m, $w_{1/2}$ = 9.5 Hz, 3-H), and 4.22 (1H, t, J = 3.5 Hz, 3-H). *m/e* (M^+) 400.3335 (calcd 400.3331), 382 ($M^+ - H_2O$), 364 ($M^+ - H_2O$), 152 ($M^+ - C_{18}H_{32}$), and 134 ($M^+ - C_{18}H_{32} - H_2O$).[9]

1-Ketoprevitamin D_3 3-Acetate (6b). A solution of 50 mg of 1-ketoprevitamin D_3 (**6a**) in 4 mL of methylene chloride was treated with 10 mg of 4-(dimethylamino)pyridine and 15 mg of acetic anhydride at room temperature for 2 h. The reaction mixture was evaporated and the residue was chromatographed on silica gel. Elution with ether gave 45 mg of 1-ketoprevitamin D_3 3-acetate (**6b**). UV λ_{max} 287, 236 nm (ϵ 10 000, 9500) and on addition of iodine and exposure to sunlight λ_{max} 320 nm (ϵ 22 000). NMR δ 0.69 (3H, s, 18-H), 1.74 (3H, s, 19-H), 1.99 (3H, s, acetate methyl), 5.45 (1H, m, 9-H), 5.90 and 6.08 (2H, ABq, J = 12 Hz, 6-H and 7-H), 5.04 (1H, heptet, J = 8.5 Hz and 4.0 Hz, 3-H). *m/e* (M^+) 440.3277 (calcd 440.3279), 396 ($M^+ - C_2H_4O$), 380 ($M^+ - C_2H_4O_2$) 220, 202.[9]

Reduction and Hydrolysis of 1-Ketoprevitamin D_3 3-Acetate (6b). A solution of 40 mg of 1-ketoprevitamin D_3 3-acetate (**6b**) in 3 mL of methanol was treated with 20 mg sodium borohydride at 0 °C for 30 min, extracted with ether, and washed with brine.

The ether extract was dried over magnesium sulfate and evaporated at 0 °C to dryness. The residue was chromatographed on silica gel. Elution with a mixture of ether–hexane (4:6) gave 25 mg of 1β-hydroxyprevitamin D_3 3-acetate (**10b**). UV λ_{max} 259 nm (ϵ 10 000) and on addition of iodine and exposure to sunlight: λ_{max} 272, 282, and 292 nm (ϵ 22 000, 25 000, 21 000). A solution of 20 mg (**10b**) in methanol was treated at 0 °C with a solution of 40 mg of potassium hydroxide in 1 mL of methanol for 4 h. The reaction mixture was extracted with ether and water and washed with brine. The ether extract was dried over magnesium sulfate and evaporated at 0 °C to dryness. The residue was chromatographed on silica gel. Elution with ether gave 15 mg of material which was identical with 1β-hydroxyprevitamin D_3 (**10a**).

1β-Hydroxyvitamin D_3 3-Acetate (5b). A solution of 10 mg of 1β-hydroxyprevitamin D_3 3-acetate (**10b**) in 2 mL of isooctane was heated under nitrogen atmosphere at 70 °C for 3.5 h. The solvent was evaporated to dryness and the residue was chromatographed on silica gel. Elution with a mixture of ether–hexane (4:6) gave 7 mg of 1β-hydroxyvitamin D_3 3-acetate (**5b**). UV λ_{max} 264 nm (ϵ 18 000) and on addition of iodine and exposure to sunlight λ_{max} 272 nm (ϵ 22 000). NMR δ 0.54 (3H, s, 18-H), 1.98 (3H, s, methyl acetate), 4.90 (1H, m, 19Z-H), 5.29 (1H, m, 19E-H), 5.87 and 6.15 (2H, ABq, J = 11.5 Hz, 6-H and 7-H), 3.97 (1H, quartet J = 9Hz and J = 4 Hz, 1-H), 4.82 (1H, heptet J = 9 Hz and J = 4 Hz 3-H).

1-Ketotachysterol$_3$ (9). A solution of 50 mg of 1-ketoprevitamin D_3 (**6a**) in 10 mL of ether was treated with 0.1 mL of 5% iodine solution in ether and exposed to visible light for 30 min. The ether solution was washed with water and evaporated under vacuum to give 35 mg of 1-ketotachysterol$_3$ (**9**). UV λ_{max} 320 nm (ϵ 22 000). NMR δ 0.70 (3H, s, 18-H), 1.82 (3H, s, 19-H), 4.1 (1H, m, 1-H), 5.77 (3H, m, 6-H, 7-H and 9-H).

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Registry No.—2, 41294-56-8; **5a,** 63181-13-5; **5b,** 63181-14-6; **6a,** 63181-15-7; **6b,** 63181-16-8; **8,** 41461-13-6; **9,** 63181-17-9; **10a,** 63181-18-0; **10b,** 63181-19-1; 1α,3β-dihydroxycholesta-5,7-diene, 43217-89-6.

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(4) The accepted notation of ring A atoms in 9,10-secosteroids is derived from the steroid-like conformations.
(5) In the alternative structure **7** the carbonyl chromophore is not expected to shift the UV band of vitamin system (λ_{max} 264 nm) considerably.
(6) The comparatively short wavelength absorption in **6a**, as well as in the other previtamin D_3 derivatives, indicates that the triene system in these compounds is not planar as in their respective tachysterol derivatives. The ring A of previtamin is probably tilted considerably in one or both directions; G. M. Sanders, J. Pot, and E. Havinga, *Fortschr. Chem. Org. Naturst.*, **27,** 131 (1969).
(7) This compound was obtained by irradiation of 1α,3β-dihydroxycholesta-5,7-diene, followed by a separation on Sephadex LH-20 column (see Experimental Section).
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(9) Full mass spectral data will be published elsewhere by Dr. Z. V. I. Zaretskii.

Reduction of Sterigmatocystin and Versicolorin A Hemiacetals with Sodium Borohydride[1]

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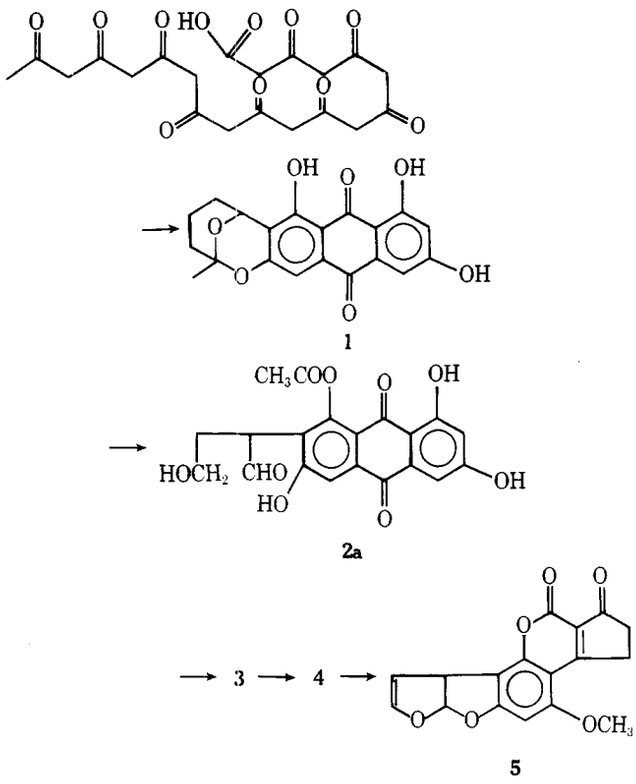
Reduction of sterigmatocysin or versicolorin A hemiacetals with a limited amount of sodium borohydride yielded two major products in each case. The hemiacetal derived from sterigmatocystin gave a new diol as the complete reduction product and a new hemiacetal as a partial reduction product, and the structure of this new hemiacetal was established by ^{13}C NMR spectroscopy and by chemical conversions. The hemiacetal derived from versicolorin A behaved similarly. The bearing of this work on the structure of versiconal acetate, isolated from *Aspergillus flavus*, is discussed.

The aflatoxins and the related sterigmatocystins are a group of toxic and carcinogenic metabolites of certain strains of the fungi *Aspergillus flavus, Aspergillus parasiticus,* and *Aspergillus versicolor,* and have aroused considerable interest because of their widespread occurrence in human and animal foodstuffs.[4,5] Previous theoretical proposals and experimental studies on the biosynthesis of these compounds have indicated that the most probable biosynthetic pathway lies from acetate through the anthraquinones averufin (**1**) and versicolorin A (**3**) to sterigmatocystin (**4**) and thence to aflatoxin B_1 (**5**) (Scheme I).[6-13] The conversion of averufin to versicolorin A is of considerable interest, since the latter contains the same

Scheme I



bisfuran ring system as sterigmatocystin and the aflatoxins B_1 and G_1, and it has been shown that two carbon atoms derived from the methyl groups of acetate have become linked in these molecules.[8,14] Since averufin is produced by a normal head-to-tail condensation of acetate units,[15] it follows that the conversion of averufin to versicolorin A involves a rearrangement of some type, and we[16] and others[6,8,17] have proposed possible pathways for this rearrangement. One possible intermediate in this conversion of averufin to versicolorin A has been identified as a yellow pigment,[18] which appears to be identical with a compound assigned the tentative structure of "versiconal acetate" (**2a**).[19] Because of the importance of "versiconal acetate" as a possible intermediate in the biosynthesis of the aflatoxins, and because of certain ambiguities in the original structural study, we undertook to attempt a synthesis of a derivative of versiconal acetate that could be used for purposes of structural confirmation. This paper describes the results of our studies.

An analysis of the spectral data in the original publication on "versiconal acetate" indicated to us that structure **2b** represented a probable structure of the compound. Our proposed pathway for the preparation of the acetylated derivative of this compound (**2c**) is shown in Scheme II. Acid treatment of versicolorin A, available from a mutant strain of *Aspergillus parasiticus*,[20] would yield the hemiacetal **6a**, which might be expected to exist in aqueous solution in equilibrium with the tautomers **6b–d**, in addition to other possible tautomers involving the peri hydroxyl group at position 1.[21] Reduction of this tautomeric mixture with a limited quantity of sodium borohydride[22] would be expected to yield a mixture of the two possible dihydro derivatives **7** and **8**, together with the fully reduced tetrahydro derivative versiconol (**9**), which has previously been isolated from *A. versicolor*.[23] Although the relative probabilities of reduction of tautomers **6b** and **6d** could not be predicted with confidence, it seemed reasonable to assume that these would be proportional to their relative concentrations in the reaction mixture, and an analogy from carbohydrate chemistry suggested that the dihydrofuran form **6b** should be preferred over the dihydropyran form **6d**.[24] Reduction should thus occur to yield the desired products **8a** and **8b** in reasonable yield. Acetylation of the anticipated mixture of these products would then yield at least some of the desired acetate **2c**, unless the equilibrium between the two forms favored **8b** to the exclusion of **8a**.

In view of the complexity of the possible products resulting from the reduction of versicolorin A hemiacetal **6a**, and because our supply of this compound was limited, the corresponding reduction of the hemicaetal derivative **12a** of sterigmatocystin (**4**) was studied first. Sterigmatocystin and its derivatives also have the advantage of being less polar than versicolorin A and its derivatives, and thus more readily handled by conventional techniques than the latter. The possible reduction products of the hemiacetal of sterigmatocystin (**12a**) are analogous to the versicolorin A derivatives, and are outlined in Scheme III.

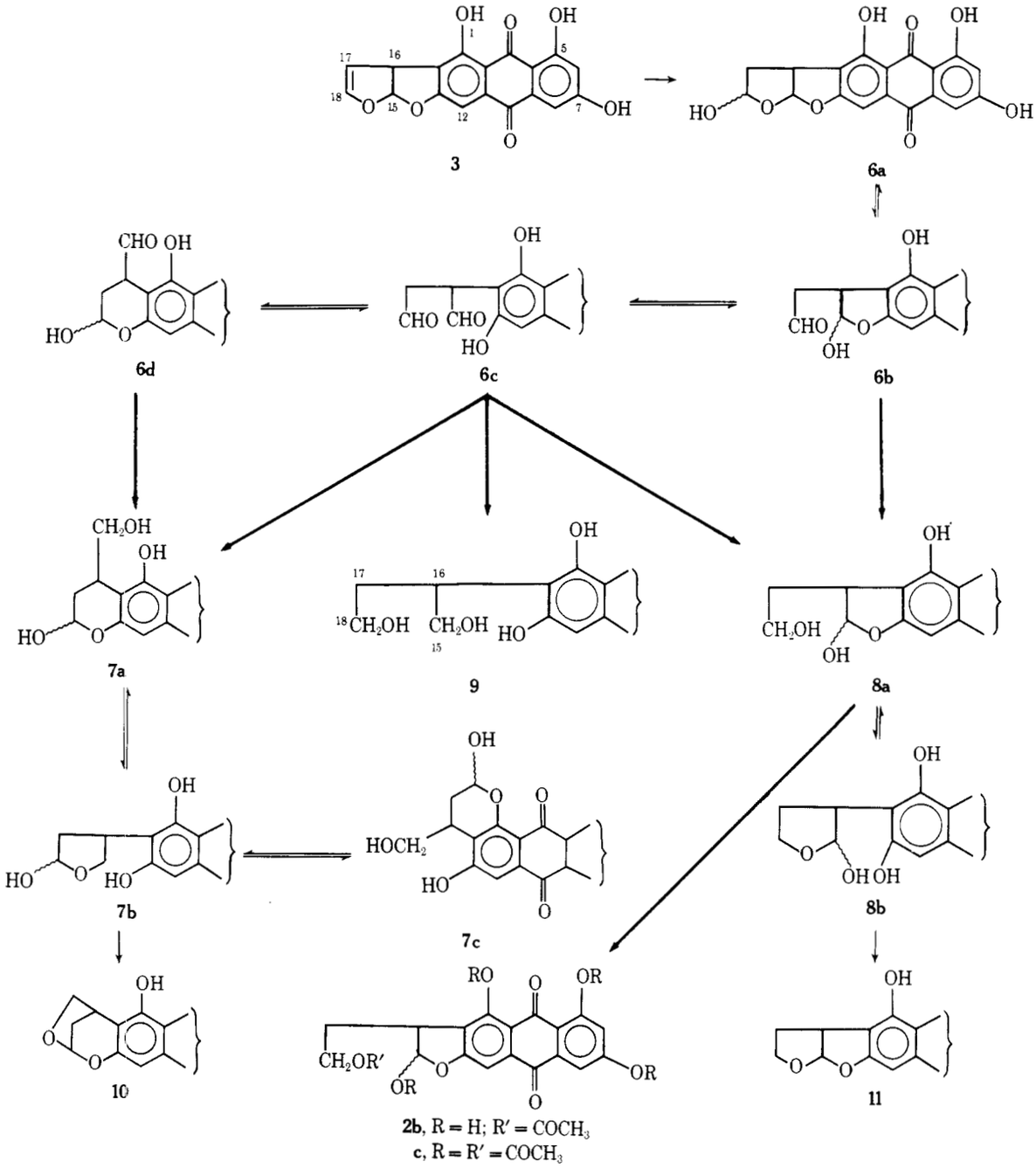
Treatment of sterigmatocystin (**4**) with dilute sulfuric acid in acetone resulted in its smooth conversion to a hydrated product which consisted of a mixture of at least three isomers. The product had ultraviolet and infrared absorption spectra and a mass spectrum consistent with its formulation as a hydrate of sterigmatocystin, but its ^1H NMR spectrum showed a more complex pattern than would have been predicted for a single compound of structure **12a**. Thus, three signals were observed for the proton of the chelated hydroxyl group, and while the presence of two of these signals could be rationalized by the existence of both epimers of structure **12a** the presence of the third signal and weak absorptions due to aldehyde protons demand that the compound exists to some extent in one or more of the open-chain forms **12b–d**, with additional possible contributions from the hydrates of these structures.

Treatment of the hemiacetal **12** with ethanol under acidic conditions resulted in its conversion to a mixture of two epimeric ethoxy acetals (**13**). The spectroscopic data for the mixture support the assignment of structure **13** as opposed to possible alternate structures; in particular, spin-decoupling experiments exclude structure **20**, based on assignments of H-17 at 6.50 ppm and H-14 at 5.34 ppm for this hypothetical compound. By implication, therefore, the hemiacetal also exists largely as the tautomer **12a**; a recent paper describes the preparation of the hemiacetal of 5-methoxysterigmatocystin, and proposes a structure corresponding to **12a** for it.[26]

Reduction of the hemiacetal **12a** with a limited amount of sodium borohydride in tetrahydrofuran–pH 7.2 phosphate buffer yielded only two isolable products. The more polar of the two was identified on the basis on its spectral data as the sterigmatocystin analogue of versiconol (**9**), and was given the trivial name of sterigmatodiol (**16**). The low optical rotation observed for this and several of the other compounds studied is attributed to the occurrence of partial racemization during the reduction process; an analogous racemization of aflatoxin B_{2a} under basic conditions has been previously reported.[27] The second reduction product was identified as a partially reduced sterigmatocystin hemiacetal (PRSTHA) by its mass spectral parent ion peak at *m/e* 344. The ^1H NMR spectrum of the isolated material, like that of compound **12a**, was rather ill-defined, but it did indicate the absence of any open-chain tautomers by the lack of any aldehyde absorption. The spectra were not capable, however, of differentiating between the possible structures **14a, 14b, 15a,** and **15b**.

Treatment of PRSTHA with dilute acid effected its smooth conversion into a new product, which lacked any hemiacetal group and which thus gave a clean, well-resolved ^1H NMR spectrum. This compound had the molecular weight and a similar mass spectrum to dihydrosterigmatocystin (**18**), prepared by hydrogenation of sterigmatocystin (**4**), but a direct comparison of samples showed that they were not identical. Assignment of the structure of the new compound as iso-

Scheme II



dihydrosterigmatocystin (17) followed from its ^{1}H NMR spectrum and from spin decoupling experiments. The latter showed that the one-proton multiplet at 5.79 ppm (H-17) was coupled with the two-proton multiplet at 2.20 ppm (H-16), which in turn was coupled with the one-proton multiplet at 3.88 ppm (H-15). Coupling between H-15 and H-14 could not be demonstrated by these experiments because of the similarity of their chemical shifts, but the pattern observed for H-14 at 4.19 ppm is consistent with these protons being coupled to one proton only at H-15; a dihedral angle between H-15 and one of the H-14 protons of nearly 90° explains the negligible coupling between them. This evidence can only be satisfied by the assignment of structure **17** to the compound, to which we have given the trivial name isodihydrosterigmatocystin. It follows from this that PRSTHA must have the structure **14a** or **14b**, since a rearrangement of the Cannizzaro type, which would be required to give isodihydrosterigmatocystin from structures **15a** or **15b**, is highly unlikely under the acidic conditions used.

A distinction between structures **14a** and **14b** for PRSTHA could not be made on the basis of its ^{1}H NMR spectrum, since as has been noted this was poorly resolved and complicated by the existence of two epimers. A distinction was made, however, on the basis of the ^{13}C NMR spectrum of compound **14** in comparison with the model compounds **16–18**. The ^{13}C NMR spectra of sterigmatocystin (**4**) and dihydrosterigmatocystin (**18**) have been published previously,[28,29] with some differences in assignments. Fortunately, the disputed assignments do not affect our conclusions, and we have chosen to use the values of Steyn[28] as the basis of our assignments. Assignments for carbons 10 and 14–18 of compounds **16, 17,** and **18,** together with predicted assignments for structures **14a** and **14b** and the experimental values for compound **14,** are given in Table I. The chemical shift assignments of compounds **16** and **17** were made on the basis of gated decoupling experiments, which revealed both directly bonded and long-range carbon–proton couplings of the indicated carbons, while the assignments of compound **18** are taken by comparison with

Scheme III

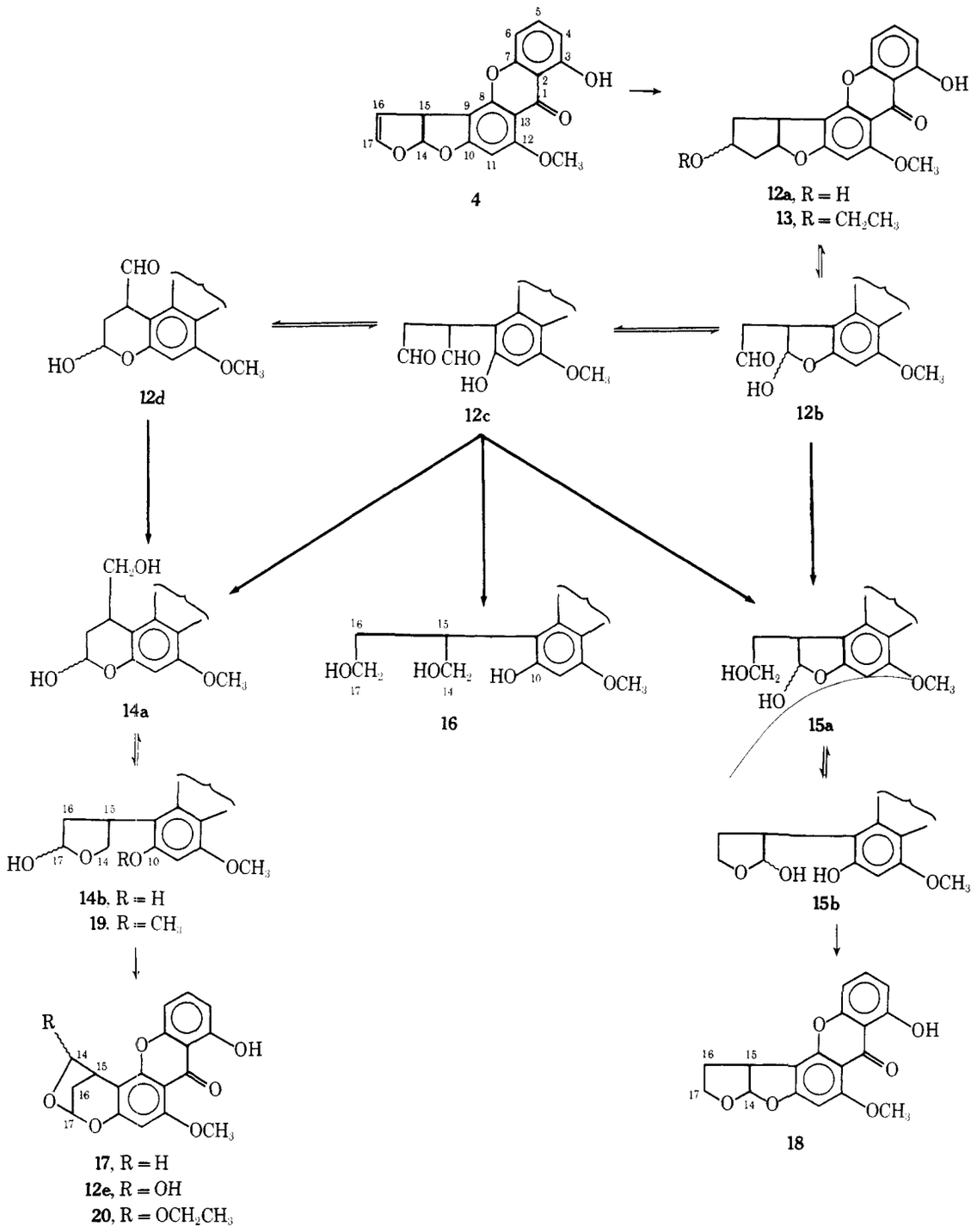


Table I. Carbon-13 Chemical Shifts for Some Sterigmatocystin Derivatives[a,b]

Carbon	16	17	18	14a, calcd	14b, calcd	14, expt
10	159.7	158.1	165.6	165.7	159.7	160.0
14	59.9	78.7	113.3	59.9	63.4	62.7
15	34.9	28.7	43.2	33.4	33.6	30.2
						32.5
16	33.2	31.5	30.5	35.8	38.7	*c*
17	63.5	99.3	67.0	99.3	99.3	95.9
				95.7	95.7	92.8
18	55.8	55.9	56.3	56.6	56.6	56.1

[a] In parts per million downfield from Me_4Si. [b] In $(CD_3)_2SO$ solution. [c] Peak hidden under the solvent peaks.

the literature assignments in $CDCl_3$. The carbons at positions 15 and 17 in compound **14** each appeared to give rise to two signals of diminished intensity, presumably because of the existence of two epimers of this structure. The assignment of these signals should be regarded as tentative, since there was insufficient material available to permit any decoupling techniques to be used in this case, but differences of 2–4 ppm for the corresponding carbons in epimeric carbohydrates have been observed and thus tend to support the assignments.[30,31] The assignment for C-14 in compound **14** is secure, since it is the only possible signal in that range, while the assignment for C-10 must lie in the range 161.1–160.0 ppm, and better agreement with the spectra of previously assigned compounds is obtained when the value of 160.0 ppm is used for this carbon.

The calculated shifts of compounds **14a** and **14b** were obtained by correcting the shifts of the model compounds in an appropriate fashion. Thus, the hydroxyl-bearing C-10 of structure **14b** was assumed to have the same shift as C-10 of structure **16**, while the "alkoxyl" substituted C-10 of structure **14a** was approximated by C-10 of structure **18**. The difference in chemical shift between these two carbons is in line with previous studies of substituent effects on aromatic systems,[32] and tends to support the assumptions made. In particular, the ring strain inherent in structure **17** makes this compound unsuitable for model purposes, since corrections for ring strain are difficult to estimate in compounds of this type. The other key assignment is of C-14 in structures **14a** and **14b**. In the case of **14a**, the shift of carbon-14 in compound **16** was taken as the best available model, since the differences in structure between **16** and **14a** occur at C-17, which should have a minimal effect on the shift of C-14. In the case of structure **14b**, the shift of C-17 of compound **18** was taken as a reference, and was then corrected by the difference in chemical shift between C-14 and C-17 of compound **16** to correct for the fact that the α carbon in **14b** is benzylic.

A comparison of the observed shifts for C-10 and C-14 of compound **14** with those calculated for structures **14a** and **14b** clearly indicates that structure **14b** offers the best agreement between theory and experiment. However, in view of the approximate nature of the calculations used to obtain the shifts for compounds **14a** and **14b**, it was deemed desirable to carry out a structural proof by chemical means also. A sample of compound **14** was thus treated with diazomethane to yield one major product. The product had a molecular weight (MS) of 358, and its ^{1}H NMR spectrum showed the presence of an additional methoxyl group. The presence of a signal in the ^{1}H NMR spectrum for a chelated proton at 13.0 ppm indicated that the hydroxyl group at carbon 3 was still intact, and the product was thus formulated as the ether **19**. Since only structure **14b**, and not **14a**, would be expected to undergo methylation with diazomethane, this work supports the assignment of structure **14b** to the partially reduced sterigmatocystin hemiacetal.

The reason for the preferential formation of **14b** over the other possible structures **14a**, **15a**, and **15b** is not clear, but it must lie either in the stability of the various ring systems involved in the tautomeric equilibria or in some special kinetic effect. If the former is the correct explanation, it would require (contrary to our earlier expectations) that the equilibrium between the reducible forms **12b–d** of the hemiacetal of sterigmatocystin must lie in favor of **12d** under the conditions of the experiment. Reduction of **12d** to **14** would then allow a new equilibrium to be established, which must lie in favor of **14b** rather than **14a**. An explanation based on a special kinetic effect seems less probable, although it cannot be completely excluded.

Having established the pathway taken by the reduction of the hemiacetal of sterigmatocystin, we turned our attention to the conversion of versicolorin A hemiacetal into its reduction products. Treatment of versicolorin A (**3**) with acid yielded the hemiacetal **6a** as the major isolable product, and reduction of this compound with sodium borohydride under the conditions previously established for the sterigmatocystin case yielded a mixture of two products, which were separated by PTLC.

The more polar of the two was assigned the versiconol structure **9** on the basis of its spectroscopic properties and by analogy with the corresponding compound from sterigmatocystin. A direct comparison of our sample with authentic versiconol showed that the two compounds had the same R_f on TLC and the same melting point, but that they differed in the fingerprint region of their infrared spectra, which were obtained as KBr pellets. The reason for this difference is presumably because our sample had undergone essentially complete racemization during the reduction process.

The second, less polar, product was shown from its mass spectrum to be a partially reduced derivative of the hemiacetal **6a**, and its ^{1}H NMR spectrum indicated that it possessed structure **7a, 7b, 8a,** or **8b**. The absence of any absorptions assignable to aldehyde protons indicated that the compound existed in the hemiacetal form, while the presence of signals for *two* chelated hydroxyl groups indicated that cyclization to the C-1 hydroxyl group, as for example in structure **7c**, had *not* occurred.

Conversion of the partially reduced hemiacetal to a stable acetal was effected by treatment with dilute acid. The spectroscopic properties of the resulting product, and especially its ^{1}H NMR spectrum, showed that it had the isoversicolorin C structure (**10**) rather than the versicolorin C structure (**11**), and the partially reduced material must thus possess the structure **7a** or **7b**. It was not possible to do a ^{13}C NMR study of the structure of this latter material, but by analogy with the sterigmatocystin case we can assign the structure **7b** to it.

The discovery that reduction of the hemiacetal **6a** yields none of the desired product **8** (or at least, none isolable by us) prevented us from achieving our initial objective of the synthesis of the acetate **2c**. However, since a crucial part of the initial structural assignment of "versiconal acetate" was its conversion to versicolorin C (**11**) in acid, it became important to confirm that this conversion did in fact yield versicolorin C and not an isomer such as isoversicolorin C (**10**). We thus compared a sample of the product from acid treatment of "versiconal acetate" with authentic versicolorin C (**11**) and isoversicolorin C (**10**), and were able to show that the retention time on HPLC[33] matched that of versicolorin C and differed from that of isoversicolorin C. This work thus offers further support, in an indirect way, for the formulation of versiconal acetate as **2b**. This conclusion has been confirmed and extended by a recent study of the ^{13}C NMR spectrum of versiconal acetate.[34]

The sterigmatocystin and versicolorin derivatives described here should be handled with extreme caution because of their structural relationship to the known carcinogens aflatoxin B_1 and sterigmatocystin.

Experimental Section[35]

Sterigmatocystin Hemiacetal (12a). Sterigmatocystin (1.0 g) was heated for 12 h under reflux in acetone (200 mL) containing 10% H_2SO_4 (10 mL). The reaction mixture was cooled, the yellow-green precipitate collected, and the filtrate concentrated, diluted with water, and extracted with ethyl acetate. The combined extracts were washed, dried, evaporated, and combined with the precipitate to yield crude product, which was recrystallized from acetone to yield 400 mg of hemiacetal, mp 210–212 °C, $[\alpha]^{27}_D$ −7° (*c* 1.4, CH_3SOCH_3). The isolated material had: λ_{max} 232 nm (ϵ 28 000), 249 (34 000), 327 (17 000); ν_{max} 3400 (OH), 1650, 1625 cm^{-1}; mass spectrum *m/e* 342 (M^+, 16), 325 (17), 324 (80), 313 (19), 306 (31), 296 (20), 295 (49), 278 (22), 277 (20), 267 (23), 266 (21), 265 (27), 181 (34), 169 (35), 152 (24), 151 (23), 149 (40); ^{1}H NMR (CH_3SOCH_3) δ 13.48, 13.40, 13.30 (1 H total area, 3s, 3-OH), 9.36, 9.50 (0.05 H total area, 2s), 7.51 (1 H, t, J = 8 Hz, H-5), 6.82 (1 H, d, J = 8 Hz, H-6), 6.62 (1 H, d, J = 8 Hz, H-4), 6.45 (1 H, s, H-11), 6.50–6.32 (1 H, m, H-14), 5.56–5.38 (1 H, m, H-17), 4.18–4.00 (1 H, m, H-15), 3.84 (3 H, s, H-18), 2.20 (2 H, m, H-16) ppm; in $CDCl_3$ solution the signal for H-14 appeared as a doublet (J = 2 Hz) at 6.53 ppm.

Anal. Calcd for $C_{18}H_{14}O_7 \cdot 0.5H_2O$: C, 61.7; H, 4.3. Found: C, 61.9; H, 4.4.

Sterigmatocystin Ethoxyacetal (13). Extraction of the hemiacetal as described above was inadvertently carried out on one occasion with a batch of ethyl acetate containing a small amount of ethanol. The crude product was shown by TLC in system A to contain two products, which were separated by PTLC in the same solvent system. The more polar of the two compounds was sterigmatocystin hemiacetal (**12a**), and the less polar was a new product identified as the ethoxyacetal **13**. The material had mp 189–192 °C after recrystallization from acetone, and had a UV spectrum essentially identical

with that of the hemiacetal **12a**. Its IR spectrum showed no hydroxyl stretching band: $[\alpha]^{27}_D$ −184° (*c* 6.9, $CHCl_3$); mass spectrum *m/e* 370 (M^+, 45), 342 (22), 341 (100), 325 (11), 313 (16), 297 (35), 295 (13), 285 (28); ^1H NMR ($CDCl_3$) δ 13.28, 13.20 (1 H, 2s, 3-OH), 7.46 (1 H, t, *J* = 8 Hz, H-5), 6.84–6.64 (2 H, m, H-4 and H-6), 6.50 (1 H, 2d, H-14), 6.36 (1 H, 2s, H-11), 5.34 (1 H, m, H-17), 4.18 (1 H, m, H-15), 4.00 (3 H, s, H-18), 3.84–3.16 (2 H, two overlapping q, $-OCH_2-$), 2.40 (2 H, m, H-16), 1.14, 0.89 (3 H, 2t, $-CH_3$). Decoupling experiments indicated that the signals at 4.18 and 6.50 ppm arose from protons on adjacent carbons, as did the signals at 5.34 and 2.40 ppm.

Reduction of Sterigmatocystin Hemiacetal with Sodium Borohydride. Sterigmatocystin hemiacetal (300 mg) was dissolved in tetrahydrofuran (300 mL) and 0.05 M phosphate buffer, pH 7.2 (80 mL), at 0 °C. The cold solution was treated dropwise over 3 h with 50 mL of buffer solution containing 90 mg of $NaBH_4$. The reaction mixture was then diluted with 50 mL of water, adjusted to pH 6 with dilute HCl, and extracted with ethyl acetate. The organic extract was washed, dried, and evaporated to yield a crude product which consisted almost completely of two new products. These products were separated by PTLC using solvent system B.

Sterigmatodiol (16). The more polar of the two products (120 mg) had mp 208–210 °C after crystallization from acetone, and $[\alpha]^{25}_D$ −8° (*c* 2.4, CH_3SOCH_3). It showed: λ_{max} 232 nm (ε 27 000), 249 (29 000), 331 (16 000); ν_{max} 3400 (OH), 1645, 1605 cm^{-1}; mass spectrum *m/e* 346 (M^+, 54) 316 (20), 315 (70), 297 (20), 285 (77), 283 (20), 271 (100); ^1H NMR (CD_3COCD_3) δ 7.56 (1 H, t, *J* = 8 Hz, H-5), 6.90 (1 H, d, *J* = 8 Hz, H-4), 6.66 (1 H, t, *J* = 8 Hz, H-6), 6.46 (1 H, s, H-11), 4.16–3.96 (3 H, m, H-14 and -15), 3.90 (3 H, s, H-19), 3.58 (2 H, t, *J* = 7 Hz, H-17); the signal for H-16 was concealed under the solvent peak; ^{13}C NMR (CD_3SOCD_3) δ 180.7, 163.6, 161.2, 159.7, 157.2, 154.3, 135.9, 110.0, 108.5, 107.9, 106.1, 103.7, 95.7, 63.5, 59.9, 55.8, 42.0–37.0 (solvent), 34.9, 33.2.

Anal. Calcd for $C_{18}H_{18}O_7$: C, 62.4; H, 5.2. Found: C, 62.6; H, 5.3.

Partially Reduced Hemiacetal (14b). The less polar of the two reduction products described above (80 mg) had mp 223–226 °C after crystallization from acetone. It showed: λ_{max} 232 (ε 22 000), 249 (ε 29 000), 325 (15 000); ν_{max} 3410, 3260, 1640, 1610 cm^{-1}; mass spectrum *m/e* 344 (M^+, 38), 326 (70), 314 (22), 313 (100), 297 (20), 285 (60), 283 (42), 255 (20), 253 (27), 169 (21), 149 (27), 131 (22), 119 (33); ^1H NMR (CD_3SOCD_3) δ 13.15 (1 H, s, 3-OH), 7.54 (1 H, t, *J* = 8 Hz, H-5), 6.84 (1 H, d, *J* = 8 Hz, H-4), 6.63 (1 H, d, *J* = 8 Hz, H-6), 6.30 (1 H, s, H-11), 5.64–5.42 (1 H, m, H-17), 5.2–4.8 (1 H, m, H-15), 3.83 (3 H, s, H-18), 4.0–3.7 (2 H, m, H-14), 2.28–2.44 (m, H-16, partially concealed under the solvent peak); ^{13}C NMR (CD_3SOCD_3) δ 180.6, 161.1 (2 overlapping signals), 160.0, 156.2, 154.5, 136.0, 110.3, 108.1, 106.2, 102.0, 95.9, 93.2, 62.7, 56.2, 42.0–37.0 (solvent), 32.5, 30.2.

Dihydrosterigmatocystin (18). Sterigmatocystin (400 mg) was hydrogenated in ethyl acetate (50 mL) over 10% Pd/C at room temperature for 4 h. The product was recovered in the usual manner and recrystallized from acetone to give dihydrosterigmatocystin, mp 226–227 °C (lit. 230 °C).[36]

Its UV and IR spectra were as expected; its mass spectrum showed *m/e* 326 (M^+, 100), 308 (20), 297 (26); ^1H NMR ($CDCl_3$) δ 13.04 (1 H, s, 3-OH), 7.36 (1 H, t, *J* = 8 Hz, h-5), 6.70 (1 H, d, *J* = 8 Hz, H-4), 6.62 (1 H, d, *J* = 8 Hz, H-6), 6.42 (1 H, d, *J* = 5 Hz, H-14), 6.24 (1 H, s, H-11), 4.16 (2 H, m, H-17), 3.93 (3 H, s, H-18), 3.63 (1 H, q, *J* = 7 Hz, H-15), 2.30 (2 H, m, H-16); ^{13}C NMR (CD_3SOCD_3) δ 180.0, 165.5, 162.8, 161.1, 154.3, 153.6, 135.6, 113.3, 110.2, 108.0, 105.8, 105.4, 90.0, 67.0, 56.3, 43.2, 42.0–37.0 (solvent), 30.5.

Isodihydrosterigmatocystin (17) The hemiacetal **14b** (20 mg) was treated with concentrated HCl (1 mL) in tetrahydrofuran (50 mL) for 4 h under reflux. Workup in the usual way yielded a homogeneous product, which was crystallized from ethyl acetate to give the product **17**, mp 226–227 °C, $[\alpha]^{27}_D$ −1.7° (*c* 2.4, $CHCl_3$). Its UV absorption was essentially identical with that of dihydrosterigmatocystin, but its IR spectrum showed differences in the fingerprint region: mass spectrum *m/e* 326 (M^+, 100), 308 (33), 297 (32), 283 (70), 265 (30); ^1H NMR ($CDCl_3$) δ 12.96 (1 H, s, 3-OH), 7.36 (1 H, t, *J* = 8 Hz, H-5), 6.69 (1 H, d, *J* = 8 Hz, H-4), 6.62 (1 H, d, *J* = 8 Hz, H-6), 6.20 (1 H, s, H-11), 5.79 (1 H, d, *J* = 2 Hz, H-17), 4.19 (2 H, ABX, J_{AB} = 8 Hz, J_{AX} = 3 Hz, J_{BX} = 0 Hz, H-14), 3.90 (3 H, s, H-18), 3.88 (1 H, m, H-15), 2.20 (2 H, m, H-16); ^{13}C NMR (CD_3SOCD_3) δ 180.1, 160.8, 160.2, 158.1, 154.1, 135.3, 109.8, 108.2, 107.8, 105.7, 99.3, 95.7, 78.7, 55.8, 42.0–37.0 (solvent), 31.5, 28.7.

Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.3, H, 4.3. Found C, 66.3; H, 4.4.

Methylation of 14b. The partially reduced sterigmatocystin hemiacetal **14b** (15 mg) in ethyl acetate (50 mL) was treated with excess diazomethane in alcohol-free ether for 2 h at 0 °C. The resulting solution was evaporated to dryness, and the product crystallized from ethyl acetate to yield the ether **18** as pale yellow crystals, mp 202–204 °C, $[\alpha]^{27}_D$ +8.5° (*c* 2.2, CH_3SOCH_3). The material had: λ_{max} 231 nm (ε 21 000), 250 (27 000), 329 (13 000); IR ν_{max} 3480, 1660, 1610 cm^{-1}; mass spectrum *m/e* 358 (M^+, 100), 340 (14), 328 (18), 327 (43), 300 (15), 299 (65), 285 (44), 273 (14), 272 (61), 255 (15), 254 (20), 242 (14), 226 (15); ^1H NMR ($CDCl_3/CD_3SOCD_3$) δ 13.02 (1 H, br s, -OH), 7.51 (1 H, t, *J* = 8 Hz, H-5), 6.82 (1 H, d, *J* = 8 Hz, H-6), 6.64 (1 H, d, *J* = 8 Hz, H-4), 6.50 (1 H, s, H-11), 5.64 (1 H, br d, *J* = 4 Hz, H-17), ~4.8 (1 H, br s, H-15), ~4.0 (2 H, complex, H-14), 3.80 (6 H, s, 2 OCH_3), and 2.2 (2 H, complex, H-16).

Anal. Calcd for $C_{19}H_{18}O_7 \cdot 0.5H_2O$: C, 62.1; H, 5.2. Found: C, 62.3; H, 5.1.

Versicolorin A Hemiacetal (6a). Versicolorin A^{20} (150 mg) was heated under reflux for 24 h in acetone (150 mL) containing 1.5 mL of 10% H_2SO_4. The reaction mixture was cooled, evaporated in vacuo to remove most of the acetone, diluted with H_2O (100 mL), and extracted with 5 × 50 mL of ethyl acetate. The combined extracts were washed, dried, and evaporated to yield a crude essentially homogeneous product which was crystallized from acetone to give orange-red crystals of the hemiacetal **6a** (90 mg), mp 269–270 °C. The material had: λ_{max} 223 nm (ε 25 000), 255 (15 000), 266 (18 000), 291 (25 000), 317 (11 000), 456 (6100); ν_{max} 3440, 3240, 1610 cm^{-1}; mass spectrum *m/e* 356 (M^+, 18), 355 (27), 328 (60), 310 (67), 309 (73), 300 (74), 299 (100), 285 (40); ^1H NMR (CD_3COCD_3) δ 7.18 (1 H, d, *J* = 2 Hz, H-8), 7.05 (1 H, s, H-4), 6.61 (1 H, d, *J* = 2 Hz, H-10), 6.49 (1 H, d, *J* = 6 Hz, H-15), 5.7–5.5 (1 H, m, H-18), 4.3–4.0 (1 H, m, H-16); signals for H-17 were concealed under the solvent peak.

Reduction of Versicolorin A Hemiacetal with Sodium Borohydride. Versicolorin A hemiacetal (80 mg) was dissolved in a mixture of tetrahydrofurn (80 mL) and 0.05 M phosphate buffer, pH 7.2, 40 mL. The solution was cooled to 0 °C and treated dropwise over 2 h with a cold solution of sodium borohydride (20 mg) in 4 mL of buffer. The reaction mixture was then diluted with water, adjusted to pH 6 with dilute HCl, and extracted with 5 × 50 mL of ethyl acetate. The extract was washed, dried, and evaporated to give a crude product which consisted largely of two new materials, which were separated by PTLC with solvent system A.

Versiconol (9). The more polar of the two reduction products was identified as versiconol (**9**). The material (10 mg) had mp 263–265 °C after crystallization from acetone, undepressed in admixture with authentic material, mp 262–266 °C, $[\alpha]^{27}_D$ 0 ± 5 (*c* 0.4, dioxane). The TLC behavior of the isolate and of authentic versiconol in solvent system A were identical. The material had: λ_{max} 224 nm (ε 22 000), 262 (7900), 296 (9400), 318 (11 000), 460 (2300); ν_{max} 3420, 1620 cm^{-1}; mass spectrum *m/e* 342 (M − 18, 10), 340 (42), 312 (40), 311 (58), 298 (25), 297 (100); using chemical ionization the sample showed *m/e* 361 (MH^+, 11), 344 (13), 343 (55), 342 (20), 341 (100); ^1H NMR (CD_3COCD_3) δ 7.24 (2 H, br, H-4 and H-5), 6.64 (1 H, d, *J* = 2 Hz, H-10), 4.2–3.8 (3 H, complex, H-15 and H-16), 3.4 (2 H, t, *J* = 6 Hz, H-18).

Partially Reduced Versicolorin A Hemiacetal (7b). The less polar of the two products from the reaction described was crystallized from acetone to give orange-red crystals (15 mg), mp >305 °C dec. The material had: λ_{max} 223 nm (ε 24 000), 255 (12 000), 267 (14 000), 318 (9000), 453 (7200); ν_{max} 3580, 3150, 1620 cm^{-1}; mass spectrum *m/e* 340 (M − 18, 84), 312 (63), 311 (92), 297 (100); ^1H NMR (CD_3SOCD_3) δ 12.62 (1 H, br s, -OH), 11.94 (1 H, br s, -OH), 6.98 (1 H, d, *J* = 2 Hz, H-8), 6.88 (1 H, s, H-4), 6.48 (1 H, d, *J* = 2 Hz, H-10), ~5.5 (1 H, m, H-15), 3.8–3.0 (3 H, m, H-16 and H-18).

Isoversicolorin C (10). Treatment of the partially reduced hemiacetal **7b** with concentrated HCl (0.5 mL) in tetrahydrofuran (20 mL) under reflux for 2 h, followed by the usual workup, yielded isoversicolorin C (**10**) as the only organic reaction product. The material had mp >350 °C after recrystallization from acetone, and λ_{max} 222 nm (ε 25 000), 255 (14 000), 265 (16 000), 294 (18 000), 318 (15 000), and 463 (6500).

It showed IR absorption at ν_{max} 3380, 1605 cm^{-1}, and its mass spectrum had *m/e* 340 (M^+, 62), 313 (20), 312 (43), 311 (100), 298 (20), 297 (84): ^1H NMR (CD_3SOCD_3) δ 12.40 and 11.94 (2 H br s, 2 -OH), 7.02 (1 H, d, *J* = 2 Hz, H-8), 6.91 (1 H, s, H-4), 6.50 (1 H, d, *J* = 2 Hz, H-10), 5.98 (1 H, br s, H-18), 4.14 (2 H, m, H-15), 3.72 (1 H, br s, H-16), 2.20 (2 H, br s, H-17). Decoupling experiments indicated that the H-17 protons at 2.20 ppm were coupled to the H-18 proton at 5.98 and the H-16 proton at 3.73 ppm; the latter was also shown to be coupled to the H-15 protons at 4.14 ppm.

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Studies on the Syntheses of Heterocyclic Compounds. 726.[1] Thermal Rearrangement of Aminomethyl Cyclopropyl Ketones and a Novel Synthesis of Pentazocine

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Thermal rearrangement of the hydrobromide of 2-benzylamino-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (**6**), obtained from 1-acetyl-1-methylcyclopropane (**2**) through 3-(4-methoxyphenyl)-1-methylcyclopropyl-2-propenone (**3**), 3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (**4**), and 2-bromo-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (**5**), gave 1-benzyl-2-(4-methoxybenzyl)-4-methylpiperidin-3-one (**7**) in 71.2% yield, which was transformed to 1-benzyl-1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (**10**) by Grignard reaction, followed by dehydration of the resulting 1-benzyl-3-hydroxy-2-(4-methoxybenzyl)-3,4-dimethylpiperidine (**8**). Since **10** had been converted to pentazocine (**1**), this work constitutes a novel synthesis of pentazocine (**1**).

The susceptibility of cyclopropane rings with suitable activating groups to several kinds of nucleophiles has been well documented[2–7] since the studies of Bone and Perkin.[8,9] Recently, Danishefsky reported[10–13] the nucleophilic homoconjugate reactions of cyclopropanes with two geminal activating groups and an enhanced activation of cyclopropanes with cyclic acylal. On the other hand, the acid-catalyzed thermal rearrangement of cyclopropylimines, which was originally reported by Cloke,[14,15] has been shown to be a useful reaction for the synthesis of Δ^1- or Δ^2-pyrrolines,[16–18] and aminomethyl cyclopropyl ketones have been transformed to 3-ketopiperidine rings.[19] In contrast to the well-studied thermal rearrangement of cyclopropylimines, there have been very limited studies regarding the thermal rearrangement of