

Griseofulvin Analogs. II. A Stereospecific Synthesis of the Ring-B Carbon Analog of Dechlorogriseofulvic Acid

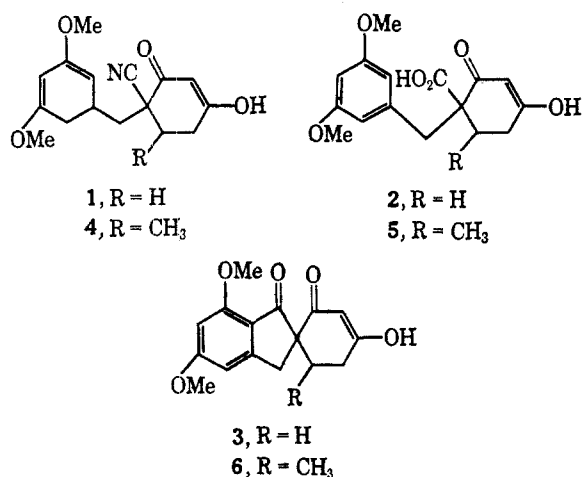
HOWARD NEWMAN AND ROBERT B. ANGIER

Organic Chemical Research Section, Lederle Laboratories,
Division of American Cyanamid Company, Pearl River, New York

Received November 22, 1965

The synthesis of 5',7'-dimethoxy-6-methyl-spiro-[cyclohexane-1,2'-indan]-1',2,4-trione, the ring-B carbon analog of dechlorogriseofulvic acid, is described.

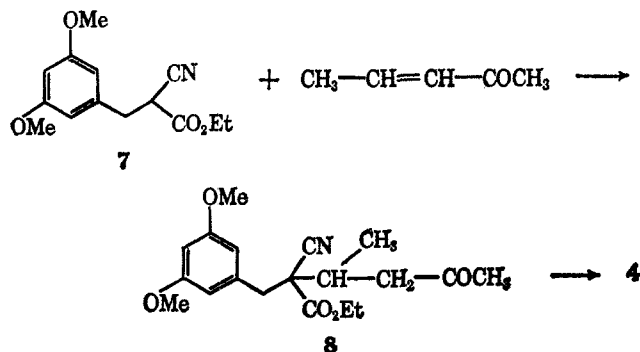
In our previous paper¹ we discussed the synthesis of the nitrile dione **1** and the acid dione **2** and the conversion of each to the spirotrione **3**. We had expected that the synthetic routes developed for **1** and **2** would also be applicable to the preparation of their methyl analogs **4** and **5**, and that ring closure of **4** and **5** to



the spirotrione **6** could be effected in the manner already described for the demethyl analogs. These expectations were only partially realized. While the nitrile dione **4** could be prepared according to the previously described route,¹ ring closure to the spirotrione **6** under the conditions previously employed did not take place. While the acid dione **5** could be converted to **6** by the method previously described, it could not be obtained according to the scheme developed for **2**.

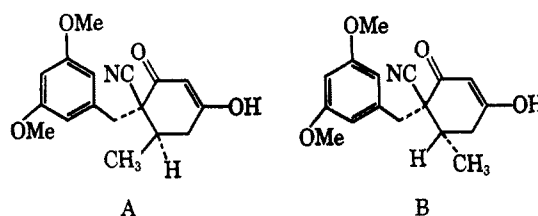
In this paper we present the differences and similarities in behavior observed in the demethyl and methyl series, outline a new stereospecific synthesis for the acid dione **5**, and describe its conversion to the spirotrione **6**.

The nitrile dione **4** was obtained by allowing ethyl 3,5-dimethoxybenzylcyanoacetate¹ (**7**) to react with

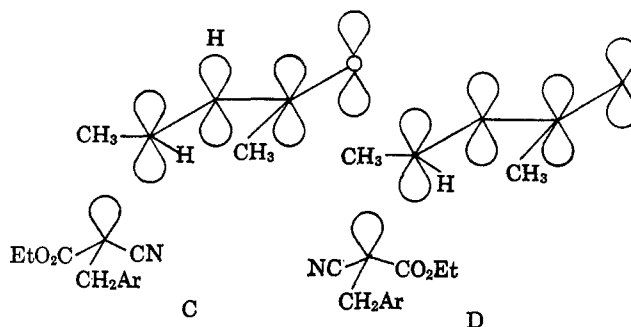


methyl propenyl ketone² to give the Michael adduct **8** which was then cyclized with methanolic sodium methoxide.

Only one of the two possible isomers A and B of **4** was isolated in crystalline form as indicated by the presence of a single 3-proton doublet due to the C₆-CH₃ substituent in the nmr spectrum of the product. We suggest that it is the *cis* (methyl, nitrile) isomer A for the following reason.



The stereochemistry of the methyl group in **4** (*cis* or *trans* to the nitrile) is actually determined by the configuration (*erythro* or *threo*) of the Michael adduct **8**, which one would expect to be predominantly *erythro* from a consideration of the possible transition states involved in its formation. Of the various relative conformation of the two substrates (the anion of the benzylcyanoacetate **7** and methyl propenyl ketone) in the transition state leading to **8**, C and D would appear to be energetically most favorable since in these, in conformity with the orientation rules outlined by Cram,³ the bulky benzylic moiety lies between the methyl and hydrogen of the methyl propenyl ketone,⁴



(1) H. Newman and R. B. Angier, *J. Org. Chem.*, **31**, 1451 (1966). Introductory remarks to the general problem will be found there. (b) Since the infrared and nmr spectra of the 1,3-cyclohexanediones to be discussed show them to be enolic, their structures are so written.

(2) V. Grignard and M. Fluchaire, *Ann. Chim. (Paris)*, [10] **9**, 5 (1928).

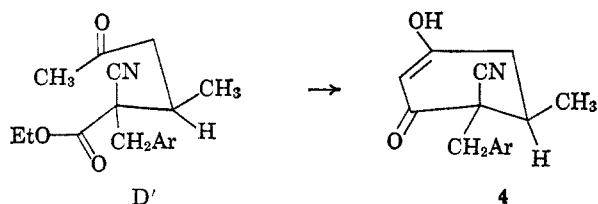
(3) D. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

(4) The relative sizes of the groups in the cyanoacetate **7** are in the order benzyl > CO₂Et > CN while in methyl propenyl ketone it is CH₃ > H. The relative sizes of carbethoxy, methyl, cyano, and hydrogen have been determined^{5,6} and are as indicated, while the relative size of benzyl was approximated taking the published value for ethyl⁵ as a lower limit.

(5) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., New York, N. Y., 1962, p 236.

(6) B. Rickborn and F. R. Jensen, *J. Org. Chem.*, **27**, 4606 (1962).

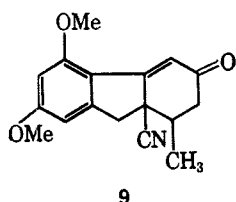
while the methyl propenyl ketone is in the energetically preferred *S-trans* form.⁷ Of these two conformations, D, in which the small nitrile substituent is in an eclipsed (or nearly eclipsed) conformation with respect to the bulky methyl group of the ketone, would be expected to predominate. The adduct resulting from D would have the *erythro*⁸ configuration (one conformation of which, D', is shown) which must necessarily lead to a *cis* relationship of the methyl and nitrile substituents in **4** obtained by subsequent intramolecular Claisen condensation. The transformation of **8** to **4** would be expected to proceed *via* the



conformer D' in which the substituents are positioned so as to correspond to their most favorable orientation in the incipient 6-membered ring with the two bulkiest groups (ArCH₂ and CH₃-) in the *trans*-equatorial conformation.⁹

X-Ray diffraction studies to be done on the stereochemically related 4'-chloro-2,5,7'-trimethoxy-6-methylspiro[2-cyclohexene-1,2'-indan]-1,4-dione, the ring-B carbon analog (gross structure) of griseofulvin (see accompanying paper¹⁰) should permit unequivocal assignment of stereochemistry.

The dione nitrile **4** did not give any spirotrione **6** on treatment with anhydrous hydrogen chloride in ether in the presence of zinc chloride but gave exclusively the tricyclic unsaturated ketone **9** in 79% yield. This is in contrast to the behavior of the



demethyl nitrile dione **1** which gave the spirotrione **3** and the demethyl analog of **9** in a ratio of 2:1,¹ and is presumably due to the inability of the nitrile substituent of **4** to form the Hoesch intermediate (imino-chloride or nitrile-hydrogen chloride complex or both¹¹) because of steric interference by the adjacent methyl substituent (*cf.* the hydrolysis of the ester dione **13** discussed below). This sensitivity of the Hoesch reaction to steric effects has been noted previously,¹² and has also been observed in the related transformation of nitriles to imino ethers.¹³

(7) (a) A. Bossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, **43**, 2071 (1960), ref 7; (b) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(8) The *erythro* isomer refers to that one in which the large, medium, and small substituents on the adjacent carbon atoms respectively eclipse each other in the fully eclipsed conformation.

(9) See ref 5, Chap 8.

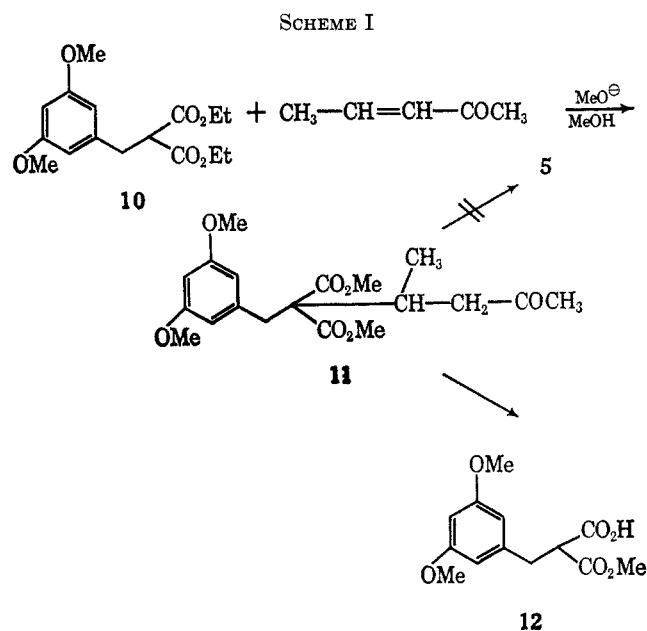
(10) H. Newman and R. B. Angier, *J. Org. Chem.*, **31**, 1462 (1966).

(11) E. N. Zilberman and N. A. Rybakova, *J. Gen. Chem. USSR*, **30**, 1972 (1960).

(12) P. E. Spoerri and A. S. Dubois, *Org. Reactions*, **5**, 387 (1949).

(13) A. Pinner, *Ber.*, **23**, 2917 (1890).

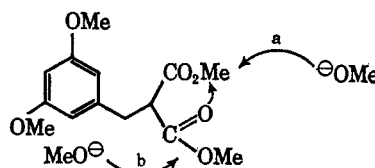
Since we had previously defined conditions whereby the dione acid **2** can be cyclized to the spirotrione **3**,¹ we turned our attention to the preparation of the methyl homolog **5** of the former. Our initial approach to the synthesis of **5** paralleled that developed for the preparation of **2** which involved the condensation of 3,5-dimethoxybenzylmalonate (**10**) (Scheme I) and methyl vinyl ketone in methanolic sodium methoxide. However, **10** did not give **5** on reaction with methyl propenyl ketone under these same conditions; the acidic product isolated was the half-acid ester **12**. We further established that the first step in the condensation, formation of the Michael adduct **11**, did take



place, but underwent reversal under the more drastic conditions used in the attempted ring closure to **5**. Thus, **11** was readily isolated when the reaction mixture was worked up after 4 hr at room temperature without heating.¹⁴

Thus we have the very interesting result that, whereas the cyano acetate **7** reacts with both methyl vinyl ketone and methyl propenyl ketone to give the dione nitriles **1** and **4**, respectively, the benzyl malonate **10** reacts only with the former to give the ester of the dione acid **2**. The fact that the benzyl and carbethoxy substituents are comparable in size (the latter is somewhat smaller) and are both considerably larger (by a factor of ten) than the cyano group⁴⁻⁶ offers a reasonable rationale for the above finding. The *erythro* Michael adduct **8** (but not the *threo*) leads to an incipient 6-membered ring in the transition state for ring

(14) The formation of **12** is most probably due to the presence of some water in the reaction medium, although it would also result from O-methyl cleavage of the diester *via* a bimolecular displacement reaction (path a or b) with methoxide.¹⁵

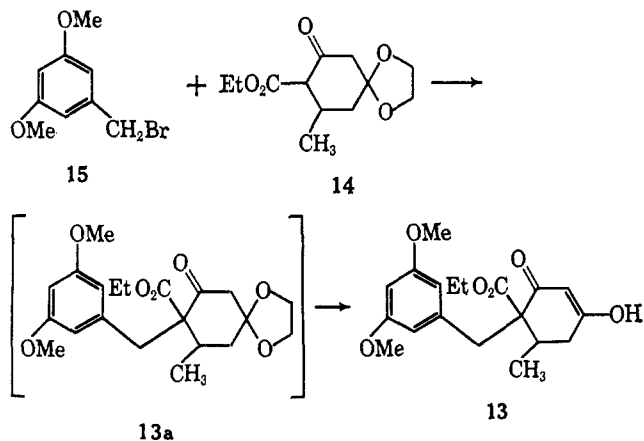


(15) J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Am. Chem. Soc.*, **72**, 2378 (1960).

closure to the dione in which cyano group is axial and the bulkier methyl and benzyl substituents are in the sterically less demanding equatorial conformation (see D'). The Michael adduct **11** arising from the benzyl malonate and methyl propenyl ketone would have either the bulkier carbethoxyl or benzyl in the axial conformation, thus giving rise to a higher energy transition state than obtained from **8** and with presumably too high an energy to compete successfully with other reaction paths (e.g., retro-Michael reaction). While it is true that in the demethyl series the benzyl malonate-methyl vinyl ketone adduct must also have either the carbethoxy or benzyl substituent axially oriented, it would still represent a lower energy species than is obtained from **11** because of the absence of the additional steric interaction of the two substituents with the adjacent methyl group.²⁰

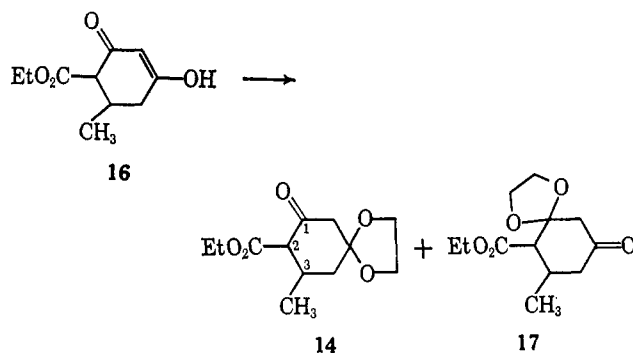
The fact that **11** is *not* converted to the ester of the acid dione **5** is also suggestive of a *cis* configuration for the nitrile dione **4**, since the transition state leading to the *trans* configuration would require an axial orientation for benzyl (or methyl and cyano depending on the chain form being considered) and, by analogy with the behavior of **11**, would not be expected to ring close.¹⁶

Our failure to obtain the dione ester **13** from **10** and methyl propenyl ketone led us to investigate an alternate route to this compound which involved the alkylation of the monoketal **14** with 3,5-dimethoxybenzyl bromide (**15**).



The monoketal **14** was readily prepared from the known dione ester **16** and ethylene glycol. Thus, treatment of **16** with an equivalent of ethylene glycol in refluxing benzene containing a catalytic amount of *p*-toluenesulfonic acid gave a product (insoluble in 2 *N* sodium hydroxide) the nmr spectrum of which was consistent with its being a mixture of predominantly **14** and the positional isomer **17** as might be expected from a consideration of the relative steric environments of the two carbonyl groups. The product showed two triplets and two doublets between δ 1.00 and 1.42 due to the carbethoxy methyl and the C₃-methyl substit-

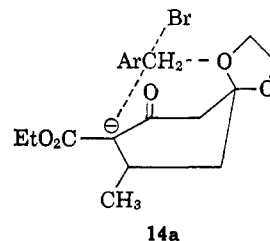
(16) Another possible explanation for the difference observed is based on the greater electronegativity of the cyano group compared to carbethoxyl (cf. the solubility of **7** but not **10** in dilute sodium hydroxide). Thus, the greater reactivity, of the ester grouping in adduct **8** than in **4** owing to a more favorable electronic effect, might be sufficient to counterbalance any adverse steric effect resulting from the proximity of the methyl group to the reaction site. This explanation, however, suffers from the disadvantage of being compatible with either a *cis* or *trans* relationship of the methyl group to the ester or nitrile.



uents in the two isomers. The two quadruplets due to the methylenic protons of the carbethoxy group in **14** and **17** appeared between δ 4.08 and 4.33 (the two-highest intensity peaks of each quadruplet were clearly discernable; the other two of each were lost in the background noise). The unequal intensities of the group of signals in both these regions indicate the unequal isomer distribution; the predominance of **14** is indicated by the intensity of the doublet centered about δ 3.00 ($J_{2,3} = 10$ cps) which is attributed to the C₂ proton in that compound in accord with the essential coincidence of its position with that of the corresponding proton in the dione ester **16** which appears at δ 3.08 ($J_{2,3} = 10$ cps). The magnitude of the coupling constant of the C₂ proton in both **14** and **16** is consistent with a *trans*-diequatorial orientation of the adjacent methyl and carbethoxyl substituents.¹⁷ In addition to the signal at δ 3.00 ($J = 10$ cps), there was also present in this region a barely discernable doublet at δ 3.03 ($J = 4$ cps) which could be due to the presence, in very small amount, of the configurational isomer of **14** in which the methyl and carbethoxy substituents are *cis* oriented. The dihedral angle between the corresponding protons would then be *ca.* 60° and they would be expected to couple to the extent observed.¹⁷

Alkylation of the sodium salt of **14** with 3,5-dimethoxybenzyl bromide in ethanol followed by hydrolysis of the resulting monoketal **13a** gave the desired ester dione **13** in *ca.* 60% yield, only one of the two possible epimers being obtained. The configuration of this product was shown to correspond to that of the nitrile dione **4**, i.e., *cis* (methyl, carbethoxyl), by converting both to the same amide dione **19** (see below).

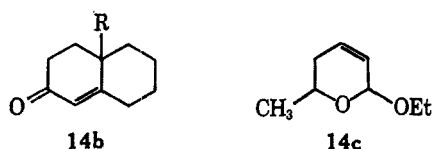
A transition state of type **14a** in which the developing positive charge on the benzyl halide interacts with the



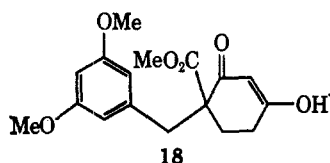
pair of electrons on the oxygen of the ketal function and the developing carbon-carbon bond is axial in character could readily account for the exclusive formation of the *cis* isomer. The preference for axial approach of an electrophile in the reaction of 6-mem-

(17) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).

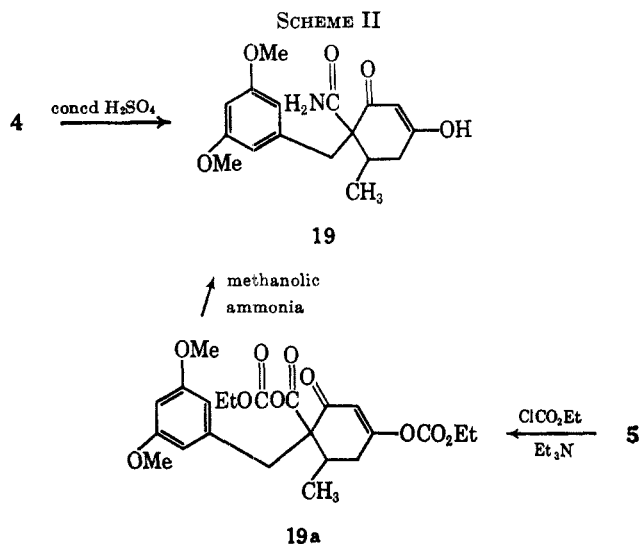
bered ketones has been previously demonstrated,¹⁸ while the directive influence resulting from dipole interactions has recently been demonstrated by McQuillin, *et al.*,^{19a,b} in the alkylation of the decalones **14b** (R = CH₃, CO₂Et). Stereodirective effects due to dipole interactions have also been very elegantly demonstrated by Henbest, *et al.*,^{19c} and also appear to be a factor in the epoxidation of the olefin **14c**.^{19d}



The ester dione **13** was hydrolyzed to the acid dione **5** in good yield by heating it, suspended in 30% aqueous sodium hydroxide, at 100° for 7.5 hr, but was recovered unchanged from its solution in 2 *N* aqueous sodium hydroxide after 24 hr at room temperature. The inertness of **13** to dilute base at room temperature is in sharp contrast to the facility with which the demethyl dione ester **18** underwent hydrolysis under these same conditions,¹ and is in accord with previously



reported rate retardation effects resulting from alkyl substitution, *cis* or *trans*, adjacent to the substituent undergoing reaction.^{20,21} [The failure of **4** to undergo the Hoesch reaction (see above) would appear to be another manifestation of this steric effect.]



(18) (a) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956); (b) *ibid.*, **76**, 175 (1954); (c) W. S. Johnson, *Chem. Ind. (London)*, 167 (1956); (d) W. S. Johnson, *et al.*, *J. Am. Chem. Soc.*, **84**, 2181 (1962).

(19) (a) C. L. Graham and F. J. McQuillin, *J. Chem. Soc.*, 4634 (1963); (b) F. J. McQuillin, and P. L. Simpson, *ibid.*, 4726 (1963); (c) reviewed by H. B. Henbest in *Proc. Chem. Soc.*, 159 (1963); (d) H. Newman, *J. Org. Chem.*, **29**, 1461 (1964).

(20) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

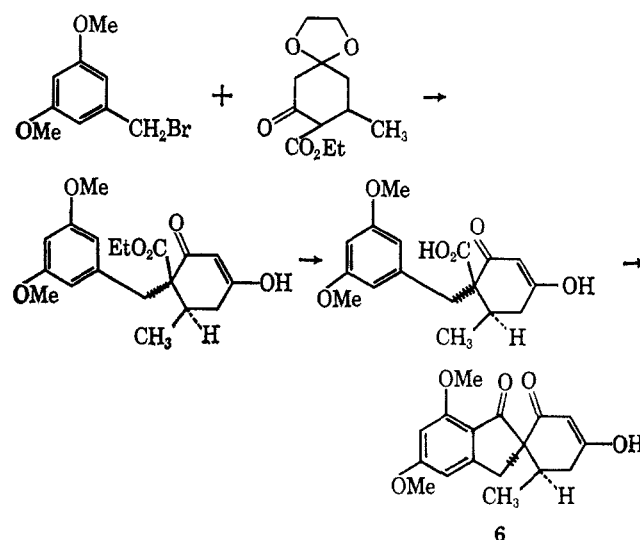
(21) The fact that **13** is an ethyl ester whereas **18** is a methyl ester could hardly be expected to account, to so significant an extent, for the rate difference observed.²²

(22) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp 211-212.

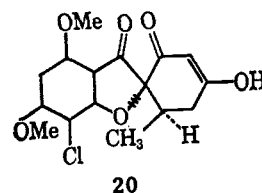
As already indicated above, the nitrile dione **4** and ester dione **13** were interrelated by conversion to the same amide dione **19**; the former by treatment with concentrated sulfuric acid, and the latter by treating the mixed carbonic anhydride derived from the acid dione **5** with saturated methanolic ammonia. (Conversion of **13** to **5** would not be expected to result in any stereochemical changes.)

The dione acid **5** was readily cyclized to the spirotrione **6** by treatment with trifluoroacetic anhydride-boron trifluoride etherate in ether as already described¹ for the transformation of **2** to **3**.

The foregoing description of the synthesis of **6** is summarized in the following equation. Since the conversion of **5** to **6** would not be expected to affect the asymmetric centers, the stereochemistry of **6** would be expected to correspond to that of the nitrile dione **4** for which a *cis* (methyl, nitrile) configuration was suggested (Scheme II).



The C₆-methyl and the indanone carbonyl would therefore be *cis* related, corresponding to the stereochemistry of these groups in griseofulvic acid (**20**).²³



Experimental Section²⁴

1-Cyano-1-(3,5-dimethoxybenzyl)-6-methyl-2,4-cyclohexanedione (4).—The condensation of ethyl 3,5-dimethoxybenzylcyanoacetate¹ and methyl propenyl ketone² was effected in two stages. To a cooled solution of 4 g (0.016 mole) of ethyl 3,5-dimethoxybenzylcyanoacetate and 1.35 ml of methyl propenyl ketone in 15 ml of dry 1,2-dimethoxyethane was added 8 drops (capillary pipet) of 1.66 *N* methanolic sodium methoxide. The reaction mixture was kept at room temperature for 16 hr and diluted with ether; the ethereal solution was washed with 2 *N*

(23) J. F. Grove, *Quart. Rev. (London)*, **17**, 1 (1963).

(24) Melting points were taken in a Hershberg apparatus using a 3-in. immersion thermometer. Infrared spectra were determined either neat (liquids or oils) or in Nujol (solids) on a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were measured in methanol on a Cary Model 11MS spectrophotometer. Magnesium sulfate was used for drying.

aqueous sodium hydroxide and salt solution, then dried, and evaporated to yield 3.7 g (0.01 mole) of the crude Michael adduct **8** which was dissolved in 7 ml of 1.66 *N* methanolic sodium methoxide (0.012 mole). The solution was heated under reflux for 3 hr, poured into cold aqueous bicarbonate solution and the mixture extracted with ether. The aqueous phase was acidified with concentrated hydrochloric acid, and the oil which separated was extracted into methylene chloride. Washing and drying the methylene chloride extracts left an oily residue which solidified on triturating with ether. The colorless solid was collected and washed with ether: yield, 1.5 g (31%); mp 157–159°. The analytical sample was obtained by recrystallization from aqueous ethanol and drying *in vacuo* over phosphorus pentoxide at 100° for 28 hr: mp 159–160°; $\lambda_{\text{max}}^{\text{MeOH}}$ 263 m μ (ϵ 15,000), 225 m μ (ϵ 9900).

The nmr spectrum in deuteriochloroform–deuterated dimethyl sulfoxide showed a somewhat broad 3-proton singlet at δ 6.40 (aromatic protons) a 1-proton singlet at δ 5.01 (olefinic proton of the enolic form of the β -diketone), a 6-proton singlet at δ 3.77 ($-\text{OCH}_3$), and a 3-proton doublet centered at δ 1.25 ($J = 6$ cps) ($\text{CH}_3-\text{CH}-$).

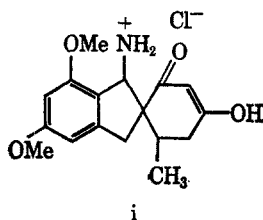
Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.39; H, 6.42; N, 4.70.

2,3-Dihydro-5,7-dimethoxy-1-methyl-3-oxo-9a(1H)-fluorene-carbonitrile (9).—Dry gaseous hydrogen chloride was bubbled through a stirred, cooled (ice–water) suspension of 1.2 g (0.004 mole) of nitrile dione **4** (dried at 78° over phosphorus pentoxide *in vacuo* for ca. 15 hr prior to use) and 0.7 g (0.005 mole) of anhydrous zinc chloride (fused, crushed under petroleum ether (bp 30–60), then dried at 140° over phosphorus pentoxide for ca. 15 hr) in 25 ml of anhydrous ether. Within 50 min the reaction mixture was homogeneous (yellow solution) and the stirring was stopped. After 1.25 hr the cooling bath was refilled with ice and then permitted to come to room temperature. After 5.25 hr a red oil began separating. The stirrer was started again. After ca. 10 hr gas passage was terminated and the reaction mixture, immersed in the water bath, was stirred for 13.5 hr (total reaction time, 23.5 hr). At the end of this time the red oil had been transformed into a yellow solid. Water was added, and the resulting mixture heated on the steam bath for ca. 15 min to evaporate the upper ethereal phase. The insoluble somewhat sticky solid was extracted into methylene chloride and the organic solution was washed with water, then bicarbonate solution, dried, and evaporated to yield 0.735 g (77% based on unrecovered starting material) of a solid which melted at 184–188°. Recrystallization from ethanol furnished analytically pure material: mp 188–189°; $\lambda_{\text{max}}^{\text{Nujol}}$ 4.48 (vw) and 6.07 μ ; $\lambda_{\text{max}}^{\text{MeOH}}$ 339 (ϵ 27,000), 254 (11,600), 246 (11,600), 227 (7500), 222 m μ (7500) (*cf.* ultraviolet spectrum of demethyl **9**¹).

Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.66; H, 6.41; N, 4.89.

Acidification of the bicarbonate extracts gave 0.18 g of starting dione nitrile **4** (15% recovery) which was isolated by extracting into methylene chloride, washing, drying, and evaporating the methylene chloride extracts and triturating the residue with ether. The infrared spectrum of the product (mp 155–158°) was identical with that of dione nitrile **4**.

To make certain that none of the spirotrione **6** was present in the form of its water soluble ketimine hydrochloride **i** which did



not undergo hydrolysis during the initial heating on the steam bath, the original aqueous phase from which **9** was separated by extraction with methylene chloride was heated under reflux for 1 hr (*cf.* preparation of **3**¹), extracted with methylene chloride and the methylene chloride extracts, in turn, extracted with bicarbonate solution. Acidification of the bicarbonate extracts, extraction with methylene chloride and drying and evaporating the latter left essentially no residue.

Reaction of Ethyl 3,5-Dimethoxybenzylmalonate (10) and Methyl Propenyl Ketone. **A.**—To a cooled solution of 1 g (3.2

mmoles) of ethyl 3,5-dimethoxybenzylmalonate in 2.1 ml of 1.53 *N* methanolic sodium methoxide (3.2 mmoles) was added 0.27 ml of methyl propenyl ketone. The reaction mixture was kept at room temperature for 3 hr, heated under reflux for 2 hr, and partitioned between cold water and ether. Acidification of the basic aqueous phase resulted in the separation of an oil which was extracted into ether. The ethereal extracts were washed, dried, and evaporated to yield 0.44 g of a very viscous yellow syrup (last traces of solvent were removed by high vacuum pumping for 17 hr): $\lambda_{\text{max}}^{\text{Nujol}}$ 5.7–5.9 μ . The nmr spectrum of the product, in deuteriochloroform showed the following absorptions: (a) δ , 3.23 doublet ($J = 7$ cps) (2 protons); (b) δ 3.80, incompletely resolved sharp doublet (9 protons); (c) δ 6.41 broad-based singlet (3 protons); (d) δ 10–11, singlet (1 proton, exchangeable) as would be expected for the half-acid ester **12** [peak assignments: (a) benzylic protons; (b) $-\text{OCH}_3$ and methyl protons of the carbomethoxy group; (c) aromatic protons; (d) $-\text{CO}_2\text{H}$]. No absorption at δ 5.00–5.35 expected for the olefinic proton of the enolic form of the methyl ester of **5** (*cf.* nmr spectrum of **4** and the methyl ester of **2**¹) was observed.

B.—To a cooled solution of 1 g (3.2 mmoles) of ethyl 3,5-dimethoxybenzylmalonate in 1.9 ml of 1.66 *N* methanolic sodium methoxide (3.2 mmoles) was added 0.27 ml of methyl propenyl ketone, the mixture kept at room temperature for 4 hr and partitioned between water and ether. The ethereal solution was washed, dried, and evaporated to yield 0.97 g of a nearly colorless liquid which solidified almost immediately upon stirring in a mixture of 3 ml of 2 *N* aqueous sodium hydroxide and 1.5 ml of methanol (it had been our intention to hydrolyze the adduct to the half-acid). The solid was collected, washed well with water, and air dried on filter paper: yield, 0.36 g (29%); mp 74–79°; $\lambda_{\text{max}}^{\text{Nujol}}$ 5.8–5.9 μ . The nmr spectrum of the product in deuteriochloroform was fully consistent with structure **11**, the Michael adduct of methyl 3,5-dimethoxybenzylmalonate and methyl propenyl ketone. The resonances and their probable assignments are δ 0.98 (doublet, $J = 6$ cps) ($\text{CH}_3-\text{CH}-$); δ 2.08 (sin-

glet) ($\text{CH}_2=\text{C}$); δ 2.17–2.91 (multiplet) ($\text{CH}-\text{CH}_2$); δ 3.18 (doublet, $J = 3$ cps) (benzylic protons); δ 3.61 and 3.70 (aromatic OCH_3); δ 3.73 ($-\text{CO}_2\text{CH}_3$); δ 6.27 (aromatic protons). The integrated ratios of the various peaks were as expected.

Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_7$: C, 62.28; H, 7.15. Found: C, 62.45; H, 7.60.

2-Carbethoxy-5-ethylenedioxy-3-methylcyclohexanone (14).—A solution of 32.5 g (0.16 mole) of 1-carbethoxy-6-methyl-2,4-cyclohexanedione (**16**)²⁵ and 9.4 ml (0.16 mole) of commercial grade ethylene glycol which had been stored over molecular sieves in 400 ml of anhydrous benzene containing 0.2 g of *p*-toluenesulfonic acid was heated under reflux 2.5 hr with continuous water separation (Dean–Stark trap). Water (3.2 ml) was separated (theory, 3 ml). The benzene solution was washed with bicarbonate solution, water, dried, and evaporated to yield a yellow liquid residue which was further purified by a quick, short-path vacuum distillation. There distilled directly 19.9 g (50%) of the colorless, fairly viscous liquid monoketal: bp 137–140° (0.1 mm); n_D^{25} 1.4758; $\lambda_{\text{max}}^{\text{Nujol}}$ 5.77, 5.84 μ (poorly resolved doublet; strong), 6.10 and 6.23 μ (weak).

Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_6$: C, 59.49; H, 7.49. Found: C, 59.45; H, 7.99.

In addition to the proton resonances in the nmr spectrum of the product already detailed in the discussion, there appeared the following: δ 3.93 (singlet; methylenic protons of the ketal function); δ 2.62 (broad singlet; methylenic protons between the carbonyl and ketal functions); and δ 1.92 (poorly resolved doublet; methylenic protons between the ketal and methyl groups).

3,5-Dimethoxybenzyl Bromide (15).—The title compound was prepared according to the general procedure of Haworth and Perkin.²⁶ Gaseous hydrogen bromide was bubbled through a cooled (ice–water) solution of 3.8 (0.023 mole) of 3,5-dimethoxybenzyl alcohol²⁷ in benzene for ca. 30 min. The flask was stoppered and kept at room temperature for an additional 1.5 hr. Most of the excess hydrogen bromide was then removed in a stream of nitrogen, ether added and the mixture poured into

(25) R. V. Schilling and D. Vorändes, *Ann.*, **306**, 195 (1899).

(26) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **1**, 1434 (1925).

(27) R. Adams, M. Harfenist, and S. Loewe, *J. Am. Chem. Soc.*, **71**, 1624 (1949).

cold water. The organic phase was washed with bicarbonate solution, dried, and evaporated to yield 3.6 g (68%) of a green-tinged white solid. The analytical sample was obtained by percolating a solution of the product in ether through a column of Woelm nonalkaline, almost neutral alumina, activity I. Evaporation of the ether eluates (ca. 100 ml) left a colorless solid which was recrystallized from cyclohexane and sublimed at 80–90° (bath temperature) under oil pump vacuum for 15 min. The solid collected on the cold finger melted at 74.5–75.5°.

Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.77; H, 4.80; Br, 34.59. Found: C, 46.72; H, 4.99; Br, 34.85.

1-Carboethoxy-1-(3,5-dimethoxybenzyl)-6-methyl-2,4-cyclohexanedione (13).—To 100 ml of a cold (ice-water), stirred solution of 0.067 mole (determined titrimetrically) of sodium ethoxide in absolute²⁸ ethanol (prepared from metallic sodium) was added 16.4 g (0.068 mole) of the monoketal mixture **14** and **17** (ca. 70:30, respectively, as estimated from its nmr spectrum) followed by 15.7 g (0.068 mole) of 3,5-dimethoxybenzyl bromide. The initial suspension gradually became homogeneous as the reaction mixture was permitted to warm to room temperature (ca. 15 min), and soon thereafter a new solid (presumably sodium bromide) began separating. The reaction mixture was stirred at room temperature for 36 hr, the precipitated solid separated by filtration; and the yellow filtrate diluted with ether, washed twice with water, dried, and evaporated. The yellow liquid residue (presumably **13a**) was heated under reflux for 1 hr in dilute ethanolic-aqueous hydrochloric acid to hydrolyze the ketal function, more water was added, and the mixture was extracted with ether. The ethereal extracts were, in turn, extracted with bicarbonate solution and the bicarbonate extracts acidified with concentrated hydrochloric acid. The oil which separated solidified almost immediately and the solid was collected, washed well with water, and air dried on filter paper overnight: yield, 9.9 g [42% calculated from the gross weight of the monoketal mixture used or 60% on the basis of the estimated net weight ($16.4 \times 0.7 = 11.5$ g) of **14** present in the mixture]; mp 150–157°. The analytical sample of the dione ester **13** was obtained by recrystallization from ethanol and drying *in vacuo* over phosphorus pentoxide at 78° for 1.5 hr: mp 161–162°; λ_{\max}^{Nujol} 5.7 μ ; λ_{\max}^{MeOH} 295 (ϵ 6400), 277 (ϵ 7900), 235 m μ (13,000).

Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.18; H, 7.21.

1-Carboxy-1-(3,5-dimethoxybenzyl)-6-methyl-2,4-cyclohexanedione (5).—A suspension of 1 g (0.0029 mole) of the dione ester **13** in 8 ml of 30% aqueous sodium hydroxide was heated with stirring at 100–105° (oil bath temperature) for 7.5 hr. (The initial suspension was oily; after ca. 1 hr. of heating, the reaction mixture became homogeneous and soon thereafter a fine white solid separated.) The reaction mixture was cooled in Dry Ice-acetone and acidified with concentrated hydrochloric acid. An off-white, very thick gum was obtained. The aqueous phase was separated by filtration and the gum triturated with fresh water. Solidification took place over a 0.75-hr period. The solid was collected and dried *in vacuo* over phosphorus pentoxide for ca. 3 hr at room temperature: yield, 0.7 g (75%); mp 99–100° eff. The analytical sample was prepared by briefly heating a portion of the product in methylene chloride and filtering the hot suspension. The solid collected melted at 99–100° eff, λ_{\max}^{Nujol} 3.10 and 5.95 μ .

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.28; H, 6.51.

5',7'-Dimethoxy-6-methylspiro[cyclohexane-1,2'-indan]-1',2,4-trione (6).—After keeping a solution of 0.58 g (0.0018 mole) of the acid dione **5** in a mixture of 6 ml of anhydrous ether and 3 ml of trifluoroacetic anhydride at room temperature for 1.25 hr, 1.25 ml of boron trifluoride etherate was added and the reaction mixture kept at room temperature for 34.5 hr. Most of the excess ether and trifluoroacetic anhydride were removed *in vacuo*, water was added to the dark green residue, and the mixture was kept at room temperature for 1 hr with intermittent shaking. Ether-methylene chloride and bicarbonate solution were then added and the mixture stirred well. The bicarbonate phase was separated, washed with ether-methylene chloride, and acidified. A green-tinged white gum separated, which solidified on standing for ca. 10 min. After stirring the mixture for an additional 15 min, the solid was collected and dried *in vacuo* at 80° over phosphorus pentoxide for 11 hr. A 0.306-g yield of a pale yellow solid was thus obtained which melted at 214–220°

dec, λ_{\max}^{Nujol} 5.95 μ . An ultraviolet spectrum of this crude product was transparent in the 330–340-m μ region indicating the absence of the carboxy analog of **9** (cf. ultraviolet spectrum of **9** and the carboxy demethyl analog of **9**). The product was further purified by heating it suspended in boiling acetone. The fine colorless solid was collected and washed with acetone: yield 0.184 g (34%). After heating *in vacuo* at 100° over phosphorus pentoxide for ca. 30 hr, the compound had mp 231–232.5° dec; λ_{\max}^{MeOH} 303 (sh) (ϵ 10,600), 273 (ϵ 29,500), 228 m μ (ϵ 21,200); λ_{\max}^{Nujol} 6.05 μ . (The heating at 100° for a considerable time is required to drive off water of hydration. The infrared spectra of the product before and after drying are different, as would be expected.)

The nmr spectrum of the spirotrione **6** in deuterated dimethyl sulfoxide exhibited the following absorptions: two poorly resolved 1-proton doublets ($J = 1-2$ cps) at δ 6.61 and 6.38 (aromatic protons), a 1-proton singlet at δ 5.31 (olefinic proton of the enolic form of the β -diketone), two 3-proton singlets at δ 3.87 and 3.78 (aromatic methoxyls), and a doublet, ($J = 6$ cps) at δ 0.80 (C_6 -methyl group). The signals due to the remaining (five) protons appeared between δ 3.50 and 2.18.

Anal. Calcd for $C_{17}H_{18}O_6$: C, 67.54; H, 6.00. Found: C, 67.49; H, 6.10.

1-Carboxamido-1-(3,5-dimethoxybenzyl)-6-methyl-2,4-cyclohexanedione (19). **A.** From 1-Cyano-1-(3,4-dimethoxybenzyl)-6-methyl-2,4-cyclohexanedione (**4**).—A solution of 0.25 g (0.83 mmole) of the nitrile dione (**4**) in 2.5 ml of concentrated (96%) sulfuric acid was kept at room temperature for 25 hr and poured into ice water. The nearly colorless solid which formed was collected after stirring the mixture for 0.75 hr at room temperature, and air dried for 24 hr: yield, 0.17 g (64%); mp 215–224° dec (darkens somewhat at ca. 180°). The crude product was heated suspended in boiling acetone. The product could not however be collected by filtration because of its fine particle size. The acetone was, therefore, evaporated and the residue heated suspended in boiling water for 30 min. The particle size of the product was now large enough to collect. The collected solid was dried *in vacuo* over phosphorus pentoxide at 100° overnight: mp 236–237° dec. Its infrared spectrum was identical throughout with that of the amide obtained from the acid dione **5** as

described below: λ_{\max}^{Nujol} 2.78 and 3.05 μ ($C-NH_2$), 6.00 μ (poorly resolved doublet, $-C-NH_2$); λ_{\max}^{MeOH} 263 m μ (ϵ 14,000), 224 m μ (ϵ 9400).

Anal. Calcd for $C_{17}H_{21}NO_6$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.66; H, 6.61; N, 4.42.

B. From 1-Carboxy-1-(3,5-dimethoxybenzyl)-6-methyl-2,4-cyclohexanedione (**5**).—To a suspension of 0.21 g (0.66 mmole) of the acid dione **5** in a mixture of 3 ml of anhydrous ether and 3 ml of methylene chloride was added 0.13 ml (1.32 mmoles) of ethyl chloroformate. The mixture was cooled in ice-water and 0.19 ml (1.32 mmoles) of triethylamine was added with stirring. After stirring at room temperature for 15.5 hr, the reaction mixture was diluted with more ether-methylene chloride and the organic solution washed successively with cold water, cold bicarbonate solution, cold water, dried, and evaporated to yield 0.278 g of an oil: λ_{\max}^{Nujol} 5.55 and 5.70 (poorly resolved doublet), 6.01 μ , presumably the mixed anhydride **19a**.

The product was cooled in ice-water and 4 ml of saturated methanolic ammonia was added. After 2.5 hr at room temperature, most of the excess methanolic ammonia was evaporated under reduced pressure, water was added, and the basic solution was acidified. The oil which separated was extracted with ether-methylene chloride and the latter extracts dried and evaporated to yield 0.18 g of a yellow gum which solidified after considerable manipulation in ether, petroleum ether, and some ethanol. After solidification took place, more ether was added, and the product was collected: yield, 10 mg; mp 223–229° dec (darkens at ca. 216°). The amide dione **19** melted at 237–238° dec after recrystallization from ethanol; mixture melting point with **19** prepared from **4** (above) was 237–238° dec. The infrared spectra of the amide dione **19** obtained by the two routes were identical.

Acknowledgments.—We wish to thank Mr. L. Brancone and staff for the microanalyses and Mr. W. Fulmor and staff for the ultraviolet and nmr spectra.

(28) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 285, method (a).