The KOH-catalyzed condensations of indene with aldehydes were carried out by adding KOH in EtOH gradually to a boiling soln of equimolar quantities of aldehyde and indene until a very dark color change appeared, then boiling for 30 min, cooling, filtering, and recrystallizing. Julolidene aldehyde, however, was difficult to condense with indene by this method, but condensed well when piperidine acetate in PhMe was the catalyst.[7] We have investigated the condensation method with the results in Table III. Unless otherwise indicated, 0.050 mole of aldehyde and 0.050 mole of indene were refluxed 10 hr in PhMe with catalyst. The soln was chilled and filtered, and then washed with 100 ml 50% MeOH, dried, and weighed. In most cases yields were only a little larger after 10 hr heating than after 5 hr. The Dean–Stark trap continued to collect a little $H_2O$.

(1) The fact that increasing indene:aldehyde ratio increased the yield slightly suggests that a by-product may be formed from 2 moles of aldehyde per mole of indene. (2) PhMe appeared much better than $C_6H_6$ or xylene. (3) Increasing the amounts of AcOH and of piperidine to 0.05 mole increased the yield. (4) Decreasing amounts of AcOH and of piperidine reduced the yields. (5) Pyrrolidine was slightly less useful than piperidine; hexamethyleneimine slightly more effective than piperidine. (6) $Bu_2NH$ was less effective, morpholine much less effective, triethylenediamine and pentylamine were ineffective. (7) Propionic acid was a little slower and succinic acid about equal to AcOH, but formic, boric, and $H_3PO_4$ acid were ineffective. (8) $Ac_2O$ in place of AcOH reduced the yield.

The Schiff base was prepared by heating a mixture of equimolar quantities of 1-(4-aminobenzylidene)indene and 4-dimethylaminobenzaldehyde 30 min in an oil bath at 125°. The methiodide of I was prepared by heating a soln of 5 g of I and 1.85 g of MeI in 50 ml of $PhNO_2$ for 8 days at 50°.

1-(4-Guanylaminobenzylidene)indene was formed by dropwise addition of a 50% aq soln of cyanamide to a boiling soln of 1-(4-aminobenzylidene)indene·HCl in *n*-BuOH, cooling, filtering, removing excess starting material by extraction with $C_6H_6$, dissolving in MeOH, making basic with NaOH, evaporating to dryness, and recrystallizing from *i*-$Pr_2O$, then from $C_6H_6$. 1-(4-Methylguanylbenzylidene)indene was prepared similarly, but the reaction mixture was refluxed for 2 hr. Its water solubility was than 2 mg/ml at room temp.

In the diazotization of 1-(4-aminobenzylidene)indene, a soln of 13.1 g of 1-(4-aminobenzyeidene)indene in 180 ml of AcOH and 12 g of 12 *M* HCl and 100 ml of ice $H_2O$ was diazotized at 0° by adding 4.2 g of $NaNO_2$ in 60 ml of ice and $H_2O$ slurry. This mixture was then added gradually to 800 ml of 25% $Me_2NH$, keeping the temp about 5°. The ppt was filtered and washed with $H_2O$.

The urea derivative was prepared by adding 0.040 mole of KCNO to 0.040 mole of 1-(4-aminobenzylidene)indene in 100 ml of glacial AcOH, allowing the mixture to stand for 1 hr, adding gradually to 200 ml of $H_2O$, and filtering. The ppt was washed with 400 ml of $H_2O$, dried, and extracted with hot $C_6H_6$ to remove $C_6H_6$-soluble starting material. The solid was dissolved in hot *i*-OPrH and $H_2O$ was added to the soln until just cloudy, then the soln was chilled and filtered.

(7) E. D. Parker and A. Furst, *J. Org. Chem.*, **23**, 201 (1958).

## 5′-Diazogriseofulvin

THOMAS L. FIELDS, HOWARD NEWMAN,* AND ROBERT B. ANGIER

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

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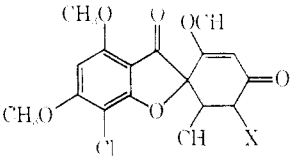
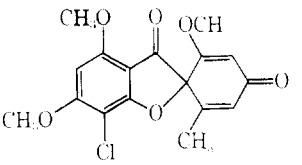
In continuing with our program to prepare analogs of the highly active antifungal drug griseofulvin[1] (**1**) we describe here the preparation of 5′-diazogriseofulvin (**2**) and a few of its transformations. Compound **2** was particularly attractive as a potential intermediate for the preparation of a variety of 5′-griseofulvin derivatives as a result of our finding[1] that 5′-bromogriseofulvin (**3**) failed to undergo the usual displacement reactions of α-halo ketones.

The preparation of **2** was achieved by allowing the readily available 5′-formylgriseofulvin[1] (**3a**) to react with tosylazide[2] in $CH_2Cl_2$ in the presence of $Et_2NH$.[3]



1. X = H
2. X = $N_2$, no 5′-H
3. X = Br
3a. X = CHO
4. X = OCOCH
7. X = SCOCH



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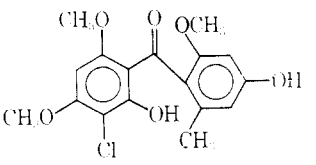


6

An attempt to convert **2** into 5′-acetoxygriseofulvin (**4**) with AcOH gave a rather complex mixture which was partially resolved by partition chromatography into a mixture of **4** and dehydrogriseofulvin **5**,[4] the major products of the reaction. Brief treatment of the mixture of **4** and **5** with Zn and AcOH converted the latter into the base-soluble phenol **6**[4] thus permitting the isolation of 5′-acetoxygriseofulvin (**4**) obtained as a mixture of cis–trans (6′-$CH_3$ *vs.* 5′-$OCOCH_3$) epimers in a 30:70 ratio (cis:trans).

With thioacetic acid, **2** was converted into 5′-thioacetoxygriseofulvin (**7**), indicated by nmr spectroscopy to be essentially a single isomer (trans 6′-$CH_3$/5′-SAc). No dehydrogriseofulvin appears to have been formed.

An attempted conversion of **2** into the 5-membered ring C derivative **8** by an Arndt–Eistert reaction using $Ag_2O$ in refluxing MeOH[5] gave instead a mixture consisting of 5′-methoxygriseofulvin (**9**) and dehydrogriseofulvin (**5**). An attempt to effect this rearrangdment photochemically[6] gave a complex mixture which could not be resolved.[7]

* To whom correspondence should be addressed.

(1) For previous papers in this series see H. Newman and T. Fields, *J. Org. Chem.*, in press, and ref cited therein.

(2) W. von E. Doering and C. H. DePuy, *J. Amer. Chem. Soc.*, **75**, 5955 (1953). Tosyl azide is now commercially available from Eastman Organic Chemicals, Rochester, N. Y.

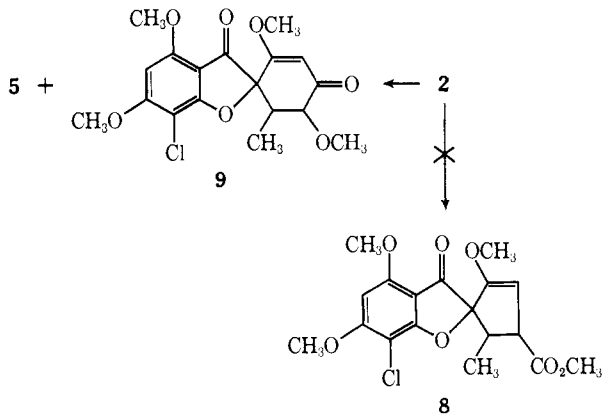
(3) M. Rosenberger, P. Yates, J. B. Hendrikson, and W. Wolf, *Tetrahedron Lett.*, 2585 (1964).

(4) D. Taub, C. H. Kuo, H. L. Slates, and N. C. Wendler, *Tetrahedron*, **19**, 1 (1963).

(5) W. E. Bachmann and W. S. Struve, *Org. React.*, **1**, 38 (1942); W. Kirmse, "Carbene Chemistry," Academic, New York, N. Y., 1964, p 119.

(6) See A. Schonberg, G. O. Schenck, and O. A. Neumuller "Preparative Organic Photochemistry" 2nd ed, Springer-Verlag, New York, N. Y., 1968, Chapter 32, p 295.

(7) For a review of the various reactions α-diazoketones undergo see F. Weygand and H. J. Bestmann, "Newer Methods of Preparative Organic Chemistry," Vol. III, Academic Press, New York, N. Y., 1964, p 451.




**Biological Data.**—Table I lists the *in vitro* antifungal activity data for the compounds indicated as determined by the agar dilution method.

TABLE I
*In Vitro* ANTIFUNGAL ACTIVITY DATA, MINIMAL INHIBITORY CONCENTRATIONS IN μg/ml[a,b]

| Compound | Ca | Cn | Mc | Mg | Pj | Tt | Tm | Tr |
|---|---|---|---|---|---|---|---|---|
| 1 | — | — | 1 | 1 | — | 10 | 2.5 | 1 |
| 2 | — | — | 5 | 10 | — | 25 | 25 | 10 |
| 3 | — | — | | 10 | — | 10 | 25 | 25 |
| 3a | — | — | 5 | 50 | — | 25 | 25 | 10 |
| 4[c] | --- | --- | --- | --- | --- | --- | --- | --- |
| 7 | — | — | 50 | 100 | — | — | — | 100 |
| 9[c] | --- | --- | 100 | 100 | --- | 100 | 50 | 50 |

[a] A solid dash denotes inactivity at 250 μg/ml; a broken dash denotes inactivity at 100 μg/ml; a blank indicates not tested. [b] The initials heading the columns represent the following fungi (from left to right) *Candida albicans*, *Cryptococcus neoformans*, *Microsporum canis*, *M. gypseum*, *Phialophthora jeanselmei*, *Trichophyton tonsurans*, *T. rubrum*, and *T. mentagrophytes*. [c] See ref 9.

As can be seen, the antifungal activity exhibited by these compounds is significantly less than that of grseiofulvin (**1**) This considerable activity difference was also observed on further *in vivo* evaluation (otpical, Carbowax) against either *Microsporum canis* or *Trichophyton mentagrophytes*.

### Experimental Section[8]

**5'-Diazogriseofulvin (2).**—$Et_2NH$ (219 mg, 3 mmoles) was added dropwise to a cooled solution (10°) of 5'-formylgriseofulvin (1.14 g, 3 mmoles) and *p*-tosylazide[2] (0.59 g, 3 mmoles) in 35 ml of $CH_2Cl_2$. The reaction mixture was stirred at room temp for 1 hr and then poured into 100 ml of $H_2O$. The organic layer was sepd and the aq layer was extracted 3 times with 70-ml portions of $CH_2Cl_2$. The combined extracts were washed with satd NaCl solution, dried ($Na_2SO_4$), and concd *in vacuo* to a yellow solid. The ir spectrum of this material exhibited typical diazo absorption at 4.80 μ. Tlc showed a mixture of starting material plus a new less polar spot. The crude diazo compd was taken up in 50 ml of $CH_2Cl_2$ and the starting 5'-formylgriseofulvin was removed by extraction with 0.5 *N* NaOH. Removal of the solvent *in vacuo* gave a yellow oil. Crystallization from EtOH gave 115 mg (10%) of product, which darkened at 160°, liquified at 175°; $\lambda_{max}^{KBr}$ 4.80 (s) (diazo). *Anal.* ($C_{17}H_{15}ClN_2O_6$) H, Cl; C: calcd, 53.90; found, 53.06; N, calcd. 7.39; found, 6.84. Attempts at further purification by recrystallization from MeOH resulted in a decrease in the N content of the product.

**5'-Acetoxygriseofulvin (4) (Mixture of Cis and Trans).**—5'-Diazogriseofulvin (**2**) (1.9 g, 5 mmoles) was added portionwise with stirring to 6 ml of glacial AcOH. The addition was accompanied by a slight evolution of gas and a mild exotherm. The reaction was stirred at room temp for 2 hr and then poured into 100 ml of $H_2O$. The white solid which pptd was collected by filtration, washed ($H_2O$), and dried *in vacuo* over $P_2O_5$. The yield of crude material was 1.6 g. Tlc ($C_6H_6$–EtOAc 1:1) and nmr indicated this to be a complex mixture containing the isomeric 5'-acetoxy griseofulvins and dehydrogriseofulvin. A portion of this mixture (1.2 g) was subjected to partition chromatography on 800 g of Celite using the system hexane–$CHCl_3$–MeOH–$H_2O$, 50:8:16:1. The majority of the eluted material came off in the 10th, 11th, and 12th hold back vol (390 mg). The nmr spectrum of this material indicated the epimeric 5'-acetoxygriseofulvins plus some dehyrogriseofulvin. This mixture was slurried in 5 ml of glacial AcOH and 400 mg of Zn dust was added. After swirling for 5 min, the mixture was dild with 35 ml of $CH_2Cl_2$ and the insolubles were removed by filtration. The filtrate was extracted with two 50-ml portions of 1 *N* NaOH. The organic layer was washed ($H_2O$), dried, and concd *in vacuo* to give 145 mg (9.6%) of the epimeric 5'-acetoxygriseofulvins, mp 115–175°. The nmr spectrum indicated a trans:cis ratio of 70:30;[9] $\lambda_{max}^{KBr}$ 5.72 (m), (OAc); $\delta_{TMS}^{CDCl_3}$ 2.18 [$COCH_3$ (trans)], 1.98 [$COCH_3$ (cis)], 1.27 [doublet, $J$ = 6 Hz, 6'-$CH_3$ (cis)], 0.97 [doublet, $J$ = 6 Hz, 6'-$CH_3$ (trans)]. *Anal.* ($C_{19}H_{19}ClO_8$) C, H, Cl.

The combined alkaline extracts were adjusted to pH 5.5. The resultant suspension was extracted with $CH_2Cl_2$. The organic extracts were washed ($H_2O$), dried, and concd *in vacuo* to give 90 mg (7.2%) of 3-chloro-2-hydroxy-4,6-dimethoxy-4'-hydroxy-2'-methoxy-6'-methylbenzophenone (**6**), mp 206–208°. The ir and nmr spectra were identical with those of an authentic sample.[4]

**5'-Thioacetoxygriseofulvin (7).**—A solution of 5'-diazogriseofulvin (190 mg, 0.5 mmole) in 1 ml of thiolacetic acid was stirred at room temp for 1 hr. The solution was dild with 20 ml of $CH_2Cl_2$ and washed 3 times with 1 *N* NaOH and 3 times with $H_2O$. The organic layer was dried and concd *in vacuo* to a yellow gum. Purification was achieved by thick-layer chromatography on silica gel using EtOAc for development. The yield of analytically pure **7** was 63 mg (30%); mp 213–216°; $\lambda_{max}^{KBr}$ 5.83 (s), 5.98 (m), $\delta_{TMS}^{CDCl_3}$, 2.37 ($SCOCH_3$). *Anal.* ($C_{19}H_{19}SClO_7$) C, H, Cl, S.

**Attempted Arndt–Eistert Reaction of 5'-Diazogriseofulvin. Formation of 5'-Methoxygriseofulvin and Dehydrogriseofulvin.**—A solution of 5'-diazogriseofulvin (190 mg, 0.5 mmole) in 50 ml of MeOH was brought to reflux and 85 mg of $Ag_2O$ added. After 30 min, an additional 85 mg of $Ag_2O$ was added. After a reflux period of 1 hr, the insolubles were removed by filtration and the filtrate was concd *in vacuo* to a red glass. This crude material was slurried in 3 ml of glacial AcOH and 200 mg of Zn dust was added. After swirling at room temperature for 10 min the mixture was dild with 50 ml of $CH_2Cl_2$ and filtered. The $CH_2Cl_2$ filtrate was extracted with 60 ml of 1 *N* NaOH, washed ($H_2O$), dried, and concd *in vacuo* to a glass. Purification by thick-layer chromatography (silica gel; $C_6H_6$–EtOAc, 1:1) gave 19 mg (10%) of 5'-methoxygriseofulvin. The product was identified by comparison of its ir, nmr, and mass spectra with those of an authentic sample.[9]

The combined alkaline extracts were adjusted to pH 6 with HCl and the resultant suspension was extracted with $CH_2Cl_2$. The organic extracts were washed ($H_2O$), dried, and concentrated *in vacuo* to a gummy solid. Purification by thick-layer chromatography (silica gel; $C_6H_6$–EtOAc, 1:1) gave 34 mg (20%) of 3-chloro-2-hydroxy-4,6-dimethoxy-4'-hydroxy-2-methoxy-6'-methylbenzophenone (**6**), mp 208–211°. The ir and nmr spectra were identical with those of an authentic sample.[4]

**Acknowledgment.**—We thank Messrs. W. Fulmor and G. Morton (nmr) and Dr. G. Van Lear (ms) for the spectral data, and Mr. L. Brancone and staff for the microanalyses. We also thank Messrs. A. Dornbush and G. Redin of our Chemotherapy Research Section for the *in vitro* and *in vivo* testing results, respectively.

(8) Melting points are uncorrected. The nmr spectra were determined on a Varian A-60 spectrometer, the mass spectra on an AEI MS-9 spectrometer. Tlc was run on phosphor containing silica gel plates (Anal. Tech., Wilmington, Del.). Thick-layer chromatograms were run on 2-mm silica gel plates containing phosphor (E. M. Reagents Division, Brinkmann Instrument Co., Westbury, N. Y.).

(9) *trans*-5'-Acetoxygriseofulvin has been previously prepared: W. Andres, W. McGahren and M. Kunstmann, *Tetrahedron Lett.*, 3777 (1969).