Synthesis in the Griseofulvin Series. II. 7-Fluoro-7-dechlorogriseofulvin, an Active Analog[1]

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Received April 29, 1963

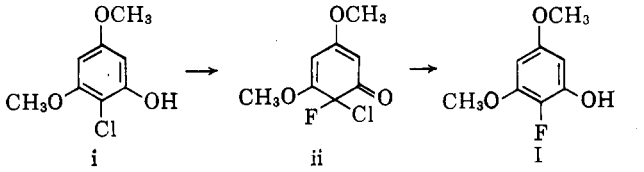
Racemic and optically active 7-fluoro-7-dechlorogriseofulvins have been prepared by total synthesis and by partial synthesis from griseofulvin, respectively.

The antifungal activity of the mould metabolites, 7-dechlorogriseofulvin (VI, F = H), 7-bromo-7-dechlorogriseofulvin (VI, F = Br), and griseofulvin (VI, F = Cl), increases strikingly in the order named.[2] It was, therefore, of interest to synthesize *inter alia* the 7-fluoro analog VI. Pursuant thereto, racemic and optically active 7-fluoro-7-dechlorogriseofulvin (VI) have been prepared by total synthesis and by partial synthesis from griseofulvin, respectively. The total synthesis pursued the same general scheme employed in our synthesis of griseofulvin[3,4] and its analogs.[1,5,6] The key intermediate in this synthesis was the fluorobenzophenone IIIa obtained by coupling 2-fluoro-3,5-dimethoxyphenol (I)[7] with 2-methoxy-4-acetoxy-6-methylbenzoic acid (II)[3] in the presence of trifluoroacetic anhydride at 20–25°.[3b] By this technique, the fluorobenzophenone acetate III could be obtained in 60% yield. During the work-up, III was partially converted to the free fluorobenzophenone IIIa, double m.p. 186–190°, 200–203°; λ_{max} 295 (18,100), sh 333 mμ (ε 6250). Saponification of III to IIIa was accomplished in quantitative yield by 2% aqueous methanolic alkali. When the trifluoroacetic anhydride acylation was carried out at 3°, a larger proportion of O-acylation to give the ester acetate IV occurred, thus indicating a temperature dependence of O- *vs.* C-acylation. In the analogous step in the griseofulvin series,[3b] trifluoroacetic anhydride at 25° produced chlorobenzophenone acetate III (F = Cl) in ~50% yield together with 25% of the corresponding chloro ester acetate IV (F = Cl).

The fluorobenzophenone IIIa was oxidized with potassium ferricyanide[8] by an improved technique[3b] both rapidly and in good yield to give (±)-7-fluoro-4,6,2′-trimethoxy-6′-methylgris-2′,5′-diene-3,4′-dione (V), m.p. 222–225°. Hydrogenation[3b] of the dienone V in 1,2-dimethoxyethane over 10% palladium on charcoal followed by conversion of unchanged V to III by treatment with zinc in acetic acid[3b] and chromatography afforded (±)-7-fluoro-7-dechlorogriseofulvin (VI) (64% conversion yield), m.p. 209–211°; λ_{max} 325 (4600), 290 (21,000), infl 245 (14,100), and 235 mμ (ε 15,000). A minor amount (10%) of the dihydro derivative VII also was formed.

The infrared spectra of the 7-fluoro compounds V, VI, and VII exhibit characteristic differences in the 6.1–6.6-μ region in comparison with the spectra of the corresponding unfluorinated analogs.[3,5,9] The C=C (double bond and aromatic) stretching bands which in the latter series normally occur near 6.15, 6.25, and 6.60 μ (in chloroform) are shifted to 6.12, 6.20, and 6.52 μ (V), 6.06, 6.16, and 6.49 μ (VI), and 6.05, 6.14, and 6.48 μ (VII). The spectra of V, VI, and VII also have a strong band near 7.85 μ not present in the spectra of the fluorine-free analogs, which may be attributed to the C—F stretching vibration.[10]

For the partial synthesis of (+)-7-fluoro-7-dechlorogriseofulvin,[11] norgriseofulvic acid (VIIa)[12] was first converted into its 4′-isopropyl ether VIII, m.p. 282–284°. The latter was obtained free of the isomeric 2′-isopropyl ether, and its structure was secured by diazomethane methylation of the C-6 phenolic hydroxyl group to give the known isopropyl ether VIIIa.[13] The phenol VIII on treatment with perchloryl fluoride in pyridine–dimethylformamide solution produced a mixture of the dienones IX and X. This mixture was reduced directly with zinc in acetic acid to a mixture of the phenols VIII and XI which was methylated in turn with diazomethane and separated by alumina chromatography and paper chromatography into the known isopropyl ether VIIIa[13] and the new fluorinated analog XIa, m.p. 144–146°. The preparation of (+)-VI itself was accomplished most conveniently by first hydrolyzing the isopropyl ether group of the mixture of VIIIa and XIa followed by methylation with diazomethane and chromatographic separation on paper. In this



(1) For a preliminary account of this work, see D. Taub, C. H. Kuo, and N. L. Wendler, *Chem. Ind.* (London), 557 (1962). For part I, see ref. 3.

(2) J. MacMillan, *J. Chem. Soc.*, 2585 (1954).

(3) (a) C. H. Kuo, R. D. Hoffsommer, H. L. Slates, D. Taub, and N. L. Wendler, *Chem. Ind.* (London), 1627 (1960); (b) D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, **19**, 1 (1963).

(4) For other syntheses of griseofulvin see: (a) A. Brossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, **43**, 1444, 2071 (1960); (b) A. C. Day, J. Dabney, and A. I. Scott, *Proc. Chem. Soc.*, 284 (1960); *J. Chem. Soc.*, 4067 (1961); (c) G. Stork and M. Tomasz, *J. Am. Chem. Soc.*, **84**, 310 (1962).

(5) (a) D. Taub, C. H. Kuo, and N. L. Wendler, *Chem. Ind.* (London), 1617 (1962); (b) D. Taub and N. L. Wendler, *Angew. Chem.*, **74**, 586 (1962).

(6) Analogs of griseofulvin have also been prepared recently by others employing different routes. In this regard see: S. R. Goodall, G. I. Gregory, and T. Walker, *J. Chem. Soc.*, 1610 (1963), and earlier papers; M. Gerecke, E. Kyburz, C. v. Planta, and A. Brossi, *Helv. Chim. Acta*, **45**, 2241 (1962).

(7) D. Taub, *Chem. Ind.* (London), 558 (1962).

(8) D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, *J. Chem. Soc.*, 530 (1956). See also: C. H. Hassall and A. I. Scott, "Chemistry of Natural Phenolic Compounds," W. D. Ollis, Ed., Pergamon Press, Oxford, 1961, p. 119.

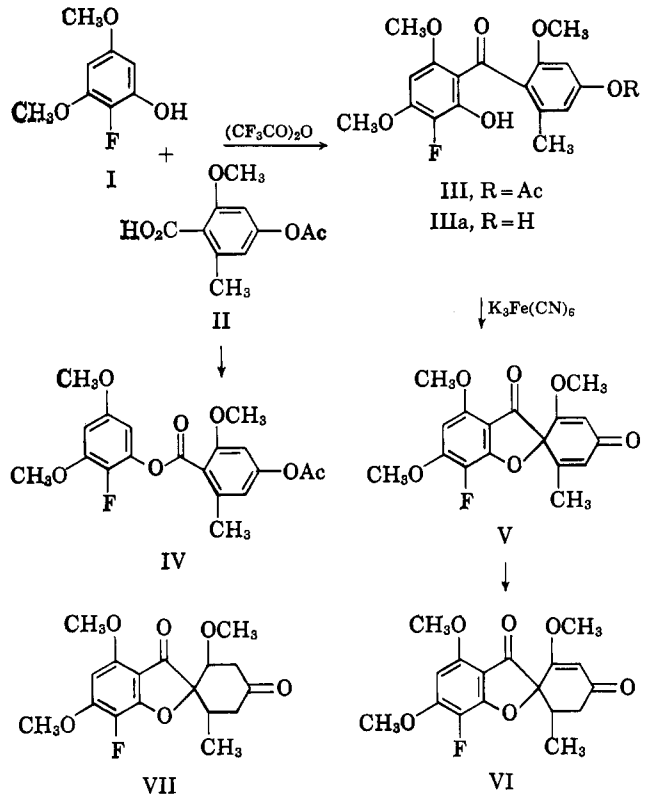
(9) See J. E. Page and S. E. Staniforth, *J. Chem. Soc.*, 1292 (1962), for discussion of the infrared spectra of griseofulvin and a number of analogs.

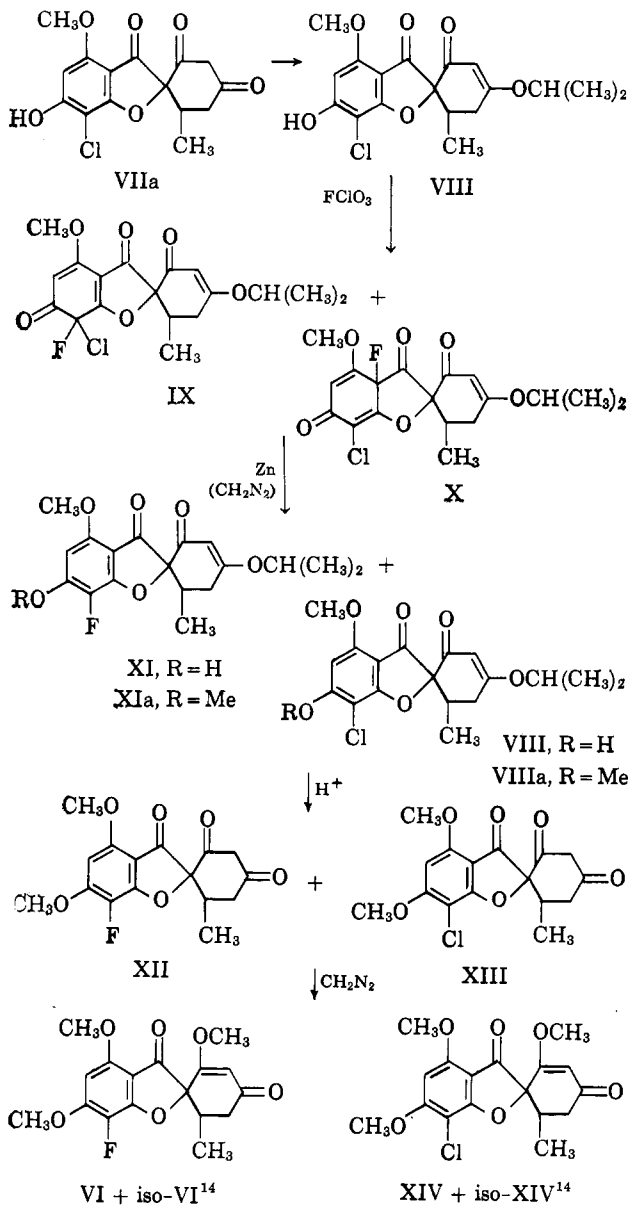
(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1958, pp. 328–329.

(11) The possibility of exchanging chlorine for fluorine in a derivative of griseofulvin itself was suggested by the observation that 2-chloro-3,5-dimethoxyphenol (i) reacted with perchloryl fluoride to give, in part, the fluorochlorodienone ii. Reductive dehalogenation of the latter with zinc in acetic acid led to selective removal of chlorine to give 2-fluoro-3,5-dimethoxyphenol (I) exclusively.[7]

(12) A. E. Oxford, H. Raistrick, and P. Simonart, *Biochem. J.*, **33**, 240 (1939); J. F. Grove, J. MacMillan, T. P. C. Mulholland, and M. A. T. Rogers, *J. Chem. Soc.*, 3949 (1952).

(13) L. A. Duncanson, J. F. Grove, and P. W. Jeffs, *ibid.*, 2929 (1958).





manner, pure (+)-7-fluoro-7-dechlorogriseofulvin (VI) was obtained as the most polar component,[14] m.p. 210–212°, $[\alpha]^{chf}D$ +316°. The spectral properties (ultraviolet, infrared, and n.m.r.), as well as the mobility of this material on paper and on alumina (t.l.c.), were identical with the corresponding properties of (±)-VI obtained by total synthesis.

Racemic VI and (+)-VI exhibited, respectively, 50% activity and the full activity of (+)-griseofulvin as determined by disk plate assay employing *Botrytis alii* as the test organism.[15]

Experimental[16]

3-Fluoro-2,4′-dihydroxy-4,6,2′-trimethoxy-6′-methylbenzophenone (IIIa) and 3-Fluoro-2-hydroxy-4′-acetoxy-4,6,2′-trimethoxy-6′-methylbenzophenone (III).—2-Methoxy-6-methyl-4-acetoxybenzoic acid (II, 2.92 g.) was added to 20 ml. of trifluoroacetic anhydride at 0°. The solution was stirred and 2.00 g. of 2-fluoro-3,5-dimethoxyphenol (I)[7] was added. The clear yellow solution was allowed to warm to 20–25° and kept at that temperature for 20 hr. The solvent was removed in a stream of nitrogen and the residue dissolved in ether. The ether solution was extracted with dilute potassium bicarbonate (acidification indicated faint opalescence) and dilute sodium hydroxide. Acidification of the alkaline extract and ether extraction gave 830 mg. (21%) of the fluorobenzophenone IIIa as a yellow solid, m.p. 180–190°, crystallized from acetone–ether, double m.p. 186–190°, 200–203°; λ_{max}^{MeOH} 295 (18,100), sh 333 mμ (ε 6250); λ_{max}^{Nujol} 2.99, 6.06, 6.19, 6.38 μ.

Anal. Calcd. for $C_{17}H_{17}O_6F$: C, 60.71; H, 5.09; F, 5.65. Found: C, 60.48; H, 5.36; F, 5.40.

Crystallization of the residue from the original ether layer (3.60 g.) from acetone–ether gave the fluorobenzophenone acetate III (1.71 g., 40%) as yellow prisms, m.p. 188–200°; analytical sample recrystallized from acetone–ether, m.p. 195–200°; λ_{max}^{MeOH} 295 (19,000), infl. 333 mμ (ε 5400); λ_{max}^{chf} 2.8–4.0, 5.72, 6.12, 6.24, 6.63, 8.2–8.4 μ. The mother liquors contained considerable additional amounts of III.

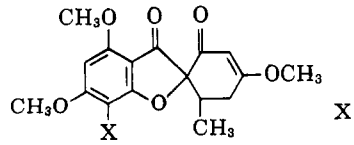
Anal. Calcd. for $C_{19}H_{19}O_7F$: C, 60.33; H, 5.06. Found: C, 60.39; H, 4.85.

Basic hydrolysis of III (950 mg.) in 30 ml. of methanol and 20 ml. of 5% aqueous sodium hydroxide at 20° under nitrogen for 2 hr. gave the fluorobenzophenone IIIa (840 mg.) in quantitative yield.

When I (500 mg.) and II (700 mg.) were allowed to react in trifluoroacetic anhydride at 3° for 68 hr., the neutral portion of the product following alumina chromatography and fractional crystallization from acetone–ether gave the fluorobenzophenone acetate III (120 mg.) and the ester acetate [2-fluoro-3,5-dimeth-

(14) The other components present in increasing order of mobility were griseofulvin XIV and the respective iso systems: iso-VI (X = F) and iso-XIV (X = Cl).

(15) The authors are indebted to H. Wallick of these laboratories for performing the assays.



(16) Melting points were taken on a microscope hot-stage apparatus and are corrected. Ultraviolet spectra were determined in methanol and rotations measured with a Zeiss photoelectric precision polarimeter employing an 0.2-decimeter tube. Whatman no. 4 paper was utilized for paper chromatography. N.m.r. spectral data for III, IIIa, IV, V, VI, VII, VIII, and XIa are in accord with the structures and are recorded and discussed elsewhere.[17]

(17) B. H. Arison, N. L. Wendler, D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, and N. R. Trenner, *J. Am. Chem. Soc.*, **85**, 627 (1963).

oxyphenyl 2′-methoxy-4′-acetoxy-6′-methylbenzoate (IV)], m.p. 145° (210 mg.); λ_{max}^{chf} 5.71, 6.29, 8.2–8.4 μ.

Anal. Calcd. for $C_{19}H_{19}O_7F$: C, 60.33; H, 5.06. Found: C, 60.45; H, 5.17.

(±)-7-Fluoro-4,6,2′-trimethoxy-6′-methylgris-2′,4′-diene-3,4′-dione (V).—To a solution of 700 mg. of the fluorobenzophenone IIIa in 20 ml. of *t*-butyl alcohol was added 12.3 g. of potassium carbonate in 88 ml. of water. The *t*-butyl alcohol was removed from the deep yellow solution by concentration under vacuum, and 2.80 g. of potassium ferricyanide in 35 ml. of water was added dropwise (5 min.) to the stirred solution. A heavy cream-colored precipitate formed. After 15 min. water was added and the mixture extracted with ethyl acetate. The organic extract was washed with cold dilute sodium hydroxide and salt solution and dried over magnesium sulfate. The neutral residue (610 mg.) crystallized from acetone–ether to give V, m.p. 222–225°; λ_{max}^{MeOH} infl. 320 mμ (ε 6800), λ_{max} 290 (31,900), infl. 247 mμ (ε 9500); λ_{max}^{chf} 5.82, 5.99, 6.12, 6.20, 6.52, 7.9 μ.

Anal. Calcd. for $C_{17}H_{15}O_6F$: C, 61.08; H, 4.52; F, 5.69. Found: C, 61.39; H, 4.91; F, 5.50.

(±)-7-Fluoro-4,6,2′-trimethoxy-6′-methylgris-2′-ene-3,4′-dione [(±)-7-Fluoro-7-dechlorogriseofulvin] (VI).—A solution of 465 mg. of the fluorodienone V in 50 ml. of 1,2-dimethoxyethane was added to a stirred suspension of 900 mg. of 10% palladium–Darco catalyst (pre-reduced) in 25 ml. of 1,2-dimethoxyethane in an atmosphere of hydrogen. Within 5 min., 0.9 equivalent of hydrogen was absorbed and the reaction was stopped. The catalyst was filtered and the solvent removed *in vacuo*. The residue was dissolved in 20 ml. of acetic acid and stirred with 800 mg. of zinc dust for 10 min. to convert any remaining V to base-soluble benzophenone IIIa. The zinc was removed by filtration, water was added, and the mixture was extracted with chloroform. The chloroform extract was washed with dilute sodium hydroxide (acidification of the basic extract and chloroform extraction gave 190 mg. of recovered benzophenone IIIa), salt solution, and dried over magnesium sulfate to give 280 mg. of neutral colorless material. Paper chromatography (mobile phase, benzene–cyclohexane 5:1; stationary phase, formamide) showed this to consist of VI contaminated with a small amount of a more mobile material, the fluorodihydro compound VII (following).

Column chromatography on 26 g. of alumina gave (±)-VI from the benzene–chloroform eluates (180 mg., 64% based on recovered III) prisms from acetone–ether, m.p. 209–211°; λ_{max}^{MeOH} 325 (4600), 290 (21,000), infl. 245 (14,100), 235 mμ (ε 15,000); λ_{max}^{chf} 5.83, 6.00, 6.06, 6.16, 6.49, 7.85 μ.

Anal. Calcd. for $C_{17}H_{17}O_6F$: C, 60.71; H, 5.09; F, 5.65. Found: C, 60.59; H, 5.40; F, 6.00.

From the benzene eluates (35 mg.) was obtained (±)-7-fluoro-4,6,2′-trimethoxy-6′-methylgrisane-3,4′-dione (VII), hexagonal prisms from acetone–ether, m.p. 180–182°; λ_{max}^{MeOH} 323 (4900), 288 (21,200), infl. 235 mμ (ε 9200); λ_{max}^{chf} 5.76, 5.87, 6.05, 6.14, 6.48, 7.82 μ.

Anal. Calcd. for $C_{17}H_{19}O_6F$: C, 60.41; H, 5.67. Found: C, 60.09; H, 5.68.

7-Chloro-6-hydroxy-4-methoxy-4′-isopropoxy-6′-methylgris-3′-ene-3,2′-dione (VIII).—A solution of 30 g. of norgriseofulvic acid[12] VIIa and 500 mg. of *p*-toluenesulfonic acid in 3200 ml. of isopropyl alcohol and 1200 ml. of toluene was refluxed with azeotropic removal of solvent and water of reaction at a rate of about 200 ml./hr. for 6 hr. The solvent removed by distillation was replaced by fresh toluene. At the end of 6 hr., the mixture was concentrated to dryness under vacuum, the resulting residue dissolved in ethyl acetate and the latter solution washed with 50% saturated sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness. Crystallization of the residue from acetone gave 7-chloro-6-hydroxy-4-methoxy-4′-isopropoxy-6′-methylgris-3′-ene-3,2′-dione (VIII), m.p. 282–284°; λ_{max}^{MeOH} 324 (10,000), 291 (17,200), 265 (21,200), 234 mμ (ε 16,400); λ_{max}^{chf} 5.91, 6.19, 6.23, 6.35 μ.

Anal. Calcd. for $C_{18}H_{19}O_6Cl$: C, 58.94; H, 5.22; Cl, 9.67. Found: C, 59.17; H, 5.12; Cl, 9.53.

(+)-7-Fluoro-4,6-dimethoxy-4′-isopropoxy-6′-methylgris-3′-ene-3,2′-dione (XIa).—To a stirred solution of 2 g. of the 4′-isopropoxy-6-phenol VIII in 18 ml. of dimethylformamide and 2 ml. of pyridine at 0°, perchloryl fluoride gas was added at the rate of 1–2 bubbles/sec. After 30 min., the temperature was raised to 25° and perchloryl fluoride addition continued at that temperature for 48 hr. At the end of that time, paper chromatography (chloroform–formamide) showed the disappearance of starting material and the predominant formation of a mobile (dienone) spot. Nitrogen was bubbled through the reaction mixture for 5 min., and 150 ml. of saturated salt solution and 2.5 *N* hydrochloric acid sufficient to make the mixture acidic were then added. The resulting mixture was extracted with 1:1 ethyl acetate–benzene. The organic extracts were combined, washed with cold 2% sodium hydroxide solution followed by saturated salt solution, dried over magnesium sulfate, and concentrated to dryness *in vacuo*. The neutral residue (800 mg.) thus obtained was a mixture containing the dienones IX and X (as shown by subsequent reactions); λ_{max}^{chf} 5.65, 5.82, 6.00, 6.30 μ. This mixture was dissolved in 10 ml. of acetic acid and 800 mg. of zinc dust added at 20° with stirring. After 30 min., an additional 800 mg. of zinc dust was added and stirring continued a further 90 min. The mixture was filtered and the filtrate concentrated almost to dryness. Saturated salt solution was added, followed by extraction with 1:1 ethyl acetate–benzene. The organic extract was washed with saturated salt solution, dried over magnesium sulfate, and concentrated to dryness to give a residue containing the phenols VIII and XI.

This phenolic residue in 10 ml. of tetrahydrofuran was methylated with diazomethane in ether at 0–5° for 15 hr. Following concentration to dryness, the residue was chromatographed over 100 g. of neutral alumina. The benzene eluates[18] were concentrated to dryness to give a residue which crystallized from ether–petroleum ether, 66 mg., m.p. 148–150°.

Anal. Calcd. for $C_{19}H_{21}O_6F$ (XIa): F, 5.2. Found: F, 4.3; Cl, 2.6.

On the basis of the halogen analysis, this material was a mixture containing ~75–80% XIa and ~20–25% VIIIa. This mixture was separated into its components by preparative paper chromatography employing 5 mg. per 15 cm. × 45 cm. sheet of Whatman no. 4 paper, ligroin–formamide system; the minor component was the known 7-chloro-4′-isopropyl ether VIIIa, m.p. 189–191°, undepressed with, and of identical mobility as, an authentic sample[13]; the major component was the slightly more polar 7-fluoro-4′-isopropyl ether XIa, m.p. 144–146°; λ_{max} 323 (5300), 288 (19,000), 268 (22,800), sh 230 mμ (ε 12,700); λ_{max}^{chf} 5.86, 6.00, 6.08, 6.23 μ.

Anal. Calcd. for $C_{19}H_{21}O_6F$: C, 62.60; H, 5.81. Found: C, 62.19; H, 5.68.

(+)-7-Fluoro-4,6,2′-trimethoxy-6′-methylgris-2′-ene-3,4′-dione (7-Fluoro-7-dechlorogriseofulvin) (VI).—A 20-g. sample of the phenol VIII was fluorinated, reduced, and methylated as in the previous experiment. The methylation product (~10 g.) was chromatographed over 370 g. of neutral alumina and the fractions (4.1 g.) containing VIIIa and XIa (paper chromatography, ligroin–formamide system) combined. A 2.8-g. sample of the latter material was refluxed for 1 hr. in 28 ml. of acetic acid and 6 ml. of 2 *N* sulfuric acid.[19] The mixture was concentrated to a small volume (25–30°) under vacuum, taken up in ethyl acetate, and extracted with 5% aqueous potassium bicarbonate. The bicarbonate extract was acidified with cold dilute hydrochloric acid, extracted with ethyl acetate, the latter dried over magnesium sulfate, and concentrated to dryness. The product (mixture of griseofulvic acids XII and XIII), on trituration with acetone–ether, deposited 100 mg. of crude crystalline 7-fluoro-7-dechlorogriseofulvic acid (XII), m.p. 233–236° (m.m.p. with authentic XIII of m.p. 252–257° was 231–246°). The crystalline material (100 mg.) and mother liquors (1.9 g.) were separately treated with diazomethane in tetrahydrofuran–ether at 0–5° for 16 hr. and taken to dryness under vacuum. The residue from methylation of the crystalline material crystallized from acetone–ether to give 22 mg. of nearly pure 7-fluoro-7-dechlorogriseofulvin (VI), m.p. 202–208°, as judged by paper chromatography (benzene–cyclohexane 1:10–formamide system). A probe of the methylation product from the mother liquors was separated by paper chromatography in this system into four components of which the most polar and most abundant had the same mobility as (±)-VI. It was followed in descending order by griseofulvin (XIV), iso-VI, and iso-XIV. A 200-mg. sample [5 mg. × 40 sheets 15 cm. × 45 cm. Whatman no. 4 paper] was chromato-

(18) The desired component was followed by paper chromatography (benzene–cyclohexane 1:5–formamide). In this system its mobility, ultraviolet absorption, and characteristic blue fluorescence were similar to those of VIIIa.

(19) Procedure of Belgian Patent 597,963, Glaxo Laboratories Ltd.; V. Arkley, J. Attenburrow, G. J. Gregory, and T. Walker, *J. Chem. Soc.*, 1260 (1962).

graphed, the most polar fluorescent band cut out, the paper triturated with methanol, and the methanol extract concentrated to near dryness. Water and chloroform were added; the chloroform extract was washed with water, dried over magnesium sulfate, and concentrated to dryness. The crystalline residue (52 mg.) on crystallization from acetone–ether gave pure (+)-7-fluoro-7-dechlorogriseofulvin (VI), m.p. 210–212°; $[\alpha]^{obs}D$ +316° (*c* 0.610); ultraviolet, infrared, n.m.r. spectra, and mobility on paper and alumina (thin layer chromatography) were identical with (±)-VI.

Anal. Calcd. for $C_{17}H_{17}O_6F$: C, 60.71; H, 5.09; F, 5.65. Found: C, 60.74; H, 5.30; F, 5.60.

Dicyanoketenimine (Cyanoform) and Its Reduction Products

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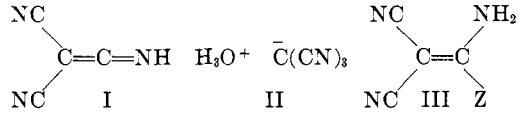
Received April 25, 1963

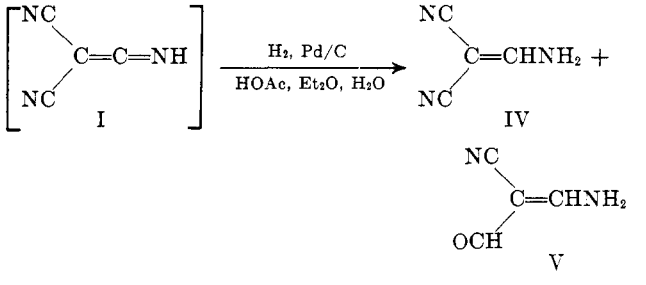
Aquoethereal cyanoform has been catalytically reduced to yield 3-amino-2-cyanoacrolein and 3-amino-2-cyanoacrylonitrile. Their properties and reactions are discussed, as is the mechanism of cyanoform reduction. High pressure reduction of 3-amino-2-cyanoacrylonitrile gives 2-amino-3,5-dicyanopyridine.

Cyanoform exists as dicyanoketenimine (I) in the free state and as hydronium tricyanomethanide (II) in aqueous or aquoethereal solutions.[1] Nevertheless, the addition of various active hydrogen compounds, HZ, to solutions of cyanoform, with the formation of compounds III, indicates the existence of an equilibrium between the ionized form and dicyanoketenimine. The



catalytic hydrogenation of aquoethereal cyanoform was undertaken in order to gain insight into the nature of this unusual ketenimine,[2] especially since catalytic reduction of such systems as $R_2C{=}C{=}NH$ or $R_2C{=}C{=}CH_2$, has, to our knowledge, not been studied.[3] It was expected that the ease of hydrogen uptake and the structure of the products would be of diagnostic value.

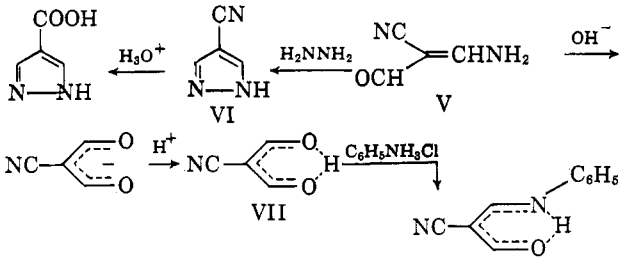
The reduction of aquoethereal cyanoform in the presence of acetic acid and 10% palladium-on-carbon catalyst proceeded very readily at room temperature and low hydrogen pressure. Two products were isolated. The major one was the expected 3-amino-2-cyanoacrylonitrile (IV) easily identified by comparison with authentic material.[4a,b] The other product, obtained in yields up to 50%, was assigned the structure 3-amino-2-cyanoacrolein (V) from spectral and chemical data as outlined.

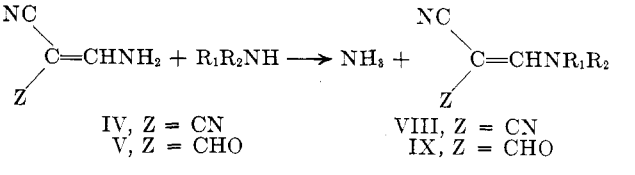


Analysis and molecular weight determination established the formula as $C_4H_4N_2O$. The infrared spectrum showed the presence of an NH_2 group and a conjugated nitrile. The n.m.r. spectrum had three peaks at 1.01, 1.35, and 2.15 τ with relative areas 1:2:1, assigned to the formyl, amino, and vinyl protons, respectively. This evidence was compatible only with structure V and was confirmed further by the following chemical studies.

The presence of the formyl group in V and its N-substituted derivatives was attested by positive, although sluggish, tests with 2,4-dinitrophenylhydrazine.[5]

Compound V reacted readily with hydrazine to form the new 4-cyanopyrazole (VI) identified by its hydrolysis to the known 4-pyrazolecarboxylic acid.[6] Mild alkaline hydrolysis of V yielded the sodium salt of cyanomalonaldehyde as a monohydrate which was converted to the free acid VII and to its reported monoanil.[7] Finally, both IV and V reacted with aliphatic amines to give N-substituted products, VIII and IX, the ultraviolet and n.m.r. spectra of which indicated considerable structural similarity.





(1) S. Trofimenko, *J. Org. Chem.*, **28**, 217 (1963).

(2) Only two other dinegatively substituted ketenimines are known: dialkylsulfonylketenimine [R. Dijkstra and H. J. Backer, *Rec. trav. chim.*, **73**, 569 (1954)] and dinitroketenimine [C. O. Parker, W. D. Emmons, H. A. Rolewicz, and K. C. McCallum, *Tetrahedron*, **15**, 79 (1962)]. Both are strong acids and resemble cyanoform in many respects.

(3) Catalytic hydrogenation of nonterminal allenes has been reported [W. R. Moore, *J. Am. Chem. Soc.*, **84**, 3788 (1962)]; so has the metal–ammonia reduction of, among others, terminal allenes [D. Devaprabrakhara and P. D. Gardner, *ibid.*, **87**, 648 (1963)].

(4) (a) O. Diels, H. Gärtner, and R. Kaack, *Ber.*, **77**, 3429 (1922); (b) M. J. Kamlet, *J. Org. Chem.*, **24**, 714 (1959).

(5) However, 3-dialkylaminoacroleins are reported not to condense with 2,4-dinitrophenylhydrazine [Z. Arnold and F. Sorm, *Collection Czech. Chem. Commun.*, **23**, 452 (1958)].

(6) R. G. Jones, *J. Am. Chem. Soc.*, **51**, 3994 (1948).

(7) F. C. Uhle and W. L. Jacobs, *J. Org. Chem.*, **10**, 81 (1945).