Synthetic Studies in the Fumagillin Series[1]

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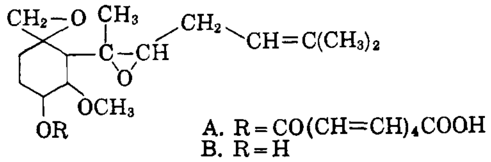
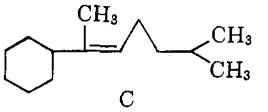
Synthetic approaches to the fumagillin structure have been explored. 2-Cyclohexyl-6-methyl-2-heptene (C) has been prepared in two ways by the Wittig reaction, and also from cyclohexyl methyl ketone, *via* the Reformatsky reaction to β-cyclohexyl-β-methylacrylic acid (G); the acid chloride with diisobutylcadmium gives 2-cyclohexyl-6-methyl-2-hepten-4-one (K), and indirect reduction of the carbonyl group gives the olefin (C). The Diels–Alder addition of 1-methoxybutadiene to 3-penten-2-one gives a mixture of the two possible isomers, 1-methyl-2-acetyl-3-methoxycyclohexene-4 (Q) and 1-methyl-2-methoxy-6-acetylcyclohexene-3 (R); the structures of these have been proven by consideration of carbonyl reactivity and by dehydrogenation to known aromatic compounds. The first isomer has been converted to 1-methyl-2-acetyl-3-methoxy-4,5-epoxycyclohexane (V), whose stereochemistry has been discussed, and various derived compounds have been prepared. 1-Methoxybutadiene and methyl crotonate give only 1-methyl-2-carbomethoxy-3-methoxycyclohexene-4 (Z), whose structure has been proved by dehydrogenation.

The elucidation of the structure of the antibiotic fumagillin and of its hydrolysis product, alcohol-I, as A and B, respectively,[4] has made the synthesis of compounds in this series a challenging problem. The present paper reports orienting experiments directed toward the synthesis of compounds related to B.

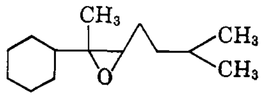


A. R = CO(CH=CH)₄COOH
B. R = H

One phase of the work has been the synthesis of 2-cyclohexyl-6-methyl-2-heptene (C) which was then to be converted to the epoxide D. Compound C was prepared in low yield by the Wittig reaction[5] between cyclohexyl methyl ketone and triphenylisohexylphosphonium bromide (E); the phosphonium compound was made by heating triphenylphosphine and isohexyl bromide in a sealed tube. The low yield in the Wittig reaction apparently was due to the very slight solubility of the phosphonium salt in suitable solvents.



C



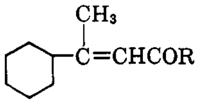
D

$(C_6H_5)_3P^+CH_2CH_2CH_2CH(CH_3)_2Br^-$

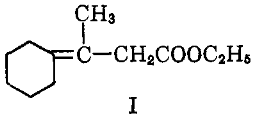
The Wittig reaction in the converse sense, using isocaproaldehyde and the rather unstable phosphonium compound from α-bromoethylcyclohexane and triphenylphosphine gave an even poorer yield of the olefin C, in a reaction which was not reproducible.

The synthesis of analogs more closely related than D to the alcohol-I structure by the Wittig procedure would involve a di-*ortho*-substituted cyclohexyl methyl ketone, and the unsatisfactory results just described made the whole approach unattractive.

The required olefin C was, therefore, elaborated as follows. The Reformatsky reaction between ethyl bromoacetate and cyclohexyl methyl ketone gave an 82% yield of the expected ethyl β-cyclohexyl-β-hydroxybutyrate; the infrared spectrum indicated that some dehydration had occurred. The β-hydroxy ester was dehydrated with phosphorus oxychloride–pyridine,[6] and the product was regarded as the conjugated α,β-unsaturated isomer F, with only insignificant amounts of the β,γ-isomer I. This conclusion was based on the infrared spectrum, which showed a conjugated ester carbonyl at 1706 cm.,$^{-1}$ and absorption in the ultraviolet with λ_{max} 222 mμ (ε 12,520).[7]

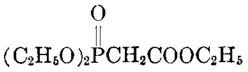


F. R = OC₂H₅
G. R = OH
H. R = Cl



I

Hydrolysis of the ester F gave the crystalline acid G, m.p. 85–86°, with carbonyl absorption at 1681 cm.$^{-1}$, and ultraviolet absorption λ_{max} 219 mμ (ε 12,000). The ester F was also obtained in 35% yield by the action of triethyl phosphonoacetate (J)[8] and sodium hydride on cyclohexyl methyl ketone.



$$(C_2H_5O)_2\overset{\overset{\displaystyle O}{\|}}{P}CH_2COOC_2H_5$$

J

The conjugated acid G was converted to the acid chloride H; treatment of this with diisobutylcadmium by the general procedure of Cason and Prout[9] gave the crude ketone K in 82% yield. Fractional distillation yielded the α,β-unsaturated isomer K in about 60% yield. The conjugated structure K was supported by the carbonyl frequency (1681 cm.$^{-1}$) and by the ultraviolet absorption, with λ_{max} 243 mμ (ε 13,100). The ketone formed a crystalline dinitrophenylhydrazone,

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[1] Aided by Grant E-1138 of the U. S. Public Health Service.

[2] Niagara Chemical Division, FMC Corporation, Middleport, New York.

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[4] (a) D. S. Tarbell, R. M. Carman, D. D. Chapman, K. R. Huffman, and N. J. McCorkindale, *J. Am. Chem. Soc.*, **82**, 1005 (1960); (b) D. S. Tarbell, R. M. Carman, D. D. Chapman, S. E. Cremer, A. D. Cross, K. R. Huffman, M. Kunstmann, N. J. McCorkindale, J. G. McNally, Jr., A. Rosowsky, F. H. L. Varino, and R. L. West, *ibid.*, **83**, 3096 (1961); (c) J. R. Turner and D. S. Tarbell, *Proc. Nat. Acad. Sciences*, **48**, 733 (1962).

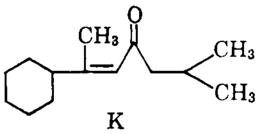
[5] G. Wittig and U. Schöllkopf, *Ber.*, **87**, 1318 (1954); U. Schöllhopf, *Angew. Chem.*, **71**, 260 (1959).

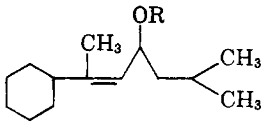
[6] This reagent in general gives less of the β-γ-unsaturated isomer and more of the α,β-isomer. [G. A. R. Kon and K. S. Nargund, *J. Chem. Soc.*, 2461 (1932).]

[7] The ε values reported by J. Cason and K. L. Rinehart, Jr., *J. Org. Chem.*, **20**, 1591 (1955), for α,β-unsaturated esters with an α-methyl group are in the range 12,800–13,800. This paper contains a discussion of the factors affecting the α,β-β,γ-equilibrium, and also contains references to earlier work by R. P. Linstead, *et al.*

[8] *Cf.* W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961), for this variant of the Wittig reaction.

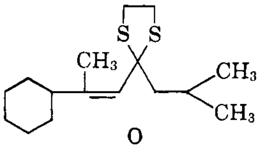
[9] J. Cason and F. S. Prout, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 601.

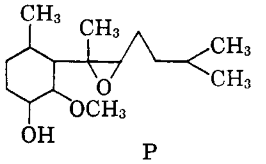

K


L. R = H
M. R = $\underset{\underset{\text{O}}{\|}}{\text{C}}\text{—C}_6\text{H}_5$

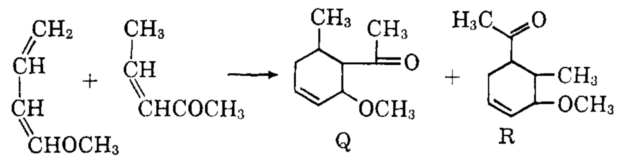
and treatment of the ketone with lithium aluminum hydride gave the corresponding alcohol L in 94% yield. The benzoate M was reduced with lithium and ethylamine[10] to the olefin C in 22% yield, with the recovery of 65% of the allylic alcohol L formed by hydrolysis during the reaction. The properties of the hydrocarbon formed in this way were identical with those prepared by the Wittig reactions. The n.m.r. spectrum of the olefin showed a triplet at τ 4.98 (one vinyl proton), a singlet at τ 7.92 (three allylic methyl protons), a broad peak around τ 8.46 (cyclohexane ring protons), and a doublet at 9.08 and 9.17 (six isopropyl protons), in agreement with structure C.

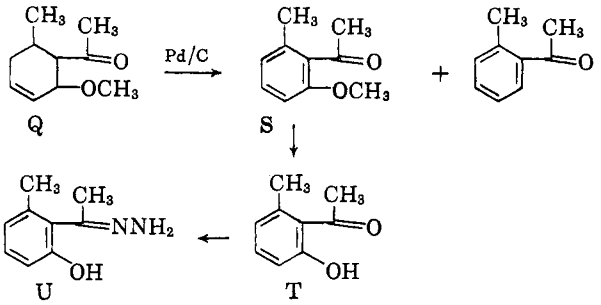
Another method of reducing the carbonyl group in the conjugated ketone K was explored. The thioketal O was prepared in 60% yield by the method of Fieser.[11] Treatment of this compound with Raney nickel,[12] hydrazine hydrate-potassium hydroxide,[13] and aluminum amalgam[14] gave only starting material, with no desulfuration product. Treatment of the thioketal O with sodium and liquid ammonia[15] gave an unidentified crystalline compound.[16]


O

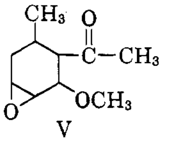

P

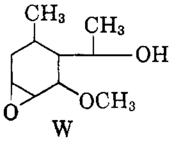
A quite different approach to the synthesis of more highly oxygenated cyclohexane derivatives, which could lead to structures such as the desoxytetrahydro alcohol-I[4b] (P), involved the Diels–Alder reaction with 1-methoxybutadiene. Condensation of this diene with 3-penten-2-one[17] in sealed tubes at 135° gave a mixture of the two possible position isomers, Q and R, which was separable by fractional distillation or, less usefully, by differences in carbonyl reactivity. One of the isomers formed carbonyl derivatives readily, but the other did not, and this allowed a tentative assignment of structure R to the isomer with the more reactive carbonyl group. This was supported by dehydrogenation of Q by palladium–charcoal at 300° to a mixture of 2-methylacetophenone and 2-methoxy-6-methylacetophenone (S), which was separated by v.p.c.[18]; the methylacetophenone was identified through a solid derivative, and S was identified by comparison of its infrared spectrum with that of a known sample previously prepared in this laboratory by an unambiguous method.[19] The identification was made conclusive by heating the crude dehydrogenation mixture with pyridine hydrochloride (to cleave the methoxyl group)[19]; the hydroxyactophenone derivative T was isolated by sublimation, was converted to the hydrazone U, and this derivative showed no depression on mixture melting point with a known sample.[19]





Epoxidation of the adduct Q by monoperphthalic acid gave a 42% yield of the crystalline epoxide V; the possibility that Baeyer–Villiger oxidation to an ester might have occurred was disproved by a positive thiosulfate test[20] for the epoxide group. Catalytic reduction of the epoxide with several catalysts and a variety of conditions was unsuccessful; the epoxide was recovered unchanged. Treatment of V with one equivalent of lithium aluminum hydride gave the crystalline alcohol W, whose structure was apparent from the disappearance of carbonyl absorption, and the appearance of hydroxyl absorption, in the infrared spectrum. Treatment of W with lithium aluminum hydride gave a mixture of diols, presumably X and Y; this mixture was oxidized to a mixture of


V


W

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[10] Cf. A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

[11] L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

[12] D. K. Fukushima, S. Lieberman, and B. Praetz, *ibid.*, **72**, 5205 (1950).

[13] V. Georgian, R. Harrison, and N. Gubisch, *ibid.*, **81**, 5834 (1959).

[14] J. D. Dutcher, J. R. Johnson, and W. F. Bruce, *ibid.*, **67**, 1737 (1945).

[15] R. R. Ireland, T. I. Wrigley, and W. G. Young, *ibid.*, **80**, 8604 (1958).

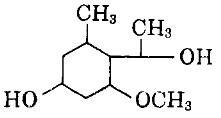
[16] See Experimental.

[17] Prepared by an improved procedure, based on that of A. Wohl and R. Maag, *Ber.*, **43**, 3284 (1910), by condensation of paraldehyde and acetone in the presence of dry hydrogen chloride, followed by dehydrochlorination by diethylaniline [*cf.* E. E. Blaise and M. Maire, *Bull. soc. chim.*, [4] **3**, 270 (1908)]. The yield was of the order of 22%, but the cheapness of the starting materials and the feasibility of large-scale runs made the compound a practical starting material.

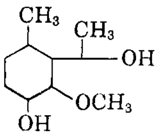
[18] It is conceivable that the dehydrogenation experiment might not be a valid structure proof, because, if the Diels–Alder reaction was reversed during dehydrogenation and if the stability relationships of R and Q were reversed at the higher temperature, R might be converted to Q (or vice versa), prior to dehydrogenation.

[19] S. E. Cremer and D. S. Tarbell, *J. Org. Chem.*, **26**, 3653 (1961).

[20] W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

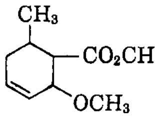


X

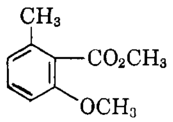


Y

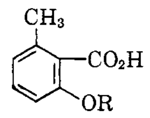
the corresponding diketones and several other compounds derived from X and Y were prepared. Work is continuing with the idea of directing the ring opening of W to form Y exclusively.[21] The Diels–Alder reaction between 1-methoxybutadiene and methyl crotonate, which was also investigated, yielded only one isomer, Z, this was readily reduced to the dihydro



Z



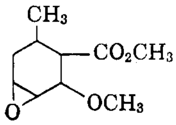
AA



BB. R = CH_3
CC. R = H

compound, which resisted attempts to saponify the ester function. The structure of Z was demonstrated by dehydrogenation with palladium–charcoal to methyl 2,6-cresotate methyl ether (AA); this ester was hydrolyzed with potassium hydroxide in ethylene glycol to the free acid BB, which showed no depression on mixed m.p. with an authentic sample of BB prepared by Cremer.[19] The acid BB was also demethylated with hydriodic acid–acetic acid to be known[22] phenolic acid CC.

Epoxidation of 1-methyl-2-carbomethoxy-3-methoxycyclohexene-4 (Z) gave the crystalline epoxide DD.



DD

Experimental[23]

Cyclohexyl methyl ketone was prepared in 42% yield by the action of cyclohexylmagnesium bromide on acetic anhydride[24] at −70°. The b.p. was 60° (9 mm.), in agreement with the reported value,[24] and it showed $n^{25}\text{D}$ 1.4481.

Isohexyl bromide (1-bromo-4-methylpentane) was prepared[25] from commercial 4-methylhexanoic acid by reduction with lithium aluminum hydride, followed by treatment with phosphorus tribromide.[26]

Triphenylisohexylphosphonium Bromide (**E**).—Isohexyl bromide (16.5 g.) and triphenylphosphine (26.2 g.) were heated in a sealed tube for 24 hr. at 135°. A colorless semisolid was removed from the tube and ground under ether. The yield of the white powder melting at 215° was 40 g. (90%). A sample was crystallized from chloroform–ether to give white needles melting at 231–233°.

Anal. Calcd. for $C_{24}H_{28}PBr$: C, 67.45; H, 6.60. Found: C, 67.24; H, 6.49.

2-Cyclohexyl-6-methylheptene-2 (**C**).—Isohexyltriphenylphosphonium bromide (10.0 g., 0.0234 mole), thoroughly dried at 100° was dispersed by stirring in 50 ml. of dry ether under a nitrogen atmosphere. Phenyllithium (19 ml., 1.25 *N*, 0.02375 mole) was added; the mixture, which turned dark red, was stirred for 3 hr. Methyl cyclohexyl ketone (2.8 g., 0.022 mole) was added and stirring was continued for 1 hr. The mixture was extracted three times with ether. The ethereal solution was washed with water, dried over anhydrous sodium sulfate and the solvent removed *in vacuo*, giving 4.0 g. of a yellow oil. The oil was chromatographed twice on activity grade I neutral alumina; the petroleum ether (30–60°) fraction yielded 0.40 g. (9%) of a colorless oil, (pot temperature 50–75° (0.07 mm.)). The infrared spectrum showed peaks at 1653 (C=C), 1379 and 1361 cm.$^{-1}$ [$(CH_3)_2CH$]. The ultraviolet spectrum showed absorption at 210 mμ, ε 2420; 220 mμ, ε 348.

Anal. Calcd. for $C_{14}H_{26}$: C, 86.51; H, 13.49. Found: C, 86.67; H, 13.50.

Ethyl β-Cyclohexyl-β-hydroxybutyrate.[27]—A mixture of 126 g. of methyl cyclohexyl ketone and 250 g. of ethyl bromoacetate in 300 ml. of dry benzene was added to 195 g. of washed zinc. The benzene solution was added slowly, and after addition the mixture was refluxed for 1 hr. The solution was hydrolyzed with 20% sulfuric acid, and the benzene layer was separated. The aqueous layer was washed with benzene and the combined benzene extracts were washed with 5% sulfuric acid, 10% sodium carbonate and water, dried over anhydrous sodium sulfate, and the solvent removed *in vacuo*. The liquid was distilled, giving 176 g. (82%) of a water-white liquid, b.p. 82–86° (0.9 mm.).[28] The infrared spectrum of the product showed the presence of some dehydration product, therefore elemental analysis was not attempted.

Ethyl β-Cyclohexyl-β-methylacrylate (**F**). **A. By Dehydration of the Hydroxy Ester.**—Pyridine (890 ml.) was added to 176 g. (0.82 mole) of the hydroxy ester and the resulting solution cooled to 5° in an ice–salt bath with stirring. To the solution was added slowly 190 g. (1.20 moles) of phosphorus oxychloride. The solution was allowed to stand for 12 hr. at room temperature and then was cooled and poured into 1.5 kg. of ice and 1.5 l. of water. The mixture was extracted three times with 400-ml. portions of hexane. Each extract was washed separately, twice with 500-ml. portions of water to pH 4. The hexane fractions were combined, dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo*. The residual oil was distilled to afford 140 g. (87%) of a colorless liquid, b.p. 60–70° (0.1 mm.), $n^{29}\text{D}$ 1.4683. The spectral properties have been described above.

B. By the Wittig Reaction.—Triethyl phosphonoacetate[8] (11.2 g., 0.05 mole) was added to a mixture of 2.6 g. of sodium hydride (49% dispersion) in 100 ml. of freshly distilled 1,2-dimethoxyethane at room temperature. Hydrogen was liberated and the solution turned orange. Stirring was continued for 1 hr. and 6.3 g. (0.05 mole) of methyl cyclohexyl ketone was added and the mixture was stirred 4 hr. more. The mixture was poured into 250 ml. of water and extracted with 500 ml. of ether. The ethereal solution was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*, which gave 10.3 g. of yellow oil. The residue was distilled to give 3.4 g. (35% of the desired product, b.p. 72–77° (0.1 mm.). The boiling point and infrared spectrum checked with those of the compound previously prepared by the alternate route.

β-Cyclohexyl-β-methacrylic Acid (**G**).—A 140-g. sample of the unsaturated ester F was added to a solution of 600 ml. of ethylene glycol, 300 ml. of 95% ethanol, 300 ml. of water and 200 g. of potassium hyroxide. The solution was refluxed for 1 hr., cooled, diluted with 3 l. of water and acidified with 600 ml. of concentrated hydrochloric acid. The solution was extracted three times with 300-ml. portions of hexane and the hexane extracts were washed with water to pH 4. The hexane extracts were dried over anhydrous sodium sulfate and the solvent removed *in vacuo*. There was obtained 120 g. of crude acid, which crystallized on cooling. The recovered crystalline product

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[21] *Cf.* E. L. Eliel and M. N. Rericks, *J. Am. Chem. Soc.*, **82**, 1362 (1960).

[22] W. K. Anslow and H. Raistrick, *Biochem. J.*, **25**, 39 (1931).

[23] Microanalyses were done by T. Montzka and V. Landeryou of this laboratory and by Micro-Tech Laboratories, Skokie, Ill.. All melting points and boiling points are uncorrected. The ultraviolet spectra (the solvent in all cases was 95% ethanol) were taken on a Cary recording spectrophotometer, Model 11 MS. All nuclear magnetic resonance spectra were taken in carbon tetrachloride on a 60-Mc. Varian spectrometer. The infrared spectra were taken as Nujol mulls, liquid films, potassium bromide disks, and chloroform or carbon tetrachloride solutions, on a Perkin-Elmer, Model 21, infrared spectrophotometer. We are indebted to Mr. Carl Whiteman for measurement of the ultraviolet spectra, and to Dr. L. D. Colebrook for the n.m.r. spectra.

[24] M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948); C. G. Overberger and A. Lebovits, *J. Am. Chem. Soc.*, **76**, 2722 (1954).

[25] We are indebted to Miss T. Huang for this preparation.

[26] R. Adams and C. R. Noller, *J. Am. Chem. Soc.*, **48**, 1084 (1926); H. A. Shonle, *et al.*, *ibid.*, **58**, 585 (1936).

[27] *Cf.* K. L. Rinehart, Jr., and E. G. Perkins, *Org. Syn.*, **37**, 37 (1957).

[28] D. Papa, H. F. Ginsberg, and F. J. Villani, *J. Am. Chem. Soc.*, **76**, 4441 (1954).

amounted to 60 g. (50%). Recrystallization of a sample from methanol–water gave colorless plates, m.p. 85–86°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.21; H, 9.54.

β-Cyclohexyl-β-methacrylyl Chloride (H).—A 16.8-g. sample of the unsaturated acid G was refluxed with 22 ml. of thionyl chloride for 4 hr., and the excess thionyl chloride was removed *in vacuo*. The product was distilled, to yield 16 g. (86%) of a water-white liquid, b.p. 97–100° (0.7 mm.). The infrared spectrum showed absorption at 1764 (C=O) and 1600 cm.$^{-1}$ (C=C).

2-Cyclohexyl-6-methylhept-2-en-4-one (K).—In a three-neck 300-ml. flask equipped with a condenser, stirrer, dropping funnel, and protected from the atmosphere by calcium chloride tubes, were placed 2.5 g. of magnesium and 50 ml. of anhydrous ether, to which was added 14 g. of 1-bromo-2-methylpropane. The solution was refluxed for 15 min. and then cooled in an ice bath; next, 9.5 g. of dried cadmium chloride was added and the mixture was stirred for 15 min. and refluxed for 45 min. The ether was removed by distillation and simultaneously replaced by anhydrous benzene (70 ml.). A solution of 16 g. of the acid chloride H in 15 ml. of dry benzene was added. The mixture was refluxed for 1 hr., cooled and decomposed with 60 ml. of ice–water and enough 20% sulfuric acid to form two clear layers. The aqueous layer was separated and washed twice with benzene. The combined benzene layers were washed with water, 5% sodium bicarbonate solution, and water. The benzene extracts were dried over anhydrous sodium sulfate and the benzene was removed *in vacuo*. The product was distilled to give 14.6 g. (82%) of a light yellow oil, b.p. 105–111° (1.3 mm.). The liquid was then distilled in a spinning band column to give four fractions. Fraction no. 1: 0.8 g., 57.5–63° (0.07 mm.), showed a weak band in the infrared spectrum at 1610 cm.$^{-1}$. Fraction no. 2: 1.4 g., 63–65° (0.07 mm.), showed bands in the infrared spectrum at 1754 and 1709 cm.$^{-1}$ in addition to the required absorption at 1681 and 1610 cm.$^{-1}$. The ultraviolet spectrum showed λ_{max} 210 mμ (ε 3000) and λ_{max} 243 mμ (ε 9400). Fraction no. 3: 6.6 g., 65–67° (0.07 mm.), showed bands in the infrared spectrum at 1754 (weak), 1681 and 1610 cm.$^{-1}$. The ultraviolet spectrum showed λ_{max} 244 mμ (ε 12,900). Fraction no. 4: 6.0 g., 67–70° (0.07 mm.), showed bands in the infrared spectrum at 1681 and 1610 cm.$^{-1}$. The ultraviolet spectrum showed λ_{max} 243 mμ (ε 13,100). The spectral data indicated that fractions no. 3 and 4 were the desired ketone K, with some impurity in fraction no. 3. A sample of fraction no. 4 was analyzed.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.31; H, 11.65.

The **2,4-dinitrophenylhydrazone** was prepared by the usual method; recrystallization from ethanol gave orange leaflets, m.p. 83–85°.

Anal. Calcd. for $C_{20}H_{28}O_4N_4$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.93; H, 7.37; N, 14.14.

2-Cyclohexyl-6-methylhept-2-en-4-ol (L).—A 10.0-g. sample of the unsaturated ketone K was dissolved in anhydrous ether and added to 3.8 g. of lithium aluminum hydride in ether. The solution was stirred for 1.5 hr. and was then decomposed with a saturated sodium sulfate solution. The aqueous layer was separated and extracted twice with ether. The combined ether layers were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The product was distilled in a molecular still to give 9.4 g. (94%) of a colorless liquid [pot temperature 100° (0.09 mm.)].

Anal. Calcd. for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.67; H, 12.62.

The **benzoate** M was prepared by allowing a mixture of 12 g. of pyridine, 9.4 g. of the alcohol L and 7 g. of benzoyl chloride to stand in 30 ml. of anhydrous benzene at 5° for 18 hr. with the exclusion of moisture. The solution was filtered to remove the pyridine hydrochloride, and the filtrate was washed twice with water, once with 5% sodium hydroxide solution, and with water until neutral. The benzene solution was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. Distillation in a molecular still gave 13.2 g. (94%) of a light yellow liquid [pot temperature 145° (0.09 mm.)].

2-Cyclohexyl-6-methylheptene-2 (C).—A 3.0-g. sample of the freshly distilled allylic benzoate M was dissolved in 50 ml. of dry ethylamine, added through a bed of anhydrous sodium sulfate. The entire flask was kept at 0° and was equipped with a stopcock to release the pressure built up in the reaction. Lithium (0.7 g.) was added, and the mixture was stirred for 15 min. after the initial appearance of a permanent blue color. The solution was diluted with ether and water was added slowly. The ethereal layer was separated and washed with 5% hydrochloric acid, 5% sodium hydroxide and with water until neutral. The ether extract was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residual oil was chromatographed on grade 1 neutral alumina to give in the petroleum ether fraction 0.4 g. (22%) of the olefin C and in the methanol–ether fraction 1.3 g. (65%) of the allylic alcohol L. The olefin fraction was distilled, [pot temperature 60° (0.09 mm.)]. The infrared spectrum was identical with those of the olefins prepared by the other routes and the elementary analysis was satisfactory.

2-Isobutyl-2-(2-cyclohexylpropene-1)-1,3-dithiolane (O).—To a solution of 2.2 g. of the unsaturated ketone K, 2 g. of ethanedithiol, and 7 ml. of acetic acid was added 0.5 ml. of freshly distilled boron trifluoride ethereate.[11] The mixture was allowed to stand at room temperature for 24 hr. The solution was diluted with ether and washed with water, 5% sodium hydroxide, and with water until neutral. The ethereal solution was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. Distillation of the residual oil in a molecular still gave 1.8 g. (60%) of a yellow liquid, [pot temperature 120° (0.09 mm.)].

Anal. Calcd. for $C_{16}H_{28}S_2$: C, 67.57; H, 9.93. Found: C, 67.98; H, 10.00.

3-Penten-2-one.—Paraldehyde (120 ml., 2.7 moles) and acetone (250 ml., 3.4 moles) were placed in a 1-l., three-neck flask and cooled in an ice bath. Dry hydrogen chloride (180 g.) was added and the mixture was allowed to stand at 5° for 2 days. Ether (500 ml.) was added to the dark brown solution, and it was washed successively with water, saturated sodium chloride solution, and potassium carbonate solution. The ethereal solution was dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo* to give a dark colored liquid residue. This was distilled under vacuum, the portion boiling at 45–55° (20 mm.) being collected. This fraction was colorless as it distilled, but turned dark red on standing at room temperature. The fraction collected was distilled immediately from twice its weight of N,N-diethylaniline. The reaction was carried out in a 3-l. one-neck flask tilted 90° from the normal position, to which was attached a short condenser. This system was found adequate for up to 150 g. of the intermediate. A rather violent evolution of gas took place with the onset of dehydrohalogenation, usually at approximately 180° pot temperature. The distillate of the above reaction was distilled and the colorless product boiling 115–125° was collected. Before use in subsequent reactions it was redistilled and the fraction boiling at 119–125° was collected and used; $n^{25}{}_D$ 1.4332. The reported[29] b.p. and index of refraction were 122–123° and $n^{25}{}_D$ 1.4350. The yield in one run was 49 g. (22%).

Diels–Alder Addition between 1-Methoxybutadiene and 3-Penten-2-one. Preparation of 1-Methyl-2-acetyl-3-methoxycyclohexene (Q) and 1-Methyl-2-methoxy-6-acetylclohexene-3 (R).—3-Penten-2-one (130 g.) freshly distilled (b.p. 119–124°) and 1-methoxybutadiene (93 g., Aldrich Chemical), freshly distilled (b.p. 88–92°) were heated together with a little hydroquinone in a sealed tube at 135° for 13 hr. The unchanged ketone was removed by distillation, leaving 146 g. of yellow oil. A sample (114 g.) of this was distilled on a spinning band column. The initial distillation gave two fractions, (1) 68.7 g., b.p. 71–74° (2 mm.), a mixture of Q and R, and (2) 29.6 g., b.p. 74–77° (2 mm.), pure R. A second distillation of fraction (1) above using a spinning band column with a pressure regulator gave two fractions (1) 42.8 g., b.p. 79–81° (4 mm.), pure Q and (2) 10 g., b.p. 81–83° (4 mm.), a mixture of Q and R.

V.p.c. analysis of fractions 1 of the second distillation on a 6.5 ft. 30% Apiezon L column at 130° and with a helium flow of 50 cc./min. showed retention times for Q of 49.5 min. and for R of 61.5 min.; the sample was 97+% pure Q.

An analytical sample of Q was prepared from an intermediate distillation fraction which had been treated with Girard's T reagent to remove isomer R. The pure Q showed infrared bands, among others at 1700, 1650, 1088, 880, 738 and 675 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_2$ (isomer Q): C, 71.39; H, 9.59. Found: C, 70.98; H, 9.66.

A pure sample of R was obtained from distillation; it showed infrared absorption at 1700, 1650, 1100, 1080, 870 and 715 cm.$^{-1}$. It was analyzed in the form of its dinitrophenylhydrazone

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derivative, which was made in the usual way, and purified by chromatography on bentonite–Celite; it melted at 157–158°.

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 55.16; H, 5.79; N, 16.08. Found: C, 55.25; H, 5.57; N, 16.19.

Aromatization of 1-Methyl-2-acetyl-3-methoxycyclohexene-4 (Q).—Isomer Q (5 g.) was heated to 280–310° for 1 hr. in the presence of 0.5 g. of 10% palladium on charcoal under a steady flow of carbon dioxide. The mixture was cooled and filtered to give 3.07 g. of orange oil, which was separated into two fractions collected by v.p.c. A 2.5-ft. Apiezon column was used at 95° with a helium flow rate of 200 cc./min. The major peaks at 13 min. and 30 min. were collected. The 2,4-dinitrophenylhydrazone, m.p. 167–169°, and the infrared spectrum of the 13 min. fraction showed it to be 2-methylacetophenone. The infrared spectrum of the 30-min. fraction was identical with a previously run spectrum of authentic 2-methoxy-6-methylacetophenone.[19]

2-Hydroxy-6-methylacetophenone (T).—The mixture (4.2 g.) of compounds from the aromatization of Q was heated with 16 g. of pyridine hydrochloride at 200° for 20 min. under a nitrogen atmosphere. The solution turned dark red and solidified on cooling. The solid was dissolved in water and extracted with ether. The ether layer was extracted with 1 *N* sodium hydroxide. The basic solution was acidified with concentrated hydrochloric acid and extracted with ether. The ethereal layer was washed with water, dried over anhydrous sodium sulfate, and the ether was removed *in vacuo,* to give 1.2 g. of a dark red oil. In an attempted distillation the oil was found to sublime at 130° (0.09 mm.) to give yellow crystals. Two recrystallizations from water and two sublimations gave a white powder, m.p. 93–98°; this compound was prepared previously,[19] but was not characterized.

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.18; H, 6.82.

The **hydrazone U** was prepared by dissolving 300 mg. of the phenolic ketone T in ethanol with 2 ml. of 95% hydrazine and a drop of glacial acetic acid. The mixture was refluxed for 3 hr. and the excess hydrazine and ethanol were removed *in vacuo.* The residual oil was crystallized from carbon tetrachloride–ether and sublimed, m.p. 135–136°. A mixture melting point with two previously prepared[19] samples showed no depression; the infrared spectra of these samples also were identical.

1-Methyl-2-acetyl-3-methoxycyclohexene 4,5-Epoxide (V).—Compound Q (5.0 g.) was dissolved in 50 ml. of ether to which was added 90 ml. of monoperphthalic acid in ether. The mixture was stirred for 5 hr. at 0°, let stand 19 hr. at 5°, and 24 hr. at room temperature. Chloroform was added to the solution and the ether was removed *in vacuo.* The chloroform solution was filtered to remove the phthalic acid, and was then washed with 10% sodium sulfite solution until unreactive to potassium iodide paper, then with 5% sodium bicarbonate solution and with water. The chloroform solution was dried over anhydrous sodium sulfate, and the chloroform removed *in vacuo,* to give 5.1 g. of yellow oil. Chromatography of the resulting oil on neutral alumina (125 g., activity grade II) gave 3.1 g. in the 50:50 petroleum ether–ether fraction. Recrystallization of the solid from petroleum ether gave 2.3 g. (42%) of white needles, m.p. 54–55°. The analytical sample, prepared in a different run, gave a positive thiosulfate test for the epoxide group.[20]

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.22; H, 8.71.

1-Methyl-2-(α-hydroxyethyl)-3-methoxycyclohexene 4-Oxide (W).—To 1 g. of the epoxide V dissolved in ether was added 0.121 g. of lithium aluminum hydride. The mixture was stirred overnight and decomposed with a saturated solution of sodium sulfate. The etheral layer was separated, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave 1.1 g. of yellow oil. The oil was found to sublime to give colorless crystals, m.p. 41–44°. Resublimation raised the melting point to 48–49°. The infrared spectrum showed disappearance of carbonyl absorption and a new peak at 3360 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.61; H, 9.67.

1-Methyl-2-carbomethoxyl-3-methoxycyclohexene-4 (Z), by Addition of 1-Methoxybutadiene to Methyl Crotonate.—1-Methoxybutadiene (24 g., freshly distilled), methyl crotonate (36 g., freshly distilled), and a little hydroquinone were heated in a sealed tube at 135–140° for 16 hr. After cooling, the tube was opened with no excess pressure and the contents were fractionally distilled. The first fraction, b.p. 30–34° (30 mm.), was starting material and the second fraction, b.p. 63–68° (0.3–1 mm.) (31 g.), appeared to be homogeneous. A second distillation of the product in a spinning band column gave a major fraction (28 g.) as a colorless oil b.p. 43.5–44.0° (0.15 mm.); the infrared spectrum showed bands, among others, at 1725 (ester carbonyl), 1655 (double bond) and 1090 cm.$^{-1}$ (ether).

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.03; H, 8.73.

Aromatization of 1-Methyl-2-carbomethoxy-3-methoxycyclohexene-4 (Z) and Conversion to 2,6-Cresotic Acid Methyl Ether (BB).—Compound Z (5 g.) was heated for 1 hr. with 0.5 g. of 10% palladium on charcoal at 230–280° under a flow of carbon dioxide. The product was cooled and filtered to give 2.1 g. of yellow oil. The product was not purified but used directly in the next reaction; it showed infrared absorption characteristic of an ester and an aromatic ring.

The crude dehydrogenation product (2.1 g.) was dissolved in a mixture of 3 g. of potassium hydroxide and 50 ml. of ethylene glycol and heated to 150° for 1 hr. The cooled mixture was diluted with water, neutralized with concentrated hydrochloric acid, and extracted three times with ether. The ether solution was allowed to stand with 5% sodium hydroxide solution for 1 hr. The basic aqueous layer was separated, neutralized with concentrated hydrochloric acid, and extracted three times with ether. The ether layer was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give 1.28 g. of yellow oil which crystallized on standing. Recrystallization from petroleum ether–ether afforded white crystals of BB, m.p. 142.5–144°. A mixture melting point with a known sample of BB prepared by Cremer[19] showed no depression.

2,6-Cresotic Acid (CC).—2,6-Cresotic acid methyl ether (100 mg.) was dissolved in 0.1 ml. of 50% hydriodic acid and 0.1 ml. of glacial acetic acid, and heated to 110–135° for 30 min. The mixture solidified on cooling and was dissolved in hot water. The cooled solution deposited crystals of the phenolic acid. Recrystallization from water gave white needles, m.p. 171.0–171.5°. The reported m.p. was 169°.[22] A water solution of the acid gave a purple ferric chloride test.

Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.31; H, 5.30.

The **acetate** was prepared from 10 mg. of the phenolic acid by heating with 0.2 ml. of acetic anhydride and a drop of 85% phosphoric acid. The resulting colorless oil was found to crystallize on standing, and on recrystallization from ether gave colorless cubic crystals, m.p. 137–138°. The reported m.p. was 131°.[22]

1-Methyl-2-carbomethoxy-3-methoxy-4,5-epoxycyclohexane (DD).—The cyclohexene derivative (Z) (5 g.) was treated with 2 equivalents of monoperphthalic acid and worked up as before to yield 1.4 g. (25%) of white rectangular crystals. Two recrystallizations from petroleum ether brought the m.p. to 85.0–85.5°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.99; H, 8.26.

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