciation to Dr. Jordan J. Bloomfield for the suggestion of the problems of this study, and for his assistance and encouragement during the course of this task. Acknowledgement is also due the late Dr. Harold Affsprung for his assistance with the hydrogen bonding study in the second portion of this work.

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TABLE OF CONTENTS

Page

LIST OF TABLES

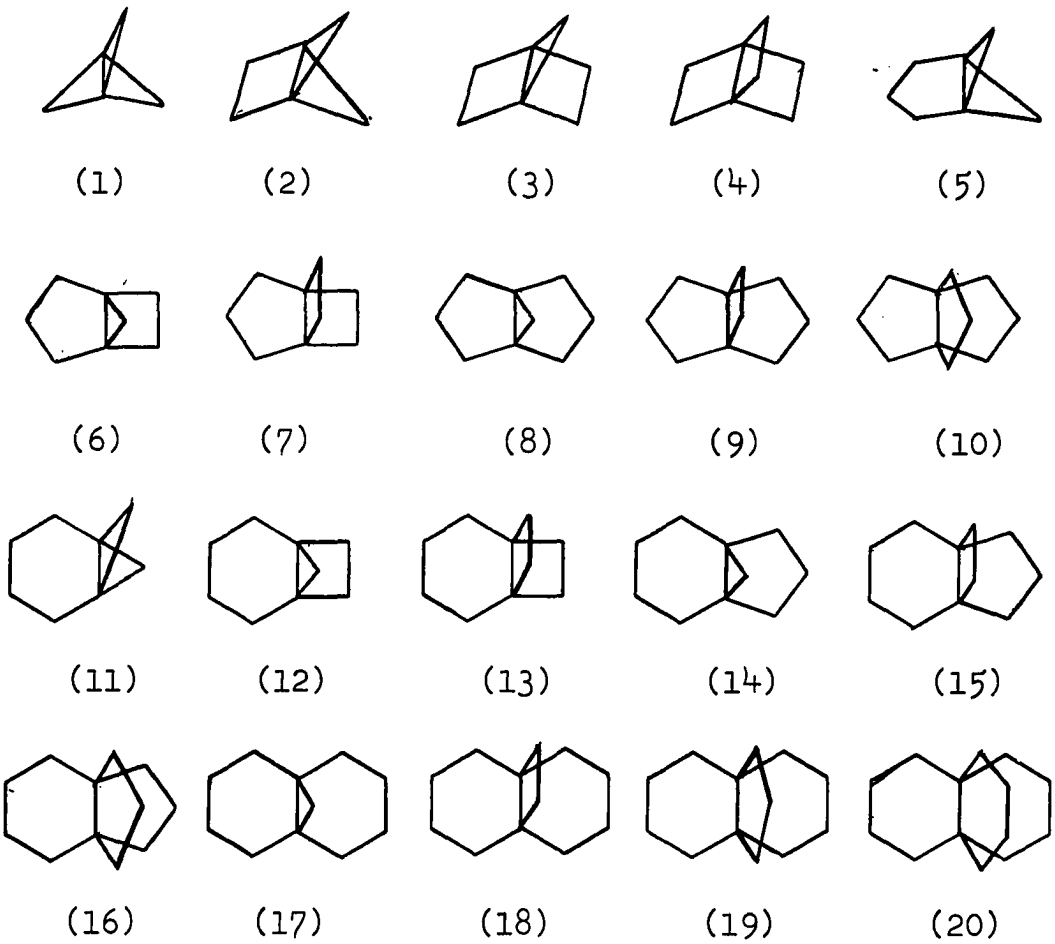
LIST OF ILLUSTRATIONS

I. SYNTHESIS OF [4.2.2], [4.2.1], AND [3.3.1] PROPELLANES

In recent years some members of a theoretically interesting class of compounds have suddenly become accessible. These are propellanes[1] or propelleranes,[2] a class of tricyclic hydrocarbons in which all three rings share a common bridge. A simplification of the rules of tricyclic nomenclature has been suggested for these systems. Compound 1 would be [1.1.1] propellane, a combination of trivial and tricycloalkane nomenclature. Propellane nomenclature has also been applied to tricyclic heterocycles in which all three rings are joined by a common carbon-carbon bond.[1]

The first twenty of these highly strained hydrocarbon skeletons are shown below. Except for propellane 9, the first twelve carbocyclic skeletons are unreported either as tricycloalkanes or as their derivatives.* Only five of the first twenty carbocyclic compounds are reported as unsubstituted tricycloalkanes. Many heterocyclic propellanes have been reported.[1]

*During the course of this work, the syntheses of [3.2.2] and [4.2.2] propellanes, (7) and (13), were reported *via* different routes than the one attempted here for propellane 13.



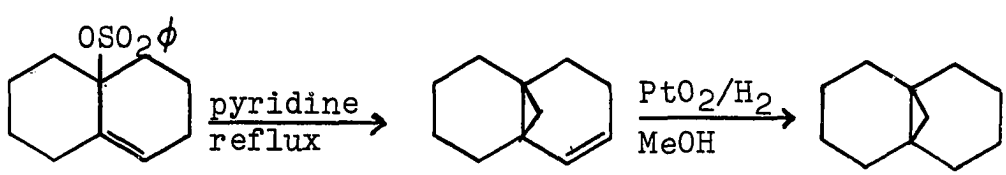
(1) (2) (3) (4) (5)

(6) (7) (8) (9) (10)

(11) (12) (13) (14) (15)

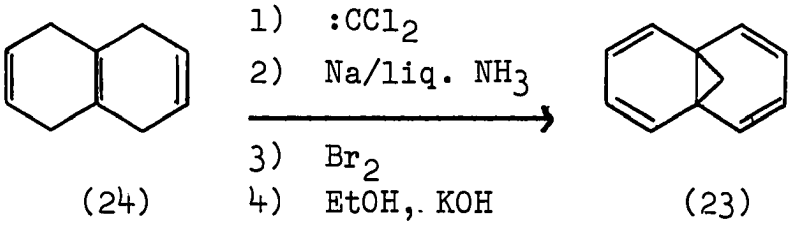
(16) (17) (18) (19) (20)

The synthesis of tricyclo [4.4.1.$0^{1,6}$] undecane, propellane 17, the first to be reported, was described in 1957.[3-4] The solvolysis of benzenesulfonate 21 produced an unsaturated propellane 22 which on hydrogenation yielded propellane 17. This method of solvolysis has been applied in syntheses of other derivatives of propellane 17, including steroids and triterpenoids.[3-11]



(21) (22) (17)

Interest in possible aromatic character of the ten π-electrons of cyclodecapentaene prompted the synthesis of 1,6-methanocyclodecapentaene 23.[12] Dichlorocarbene was added selectively to the central double bond of triene 24, which was then reduced with sodium in liquid ammonia, was brominated and finally was dehydrobrominated with alcoholic potassium hydroxide to produce 1,6-methanocyclodecapentaene 23, which indeed showed extensive π-electron delocalization suggesting structures 25-26.



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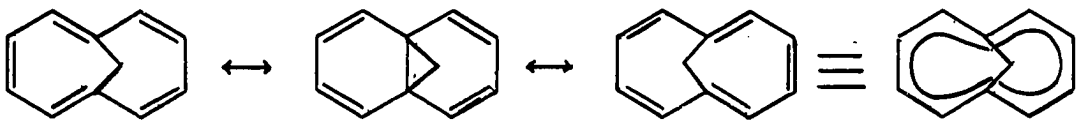
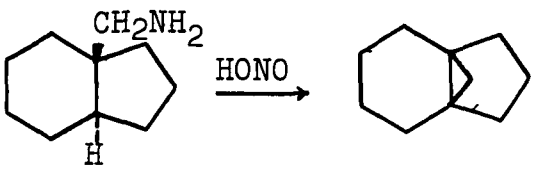


(25) (23) (26)

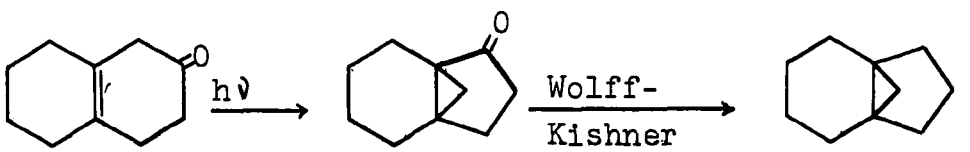
Other derivatives of propellane 17 have been produced by carbene addition[13-15] and by the Simmons-Smith reaction.[16-18] Other steroidal and triterpenoid derivatives are known.[19-22]

Investigation of the reaction of trans-8-hydrindanylcarbinylamine 27 and nitrous acid revealed tricyclo [4.3.1.$0^{1,5}$] decane, propellane 14, as the major product.[23] Application of this and another carbonium ion method have provided steroidal propellane derivatives related to 14.[23-24] Alternate syntheses of propellane 14 *via* dihalocarbene or diazomethane addition[25-26]

and by photochemical rearrangement of β,γ-unsaturated ketone 28[27] have proved interesting.

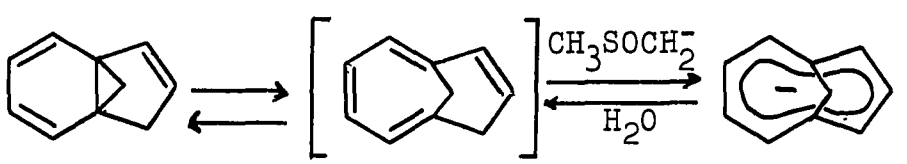


(27) (14)



(28) (14)

Almost simultaneously, reports appeared of the preparation of 1,5-methanocyclononatetraenyl anion 29, another methano-bridged ten π-electron aromatic specie.[26,28-29] Each route proceeded to triene 30 by the initial introduction of a cyclo-propane ring into a dihydroindane system either by the Simmons-Smith reaction[28] or dichlorocarbene addition.[26] 1,5-Methano-cyclononatetraenyl anion 29 was generated by treatment of

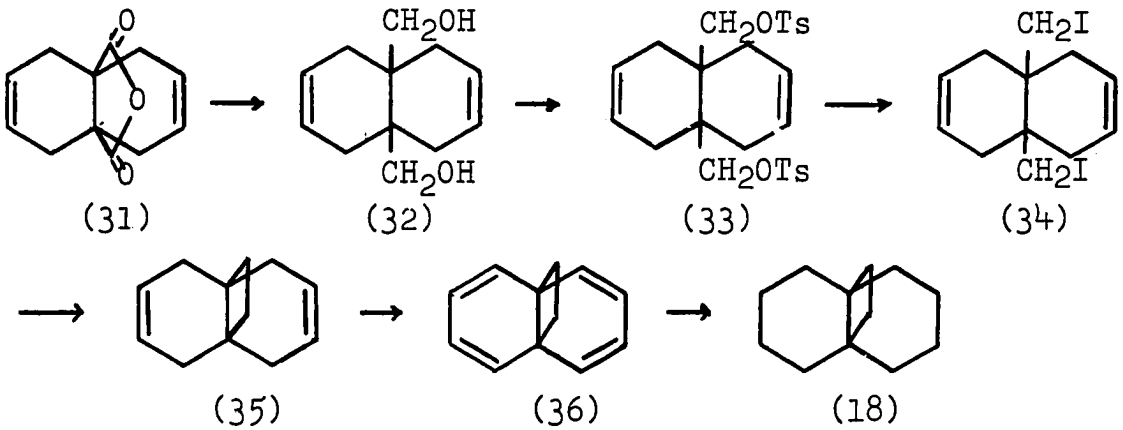


(30) (29)

compound 30 with sodium methylsulfinylmethylide. Ring current was evident from the nmr and uv spectra. Several other propel-lane 14 derivatives have been reported. They were prepared by

the Simmons-Smith reaction,[17-18,30-31] from diazoacetates,[13,32] and from dichlorocarbenes.[30,33]

Continued interest in the ten π-electrons of cyclodecapentaene led to the synthesis of tricyclo [4.4.2.$0^{1,6}$] dodecane, propellane 18, by two independent routes. Vogel and co-workers[34] reduced anhydride 31 to diol 32 then prepared ditosylate 33. Diiodide 34 was easily formed and ring closure was effected with phenyllithium to form 1,4,5,8,9,10-hexahydro-9,10-ethano-naphthalene (35). Bromination followed by dehydrobomination in quinoline produced tetraene 36. Hydrogenation yielded propellane 18.

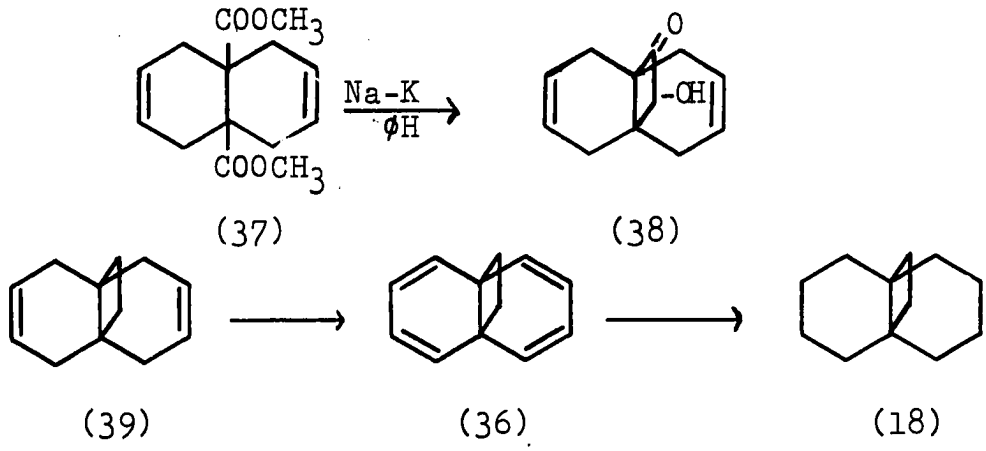


(31) (32) (33) (34)

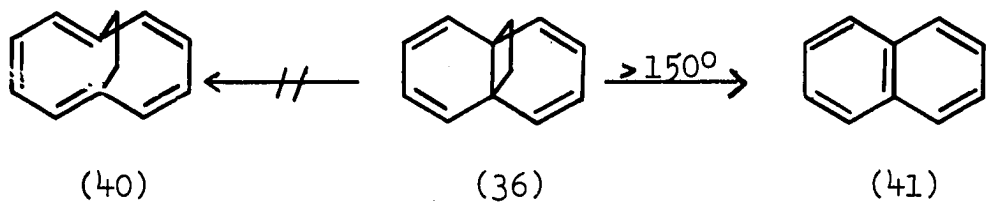
(35) (36) (18)

An alternate route described by Bloomfield and Irelan[2] included a novel method of closure of diester 37 to a four-membered ring, compound 38, via an acyloin condensation using sodium-potassium alloy. Acyloin 38 was reduced to diene 39, was subsequently brominated, then was dehydrobominated with potassium t-butoxide in dimethylsulfoxide to give tetraene 36.

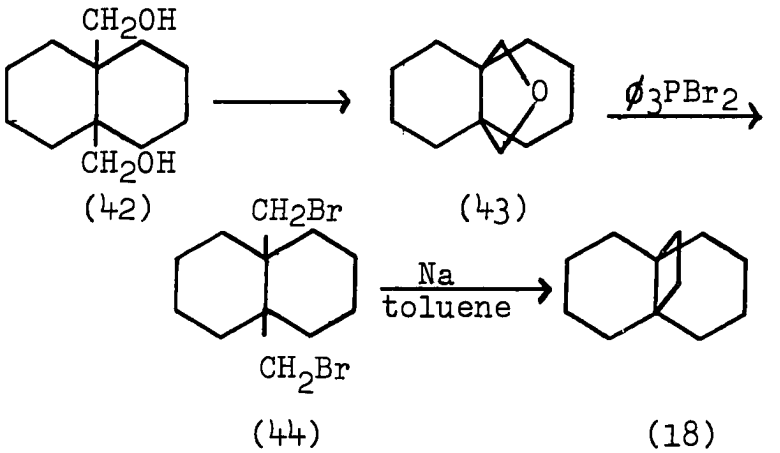
Hydrogenation yielded propellane 18.



Both laboratories reported that tetraene 36 could not exist in tautomeric equilibrium with the bridged cyclodecapentaene 40, instead 36 decomposed on heating to produce naphthalene and ethylene.

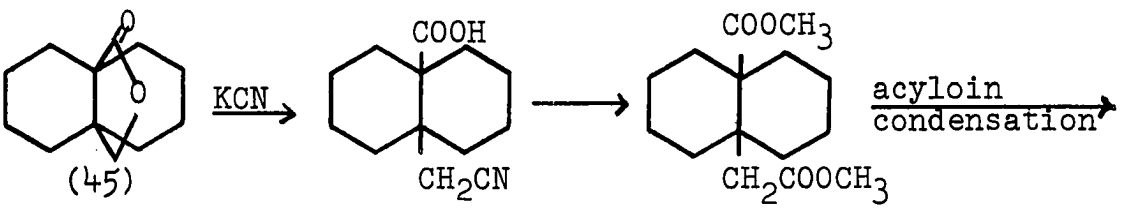


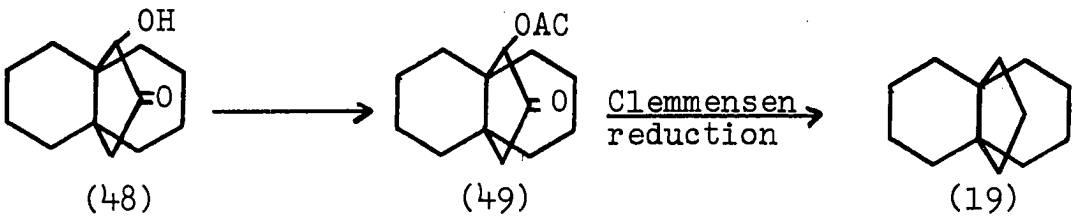
A third route to propellane 18 has been demonstrated with the cyclization of diol 42 to produce a tetrahydrofuran derivative, 43.[1] Treatment of compound 43 with triphenylphosphine dibromide led to dibromide 44 which was cyclized with sodium in toluene giving propellane 18. An alternate and longer route is also described.[1]



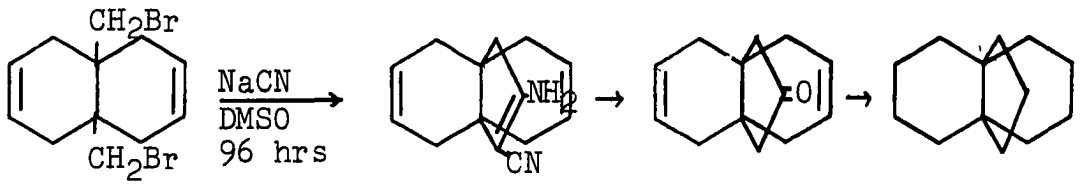
Tricyclo[4.4.2.$0^{1,6}$]3,8,11-dodecatriene has recently been reported.[35-36] A derivative of the [4.4.2] propellane skeleton is the tetramer of cyclohexyne.[37-38]

A communication has described the synthesis of propellane 19, tricyclo[4.4.3.$0^{1,6}$]tridecane, proceeding through the opening of lactone 45 with potassium cyanide.[39] Nitrile 46 was hydrolyzed and esterified, giving a diester, 47, which was cyclized by an acyloin condensation. Acyloin 48 was acetylated and compound 49 was reduced to propellane 19.





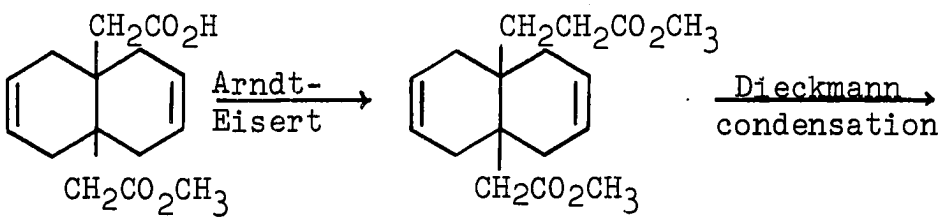
A different procedure utilized the Thorpe condensation of an intermediate dinitrile produced from dibromide 50.[1] Acid hydrolysis transformed 51 into ketone 52 which was hydrogenated and subjected to a Wolff-Kishner reduction to give propellane 19.



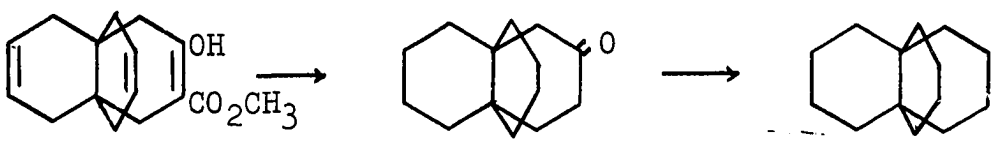
(50) (51) (52) (19)

Related methods have yielded tricyclo[4.4.3.$0^{1,6}$]tridecane derivatives.[40-44]

Propellane 20, tricyclo[4.4.4.$0^{1,6}$]tetradecane, has been prepared in a similar manner.[41,45] Arndt-Eisert homologation of half-ester 53 led to the diester 54. Dieckmann cyclization gave the expected keto-ester 55, which was hydrolyzed with base and hydrogenated which led to ketone 56. Wolff-Kishner reduction of ketone 56 gave propellane 20.

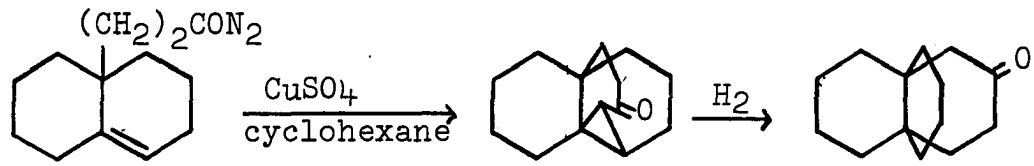


(53) (54)



(55) (56) (20)

An alternate route[45] converted diazoketone 57 into cyclopropane ketone 58 which led to ketone 56 on hydrogenation. Ketone 56 was reported earlier by Snatzke and Zanati.[42]

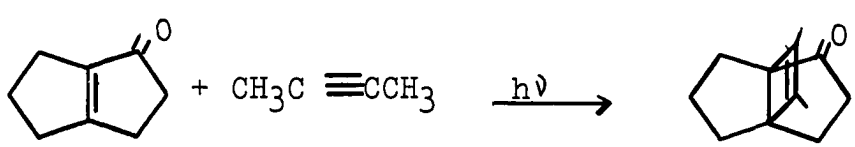


(57) (58) (56)

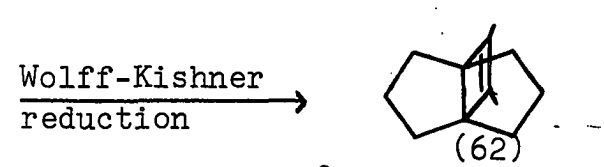
The tricyclo[4.4.4.$0^{1,6}$]tetradecane skeleton occurs also in several quinones obtained in Diels-Alder reactions,[46-48] as well as several acyloin products.[49]

The remaining carbocyclic propellanes are unknown,* although derivatives of some of these have been synthesized.

Photochemical induced 1,2-cycloaddition of 2-butyne to α,β-unsaturated ketones has been successful in the preparation of derivatives of propellanes 9 and 15.[50-51] The light catalyzed addition of 2-butyne (59) to bicyclo[3.3.0]oct-1(5)-en-2-one(60) gave adduct 61 which was reduced via a Wolff-Kishner reaction to produce the tricyclic olefin 62, a derivative of propellane 9.



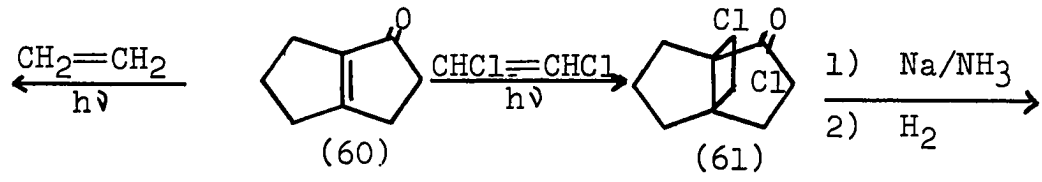
(60) (59) (61)



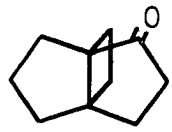
(62)

*See footnote p 1, Reference 89.

More derivatives were obtained with the photochemical addition of ethylene or dichloroethylene to ketone 60. Subsequent dehalogenation of the dichloroadduct 61 followed by hydrogenation gave ketone 62.[51]



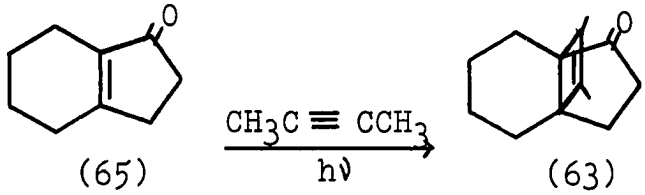
(60) (61)



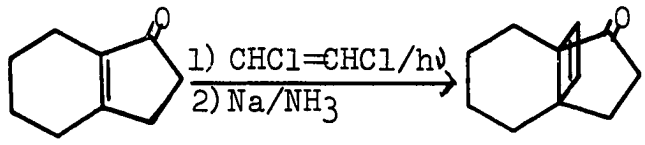
(62)

Perchloro-(4,8-dimethylenetricylo[3.3.2.$0^{1,5}$]deca-2, 6-diene is another propellane 9 derivative.[52]

Similar reaction sequences provided propellane 15 derivatives 63, 64 from ketone 65.[50,53]

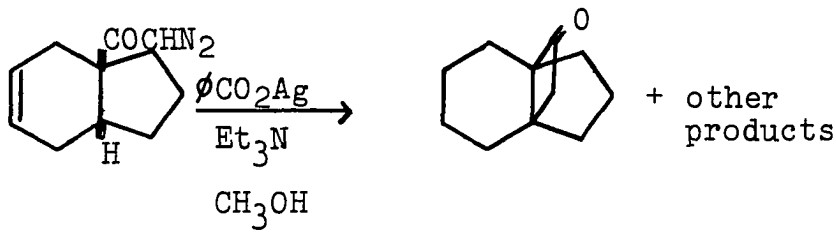


(65) (63)



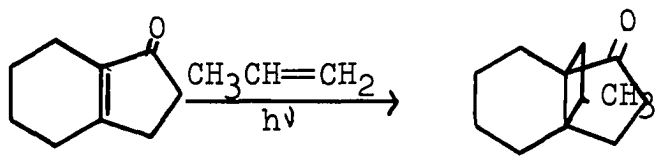
(65) (64)

Ketone 66, another derivative, was detected among other products from the insertion of diazoketone 67 when treated with silver benzoate and triethylamine.[54]



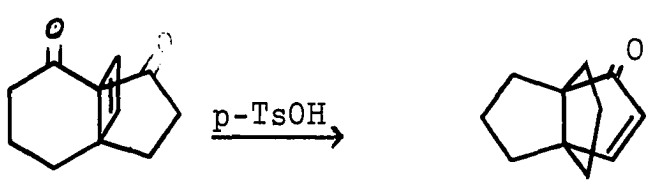
(67) (66)

In connection with efforts to develop new methods in the synthesis of Lycopodium alkaloids, model compound 68 added propene readily to give propellane ketone derivative 69.[55]



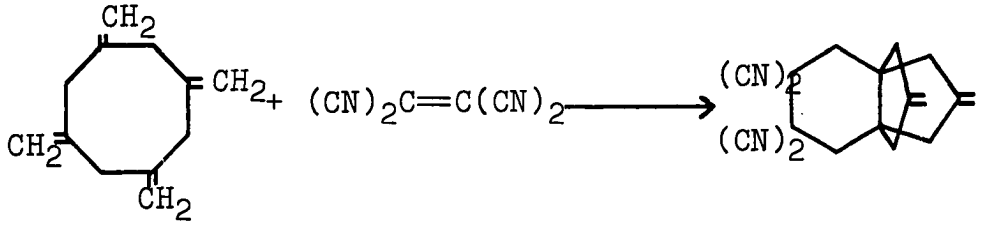
(68) (69)

Occasionally a propellane derivative may be converted to a derivative of another propellane by rearrangement. For example, acid catalysis transformed ketone 64 to ketone 70, a derivative of propellane 10.[53] Two other derivatives of tricyclo[3.3.3.$0^{1,5}$]undecane also has been synthesized.[56-57]



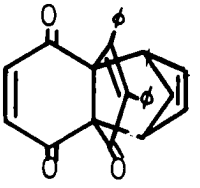
(64) (70)

Tetracyanoethylene 71 has been shown to undergo a 1,7-addition with allene tetramer 72 to form a tricyclo[4.3.3.$0^{1,6}$]dodecane derivative, 73, of propellane 16.[58]



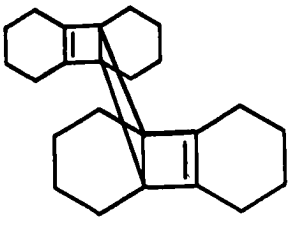
(72) (73)

Another derivative, 74, was obtained in a Diels-Alder reaction.[59]



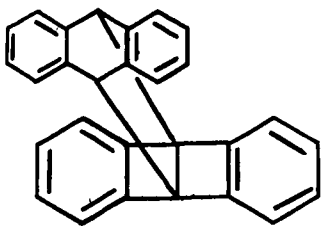
(74)

A tetramer of cyclohexyne also contains the tricyclo-[4.2.2.$0^{1,6}$]decane skeleton. Structure 75 has been suggested but not rigorously proved.[37-38]

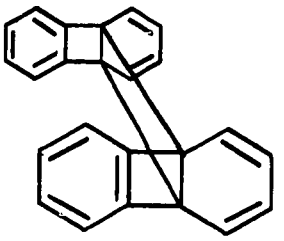


(75)

Other "Dewar" benzene derivatives of propellane 13 have been reported, compounds 76a[60-61] and 76b.[62]



(76a)



$(76b)^{-}$

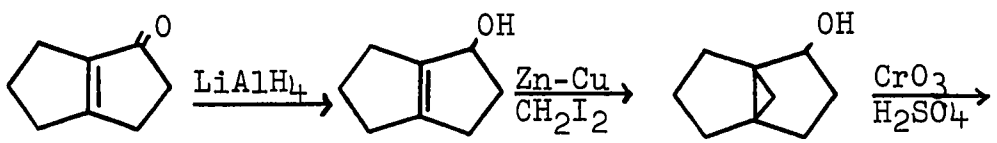
Examination of the unreported propellane hydrocarbons suggested several interesting propellanes (8, 12, 13) that might be synthesized either as hydrocarbons or their derivatives.

RESULTS AND DISCUSSION

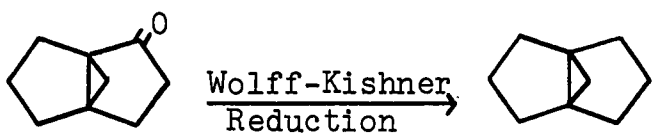
Part I

[3.3.1] Propellane

Bicyclo[3.3.0]oct-1(5)-en-2-one (60), previously used in the preparation of propellane derivatives,[50-51] suggested a route to a [3.3.0] propellane *via* introduction of a cyclopropyl group. Careful reduction of 60 with lithium aluminium hydride at -5° provided the allylic alcohol 77, an olefinic compound containing a hydroxyl group in close proximity to the site of unsaturation, a factor that is known to enhance[63] the Simmons-Smith[64] reaction. Thus tricyclo[3.3.1.$0^{1,5}$]nonan-2-ol (78) was obtained, which exhibited the requisite spectral properties. The *cis*-directing effects[63,65-66] of a neighboring hydroxyl group participating in a Simmons-Smith reaction suggest that



(60) (77) (78)



(79) (8)

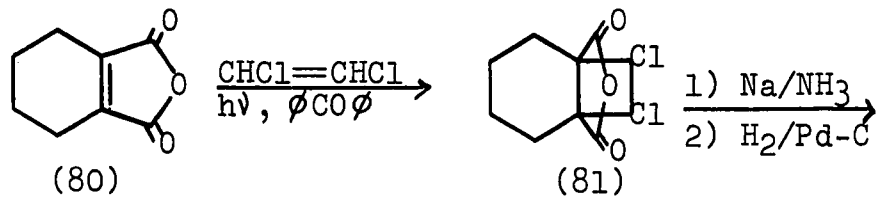
the hydroxyl and cyclopropyl groups are cis in 78. This is substantiated by the position of the chemical shifts of the cyclopropyl protons (δ 0.98, 0.47 ppm), for the cyclopropyl proton cis to a α-hydroxyl group in bicyclo[3.1.0]alkanes is shifted downfield by deshielding.[67]

Oxidation of alcohol 78 with Jones' Reagent[68] provided ketone 79, which underwent a Wolff-Kishner reduction to propellane 8. Tricyclo[3.3.1.$0^{1,5}$]nonane (8) exhibited infrared absorptions at 3065, 3005, 1010 cm^{-1} (cyclopropyl) and nmr absorptions at δ 1.6 and 0.45 ppm (cyclopropyl).

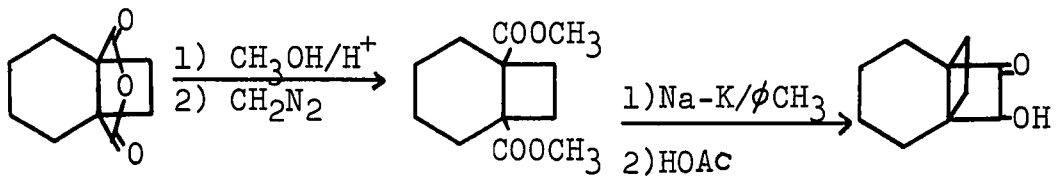
Part II

Derivatives of [4.2.2] Propellane

Photochemical 1,2-cycloadditions of olefins to α,β-unsaturated ketones has also provided propellane derivatives.[50-51] Anhydrides, although used less often than unsaturated ketones in 1,2-cycloaddition reactions, provide more diversified derivatives than ketones. The following scheme was devised to synthesize derivatives of [4.2.2] propellane, beginning with the photochemical-induced addition of dichloroethylene to anhydride 80, followed by reduction, esterification, and finally ring closure via an acyloin condensation.



(80) (81)

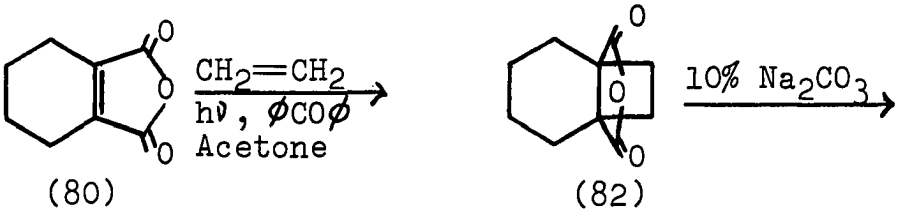


(82)

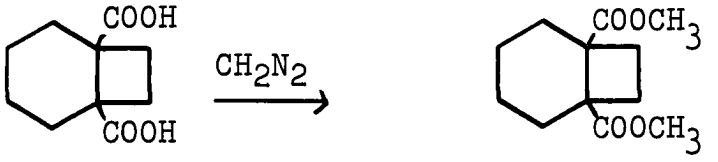
Anhydride 80 successfully added dichloroethylene when photolyzed but the low yield and difficulty of isolation of 81 encouraged more experimentation. The photoaddition of alkynes and alkenes to maleic anhydride derivatives[69-73] and ethylene to α,β-unsaturated ketones[74-76] suggested an alternate

route to anhydride 82.

The benzophenone sensitized photochemical addition of ethylene to anhydride 80 went smoothly in 85% yield, giving 82. Hydrolysis gave diacid 83 which upon esterification with diazomethane gave 84 in excellent overall yield.

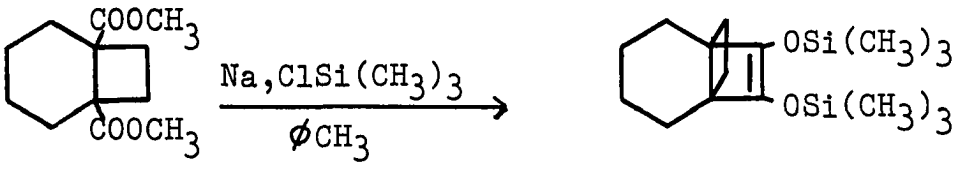


(80) (82)



(83) (84)

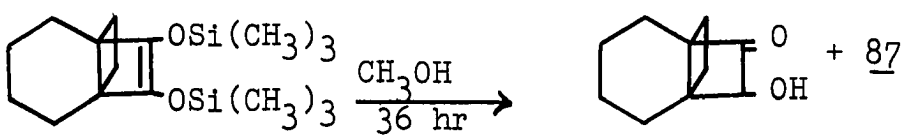
Compounds 82-84 have been prepared earlier by a tedious and much less efficient method.[77] Ring closure of diester 84 was accomplished with an acyloin condensation which has only recently become generally applicable in the synthesis of four-membered rings.[2,49,78-80] Isolation of the intermediate enediolate as a derivative of trimethylsilyl ether 85 occurred when chlorotrimethylsilane was introduced into the reaction mixture. It is unlikely such a strained system



(84) (85)

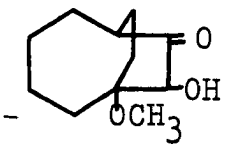
could be formed without the use of some means of forcing the reaction to completion, but once the cyclobutene derivative 85 is formed, it should be relatively stable. Thermal ring opening of cyclobutenes proceed in conrotatory fashion but this event is unlikely with 85 for it would lead to a cis-trans-1,3-bicyclooctadiene derivative, a very unstable and unlikely molecule, complicated by two violations of Bredt's rule.

Hydrolysis of silyl ether 85 with methanol led to a mixture of two compounds, one a hydroxyketone 86 whose infrared absorption is characteristic of cyclobutanones. The other compound is a hydroxyketone containing a methoxyl group, as indicated by its IR and nmr spectra. Examination of an nmr spectrum conducted in dimethyl sulfoxide-d_6 revealed a secondary hydroxyl group. It also appears that 86, on standing with methanol, decomposes to 87. This information suggests structure 87a⁻ or 87b, which could result from ring cleavage with methanol.

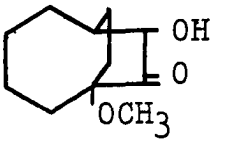


(85) (86)

Structure 87a has been tentatively chosen for the compound on the basis of a multiplet appearing at δ 2.6 ppm which can be assigned to the bridgehead proton alpha to the carbonyl group.

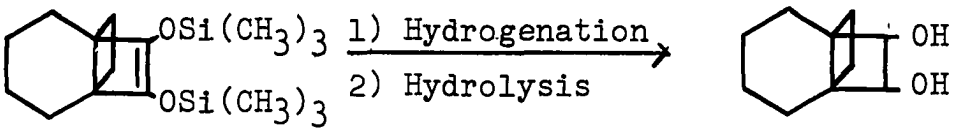


(87a)



(87b)

To avoid rearrangement, an alternate scheme was designed which commenced with the hydrogenation of 85 and hydrolysis to give diol 88. Low pressure hydrogenation was attempted with several catalyst/solvent systems with little success. In addition to unchanged 85, another compound appeared with a band in the IR spectrum at 1775 cm^{-1}, which corresponded to a similar

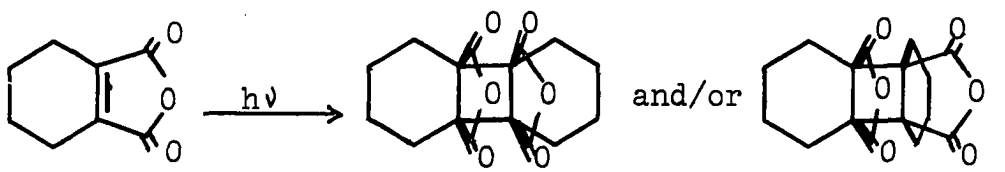


(85) (88)

band for the C=O of cyclobutanone 86. Rather than hydrogenation, partial hydrogenolysis of the O-Si bond was suspected. An attempt at complete hydrogenolysis with five times the required catalyst produced approximately 60% of suspected 86. Indications were that some type of poisoning of the catalysts had occurred.

One routine irradiation experiment with ethylene and cyclohex-1-ene-1,2-dicarboxylic acid anhydride gave an unexpected result when the dimer of cyclohex-1-ene-1,2-dicarboxylic acid anhydride (89) was isolated. Apparently insufficient ethylene, during the course of the reaction, resulted in dimerization as well as the expected product. It is interesting

speculation whether the dimer is cis-syn-cis (89a) or cis-anti-cis (89b) or both.



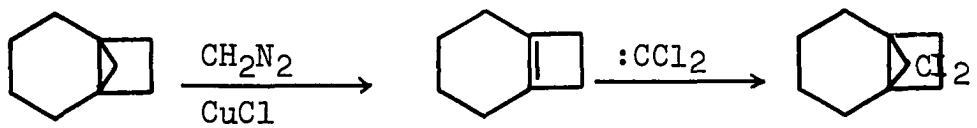
(80) (89a) (89b)

Dimerization of α,β-unsaturated ketones generally produces[81-2] anti-structures, especially if the reaction is sensitized and conducted in polar solvents.[83] These results support the prediction that structure 89b is the correct dimer.

Part III

Derivatives of [4.2.1] Propellane

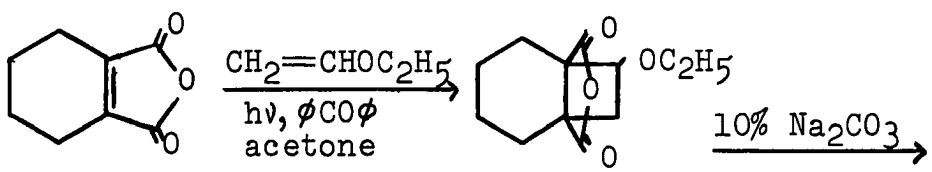
Bicyclo[4.2.0]octane-1,6-dicarboxylic acid (83) suggested a facile route to an interesting bicyclic olefin 89 reported earlier[84-85] by two elaborate processes. Bisdecarboxylation with lead tetraacetate gave bicyclo[4.2.0]oct-1(6)-ene (90) in about 32% yield. Olefin 90 seemed a likely intermediate for the synthesis of tricyclo[4.2.1.$0^{1,6}$]nonane (12) or a derivative. Methylene addition *via* diazomethane catalyzed by copper(I) chloride and dichlorocarbene, generated by several methods, was attempted with little success.



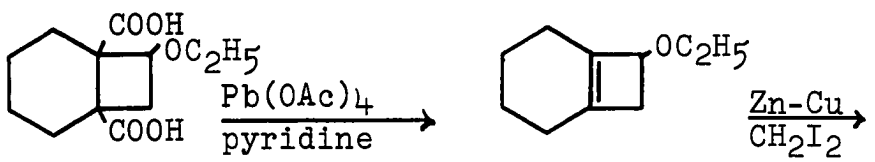
(12) (90)

One reaction of 90 with dichlorocarbene, generated from ethyl trichloroacetate and sodium methoxide, gave an unstable crystalline compound, 91, which upon elemental analysis, suggested the addition of two equivalents of dichlorocarbene. Hydrogen chloride was evolved on standing or application of heat, giving 92, which analyzed as $C_{10}H_{11}Cl_3$. The elemental analysis of 91, although poor, suggested $C_{10}H_{12}Cl_4$ rather than $C_9H_{12}Cl_2$ for the monoadduct.

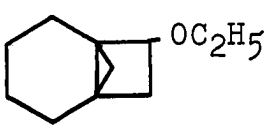
These results necessitated an alternate route to propellane 12. The initial success of cycloaddition of ethylene to cyclohex-1-ene-1,2-dicarboxylic acid anhydride (80) gave impetus to an alternate route. Ethyl vinyl ether was added photochemically to anhydride 80. The crude anhydride adduct was hydrolyzed to diacid 93 without purification. Olefin 94 was obtained from the bisdecarboxylation of diacid 93. A



(80)



(93) (94)



(95)

Simmons-Smith reaction gave 7-ethoxytricyclo[4.2.1.$0^{1,6}$]nonane (95), a derivative of propellane 12. Again the neighboring saturated oxygen group facilitated the methylene addition to olefin 94. The infrared spectrum exhibited characteristic cyclopropane absorptions in the infrared region (3050 and 3010 cm^{-1}). The nmr spectrum, which included clear assignments

of chemical shifts of an ethoxy group, displayed several more complex splitting patterns for the various types of methylene protons. The cyclopropane protons might be expected to appear as basic AB doublets considering their different environments. The actual spectrum displayed complex multiplets between δ 0.87 and 0.29 ppm which could be roughly described as two sets of quartets, with perhaps some extraneous contribution. Simplicity aside, the complex patterns of the very strained molecule can be explained by different environments of the two cyclopropyl protons one of which is affected by the adjacent cyclobutane ring and cis-ethoxy group and the other by the cyclohexane ring. This long-range coupling could produce a more complicated spectrum. It is probable the cyclopropane ring and the ethoxy group are cis as expected in Simmons-Smith reactions, but there is a possibility of some trans-product being formed, for the reaction is not entirely stereospecific. If this were true, further complications would enter the nmr spectrum.

SUMMARY

Several new propellanes, a class of tricyclic hydrocarbons in which all three rings share a common bridge, have been synthesized either as hydrocarbons or as derivatives containing the basic tricyclic skeleton. Among these are [3.3.1] propellane (tricyclo[3.3.1.$0^{1,5}$]nonane) and derivatives of [4.2.1] and [4.2.2] propellane. Other related compounds were obtained during the course of this study.

EXPERIMENTAL

All melting and boiling points are uncorrected. Elemental analyses are by A. Bernhardt, Microanalytical Laboratories, Mülheim (Ruhr), West Germany. Nmr spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. IR spectra were obtained with a Beckman IR-8 Instrument.

Bicyclo[3.3.0]oct-1(5)-en-2-ol (77). To a one liter 3-necked round bottom flask, fitted with a mechanical stirrer, addition funnel, and calcium chloride drying tube were added 12.0 g (0.316 mole) of lithium aluminium hydride and 400 ml of anhydrous ether. The flask was cooled in a -5° cold bath and stirred as 73.2 g (0.60 mole) of bicyclo[3.3.0]oct-1(5)-en-2-one (60)* was added quickly within 10 min. The flask was kept cold and stirred for 4.5 hr. Water (24 ml) was cautiously added and the mixture stirred overnight. The precipitate was filtered and washed with ether. The ethereal solutions were combined, dried (Na_2SO_4), filtered, concentrated, and distilled giving 53.3 g (72%) of bicyclo[3.3.0]oct-1(5)-en-2-ol (77): bp 57-63°/0.8-0.9 mm; IR (film) 3500-3200 cm^{-1} (alcohol OH); nmr (CCl_4) δ 4.70-4.35 (broad s, 2), and 2.20 ppm (broad s, 10); nmr (neat) δ 5.07 (broad s, 1, C<u>H</u>OH), 4.75-4.40 (mound, 1, O<u>H</u>), 2.20 ppm (broad s, 10 C<u>H</u>$_2$). Glc analysis revealed a 10%

*Generous sample courtesy of Badische Anilin & Soda Fabrik, Germany.

impurity of shorter retention time than bicyclo[3.3.0]oct-1(5)-en-2-ol (77), which failed to separate upon distillation with a Nestor/Faust spinning band column. Compound 77 decolorized sufficient bromine water and gave a positive tetranitromethane test.

Tricyclo[3.3.1.$0^{1,5}$]nonan-2-ol (78). To a 500 ml 3-necked round bottom flask, equipped with a condenser, dropping funnel, and magnetic stirrer were added zinc-copper couple prepared[86] from 53.6 g (0.82 mole) of powdered zinc (Fisher) and 300 ml anhydrous ether. The system was placed under a blanket of nitrogen and 0.15 g iodine and 172.8 g (0.645 mole) of methylene iodide were added to the stirred mixture. A heat lamp was used to initiate the reaction until the ether refluxed unaided. After the initial reaction had subsided, heat was applied and the contents were heated under reflux for 0.5 hr. Reflux was continued as 37.8 g (0.30 mole) of bicyclo[3.3.0]oct-1(5)-en-2-ol (77) and 70 ml of anhydrous ether were added slowly in 0.5 hr. The contents were refluxed 2 hr additional. The flask was cooled and approximately 70 ml of saturated ammonium chloride solution was added cautiously to the reaction mixture. The residue was filtered and washed with ether. The ethereal solution was washed with saturated potassium carbonate solution (4 x 120 ml), saturated sodium chloride solution (2 x 120 ml), and dried ($MgSO_4$). The solution was concentrated and combined with 100 ml of saturated sodium methoxide in methanol. The methanolic solution was stirred under a blanket of nitrogen

overnight and then poured into 600 ml of anhydrous ether. The ether was extracted with saturated sodium chloride solution until the wash solution was no longer basic. The ethereal solution was dried ($MgSO_4$), filtered, concentrated, and fractionally distilled, giving 36.05 g (87.1%) of oil which contained some starting material. Purer fractions were combined and redistilled: bp 64°/0.55 mm; n_D^{25} 1.5020; IR (film) 3550-3150 (alcohol OH), 3070, 3010 (cyclopropane); nmr (CCl_4) δ 4.40-4.08 (m, 2, CHOH and CHOH), 2.3-1.3 (m, 10, CH), 0.98 (d, 1, J = 6 Hz, Δ-H), and 0.47 ppm (d, 1, J = 6 Hz, Δ-H).

Anal. Calcd for $C_9H_{10}O$: C, 78.21; H, 10.21. Found: C, 78.13; H, 10.17.

Tricyclo[3.3.1.$0^{1,5}$]nonan-2-one (79). To a 125 ml 3-necked round bottom flask fitted with thermometer, dropping funnel, and magnetic stirrer, were added 6.89 (0.0507 mole) of tricyclo-[3.3.1.$0^{1,5}$]nonan-2-ol (78) and 50 ml of acetone. Jones' Reagent[68] (approximately 20 ml) prepared from 17.5 g (0.175 mole) of chromium trioxide, 75 ml water, and 15 ml concentrated sulfuric acid, was added dropwise to the stirred solution as the internal temperature was maintained at 5-10° with an ice-water bath. The oxidant was added until the color was slow to disperse, then the mixture was stirred for 20 min additional. Solid sodium bisulfite was carefully added until the mixture was neutral. The acetone layer was decanted and combined with acetone washes (2 x 25 ml) from the residue. The acetone solution was concentrated to about 15 ml with a

rotary evaporator and then was added to 25 ml of saturated sodium chloride solution. This solution was extracted with ether (2 x 20 ml). The ethereal solution was dried (Na_2SO_4), filtered, concentrated, and distilled in two fractions, bp 59.5-61.0°/0.7 mm and 63.0-64.0°/0.8 mm, giving 4.96 g (71.9%) of tricyclo[3.3.1.$0^{1,5}$]nonan-2-one (79): n_D^{20} 1.5034; IR (film) 3070, 3000 (cyclopropane), 1715 (ketone C=O); nmr (CCl_4) δ 2.8-1.55 (m), 1.46 (d, 1, $\underline{J}$ = 6 Hz, Δ-$\underline{H}$), and 1.23 ppm (d, 1, $\underline{J}$ = 6 Hz, Δ-$\underline{H}$).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.22; H, 8.89.

Tricyclo[3.3.1.$0^{1,5}$]nonane (8). A mixture of 2.68 g (0.02 mole) of tricyclo[3.3.1.$0^{1,5}$]nonan-2-one (79), 35 ml of diethylene glycol, 0.5 g potassium hydroxide, and 3.0 ml of hydrazine (95%, Eastman) was refluxed for 6 hr in a 50 ml round bottom flask fitted with a chilled-water condenser. The mixture was cooled and extracted with pentane (4 x 30 ml). Most of the pentane was removed by distillation through a Vigreaux column. The concentrate was placed on 15 g neutral alumina and was eluted with 150 ml of pentane. The pentane was removed by distillation through a Vigreaux column and careful concentration with a rotary evaporator, giving 0.4 g (16.4%) of tricyclo[3.3.1.$0^{1,5}$]nonane (8); n_D^{25} 1.4750; IR (film) 3065, 3005, and 1010 cm^{-1} (cyclopropane); nmr (CCl_4) δ 1.6 (m, 12, $C\underline{H}_2$) and 0.45 ppm (s, 2, $\Delta\underline{H}$).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.62; H, 11.29.

Bicyclo[4.2.0]octane-1,6-dicarboxylic acid anhydride (82). In a 750 ml 3-necked Pyrex irradiation vessel fitted with a fritted glass bubbler for an ethylene inlet, magnetic stirrer, and calcium chloride drying tube, were placed 30.4 g (0.2 mole) of cyclohex-1-ene-1,2-dicarboxylic acid anhydride (80), 5.0 g benzophenone, and 725 ml of acetone. Ethylene was bubbled gently through the stirred solution during 11-20 hr irradiation with a Hanovia 200 watt mercury arc quartz immersion lamp cooled with 0° chilled water. The internal temperature was 5-10°. The solution was concentrated, the solid recrystallized from ethyl acetate-hexane, giving 30.6 g (85.0%) of bicyclo[4.2.0]-octane-1,6-dicarboxylic acid anhydride (82): mp 106.3-110.0° (sample recrystallized for analysis, mp 108.5-109.4°) [lit.[77] mp 111.0-111.5°]; IR (KBr) 1850 and 1790 cm^{-1} (anhydride C=O); nmr (CCl_4) δ 2.34 (s, 4, cyclobutane), 1.88 (m, 4), and 1.5 ppm (m, 4).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.50; H, 6.79.

Bicyclo[4.2.0]octane 1,6-dicarboxylic acid (83). A magnetically stirred mixture of 30.6 g (0.17 mole) of bicyclo[4.2.0]-octane-1,6-dicarboxylic acid anhydride (82) and 150 ml of aqueous 10% sodium carbonate was heated with a steam bath until solution was effected. The solution was cooled and acidified with concentrated hydrochloric acid. The solid diacid was filtered, washed with water, and dried, giving 30.5 g (90.6%) of bicyclo[4.2.0]octane 1,6-dicarboxylic acid; mp 169-70°;

recrystallized from ethanol-water, mp 164.2-164.8° [lit.[77] 159° recrystallized from water]; IR ($CHCl_3$) 3500-3000 (acid OH) and 1705 cm^{-1} (acid C=O).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.43; H, 7.32.

Dimethylbicyclo[4.2.0]octane-1,6-dicarboxylate (84). Bicyclo[4.2.0]octane-1,6-dicarboxylic acid (83) (19.8 g, 0.1 mole) was esterified with diazomethane, giving 21.6 g (95.3%) of dimethylbicyclo[4.2.0]octane-1,6-dicarboxylate (84): bp 90-92°/0.4 mm; n_D^{20} 1.4771; [lit.[77] bp 107°/1.5 mm; n_D^{20} 1.4750]; IR (film) 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 3.57 (s, 6, OCH_3), and 2.5-1.4 ppm (m, 12, CH_2).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.25; H, 8.02. Found: C, 63.44; H, 7.89.

7,8-Di[trimethylsiloxy]tricyclo[4.2.2.$0^{1,6}$]dec-7-ene (85). Approximately 750 ml of dry toluene (refluxed overnight with and distilled from calcium hydride) was distilled directly into a two liter 3-necked round bottom flask fitted with a sintered glass disc*, condenser, mechanical stirrer, nitrogen inlet, and addition funnel. The system was swept with nitrogen and maintained under a nitrogen blanket as the toluene was brought to reflux. Clean sodium (0.66 g-atom, 15.18 g) was added in small pieces and dispersed with a 5000 rpm stirrer. Chlorotrimethylsilane (40 g) was added. A mixture of 33.9 g

*Similar to a commercial flask, Cat. No. LG-7950, Lab Glass, Inc.

(0.15 mole) of dimethyl bicyclo[4.2.0]octane-1,6-dicarboxylate (84), 41.5 g (a total of 0.75 mole) of chlorotrimethylsilane, and 40 ml of toluene was added in 2.5 hr with high speed stirring. The stirrer was slowed and the mixture was refluxed 26 hr. The flask was cooled and the toluene was freed of unreacted sodium and other debris by filtration through the sintered glass bottom of the flask. The toluene solution was concentrated in vacuo, and distilled, giving 17.54 g (37.6%) of 7,8-di[trimethyl]siloxy tricyclo[4.2.2.0^{1,6}]dec-7-ene (85); bp 85-86.5°/0.05 mm; n_D^{20} 1.4666; IR (film) 1695 cm^{-1} (C=C); nmr (CCl_4) δ 1.95-1.2, broad singlets at 1.84 and 1.31 (12, CH_2) and 0.18 ppm (s, 18, $SiCH_3$).

Anal. Calcd for $C_{16}H_{30}O_2Si_2$: C, 61.88; H, 9.74; Si, 18.09. Found: C, 62.09; H, 9.57; Si, 18.00, 17.89.

Hydrolysis of 7,8-Di[trimethylsiloxy]tricyclo[4.2.2.0^{1,6}]-dec-7-ene (85). Dry methanol (110 ml) and 17.5 g (0.056 mole) of 7,8-di[trimethylsiloxy]tricyclo[4.2.2.0^{1,6}]dec-7-ene (85) were mixed and stored at room temperature for 36 hr. The methanol was removed at room temperature with a water aspirator, giving 11.7 g of pink oil. The infrared spectrum indicated the desired hydroxycyclobutanone derivative was a minor component. A portion (6.7 g) of the oil was placed in a refrigerator for several days which induced partial crystallization. Fluffy white crystals were collected and recrystallized from hexane-benzene, giving 1.3 g: mp 104-106°; recrystallized again from hexane-benzene; mp 107.7-108.6°; IR (KBr)

3340 (OH) and 1715 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 3.73 (s, 1, C<u>H</u>OH), 3.5 (s, 1, CHO<u>H</u>), 3.29 (s, 3, $OC\underline{H}_3$), and multiplets centered at 2.6, 2.13, and 1.75 ppm (13); nmr (DMSO-d_6) δ 5.6 (d, 1, CHO<u>H</u>) and 3.6 ppm (d, 1, C<u>H</u>OH).

<u>Anal</u>. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.51; H, 9.05.

<u>Attempted Reduction of 7,8-Di[trimethylsiloxyl]tricyclo-[4.2.2.$0^{1,6}$]dec-7-ene (85)</u>. The catalyst, 25 ml of dry solvent and 1.0 g 7,8-di[trimethylsiloxyl]tricyclo[4.2.2.$0^{1,6}$]dec-7-ene (85) were placed in a Parr low pressure hydrogenation apparatus for 3-5 days at 35-60 lbs pressure. Little indication of hydrogenation was detected although 30-60% of <u>85</u> had disappeared with the appearance of a new band in the IR spectrum at 1775 cm^{-1}. This band corresponded to a similar one for cyclobutanone <u>86</u>. The following systems were attempted: 0.1 g 5% Pd-C/ethyl acetate, 0.1 g PtO_2 (Adam's catalyst)/cyclohexane, 0.1 g 5% Rh-Al_2O_3/ethyl acetate, and 0.5 g 5% Pd-Al_2O_3/ethyl acetate. The latter system (5 x normal amount of catalyst) was an unsuccessful attempt at complete hydrogenolysis of the O-Si bonds.

<u>7,8-Dichlorobicyclo[4.2.0]octane-1,6-dicarboxylic acid anhydride (81)</u>. In a 225 ml three-necked Pyrex irradiation vessel equipped with a magnetic stirrer, nitrogen inlet, and drying tube, were placed 4.0 g (0.026 mole) of cyclohex-1-ene-1,2-dicarboxylic acid anhydride (80), 0.5 g benzophenone, and 200 ml of <u>cis</u>-dichloroethylene. The solution (under a

nitrogen blanket) was irradiated 42 hr with a Hanovia 450 watt mercury arc quartz immersion lamp cooled by circulated 0° chilled water. Excess cis-dichloroethylene was removed and the residue allowed to stand with hexane several days. A small amount of brownish crystals formed, were collected, and recrystallized from hexane:ethyl acetate (4:1), giving 0.2 g (3%) of 7,8-dichlorobicyclo[4.2.0]octane-1,6-dicarboxylic acid anhydride (81): mp 157-159°; IR (KBr) 1845 and 1787 cm^{-1} (anhydride C=O).

Anal. Calcd for $C_{10}H_{10}O_3Cl_2$: C, 48.22; H, 4.05; Cl, 28.47. Found: C, 48.42; H, 4.15; Cl, 28.32.

Dimer of cyclohex-1-ene-1,2-dicarboxylic acid anhydride (89). On one occasion during the preparation of bicyclo[4.2.0]-octane-1,6-dicarboxylic acid anhydride (82), the ethylene flow diminished for several hours. Recrystallization produced two types of crystals, needles of bicyclo[4.2.0]octane-1,6-dicarboxylic acid anhydride (82) and platelets of the dimer of cyclohex-1-ene-1,2-dicarboxylic acid anhydride (80). The platelets were collected and recrystallized from ethyl acetate, giving 5.4 g (17.7%) of dimer 89: mp 277.0-278.5°; IR ($CHCl_3$) 1865, 1835, and 1790 cm^{-1}(anhydride C=O).

Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.15; H, 5.45.

7-Ethoxyoctane-bicyclo[4.2.0]1,6-dicarboxylic acid (93). In a 750 ml three-necked Pyrex irradiation vessel fitted with a fritted glass bubbler for a nitrogen inlet, magnetic stirrer,

and calcium chloride drying tube, were placed 30.4 g (0.2 mole) cyclohex-1-ene-1,2-dicarboxylic acid anhydride (80), 5.0 g benzophenone, 100.8 g (1.4 moles) of ethyl vinyl ether, and 500 ml of acetone. Nitrogen was bubbled for 1 hr through the stirred solution, then discontinued during 20 hr of irradiation with a Hanovia 200 watt mercury arc quartz immersion lamp cooled with circulated 0° chilled water. The acetone and unreacted ethyl vinyl ether were removed, leaving 50-55 g of a yellow oil that failed to crystallize.

The oily products of three such runs were combined and hydrolyzed by heating with 500 ml of 10% aqueous sodium carbonate for 5.5 hr. The contents were cooled and extracted with ether (2 x 100 ml). An oil was formed on acidification of the aqueous layer with concentrated hydrochloric acid. The oil later crystallized on standing, was collected, and washed with water, giving 113.4 g (78.1%) of 7-ethoxybicyclo[4.2.0]octane-1,6-dicarboxylic acid (93); mp 143.5-148.5° dec.; IR ($CHCl_3$) 3300-3100 (acid OH) and 1705 cm^{-1} (acid C=O).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.35; H, 7.54.

Bicyclo[4.2.0]oct-1(6)-ene (90). In a 500 ml round bottom flask equipped with a magnetic stirrer and reflux condenser, were placed 200 ml of dry pyridine and 17.82 g (0.09 mole) of bicyclo[4.2.0]octane-1,6-dicarboxylic acid (83). Lead tetraacetate (70.75 g, 0.159 mole) (Arapahoe, pumped

free of acetic acid and acetic anhydride) was added and the flask placed in a 45° oil bath. Evolution of carbon dioxide began immediately and the flask was quickly removed from the oil bath as the pyridine began to reflux. The reaction subsided within 7-8 min, was cooled and 300 ml of 6N nitric acid (cold) was added with cooling. The aqueous solution was extracted with ether (3 x 200 ml) which was subsequently washed with saturated sodium bicarbonate solution (1 x 150 ml, 1 x 50 ml) and dried ($MgSO_4$). The solution was concentrated and distilled, giving 3.1 g (31.9%) of bicyclo[4.2.0]oct-1(6)-ene (90): bp 55°/34 mm; n_D^{20} 1.4812; IR (film) exhibited only a few bands, 1445 (m), 1260 (m), and 1135 (w) cm^{-1}; nmr (CCl_4) δ 2.42 (finely split singlet, 4, cyclobutane) and two multiplets centered at 1.85 and 1.67 ppm (allylic and methylene).

Anal. Calcd for C_8H_{12}: C, 89.00; H, 11.00. Found: C, 88.86; H, 10.88.

7-Ethoxybicyclo[4.2.0]oct-1(6)-ene (94). To a 500 ml round bottom flask fitted with a magnetic stirrer and reflux condenser were added 300 ml of dry pyridine and 29.04 g (0.12 mole) of 7-ethoxybicyclo[4.2.0]octane-1,6-dicarboxylic acid (93). Lead tetraacetate (79.8 g, 0.16 mole) (free of acetic acid and acetic anhydride) was added and the flask placed in a 45° oil bath. The reaction began, the pyridine refluxed gently, then subsided within 10 min. The reaction mixture was cooled and 750 ml of 5N nitric acid (cold) was added slowly with more cooling. This was followed by ether

extraction (4 x 250 ml) of the aqueous solution. The ethereal layer was washed with saturated sodium bicarbonate solution (100 ml), saturated sodium chloride solution (50 ml), water (50 ml), dried ($MgSO_4$), and concentrated, giving 15 g of residue. This material was placed on a column of Florisil (200 g) and eluted with pentane, giving 7.16 g (39.2%) of 7-ethoxybicyclo[4.2.0]oct-1(6)-ene (94): n_D^{25} 1.4710; IR (film) 1650 cm^{-1} (weak C=C); nmr (CCl_4) δ 4.32 (broad s, 1, C$\underline{H}$OC), 3.45 (q, 2, $\underline{J}$ = 7 Hz, OC$\underline{H}_2$), 2.8-1.5 (various multiplets), and 1.13 ppm (t, 3, $\underline{J}$ = 7 Hz, C$\underline{H}_3$).

<u>Anal</u>. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: 79.02; H, 10.78.

<u>7-Ethoxytricyclo[4.2.1.$0^{1,6}$]nonane (95)</u>. In a 50 ml three-necked round bottom flask fitted with a reflux condenser, magnetic stirrer, addition funnel, and drying tube, were placed 2.61 g (0.04 mole) of zinc-copper couple,[86] 20 ml of anhydrous ether, a trace of iodine, and 8.04 g (0.03 mole) of methylene iodide. Reaction was initiated with a heat lamp and then was heated under reflux for 0.5 hr additional. 7-Ethoxybicyclo-[4.2.0]oct-1(6)-ene (94) (2.22 g, 0.0146 mole) in 10 ml of ether was added in 0.5 hr to the refluxing mixture. After 1 hr of additional reflux, the flask contents were cooled and approximately 5 ml of saturated aqueous ammonium chloride solution was added cautiously and stirred 1.5 hr. The precipitate was filtered and washed with ether. The combined ethereal solutions were extracted with saturated potassium carbonate

solution (4 x 10 ml), saturated sodium chloride solution (2 x 10 ml), dried ($MgSO_4$), and concentrated *in vacuo* at room temperature. The residue was placed on a column of Florisil (60 g) and eluted with pentane, giving 0.5 g (20.0%) of 7-ethoxytricyclo[4.2.1.$0^{1,6}$]nonane (95). A pure sample of 95 was obtained by preparative glc on a 20% SE-30 on Chromsorb Z, 3/8 in x 20 ft column at 150°: n_D^{25} 1.4826; IR (film) 3050, 3010 cm^{-1} (cyclopropane); nmr (CCl_4) δ 3.3 (q, 2, J = 7 Hz, OCH_2), 2.3-1.25 (multiplet), 1.02 (t, 3, J = 7 Hz, CH_3, and 0.87-0.29 ppm (two complex multiplets, ΔH).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.40; H, 10.91. Found: C, 79.21; H, 11.06.

Attempted Reaction of Diazomethane with Bicyclo[4.2.0]oct-1(6)-ene (90). Between 0.06-0.07 mole of diazomethane* was generated[87] and gently swept through a KOH drying tower into a 50 ml erlenmeyer flask containing a stirred mixture of 0.3 g copper(I) chloride (freshly prepared[80]), 15 ml ether, and 1.5 g (0.014 mole) of bicyclo[4.2.0]oct-1(6)-ene (90). The diazomethane was bubbled into the ether solution in the flask which was immersed in an ice-water bath. An aliquot was taken and glc analysis revealed no new components. Again 0.06-0.07 mole diazomethane was generated and swept into the reaction flask. Again only unreacted olefin was present.

Attempted Addition of Dichlorocarbene to Bicyclo[4.2.0]-oct-1(6)-ene (90), Method A. In a 25 ml round bottom flask were placed 2.5 g (0.023 mole) of bicyclo[4.2.0]oct-1(6)-ene

*From Bis-(N-methyl-N-nitroso)terephthalamide, E. I. du Pont de Nemours and Co.

(90), 12-15 ml of 1,2-dimethoxyethane (distilled from calcium hydride), 5.56 g (0.03 mole) of dry sodium trichloracetate. The magnetically stirred mixture was refluxed 12 hr. The ether and unreacted olefin were removed leaving a brown tar that exhibited no cyclopropane absorption (1000 cm^{-1}) in the infrared spectrum.

Method B. In a 25 ml round bottom flask were placed 1.42 g (0.013 mole) of bicyclo[4.2.0]oct-1(6)-ene (90), 5 ml of pentane (olefin-free), 5 ml of anhydrous ether, and 2.04 g (0.0182 mole) of potassium t-butoxide. The flask was cooled and stirred as 2.4 g (0.02 mole) of chloroform was added dropwise. The contents were stirred for 15 min additional, poured into 25 ml of water, and extracted with pentane (2 x 15 ml). The aqueous layer was washed with ether. Both pentane and ether solutions were concentrated separately, but revealed nothing that indicated a dichlorocyclopropane structure (1000, cyclopropane or 800-600 cm^{-1}, chlorine) in the infrared spectrum.

Method C. In a 100 ml three-necked round bottom flask equipped with a dropping funnel, magnetic stirrer, and nitrogen inlet, were placed 6.48 g (0.06 mole) of bicyclo[4.2.0]-oct-1(6)-ene, 13.0 g (0.24 mole) of sodium methoxide, and 90 ml of olefin-free pentane. The reaction flask was placed under a blanket of nitrogen, cooled with an ice-salt water bath, and 38.3 g (0.2 mole) ethyl trichloracetate was added within 3 hr. The flask contents were allowed to warm to room

temperature overnight and then were poured into 300 ml of water and extracted with pentane. The pentane layer was dried (Na_2SO_4), concentrated, giving a brown mobile liquid which was placed in a refrigerator for several days. Crystallization and filtration gave 3.8 g and 0.5 g (second crop) of 91, brownish-white crystals, mp 70.5-71.5° dec. Recrystallization was effected from ether-hexane by chilling a room temperature solution to -76°. The melting point ranged from 67-71°, depending on the extent of decomposition as evidenced by the evolution of hydrogen chloride at room temperature. IR (KBr) 3020, 1480, 1090, 835, 800, 655; nmr (CCl_4) δ 3.0-1.5 ppm.

Anal. Calcd for $C_{10}H_{12}Cl_4$: C, 43.83; H, 4.41; Cl, 51.75. Found: C, 45.31; H, 4.78; Cl, 49.90.

Attempted Recrystallization of 91, Isolation of 92. A portion of 91 was dissolved in hot ethanol-water. An oil was recovered and chromatographed on Florisil (eluted with hexane): n_D^{25} 1.5643; IR (film) 3030, 1620, 1590, 1040, 805, 745, 705; nmr (CCl_4) 5.94 (d, J = 4.5 Hz), 5.81 (d, J = 4.5Hz), 3.33-1.10 with multiplets superimposed at 2.75-2.60, 1.90, and 1.7-1.5 ppm. 91 later crystallized: mp 276-9° dec; IR (KBr) 1605, 1570 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}Cl_3$: C, 50.55; H, 4.67; Cl, 44.77. Found: C, 50.20; H, 4.85; Cl, 44.63.

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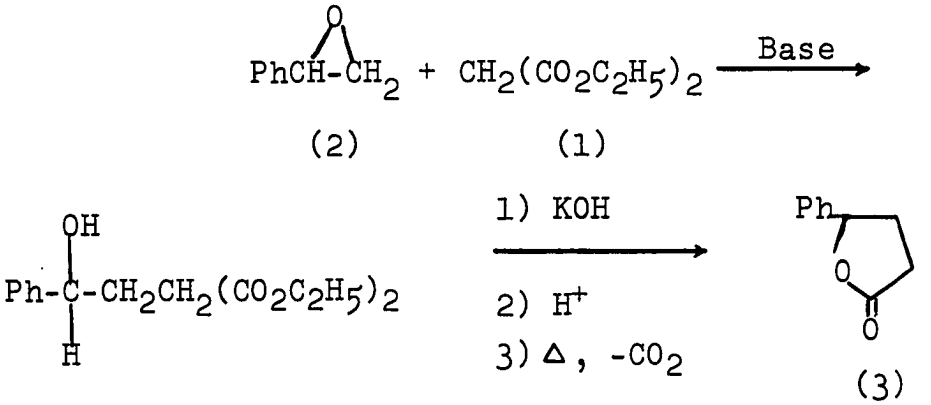
II. SOLVENT EFFECTS IN THE REACTION OF DIETHYLMALONATE ANION WITH STYRENE OXIDE

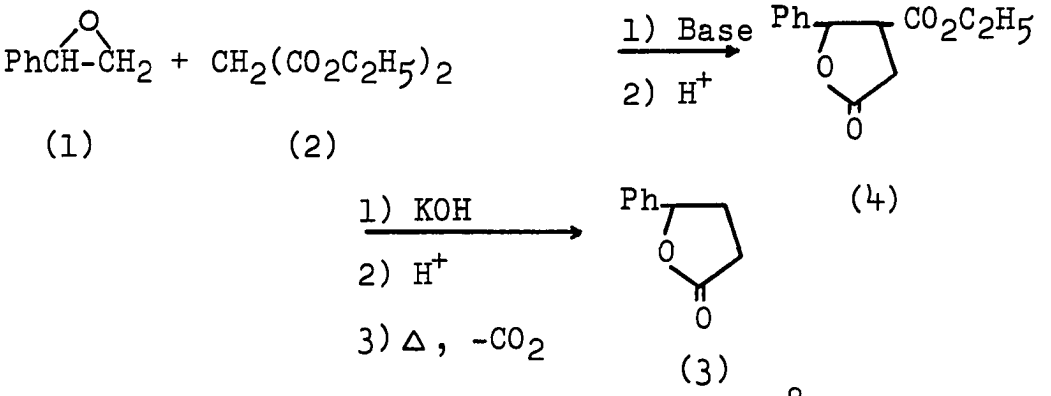
INTRODUCTION

Recently, re-examination of the reaction of diethylmalonate anion with styrene oxide has produced some interesting results. Originally, Russell and VanderWerf[1] reported that the addition of diethylmalonate (1) to styrene oxide (2) led to an unisolated hydroxyester which upon saponification, lactonization, and decarboxylation produced γ-phenyl-γ-butyrolactone (3).



Van Zyl and van Tamelen[2] repeated the synthesis of 3, with isolation of the intermediate α-carbethoxy-γ-phenyl-γ-butyrolactone (4), which was then subjected to saponification and decarboxylation, confirming the earlier report.[1] These conclusions pertaining to the supposed specificity have been

utilized or quoted widely.[3-7]



(1) (2) (4) (3)

In fact, Bavin, Hansell, and Spickett[8] in a re-examination of this method, established that the reaction between styrene oxide and diethylmalonate anion gave in addition to lactone 3, its isomer, β-phenyl-γ-butyrolactone (5). These isomers, 3 and 5, are the result of attack of diethylmalonate anion at both the α- and β-carbons of styrene oxide.

(3) (5)

Infrared spectra had suggested the presence of an isomeric lactone. Pure specimens of compounds 3 and 5 were prepared by unambiguous means and their melting points recorded: γ-phenyl-γ-butyrolactone, mp 35-36°, and β-phenyl-γ-butyrolactone, mp 47-48°. Crystallization of the oily mixture gave impure lactone 5 rather than the γ-phenyl isomer (3), and the melting point (45.5-46.0°) recorded by Russell and VanderWerf[1]

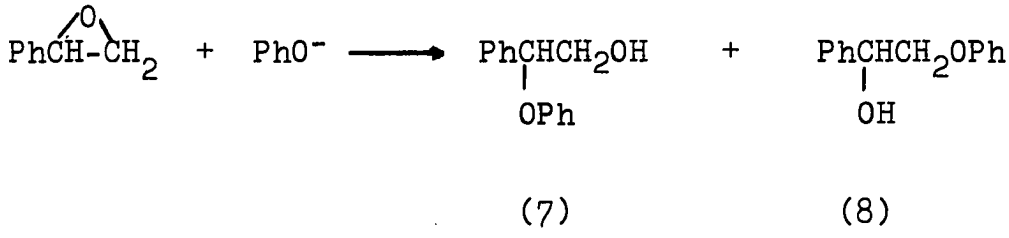
suggested that they obtained only 5 in a state of purity.

At approximately the same time DePuy and coworkers[9] confirmed these results with structural assignments for the respective isomers, 3 and 5, using nmr spectra. The pure components were separated by column chromatography on silica gel.

The reaction solvent of choice in these reports[1-2,8-9] was absolute ethanol, although Bavin and coworkers[8] also used 2-propanol and methanol. The latter authors reported compound 5 composed 35-50% (estimated from the infrared spectra) of the lactone mixture and only small variations were associated with changes of temperature and solvent. However DePuy and coworkers[9] have shown that compound 5 was 60% of the lactone mixture (integration of the nmr spectrum).

This lack of a solvent effect is curious since a solvent dependence has been shown with other nucleophilic openings of styrene oxide.[10-12]

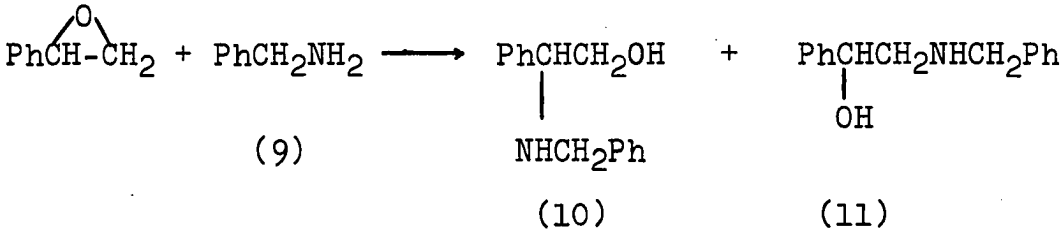
Nucleophilic ring opening of epoxides occurs most readily in solvents which are not only highly polar but hydroxylic.[10,12-14] This dependence on the medium suggests that the solvent might act as an electrophilic catalyst as well as non-specifically as a charge-dispersing medium. Guss and Williams[10] observed an increase in the rate of reaction between phenoxide and styrene oxide as the capacity for the solvent to form hydrogen bonds with the oxide was augmented.



(7) (8)

In this reaction, the isomeric phenoxyalcohols (7) and (8) were produced in varying ratios in ten different solvents. Alcohol 7 varied from 43% (tetrahydrofuran) to 77% (water) for this reaction (Table 1).

Solvent effects were reported also[11-12] in the reaction of styrene oxide and benzylamine (9), with the production of isomeric aminoalcohols, (10) and (11). These results have shown that the "single expected product," compound 11, actually ranged from 60-100% of a mixture of isomers, (10) and (11) (Table 2).



(9) (10) (11)

From the beginning, the study of the mechanism of the ring opening of styrene oxide with diethylmalonate anion proved interesting when earlier reports cited only one product, 3. It was first suggested that the preferential nucleophilic attack was a bimolecular displacement favored by the

TABLE 1

The Effect of Solvent on the Composition of the Mixture of Isomers Obtained with the Reaction of Phenoxide and Styrene Oxide[a,b]

Solvent	Temp., °C	Total Yield %	α-Isomer (7)[c]
Tetrahydrofuran, 75 ml plus methanol, 3.2 g	70	41	28
Tetrahydrofuran, 25 ml	93	81	43
Dioxane, 25 ml	100	77	47
Acetal, 25 ml	100	65	55
Ethanol, 25 ml	94	84	57
Allyl alcohol, 25 ml	100	80	64
Methanol, 25 ml	70	85	69
Nitrobenzene,[d] 25 ml	100	56	71
Toluene,[d] 25 ml	100	70	72
Thiophene,[d] 25 ml	94	61	73
Water, 7.5 ml	100	80	77
Phenol,[e] 14.1 g	100	50	88

[a]Reference 10.

[b]Reactants: styrene oxide (0.05 mole), phenol (0.15 mole), sodium (0.05 mole), sodium hydroxide (0.05 mole) with water as the solvent.

[c]α-Phenoxy-α-phenylethanol.

[d]Some sodium phenoxide remained undissolved.

[e]This amount was in addition to the quantity present in all runs.

TABLE 2

Rate Constants for the Normal[a] and Abnormal Isomers and the Percentage of the Normal Isomer in the Reaction of Styrene Oxide with Benzylamine (59.6° C., k_N and k_A in l.mole^{-1} sec.$^{-1}$)[b]

Solvent	Normal[a] Product (%)	$10^7 k_N$	$10^7 k_A$
Methanol	64	2500	1410
Ethanol	73	1850	680
n-Propanol	74	1690	590
n-Butanol	72	1400	550
Butan-2-ol	74	1132	398
t-Butyl alcohol	75	454	151
2-Methylbutan-2-ol	75	264	88
Dimethyl sulfoxide	87	102	17.0
Sulfolane	100	44.5	0.0
Acetonitrile	83	15.4	3.1
Nitrobenzene	80	10.8	2.7
Diglyme	92	5.5	0.5

[a]The normal isomer is the aminoalcohol (11) produced by attack of benzylamine on the β-carbon of styrene oxide.

[b]Reference 11 and 12.

electron-donating phenyl group.[1] A transition state of the type shown in Figure 1 is expected for an S_N2 reaction of epoxides,[4] provided the group R has no very marked polar or inductive effects. Thus the normal isomer would be formed for steric reasons.

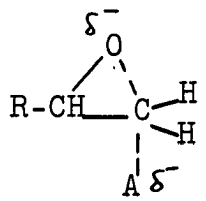
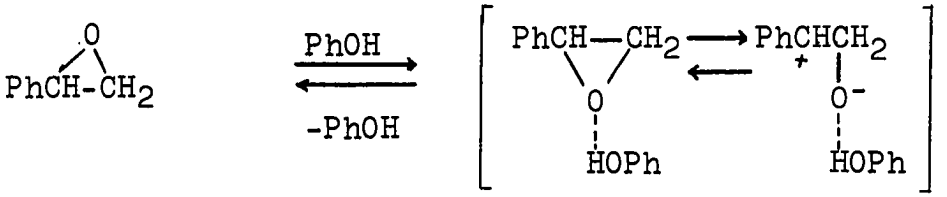
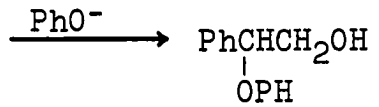


Figure 1

Guss has suggested a unimolecular mechanism for the formation of the primary phenoxyalcohol (7). The phenol can assist the rate-determining unimolecular ring opening, and the carbonium ion is solvated and also stabilized by resonance. Support is derived from the results of the reaction of phenoxide



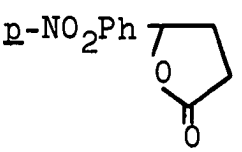


(7)

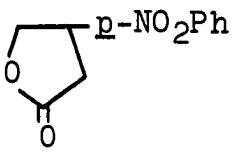
anion and p-nitrostyrene oxide. If the bimolecular reaction were responsible for the abnormal product (7), then the

utilization of p-nitrostyrene oxide should facilitate reaction at the α-carbon due to the electron withdrawing effect of a p-nitro-group and more primary alcohol would be formed than with styrene oxide. Actually less primary alcohol is formed (76% α-attack, styrene oxide; 36% α-attack, p-nitrostyrene oxide.)[15]

Recently Cristol and Osman[16] corrected an earlier report[17] concerning the product of the reaction of p-nitrostyrene oxide and diethylmalonate. Originally, γ-phenyl lactone (12) was considered the only product of this condensation. Re-investigation with nmr analyses and the independent syntheses of authentic samples of both isomeric γ-lactones proved the other isomer, β-p-nitrophenyl-γ-butyrolactone (13) to be the only product. This wholly α-attack provides reason to doubt that steric factors attributed to the bulky phenyl group, as suggested by Guss, are important. It appears that the inductive effects of ring-substituted and unsubstituted styrene oxides are more important in this instance.



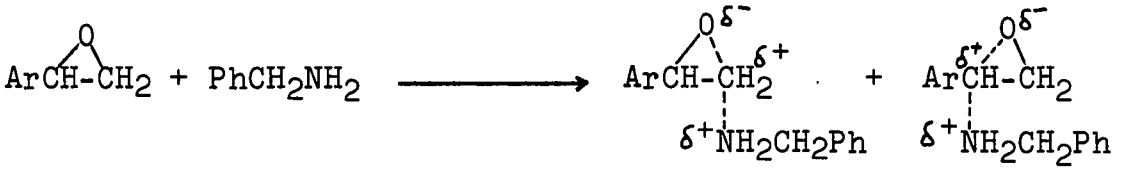
(12)



(13)

Laird and Parker[18] do not consider an S_N1 mechanism for the reaction of benzylamine with a series of m- and p-substituted styrene oxides in ethanol. They propose an S_N2 mechanism

for the normal product and a "borderline" S_N2 mechanism for the abnormal transition state.[4] Both reactions involve the opening of the highly strained three-membered ring, a process in which it could be expected that bond breaking will have progressed further than bond making in the transition state. Thus the attacked carbon would be more positive than initially. Their kinetic results show increased rates of abnormal attack with a p-electron-releasing substituent and decreased rates with electron-withdrawing substitutents. The opposite is true with the normal reaction rate. Electron-releasing substituents stabilize the increased positive charge on the attacked carbon atom during the transition state while electron-withdrawing substituents destabilize the partial positive charge.



Recently, the rates of abnormal and normal attack coupled with product analyses have been published for the reaction of styrene oxide and benzylamine in various protic and aprotic solvents.[12] In methanol, the reaction is less selection (62% normal product) but faster at both abnormal and normal positions. A constant 73.5 ± 1.5% normal product was obtained in six other alcohols. This invariant ratio is rationalized by the mode of interaction of the solvents with the reactants in the transition state. The principal interaction probably

occurs by hydrogen bonding of the hydroxyl group of the solvent molecule to the epoxide oxygen atom. Variation of the solvent will affect the magnitude of this interaction and hence the rate of reaction, but not the product ratio. The latter would be determined by electronic and steric effects on the site of bond formation. However, methanol is an exception to this regular pattern.

In aprotic, as in, protic solvents, rates of normal and abnormal reactions increased with an increase in the dielectric constant of the solvent. The rates in protic solvents were much faster than in aprotic solvents of higher dielectric constant. This is attributed to the ability of the protic solvent to hydrogen bond to the epoxide oxygen and assist ring-cleavage.

The reaction of styrene oxide and diethylmalonate presented several unanswered questions for study: among these are; 1) the actual percentage of β-phenyl-γ-butyrolactone (5) in the product mixture obtained in the solvent ethanol; 2) the effect of a change of solvent on this percentage; and 3) the possibility of hydrogen bonding in the transition state of the reaction.

RESULTS AND DISCUSSION

In order to detect some of the important factors involved in solvent effects on the epoxide ring opening of styrene oxide, consideration was given to solvents of various properties. With respect to polarity, these solvents range from a dielectric constant of 2.2 (*p*-dioxane) to 48.5 (dimethyl sulfoxide) as shown in Table 3. Polar hydroxylic solvents with increasing bulkiness were selected for hydrogen bonding interactions. And finally, dipolar aprotic solvents such as dimethyl sulfoxide, dimethylformamide, etc., were chosen to study the effects of high polarity with negligible hydrogen bonding.

In this work it was found that the reaction of styrene oxide and diethylmalonate anion produced isomeric *γ*-lactones in varying ratios, depending upon the reaction solvent utilized. Table 4 records the total yield of *γ*-lactones and the percentage of *β*-phenyl-*γ*-butyrolactone (5), the so-called abnormal product resulting from nucleophilic attack by diethylmalonate anion on the *α*-carbon of styrene oxide. A 70% yield of *γ*-lactones was obtained with ethanol as the reaction solvent; lactone 5 composed 59% of this isomeric mixture. These results agree favorably with those of DePuy and coworkers[9] who obtained 62 and 60% respectively, but are contrary to another report[8] of 45 and 35-50% of lactone 5. This latter discrepancy might be explained by an examination

TABLE 3

Dielectric Constants of Selected Solvents

Solvent	Dielectric Constant at 25° C.	Reference
Methanol	32.63	19
Ethanol	24.3	19
2-Propanol	18.3	19
t-Butyl alcohol	10.9[a]	19
p-Dioxane	2.209	19
Benzene	2.274	19
Sulfolane	44[a]	20
Diglyme	6.8	21
Tetrahydrofuran	7.2	21
Dimethylformamide	36.71	22
N-Methyl-2-pyrrolidone		

[a]Dielectric constant at 30° C.

TABLE 4

The Percentage of α-Attack of Styrene Oxide by Diethylmalonate Anion and the Total Yield of Isomeric γ-Lactones Produced in Various Solvents

Solvent	Temp.	Lactone 5 (α-attack)[a] (%)	Yield[b] γ-Lactones g (%)
Methanol	Reflux	76.2 (74.3)	28.4 (58.5)
Ethanol	Reflux	59.4 (59.3)	34.0 (70.0)
2-Propanol	Reflux	41.5 (45.5)	31.2 (64.1)
t-Butyl alcohol	Reflux	40.7 (42.0)	28.7 (59.0)
p-Dioxane	Reflux	34.3 (33.9)	24.5 (50.4)
Benzene	Reflux	34.0 (33.4)	15.7 (32.3)
Sulfolane	60°	31.7 (33.6)	7.5[c](15.4)
Diglyme	70°	30.3 (31.7)	27.2 (56.0)
Tetrahydrofuran	Reflux	27.3 (30.8)	24.2 (49.7)
Dimethylformamide	RT	26.0 (26.9)	3.0[d](6.0)
Dimethylsulfoxide	RT	25.5 (25.2)	1.0[d](2.0)
N-Methyl-2-pyrrolidone	RT	19.5 (19.7)	2.5[d](4,0)

[a]Results of duplicate experiment shown in parentheses.

[b]Yield shown for Run 1 of duplicate experiments.

[c]After two distillations.

[d]Glc estimate of the distillate.

of the experimental portion of the report in question. These authors illustrated a typical experiment with isopropyl alcohol as a solvent, obtaining 47% lactones; lactone 5 was 41% of the total. Their experiment was in excess of 200 mole scale, actually a pilot plant operation. In the present case the lactone yield was 64%, of which 5 comprised 41-45% of the total when isopropyl alcohol was used as the reaction solvent. However the results for ethanol and methanol (59.4 and 76.2%) do not fall within the range of values for lactone 5 (35-50%) previously reported.[8]

Also indicated in Table 4 are the poor yields (2-15%) of lactones 3 and 5 obtained in dipolar aprotic solvents. These results exclude polarity alone as an important consideration in this reaction. Only slightly lower yields were recorded in relatively nonpolar solvents such as p-dioxane, tetrahydrofuran, and diglyme than in polar alcohols. Although the reaction was conducted at room temperature in three of the four dipolar aprotic solvents, temperature is only a minor consideration with dipolar aprotic solvents.

In these reactions for which dipolar aprotic solvents have been reported to give higher yields, often with shorter reaction times than conventional solvents, one of the reactants is usually an anion and the reactions probably are bimolecular.[24-25] Most anions in dipolar aprotic solvents are much less solvated than in protic solvents, but polarizable charged transition states in dipolar aprotic solvents are more solvated than in

protic solvents.[26] S_N1 ionization in dipolar aprotic solvents is not common because both ionized groups are weakly solvated, the anion because it cannot form a hydrogen bond with the solvent, the carbonium ion because it has a well-shielded charge.

Although anionic reactions are faster in dipolar aprotic solvents, positions of equilibria are similar in protic and dipolar aprotic solvents, unless the nucleophile and the leaving group have very different polarizabilities, sizes, or different charge types.[27] The equilibrium lies much further to the left in dipolar aprotic solvents than in protic solvents of the same dielectric constant.[25-26]

$$CH_3Br + (CH_3)_2S \rightleftharpoons (CH_3)_3S^+ Br^-$$

This could explain the low yield of γ-lactones in dipolar aprotic solvents. The major product isolated from the reaction in dimethyl sulfoxide, dimethylformamide, and N-methyl-2-pyrrolidone appears to be phenylethylene glycol (16), a hydrolysis product of styrene oxide.

$$PhCH\!-\!CH_2 \;(O) \xrightarrow[H_2O\text{-}C_2H_5OH]{NaOH} PhCHOHCH_2OH \quad (16)$$

Melting point,[28] analyses and the nmr spectrum agree quite well. Phenylethylene glycol (16) probably resulted from the hydrolysis of styrene oxide during the saponification procedure in aqueous ethanolic sodium hydroxide.

Tables 5 and 6 contain data obtained from experiments with various concentrations of reactants. The percentage of α-attack varied little with dilution or excess diethylmalonate or diethylmalonate anion.

An S_N2 mechanism has been generally accepted for the attack at the β-position of styrene oxide by various nucleophiles such as phenoxide,[10] methoxide,[29] benzylamine,[12] and diethylmalonate anion.[1] The experimental results reported here do not disagree with this mechanism. However, a discrepancy quickly arises when one considers attack at the α-position of styrene oxide. Guss has proposed[10] a unimolecular ring opening assisted by solvent hydrogen bonding interactions and subsequent attack by the nucleophile. Alternatively, Parker has suggested[4] a "borderline S_N2" mechanism where bond-breaking has progressed further than bond-making in the transition state for reactions in basic or neutral solutions. When both partial bonds in the transition state are longer than usual, the central carbon atom will carry a partial positive charge, Figure 2.

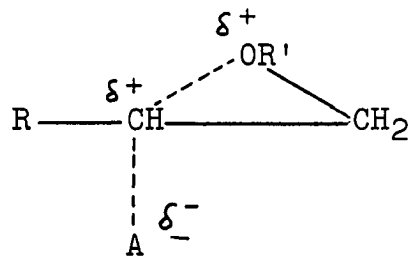


Figure 2

TABLE 5

The Percentage of Lactone 5 and the Total Yield of γ-Lactones Produced with Various Concentrations of Diethylmalonate Anion

Solvent	Diethyl-malonate (Equivalents)[a]	Base (Equivalents)[a]	Lactone 5 (%)[b]	Yield γ-Lactones g (%)[b]
Ethanol	1.0	1.0	59.4 (59.3)	34.0 (70.0)
Ethanol	1.5	1.5	58.8 (59.3)	39.0 (80.4)
Ethanol	1.5	1.0	58.4 (60.6)	34.4 (70.6)
Ethanol	10.0	10.0	58.8[c]	21.5 (88.5)[c]
Tetrahydrofuran	1.0	1.0	27.3 (30.8)	24.2 (49.7)
Tetrahydrofuran	1.5	1.5	26.9 (25.9)	26.8 (55.1)
Tetrahydrofuran	1.5	1.0	25.8 (25.8)	24.7 (50.8)
Tetrahydrofuran	10.0	10.0	29.9[c]	20.6 (84.7)[c]

[a]One equivalent of styrene oxide used in all these experiments.
[b]Results of a duplicate experiment shown in parentheses.
[c]No duplicate run; scale one-half of other experiments.

TABLE 6

The Percentage of Lactone 5 and the Total Yield of γ-Lactones Produced with Various Amounts of Solvent

Solvent	ml	Lactone 5 (%)[a]	Yield γ-Lactones g (%)[b]
Ethanol	200	59.7 (64.9)	33.9 (69.8)
Ethanol	300	59.4 (59.3)	34.0 (70.0)
Ethanol	500	62.0 (62.3)	30.1 (61.8)
Tetrahydrofuran	200	24.1 (24.6)	28.4 (58.3)
Tetrahydrofuran	300	27.3 (30.8)	24.2 (49.7)

[a]Results of duplicate experiments shown in parentheses.

[b]Calculations shown for only Run 1 of duplicate experiments.

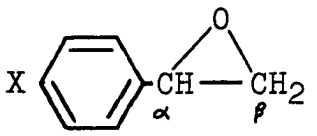
The R group can stabilize this partial positive charge by electron donation, in the manner of an S_N1 mechanism. Essentially the same ideas are presented by Thornton[30] and by Gold.[31]

Either theory can explain the position of attack of various nucleophiles on substituted styrene oxides shown in Table 7, except the attack of diethylmalonate anion on the α-carbon of p-nitrostyrene oxide. The most reasonable mechanism for this example is an S_N2 attack at the most positive site, the α-carbon atom, to which the electron-withdrawing p-nitrophenyl group is attached. In a previously mentioned study by Parker and Rockett,[12] a constant normal/abnormal product and rate ratio was found in six of seven alcohols used as solvents with methanol the exception. This suggested very similar mechanisms were operating for both normal and abnormal attacks. Therefore, either an S_N2 or more likely a "borderline S_N2" was the mode of attack at the α-carbon.

Table 4 shows that in the reaction with diethylmalonate ion, two of four alcohols gave 43 ± 2.4% of attack at the α-carbon. Deviation from constancy is more in non-hydroxylic solvents where 29.7 ± 4.6% α-attack occurred. A similar effect was also noted by Parker and Rockett.[12] The present results are in line with the "borderline S_N2" concept rather than a classical S_N1 mechanism. The results in the nonpolar solvents, such as benzene and p-dioxane show only 6-7% less attack in the α-position than with the polar alcohols

TABLE 7

The Percentage of α-Attack by Various Nucleophiles on Some p-Substituted Styrene Oxides



X	Nucleophile	α-Attack (%)	Reference
$-OCH_3$	$LiBH_4$	95	33,34
$-CH_3$	$LiBH_4$	67	33,35
-H	$LiBH_4$	26	34
$-NO_2$	$LiBH_4$	62	34
$-OCH_3$	PhONa	100	36
-H	PhONa	76	37
$-NO_2$	PhONa	36	37
-H	$NaCH(CO_2C_2H_5)_2$	60	9
$-NO_2$	$NaCH(CO_2C_2H_5)_2$	100	16
$-CH_3$	$PhCH_2NH_2$	55	18,38
-H	$PhCH_2NH_2$	17	18,39

isopropyl and t-butyl. The nonpolar solvents would not be expected to aid a charge separation required by an S_N1 mechanism but could aid an S_N2 or "borderline S_N2", where the separation of charges is much less.

More evidence opposing an S_N1 mechanism has been published[39] recently. The rates and equilibria for reactions of three derivatives of malachite green [4,4'-bis(dimethylamino)triphenylmethyltetrafluoroborate] with several nucleophiles has been studied. These stabilized carbonium ions react faster with the nucleophiles, azide, cyanide, hydroxide, and methoxide in this solvent order, dimethyl sulfoxide > dimethylformamide > methanol > water. Thus this work shows results for α-attack that are the opposite of what would be expected from attack on a carbonium ion generated in a S_N1 mechanism. As the solvent becomes more polar and also hydroxylic, the reaction may be approaching the S_N1 mechanism which is influenced by increased polarity and hydrogen bonding assistance to the ring opening.

The decrease of α-attack of diethylmalonate on styrene oxide in dipolar aprotic solvents might be considered evidence that an S_N1 mechanism is contributing to the reaction in other solvents because the contribution of an S_N1 mechanism in dipolar aprotic solvents is negligible.[24-25] However the results show in Table 4 that reaction still occurs at the α-position when unfavorable solvents for an S_N1 mechanism are utilized (low polarity and non-hydroxylic) such as benzene

and p-dioxane. Here lies the appeal of the "borderline S_N2" mechanism for attack at the α-position of styrene oxide. This mechanism could function in solvents of low polarity and increase in importance with a change to more polar, hydroxylic solvents.

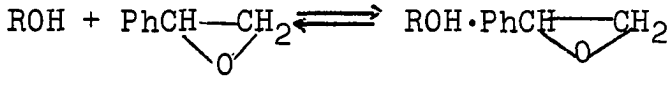
The importance of hydrogen bonding of the reactant, styrene oxide, and alcoholic solvents has been suggested earlier.[11-12,15] The magnitude of this interaction could not be expected to be as great as that exhibited by alcohol-amine or alcohol-alcohol interactions for these involve more basic substrates than styrene oxide.

Searles and Tamres[40] studied the extent of hydrogen bonding of 0.1 M methanol-d with various cyclic ethers as solvents. Their results from spectroscopic measurements of the frequency shift of the monomer -OD band in the infrared spectrum and the heat of mixing in chloroform solution show the extent of hydrogen bonding of cyclic ethers varies with the number of atoms in the ring in the following order: $4 > 5 > 6 > 3$. No association constants were reported ($K_{ass.}$). Of the seventeen cyclic ethers in the study, styrene oxide exhibited the second weakest interaction. It appears the combination of a three-membered ring structure and an electron-withdrawing inductive effect of a phenyl group decreases the basicity and donor ability of styrene oxide.

Coggeshall and Saier[41] utilized a slightly different spectral method in their report of the interactions of various

alcohols with p-dioxane and several ketones. A decrease in absorption of the monomer -OH band of dilute (10^{-3} M) alcohols in carbon tetrachloride occurred when p-dioxane or acetone was introduced. This decrease in the concentration of the monomer species is attributed to association between the alcohol and the added substrate. This method presented some experimental advantages over the method of Searles and Tamres[40] and was selected for examination of the hydrogen bonding interaction of styrene oxide with alcohols.

A comparison of two 2.5×10^{-3} M solutions of each alcohol, one of which contained 0.1 M styrene oxide, revealed differences in absorptions of the monomer -OH band in the infrared spectrum. Styrene oxide (0.1 M) absorbs slightly in the 2.7-2.9 μ region, thus it was necessary to subtract its contribution from the recorded absorbance of the ternary mixture. These data are recorded in Table 8. Equilibrium constants for the association of styrene oxide and the respective alcohols were calculated from Beer's Law where A is absorbance, ε is molar absorptivity, b is cell path length and c is concentration in moles per liter.



$$K = \frac{[\text{ROH}\cdot\text{PhCH}\text{—}\text{CH}_2\text{(O)}]}{[\text{ROH}]\,[\text{PhCH}\text{—}\text{CH}_2\text{(O)}]}$$

$$A = \varepsilon bc$$

TABLE 8

Calculated Association Constants (K) for Styrene Oxide and Various Alcohols in Carbon Tetrachloride[a]

Alcohol (2.5×10^{-3} Molar)	K (25° C.)
Methanol	2.80 ± 0.1
Ethanol	1.90 ± 0.1
2-Propanol	0.77 ± 0.1
t-Butyl alcohol	0.22 ± 0.1

[a]This work.

TABLE 9

Association Constants (K) for Various Epoxides and Phenol in Carbon Tetrachloride[a]

Epoxide	K in liters per mole 20°C.	60°C.
Cyclohexene oxide	7.54	3.35
cis-Methylstyrene oxide	3.59	1.67
trans-Methylstyrene oxide	3.57	1.88
cis-Stilbene oxide	2.68	1.79
trans-Stilbene oxide	2.03	1.12

[a]Reference 42.

The value of ε was calculated and applied to the following equation, where ΔA is the difference of absorbances of alcohol and alcohol plus styrene oxide.

$$\Delta A = \varepsilon bc$$

The value of c represents the concentration of the complex ROH·PhCH—$\overset{O}{\diagdown\diagup}$$CH_2$. The equilibrium concentrations of alcohol and styrene oxide can be found and applied to calculate the equilibrium constant. The error ($\pm$ 0.1) is derived from the probable photometric error (about 1% in transmittance of the samples) and does not include other sources of error. These K values are calculated only for comparison; a more thorough study with varying concentrations of styrene oxide is necessary to confirm these values. Although no direct comparisons of the equilibrium or association constants are available, a study of the association of phenol with various phenyl-substituted oxides has been reported[42] as shown in Table 9. The K for methanol (Table 8) agrees with the values for cis- and trans-methylstyrene oxide (3.59 and 3.57) if one considers that phenol is a stronger acid than methanol and would have a larger association constant.

It was suggested earlier that hydrogen bonding favors α-attack bonding rather than β-attack by a nucleophile, Figure 3.

Figure 3

A plot of the percentage α-product of the reaction between styrene oxide and diethylmalonate versus K from Table 8 is shown in Figure 4. The linear relationship shown indicates some correlation of hydrogen bonding ability of the solvent and the amount of α-product. It is assumed that α- and β-products are the result of competition of the α- and β-sites for the nucleophile and that neither product is preferentially destroyed.

The results of these hydrogen bonding experiments neither proves nor disproves the suggestion that a "borderline S_N2" mechanism occurs when diethylmalonate attacks the α-position of styrene oxide. The extent of alcohol-styrene oxide association appears to be less than the association of alcohols with aliphatic and most alicyclic ethers, which is much less than typical alcohol-alcohol or alcohol-amine associations. The alcohol-styrene oxide association encourages a "borderline S_N2" mechanism but appears of less value in application to an S_N1 mechanism. The results show that methanol and ethanol exhibit more hydrogen bonding interactions than t-butyl alcohol or 2-propanol. Perhaps the former pair of alcohols

interact enough with styrene oxide to assist an S_N1 mechanism, but it is more difficult to visualize such a mechanism for the reaction in t-butyl alcohol and 2-propanol since the α-product is only about 10% greater than in the non-polar solvents benzene and p-dioxane. S_N1 mechanisms are less likely to occur in these non-polar solvents, yet about 34% α-product is recorded in some of these solvents. The α-attack in non-polar solvents is a fact explained by a "borderline S_N2" mechanism, a mechanism which becomes a more important contributor in polar, hydroxylic reaction solvents.

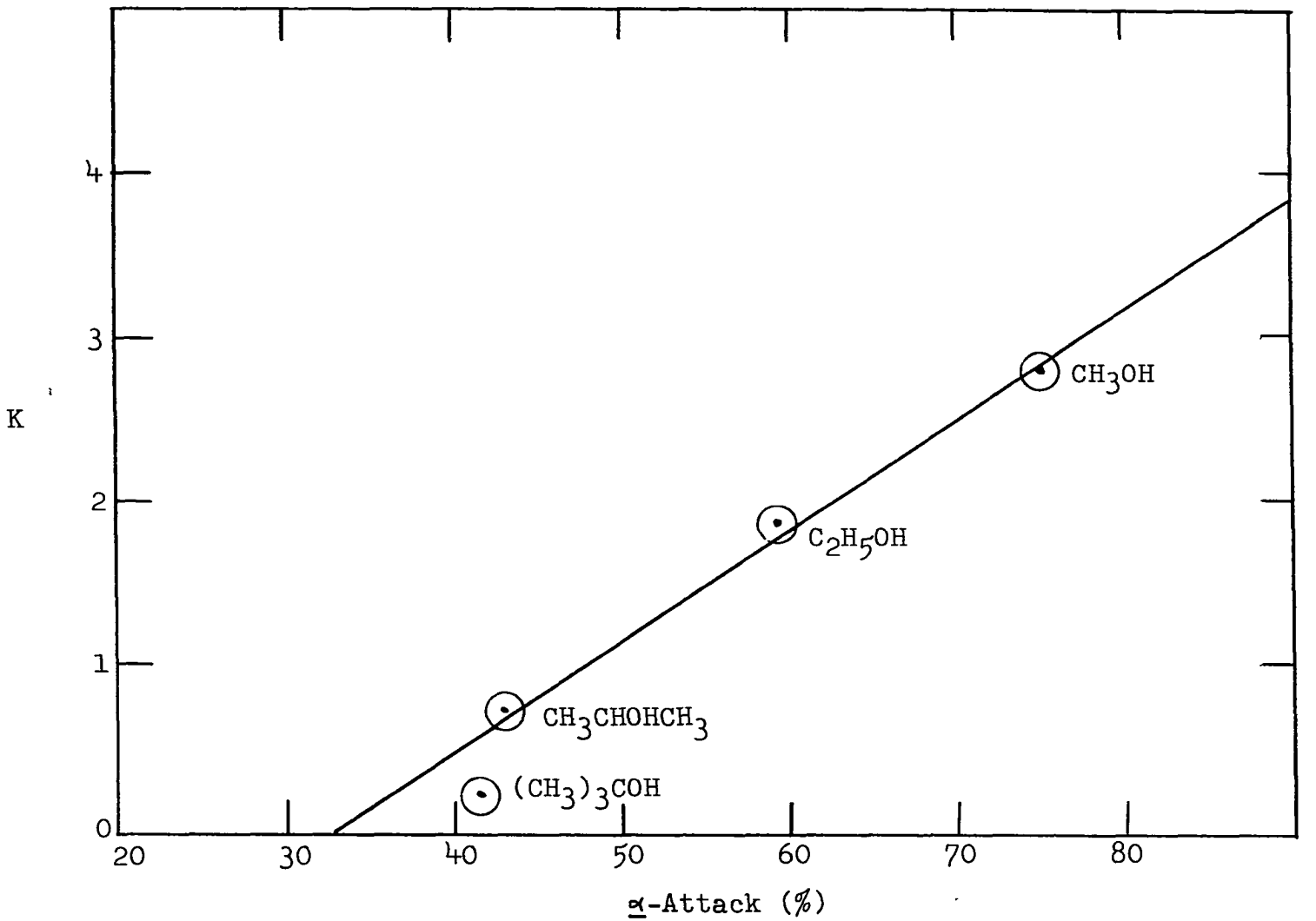


Figure 4. Plot of association constant (K) versus α-attack

SUMMARY

Solvent effects indeed contribute in the reaction of diethylmalonate anion with styrene oxide. After hydrolysis and decarboxylation, two isomeric γ-lactones are formed, their ratio dependent upon the solvent used. It is suggested that a "borderline S_N2" mechanism is contributing to the reaction. Correlation was attempted with the percentage of β-phenyl-γ-butyrolactone produced and various solvent properties.

EXPERIMENTAL

All melting and boiling points are uncorrected.

Elemental analyses are by A. Bernhardt, Microanalytical Laboratories, Mülheim (Ruhr), Germany.

Nmr spectra were obtained with a Varian A-60 instrument using tetramethylsilane as an internal standard.

Gas chromatographic quantitative analyses were performed with a 20% diethylene glycol succinate (DEGS) on a 60-80 mesh Chromosorb W column at 180°. Retention time of γ-phenyl-γ-butyrolactone (3) was 17.5 minutes and β-phenyl-γ-butyrolactone (5) was 20.5 minutes. The composition of the product mixture was calculated by the area under the peak method, the peak areas being determined by half-width and peak-height measurements.

Most of these experiments were run with duplicates. Only the yields of the first series are shown in experimental detail.

The solvents used in these studies were carefully dried. Methanol and 2-propanol were dried with magnesium turnings and distilled. Ethanol was used directly from freshly opened bottles. t-Butyl alcohol, sulfolane, dimethyl sulfoxide, dimethylformamide, N-methyl-2-pyrrolidone, diglyme, p-dioxane, and benzene were refluxed with calcium hydride and distilled. Tetrahydrofuran was refluxed and

distilled from lithium aluminium hydride.

Experiment I. Reaction of Diethylmalonate Anion with Styrene Oxide in Absolute Ethanol. This is basically the method of DePuy.[9] In a three-necked round bottom flask equipped with a condenser, dropping funnel, nitrogen inlet, and magnetic stirrer, were placed sodium (7.0 g, 0.304 g-atom) and 300 ml absolute ethanol. Diethylmalonate (48 g, 0.3 mole) was added with stirring. The contents were brought to reflux and styrene oxide (36 g, 0.3 mole) was added over 2 hours. After 2 hours of additional reflux, 300 ml of 2% sodium hydroxide solution was added and the ethanol was removed by distillation. The remaining solution was cooled, 45 ml of concentrated hydrochloric acid was added with stirring. The mixture was extracted with methylene chloride (2 x 100 ml) and the methylene chloride was removed under reduced pressure, and the remaining oil was heated in a 145° oil bath until carbon dioxide evolution ceased. The oil was distilled and two fractions were collected, the lower boiling cut was ignored after gas-liquid chromatographic separation revealed only small amounts of lactones 3 and 5. The yield was 34.0 g (70.0%), bp 103-111°/0.06-0.15 mm.

Experiment II. Reaction of Diethylmalonate Anion with Styrene Oxide in Absolute Methanol. This was a 0.3 mole scale experiment, same as Experiment I. The yield was 28.4 g (58.5%), bp 95-116°/0.06-0.15 mm.

Experiment III. Reaction of Diethylmalonate Anion with Styrene Oxide in Dry 2-Propanol. This was a 0.3 mole scale

experiment, same as Experiment I. The yield was 31.2 g (64.1%), bp 100-118°/0.15-0.2 mm.

Experiment IV. Reaction of Diethylmalonate Anion with Styrene Oxide in Tetrahydrofuran. Sodium hydride (0.304 mole) as an oil dispersion was washed with dry benzene (3 x 35 ml) in a modified three-necked 1-liter round bottom flask fitted with a mechanical stirrer, dropping funnel, condenser, and nitrogen inlet. The design of the flask* allowed removal of the benzene washes through the sintered glass disk bottom while under a nitrogen atmosphere. Three hundred milliliters dry tetrahydrofuran (distilled from calcium hydride) was introduced and the previous procedure for Experiment I was followed. The yield was 24.2 g (49.7%), bp 107-122°/0.1-0.15 mm.

Experiment V. Reaction of Diethylmalonate Anion with Styrene Oxide in t-Butyl Alcohol. This was a 0.3 mole scale experiment, the same procedure as Experiment IV. The yield was 28.7 g (59.0%), bp 99-111°/0.05-0.06 mm.

Experiment VI. Reaction of Diethylmalonate Anion with Styrene Oxide in p-Dioxane. This was a 0.3 mole scale experiment with 150 ml of dry p-dioxane as a solvent, otherwise the procedure was the same as Experiment IV. The yield was 24.5 g (50.4%), bp 105-125°/0.1-0.2 mm.

Experiment VII. Reaction of Diethylmalonate Anion with Styrene Oxide in Benzene. This was a 0.3 mole scale experiment. Diethylmalonate anion formation was effected by slow addition of diethylmalonate over 1.5 days to refluxing benzene

*Similar to a commercial flask, Cat. No. LG-7950, Lab Glass, Inc.

(400 ml) and sodium hydride (0.304 mole), followed by 12 hours reflux. Styrene oxide (36.0 g, 0.3 mole), was added over 1.25 hours. Subsequent workup was the same as Experiment IV. The yield was 15.7 g (32.3%), bp 107-116°/0.08-0.10 mm.

Experiment VIII. Reaction of Diethylmalonate Anion with Styrene Oxide in Diglyme. Sodium hydride (0.304 mole) was washed with dry benzene (3 x 35 ml) and 150 ml diglyme was added. Diethylmalonate (48 g, 0.3 mole) was introduced, the contents were brought to 70°, and styrene oxide (36 g, 0.3 mole) was added in 1 hour. The temperature was maintained at 70° for 3 additional hours, and the contents were poured into seven-fold ice-water and acidified with hydrochloric acid. This mixture was extracted with 300 ml ether followed by additional extractions with ether (2 x 250 ml). The ether was removed under reduced pressure, 300 ml 95% ethanol and 300 ml of 6% sodium hydroxide were added (this additional base was added to compensate for earlier neutralization with acid). The ethanol was distilled and the workup was continued similar to the Experiment I. The yield was 27.2 g (56.0%), bp 103-116°/0.07-0.12 mm.

Experiment IX. Reaction of Diethylmalonate Anion with Styrene Oxide in Sulfolane (Tetrahydrothiophene-1,1-dioxide). This was a 0.3 mole scale experiment similar to Experiment VIII. Heat was required to effect diethylmalonate anion formation. The temperature was maintained at 60-70° throughout. The product was distilled, bp 95-122°/0.1-0.3 mm, 29.6 g

The product was redistilled after it was shown by glc analysis that the γ-lactones were about 40% of the distillate. The yield was 7.5 g (15.4%), bp 83-84°/0.04-0.05 mm.

Experiment X. Reaction of Diethylmalonate Anion with Styrene Oxide in Dimethyl Sulfoxide. This was a 0.3 mole scale experiment, similar to Experiment VIII, except the reaction was maintained at room temperature throughout. The product (9.7 g), bp 95-134°/0.13-0.15 mm was about 10% γ-lactones by glc analysis, for a yield of about 2%.

Experiment XI. Reaction of Diethylmalonate Anion with Styrene Oxide in Dimethylformamide. This was a 0.3 mole scale experiment, the same as Experiment X. The product was distilled, bp 92-112°/0.10-0.12 mm, and 10.1 g distillate was collected. γ-Lactones 3 and 5 composed about 30% of the distillate (glc analysis) for a yield of about 6%.

Experiment XII. Reaction of Diethylmalonate Anion with Styrene Oxide in N-Methyl-2-pyrrolidone. This was a 0.3 mole scale experiment similar to Experiment X. The product was distilled, bp 106-127°/0.09-0.35 mm, and 7.4 g distillate was collected. γ-Lactones 3 and 5 composed about 30% of the distillate (glc analysis), for a yield of about 4%.

Experiment XIII. Reaction of 0.5 Equivalent Excess Diethylmalonate Anion with Styrene Oxide in Absolute Ethanol. This was a 0.3 mole scale experiment similar to Experiment I except 0.15 mole excess diethylmalonate anion was utilized and later 450 ml of 2% sodium hydroxide solution was used in

the saponification procedure. The ethanol was distilled and 67.5 ml concentrated hydrochloric acid was added. The yield was 39.0 g, (80.4%), bp 102-122°/0.075-0.12 mm.

Experiment XIV. Reaction of Ten-fold Concentration of Diethylmalonate Anion with Styrene Oxide in Absolute Ethanol. This was a 0.5 mole experiment, similar to Experiment XIII, except 1.5 moles diethylmalonate was added to 1.52 g-atoms sodium dissolved in 500 ml absolute ethanol and saponification was effected with 750 ml 4% sodium hydroxide solution. The ethanol was distilled and 225 ml concentrated hydrochloric acid was added, followed by extraction with methylene chloride (2 x 300 ml). The yield was 21.5 g (88.5%), bp 97-132°/0.2-0.3 mm.

Experiment XV. Reaction of Diethylmalonate Anion Plus Excess Diethylmalonate with Styrene Oxide in Absolute Ethanol. In a 0.3 mole scale experiment, 0.45 mole diethylmalonate and 0.3 g-atom sodium were reacted with 0.3 mole styrene oxide. The yield was 34.4 g (70.6%), bp 108-117°/0.09-0.11 mm.

Experiment XVI. Reaction of Diethylmalonate Anion with Styrene Oxide in 500 Milliliters of Absolute Ethanol. In a 0.3 mole scale experiment similar to Experiment I, 500 ml of absolute ethanol was used. The yield was 30.1 g (61.8%), bp 98-114°/0.09-0.10 mm.

Experiment XVII. Reaction of Diethylmalonate Anion with Styrene Oxide in 200 Milliliters of Absolute Ethanol. In a 0.3 mole scale experiment similar to Experiment I, 200 ml of

absolute ethanol was used as the solvent. The yield was 33.9 g (69.8%), bp 105-114°/0.06-0.20 mm.

Experiment XVIII. Reaction of 0.5 Equivalent Excess Diethylmalonate Anion with Styrene Oxide in Tetrahydrofuran. This was a 0.3 mole scale experiment similar to Experiment IV, except 0.15 mole excess diethylmalonate anion was utilized and later 450 ml of 2% sodium hydroxide solution was used in the saponification procedure. The ethanol was distilled and 67.5 ml concentrated hydrochloric acid was added. The yield was 26.8 g (55.1%), bp 110-126°/0.11-0.20 mm.

Experiment XIX. Reaction of Ten-fold Concentration of Diethylmalonate Anion with Styrene Oxide in Tetrahydrofuran. This was a 0.15 mole scale experiment, corresponding with Experiment XIV. The yield was 20.6 g (84.7%), bp 110-120°/0.09 mm.

Experiment XX. Reaction of Diethylmalonate Anion and Excess Diethylmalonate with Styrene Oxide in Tetrahydrofuran. This was a 0.3 mole scale experiment corresponding to Experiment XV. The yield was 24.7 g (50.8%), bp 106-128°/0.10-0.20 mm.

Experiment XXI. Reaction of Diethylmalonate Anion with Styrene Oxide in 200 Milliliters Tetrahydrofuran. This was a 0.3 mole scale experiment corresponding to Experiment XVII. The yield was 28.4 g (58.3%), bp 115-127°/0.15-0.24 mm.

Separation of Lactones (3) and (5) with Column Chromatography. A mixture of the γ-lactones (1.5 g) was placed on a

column of 60 g silicic acid and was eluted with benzene-ethyl acetate (3:1). Lactone 5 was eluted first and was confirmed by its nmr spectrum.[9]

Identification of Phenylethylene Glycol (16). The distillate from Experiment XI was distilled through a spinning band column in six fractions. The first three fractions were largely lactones (3) and (5). The sixth fraction solidified, giving 3.0 g of solid: bp 108°/0.5 mm. The solid was recrystallized from carbon tetrachloride as long white needles; mp 58-60°. The collected crystals were recrystallized three times from hexane-chloroform: mp 64.8-66.0° (lit.[29] mp 65-66°); IR (KBr) 3320-3220 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.28 (s, 5, $C_6\underline{H}_5$), 4.68 (t, 1, $\underline{J}$ = 1 cps, C$\underline{H}$OH), 4.1 (broad s, 2, O$\underline{H}$), 3.58 ppm (d, 2, $\underline{J}$ = 1 cps, $C\underline{H}_2$OH).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.29. Found: C, 69.56; H, 7.06.

Hydrogen Bonding Study of Styrene Oxide with Various Alcohols in Carbon Tetrachloride. Infrared spectra were determined with a Beckman Model DK-1 double beam recording spectrophotometer. Spectra were recorded from 2.7-2.9 μ using 5 cm. near infrared silica cells (Beckman) in a sample holder thermostated at 24.8 $\pm$ 0.2° C.

Carbon tetrachloride (Matheson, Coleman & Bell) was distilled from phosphorus pentoxide through a 90 cm column packed with glass helices. The middle 70% fraction was collected, discarding the first 10%. The carbon tetrachloride

was stored over molecular sieves (3A Linde) until used. Methyl and isopropyl alcohols were dried with magnesium turnings before distillation. Tert-butyl alcohol was dried with calcium hydride and distilled. Ethyl alcohol was used directly from a freshly opened bottle. All alcohols were stored over molecular sieves (3A Linde) before use. Styrene oxide (Aldrich) was distilled (bp 69°/8.9 mm) and an intermediate fraction collected.

0.1 M solutions of alcohols in carbon tetrachloride were prepared and diluted. A 2.438 M solution of styrene oxide in carbon tetrachloride was prepared.

Dilute alcohols of 10^{-3} M exist largely as monomers. A Beer's Law plot suggested a 2.5×10^{-3} M concentration of alcohols would be convenient for a hydrogen bonding study. Three different solutions were prepared: 0.0975 M styrene oxide, 2.5×10^{-3} M alcohol, and 0.0975 M styrene oxide plus 2.5×10^{-3} M alcohol. The 100 ml volumetric flasks containing these solutions were fitted with drying tubes and allowed to equilibrate for 24 hours at room temperature ($25.5 \pm 0.5°$).

The spectra of these solutions were recorded. At the wavelength of the absorption of the monomer -OH stretch, the absorbance of 0.0975 M styrene oxide was subtracted from the absorbance of the ternary mixture of alcohol, styrene oxide, and carbon tetrachloride. The difference between the absorbances of the 2.5×10^{-3} M alcohol and the ternary mixture less the absorbance of styrene oxide was considered a measure of the extent of hydrogen bonding between the alcohol and styrene oxide.

TABLE 10

Absorbance Data of Various Alcohols and Alcohols plus Styrene Oxide

Alcohol	λ (μ)	Absorbance: Alcohol (2.5 x 10^{-3} M)	Absorbance: Styrene Oxide (0.1 M)	Absorbance: Alcohol and Styrene Oxide (2.5 x 10^{-3} M and 0.1 M)	ΔA
Methanol	2.7415	0.721	0.328	0.886	0.163
Ethanol	2.7470	0.611	0.284	0.796	0.099
2-Propanol	2.7540	0.638	0.276	0.870	0.044
t-Butyl alcohol	2.7595	0.639	0.197	0.822	0.013

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III. SYNTHESIS OF FIVE- AND SIX-MEMBERED OXYGEN AND SULFUR HETEROCYCLES VIA CONCOMITANT MICHAEL AND DIECKMANN CONDENSATIONS

INTRODUCTION

Individually the Michael condensation[1-2] and the Dieckmann condensation[3-4] are well known reactions of synthetic importance. Combined in one sequence, these condensations present a technique for the synthesis of heterocycles that has hardly been exploited.

Originally the Michael condensation was the addition of an activated carbanion to an acceptor such as an α,β-unsaturated carbonyl compound. Now, the Michael condensation has been expanded to include simply, anionic donors and acceptors activated by groups other than carbonyl and carbalkoxyl. An example of this extension includes the addition of a mercaptan to an olefin to produce a thioether. Thus ethyl thioglycolate (1) and ethyl acrylate (2) condense to produce carbethoxymethyl β-carbethoxyethyl thioether (3).[5]

$$\underset{(1)}{HSCH_2CO_2C_2H_5} + \underset{(2)}{H_2C{=}CH_2CO_2CH_3} \longrightarrow \underset{(3)}{C_2H_5O_2CCH_2SCH_2CH_2CO_2C_2H_5}$$

Similarly methyl glycolate (4) and methyl acrylate (5) produce carbomethoxymethyl β-carbomethoxyethyl ether (6).[6]

$$HOCH_2CO_2CH_3 \quad + \quad H_2C{=}CH_2CO_2CH_3 \longrightarrow CH_3O_2CCH_2OCH_2CH_2CO_2CH_3$$

(4) (5) (6)

The Dieckmann condensation is a base catalyzed acetoacetic ester condensation in which a dicarboxylic ester containing at least one α-hydrogen atom, is cyclized to a β-keto ester. One example of the numerous applications of the Dieckmann condensation to the syntheses of heterocycles is the cyclization of dimethyl β-thiodipropionate (7) to produce 3-carbomethoxytetrahydrothiopyran-4-one (8).[7-8]

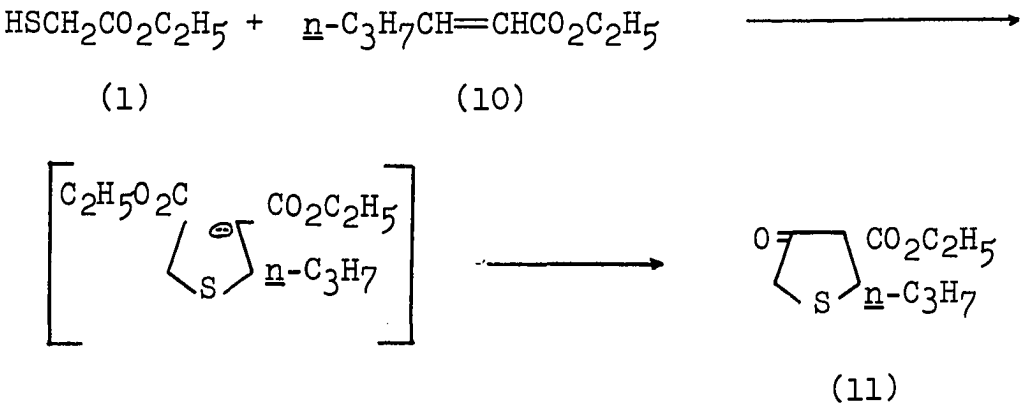
(7) (8)

Also 4-carbomethoxy-3-ketotetrahydrofuran (9) is the result of condensation of carbomethoxymethyl β-carbomethoxyethyl ether (6).[6]

(6) (9)

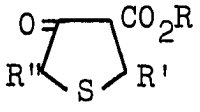
The latter example of the Dieckmann condensation coupled with the Michael condensation cited earlier (formation of compound 6) is a reaction sequence that usually can be simplified. Rather than two separate condensations with isolation of products, it is often possible to obtain the desired

cyclized end product without isolation of the Michael adduct. This method has been applied in the preparation of numerous five-membered nitrogen heterocycles but seldom utilized for other types of heterocycles. The first reported use of this simplified sequence to produce oxygen or sulfur heterocycles was the condensation of ethyl thioglycolate (1) and ethyl 2-hexenoate (10) which cyclized to 2-propyl-3-carbethoxytetrahydrothiophen-4-one (11).[9]



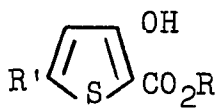
(1) (10) (11)

A total of five tetrahydrothiophenones (11) and (12) and four thiophenes (13) have been synthesized in this manner,



(12)

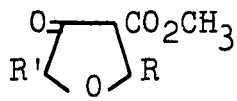
(11, R = C_2H_5, R' = n-C_3H_7, R'' = H)[9]
(12a, R = CH_3, R' = CO_2CH_3, R'' = H)[10]
(12b, R = CH_3, R' = n-C_3H_7, R'' = H)[9]
(12c, R = CH_3, R' = $(CH_2)_3OC_6H_5$, R''=H)[9]
(12d, R = CH_3, R' = H, R'' = $(CH_2)_3OC_6H_5$)[9]



(13)

(13a, R = CH_3, R' = H)[11]
(13b, R = C_2H_5, R' = H)[11]
(13c, R = C_2H_5, R' = C_6H_5)[11]
(13d, R = CH_3, R' = CO_2CH_3)[10]

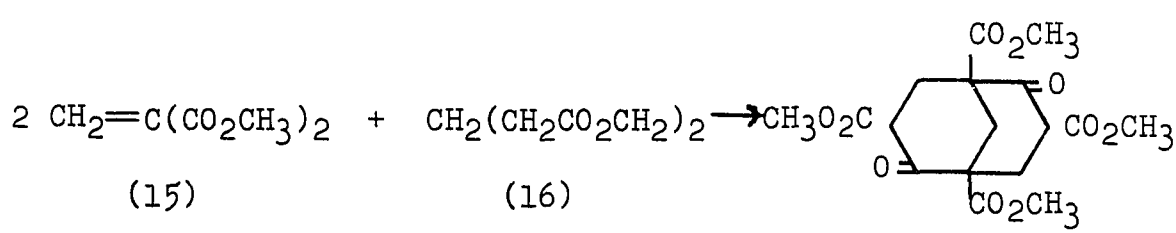
Other examples of this version of the Dieckmann condensation include the preparation of the tetrahydrofuranones (14).



(14)

(14a, R = H, R' = H)[12]
(14b, R = CH_3, R' = H)[12]
(14c, R = H, R' = CH_3)[12]

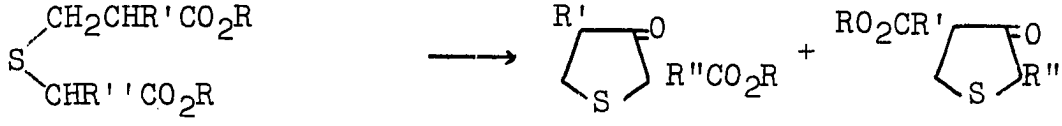
No example of the formation of a six-membered ring heterocycle by means of this Michael-Dieckmann reaction sequence has been reported. In fact, there is only one reported example of a six-membered carbocyclic produced by this sequence.[13-14] The condensation of two equivalents of dimethylmethylenemalonate (15) with dimethyl glutarate (16) gave the bicyclononane derivative 17.



(15) (16) (17)

The Dieckmann cyclization of unsymmetrical diesters potentially may lead to two isomeric keto esters. This is illustrated

by the following sequence with the formation of isomeric tetrahydrothiophenones 18 and 19. The type of α-substituent, the reaction temperature, and the solvent may influence the direction

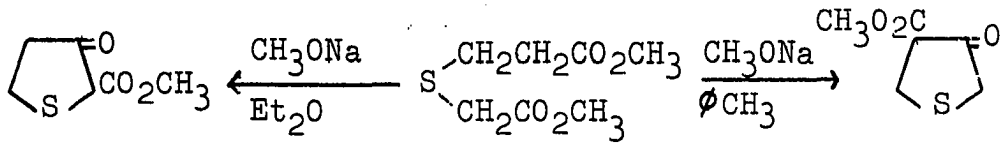


(20) (18) (19)

of ring closure. With unsubstituted diester 20 (R' = R'' = H), two intermediary anions, 21 and 22 are possible. The α-hydrogens adjacent to sulfur are the most acidic,

(21) (22)

thus anion 22 is formed more rapidly, leading to compound 18. At higher temperatures and equilibrium conditions, product 19 is formed *via* anion 21. This has been shown with the cyclization of dimethyl ester 23 to largely 2-carbomethoxytetrahydrothiophen-3-one (24) in refluxing diethyl ether to exclusively 4-carbomethoxytetrahydrothiophen-3-one (25) in refluxing toluene.[15]

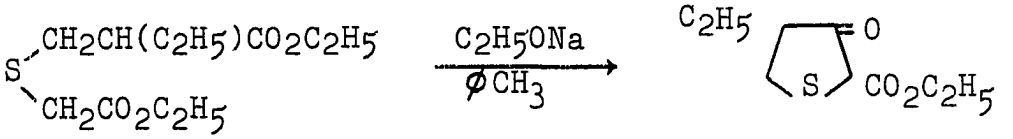


(24) (23) (25)

An alkyl substituent on only one of the active methylenes of diester 18 (R' or R'' = alkyl) decreases the acidity of the hydrogen at the substituted site, favoring the unsubstituted anion. The condensation of ethyl α-(2-carbethoxyethylmercapto) propionate (26) gave 2-methyl-4-carbethoxytetrahydrothiophen-3-one (27).[5,16]

(26) (27)

Similarly, tetrahydrothiophenone 28 is the product of cyclization of diester 29.[17]

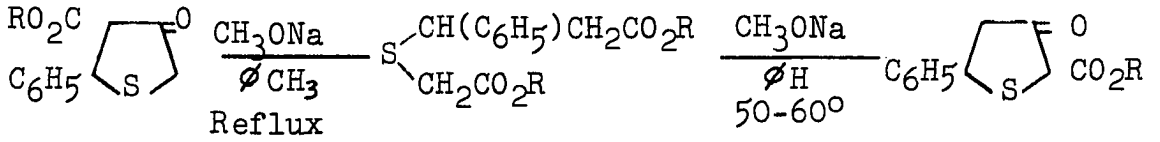


(29) (28)

Substitution of the β-methylene again presents a choice of directions for ring closure. β-Methyl substitution, compound 30, produced tetrahydrothiophenone 31.[18-19]

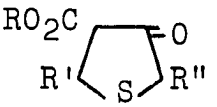
(30) (31)

Product control was demonstrated when compound 32 was formed in refluxing toluene from β-phenyl diester (33).[19] The same diester gave the isomeric ketoester 34 in benzene at 50-60°.[19]



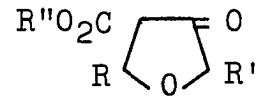
(32) (33) (34)

The combined Michael-Dieckmann sequence without isolation of intermediates has accounted for several previously mentioned 5-substituted-4-carbalkoxytetrahydrothiophen-3-ones (12) (R'' = H).[9] These reactions were conducted in diethyl ether at room temperature or refluxing benzene.



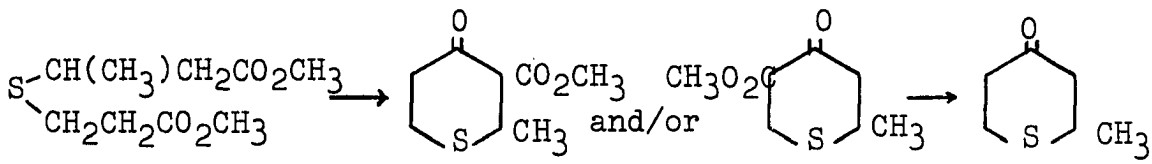
(12)

Isomeric ketoester products has not become a problem in tetrahydrofuranone, tetrahydrothiopyranone, or tetrahydropyranone synthesis. Most of the four reported syntheses of tetrahydrofuranones via Dieckmann condensations could theoretically have closed in two directions. Only 4-carbalkoxytetrahydrofuran-3-ones (14) have been reported.[6,12]



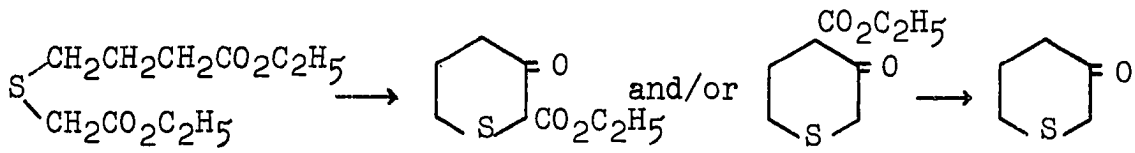
(14)

The exact direction of Dieckmann ring closure of certain substituted diesters leading to substituted tetrahydrothiopyranones, has not been determined. Intermediate ketoesters were not usually identified and were isolated only in one example. The synthesis of 2-methyltetrahydrothiopyran-4-one (35) is typical of the few examples reported.[20]



(35)

The intermediate ketoester(s) 36 was isolated yet unidentified in the synthesis of tetrahydrothiopyran-3-one (37) from diester 38.[21]

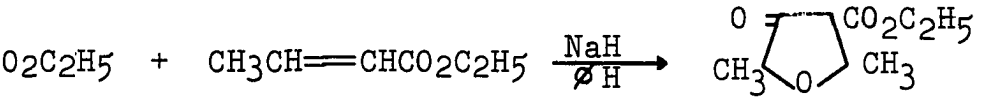


(38) (36) (37)

In view of the small amount of work previously devoted to the synthesis of five- and six-membered oxygen and sulfur heterocycles *via* a combined Michael-Dieckmann condensation, there remained 1) the first application of this method for the synthesis of tetrahydropyranones and tetrahydrothiopyranones, 2) extension of this method in the synthesis of unreported tetrafuranones, tetrahydrothiophenones, tetrahydropyranones, and tetrahydrothiopyranones, 3) the extension of this simplified sequence for improved and more efficient syntheses of previously reported oxygen and sulfur heterocycles obtained by other means.

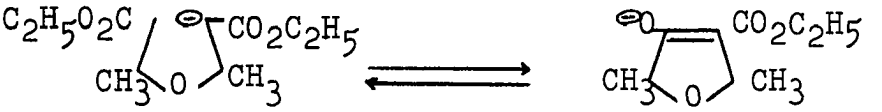
RESULTS AND DISCUSSION

The previously unreported compound, 2,5-dimethyl-3-carbethoxytetrahydrofuran-4-one (39) was obtained from ethyl lactate (40) and ethyl crotonate (41) without isolation of the Michael adduct. This combined sequence of Michael and Dieckmann condensations without isolation of intermediates is an efficient and time-saving method of synthesis of heterocycles, formerly obtained by other methods or by individual condensations.



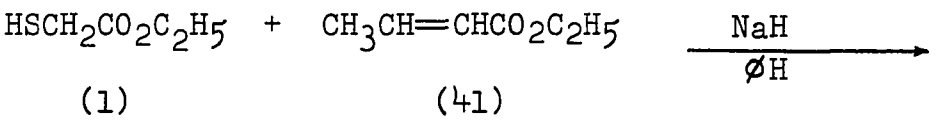
(40) (41) (39)

The formation of the enolate of the keto ester is the driving force of the Dieckmann condensation.[4] The ethanol formed in the Dieckmann cyclization was removed by azeotropic distillation with the solvent, benzene. Removal of the alcohol shifted the equilibrium (42-43) of the Dieckmann condensation in favor of the enolate. This is a technique seldom utilized but applicable in almost every Dieckmann condensation.

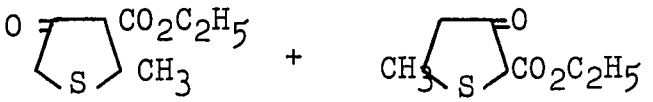


(42) (43)

These techniques were also applied in the reaction of ethyl thioglycolate (1) with ethyl crotonate (41) to give isomeric keto esters, 2-methyl-3-carbethoxytetrahydrothiophen-4-one (45) and 2-carbethoxy-5-methyltetrahydrothiophen-3-one (46). The presence of isomeric keto esters was suspected

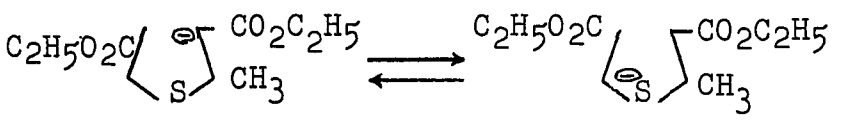


(1) (41)



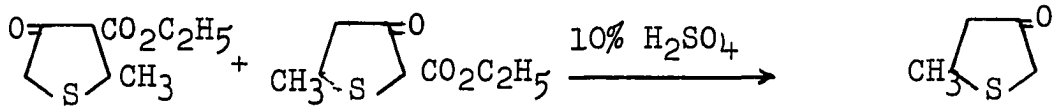
(45) (46)

when the nmr spectrum appeared more complex than expected. The probability of disastereomers further compounded the analysis. The mixture of keto esters is the result of at least partial equilibration of the Michael adduct anion (47-48) followed by cyclization.



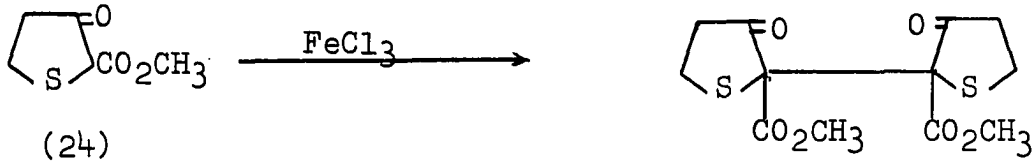
(47) (48)

Hydrolysis and decarboxylation of the mixture gave a single product, 5-methyltetrahydrothiophen-3-one (49). Interpretation of the nmr spectrum of 49 revealed a singlet at δ 3.25 ppm



(45) (46) (49)

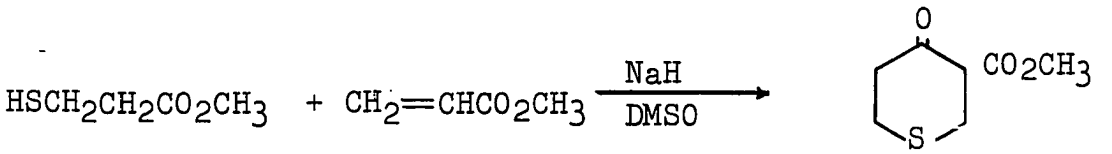
which was assigned to the C-2 protons. A similar singlet of less magnitude appeared at δ 3.4 ppm in the spectrum of a mixture of isomers 45 and 46. Woodward[15] has reported a sensitive method for the quantitative determination of 2-carbomethoxytetrahydrothiophen-3-one in the presence of 4-carbomethoxytetrahydrothiophen-3-one. Titration with ferric chloride until a red color persisted, oxidized 24 to its dimer 50. Results of the application of this method to the mixture of isomers 45 and 46 revealed the 2-carbethoxy-5-methyltetrahydrothiophen-3-one (46) was 63% of the product.



(24) (50)

In analogy with the results of Woodward,[15] the ratio of the kinetic product, isomer 46, and the thermodynamic product, isomer 45, should vary with the proper selection of solvent and reaction conditions.

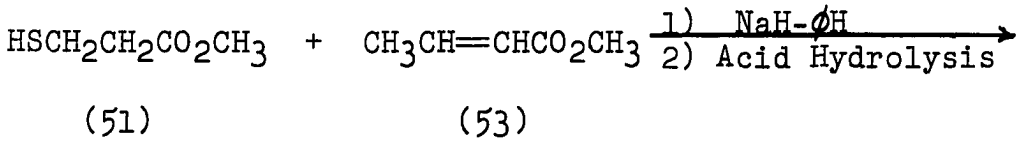
A variation of the combined Michael-Dieckmann condensations was successful in the reaction of methyl β-thiopropionate (51) with methyl acrylate (52) to give 3-carbomethoxytetrahydrothiopyran-4-one (8).



(51) (52) (8)

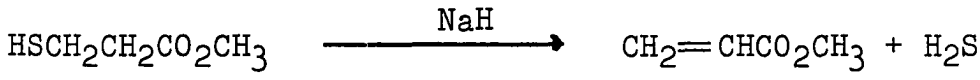
This appears to be the first application of the combined Michael-Dieckmann condensation for the synthesis of a six-membered heterocycle. Only one six-membered carbocyclic has been reported by this sequence.[13-14] Convenience dictated the conduction of the reaction in dimethyl sulfoxide at room temperature, as the reaction was vigorous and unpredictably exothermic when conducted in benzene. The yield of 3-carbomethoxytetrahydrothiopyran-4-one (8) compared very favorably with that obtained from the two step sequence previously reported.[7]

Investigation of the generality of this sequence for the synthesis of substituted tetrahydrothiopyran-4-ones revealed the method has limitations. The reaction of methyl β-thiopropionate (51) and methyl crotonate (53) followed by hydrolysis and decarboxylation gave 2-methyltetrahydrothiopyran-4-one (54) in addition to tetrahydrothiopyran-4-one (55), both in low yield. Compound 8 apparently is the result of β-elimination of hydrogen sulfide from methyl β-thiopropionate (51) to give methyl acrylate (52) which competes for methyl β-thiopropionate anion.



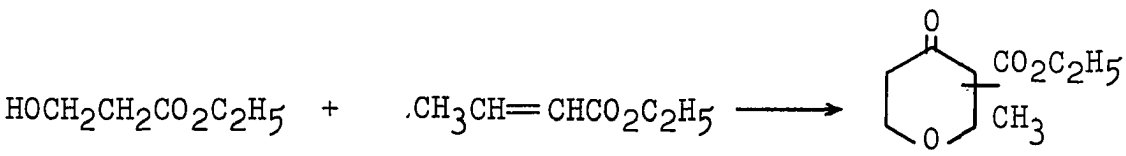
(51) (53)

(54) (55)

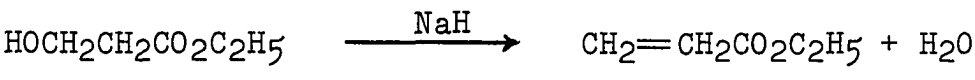


(51) (52)

The previously mentioned methods were unsatisfactory when applied in the attempted synthesis of a methyl substituted carbethoxytetrahydropyran-4-one (56) from ethyl β-hydroxypropionate (57) and ethyl crotonate (41). β-Elimination is a greater problem with ethyl β-hydroxypropionate (57) than with methyl β-thiopropionate which was discussed earlier.



(57) (41) (56)



(57)

SUMMARY

In summary, the generality of a combined Michael-Dieckmann condensation as applied to the synthesis of five- and six-membered sulfur and oxygen heterocycles was investigated. This method included the simultaneous addition of reactants followed by azeotropic distillation of the alcohol produced to force the equilibrium in favor of products. These methods gave an unreported tetrahydrofuranone in good yield, produced two tetrahydrothiophenones, and tetrahydrothiopyran-4-one, previously obtained by less efficient methods. Although tetrahydrothiopyran-4-one is the first reported six-membered heterocycle obtained by a combined Michael-Dieckmann condensation, extension to the synthesis of substituted tetrahydrothiopyranones and tetrahydropyranones was less successful and failed completely in the latter case.

EXPERIMENTAL

All melting and boiling points are uncorrected. Elemental analyses are by A. Bernhardt, Microanalytical Laboratories, Mülheim (Ruhr), Germany. Nmr spectra were obtained with a Varian A-60 instrument using tetramethylsilane as an internal standard. IR spectra were obtained with a Beckman IR-8 instrument. The solvents used in these experiments were carefully dried. Benzene and dimethyl sulfoxide were refluxed with calcium hydride, distilled (reduced pressure for the latter), and stored over a column of molecular sieves (Linde, 4A). The solvents were drawn through the column of molecular sieves as needed.

Synthesis of 2,5-Dimethyl-3-carbethoxytetrahydrofuran-4-one (39). Sodium hydride (0.11 mole) as an oil dispersion was washed free of oil with dry benzene (3 x 30 ml) in a modified three-necked 500 ml round bottom flask * fitted with a Trubore** stirrer, dropping funnel, condenser, and a calcium chloride drying tube. Benzene (300 ml) was introduced. A mixture of 12.54 g (0.11 mole) ethyl crotonate, 11.8 g (0.10 mole) ethyl lactate, and 15 ml of dry benzene was added to the stirred suspension in 3.5 hours. The contents of the flask were

*A comparable flask is available, Labglass Inc., LG 7950

**Trademark, Ace Glass, Inc.

brought to reflux and ethanol azeotroped until a constant refractive index was obtained. The mixture was allowed to cool and then cautiously acidified with 6N hydrochloric acid. The benzene layer was separated, washed with 60 ml of saturated sodium chloride solution, followed by 60 ml of water. The benzene layer was dried ($MgSO_4$), concentrated, and distilled, bp 68-71°/0.85-1.1 mm, giving 10.87 g (58.4%) of 2,5-dimethyl-3-carbethoxytetrahydrofuran-4-one. A sample was redistilled, for analysis: bp 78°/2.0 mm; n_D^{20} 1.4400; IR (film) 1775 (ketone C=O), 1735 (ester C=O), 1675 (enol C=O), 1640 cm^{-1} (C=C); nmr (CCl_4) δ 4.0-4.72 (m, 4), 3.12 (d, 1, $COC\underline{H}CO_2$), 1.13-1.43 ppm (m, 9).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.95; H, 7.51.

Synthesis of 2-methyl-3-carbethoxytetrahydrothiophen-4-one (45) and 2-carbethoxy-5-methyltetrahydrothiophen-3-one (46). To a stirred suspension of 0.11 mole of sodium hydride (washed free of oil) in 300 ml of dry benzene in the specially designed 500 ml round bottom flask (see above) were added in 2.5 hours a mixture of 12.0 g (0.1 mole) ethyl thioglycolate*, 11.54 g (0.1 mole) ethyl crotonate and 15 ml of dry benzene. The flask contents were stirred for an additional 1 hr. at which time the reaction became exothermic which required cooling with an ice-water bath. The solution was carefully brought to

*A generous sample was supplied by Evans Chemetics.

reflux and ethanol azeotroped until a constant refractive index was obtained. The reaction mixture was allowed to cool and then acidified with 6N hydrochloric acid. The benzene layer was washed with 50 ml of saturated sodium chloride solution, followed by 50 ml of water. The benzene layer was dried ($MgSO_4$), concentrated, and distilled, bp 89-96°/0.5-1.1 mm, giving 13.32 g (70.9%) of a faint yellow foul-smelling oil. A sample was redistilled for analysis: bp 91°/1.0 mm; n_D^{25} 1.4935; IR (film) 1755 (ketone C=O), 1730 (ester C=O), 1660 (enol C=O), 1615 cm^{-1} (C=C).

Anal. Calcd for $C_8H_{12}SO_3$; C, 51.04; H, 6.37; S, 17.03. Found: C, 50.88; H, 6.22; S, 16.87.

A 0.2026 g sample in 3 ml of 95% ethanol was titrated with 0.100 N ferric chloride. A pink endpoint required 6.75 ml of ferric chloride. From this result, approximately 63% of the above product is 2-carbethoxy-5-methyltetrahydrothiophen-3-one and the remainder, its isomer, 2-methyl-3-carbethoxy-tetrahydrothiophen-4-one. The basis of this conclusion comes from the result of a similar titration of 2-carbomethoxytetrahydrothiophen-3-one and 4-carbomethoxytetrahydrothiophen-3-one by Woodward.[15]

Synthesis of 3-carbomethoxytetrahydrothiopyran-4-one (8). To a stirred suspension of 0.11 mole sodium hydride (washed free of oil) in 50 ml of dry dimethyl sulfoxide in a specially designed 250 ml round bottom flask (see above were added slowly with cooling, 12.0 g (0.1 mole) of methyl

β-thiopropionate*. The flask contents were stirred for an additional 1 hour. Methyl acrylate (8.71 g, 0.1 mole) was added slowly in 5.5 hours. The reaction mixture was stirred for an additional 15 hours, and then poured into 400 ml of acidified ice-water and extracted with ether (3 x 150 ml). The ether layer was washed with saturated sodium chloride solution (1 x 100 ml), followed by water (1 x 75 ml). The ether layer was dried ($MgSO_4$), concentrated, and distilled giving 7.16 g (44.2%) of 3-carbomethoxytetrahydrothiopyran-4-one (8): bp 85-86.5°/0.3-0.4 mm; $n_D^{19.5}$ 1.5263; [lit.[7] bp 120-5°/5 mm, n_D^{20} 1.5234]; IR (film) 1745 (ester C=O), 1715 (ketone C=O), 1655 (enol C=O), 1612 cm^{-1} (C=C).

Anal. Calcd for $C_7H_{10}SO_3$: C, 48.26; H, 5.79; S, 18.40. Found: C, 48.12; H, 5.53; S, 18.53.

Hydrolysis and Decarboxylation of 3-Carbomethoxytetrahydrothiopyran-4-one (8). 1.62 g (0.01 mole) 3-Carbomethoxytetrahydrothiopyran-4-one (8) and 11 ml of 10% sulfuric acid were refluxed and stirred for 3.5 hours. The mixture was cooled and extracted with ether (2 x 10 ml). The ether layer was dried (Na_2SO_4), filtered, concentrated, giving 1.2 g (100%) of a white waxy solid. The solid tetrahydrothiopyran-4-one (55) was recrystallized 2 times from hexane, mp 60-2°, 62-4°; [lit.[7,20,22] mp 58-62°, 65-66°].

*A generous sample was supplied by Evans Chemetics.

Synthesis of 2-Methyltetrahydropyran-4-one (54). To a stirred suspension of 0.11 mole sodium hydride (washed free of oil) in 250 ml of dry benzene were added in 1 hr. 12.0 g (0.1 mole) of methyl β-thiopropionate, 10.0 g (0.1 mole) of methyl crotonate, and 15 ml dry benzene. The mixture was slowly brought to reflux in 6 hrs. and refluxed for 2 hrs. Slow distillation was begun and continued until a constant refractive index was obtained. The flask contents were allowed to cool and then neutralize with 20 ml 6N hydrochloric acid. The benzene layer was separated and washed with 50 ml of saturated sodium chloride solution. The organic layer was dried ($MgSO_4$), filtered, concentrated, and distilled, bp 80-100°/0.15-0.25 mm, until the distillate no longer contained keto esters as determined by IR spectra. The distillate, 7.2 g, and 60 ml of 10% sulfuric acid were refluxed for 3.5 hrs. The contents were cooled, extracted with ether (3 x 25 ml). The ether layer was washed with 25 ml of saturated sodium bicarbonate solution, dried (Na_2SO_4), concentrated, and distilled, giving 1.3 g (10%) of product: bp 68-72°/2.7-3.5 mm [lit.[20] bp 41-5°/2 mm]; IR (film) 1715 cm^{-1} (C=O). Thin layer chromatography revealed a mixture of two components, one of which appeared to be tetrahydrothiopyran-4-one (55) and the other assumed to be 2-methyltetrahydrothiopyran-4-one (54).

Attempted Synthesis of 2-Methyl-5-carbethoxytetrahydropyran-4-one (56). The procedures described above failed to produce any enolic products.

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