zation from methanol did not alter the melting point. A portion of the oxalate was treated with 5% hydrochloric acid to yield the **hydrochloride**, mp 258–260°. The ultraviolet spectrum and R_f (paper chromatography) were identical with those of naturally occurring cephaeline hydrochloride.

Anal. Calcd for $C_{28}H_{38}N_2O_4\cdot 2HCl\cdot 2H_2O$: C, 58.5; H, 7.4; N, 4.9. Found: C, 58.3; H, 7.2; N, 4.9.

The free base was prepared from the oxalate and recrystallized from 150 parts of ether to give woolly fine needles, double mp 115–116 and 150°.

Anal. Calcd for $C_{28}H_{38}N_2O_4\cdot H_2O$: C, 69.7; H, 8.3; N, 5.8. Found: C, 69.9; H, 8.2; N, 6.0.

The mother liquor from the cephaeline oxalate was evaporated to dryness, converted to the hydrochloride, and recrystallized repeatedly from ethanol-water until a paper chromatogram showed only one spot with an R_f corresponding to isoemetine. In this manner, 50 mg of isocephaeline hydrochloride, mp 270°, was obtained.

Anal. Calcd for $C_{28}H_{38}N_2O_4\cdot 2HCl$: C, 62.3; H, 7.5; N, 5.2. Found: C, 62.0; H, 7.5; N, 5.0.

Isocephaeline base, mp 176°, was obtained from the hydrochloride and recrystallized from about 1000 parts of ether.

Methylation of racemic cephaeline and isocephaeline bases with diazomethane yielded products which were similar to those (infrared spectra, paper chromatography, and derivatives) of authentic emetine and isoemetine.

Racemic Emetine (XIV).—The crude mixture of cephaeline and isocephaeline as obtained above was methylated with diazomethane to yield a mixture of emetine and isoemetine. This mixture was separated by crystallization of the oxalate salts as described.[8] The yield of pure emetine was 50% based upon protoemetine.

(−)-Emetine (XIV*).—An aqueous suspension of optically active protoemetine (X*) perchlorate (3.0 g) was covered with an ether layer and basified with sodium hydroxide, with cooling. The layers were separated and the aqueous layer was extracted many times with ether. The combined ether extracts were washed with water, dried, and evaporated to dryness under vacuum to yield 2.16 g of an oily product. This material was combined with 60 ml of water, 3 g of 3-hydroxy-4-methoxyphenethylamine (XI) hydrochloride, and 6.6 ml of acetic acid. The solution (pH 4–4.5) was allowed to stand at 25° until a negative protoemetine test (2,4-dinitrophenylhydrazine) was obtained (44 hr). The aqueous solution was basified with solid sodium carbonate and the base that precipitated was collected and dried over phosphorus pentoxide to yield 2.25 g, mp 85–130°. An additional 0.51 g was obtained by partially concentrating the mother liquor under nitrogen and *in vacuo*. Further concentration yielded the excess of XI originally added. Paper chromatography showed that both fractions (total, 2.76 g, 87%) were identical and that each contained about 75% cephaeline and 25% isocephaeline.

A sample of the mixture of bases (1.7 g) was dissolved in 20 ml of ethanol and treated with an excess of ethereal diazomethane. The solution was allowed to stand overnight and evaporated to dryness. The residue was dissolved in ether, washed with 2 *N* sodium hydroxide and water, dried, and evaporated to yield 1.60 g of a resinous product which was dissolved in 10 ml of methanol and acidified with 48% hydrobromic acid. The solution was kept at 5° overnight and the crystals which precipitated were collected to yield 1.12 g of crude emetine hydrobromide, mp 228–240°. Repeated recrystallization from methanol yielded pure product, mp 244–245°, lit. 243–245[32] and 250–254°.[10]

When the hydrobromide was dissolved in water and basified with ammonium hydroxide, emetine base was obtained: $[\alpha]^{21\circ}_{\mathrm{D}}$ −49.2 ± 1° (*c* 2.8 in chloroform), lit.[28] $[\alpha]^{23\circ}_{\mathrm{D}}$ −49.2 ± 1° (*c* 3.56 in chloroform). The synthetic products, both salts and free base, were identical (melting point, mixture melting point, infrared spectra, and paper chromatography) with natural materials.

The mother liquor from the crystallization of emetine hydrobromide was evaporated to dryness and the residue was dissolved in water and basified with ammonium hydroxide. The precipitated base was dried, dissolved in 5 ml of pyridine and treated with benzoyl chloride (0.2 ml). The reaction mixture was processed in the usual manner to obtain 0.060 g of N-benzoylisoemetine, mp 202°, lit.[26] 201.5–203°.

Acknowledgment.—We are indebted to Mrs. Ilona Balogh and Mrs. Sarolta Viszt for the microanalyses and to Dr. P. Sohar for the infrared spectra. The work was supported by the Hungarian Academy of Sciences and the Chinoin Pharmaceutical Works.

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(29) The paper chromatography was carried out in the system: 2 *N* hydrochloric acid, methyl ethyl ketone, applying descending technic.[7,30] The chromatography was evaluated for 24 hr and the spots were developed with platine iodide solution. For comparison, parallel experiments were conducted in each case with emetine and isoemetine (prepared according to the literature[31]); the R_f value of these two compounds show the ratio 1:0.62.[31] The cephaeline has the same R_f value as emetine, while the isocephaeline shows the same migration as isoemetine.

(30) M. Barash, I. M. Osbond, and J. C. Wickens, *J. Chem. Soc.*, 3530 (1959).

(31) P. Karrer, C. H. Eugster, and O. Ruttner, *Helv. Chim. Acta*, **31**, 1219 (1948).

(32) A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, 717 (1960).

Griseofulvin Analogs. I. 5′,7′-Dimethoxyspiro(cyclohexane-1,2′-indan)-1′2,4-trione, the Ring-B Carbon Analog of Dechlorodemethylgriseofulvic Acid

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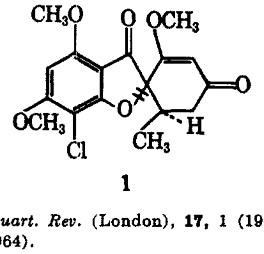
Received November 22, 1965

The synthesis of the title compound is described.

The potent antifungal properties of the mold metabolite griseofulvin (1)[1] made it of interest to prepare some related compounds for biological evaluation.



1

Since no work on structural variations in ring B had been reported,[2] we decided to direct our efforts toward the modification of this part of the molecule. Spe-

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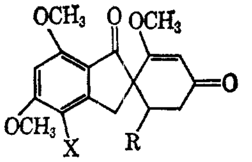
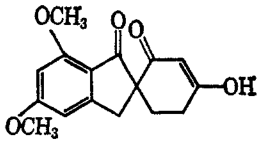
(1) J. F. Grove, *Quart. Rev.* (London), **17**, 1 (1963); *Prog. Chem. Org. Nat. Prod.*, **22**, 203 (1964).

(2) Rings A and C have been extensively manipulated: (a) D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **28**, 2752, 3344 (1963); (b) S. H. Crowdy, J. F. Grove, and P. McCloskey, *Biochem. J.*, **72**, 241 (1959); (c) A. Brossi, M. Baumann, and F. Burkhart, *Helv. Chim. Acta*, **45**, 1292 (1962); (d) M. Gerecke, E. Kyburz, C. V. Planta, and A. Brossi, *ibid.*, **45**, 2241 (1962); (e) E. Kyburz, H. Geleick, J. R. Frey, and A. Brossi, *ibid.*, **43**, 2083 (1960); (f) J. E. Page and S. E. Staniforth, *J. Chem. Soc.*, 1814 (1963), *ibid.*, 1292 (1962).

(2a) NOTE ADDED IN PROOF.—Very recently, Mulholl, *et. al.* [*ibid.*, 4939 (1965)], reported on the preparation of ring B sulphur and nitrogen analogs of griseofulvin-like compounds in which ring A was either unsubstituted or mono chlorinated.



2, X = Cl; R = CH_3
3, X = H; R = H

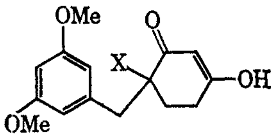


4

cifically, we chose to replace the ring oxygen with $-CH_2-$ and thus obtain the carbon analog **2**.

We set as our immediate goal the preparation of the potential spirotrione precursor **4** of the somewhat simpler demethyl dechloro carbon analog **3**.[3] We report here the synthesis of **4**.

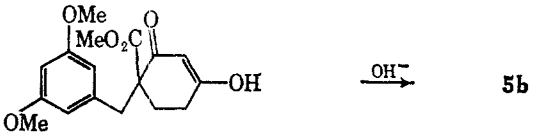
The immediate precursor of **4** was either the dione nitrile **5a** or the dione acid **5b**. The dione nitrile **5a**



5a, X = CN
b, X = COOH
c, X = $-\overset{\text{NH}}{\overset{\|}{\text{C}}}-\text{Cl}$
d, X = $-CONH_2$

was obtained in the manner shown in Scheme I. Condensation of 3,5-dimethoxybenzaldehyde with ethyl cyanoacetate gave the benzylidene derivative **6** (Scheme I) which was hydrogenated to **7**. Reaction of **7** with methyl vinyl ketone gave the Michael adduct **8** which underwent an intramolecular Claisen condensation to give **5a**.

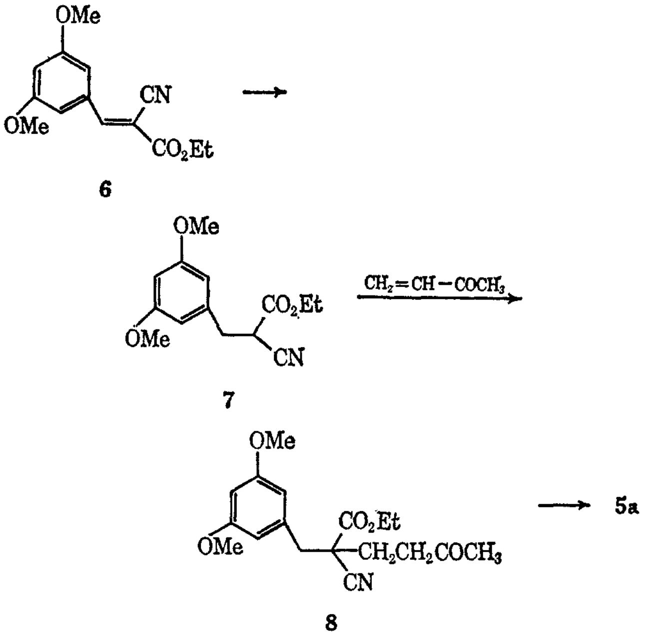
In a similar fashion, using diethyl malonate in place of ethyl cyanoacetate, the dione ester **9** was obtained (the methyl vinyl ketone condensation was conducted in methanol) and was, in turn, hydrolyzed to **5b** with dilute aqueous sodium hydroxide.[4]

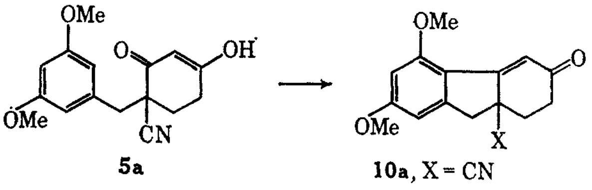


9

The ring closure of the nitrile dione **5a** to the spirotrione **4** was effected with anhydrous hydrogen chloride in dry ether in the presence of zinc chloride at room temperature, the usual conditions for the Hoesch condensation of nitriles with phenols or phenolic ethers.[5] Along with the spirotrione **4** there was obtained, in addition to some starting material **5a**, the neutral tricyclic unsaturated ketone **10a** (relative yields of **4** and **10a**, 2:1, respectively) formed from a Friedel–Crafts-type condensation between the β-dicarbonyl moiety and the aromatic ring.[6]

SCHEME I





5a **10a**, X = CN
b, X = COOH

Treatment of **5a** with boron trifluoride etherate at steam bath temperature resulted in its complete conversion to **10a**. In view of the demonstrated greater reactivity of the Hoesch intermediate compared to the β-dicarbonyl moiety (ref 6), this would appear to be reasonably explained on the basis of the much greater basicity of cyclohexanediones compared with nitriles[8] which results in considerably greater concentrations of the protonated form of the former. (The acid species in the Hoesch reaction is presumably too

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(3) Conversion of **4** to **3** (X = R = H) should present little difficulty, by analogy with the ready conversion of griseofulvic acid to **2** (and its positional isomer) with diazomethane. [A. E. Oxford, H. Raistrick, and P. Simonart, *Biochem. J.*, **33**, 240 (1939).]

(4) The 1,3-diones **5** and **9** were isolated from reaction mixtures which were homogeneous throughout the course of the reaction. This is in contrast to the results of Spencer, *et al.* [*J. Org. Chem.*, **29**, 787 (1964)], who reported that no reasonable yields of 1,3-diones could be obtained from this general type of reaction unless conditions for the precipitation of the enolate of the dione could be found.

(5) (a) P. E. Spoerri and A. S. DuBois, *Org. Reac.*, **5**, 387 (1949); (b) for a comprehensive discussion of the mechanism of this reaction, see E. N. Zilberman and N. A. Rybakova, *J. Gen. Chem. USSR*, **30**, 1972 (1960).

(6) Most recent studies on the mechanism of the Hoesch reaction[5b] indicate that the reactive species is not solely the iminochloride formed *in situ* from the nitrile and hydrogen chloride,[5a] but, depending on reaction conditions, involves, in addition, other reactive intermediates (*e.g.*, nitrile–hydrogen chloride complex) to a greater or lesser degree. Referring, therefore, to the reactive species (one or more) involved in the reaction described as the "Hoesch intermediate" it would appear that it is more reactive than the β-dicarbonyl moiety in **5a**.

There are, apparently, alternative reaction paths available to nitrile–hydrogen chloride adducts on treatment with water; the acetonitrile–hydrogen chloride adduct is reported to revert back to acetonitrile,[7a] whereas the trichloroacetonitrile adduct is converted to trichloroacetamide.[7b] Therefore, a more quantitative estimate of the reactivity difference between the "Hoesch intermediate" and the β-dicarbonyl moiety in **5a** based on the starting material recovered and the relative amounts of **4** and **10a** formed would not be possible, since it would not be known whether the recovered nitrile dione **5a** is merely unreacted starting material, or is a result of the decomposition of the "Hoesch intermediate" in the manner observed with the acetonitrile–hydrogen chloride adduct.

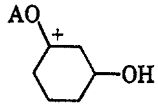
(7) (a) L. E. Hinkel and G. Treharne, *J. Chem. Soc.*, 866 (1945); (b) J. Houben and W. Fischer, *Ber.*, **60**, 1759 (1927).

(8) p*K* measurements establish this difference as enormous—on the order of 9 p*K* units. See E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

strong to show this selective protonation.) This concentration differential in the protonated forms of the two species is presumably large enough to offset the greater reactivity expected for the protonated nitrile B compared to the protonated β-diketone B′ (or more sophisticated representations thereof). The greater basicity of the β-diketone would be expected on the basis of qualitative resonance considerations which would also account for the greater reactivity of the protonated nitrile. With 96% sulfuric acid at room temperature, **5a** was hydrolyzed to the amide dione **5d**.

$\overset{NA}{\overset{\|}{R{\cdot}C^{+}}}$

B A = general acid



B′

Spirotrione **4**, possibly accompanied by relatively small amounts of **10** (X = H) (Experimental Section), was also obtained from the dione acid **5b** on treatment with trifluoroacetic anhydride in ether followed by boron trifluoride etherate, presumably *via* the trifluoroacetylated mixed anhydride i (ref 10). In the absence of boron trifluoride etherate, **5b** was recovered unchanged.[9,10]

The dione acid **5b**, treated with boron trifluoride etherate at steam bath temperature, behaved in a manner similar to **5a**, and gave the tricyclic ketonic acid **10b** as the sole acidic product, presumably for the reasons already outlined for **5a**. (p*K* measurements indicate cyclohexanediones to be on the order of one million times more basic than carboxylic acids.[8])

Concentrated (96%) sulfuric acid at room temperature for *ca.* 18 hr left **5b** unchanged.

In summary, formation of the spirotrione **4** and/or the tricyclic ketone **10** from **5** is seen to depend on the reactivity of the substituent X in **5** relative to the β-dicarbonyl moiety.

Experimental Section[17a]

Ethyl 3,5-Dimethoxybenzylidenecyanoacetate (6).—A mixture of 10 g (0.06 mole) of 3,5-dimethoxybenzaldehyde[17b] 6.8 g (0.06 mole) of ethyl cyanoacetate, and 8 drops of piperidine was heated on the steam bath for *ca.* 30 min. The reaction mixture solidified on cooling. The yellow solid was triturated with ethanol and collected to yield 14 g (90%) of the benzylidenecyanoacetate, mp 82.5–86°. Recrystallization from ethanol furnished the analytical sample as a pale yellow crystalline solid, mp 89.5–90.5°.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.86; H, 5.77; N, 5.53.

Ethyl 3,5-Dimethoxybenzylcyanoacetate (7).—A solution of 7 g (0.027 mole) of ethyl 3,5-dimethoxybenzylidenecyanoacetate in 100 ml of ethyl acetate was hydrogenated in a Parr apparatus over 0.7 g of 10% palladium on charcoal for 2.25 hr. (The theoretical amount of hydrogen, *ca.* 2.4 lb, was consumed within 1.5 hr.) The catalyst was removed by filtration through Celite, and the filtrate evaporated to yield 7 g of the dihydro derivative as a pale yellow liquid which was transformed to an oily solid on standing for 2 days. A 2-g sample of the product in ether was further purified by percolating through a 2 × 5 cm column of Woelm almost neutral (nonalkaline) alumina, activity I. Evaporation of the ethereal eluate (*ca.* 50 ml) left a 1.8 g of pale yellow liquid residue which was kept under high vacuum for 4.5 hr. After standing at room temperature for 6 days, the liquid was agitated. Solidification took place overnight to yield an essentially colorless, crystalline solid, mp 45–47°.

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.88; H, 6.66; N, 5.58.

1-Cyano-1-(3,5-dimethoxybenzyl)-2,4-cyclohexanedione (5a).—The condensation of the 3,5-dimethoxybenzylcyanoacetate and methyl vinyl ketone was effected in two stages. To a cooled solution of 7 g (0.027 mole) of the 3,5-dimethoxybenzylcyanoacetate and 1.9 ml of methyl vinyl ketone in 10 ml of dry 1,2-dimethoxyethane was added 16 drops (capillary pipet) of 1.66 *N* methanolic sodium methoxide. The reaction mixture was kept at room temperature for *ca.* 15 hr and diluted with ether; the ethereal solution was washed with 2 *N* aqueous sodium hydroxide, salt solution, dried, and evaporated to yield the crude Michael adduct **8** which was dissolved directly in 16 ml of 1.66 *N* methanolic sodium methoxide (0.027 mole). The solution was heated under reflux for 2.5 hr and poured into cold water; the mixture was extracted with ether. The aqueous phase was acidified. A nearly colorless oil separated which solidified within 10–15 min. After another 15 min, the colorless solid was collected and air dried on filter paper: yield 4.4 g (57%); mp 170–174°.

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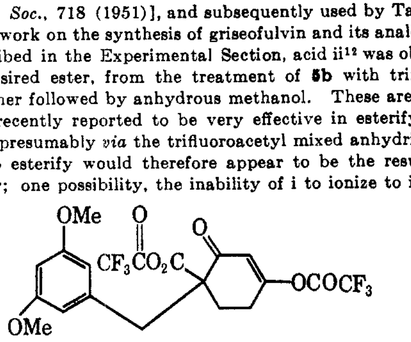
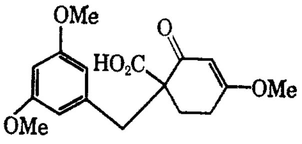
[9] Acylations in trifluoroacetic anhydride were first reported by Bourne, *et al.* [*J. Chem. Soc.*, 718 (1951)], and subsequently used by Taub, *et al.*,[11] in their elegant work on the synthesis of griseofulvin and its analogs.

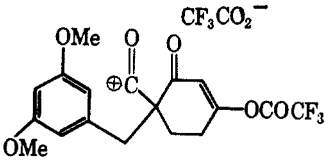
[10] As described in the Experimental Section, acid ii[12] was obtained, instead of the desired ester, from the treatment of **5b** with trifluoroacetic anhydride in ether followed by anhydrous methanol. These are essentially the conditions recently reported to be very effective in esterifying highly hindered acids, presumably *via* the trifluoroacetyl mixed anhydride.[14] The failure of **5b** to esterify would therefore appear to be the result of some electronic factor; one possibility, the inability of i to ionize to iii owing to the destabilization of the latter species by the electron-deficient trifluoroacetylated β-dicarbonyl moiety. The unionized mixed anhydride i would be expected[15,16] to react with methanol preferentially at the carbonyl group of the trifluoroacetyl moiety to regenerate the free acid. The inability to form the acylium ion iii in the absence of boron trifluoride etherate would also account for the failure of **5b** to cyclize to **4** in trifluoroacetic anhydride alone.



i

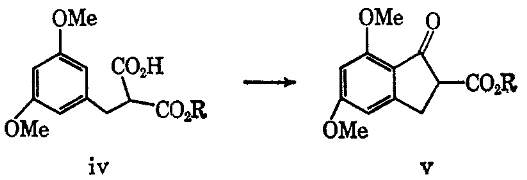


ii



iii

We also found (Experimental Section) that malonic acid iv (R = H) is rapidly converted to v (R = Me) with trifluoroacetic anhydride in ether at room temperature (3 hr) followed by treatment with methanol. By contrast, iv (R = Me) was recovered unchanged under these conditions.



iv v

[11] See ref 2a and earlier work.

[12] The facts in hand do not eliminate the isomeric enol ether as a possible structure for the product. However, structure **12** is preferred by analogy with the preferential formation of the 4′ enol ether in the acid catalysed alcoholysis of griseofulvic acid, presumably for steric reasons.[13]

[13] L. A. Duncanson, J. F. Grove, and P. W. Jeffs, *J. Chem. Soc.*, 2929 (1958).

[14] (a) R. C. Parish and L. M. Stock, *Tetrahedron Letters*, **No. 20**, 1285 (1964); (b) *J. Org. Chem.*, **30**, 927 (1965).

[15] E. J. Bourne, S. H. Henry, C. E. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952).

[16] A. R. Emery and V. Gold, *ibid.*, 1443, 1447, 1455 (1950).

[17] (a) Melting points were taken in a Hershberg apparatus using a 3-in. immersion thermometer. Infrared spectra were determined in 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 11A, spectrophotometer. Magnesium sulfate was used for drying. (b) Aldrich Chemical Co., Inc., Milwaukee, Wis.

Recrystallization from ethanol furnished the analytical sample: mp 176–177°, λ_{max}^{MeOH} 260 mμ (ϵ 15,000), 224 mμ (ϵ 10,000); λ_{max}^{Nujol} 4.45 μ (very weak).

The nmr spectrum in deuteriochloroform–deuterated dimethyl sulfoxide showed a 6-proton multiplet at δ 2.00–3.45 (benzylic protons and α and β methylenic protons of the cyclohexanedione ring), a 6-proton singlet at δ 3.83 ($-OCH_3$), a 1-proton singlet at δ 5.49 (olefinic proton of the enolic form of the β-diketone), and a somewhat broad based 3-proton singlet at δ 6.49 (aromatic protons).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.71; H, 6.12; N, 4.62.

Ethyl 3,5-Dimethoxybenzylidenemalonate. The general procedure of Cope, *et al.*, was followed.[18] A solution of 50 g (0.3 mole) of 3,5-dimethoxybenzaldehyde, 50 g (0.3 mole) of diethyl malonate, 1.5 ml of piperidine, and 5 ml of acetic acid in 50 ml of anhydrous benzene was heated under reflux for 14 hr with continuous water separation by means of a Dean-Stark trap. The benzene was removed under reduced pressure and the residue distilled directly at 0.2 mm using a short-path distilling apparatus and a free flame as a heat source. After a 6-g forerun which distilled up to 170°, 61 g (64%) of the benzylidenemalonate was obtained as a moderately viscous liquid, bp 170–178°. The liquid solidified on rubbing with a glass rod, after standing at room temperature for *ca.* 30 min. The colorless solid was suspended in petroleum ether (bp 30–60°). The lumps were broken up, and, after an additional 1.5 hr, collected: yield 60 g; mp 45–48°.

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.25; H, 6.48.

Ethyl 3,5-Dimethoxybenzylmalonate.—A solution of 53 g (0.17 mole) of the benzylidene malonate in 70 ml of ethyl acetate was hydrogenated over 0.4 g of 10% palladium-on-charcoal in a Parr apparatus for 2 hr (hydrogen pressure remained constant after *ca.* 30 min). The catalyst was removed by filtration through Celite and the filtrate evaporated to yield 51 g (97%) of the colorless, liquid dihydro derivative. Distillation of *ca.* 1 g of the product furnished the analytical sample, bp 140–145° (0.2 mm), $n^{24}\text{D}$ −1.4998. (The distillate was collected in three arbitrary fractions; a portion of the third was analyzed.)

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.02; H, 7.18.

1-Carbomethoxy-1-(3,5-dimethoxybenzyl)-2,4-cyclohexanedione (**9**).—To a cooled solution of 47 g (0.15 mole) of ethyl 3,5-dimethoxybenzylmalonate in 98 ml of 1.53 *N* methanolic sodium methoxide (0.15 mole) was added 10.5 ml of methyl vinyl ketone, dropwise with swirling over a 5–10-min period, the temperature of the exothermic reaction being kept between 5 and 10°. After an additional 5 min in the cooling bath (ice–water), the reaction mixture was kept at room temperature for 2.75 hr, heated under reflux for 2 hr, and partitioned between cold water and methylene chloride–ether. Acidification of the basic aqueous phase resulted in the separation of an oil which partially solidified on short standing. This was taken up in methylene chloride and the solution was dried and evaporated to yield a partially solid residue which was triturated with ether. The resulting colorless, ether-insoluble solid was collected, washed thoroughly with ether, and air dried: yield 17.4 g (36%); mp 177–179°. Recrystallization from ethanol and drying *in vacuo* at 78° over phosphorous pentoxide for 2 hr furnished the analytical sample: mp 178–180.5°; λ_{max}^{MeOH} 260 mμ (ϵ 16,000), 225 mμ (ϵ 11,200); λ_{max}^{Nujol} 5.80 μ.

The carbomethoxy methyl, methoxy, enolic, and aromatic protons appeared, respectively, in the nmr spectrum (deuteriochloroform–deuterated dimethyl sulfoxide), at δ 3.70 (sharp overlapping 9-proton doublet), 5.35 (1-proton singlet), and 6.25 (3-proton singlet).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.70; H, 6.62.

Note that unlike the 3,5-dimethoxybenzylcyanoacetate, the 3,5-dimethoxybenzylmalonate was insoluble in 2 *N* aqueous sodium hydroxide, presumably because of the lower electronegativity of the carbethoxy group compared with cyano.

1-Carboxy-1-(3,5-dimethoxybenzyl)-2,4-cyclohexanedione (**5b**).—Five grams (0.0155 mole) of the carbomethoxy dione **9** was dissolved in cold aqueous 2 *N* sodium hydroxide. The solution was kept at room temperature for 15.5 hr, cooled in Dry Ice–acetone, and acidified with concentrated hydrochloric acid, the temperature of the mixture being kept below 10°. The colorless gum which separated, solidified on short standing, and was collected and air dried on filter paper overnight: yield 4.45 g (97%); mp 96–97° eff. The analytical sample, mp 99–100° eff, was obtained by suspending a portion of the product in methylene chloride, in which it is sparingly soluble, for 2.25 hr, collecting and keeping under high vacuum for 3 hr: λ_{max}^{MeOH} 258 mμ (ϵ 14,300), 225 mμ (ϵ 11,400); λ_{max}^{Nujol} 5.88 μ.

Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.42; H, 6.16.

5′,7′-Dimethoxyspiro[cyclohexane-1,2′-indan]-1′,2,4-trione (**4**). **A. From 1-Cyano-1-(3,5-dimethoxybenzyl)-2,4-cyclohexanedione** (**5a**).—To 25 ml of anhydrous ether contained in a flame dried three-necked flask was added 1.15 g (0.004 mole) of dried (at 78° over phosphorous pentoxide *in vacuo* overnight) nitrile dione **5a** and 0.68 g (0.005 mole) of anhydrous zinc chloride (fused, crushed under benzene, then heated at *ca.* 140° over phosphorous pentoxide for 14.5 hr). The suspension was cooled in ice water and dry gaseous hydrogen chloride was bubbled through. The reaction mixture was a homogeneous yellow solution after 1.5 hr, and after 2.5 hr, a red-brown oil separated. The cooling bath was refilled with ice once, after 2.5 hr. After *ca.* 10 hr, the gas passage was terminated, the flask stoppered, and kept for an additional 14 hr (total reaction time, 25 hr). Water (20 ml) was then added and the mixture heated on the steam bath for *ca.* 20 min to evaporate the ether. The hot aqueous solution was then decanted from an insoluble brown-red oil, heated under reflux for 1.5 hr, again decanted from a small amount of dark brown gum which had separated, cooled, and extracted with methylene chloride. The methylene chloride extracts were, in turn, extracted with bicarbonate solution and the latter acidified. A nearly colorless gum separated which was taken up in methylene chloride, a small amount of ether added, and the solution washed, dried, and evaporated to yield 0.25 g of a white froth which solidified on trituration with ether. After *ca.* 1 hr the solid was collected: yield 0.18 g; mp 210–216° dec. After recrystallization from ethanol and drying at 80° for 4 hr then at room temperature overnight over phosphorus pentoxide under high vacuum, the compound had mp 224–226° dec; λ_{max}^{MeOH} 229 mμ (ϵ 20,400), 274 (28,000), 301 sh (9350); λ_{max}^{Nujol} 5.90 mμ.

Its nmr spectrum in deuteriochloroform showed a 6-proton broad multiplet at δ 2.15–3.56 (benzylic protons plus the α and β methylenic protons in the cyclohexanedione), a 6-proton singlet at δ 4.00 ($-OCH_3$), a 1-proton singlet at δ 5.51 (olefinic proton of the enolic form of the β-diketone), and two 1-proton singlets (not very sharp) at δ 6.51 and 3.66 (aromatic protons).

The relative ratio of the δ 3.83 signal ($-OCH_3$ of the nitrile dione, see above) and the δ 4.00 signal ($-OCH_3$ of the spirotrione) in the nmr spectrum of the product before recrystallization from ethanol indicated contamination by *ca.* 15% of starting nitrile dione.

As already indicated above, the reaction mixture was worked up by adding water to the ethereal mixture, evaporating the ether on the steam bath, and decanting the hot aqueous solution from an insoluble red-brown oil. In another experiment, this oil was processed by dissolving it in methylene chloride and washing the solution with water, treating with Norit and, after separating the Norit, extracting with bicarbonate solution. Drying and evaporating the methylene chloride solution left an oily residue which solidified on rubbing (metal spatula) in ethanol. The solid obtained melted at 165–170°, and its infrared spectrum was identical with that of the neutral tricyclic unsaturated ketone **10a** obtained from the reaction of **5a** and boron trifluoride etherate (see below).

Acidification of the bicarbonate extracts gave a water insoluble oily product which solidified on short standing. The solid melted at 172–174°, and its infrared spectrum was identical with that of starting nitrile dione **5a**.

The spirotrione was isolated from this experiment as already described. The relative yields of the three products isolated (crude) were *ca* 1:1:2 (**10a**:**5a**:**4**).

B. From 1-Carboxy-1-(3,5-dimethoxybenzyl)-2,4-cyclohexane dione (**5b**).—After keeping a solution of 0.295 g (0.96 mmole) of the dione acid in a mixture of 3 ml of anhydrous ether and 1.5 ml of trifluoroacetic anhydride at room temperature for 1.25 hr, 0.65 ml of boron trifluoride etherate was added and the reaction mixture kept at room temperature for 35 hr. Most of the excess ether and trifluoroacetic anhydride was removed *in vacuo*, water added to the very dark green residue and the

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[18] A. C. Cope, C. M. Hofman, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

mixture kept at room temperature for *ca.* 1 hr. The dark green gummy product was dissolved in methylene chloride–ether and the solution extracted with aqueous sodium bicarbonate. A dark green gum separated upon acidification of the bicarbonate extracts which was taken up in methylene chloride. The methylene chloride solution was treated with Norit, dried (single operation), and evaporated to give a green froth which solidified on trituration with ether. The pale green solid, collected after 1 hr, melted at 210–218° dec; the yield was 65 mg (24%). Its infrared spectrum was practically the same as that of analytically pure spirotrione **4**.

The bicarbonate extracted methylene chloride–ether solution was dried and evaporated to yield 76 mg of a dark green gum which appeared to partially solidify on trituration with ether. The ultraviolet spectrum of this material showed four peaks of comparable intensities at 333, 312, 285, and 263 mμ, the 285-mμ peak being somewhat more intense than the rest. If the 312-, 285-, and 263-mμ peaks were all due to a single substance, and if their extinction coefficients were comparable in magnitude (*ca.* 25,000) to that of the 333-mμ peak [assumed to be due to **10** (X = H), *cf.* the ultraviolet spectra of **10a** and **10b**], the amount of **10** (X = H) in the neutral fraction could not exceed 38 mg (50% of the total). Leaving aside the second condition, the comparable intensities of the 312-, 285-, and 263-mμ peaks makes it unlikely that the first condition applies and the amount of **10** (X = H) present would be even lower.

The ultraviolet spectrum of the residue obtained by evaporating the ethereal mother liquor from which the spirotrione **4** separated was also essentially transparent in the 300–350-mμ region, thus ruling out the presence of **10b** in the acid fraction.

7,8-Dihydro-2,4-dimethoxy-6-oxo-8a(6H)-fluorenecarbonitrile (10a).—A solution of 0.5 g (0.0017 mole) of nitrile dione **5a** in 5 ml of boron trifluoride etherate was heated on the steam bath for 40 min (a yellow solid separated after *ca.* 20 min), and the reaction mixture poured into ice-water. The organic product was extracted with methylene chloride, and the methylene chloride extracts were washed with water then bicarbonate solution, dried, treated with Norit, and evaporated to yield 0.32 g (70%) of a yellow oil which solidified almost immediately on trituration with ethanol. The product was recrystallized three times from ethanol and dried at 78° over phosphorus pentoxide *in vacuo* for 3 hr to give 0.15 g of a light yellow, crystalline solid: mp 172–173°; $\lambda_{\max}^{\text{Nujol}}$ 6.05 μ; $\lambda_{\max}^{\text{MeOH}}$ 338 mμ (ε 25,200), 256 (10,700), 250 (10,700), 227 (7000), and 222 (7000).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 70.85; H, 5.75; N, 5.08.

The nmr spectrum of the compound in deuteriochloroform was fully consistent with structure **10a**. It showed a 4-proton multiplet at δ 2.00–2.97 (α and β methylenic protons in the unsaturated ketone), 2-proton double doublet centered at δ 3.11 and 3.62 (J = 16 cps) (benzylic protons), a sharp 6-proton overlapping doublet at δ 3.98 ($-OCH_3$), a two 1-proton singlet (not very sharp) at δ 6.43 and 6.55 (aromatic protons), and a sharp 1-proton singlet at δ 6.70 (α olefinic proton of the unsaturated ketone function).

7,8-Dihydro-2,4-dimethoxy-6-oxo-8a(6H)-fluorenecarboxylic acid (10b).—A solution of 0.25 g (0.82 mole) of acid dione **5b** in 2.5 ml of boron trifluoride etherate was heated on the steam bath for 35 min. (A yellow solid separated within 2 min which largely dissolved by the end of 20 min. A yellow solid again separated after 25 min.) The reaction mixture was poured into ice water, the mixture extracted with methylene chloride–ether, and the organic solution extracted with aqueous bicarbonate. Acidification of the bicarbonate extracts gave a water insoluble pale yellow solid which was collected and air dried: yield 145 mg (61%); mp 96–97° eff. Its infrared spectrum was clearly different from that of starting carboxy dione **5b**. The product was further purified by keeping it suspended in ethanol for *ca.* 3 hr at room temperature, collecting, and drying *in vacuo* at room temperature over phosphorus pentoxide for 27 hr: mp 120–121.5° eff; $\lambda_{\max}^{\text{Nujol}}$ 5.89 (sharp) and 6.32 μ (moderately broad and very strong); $\lambda_{\max}^{\text{MeOH}}$ 334 mμ (ε 24,000), 250 (11,000), 224 (8000).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.70; H, 5.97.

1-Carboxamido-1-(3,5-dimethoxybenzyl)-2,4-cyclohexanedione.—A suspension of 0.7 g (0.0024 mole) of the nitrile dione **5a** in 5 ml of 96% sulfuric acid was shaken intermittently for 1–1.5 hr, at the end of which time the reaction mixture was homogeneous. The red-orange solution was kept at room temperature for 23 hr and poured into ice-water. A gummy solid separated which was collected after stirring the aqueous mixture for *ca.* 0.75 hr. The product was dissolved in sodium bicarbonate solution, the solution treated with Norit and acidified. An almost colorless solid separated which was collected after 30 min.: yield 0.49 g (66%); mp 193–194.5°. After recrystallization from ethanol and drying at 80° over phosphorus pentoxide *in vacuo* overnight, the product had mp 193.5–195°; $\lambda_{\max}^{\text{Nujol}}$ 6.0 μ; $\lambda_{\max}^{\text{MeOH}}$ 264 mμ (ε 14,000), 222 mμ (ε 10,000).

Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.76; H, 6.49; N, 4.60.

6-Carboxy-6-(3,5-dimethoxybenzyl)-3-methoxy-2-cyclohexen-1-one (ii).—A solution of 0.1 g (0.33 mmole) of the dione acid **5b** in a mixture of 1 ml of anhydrous ether and 1 ml of trifluoroacetic anhydride was kept at room temperature for 55 min, cooled in Dry Ice–acetone and 1.5 ml of cooled absolute methanol was added. After 0.75 hr at room temperature a good portion of the volatile components were evaporated *in vacuo;* water was added to the residue. The oil which separated was taken up in methylene chloride ether, and the solution was dried and evaporated to yield an oily residue which solidified on trituration with ether: yield 38 mg (36%); mp 103–104° eff; $\lambda_{\max}^{\text{Nujol}}$ 5.82 (relatively sharp), 6.32 μ (broad, very strong).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.73; H, 6.51.

3,5-Dimethoxybenzylmalonic Acid.—A suspension of 1 g (3.2 mmole) of ethyl 3,5-dimethoxybenzylmalonate in 5 ml of aqueous sodium hydroxide (1:1 wt/v) was heated on the steam bath for 1 hr. The reaction mixture was cooled in Dry Ice–acetone, diluted with water, and acidified with concentrated hydrochloric acid (the temperature during the acidification did not rise above 20°). The solid which formed was collected, washed well with water, and dried under high vacuum over phosphorus pentoxide at room temperature for 26 hr: yield 0.45 g (55%); mp 156–157.5° eff (shrinks *ca.* 152°).

Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 57.06; H, 5.65.

2-Carbomethoxy-5,7-dimethoxy-1-indanone.—Two hundred and fifty milligrams (0.001 mole) of 3,5-dimethoxybenzylmalonic acid was dissolved in a mixture of 3 ml of anhydrous ether and 1.5 ml of trifluoroacetic anhydride. Within a minute a new solid separated. The reaction mixture was kept at room temperature for 3 hr during which time partial solution of the suspended solid appeared to take place. The reaction mixture was cooled in Dry Ice–acetone, and 5 ml of Dry Ice–acetone cooled absolute methanol was added. After 70 min at room temperature, the volatile components were partially evaporated and water was added. The oil which separated was extracted with methylene chloride–ether and the extracts washed with bicarbonate solution, dried, and evaporated to yield an oil which solidified on trituration with ether: yield 128 mg (51%); mp 79–94°. The product was recrystallized from ethyl acetate–ether, and the somewhat tacky solid obtained was washed well with ether and kept suspended in that solvent overnight. The resulting very pale yellow solid melted at 104–105°: $\lambda_{\max}^{\text{Nujol}}$ 5.82 and 5.92 μ (ester and ketone, respectively); $\lambda_{\max}^{\text{MeOH}}$ 300 mμ sh (ε 6900), 277 (18,100), 230 (16,900).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.32; H, 5.68.

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