Experimental Section[14]

Velutin (4′,5-Dihydroxy-3′,7-dimethoxyflavone) (Ia).—A collection of *Ceanothus velutinus* was made in late October 1969, about 5 km north along the Lake Kachess Dam Road, near Snoqualmie Pass, Wash. The leaves were air-dried for 1 week, and then ground in a Wiley mill and extracted with hot pentane for 10 days. On standing, the dark solution deposited a yellow powder, which was collected, washed, dried, and crystallized from a large volume of ethyl acetate to yield the analytical sample (0.80 g, from 1.6 kg of leaves): mp 225–227° (lit.[10] 223–224°); R_f 0.66; ν_{max} 3440 (OH), 2950 (CH), 1660 (C=O), 1605 (C=C), and 847 cm^{-1} (1,2,3,5 tetrasubstitution); λ_{max} 238, 250, 268, and 348 mμ (log ε 4.04, 4.05, 4.01, and 4.16); δ 3.85 (OCH_3), 3.92 (OCH_3), 6.35 and 6.75 (6-H and 8-H), 6.90 (3-H), 7.01 (5′-H), 7.5–7.7 (6′,2′-H), and 12.93 (5-OH); mass spectrum 314 (parent), 284 (M − 30), and 137 ($C_7H_5O_3$). The flavone produced a brown color with ferric chloride, and a red-orange with magnesium–hydrochloric acid. The ultraviolet shifts with aluminum chloride (10%) were almost identical with those of 3′,7-di-*O*-methylluteolin.[10]

Anal. Calcd for $C_{17}H_{14}O_6 \cdot {}^1/_2H_2O$ (323.29): C, 63.15; H, 4.61. Found: C, 63.51; H, 4.29.

Treatment with acetic anhydride and a drop of sulfuric acid formed the diacetate (Ib), as colorless needles from benzene, mp 207° (lit.[12] 207°).

Methylation with dimethyl sulfate–potassium carbonate afforded luteolin tetramethyl ether (Ic), purified by sublimation at 175° (0.01 mm): mp 192–194° (lit.[15] 192–193°); mass spectrum 342 (parent), 313 (M − 29), 312 (M − 30), 181 ($C_9H_9O_4$), 180 ($C_9H_8O_4$), 162 ($C_{10}H_{10}O_2$), 152 ($C_8H_8O_3$), 147 ($C_9H_7O_2$), and 137 ($C_7H_5O_3$).

Demethylation with hydrogen iodide (49%) gave luteolin (Id), as yellow crystals from ethanol, mp 328–330° (lit.[15] 330–331°).

Registry No.—Ia, 25739-41-7.

Acknowledgment.—We thank the National Center for Urban and Industrial Health (Public Health Service Grant No. U1 00697) for the support of this work.

(14) Melting points are uncorrected. Microanalyses were provided by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Spectral measurements were made as follows: infrared (potassium bromide), ultraviolet (95% ethanol), and nuclear magnetic resonance (deuteriodimethyl sulfoxide, internal tetramethylsilane, 60 MHz). The mass spectrum was obtained on a double-focusing instrument. Thin layer chromatography employed silica gel G as the support, ethyl acetate as the developer, and iodine for detection.

(15) J. Gripenberg in "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., Macmillan, New York, N. Y., 1962, p 406.

Epoxidation of Griseofulvin. A New Reaction of the β-Methoxyenone System

HOWARD NEWMAN

Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

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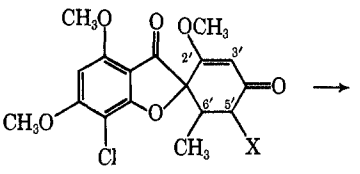
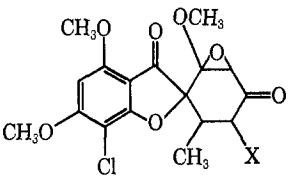
We would like to report that griseofulvin (**1**) and its 5′-bromo analog (**8**) are converted to their corresponding epoxy derivatives **2** and **9** in good yield by treatment with hydrogen peroxide and base. Epoxidation of **1** and its 5′-methylsulfonyl analog **5** was also achieved with benzoyl peroxide–methoxide in good yield but with poor conversion.

To the best of our knowledge this represents a new reaction of an enol ether of a β-diketone and would be expected to be generally applicable. We were led to this finding in the following manner.



1, X = H
5, X = SO_2CH_3
8, X = Br



2, X = H
5a, X = SO_2CH_3
9, X = Br

When we previously[1] attempted to introduce oxygen at C-5′ in griseofulvin (**1**) by allowing 5′-formylgriseofulvin (**3**)[2] to react as its sodium salt with benzoyl peroxide in methanol, we obtained the overoxidized product, 5′-hydroxydehydrogriseofulvin (**4**), presumably owing to the ready decarbonylation of an initially formed 5′-oxygenated-5′-formyl intermediate. We hoped to circumvent this difficulty by using 5′-methylsulfonylgriseofulvin (**5**) in place of **3**; however, we encountered another unexpected result.

Thus, on treating **5**, readily obtainable from 5′-methylthiogriseofulvin[3] by peracid oxidation, with **1** equiv of sodium methoxide in methanol followed by 1 equiv of benzoyl peroxide, we obtained a product which was indicated by its nmr spectrum to be a 2-component mixture, in approximately a 1:1 ratio, consisting of unreacted **5** and a new substance in which the C-2′–C-3′ double bond appeared to have been transformed. This was suggested by the appearance of a new OCH_3 signal in the spectrum at δ 3.27, 0.39 upfield from the OCH_3 in signal in **5**, and a decrease in intensity (to ~0.5) of the vinyl proton of **5**. Further characterization as detailed in the Experimental Section established its structure as the epoxide **5a**.

Treating griseofulvin (**1**) in a similar manner gave a comparable result. The new product was isolated by thick layer chromatography and was formulated as epoxygriseofulvin (**2**) on the basis of its spectral (ir, nmr, mass spectrum) and analytical data. Its nmr spectrum additionally indicated it be a single isomer.

A significant improvement in the conversion of **1** to **2** was achieved by using hydrogen peroxide–base, the reagent commonly employed for epoxidizing α,β-unsaturated ketones. (The epoxidation with benzoyl peroxide–methoxide is presumed to take place in a manner similar to that postulated for the hydrogen peroxide–base epoxidation,[4] the required benzoyl peroxy anion, $PhCOOO^-$, being generated by methoxide attack on benzoyl peroxide. The poorer conversion obtained with $PhCO–OOCOPh^-–OCH_3$ could be due to the

(1) H. Newman, *J. Heterocycl. Chem.*, **7**, 957 (1970).

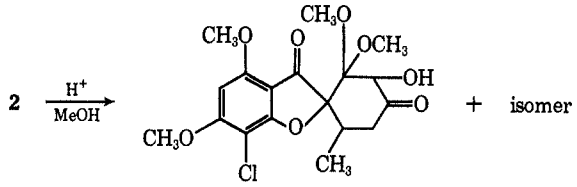
(2) H. Newman and T. L. Fields, *J. Org. Chem.*, **35**, 3156 (1970).

(3) (a) The facile preparation of this compound from **3** and methylthiotosylate[3b] will be published elsewhere shortly. (b) See R. C. Autrey and P. W. Scullard, *J. Amer. Chem. Soc.*, **90**, 4921 (1968).

(4) See the review on epoxy ketones by J. L. Pierre, *Ann. Chim. (Paris)*, 159 (1966).

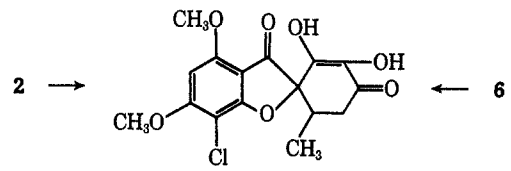
competitive destruction of the oxidizing species by another route.)

Treatment of compound **2** in methanol containing a very small amount of concentrated sulfuric acid at room temperature led to its immediate transformation to the dimethyl ketal **6** and an isomeric product in roughly equal amounts. The structure of **6** follows

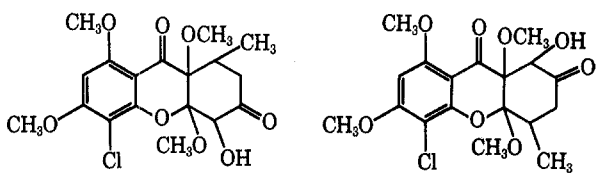


6

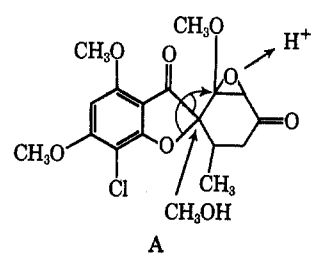
from its spectral (ir, nmr, mass spectrum) and analytical data (See Experimental Section) and its hydrolysis to 3′-hydroxygriseofulvic acid (**7**).[5] also obtained from the direct aqueous hydrolysis of **2**.



The isomeric product, indicated as such by its M^+ at m/e 400 in the mass spectrum and its analytical data, exhibits an nmr spectrum (See Experimental Section) which would be consistent with its formulation as the rearrangement product **8** or **8a** (no stereochemistry implied in the structures) and which could arise as indicated by the arrows in A, where epoxide opening is accompanied by migration of either the ring B oxygen or ring B carbonyl followed by methanolysis of the resulting electron deficient center.



8 **8a**



A

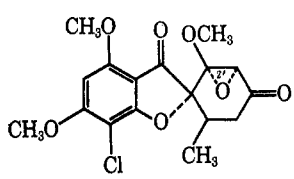
The formation of **8** or **8a** is interesting in that it represents a skeletal rearrangement of **2** under mildly acidic conditions. By contrast, the carbon framework of griseofulvin is stable to acid.[6]

The nmr signals of the two ketal OCH_3 groups in **6** were well separated, appearing at δ 3.57 and 3.40. It would appear not unreasonable to assign the higher field signal to the OCH_3 cis to the ring B carbonyl group, it being closer in this configuration to the shielding cone of this group.[7]

With regard to the stereochemistry of the epoxidation, it will become unequivocally known when an X-ray study of 5′-bromoepoxygriseofulvin **9** (by Dr. D. B. Cusulich of our laboratories) currently in progress will be completed. **9** was obtained by epoxidizing 5′-bromogriseofulvin (**8**) as described above, and was related to **2** by converting it to the common intermediate **6** with triphenylphosphine in methanol. The ketal **6** was isolated directly from the reaction mixture which proved to be acidic, the result of rapid acid-catalyzed opening of the initially formed reduction product **2**.

A chemical approach to the solution of the stereochemical problem was attempted, however, predicated on the nmr assignments made above for the two ketal OCH_3's in **6**. It was reasoned that acid-catalyzed opening of the epoxide in **2** in CD_3OH should lead, ideally in a completely trans diaxial opening, to the disappearance of one of the OCH_3 signals. The stereochemistry of the epoxide ring would then follow. The acidic conditions of the reaction and the methoxy substituent on the epoxide ring makes a ring opening *via* an SN1-like pathway more likely and the stereospecificity of the opening, therefore, questionable. It would, however, still appear reasonable to expect that, to the extent that one isomer does predominate, it would be that one arising from a trans diaxial opening.

The result of the experiment was that both OCH_3 signals were, in fact, present with the lower field signal predominating in a ratio of ~3:1. If one accepts the foregoing argument, one would conclude that the epoxide ring must have been α oriented (*i.e.*, trans to the ring B carbonyl) as in B resulting in a predominant approach of CD_3OH from the β face or cis to the ring B carbonyl. (In the process the stereochemistry of the OCH_3 at C-2′ is inverted.)



B

We however, emphasize again that the stereochemistry shown in B is at, this point, only tentative, based as it is on intuitively reasonable, but nevertheless unproven assumptions.

Experimental Section[8]

Epoxygriseofulvin (2). A. Hydrogen Peroxide–KOH.—To a cooled (ice water) stirred suspension of 2.8 g (0.008 mol) of griseofulvin (**1**) in 80 ml of methanol containing 5 ml of 30% H_2O_2 (~0.044 mol) was added ~400 mg of potassium hydroxide (pellets) (~0.007 mol). The reaction mixture was stirred in the cooling bath for 15 min, allowed to come to room temperature (with stirring) during 15 min, and then diluted with ice water,

(5) The tautomeric form shown is done so arbitrarily.

(6) J. F. Grove, J. MacMillan, T. P. C. Muholland, and M. A. T. Rogers, *J. Chem. Soc.*, 3949 (1952).

(7) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 28.

(8) Melting points are uncorrected. Nmr spectra were determined on a Varian A-60A spectrometer using tetramethylsilane as an internal standard and mass spectra on an AEI MS-9 spectrometer. Thin layer chromatograms were run on phosphor-containing silica gel plates (Analtech, Inc., Wilmington, Del.); thick layer chromatograms were run on 2-mm silica gel plates (E. Merck Ag., Darmstadt, Germany; distributed by Brinkmann Instrument Inc., Westbury, N. Y.).

and the colorless solid was collected by filtration, washed well with water, and air-dried, yield 2.8 g. The crude product was heated in boiling ethyl acetate and the mixture filtered to separate an insoluble gummy material. Addition of *n*-hexane to the colorless filtrate caused a colorless crystalline solid to separate, yield 1.75 g. Thin layer chromatography indicated very minor contamination with unreacted griseofulvin, which was removed most efficiently by partition chromatography (on Celite 545 using heptane–$CHCl_3$–methanol–water 50:8:16:1) to yield 1.17 g (41%) of epoxygriseofulvin (**2**), mp 142–160°, which showed a single spot (R_f ~0.6) on tlc (PhH–EtOAc 1:1) and exhibited ir, nmr, and mass spectra identical with those of the analytical sample of **2** prepared as described below.

B. Benzoyl Peroxide–Methoxide.—A stirred suspension of 0.35 g (0.001 mol) of griseofulvin (**1**) and 0.48 g (0.002 mol) of benzoyl peroxide in 10 ml of methanol at room temperature was treated with 2 ml of ~1 *M* NaOMe in methanol (0.002 mol). The mixture was stirred at room temperature for 15 min (after 10 min. the original strongly basic solution was essentially neutral) and filtered to separate 150 mg of insoluble solid corresponding in R_f to griseofulvin. The slightly turbid filtrate was poured into ice water and the solid which formed (during 15 min) was collected and air-dried to yield 130 mg of product which showed two spots on tlc (PhH–EtOAc 1:1), R_f ~0.45 and 0.6, the former corresponding to that of griseofulvin. The products corresponding to the two spots were separated by thick layer chromatography using PhH–EtOAc 1:1 for development and were obtained in A a 1:2 ratio (faster:slower). The colorless faster running product, epoxygriseofulvin (**2**), melted at 149–155° after triturating with methanol: λ_{max}^{KBr} 5.80 and 5.87 μ; $\delta_{TMS}^{CDCl_3}$ 6.16 (aromatic H), 4.05, and 4.00 (aromatic OCH_3's), 3.80 (epoxy H), 3.24 (epoxy OCH_3), 2.65–2.46 (mainly 2.65, C-5′ and C-6′ H's), and 0.83 (doublet J = 6 Hz, C-6′ CH_3). The mass spectrum showed an M^+ at m/e 368 (with the expected 370 peak at *ca.* one-third the intensity owing to Cl isotope 37).

Anal. Calcd for $C_{17}H_{17}O_7Cl$ (368.77): C, 55.50; H, 4.62; Cl, 9.66. Found: C, 55.82; H, 4.82; Cl, 9.72.

5′-Methylsulfonylgriseofulvin (**5**).—A solution of 2 g (0.005 mol) of 5′-methylthiogriseofulvin[3] in 100 ml of methylene chloride was treated with 2 g (0.01 mol) of 85% *m*-chloroperbenzoic acid (K & K Laboratories Inc., Plainview, N. Y.) at room temperature. After 1 hr, the reaction mixture was diluted with methylene chloride and washed with cold aqueous sodium bisulfite, bicarbonate, dried, and evaporated to yield a gummy residue which solidified on heating in methanol: yield 1.4 g (64%) of colorless solid; mp 170–173°; λ_{max}^{KBr} 5.83 (s), 6.02 (m), and 6.17, 6.27 (vs); $\delta_{TMS}^{CDCl_3}$ 6.16 (aromatic H), 5.63 (vinyl H), 4.05 and 3.99 (aromatic OCH_3's), 3.66 (vinyl OCH_3), 3.28 ($-SO_2CH_3$), and 1.25 (doublet, J = 6 Hz, C-6′ CH_3).

Anal. Calcd for $C_{18}H_{19}ClSO_3$ (430.86): C, 50.17; H, 4.44; S, 7.44; Cl, 8.23. Found: C, 49.50; H, 4.46; S, 7.05; Cl, 8.37.

5′-Methylsulfonylepoxygriseofulvin (**5a**).—The addition of 0.52 ml (0.52 mmol) of ~1 *M* NaOMe in methanol to a suspension of 220 mg (0.52 mmol) of **5** in 5 ml of methanol gave a yellow solution to which 126 mg (0.52 mmol) of benzoyl peroxide was added (with stirring) at room temperature. A new solid separated 1–2 min after stirring at room temperature for 15 min, and the solid was collected and washed with methanol to yield 148 mg of product, mp 170–176°, whose nmr spectrum in chloroform showed, in addition to the signals corresponding to the various protons in starting **5**, new signals at δ 3.27 (epoxy OCH_3, *cf.* corresponding chemical shift for these protons in **2** and **9**), 3.09 ($-SO_2CH_3$ in **5**), and 1.11 (doublet, J = 6 Hz, C-6′–CH_3 in **5a**) corresponding to the epoxide **5a**. The chemical shift of the new epoxy H is most probably part of the 3.99 aromatic OCH_3 signal as indicated by the increase in intensity of this signal relative to that of the other aromatic OCH_3 at 4.05. (The two were essentially equal in intensity in starting (**5**). The ratio of the two products, estimated from the relative peak intensities, was 1:1. The two compounds ran very close to each other on tlc (PhH–EtOAc 1:1), the front of the slower running **5** touching the rear of the faster running **5a**.

By recycling the product mixture twice more as described above, virtually all the starting **5** was converted to **5a** as indicated by nmr spectral analysis. The product thus obtained (34 mg) melted at 177–180° (shrinks 174°).

Anal. Calcd for $C_{18}H_{19}ClSO_9$ (446.86): C, 48.38; H, 4.29; Cl, 7.94; S, 7.18. Found: C, 48.54; H, 4.20; Cl, 7.96; S, 6.81.

5′-Bromoepoxygriseofulvin (**9**).—A stirred suspension of 1 g (0.0023 mol) of 5′-bromogriseofulvin (**8**) in 40 ml of methanol containing 2.5 ml (~0.0022 mol) of 30% H_2O_2 was cooled in ice water and treated with 200 mg (0.0035 mol) of potassium hydroxide (pellets). After stirring in the cold for 15 min (the system was homogeneous after ~5 min), the mixture was poured into ice water and extracted first with methylene chloride and then with methylene chloride–ether. The organic extracts were washed with aqueous bisulfite, dried, and evaporated to yield 0.47 g of a pale yellow crystalline solid which showed a single spot on tlc (PhH–EtOAc 1:1), R_f ~0.5, and which melted at 157–160° after recrystallization from ethyl acetate (colorless product): λ_{max}^{KBr} 5.80 and 5.89 μ; $\delta_{TMS}^{CDCl_3}$ 6.16 (aromatic H), 4.35 (doublet, J = 10 Hz, C-5′ H), 4.05 and 4.00 (aromatic OCH_3's), 3.27 (epoxy OCH_3), and 1.00 (doublet, J = 6 Hz, C-6′ CH_3).

Anal. Calcd for $C_{17}H_{16}O_7BrCl$ (447.68): C, 45.61; H, 3.60; Cl, 7.92; Br, 17.85. Found: C, 45.62; H, 3.62; Cl, 7.79; Br, 17.56.

Treatment of Epoxygriseofulvin (2) with Dilute Methanolic Acid. Formation of the Dimethyl Ketal 6 and 5-Chloro-4-hydroxy-1,4,4a,9a-tetrahydro-4a,6,8,9a-tetramethoxy-1-methylxanthene-3(2H),9-dione (**7**).—To 5 ml of commercial grade absolute methanol containing 1 drop (Pasteur pipet) of concentrated sulfuric acid was added 170 mg (0.46 mmol) of epoxygriseofulvin, (**2**) at room temperature. A colorless homogeneous solution formed virtually instantaneously. After 4 min at room temperature, the colorless solution was poured into ice water and the mixture was extracted with methylene chloride. The methylene chloride extract was washed with aqueous bicarbonate, dried, and evaporated to yield ~140 mg of a light yellow gum indicated by tlc (PhH–EtOAc 1:1) to be a two component mixture which was separated by partition chromatography on Celite 545 using heptane–chloroform–methanol–water 50:8:16:1.

Faster Moving Component 6.—A colorless solid, 63 mg, had mp 191–193.5°; λ_{max}^{KBr} 5.81, 5.92 (s), and 6.20, 6.30 μ (vs); $\delta_{TMS}^{CDCl_3}$ 6.17 (aromatic H), 5.27 (doublet, J = 7 Hz which collapses to a singlet on proton exchange, C-3′ H), 4.03 and 4.00 (aromatic OCH_3's), 3.57 (C-2′ OCH_3 trans to ring B carbonyl), 3.40 (C-2′ OCH_3 cis to ring B carbonyl), 0.88 (doublet J = 6 Hz C-6′ CH_3); mass spectrum showed M^+ at m/e 400 (with the expected 402 peak at one-third the intensity); R_f ~0.6 (tlc PhH–EtOAc 1:1).

Anal. Calcd for $C_{18}H_{21}O_8Cl$ (401.82): C, 53.93; H, 5.28; Cl, 8.85. Found: C, 54.22; H, 5.31; Cl, 8.78.

Slower Moving Component 7.—A solid, 52 mg, was rendered colorless by triturating with a small amount of methanol: mp 217–221°; λ_{max}^{KBr} 5.80 (infl) (m), 5.90 (s), and 6.20, 6.30 μ (vs); $\delta_{TMS}^{CDCl_3}$ 6.13 (aromatic H), 4.00 and 3.95 (aromatic OCH_3's), 3.54 and 3.27 (the two junction OCH_3's), 0.93 (doublet, J = Hz, C-6′ CH_3). On proton exchange, a somewhat broadened singlet appeared at δ 4.95 and is assigned to the proton α to the OH group; mass spectrum showed M^+ at m/e 400 [and at 402 (1/3 as intense as that at 400)]; R_f ~0.55 (tlc, PhH–EtOAc 1:1).

Anal. Found: C, 53.46; H, 5.43 (calcd as for **6** above).

Repeating the above reaction in CD_3OD gave **6** in which the C-2′ OCH_3 signals in the nmr spectrum appeared in a ratio of 3:1, lower field (δ 3.57, higher field (δ 3.40). (**6** was separated in this experiment by thick layer chromatography using PhH–EtOAc 1:1 for development.)

Refluxing **2** in neat CD_3OD left it unchanged.

Hydrolysis of Epoxygriseofulvin (**2**). **Formation of 3′-Hydroxygriseofulvic Acid** (**7**).—A suspension of 1.75 g of epoxygriseofulvin (**2**) (slightly contaminated with griseofulvin) in 10 ml of commercial grade spectro quality dioxane and 10 ml of 1 *N* HCl was heated on the steam bath with swirling for 1.5 min. A homogeneous system formed. After allowing the solution to cool for 2 min, it was poured into ice water and the colorless solid collected. The product was dissolved in aqueous bicarbonate, and the solution was washed with methylene chloride–ether (to remove the griseofulvin contaminant; griseofulvin does not hydrolyze under these conditions) and reacidified. The precipitated solid was collected washed well with water and air-dried: yield 0.65 g; mp 155–165° (foaming; sample underwent prior shrinking and wetting); λ_{max}^{KBr} 3.0 (broad, s), 5.91 (s), and 6.20, 6.30 μ (vs); $\delta_{TMS}^{CDCl_3-DMSO-d_6}$ 6.20 (aromatic H), 4.05 and 3.99 (aromatic OCH_3's), 3.5–2.3 (methylene and methine H's), 1.00 (C-6′ CH_3).

Anal. Calcd for $C_{16}H_{15}O_7Cl \cdot 2H_2O$ (390.77): C, 49.17; 4.90; Cl, 9.07; H_2O; 9.2. Found: C, 49.81; H, 3.97; Cl, 9.78; H_2O; 7.6.

3′-Hydroxygriseofulvic Acid 7 from the Hydrolysis of 6.—Half of a solution of 14 mg of **6** in 0.3 ml of commercial grade spectro quality dioxane and 0.5 ml of 1 *N* HCl was heated on the steam bath in an open test tube for 15 min and water was added. The gum which separated, rapidly solidified. The light yellow solid was collected and washed well with water. It was soluble in aqueous bicarbonate and showed an infrared spectrum which was essentially identical with that of 3′-hydroxygriseofulvic acid (**6**) obtained above from the hydrolysis of epoxygriseofulvin (**4**).

(The other half of the solution was kept at room temperature for 16 hr and then poured into water. The solid which separated showed a tlc and infrared spectrum identical with those of starting **6**.)

Formation of 6 by Reductive Hydrolysis of 5′-Bromoepoxygriseofulvin (9).—A suspension of 1.1 g (0.0025 mol) of **9** and 0.65 g (0.0025 mol) of triphenylphosphine in 20 ml of methanol was heated on the steam bath for 1 min during which time the system became homogeneous. After allowing it to cool for 5 min, the reaction mixture was poured into ice water and the organic product extracted with ether–methylene chloride. Drying and evaporating the organic extract left 1.49 g of a light yellow foam which showed one major new spot on tlc (PhH–EtOAc 1:1) corresponding in R_f to that of **6** prepared above. The product corresponding to this spot was separated by thick layer chromatography (of *ca.* a 300-mg sample) using PhH–EtOAc 1:1 for development and was identified as **6** by ir, nmr, and mass spectral comparisons.

Registry No.—**2**, 25966-68-1; **5**, 25966-69-2; **5a**, 25966-70-5; **6**, 26039-32-7; **7**, 25966-71-6; **9**, 25966-72-7.

Acknowledgments.—I thank Messrs. W. Fulmor and G. Morton (nmr) and Dr. G. Van Lear (mass spectrum) and staffs for the spectral data, Mr. L. Brancone and staff for the microanalyses, and Mr. C. Pidacks and staff for the partition chromatography. I also thank Dr. R. B. Angier for his interest.

Action of *N*-Halosuccinimide on 8-Quinolinol[1]

HERMAN GERSHON* AND MAYNARD W. MCNEIL

Boyce Thompson Institute for Plant Research, Yonkers, New York 10701

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A reinvestigation of the action of *N*-halosuccinimide on bis(8-quinolinolato)copper(II) revealed that, on monochlorination, a mixture of 5- and 7-chloro chelates resulted. On monobromination, only the 5-bromo chelate formed, and on monoiodination, the 7-iodo chelate was obtained.[2] This was in disagreement with the results of Prasad, *et al.*,[3] who reported that on monohalogenation of the same chelate with *N*-halosuccinimide, substitution took place exclusively in the 5 position. On the basis of dihalogenation studies of metal chelates with elemental chlorine and bromine and a list of reactivities of free and coordinated ligands found in the literature, Maguire and Jones[4] concluded that, with the exception of tropolone, there are no authenticated instances where coordination changes the reactive position of an aromatic ligand toward electrophilic reagents. Hix and Jones[5] attempted to further strengthen this view by citing 109 reactions tabulated by Blatt[6] and 73 additional reactions listed by Berliner[7] where coordination does not affect orientation. Competitive bromination studies of mixtures of 8-quinolinol and its chelates with iron(III), chromium(III), and cobalt(III) using insufficient bromine indicated that the rate of bromination of the chelates was about 35 times as rapid as that of the free ligands.

The present work was undertaken to further study what appeared to be the anomalous orientation of halogen when bis(8-quinolinolato)copper(II) was treated with *N*-halosuccinimide.[2] It was also of interest to reexamine the concept that chelation does not affect orientation of substituents in electrophilic substitution of aromatic ligands.

To approach the first problem, 8-quinolinol was reacted with *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and *N*-iodosuccinimide (NIS) in chloroform, and the molar ratios of halogenating agent to substrate were 1:1, 2:1, and 3:1. The reaction time was 3 hr and two reaction temperatures were employed, ambient and 40–60°. The rationale for this approach and the identification and quantitation of the products were previously discussed.[2]

Table I contains the results obtained from the halogenation of 8-quinolinol with *N*-halosuccinimide. It

TABLE I

ACTION OF *N*-HALOSUCCINIMIDE ON 8-QUINOLINOL IN CHLOROFORM

Halogenating agent NCS[a]	Molecular ratio of *N*-halosuccinimide to 8-quinolinol	Temp, °C	Products, % Ox[b]	5-ClOx	7-ClOx	5,7-Cl_2Ox
	1	ambient	95	1	4	0
	2	ambient	94	1	5	0
	3	ambient	94	1	5	0
	1	40–60	82	3	15	Tr[c]
	2	40–60	81	4	15	Tr
	3	40–60	77	6	17	Tr
NBS			Ox	5-BrOx	7-BrOx	5,7-Br_2Ox
	1	ambient	16	14	50	20
	2	ambient	0	0	0	100
	3	ambient	0	0	0	100
	1	40–60	14	12	58	16
	2	40–60	0	Tr	Tr	99
	3	40–60	0	0	0	100
NIS			Ox	5-IOx	7-IOx	5,7-I_2Ox
	1	ambient	Tr	94	Tr	5
	2	ambient	Tr	7	Tr	92
	3	ambient	0	Tr	0	99
	1	40–60	12	77	0	11
	2	40–60	Tr	10	0	90
	3	40–60	0	Tr	0	99

[a] NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide. [b] Ox = 8-quinolinol. [c] Tr = trace (<1%).

* To whom correspondence should be addressed.

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