

Separation of the isomers was effected by rechromatographing the 1.48 g. of isomer mixture on 250 g. of alumina by the identical gradient elution procedure and monitoring the various fractions by gas-phase chromatography. In this fashion, there was isolated from the earlier eluted portion 0.46 g. of oil, $\lambda_{\text{max}}^{\text{cnpil}}$ 6.00, 6.20, 10.20, and 11.70 μ , the optical rotatory dispersion curve (Fig. 4) of which demonstrated that it was the desired 7 α -isopropyl-10 β -methyl- $\Delta^{1(9)}$ -octalone-2 (XVIII). After an intermediate fraction (0.741 g.), consisting of varying amounts of both isomers XVIII and XIX, there was finally eluted 68 mg. of the pure 7 α -isopropyl-10 α -methyl- $\Delta^{1(9)}$ -octalone-2 (XIX) ($\lambda_{\text{max}}^{\text{cnpil}}$ 6.00, 6.20, 8.20, and 11.60 μ) the optical rotatory dispersion curve (Fig. 4) of which established the configuration at C-10.

Mannich Base Condensation of (–)-Tetrahydrocarvone (XVI).—(–)-Tetrahydrocarvone (XVI) (5.0 g.) was heated for 1 hr. at 85° in an atmosphere of nitrogen with a small piece (size of small pea) of sodium, and after all of it had dissolved, there was added 3.3 g. of 1-diethylamino-3-butanone²⁹ and heating (92°) continued with stirring for 2.3 hr. Isolation with ether in the conventional manner yielded 5.3 g. of orange colored oil, from which unreacted starting ketone XVI was removed by distillation at 33–39° (0.3 mm.). The distillation residue was dissolved in 20 cc. of methanol containing 0.2 g. of sodium and was heated under reflux for 4 hr. in an atmosphere of nitrogen. After neutralization with acetic acid, the product was isolated with ether and chromatographed on 125 g. of activity II neutral alumina. Elution with 10% ether in petroleum ether afforded 1.78 g. of 7 α -isopropyl-10 β -methyl- $\Delta^{1(9)}$ -octalone-2 (XVIII) ($\lambda_{\text{max}}^{\text{EtOH}}$ 239 m μ , ϵ 16,100; $\lambda_{\text{max}}^{\text{cnpil}}$ 6.00, 6.20, 10.20, and 11.70 μ ; $[\alpha]_D^{+65}$ (c 1.44, methanol) the identity of which was established by infrared spectrometric, optical rotatory dispersion, and gas-phase chromatographic comparison with isomer XVIII from the chloroketone route. The 2,4-dinitrophenylhydrazone was recrystallized from methanol-ethyl acetate, whereupon it exhibited m.p. 195–197°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 390 m μ (ϵ 34,000).

Anal. Calcd. for $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.00; H, 6.70; N, 14.37.

***cis*-7 α -Isopropyl-10 β -methyl-2-decalone (XXIII).**—Catalytic hydrogenation of 150 mg. of the octalone XVIII in 5 cc. of ethyl

acetate and 15 mg. of 5% palladium-on-charcoal catalyst provided 148 mg. of a partially crystalline reduction product, which by gas-phase chromatography (diethylene glycol succinate column operated at 146°) was shown to consist of seven parts *cis* (XXIII) and one part *trans* (XXII) ketones. A pure specimen of the *cis*-ketone XXIII was secured by chromatography on neutral alumina (activity II) and elution with petroleum ether, followed by sublimation at 42° (0.1 mm.) and low temperature crystallization from pentane; m.p. 55–57°, $\lambda_{\text{max}}^{\text{KBr}}$ 5.88 μ ; R.D. (Fig. 2) in methanol (c 0.2): $[\phi]_{589}^D - 32^\circ$, $[\phi]_{366}^D - 221^\circ$, $[\phi]_{275}^D - 115^\circ$, $[\phi]_{250}^D - 147^\circ$.

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}$: C, 80.71; H, 11.61. Found: C, 80.46; H, 11.31.

***trans*-7 α -Isopropyl-10 α -methyl-2-decalone (XXII).**—The chemical reduction of 330 mg. of the octalone XVIII was performed in the usual manner³⁰ by adding an ethereal solution of it to 70 mg. of lithium dissolved in 40 cc. of liquid ammonia (condensed directly from tank by the use of a Dry Ice-acetone bath). An additional 30 mg. of lithium was added and after 10 min., the blue color had disappeared, whereupon solid ammonium chloride was added and the ammonia allowed to evaporate. The product, isolated by ether extraction, exhibited both hydroxyl and carbonyl absorption (5.88 μ due to reduction product and 6.00 μ due to unreacted octalone) in the infrared and was, therefore, oxidized in 15 cc. of acetone with 0.4 cc. of 8 *N* chromium trioxide solution.²⁷ The resultant oil (325 mg.) was purified by chromatography on 40 g. of neutral alumina and elution with petroleum ether. Gas-phase chromatographic analysis of the various crystalline fractions (70 mg.) showed that none contained more than 6–9% of the *cis*-decalone XXIII as a contaminant. Recrystallization of the solid *trans*-decalone XXII from pentane at low temperatures afforded the pure isomer, m.p. 103–105°, $\lambda_{\text{max}}^{\text{KBr}}$ 5.88 μ ; R.D. (Fig. 2) in methanol (c 0.13): $[\phi]_{589}^D + 84^\circ$, $[\phi]_{367}^D + 2500^\circ$, $[\phi]_{290}^D 0^\circ$, $[\phi]_{267}^D - 3160^\circ$, $[\phi]_{256}^D - 2690^\circ$.

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}$: mol. wt., 208. Found: mol. wt., 208 (mass spec.). Further elution with ether-petroleum ether (1:4) yielded 170 mg. of recovered octalone XVIII.

(29) See J. E. Starr in C. Djerassi, Ed., "Steroid Reactions: An Outline for Organic Chemists," Holden-Day, San Francisco, Calif., Chapter 7.

[CONTRIBUTION FROM THE CHANDLER LABORATORIES OF COLUMBIA UNIVERSITY, NEW YORK 27, N. Y.]

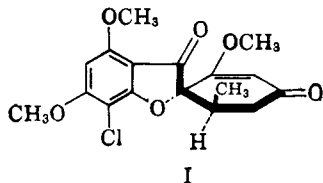
A New Synthesis of Cyclohexenones: The Double Michael Addition of Vinyl Ethynyl Ketones to Active Methylene Compounds. Application to the Total Synthesis of *dl*-Griseofulvin¹

BY GILBERT STORK AND MARIA TOMASZ

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It is shown that certain vinyl ethynyl ketones can undergo Michael addition with suitable molecules to form cyclohexenones. This new synthesis, applied to the specific case of the hitherto unknown ethoxyethynyl vinyl ketones, has been used to synthesize the antibiotic griseofulvin.

The important orally active antifungal antibiotic griseofulvin (I) has established itself in medicine over the last few years.² Originally isolated from *penicillium griseofulvum*,³ the antibiotic was eventually shown to have the structure⁴ and stereochemistry⁵ indicated in I. This stereochemistry has now been confirmed by X-ray analysis.⁶



(1) Preliminary communication: G. Stork and M. Tomasz, *J. Am. Chem. Soc.*, **84**, 310 (1962).

(2) For a recent review, see J. F. Grove, *Quart. Rev. (London)*, **17**, 1 (1963).

(3) A. E. Oxford, H. Raistrick, and P. Simonart, *Biochem. J.*, **33**, 240 (1939).

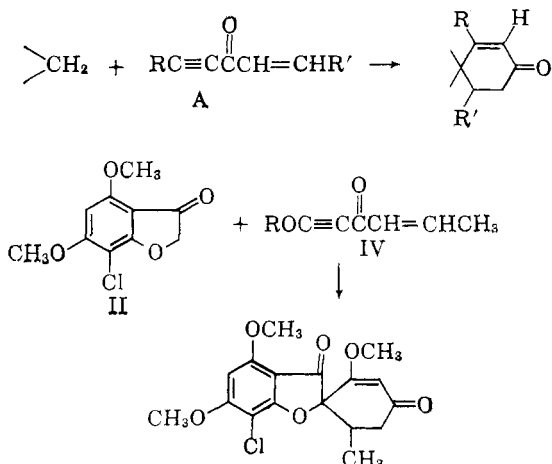
(4) J. F. Grove, J. McMillan, T. P. C. Mulholland, and M. A. T. Rogers, *J. Chem. Soc.*, 3977 (1952).

(5) J. McMillan, *ibid.*, 1823 (1959).

(6) W. A. C. Brown and G. A. Sim, *ibid.*, 1050 (1963).

Two of the interesting features of griseofulvin which caught our attention when we began considering possible routes to its total synthesis were the presence of the spiro system formed by the two ketonic rings and the fact that one of the rings is the enol ether of an *unsymmetrical* β -diketone. Should it be possible to construct cyclohexenone derivatives by double Michael reactions involving the addition of a suitable active methylene compound to a cross-conjugated vinyl ethynyl ketone (cf. A), the specific use of the coumaranone II as the active methylene compound and of methoxyethynyl propenyl ketone IV, R=CH₃, as the acceptor could produce directly the griseofulvin structure (we will defer a discussion of the stereochemical problem at this point).

It was especially attractive that such a process would lead to the proper enol ether as well as allow the synthesis of the griseofulvin system in essentially one operation. The simplicity of the scheme served to emphasize that a number of serious problems had to be resolved before its success could be contemplated. The most serious of these problems were: (1) Alkoxyethynyl ketones were still unknown in spite of attempts

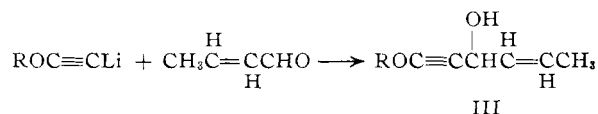


at their preparation.⁷ (2) The double Michael addition to a cross-conjugated vinyl ethynyl ketone was not a known reaction. It is the existence of these problems which made the projected synthesis of particular interest. We will discuss them in turn.

I. Synthesis of Alkoxyethynyl Propenyl Ketones.—

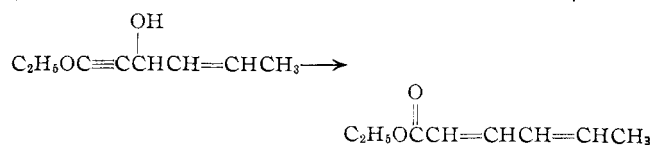
As we have just stated, alkoxyethynyl ketones had not previously been prepared. This is apparently due to their great lability rather than to any intrinsic difficulty with the system *per se*. The corresponding alkylthioethynyl ketones are readily prepared.⁸ It will be noted that the alkoxyethynyl ketone we needed is additionally conjugated with a vinyl group. This feature might well have been a source of even greater lability and difficulty, but we felt that it was likely to facilitate the obtention of the compound since one could anticipate that the corresponding secondary alcohol would be oxidized particularly easily by manganese dioxide. This latter reagent appeared ideally suited to our purpose, as it can be used under the essentially anhydrous and neutral conditions which the expected properties of alkoxyethynyl vinyl ketones appeared to make mandatory.

The availability of ethoxyacetylene⁹ led us to examine first the preparation and properties of ethoxyethynyl propenyl ketone: the required secondary alcohol III, R = C₂H₅, was readily prepared by the reaction of the lithium salt of ethoxyacetylene with crotonaldehyde, in ether solution at -15°. The product, worked up in the careful absence of acid, was a colorless oil, b.p. 65–70° (diffusion pump), which was obtained in yields varying from 43 to 63%. The structure of the substance was proved by its analysis, the rapid quantitative uptake of three equivalents of hydrogen over platinum in ethyl acetate, and the infrared spectrum which showed bonded and nonbonded hydroxyl (ν 3450 and 3600 cm.⁻¹), triple bond (2270 cm.⁻¹), and double bond (1670 cm.⁻¹).



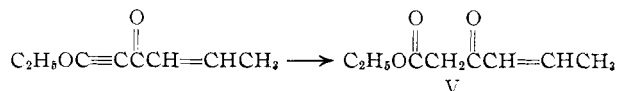
The secondary carbinol was quite unstable. Even simple standing at room temperature appeared to allow rearrangement to ethyl sorbate. This rearrangement could be effected rapidly by treatment with ethanol containing sulfuric acid. It could be fol-

lowed easily by the disappearance of the hydroxyl and triple bond bands in the infrared, and the appearance of the characteristic maximum at 259 m μ .¹¹



Oxidation of the secondary alcohol to the corresponding ketone was successfully effected with dry manganese dioxide¹² in methylene chloride solution. The manganese dioxide had to be washed to as close to neutrality as possible because of the lability of the vinyl ethynyl ketone to bases (as well of course as to acids). The manganese dioxide oxidation could be followed most easily by the shift of the triple bond band from its original position at 2270 to 2230 cm.⁻¹. Ethoxyethynyl propenyl ketone (IV), R = C₂H₅, was isolated at the completion of the oxidation as a colorless oil, b.p. 53–54° (diffusion pump). The infrared spectrum was consistent with structure IV. It showed the absence of hydroxyl bands and the presence of strong bands for the triple bond (2230 cm.⁻¹), carbonyl (1650 cm.⁻¹), and double bond (1630 cm.⁻¹). The ultraviolet spectrum showed $\lambda_{\text{max}}^{\text{EtOH}}$ 228 m μ (11,600) and 249 m μ (9100). The substance is unstable at room temperature, but can be kept under nitrogen at -15°.

On treatment with aqueous acid, the expected hydration to ethyl crotonylacetate (V) took place rapidly. The β -keto ester, which gave a purple ferric chloride test, was characterized by its 2,4-dinitrophenylhydrazones, m.p. 120–121°, and by its known¹³ copper chelate, m.p. 161°.



Addition of water to the triple bond also takes place readily in the presence of traces of base; an aqueous alcoholic 0.02 N sodium hydroxide solution of IV showed complete disappearance of the triple bond band after half an hour at room temperature. Even in neutral medium, water is readily added. Thus, whereas refluxing in *absolute* alcohol for 1 hr. left the ethoxyethynyl ketone IV, R = C₂H₅, essentially unchanged, refluxing for 4 hr. in 60% aqueous ethanol gave an oil which had the infrared spectrum of ethyl crotonylacetate.

The methoxy analogs III and IV, R = CH₃, were prepared analogously and exhibited similar properties.

II. Cycloadditions to Ethynyl Vinyl Ketones.—

Double Michael additions of ethynyl vinyl ketones had not been described until our preliminary communication and, as we then pointed out, their success is critically dependent on having the initial addition take place at the triple bond. Initial addition to the double bond would lead to an intermediate such as B in which the second addition would not be expected to give a six-membered ring, since ease of approach to the triple bond is now obviously greatly in favor of a five-membered ring. At the same time no special advantage accrues from addition to the β -position of the conjugated acetylene group, as the carbonyl could not help stabilize the developing anion which would not be in a position to overlap with it. Put in other terms, effective over-

(7) J. F. Arens in "Advances in Organic Chemistry," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1960, p. 117 ff.

(8) J. Bonnema and J. F. Arens, *Rec. trav. chim.*, **79**, 1137 (1960).

(9) Cf. Experimental. This later became available from Pfister Chemical Works, Inc., Ridgefield, N. J.

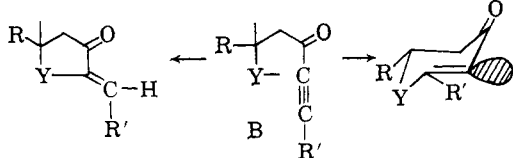
(10) This method was described by J. C. Postma and J. F. Arens, *Rec. trav. chim.*, **75**, 1408 (1958), with other aldehydes.

(11) H. E. Ungnade and T. R. Hopkins, *J. Am. Chem. Soc.*, **73**, 3091 (1951).

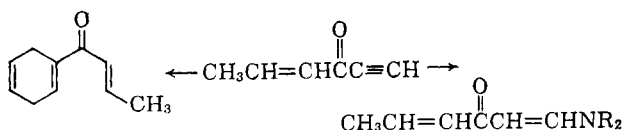
(12) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans; B. A. Hems, A. B. A. Jensen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(13) D. Breslow and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944).

lap would require the energetically very unfavorable geometry of an allene within a six-membered ring.

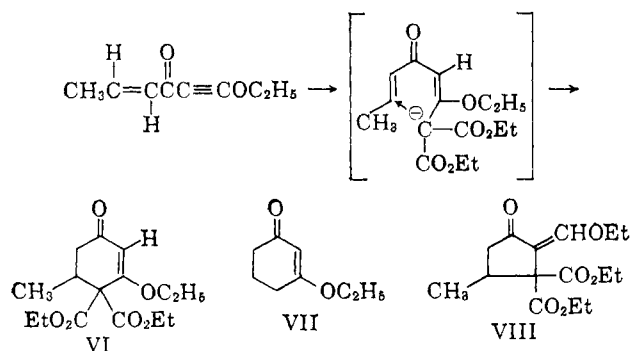


There was in fact some evidence that in systems in which a carbonyl is cross-conjugated with both a double and a triple bond,¹⁴ the latter is the more reactive. For instance, the addition of amines to 4-hexen-1-yn-3-one takes place exclusively at the triple bond. Similarly, Diels-Alder addition of butadiene to the same substance gives a monoadduct in which it is the triple bond which has undergone addition.¹⁵ This greater



reactivity of the triple bond is not unexpected since even unactivated acetylenes can add amines and alkoxides.¹⁶ The specific system of interest to us differs from the simple case above in that the triple bond also carries an alkoxy group which might decrease the reactivity of the acetylenic system by increasing the electron density in the triple bond. Since, however, conjugation would not be expected to be very effective through a triple bond, addition could actually be favored by the inductive effect of the alkoxy group. One encouraging fact, already mentioned, was the very rapid transformation of ethoxyethynyl propenyl ketone into V under the action of water, a transformation which suggests that either hydroxide ion or water adds selectively to the triple bond, alkoxy group notwithstanding.

The first experiment to study whether the anticipated double Michael addition would take place in the proper sense was the reaction of diethyl malonate with IV, $R = C_2H_5$, in the presence of a catalytic amount of potassium *t*-butoxide in dry *t*-butyl alcohol. After 2 hr. at room temperature a crude, but crystalline, material was isolated in 73% yield. The substance was purified by molecular distillation and recrystallization from hexane. The new compound, m.p. 61–62°, had the proper carbon-hydrogen analysis for a 1:1 adduct and showed $\lambda_{max}^{CCl_4}$ 5.83, 6.09, and 6.22 μ and λ_{max}^{EtOH} 251 μ (ϵ 17,000). These properties were certainly compatible with the structure VI (*cf.*, for instance the enol ether VII which has λ_{max}^{EtOH} 250 μ (17,000)¹⁷ and 1660



(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(15) K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 45 (1946).

(16) Cf. R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworths Scientific Publications, London, 1955, p. 21 ff.

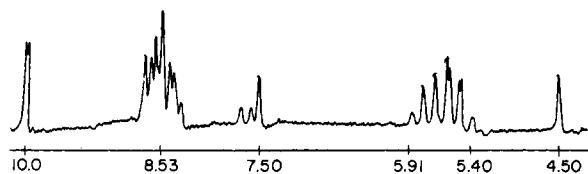
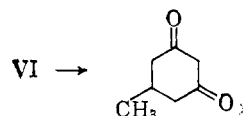


Fig. 1.—N.m.r. spectrum of VI in CCl_4 .

and 1625 cm^{-1})¹⁸ but did not uniquely require it. Similarly, the n.m.r. spectrum (see Fig. 1) could not be used to differentiate with confidence between VI and VIII, but it made it clear that the product was indeed the result of a *double* Michael addition, since only one vinyl proton was present in the spectrum, at $\tau = 4.5$.

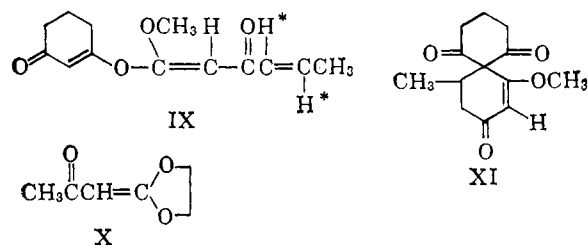
Final decision in favor of VI was easily reached by hydrolysis with aqueous potassium hydroxide, followed by heating with acid to decarboxylate the intermediate. This gave the known¹⁹ 5-methylcyclohexane-1,3-dione, m.p. 131–132°, undepressed on admixture with an authentic sample.



It is thus demonstrated that the double Michael addition of ethynyl ketones constitutes a new synthesis of certain cyclohexenones.²⁰

One other example was studied before turning to the case of the coumaranone II. Dihydroresorcinol was chosen as an example of a *cyclic* active methylene compound which would produce the type of spiro system characteristic of griseofulvin. Reaction of equimolar amounts of the methoxypentenynone IV, $R = CH_3$, with dihydroresorcinol at room temperature in the presence of a catalytic quantity of potassium *t*-butoxide in *t*-butyl alcohol followed by chromatography of the reaction mixture over silica gel, led to the separation of two crystalline substances: one melting at 81° and the other at 146–147°, in approximately equal amounts. The two compounds were both 1:1 adducts on the basis of their analysis.

The product melting at 81° is tentatively assigned structure IX. The ultraviolet spectrum (λ_{max}^{MeOH} 250 μ , ϵ 37,000) showed the presence of at least two



chromophores of the required type. The maximum of the enol ether is at 250 μ and the acyl ketene acetal system would be expected to absorb in the same area (the acetyl ketene acetal X has λ_{max}^{THF} 250 μ , ϵ 23,600).²¹ In accord with the postulated structure, mild acid hydrolysis split IX into methyl crotonylacetate and di-

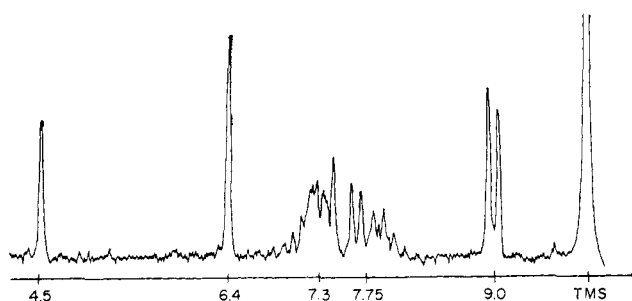
(17) W. E. Gannon and H. O. House, *Org. Syn.*, **40**, 41 (1960).

(18) Cf. L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 144.

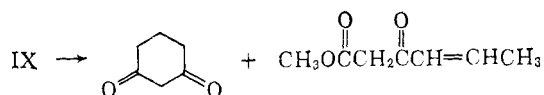
(19) A. W. Crossley and N. Renouf, *J. Chem. Soc.*, **107**, 602 (1915).

(20) It will be noted that the initial adduct could have two different configurations around the double bond formed by initial addition to the acetylenic function. The kinetically formed product which would be expected to result from *trans* addition to the acetylene would have the necessary stereochemistry for further cyclization in the desired manner. The initial adducts we are dealing with here are in any case vinylogous β -dicarbonyl compounds and could be expected to equilibrate (*via* enolization and reprotonation) should they possess the unfavorable stereochemistry.

(21) C. O. Parker, *J. Am. Chem. Soc.*, **78**, 4944 (1956).

Fig. 2.—N.m.r. spectrum of XI in CHCl_3 .

hydroresorcinol. Although this seems to establish the structure, some features of the infrared and n.m.r. spectrum are unusual. The absorption at 1740 cm^{-1} (in addition to the expected 1660 and 1623 cm^{-1} peaks) suggests an ester, although it might possibly be the modified ketene acetal double bond.²² Further, the

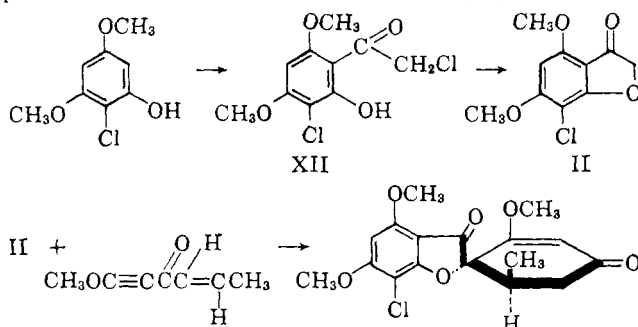


n.m.r. spectrum (see Fig. 3), although showing the required features of a methyl doublet at $\tau = 8.1$, methoxyl at $\tau = 6.4$, and four hydrogens in the vinylic region, appeared to be explicable on the basis of structure IX only if one assumed essentially the same chemical shift for the two vinyl protons marked by an asterisk as they both would have to appear around $\tau = 3.85$.

Whether or not structure IX is correctly assigned to the 87° product, there can be no doubt about the structure of the 146° isomer which must be represented by the expression XI on the basis of its infrared spectrum ($\lambda_{\text{max}}^{\text{CHCl}_3}$ 1740 , 1710 , 1655 , and 1620 cm^{-1}), its ultraviolet spectrum ($\lambda_{\text{max}}^{\text{MeOH}}$ $249\text{ m}\mu$, ϵ $15,220$), and its n.m.r. spectrum in chloroform (Fig. 2). This showed only one vinyl hydrogen ($\tau = 4.5$) as a singlet, a methyl as a doublet ($\tau = 9.0$), and the methoxyl hydrogens at $\tau = 6.4$. The expected multiplets at *ca.* 7.3 and 7.75τ accounted for the other eight protons.

Here again the desired cycloaddition had taken place with the formation of a cyclohexenone ring

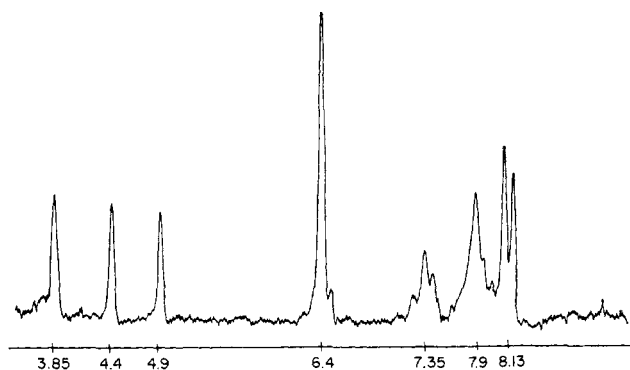
Synthesis of *dl*-Griseofulvin.—We were now ready to apply the new cycloaddition synthesis to the case of griseofulvin. The required 7-chloro-4,6-dimethoxycoumaranone (II) had previously been synthesized by McMillan, *et al.*,²³ from 2-chloro-3,5-dimethoxyphenol. Reaction of the coumaranone (II) with meth-



oxyethynyl propenyl ketone (IV, $\text{R} = \text{CH}_3$) in diglyme-*t*-butyl alcohol, in the presence of potassium *t*-butoxide at room temperature gave a mixture which was chromatographed over acid-washed alumina. Initial fractions contained recovered coumaranone II, and later eluates gave fractions which were shown to contain

(22) Cf. P. Yates and E. W. Robb, *J. Am. Chem. Soc.*, **79**, 5760 (1957).

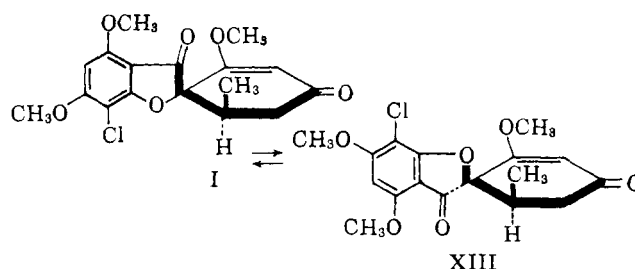
(23) J. McMillan, T. P. C. Mulholland, A. W. Dakin, and J. Ward, *J. Chem. Soc.*, 429 (1954).

Fig. 3.—N.m.r. spectrum of IX in CCl_4 .

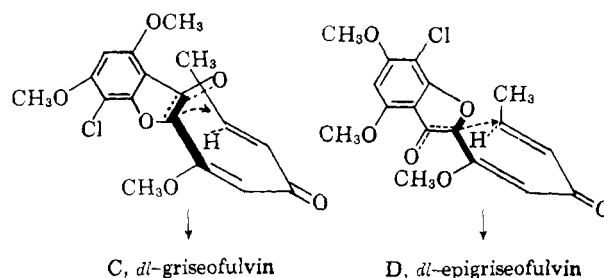
dl-griseofulvin by thin layer chromatography on silica gel. Rechromatography of these fractions then led to pure *dl*-griseofulvin (I), m.p. 224 – 226° . Sublimation and recrystallization from ethyl acetate-hexane gave plates melting at 212 – 213° and again at 225 – 226° . Previously reported melting points have been 214 – 216° ,^{24a} 228 – 230° ,^{24b} and 222 – 224° .^{24c} The ultraviolet spectrum [$\lambda_{\text{max}}^{\text{MeOH}}$ $318\text{ m}\mu$ (5200), $286\text{ m}\mu$ ($23,000$), $245\text{ m}\mu$ (sh) ($16,000$), and $230\text{ m}\mu$ ($21,300$) (see Fig. 4 and 5)] and the infrared spectrum [$\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.93 , 6.07 , 6.24 , $6.33\text{ }\mu$ (see Fig. 6 and 7)] were identical with those of natural (+)-griseofulvin. The behavior on thin layer chromatography was also identical with that of the natural material.

It is of considerable interest that the synthesis appears to have produced *dl*-griseofulvin (I) free from its epimer *dl*-epigriseofulvin (XIII). This, of course, makes this synthesis of *dl*-griseofulvin stereospecific. We believe also that this result may have important mechanistic significance with respect to the course of other Michael reactions.

We first note that the epimer actually obtained is known to be the *less stable* one. Equilibration of (+)-griseofulvin has been shown to produce an equilibrium mixture containing 60% of the epimer in which the carbonyl group of the coumaranone ring is *trans* to the neighboring methyl group.⁵ The formation of *dl*-



griseofulvin must therefore be under kinetic control. We would like to suggest that the stereospecificity observed here is the result of better overlap of the elec-



(24) (a) A. Brossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, **43**, 2071 (1960); (b) A. C. Day, J. Nabney, and A. I. Scott, *J. Chem. Soc.*, 4067 (1961); (c) C. H. Kuo, R. D. Hoffsommer, H. L. Slates, D. Taub, and N. I. Wendler, *Chem. Ind. (London)*, 1627 (1960).

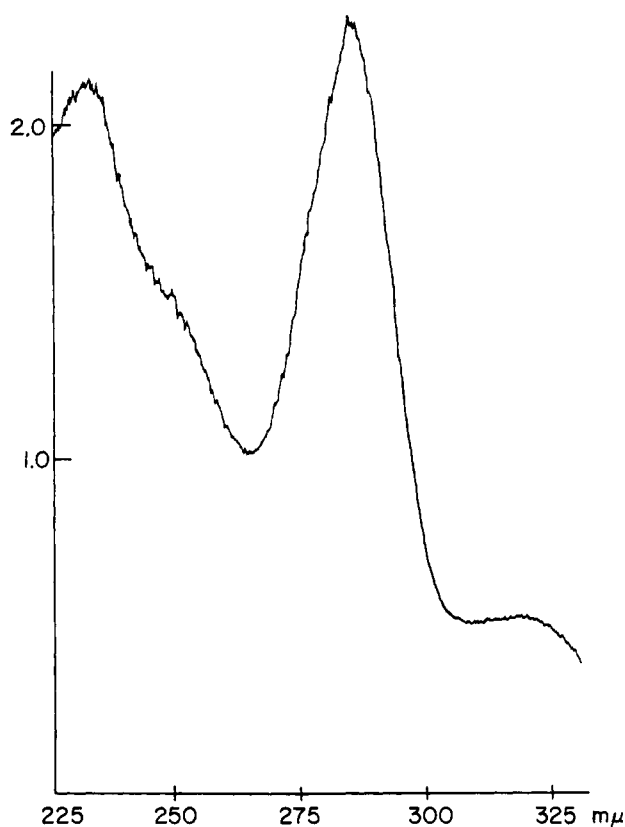


Fig. 4.—Ultraviolet spectrum of synthetic *dl*-griseofulvin in CH_3OH .

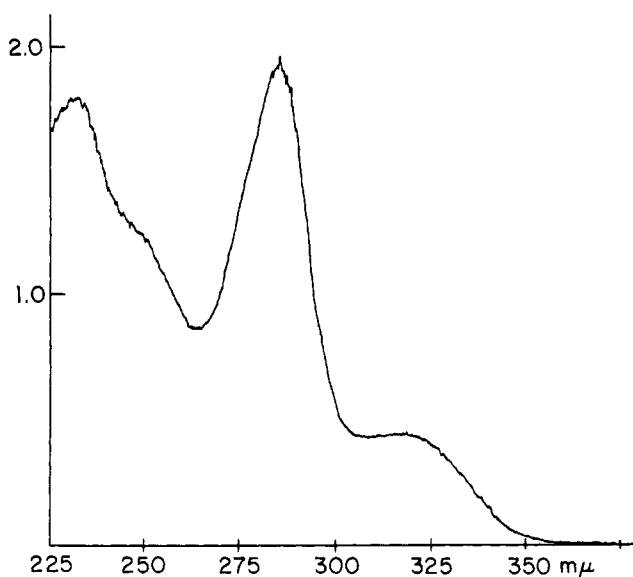


Fig. 5.—Ultraviolet spectrum of natural (+)-griseofulvin in CH_3OH .

tron donor system of the enolate ion with the unsaturated ketone acceptor in the transition state C which leads to *dl*-griseofulvin than in the transition state D which leads to *dl*-epigriseofulvin. Whether this result applies to other Michael additions is not known at present.

Experimental

Ethoxy- and methoxyacetylene were originally prepared from the corresponding β -bromovinyl ethers and lithium amide. This new method was preferred to the simpler use of diethyl or dimethyl chloroacetal and sodamide in liquid ammonia²⁵ because

(25) (a) E. R. H. Jones, G. Eglinton, M. C. Whiting, and B. L. Shaw, *Org. Syn.*, **34**, 46 (1954); (b) for an improvement of (a), see H. H. Wassermann and P. S. Wharton, *J. Am. Chem. Soc.*, **82**, 661 (1960).

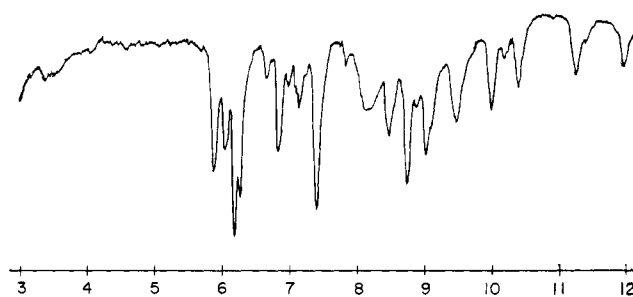


Fig. 6.—Infrared spectrum of natural (+)-griseofulvin in CHCl_3 .

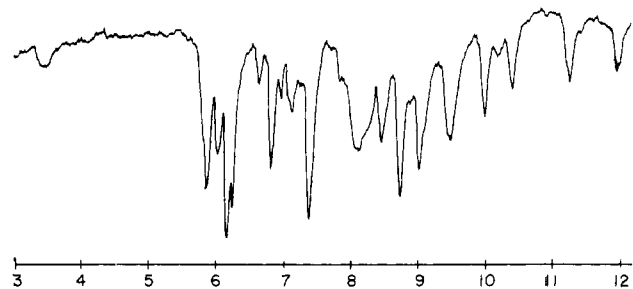


Fig. 7.—Infrared spectrum of synthetic *dl*-griseofulvin in CHCl_3 .

of the reduced hazard of fire during the decomposition of the alkali metal salt with water. Ethoxyacetylene has now become commercially available.⁹

β -Bromovinyl Ethyl Ether.²⁶—Vinyl ethyl ether (225 g., 3.12 moles) was slowly added, under vigorous stirring, to 500 g. (3.12 moles) of bromine. The temperature of the reaction mixture was kept between -10 and -15° by cooling the flask in an acetone–Dry Ice bath. The addition took about 5 hr.; then the resulting clear, slightly yellow α,β -dibromoethyl ethyl ether was allowed to stand overnight at room temperature. Diethylaniline (1000 cc., dried over magnesium sulfate and distilled) was placed into a 3-necked 3-l. flask fitted with a stirrer, a Vigreux column, an ice-cooled receiver, and a dropping funnel containing the above α,β -dibromoethyl ethyl ether. The flask was heated in an oil bath (93 – 98°), and a vacuum of 20–25 mm. was established in the system. The α,β -dibromoethyl ethyl ether was then added dropwise over a period of 6 hr. while the β -bromovinyl ethyl ether formed simultaneously distilled into the receiver. Redistillation yielded 225 g. (48% of the theoretical) of the pure compound, b.p. 36 – 50° (14–24 mm.); reported²⁶ b.p. 42 – 46° (12 mm.).

β -Bromovinyl Methyl Ether.—Methyl vinyl ether (46.6 g., 0.80 mole) was condensed (b.p. 8°) in a flask by cooling in ice. It was then slowly distilled with vigorous stirring into a 3-necked flask containing 128 g. (0.80 mole) of bromine. The reaction mixture was kept at -5 to -10° (Dry Ice–acetone bath). The addition took about 3 hr., and the mixture was then allowed to stand overnight in an ice bath. The resulting α,β -dibromoethyl methyl ether was added to 250 cc. of diethylaniline in the manner described above. On distillation, β -bromovinyl methyl ether was obtained, b.p. 69 – 70° (120 mm.), yield 57 g. (52%).

Anal. Calcd. for $\text{C}_3\text{H}_5\text{OBr}$: C, 26.28; H, 3.65. Found: C, 25.92; H, 3.67.

Ethoxyacetylene.—Lithium (27.38 g., 3.94 g.-atoms) was dissolved in 3 l. of liquid ammonia to which about 0.5 g. of anhydrous ferric chloride had been added. When the lithium amide formation was complete (the previously blue mixture became light gray), 312.6 g. (2.07 moles, 5% excess) of β -bromovinyl ethyl ether was added to the stirred suspension, during 1 hr. The ammonia was then allowed to evaporate while a slow stream of prepurified nitrogen passed through the system which was kept sealed from the air by a mercury trap. After 48 hr., the evaporation was practically complete. The flask containing dry lithium ethoxyacetylide was cooled to -70° in Dry Ice, and the flow rate of the nitrogen stream was increased so that no air would enter the system during the cooling.

A saturated aqueous calcium chloride solution (1 l.), which had been freed of air by boiling *in vacuo* and was kept under nitrogen, was cooled to -50° , and poured into the flask through a powder funnel as rapidly as possible and without stirring or swirling. (Free passage of the nitrogen through the flask was ensured by inserting a thick bent wire between the stem of the funnel and the neck of the flask.) The funnel then was replaced by

(26) I. N. Nazarov, Th. A. Krasnaya, and V. P. Vinogradov, *J. Gen. Chem. USSR*, **28**, 451 (1958).

a stopper, and the flow of nitrogen was discontinued. (The system remained sealed from the air by the mercury trap.) The mixture was allowed to warm to room temperature, then was stirred well for 5 min. After some swirling by hand, the contents of the flask were transferred into a large separatory funnel and the two layers were allowed to separate. Most of the lower layer was discarded. (Complete separation was not possible because of emulsion formation at the boundary of the phases.) The remaining mixture was distilled from an oil bath, through a short Vigreux column, into a Dry Ice-cooled receiver. The distillation of ethoxyacetylene began when the bath temperature reached 80° (inner temperature 46°). A large amount distilled at 46–50°; then the bath temperature was raised gradually up to an inner temperature of 80°, at which point the distillation was stopped.

The receiver contained a frozen lower and a liquid upper layer. The latter was decanted, dried over calcium chloride overnight, and filtered (under cover, to prevent evaporation). Its weight was 104 g. (75% of the theoretical) and was almost pure ethoxyacetylene according to the infrared spectrum. On distillation through a short Vigreux column under nitrogen, 87 g. (62% of the theoretical) of ethoxyacetylene was obtained, b.p. 53° (reported^{25a} b.p. 51°).

Methoxyacetylene.—Lithium (7.92 g., 1.14 g.-atoms) was dissolved in 800 cc. of liquid ammonia containing a small amount of anhydrous ferric chloride. In a manner completely analogous to that described above for ethoxyacetylene, 82.4 g. (0.60 mole, 5% excess) of β -bromovinyl methyl ether was added and the ammonia was evaporated; then 500 cc. of saturated calcium chloride solution was added. When the mixture had warmed up to room temperature, it was stirred for 5 min., then swirled by hand several times to flush the sides. A Vigreux column and Dry Ice-cooled receiver were then attached to the flask (note that no separation of the layer was carried out in this case) and the mixture was distilled from an oil bath, up to 90° bath temperature (inner temperature 30–60°) under nitrogen. The distillate weighed 20 g. To this, 50 ml. of ice-cold *n*-heptane and a drop of phenolphthalein solution was added. Saturated aqueous sodium dihydrogen phosphate solution was added to neutrality, with vigorous swirling of the flask which was cooled in an ice bath. The aqueous layer was frozen out by cooling in Dry Ice; the upper layer was decanted and dried over calcium chloride overnight at 0°. It was filtered under cover and distilled through a short Vigreux column under nitrogen, yielding methoxyacetylene (15.7 g., 50% of the theoretical), b.p. 34°, reported^{25b} b.p. 22.5–24°.

Ethoxyethynylpropenylcarbinol (III, R = C₂H₅).—To an ethereal solution of phenyllithium²⁷ from 2.98 g. of lithium and 30.66 g. (0.195 mole) of bromobenzene, ethoxyacetylene (12.67 g., 0.195 mole) was added in a period of 5 min., under ice-cooling and a nitrogen atmosphere, with stirring. A white precipitate was formed. The mixture was then cooled to –15° to –20° (Dry Ice-acetone bath) and 15.05 g. (0.215 mole, 10% excess) of dry, distilled crotonaldehyde in 70 ml. of absolute ether was added in a period of about 45 min., with vigorous stirring. The precipitate disappeared by the end of the addition. To the resulting solution, 150 cc. of saturated aqueous sodium chloride (cooled to 0°) was added at once with stirring. The ether layer was separated and dried over magnesium sulfate overnight at 0°, and the ether was then evaporated *in vacuo*. (The residue was not allowed to warm to the steam bath temperature after evaporating the ether.) The residual oil weighed 27 g. It was distilled through a short Vigreux column to yield ethoxyethynylpropenylcarbinol (III, R = C₂H₅) as a colorless oil, b.p. 65–70° (diffusion pump), weight 17.0 g. (62% yield); $\lambda_{\text{max}}^{\text{C}^{14}}$ 3600 (w), 3450 (broad), 2270 (s), 1675 (w) cm.⁻¹.

Anal. Calcd. for C₈H₁₂O₂: C, 68.54; H, 8.63. Found: C, 68.78; H, 8.69.

The substance is stable when kept at –15° under nitrogen (usually solidifies). On standing at room temperature, strong bands in the 1700–1740 cm.⁻¹ region were observed after 1 week.

On catalytic hydrogenation, 0.1367 g. (0.00098 mole) of III, R = C₂H₅, in 10 cc. of ethyl acetate over reduced platinum (from 0.0067 g. of platinum oxide) consumed 72.06 cc. of hydrogen (theoretical for 3 moles of hydrogen at 27°: 72.40 cc.) in a period of 20 min., then stopped.

Rearrangement of Ethoxyethynylpropenylcarbinol into Ethyl Sorbate.—Ethoxyethynylpropenylcarbinol (0.4 g.) was dissolved in 10 cc. of absolute ethanol containing 1 drop of concentrated sulfuric acid. The solution was refluxed for 1 hr., then poured into water, extracted with ether (3 times), washed with water (once), dried over magnesium sulfate, and filtered; the solvent was then evaporated *in vacuo*. The residue was a pale yellow oil, the spectral properties of which indicated that it was the anticipated ethyl sorbate: $\lambda_{\text{max}}^{\text{OH}}$ 259 m μ (reported 259 m μ); $\lambda_{\text{max}}^{\text{C}^{14}}$ 1710 (s), 1650 (m), 1620 (w), 1605 (w) cm.⁻¹ (no OH, no triple bond).

(27) H. Gilman and J. W. Morton, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 286.

Methoxyethynylpropenylcarbinol. A procedure, analogous to that used for III, R = C₂H₅, was applied: phenyllithium was prepared from 3.5 g. (0.5 g.-atom) of lithium and 39.5 g. (0.25 mole) of bromobenzene in 200 ml. of ether. Methoxyacetylene (14.0 g., 0.25 mole) was then added, followed by the addition of 19.25 g. (0.275 mole) of crotonaldehyde, in the manner described above for III, R = C₂H₅, with the exception that here the reaction flask was equipped with a Dry Ice condenser because of the low boiling point of methoxyacetylene (34°). The work-up was also identical. On distillation through a short Vigreux column, methoxyethynylpropenylcarbinol was obtained as a colorless oil, b.p. 60° (diffusion pump), weighing 20.2 g. (64% yield); $\lambda_{\text{max}}^{\text{C}^{14}}$ 3620 (w), 3450 (broad), 2270 (s), 1670 (w) cm.⁻¹. Good analytical values could not be obtained on this compound, probably because of its instability.

Anal. Calcd. for C₇H₁₀O₂: C, 66.64; H, 7.99. Found: C, 65.10; H, 7.72.

Ethoxyethynyl Propenyl Ketone (IV, R = C₂H₅).—Ethoxyethynylpropenylcarbinol (10.0 g.) was added to a suspension of finely powdered manganese dioxide (100 g.; for preparation, see below) in dry methylene chloride (1 l.) in a period of 15 min., with vigorous stirring. The reaction mixture was warmed up slightly during the addition. It was stirred for 4 hr. at room temperature. The infrared spectrum of a sample indicated a complete shift of the 2270 band to 2230 cm.⁻¹. The mixture was filtered by suction through a layer of anhydrous magnesium sulfate placed on the filter paper. The manganese dioxide was washed with 100 cc. of methylene chloride and the filtered washings were combined with the main filtrate. The methylene chloride was evaporated *in vacuo* and the residual oil (6 g.) was distilled from an oil-jacketed flask under high vacuum. The first fraction, b.p. 30–40° (bath; diffusion pump), weighed 1.6 g. and was a mixture; the combined second and third fractions were ethoxyethynyl propenyl ketone, obtained as a colorless oil, b.p. 40–60° (bath; diffusion pump) which weighed 4.0 g. (40% yield); $\lambda_{\text{max}}^{\text{OH}}$ 249 m μ (ϵ 9100), 228 m μ (ϵ 11,600); $\lambda_{\text{max}}^{\text{C}^{14}}$ 2230 (s), 1650 (s), 1625 (s) cm.⁻¹. Repeated distillation did not improve the analytical figures.

Anal. Calcd. for C₈H₁₀O₂: C, 69.54; H, 7.30. Found: C, 68.97; H, 7.32.

In another experiment, the crude oil (10 g., from 16 g. of carbinol) was distilled through a Claisen head. A low yield (4.4 g., 28%) was obtained, b.p. 53–55° (diffusion pump), and a large amount of undistillable residue was left in the flask. The distillation from an oil-jacketed flask thus seems preferable.

The ketone IV, R = C₂H₅, can be kept in the freezer under nitrogen for a prolonged time. At room temperature it slowly decomposes.

On adding IV, R = C₂H₅, to DNP reagent the DNP derivative of ethyl crotonyl acetate (for the preparation of an authentic sample, see below) was formed as an orange solid. On recrystallization from ethanol it formed leaflets, m.p. 120–121°, $\lambda_{\text{max}}^{\text{C}^{14}}$ 1740 (s) cm.⁻¹ (ester carbonyl).

Anal. Calcd. for C₁₄H₁₆O₆N₄: C, 50.00; H, 4.80; Found: C, 49.88; H, 4.88.

Methoxyethynyl Propenyl Ketone (IV, R = CH₃).—Methoxyethynylpropenylcarbinol (12.6 g.) was oxidized in an analogous manner for 6 hr. with 126 g. of freshly prepared manganese dioxide suspended in 1.2 l. of dry methylene chloride. On distillation of the crude oil from an oil-jacketed flask, methoxyethynyl propenyl ketone was obtained as a colorless oil, b.p. 65–80° (bath; diffusion pump), yield 3.7 g. (30% of the theoretical); $\lambda_{\text{max}}^{\text{OH}}$ 2230 (s), 1650 (s), 1625 (s) cm.⁻¹. It was redistilled for an analytical sample.

Anal. Calcd. for C₇H₈O₂: C, 67.73; H, 6.50. Found: C, 67.10; H, 6.84.

On adding 88 mg. of IV, R = CH₃, to methanolic DNP reagent, the DNP derivative of methyl crotonylacetate was formed as an orange solid in 81% yield. On repeated recrystallization from methanol it melted at 172° (leaflets), $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.80 μ (ester carbonyl).

Anal. Calcd. for C₁₃H₁₄O₆N₄: C, 48.45; H, 4.35. Found: C, 48.19; H, 4.41.

Preparation of Active Manganese Dioxide.¹²—A solution of manganese sulfate monohydrate (417 g. in 750 ml. of water) and 40% sodium hydroxide solution (585 ml.) were added simultaneously to a hot stirred solution of 480 g. of potassium permanganate in 3 l. of water over a period of 1 hr. The boiling mixture was stirred for an additional hour, and it was then allowed to stand overnight. The precipitate was collected with the help of a centrifuge, then washed until the pH of a wetted sample reached 8. Each washing was done in the following way: the centrifuged precipitate was transferred into a beaker, boiled with water for 5 min., with occasional stirring, then centrifuged while still hot. The most active manganese dioxide was obtained when the washing was done within a day. The precipi-

tate was dried at 110° overnight and powdered before use; yield about 300 g. of manganese dioxide.

Ethyl Crotonylacetate (V) via Hydration of Ethoxyethynyl Propenyl Ketone.—(a) Ethoxyethynyl propenyl ketone (0.31 g.) was dissolved in 5 ml. of ether. Aqueous hydrochloric acid (5%, 10 ml.) was added, and the heterogeneous mixture was stirred at room temperature for 3 hr. The ether layer was separated, washed once with saturated sodium bicarbonate solution and once with saturated salt solution, and dried over magnesium sulfate; the ether was removed *in vacuo*. The residual oil was ethyl crotonylacetate as proved by its properties: $\lambda_{\text{max}}^{\text{EtOH}}$ 267 and 226 μ ; $\lambda_{\text{max}}^{\text{CCl}_4}$ 1740 (s), 1700 (m), 1660 (s), 1640 (s), 1600 (s) cm^{-1} . It gave a purple ferric chloride test and formed a green crystalline copper chelate, m.p. 161° (reported¹³ 159°); it gave a crystalline DNP derivative identical with that obtained directly from IV, R = C₂H₅, (characterized by its m.p., infrared, and C-H analysis, see above).

(b) A small sample of IV, R = C₂H₅, was refluxed in 60% aqueous ethanol for 4 hr.; then the solvent was evaporated. The residual oil had an infrared spectrum identical with that of ethyl crotonylacetate, obtained in a.

4,4-Dicarbethoxy-3-ethoxy-5-methyl-2-cyclohexenone (VI).—To a solution containing 3.12 g. (0.0195 mole) of diethyl malonate (dry, distilled) and potassium *t*-butoxide (from 0.097 g. (0.025 g.-atom) of potassium) in absolute *t*-butyl alcohol (60 cc.), 2.035 g. (0.017 mole) of ethoxyethynyl propenyl ketone (freshly distilled) was added, and the clear yellow solution was stirred at room temperature for 2 hr. under nitrogen. Then 0.13 g. (0.025 mole) of glacial acetic acid in 5 cc. of *t*-butyl alcohol was added, and the mixture was poured into water and extracted with ether (3 times). The combined ether extracts were washed once with water and once with saturated salt solution, dried over magnesium sulfate, and filtered; the ether was then evaporated *in vacuo*. The residual oil solidified on scratching. It was purified by molecular distillation (90–130° bath temperature; diffusion pump) affording VI in 50% yield, m.p. 60–62°. On recrystallization from *n*-hexane it melted at 61–62° (prisms): $\lambda_{\text{max}}^{\text{EtOH}}$ 250 μ (ϵ 17,100); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.83 (s), 6.09 (m), 6.22 (s) μ ; for n.m.r. (in CCl₄) see Fig. 1; t.l.c. on silica plate, *n*-butyl acetate as solvent: R_f ~0.58 (0.2% KMnO₄; yellow spot).

Anal. Calcd. for C₁₆H₂₂O₆: C, 60.39; H, 7.43. Found: C, 60.47; H, 7.35.

The total amount of VI formed in the reaction could be estimated as about 73% on the basis of a quantitative ultraviolet determination on the crude crystalline product which had exactly the theoretical weight (5.0 g.).

4,4-Dicarbethoxy-3-methoxy-5-methyl-2-cyclohexenone.—Diethyl malonate (0.242 g., 0.0015 mole) was allowed to react with 0.164 g. (0.0013 mole) of methoxyethynyl propenyl ketone in 6 ml. of absolute *t*-butyl alcohol containing potassium *t*-butoxide (from 8 mg. of potassium) under the conditions described above. A similar work-up resulted in a crude oil (0.326 g.) which could not be crystallized even after a molecular distillation (130° (diffusion pump)). Its infrared spectrum was very similar to that of VI; $\lambda_{\text{max}}^{\text{EtOH}}$ 250 μ (ϵ 13,800); t.l.c., identical with that of VI. Its structure was proved by conversion to 5-methylcyclohexane-1,3-dione (see below).

5-Methylcyclohexane-1,3-dione via Hydrolysis and Decarboxylation (a) of VI and (b) of its Methoxy Analog.—(a) A solution of VI (2.0 g.) in a mixture of 10 ml. of water and 10 ml. of ethanol containing 1.7 g. of potassium hydroxide was refluxed for 6 hr. under nitrogen. It was then acidified with 1:2 hydrochloric acid–water, to pH 7. Most of the alcohol was distilled off, then more acid was added. On heating the mixture for 10 min. strong gas evolution was observed. The mixture was extracted with ether (3 times), the combined extracts were washed once with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to dryness. On adding some ether to the residue, white crystals separated which were removed from the ethereal mother liquor by filtration, yielding 5-methylcyclohexane-1,3-dione,¹⁹ m.p. 130–132°; $\lambda_{\text{max}}^{\text{EtOH}}$ 253 μ ; base (NaOEt) 280 μ ; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.82 (w), 5.90 (s), 6.24 (s, broad) μ . It was identical with an authentic preparation.

(b) In this case an improved, more quantitative procedure was worked out, on a very small scale, to characterize the non-crystalline starting material available only in small quantity. A solution of 25 mg. of the cyclic enol ether was refluxed in 1 ml. of 10% aqueous potassium hydroxide under nitrogen for 4 hr. Then 2 ml. of 10% sulfuric acid was added and the mixture was heated for 5 min. Extraction with chloroform (3 times), washing the combined extracts with saturated sodium chloride solution (once), drying over magnesium sulfate, and evaporation of the solvent yielded 6 mg. (55%) of pure 5-methylcyclohexane-1,3-dione, m.p. 131–132°, identical with an authentic preparation.

Michael Addition of Dihydroresorcinol to Methoxyethynyl Propenyl Ketone.—To a solution of potassium *t*-butoxide in absolute *t*-butyl alcohol (prepared by adding 20 mg. (0.0005 g.-atom) of potassium to 25 ml. of absolute *t*-butyl alcohol), 0.509

g. (0.0045 mole) of dihydroresorcinol (m.p. 105–106°, dried over phosphorus pentoxide in a desiccator) and 0.480 g. (0.0038 mole) of freshly distilled methoxyethynyl propenyl ketone (IV, R = CH₃) were added successively. The solution was stirred in a nitrogen atmosphere for 4.5 hr. at room temperature. By the end of this time the band at 2230 cm^{-1} (triple bond) completely disappeared from the infrared spectrum of the mixture. Two drops of glacial acetic acid in 2 ml. of *t*-butyl alcohol was added and the mixture was poured into water. Extraction with methylene chloride (3 times), washing the combined extracts with water (3 times), drying over magnesium sulfate, and evaporation of the solvent yielded 0.806 g. of an oil containing some crystals. Efforts were made to isolate a pure substance by fractional crystallization, but only a small amount (27 mg.) of a crystalline material (m.p. 145–147°) was obtained. During these manipulations, 0.208 g. (25% of the crude product) was lost, probably during a charcoal treatment. The remaining 0.565 g. was chromatographed over a column of 30 g. of silica gel made up in benzene. Elution with 10% ether–benzene gave 0.206 g. of an oil (fractions 5–9) followed by a crystalline substance (fractions 11–20), m.p. 140–144° (0.200 g.). The oil was rechromatographed over 30 g. of silica gel, and on elution with 5% ether–benzene 0.180 g. of a crystalline material, m.p. 76–80°, was obtained.

The compound with m.p. 140–144° was further purified by sublimation (80° (diffusion pump)) and recrystallization from 10% benzene–*n*-heptane, giving 87 mg. of analytically pure 7-methoxy-11-methyl-spiro[5.5]undec-7-en-1,5,9-trione (XI), m.p. 146–147° (plates, Kofler microscope); $\lambda_{\text{max}}^{\text{MeOH}}$ 249 μ , ϵ 15,200; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 1740 (w), 1710 (s) 1655 (s), 1620 (s) cm^{-1} ; for n.m.r. see Fig. 2; t.l.c. on silica plate, *n*-butyl acetate as solvent: R_f 0.4 (0.2% KMnO₄; yellow).

Anal. Calcd. for C₁₈H₁₆O₄: C, 66.08; H, 8.63. Found: C, 66.34; H, 6.74.

The yield, calculated on the basis of 0.200 + 0.027 g. = 0.227 g. of chromatographically pure substance, was 28% of the theoretical.

The compound with m.p. 76–80° was recrystallized from *n*-hexane, affording the presumed 2-methoxy-2-(3-ketocyclohexenyl-oxy)-vinyl propenyl ketone (IX, 97 mg.) as colorless soft needles, m.p. 80–82°; $\lambda_{\text{max}}^{\text{MeOH}}$ 250 μ (ϵ 37,100); $\lambda_{\text{max}}^{\text{CCl}_4}$ 1740 (s), 1660 (s, broad), 1623 (s) cm^{-1} ; for its n.m.r. spectrum see Fig. 3; t.l.c., silica plate, *n*-butyl acetate: R_f 0.5 (0.2% KMnO₄; yellow).

Anal. Calcd. for C₁₈H₁₆O₄: C, 66.08; H, 6.83. Found: C, 65.96; H, 6.84.

The yield, calculated on the basis of 0.180 g. of chromatographically homogeneous substance, was 22% of the theoretical.

Acidic Hydrolysis of IX.—A small sample of IX (18 mg.) was dissolved in 2 drops of purified dioxane, 0.5 ml. of 2 *N* sulfuric acid was added, and the solution was allowed to stand at room temperature; t.l.c. analysis (silica plate, *n*-butyl acetate) indicated the gradual disappearance of the starting material (R_f 0.57) and the appearance of two new spots: one at the height of the solvent front, giving a purple color with ferric chloride, and one close to the origin (same as dihydroresorcinol). After 3 hr., the reaction was complete. Excess saturated sodium bicarbonate solution was added and the mixture was extracted with ether (3 times), the combined ether extracts were washed with water, and the solvent was evaporated. The residual oil gave a crystalline DNP derivative which, after recrystallization from methanol, melted at 172° and was identical by melting point and mixture melting point with the DNP derivative of methyl crotonylacetate (see above).

The aqueous sodium bicarbonate layer was acidified with 2 *N* sulfuric acid and extracted with chloroform (3 times). The combined chloroform extracts were dried over a small amount of magnesium sulfate, filtered, and evaporated. The white crystalline residue was identified as dihydroresorcinol, by its infrared and ultraviolet spectra ($\lambda_{\text{max}}^{\text{EtOH}}$ 253 μ ; in base 280 μ), m.p. 104–106°, and mixture m.p. with an authentic sample.

3,5-Dimethoxyphenol.²⁸—Phloroglucinol (20 g., techn.) was dissolved in 250 ml. of absolute methanol and cooled to 0° in an ice bath. Dry hydrogen chloride was introduced to saturation (this required about 4 hr.). The temperature was kept between 10 and 27° by cooling in ice during the saturation. The solution was refluxed for 1 hr., then saturated again with hydrogen chloride. The mixture was allowed to stand overnight at room temperature. The methanol was then evaporated *in vacuo* and the residual brown oil was dissolved in ether and washed with water (once), with saturated sodium bicarbonate solution (3 times), and with saturated salt solution (once). The ether layer was dried over magnesium sulfate and the solvent was then removed *in vacuo*. The residual oil was then distilled through a Vigreux column to give 3,5-dimethoxyphenol, b.p. 128–129° (1.5 mm.), m.p. 32–34° (reported²⁸ b.p. 161–164° (10 mm.), solidifying).

(28) K. Freudenberg, H. Fikentscher, and W. Wenner, *Ann.*, **442**, 318 (1925).

2-Chloro-3,5-dimethoxyphenol.²⁹—To a solution of 3,5-dimethoxyphenol (20 g.) in 240 cc. of distilled chloroform, 20 g. of sulfuric chloride (distilled) dissolved in 80 cc. of chloroform was added dropwise in a period of 1 hr., under reflux. The resulting solution was refluxed for 3 hr. more and was then allowed to stand at room temperature for 48 hr. After evaporation to dryness, the residual dark oil was twice extracted with boiling *n*-hexane (first extract, 400 ml.; second, 200 ml.). The combined extracts were allowed to cool. After filtering off 1.1 g. of 4-chloro-3,5-dimethoxyphenol, m.p. 115–130° (reported²³ 132–133°), as the first crop, 10 g. of 2-chloro-3,5-dimethoxyphenol separated as colorless needles, m.p. 58–60°. After recrystallization it melted at 64–65° (reported²³ m.p. 58–59°). In another experiment, the crude mixture was chromatographed over thirty times its weight of alumina (acid-washed). Elution with benzene gave about the same yield as before, m.p. 65°.

2-Hydroxy-3 α -dichloro-4,6-dimethoxyacetophenone (XII).²³—2-Chloro-3,5-dimethoxyphenol (2.62 g.) was dissolved in 3.7 g. of nitrobenzene and to the resulting solution 3.27 g. of chloroacetyl chloride and 3.5 g. of anhydrous aluminum chloride were added successively. The mixture was stirred for 20 hr. at room temperature, then a mixture of 40 ml. of ice-cold water and 10 ml. of concentrated hydrochloric acid was added, and the nitrobenzene was removed by steam distillation. The residual mixture was filtered, and the solid was collected and washed with water, methanol, and ether, successively. The resulting light yellow powder was recrystallized from dioxane, affording 2 g. of XII as yellow needles, m.p. 216° dec. (reported²³ m.p. 211° dec.).

7-Chloro-4,6-dimethoxycoumaran-3-one (II).²³—A solution of 10 g. of XII in 120 ml. of 95% ethanol containing 11.8 g. of hydrated sodium acetate was refluxed for 2 hr. The solvent was then removed *in vacuo*, and the solid residue was thoroughly washed with water on a filter. The remaining solid was recrystallized from dioxane giving 7.2 g. of 7-chloro-4,6-dimethoxycoumaran-3-one (II) as colorless needles, m.p. 218–225° dec. (reported²³ m.p. 210–220° dec.; t.l.c. silica plate, *n*-butyl acetate: R_f 0.50 (blue fluorescence in ultraviolet light)).

Epimerization of Natural (+)-Griseofulvin.—In order to check the ability of the silica plates to separate griseofulvin from epigriseofulvin (XIII), (+)-griseofulvin was partially converted to (+)-epigriseofulvin by the method of Brossi, *et al.*^{24a}: Natural (+)-griseofulvin (27 mg.) was dissolved in 2 ml. of 1 *N* methanolic sodium methoxide. The solution was heated at 70° under nitrogen for 3 hr., then cooled to room temperature. This solution was used for t.l.c., silica plate, *n*-butyl acetate, solvent front 11 cm.: two ultraviolet fluorescent (violet) spots (R_f 's 0.36 (griseofulvin) and 0.33 (epigriseofulvin); close, but but definite separation). On spraying with 0.2% KMnO_4 , griseofulvin appears as a bright yellow spot; epigriseofulvin is invisible.

(29) A slight modification of the procedure of J. McMillan, T. P. C. Mulholland, A. W. Dakins, and G. Ward, *J. Chem. Soc.*, 429 (1954).

***dl*-Griseofulvin (I).**—A solution of potassium *t*-butoxide (prepared by adding 0.048 g. of potassium to 10 ml. of absolute *t*-butyl alcohol) was added to 500 ml. of diglyme (distilled from lithium aluminum hydride under nitrogen). In this mixture 7-chloro-4,6-dimethoxycoumaran-3-one (II) (2.00 g., 0.0088 mole) was dissolved; then 1.00 g. (0.0081 mole) of methoxyethynyl propenyl ketone (freshly distilled) was added at once. The resulting solution was stirred at room temperature for 20 hr. under nitrogen. Glacial acetic acid (2 ml.) was then added and the mixture was poured into water (about 1 l.) and extracted with chloroform (3 times); the combined chloroform extracts were washed with water (3 times), then dried over magnesium sulfate. After evaporating the chloroform, the remaining diglyme was removed by heating to 60° at 0.001 mm. The residual reddish powder was chromatographed over acid-washed alumina (200 g.). Elution with benzene and 5, 10, and 20% ether–benzene, successively, yielded 0.63 g. of the starting material II. Further elution with 20, 50, and 100% ether–benzene gave 0.220 g. of partially crystalline material which was shown to contain *dl*-griseofulvin, as its main component, by t.l.c. analysis. A further 1.2 g. of amorphous solid, which also contained a small amount of griseofulvin according to t.l.c., was eluted with chloroform.

The middle fraction was rechromatographed over 8 g. of Woelm nonalkaline alumina, activity grade I, and the band which gave a blue fluorescence under ultraviolet light was eluted with 50% ether–benzene, giving 100 mg. of *dl*-griseofulvin, m.p. 224–226° (Kofler hot stage), homogeneous by t.l.c. analysis. It was sublimed (150–160° (diffusion pump)) and recrystallized from ethyl acetate–*n*-hexane, giving plates, m.p. 212–213°, then 225–226° (Kofler hot stage) (reported 214–216°,^{24a} 228–230°,^{24b} 222–224°^{24c}); $\lambda_{\text{max}}^{\text{MeOH}}$ 318 (ϵ 5200), 286 (ϵ 23,000), 245 (sh) (ϵ 16,000), 230 μ (ϵ 21,300) (for comparison with the ultraviolet spectrum of natural (+)-griseofulvin, see Fig. 4, 5); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.93 (s), 6.07 (m), 6.24 (s), 6.33 (s) μ . (For comparison with the infrared spectrum of natural (+)-griseofulvin, see Fig. 6, 7.) Analysis by t.l.c., silica plate, *n*-butyl acetate, gave R_f 0.36 (0.2% KMnO_4 , yellow; ultraviolet, violet fluorescence).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{O}_6\text{Cl}$: C, 57.80; H, 4.86. Found: C, 58.00; H, 4.87.

An additional 43 mg. of *dl*-griseofulvin was obtained by rough rechromatographing of the last fraction from the first chromatography over 30 g. of acid-washed alumina. The combined material from the benzene, 50% ether–benzene, and ether eluates (0.130 g.) was further purified by preparative t.l.c. in two batches, affording 43 mg. of *dl*-griseofulvin, m.p. 224–226°. Thus the total yield of *dl*-griseofulvin was 0.143 g. (5% of the theoretical; 7%, if the recovery of 0.63 g. of II is taken into account).^{30,31}

(30) The over-all yield by this relatively short route does not compare unfavorably with that obtained in the other reported syntheses; *cf.* ref. 24.

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Total Synthesis of Longifolene¹

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An account is given of a total synthesis of longifolene starting from resorcinol by operations which generate structure II unambiguously. The complex bridged-ring system of longifolene was produced by internal cyclization of a homodecalin derivative which in turn was constructed from 1,6-dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (IX) by a novel ring expansion. Resolution was accomplished using L(+)-2,3-butanedithiol which served an additional role in carbonyl protection and reduction.

Introduction

The virtuosity of Nature in the construction of intricate molecules is nowhere more evident than in those families which are described broadly as isoprenoids. Within this group an especially concentrated and impressive display of this synthetic expertise can be found in the sesquiterpene class. Here diverse and unusual arrangements of rings and functionality abound notwithstanding a common origin from the same acyclic C_{15} -precursor, as now seems probable. This remarkable variety of design is perhaps the principal reason for the structural chemist's deep inter-

est in this field of natural products, a concern which is out of all proportion to present practical value. At the same time these structures are highly relevant to the study of chemical synthesis since they challenge present principles and methodology, especially in respect to a fundamental element of synthesis, the construction of ring systems and networks of carbon. In this paper and that which follows we report synthetic studies on two of the most interesting sesquiterpene structures, longifolene and caryophyllene.^{2,3}

(2) For previous publications from our group on the synthesis of sesquiterpenes in the santalene series see (a) E. J. Corey, S. W. Chow, and R. A. Scherrer, *ibid.*, **79**, 5773 (1957); (b) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *ibid.*, **84**, 2611 (1962).

(3) A measure of current interest and progress in the synthesis of sesquiterpenes is provided by a partial list of other recently solved problems

(1) For a preliminary communication on this work see E. J. Corey, M. Ohno, P. A. Vatakencherry, and R. B. Mitra, *J. Am. Chem. Soc.*, **83**, 1251 (1961).