co-workers[5] had ascribed the configuration L_s to the α-carbon, both Gawron's group and the report from this laboratory gave the configuration of isocitric acid as L_sD_g, the optical enantiomorph of I. However, a series of papers by Katsura and Kaneko and their co-workers[6] have reported independent determinations by classical methods of the configurations of the α and β carbons of *d*-isocitric acid. They ascribe the configuration I to isocitric acid in contradiction to Greenstein's result, but in agreement with the *threo* configuration required by Gawron's work and our own. Although this latter fact was a strong indication that the Katsura absolute configuration was correct, it seemed worth while for us to obtain an independent check on this very important result by X-ray dispersion techniques as we had already planned.[2]

TABLE I

SOME DISPERSION DATA FOR POTASSIUM AND RUBIDIUM MONO-SALTS OF ISOCITRIC LACTONE

Values of $100\,(|F_+|^2 - |F_-|^2)/{}^1/_2(|F_+|^2 + |F_-|^2)$

	Mo Kα-Rb salt		Cu Kα-K salt		Cr Kα-K salt	
(*hkl*)	Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	Obsd.
(111)	−38.0	−39.3	−26.5	−28.9	−50.2	−54.0
(282)	+27.8	+29.9	+45.1	+41.5	+82.9	+78.8
(331)	−15.3	−17.7	−16.2	−13.5	−31.1	−27.9
(241)	+15.5	+11.9	+12.5	+ 8.0	+23.7	+18.1
(243)	−22.0	−19.4	−25.6	−21.1	−48.8	−45.4
(212)	−18.0	−15.5	−15.8	−13.2	−30.2	−23.3
(141)	− 8.1	− 8.6	−14.6	−14.5	−27.8	−29.0
	$\Delta f' = -0.9^a$		$\Delta f' = +0.2^b$		$\Delta f' = +0.1^b$	
	$\Delta f'' = +3.2^a$		$\Delta f'' = +1.2^b$		$\Delta f'' = +2.3^b$	

[a] Ref. 10. [b] Extrapolated from ref. 10.

We have therefore made an absolute determination of the two isomorphous lactone salts by the method of Bijvoet[7] and find that the Crassulacean *d*-isocitric acid has the configuration I in agreement with Katsura. Thus this acid can be described as D_sL_g isocitric acid, as *threo*-D_s-isocitric acid,[8] or in the Cahn–Ingold–Prelog notation[9] as (1R:2S) - 1 - hydroxy - 1,2,3 - propanetricarboxylic acid.

Diffraction measurements were made on two different crystals of the rubidium salt using Mo Kα radiation and on two different crystals of the potassium salt using Cr Kα radiation. Measurements also were made on one of the latter with Cu Kα radiation. In the table, results of typical experiments are shown. Observed and calculated values of the quantity $100(|F_+|^2 - |F_-|^2)/{}^1/_2(|F_+|^2 + |F_-|^2)$ are shown for 21 of the 47 experiments carried out. In this expression $|F_+|$ corresponds to the reflection *hkl* and its space group equivalents $(h\bar{k}\bar{l},\bar{h}k\bar{l},\bar{h}\bar{k}l)$ while $|F_-|$ corresponds to $\bar{h}\bar{k}\bar{l}$ and its equivalents $(\bar{h}kl,h\bar{k}l,hk\bar{l})$. The table also includes the values of the dispersion constants $\Delta f'$ and $\Delta f''$ used in the structure factor calculations.[10] The atomic coördinates, which will be presented elsewhere, are available on request from the undersigned. In all experiments at least two equivalent reflections of each type were measured. In some experiments all four equivalent reflections were available. For example in the case of the reflection 412 (K:crystal #1:Cr Kα) the counts were: $|F^-|^2$ −7,780, 7,750, 7,540, 7,560: $|F_+|^2$ −11,140, 11,560, 11,190, 10,860. In no case was a dispersion effect observed which differed in sign from that calculated. Thus it is quite clear that the Katsura configuration on which our calculation was based is correct.

We are very much indebted to Dr. H. B. Vickery, not only for his provision of these and other crystals, but also for his continued interest in and discussion of this work.

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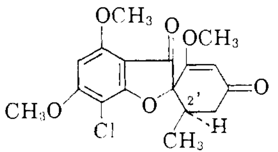
RECEIVED NOVEMBER 27, 1961

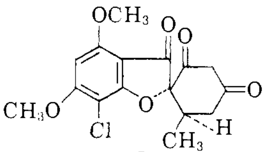
A STEREOSPECIFIC TOTAL SYNTHESIS OF GRISEOFULVIN

Sir:

The synthesis of the orally active antifungal antibiotic griseofulvin (I) presents interesting structural and stereochemical problems. These problems are well illustrated by one of the two previous syntheses[1,2] of this substance: both epimers at the 2′ carbon are obtained while the intermediacy of the β-diketone II (griseofulvic acid) leads to the two possible enol ethers with diazomethane.[1]



I



II

An interesting solution to these difficulties, based on a biogenetically likely pathway, has been recorded.[2]

We now report a one-step total synthesis of *dl*-griseofulvin which provides a model for the synthesis of poly-β-dicarbonyl compounds or their enol ethers.

Reaction of the known 7-chloro-4,6-dimethoxycoumaranone (III)[3] with methoxyethynylpropenyl ketone (IV), in the presence of potassium *tert*-

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[5] (a) J. P. Greenstein, N. Izumiya, M. Winitz, and S. M. Birnbaum, *J. Am. Chem. Soc.*, **77**, 707 (1955); (b) M. Winitz, S. M. Birnbaum, and J. P. Greenstein, *ibid.*, **77**, 716 (1955).

[6] (a) T. Kaneko, H. Katsura, H. Asano, and K. Wakabayashi, *Chem. and Ind.*, 1187 (1960); (b) T. Kaneko and H. Katsura, *ibid.*, 1188 (1960); (c) H. Katsura, *J. Chem. Soc. Japan*, **82** [1], 91 (1961); (d) H. Katsura, *ibid.*, **82** [1], 92 (1961); (e) H. Katsura, *ibid.*, **82**, [1], 98 (1961).

[7] J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature*, **168**, 271 (1951).

[8] *Cf.* H. B. Vickery, *Science*, in press.

[9] (a) R. S. Cahn and C. K. Ingold, *J. Chem. Soc.*, 612 (1951); (b) R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956).

[10] C. H. Dauben and D. H. Templeton, *Acta Cryst.*, **8**, 841 (1955).

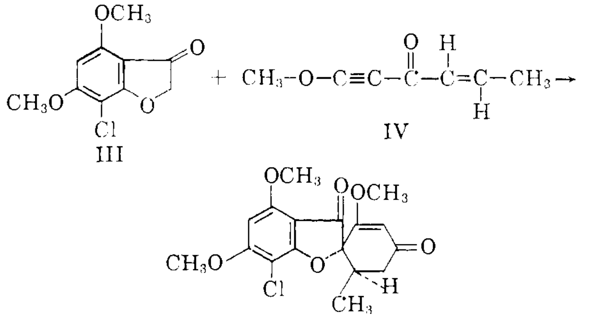
[11] American Cancer Society Post-Doctoral Research Fellow (PF-87).

[1] A. Brossi, M. Baumann, M. Gerecke and E. Kyburz, *Helv. chim. acta*, **43**, 2071 (1960).

[2] (a) A. C. Day, J. Nabney and A. J. Scott, *J. Chem. Soc.*, 4067 (1961). (b) See also C. H. Kuo, R. D. Hoffsommer, H. L. Slates, D. Taub and N. L. Wendler, *Chemistry and Industry*, 1627 (1960).

[3] J. MacMillan, T. P. C. Mulholland, A. W. Dawkins and G. Ward *ibid.*, 429 (1954).

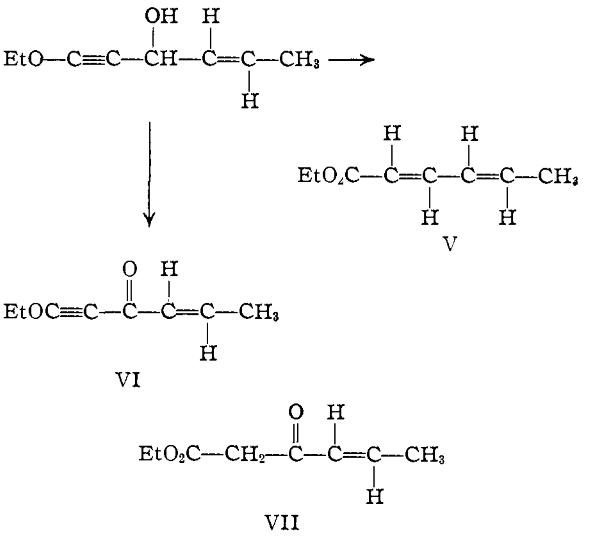
butoxide in diethyleneglycol dimethyl ether, overnight at room temperature gave *dl*-griseofulvin, m.p. 212–213°; 225–226° (reported m.p. 214–216°[1]; 222–224°)[2b] after chromatography of the reaction product on neutral alumina.


III

IV

Identity of the substance was further indicated by the superposability of the very characteristic ultraviolet and infrared spectra of our synthetic material with those of natural (+) griseofulvin.[4,5]

The alkoxyethynyl ketone IV which is required for this synthesis is a new and interesting type of substance. It is the first alkoxyethynyl ketone to be synthesized: previous attempts at making such systems have been unsuccessful.[6] Reaction of the lithium salt of ethoxyacetylene with crotonaldehyde in ether at −15° gave the anticipated ethynyl carbinol, b.p. 67° (mercury pump) (Found: C, 68.78; H, 8.69) $\lambda_{\max}^{\mathrm{CCl_4}}$ 2270 cm.$^{-1}$ $\lambda_{\max}^{\mathrm{EtOH}}$ 259 mμ. This substance is very unstable and reacts rapidly with acid to give the corresponding sorbic ester V.

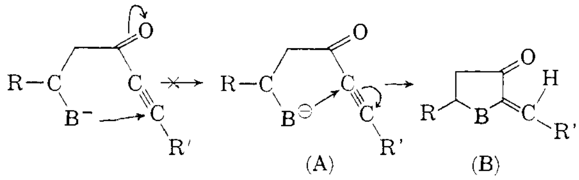

V

VI

VII

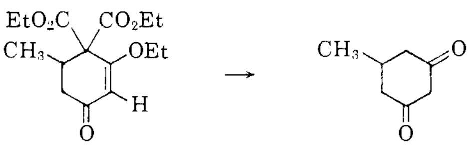
Oxidation with manganese dioxide to VI could be carried out successfully only with dioxide[7] which had been exhaustively washed to as complete neutrality as possible because of the inordinate sensitivity of the alkoxyethynyl ketones to base, as well as acid. Treatment of the ethynyl carbinol in dry methylene chloride with ten times its weight of freshly prepared manganese dioxide, for three hours at room temperature, gave the desired ketone VI, b.p. 40–50° (bath, diffusion pump) (Found: C, 68.97; H, 7.32). The substance had $\lambda_{\max}^{\mathrm{EtOH}}$ 249 mμ (9,100); 228 mμ (11,600) and $\lambda_{\max}^{\mathrm{CCl_4}}$ 2230, 1630, 1655 cm.$^{-1}$ (all strong). The instability to base is illustrated by the disappearance of the triple bond (infrared) after half an hour at room temperature with aqueous base, or after an hour at room temperature with a trace of *tert*-butoxide in *tert*-butanol. Hydration with 5% aqueous hydrochloric acid at room temperature for three hours gave ethyl crotonylacetate (VII) characterized as its 2,4-dinitrophenylhydrazone, m.p. 120–121° (Found: C, 49.88; H, 4.88) and the known copper salt,[8] m.p. 161° (reported,[8] m.p. 159°). The same β-keto ester was obtained by simple refluxing with aqueous ethanol for four hours.

The possibility of forming a six-membered ring by double Michael addition with ethynyl vinyl ketones requires that the first addition take place at the triple bond. Should addition start at the *double* bond, the second addition would lead to an anion which would derive no resonance stabilization from the carbonyl group (cumulene in 6-ring) and addition, if it took place at all, would be to the geometrically favored α-carbon to the carbonyl group (*cf.* A → B).


(A)

(B)

A triple bond is intrinsically more reactive to anions than a double bond, but the effect of the alkoxyl in our system is difficult to predict. In any event, the easy formation of crotonylacetic ester by OH$^-$ addition to VI shows that the required selective addition to the triple bond was taking place. Alkoxyethynyl ketones should therefore give cyclic enol ethers of β-diketones with a variety of substances: Reaction of the ethoxyethynyl ketone VI with malonic ester in *tert*-butanol–potassium *tert*-butoxide at room temperature for two hours gave in about 70% yield the enol ether VIII, m.p. 61–62° (Found: C, 60.47; H, 7.35) $\lambda_{\max}^{\mathrm{EtOH}}$ 251 mμ (17,100) $\lambda_{\max}^{\mathrm{CCl_4}}$ 5.83, 6.09, 6.22 μ.


VIII

The n.m.r. spectrum showed the presence of only one vinyl hydrogen, as required, as a single line

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[4] The C$_2'$ epimer, epigriseofulvin, has a very different infrared spectrum (ref. 1).

[5] Although the yield in this synthesis is low (5%), this is higher than the yield obtained in one synthesis (ref. 1) and about the same as that of the improved version of the other (ref. 2).

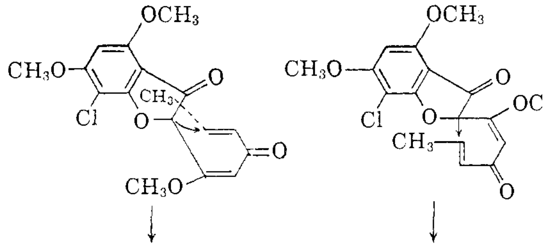
[6] J. F. Arens, in "Advances in Organic Chemistry, Methods and Results," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p. 117 ff.

[7] 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).

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

with $\tau = 4.5$. Hydrolysis with 6% aqueous potassium hydroxide gave the known 5-methylcyclohexane-1,3-dione,[9] m.p. 130–132°, undepressed on mixing with an authentic sample. Similarly, the methoxyethynyl ketone IV gave the related adduct with malonic ester. This was hydrolyzed directly with aqueous 10% potassium hydroxide to give a 64% yield of the above dione.

The stereospecificity in the desired sense of the addition of IV to the coumaranone III to produce *dl*-griseofulvin requires comment. Since the two possible C_2' epimers are of roughly the same stability. the formation of *dl*-griseofulvin in our synthesis must be under kinetic control. We believe that it is significant that the product actually obtained is that which would correspond to the greatest overlap of electron donor and acceptor systems in the transition state for the second Michael addition.



dl-griseofulvin *dl*-epigriseofulvin

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(9) A. J. Birch and R. W. Rickards, *Austral. J. Chem.*, **9**, 241 (1956).

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tert-BUTYL PEROXYFORMATE. A HIGHLY STABLE PEROXIDE AND A NEW FORM OF INDUCED PEROXIDE DECOMPOSITION[1]

Sir:

The rate of decomposition of diacyl peroxides and of peresters often is increased by a concurrent series of free radical chain steps involving reaction of a solvent radical with undecomposed peroxide. The induced decomposition of benzoyl peroxide in ether has been shown to involve attack by an α-ethoxyethyl radical on one of the oxygens of the peroxide link.[2] We wish to report a highly stable perester which undergoes a new form of induced radical decomposition.

tert-Butyl peroxyformate (b.p. 41° at 24 mm., $n^{25}D$ 1.3973) prepared by reaction of *tert*-butyl hydroperoxide and formyl fluoride[3] in ether at 0° was shown to be pure by vapor phase chromatography and by its analysis. *Anal.* Calcd. for $C_5H_{10}O_3$: C, 50.83; H, 8.53. Found: C, 50.62; H, 8.61. Kinetic studies were carried out in dilute solutions using degassed sealed ampoules and the perester decomposition followed by loss of its carbonyl absorption at 1760 cm.$^{-1}$.[4] Representative rate measurements are shown below.

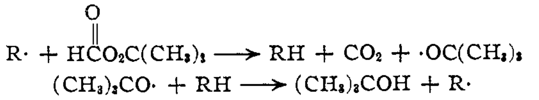
RATES OF DECOMPOSITION OF *tert*-BUTYL PEROXYFORMATE

Solvent	Peroxide concn., *M*	Temp., ° C.	$k \times 10^4$, sec.$^{-1}$
Chlorobenzene	0.135	140.8	1.71
	.0274	140.8	1.62
	.0260	140.8	1.67
	.138	130.8	.538
	.0249	130.8	.571
	.0243	130.8	.548
Cumene	.0296	140.8	5.03
	.0300	140.8	5.41
	.097	140.8	5.58
	.141	140.8	6.76

tert-Butyl peroxyformate decomposed in chlorobenzene with first order kinetics and a half-life of 70 min. at 140.8° (ΔH^* 38 kcal., ΔS^* 15 e.u.). This rate of decomposition is only about twice as great as that of *tert*-butyl peroxide[5] and makes this simple *t*-butyl perester the most stable of its class. The products of decomposition in chlorobenzene include 45% carbon dioxide, 33% formic acid as well as products derived from addition of formyloxy radicals to the solvent. No hydrogen was formed by decomposition in chlorobenzene or in cumene. The slow rate and the products of decomposition in chlorobenzene indicate simple unimolecular breakage of the peroxide bond giving rise to formyloxy and *tert*-butoxy radicals. The resonance of the formyloxy radical produced seems to have little accelerative effect but increased stability of the peroxide bond may be a result of electron withdrawal from the peroxide oxygens by the formyl group similar to inductive effects in other peroxide decompositions. In contrast to acetoxy radicals,[6] formyloxy radicals do not quickly decarboxylate presumably because of the higher energy required to break a carbon hydrogen bond.

A change in solvent from chlorobenzene to cumene results in a threefold increase in rate of decomposition and leads to increased yields of carbon dioxide (86% carbon dioxide, 8% formic acid). The rate of decomposition is increased slightly at higher concentrations of perester but is decreased toward the rate in chlorobenzene by 0.2 molar quinone or 0.5 molar styrene in cumene.

From these results it appears that the increased decomposition in cumene is caused by attack of solvent derived radicals on the aldehydic hydrogen of *tert*-butyl peroxyformate rather than by attack on either of the peroxide oxygens.



$$R\cdot + H\overset{\overset{O}{\|}}{C}O_2C(CH_3)_3 \longrightarrow RH + CO_2 + \cdot OC(CH_3)_3$$

$$(CH_3)_3CO\cdot + RH \longrightarrow (CH_3)_3COH + R\cdot$$

This type of induced decomposition would give rise to the higher yield of carbon dioxide observed in cumene and the yields of *tert*-butyl alcohol and dicumyl, about 80% and 28%, respectively, are

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(1) Supported by a grant from the National Research Council of Canada.

(2) (a) D. B. Denney and G. Feig, *J. Am. Chem. Soc.*, **81**, 5322 (1959); (b) J. C. Martin and E. H. Drew, *ibid.*, **83**, 1232 (1961); other types of induced decomposition of peroxides have been discussed and reviewed by C. Walling and E. S. Savas, *ibid.*, **82**, 1738 (1960), and by C. G. Swain, L. J. Schaad and A. J. Kresge, *ibid.*, **80**, 5313 (1958).

(3) G. A. Olah and S. J. Kuhn, *ibid.*, **82**, 2380 (1960).

(4) P. D. Bartlett, E. P. Benzing and R. E. Pincock, *ibid.*, **82**, 1767 (1960).

(5) J. H. Raley, F. F. Rust and W. E. Vaughan, *ibid.*, **70**, 88 (1948).

(6) H. J. Shine and D. M. Hoffman, *ibid.*, **83**, 2783 (1961); L. Herk, M. Feld and M. Szwarc, *ibid.*, **83**, 2998 (1961).