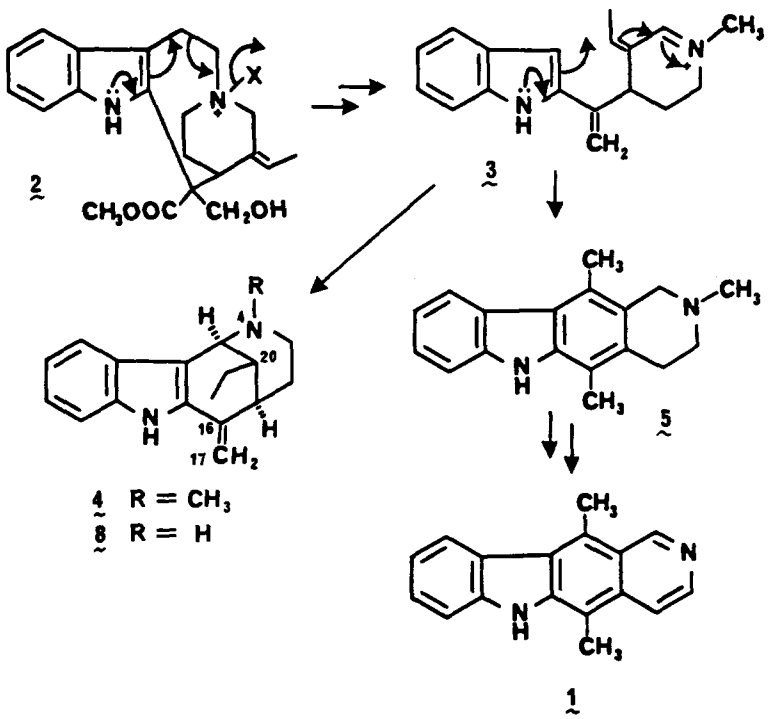
STUDIES ON THE ULEINE ALKALOIDS. III. SOME MICROBIAL TRANSFORMATIONS OF ULEINE[1,2]

ROBERT P. BORRIS and GEOFFREY A. CORDELL

Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612

ABSTRACT.—Four organisms were studied preparatively for the microbial transformation of uleine (**4**). *Penicillium adametzi* and *P. chrysogenum* produced the diastereomeric N_b-oxides of uleine **7** and **9**, and the two C-16 isomers of 16-hydroxy-16,17-dihydrouleine **10** and **11**. *Streptomyces purpurescens* and *S. rimosus* afforded the (4*S*)-N_b-oxide of uleine, the two 16-hydroxy-dihydro derivatives, and des-N-methyl uleine (**8**). The (4*R*)-N_b-oxide of uleine had not been obtained previously by chemical oxidation of uleine (**4**).

The pyridocarbazole alkaloid ellipticine (**1**) is of interest for two principal reasons (1). Firstly, it displays anticancer activity against several leukemia systems, and derivatives of improved activity have been obtained by semi-synthesis (2–6). Indeed, the 9-methoxy derivative has been evaluated clinically in France (7). Secondly, from an academic point of view, ellipticine is of interest because the characteristic two-carbon bridge of an alkaloid derived from tryptophan is absent. Potier and co-workers (8,9) have proposed an interesting biogenetic scheme for ellipticine (**1**) from a stemmadenine (**2**) derivative, which, at a critical juncture, passes through the intermediate **3**. This same intermediate may also be involved in the biosynthesis of uleine (**4**) (8,10). The availability of uleine (**4**) led us to consider a retrobiomimetic approach to the intermediate **3** or a close

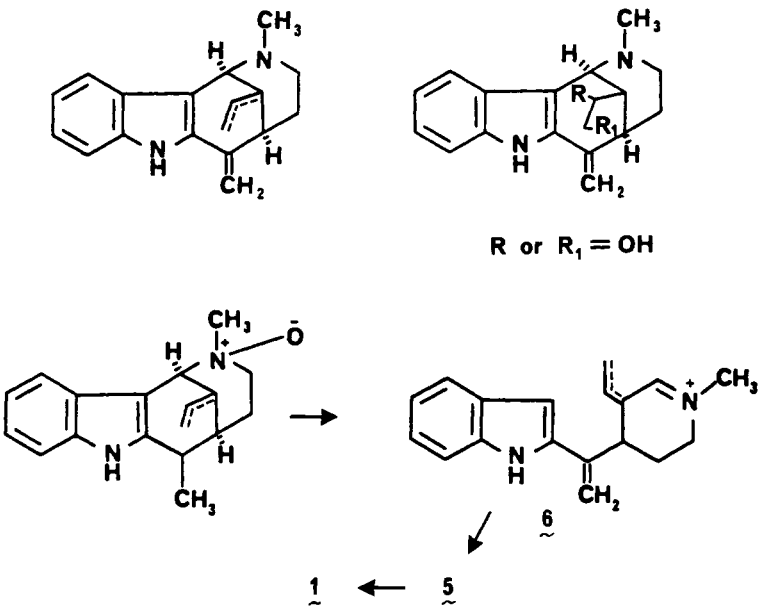


[1]For Paper II in this series, see R. P. Borris, D. C. Lankin and G. A. Cordell, *J. Nat. Prod.*, **46**, 206 (1983).

[2]Portions of this work were submitted by R.P.B. in partial fulfillment of the Ph.D. degree requirements of the Graduate College, University of Illinois at the Medical Center, August 1981, and were first reported at the Joint Meeting of the American Society of Pharmacognosy and the Society for Economic Botany, Boston, Mass., July, 1981.

relative, which could then be transformed to **5**, a compound previously transformed into ellipticine (**1**) through oxidative processes (1).

Four possible oxidation products were identified as being reasonable for the subsequent modifications (scheme 1), which involve a modified Polonovskii reaction to eventually afford the intermediate **6**. Since none of the dehydro- or side chain hydroxy derivatives of uleine are known as natural products[3] and the 18 and 19 carbon atoms are chemically unreactive, it was decided to attempt functionalization of these atoms through microbial transformation.



Scheme 1

Fourteen organisms from our collection were selected for their potential to carry out this transformation, and four were subsequently selected for preparative scale fermentation after it was shown that a number of products other than the N_b-oxide derivative of uleine were being produced in trial experiments. The organisms selected were *Penicillium adametzi* (ATCC-10407), *P. chrysogenum* (ATCC-11709), *Streptomyces purpurescens* (NRRL-B148) and *S. rimosus* (ATCC-10970). A summary of the isolates from these organisms is shown in table 1.

TABLE 1. Summary of the products from the microbial transformation of uleine.

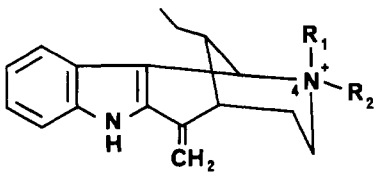
Compound	*Penicillium chrysogenum*	*Penicillium adametzi*[a]	*Streptomyces rimosus*	*Streptomyces purpurescens*[a]
(4*S*)-Uleine-N_b-oxide	2.5%	+	1.6%	+
(4*R*)-Uleine-N_b-oxide	0.7%	+	not detected	not detected
(16*R*)-16-Hydroxy-16, 17-dihydrouleine	0.8%	+	0.8%	+
(16*S*)-16-Hydroxy-16, 17-dihydrouleine	0.9%	+	0.9%	+
Des-*N*-methyl uleine	not detected	not detected	2.3%	+

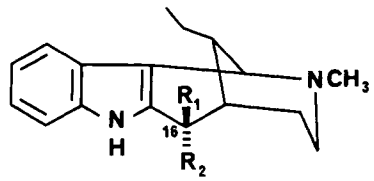
[a]Analyzed by tlc only, no isolation conducted.

[3]The only dehydro-uleine derivative thus far reported is 18,19-(or 19,20)-dehydro-N-desmethyluleine isolated by Djerassi *et al.* (11,12) from *Aspidosperma dasycarpon* A. DC. Only 3 mg of this compound were obtained.

With two exceptions, each was identified by direct comparison with samples obtained semisynthetically (13,14).

One exception was (4*R*)-uleine-N_b-oxide (**7**) which, although produced through microbial transformation by *P. chrysogenum* and *P. adametzi*, was not a product of the chemical N_b-oxidation of uleine (13). The second exception was the metabolite of *S. rimosus* and *S. purpurescens* identified as des-*N*-methyl uleine (**8**), previously isolated as a natural product from extracts of *Aspidosperma dasycarpon* A. DC. (11,12).





4R **7** $R_1=CH_3$, $R_2=-O^-$ 16R **10** $R_1=OH$, $R_2=CH_3$

4S **9** $R_1=-O^-$, $R_2=CH_3$ 16S **11** $R_1=CH_3$, $R_2=OH$

EXPERIMENTAL[4]

SOURCE OF ULEINE (**4**).—The uleine used in these experiments was obtained from a bark extract of *Aspidosperma subincanum* K. von Mart. (Apocynaceae) as described previously (13).

FERMENTATION CONDITIONS AND SCREENING PROTOCOL.—Slant cultures of micro-organisms were obtained from our departmental culture collection and propagated through at least three transfers at four-day intervals prior to use. Organisms were grown on recommended media (50 ml) (15) in cotton-plugged Erlenmeyer flasks (250 ml) on a reciprocating shaker operating at 125 cpm. A 10% inoculum size was used and the temperature was maintained at 24±1°.

Nine flasks were inoculated with each organism: six as test cultures and three acting as controls. Seventy-two hours after inoculation, the test cultures were fed uleine (10 mg) in ethanol (95%, 0.5 ml). Three test cultures were harvested after 72 hours of incubation, while the remaining test cultures and controls were recovered 128 hours after feeding. To one flask of each medium, with no organism present, was added uleine (10 mg) in ethanol (95%, 0.5 ml) and the product was recovered after 128 hours. A standard procedure for work-up and preliminary fractionation was established as follows. Cultures were filtered and the filtrate rendered alkaline (28% NH_4OH) and extracted with ethyl acetate (3 x 100 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to afford fraction 1.

The cells were extracted with methanol (100 ml); the methanol extract was concentrated *in vacuo* and partitioned between dilute (5%) ammonium hydroxide solution (100 ml) and ethyl acetate (3 x 100 ml). After drying (Na_2SO_4), the organic phase was filtered and evaporated *in vacuo* to yield fraction 2. The marc from the methanol extraction was suspended in 1N HCl (100 ml) and filtered; the filtrate was adjusted to pH 10 and extracted with ethyl acetate (3 x 100 ml). After drying (Na_2SO_4), the organic phase was evaporated *in vacuo* to yield fraction 3. The results of this screening are presented in table 2. No alkaloids were detected in fractions 2 or 3 of the cultures from any of the organisms.

PREPARATIVE SCALE MICROBIAL TRANSFORMATIONS OF ULEINE (**4**).—From the screening experiments *Penicillium adametzi* (ATCC-10407), *P. chrysogenum* (ATCC-11709), *Streptomyces purpurescens* (NRRL-B148), and *S. rimosus* (ATCC-10970) were selected for the preparative scale transformation of uleine. Each organism was inoculated into seven Erlenmeyer flasks (2 liter) containing medium (350 ml), a 10% inoculum size was used. Forty-eight hours after inoculation, uleine (50 mg) in DMSO-ethanol (2:1, 3 ml) was added to each flask and the fermentation allowed to proceed for fourteen days. At the end of this time, the cultures for each organism were pooled and filtered; the filtrate was adjusted to pH 10 with 28% ammonium hydroxide solution and extracted with ethyl acetate (3 x 1.2 liters). After drying (Na_2SO_4), the pooled organic phase was evaporated *in vacuo* to afford a crude alkaloidal extract.

ISOLATION OF *Penicillium chrysogenum* METABOLITES.—The alkaloid extract from the *P. chrysogenum* cultures was chromatographed over a column of Silica gel-60[5] (40 g, 2 x 40 cm) packed in ethyl acetate. Elution was commenced with ethyl acetate, followed by ethyl acetate-isopropanol-ammonium hydroxide mixtures (95:5:1–10:10:1) of increasing polarity,

[4]Proton magnetic resonance spectra were recorded in $CDCl_3$ with a Varian T-60A instrument operating at 60 MHz with a Nicolet Model TT-7 Fourier Transformation attachment. Tetramethylsilane was used as an internal standard and chemical shifts are recorded in δ (ppm). Mass spectra were determined with a Varian MAT 112S double focusing mass spectrometer operating at 70 eV.

[5]E. Merck, Darmstadt, W. Germany.

TABLE 2. Screening results for the microbial transformation of uleine.

Organism	Culture	Fraction	R_f of CAS reactive products[a,b]
1. *Aspergillus niger* ATCC-9029	Control	1,2,3	none
	72 hours[c]	1	0.64, 0.20
	168 hours[c]	1	0.64, 0.20
2. *Beauveria bassiana* ATCC-7159	Control	1,2,3	none
	72 hours	1	0.64, 0.20
	168 hours	1	0.64, 0.20
3. *Penicillium adametzi* ATCC-10407	Control	1,2,3	none
	72 hours	1	0.64, 0.29, 0.20
	168 hours	1	0.64, 0.29, 0.20
4. *Penicillium chrysogenum* ATCC-11709	Control	1,2,3	none
	72 hours	1	0.64, 0.29, 0.20
	168 hours	1	9.64, 0.29, 0.20 (15%)
5. *Rhizoctonia solani* ATCC-6221	Control	1,2,3	none
	72 hours	1	0.64
	168 hours	1	0.64
6. *Streptomyces bambergiensis* ATCC-13879	Control	1,2,3	none
	72 hours	1	0.64, 0.20
	168 hours	1	0.64, 0.20
7. *Streptomyces ederensis* ATCC-15304	Control	1,2,3	none
	72 hours	1	0.64, 0.20
	168 hours	1	0.64, 0.20
8. *Streptomyces erythreus* ATCC-11635	Control	1,2,3	none
	72 hours	1	0.64, 0.20
	168 hours	1	0.64, 0.20
9. *Streptomyces geysiriensis* ATCC-15303	Control		none
	72 hours	1	0.64, 0.20
	168 hours	1	0.64, 0.20
10. *Streptomyces griseus* forma *farinosus* ATCC-13741	Control	1,2,3	none
	72 hours	1	0.64, 0.20
	168 hours	1	0.64, 0.20
11. *Streptomyces paucisporogenes* ATCC-12596	Control	1,2,3	none
	72 hours	1	0.64, 0.20
	168 hours	1	0.64, 0.20
12. *Streptomyces platensis* ATCC-13865	Control	1,2,3	none
	72 hours	1	0.64, 0.20
	168 hours	1	0.64, 0.20
13. *Streptomyces purpurescens* NRRL-B148	Control	1,2,3	none
	72 hours	1	0.64, 0.43, 0.33, 0.20
	168 hours	1	0.64, 0.43, 0.33, 0.20
14. *Streptomyces rimosus* ATCC-10970	Control	1,2,3	none
	72 hours	1	0.64, 0.43, 0.33, 0.20
	168 hours	1	0.64, 0.43, 0.33, 0.20
Media Controls			
Potato dextrose broth	168 hours	1	0.64
Saboraud's dextrose broth	168 hours	1	0.64
Malt extract broth	168 hours	1	0.64
Yeast salt extract broth	168 hours	1	0.64
Sporulation broth	168 hours	1	0.64

[a]Silica gel-60 F_{254} developed with ethyl acetate:-isopropranol-ammonia (22:15:1).
[b]The spot of R_f 0.64 represents the starting material, uleine.
[c]No alkaloids were detected in fractions 2 and 3 in any of the cultures at 72 and 168 hours.

and finally methanol. Twenty fractions (125 ml per fraction) were collected. Thin-layer chromatographic comparison of the fractions indicated that fractions 2–7 (95:5:1–90:10:1) consisted primarily of uleine, while fractions 8–13 contained the suspected metabolites.

Fractions 12 and 13 (40:10:1) from the column were pooled and filtered through neutral alumina[6] (Brockman activity I); and the residue, after removal of solvent, was subjected to

[6]M. Woelm, Eschwege, W. Germany.

preparative tlc on Silica gel 60 F_{254}[5] with ethyl-acetate-isopropanol-ammonium hydroxide (45:30:1) as the developing solvent to afford (4*S*)-uleine-N_b-oxide (**9**) as a yellow-brown amorphous gum (8.7 mg, 2.5%): ^{1}H-nmr ($CDCl_3$) δ 0.89 (5H, m, 18-H_3, 19-H_2), 3.16 (3H, s, 5-H_3), 4.46 (1H, d, J=2.3 Hz, 21-H), 5.22 (1H, s, 17-H), 5.93 (1H, s, 17-H), 7.10–7.60 (4H, m, 4 x Ar-H), and 11.10 (1H, br s, N-H); ms, *m/z* 282 (M^+, 9%), 266 (12), 237 (8), 236 (5), 235 (4), 234 (4), 224 (15), 223 (80), 222 (38), 221 (9), 220 (5), 209 (19), 208 (42), 207 (20), 206 (16), 205 (7), 204 (8), 195 (9), 194 (24), 193 (8), 192 (6), 191 (6), 181 (7), 180 (16), 167 (8), and 60 (100). The sample was identical to **9** prepared by the chemical oxidation of uleine (**4**) (13).

Preparative tlc of column fraction 9 (90:10:1) on Silica gel-60 F_{254} with ethyl acetate-isopropanol-ammonium hydroxide (45:30:1) as the developing solvent afforded (4*R*)-uleine-N_b-oxide (**7**) as a brown oil (2.4 mg, 0.7%): ^{1}H-nmr ($CDCl_3$) δ 0.85 (5H, m, 18-H_3, 19-H_2), 3.43 (3H, s, 5-H_3), 5.10 (1H, m, 21-H), 5.30 (1H, s, 17-H), 5.90 (1H, s, 17-H), 7.00–7.70 (4H, m, 4 x Ar-H), and 8.45 (1H, br s, N-H); ms, *m/z* 282 (M^+, 4%), 231 (5), 266 (22), 265 (9), 252 (19), 251 (10), 237 (13), 235 (14), 223 (26), 222 (29), 221 (22), 220 (10), 211 (15), 210 (15), 209 (31), 208 (24), 207 (17), 206 (27), 205 (7), 204 (12), 198 (9), 197 (12), 196 (12), 195 (24), 194 (46), 193 (18), 192 (10), 191 (9), 181 (14), 180 (32), 171 (10), 168 (12), 167 (18), and 159 (11).

Preparative tlc of column fractions 10 and 11 (40:10:1) on Silica gel-60 F_{254} eluting with ethyl acetate-isopropanol-ammonium hydroxide (25:15:1) permitted the separation of two metabolites (R_f 0.44, 0.33). Further preparative tlc of the band at R_f 0.44 in the same solvent system afforded (16*R*)-16-hydroxy-16,17-dihydrouleine (**10**) as a yellow-brown amorphous gum (2.9 mg, 0.8%): ^{1}H-nmr, ($CDCl_3$) δ 0.96 (5H, m, 18-H_3, 19-H_2), 1.66 (3H, s, 17-H_3), 2.30 (3H, s, 5-H_3), 4.08 (1H, br s, 21-H), 7.10–7.60 (4H, m, 4 x Ar-H), and 9.10 (1H, br s, N-H); ms, *m/z* 284 (M^+, 26%), 267 (4), 266 (11), 265 (3), 241 (7), 238 (7), 237 (15), 224 (13), 223 (36), 213 (10), 210 (24), 209 (38), 208 (13), 210 (17), 198 (8), 197 (9), 196 (12), 194 (15), 185 (11), 184 (11), 183 (12), 182 (8), 181 (8), 180 (13), 173 (21), 172 (56), 171 (10), and 170 (7). The sample was identical to **10** prepared from uleine (**4**) by $LiAlH_4$ reduction (14).

Further preparative tlc of the band at R_f 0.33 in the same system afforded (16*S*)-16-hydroxy-16,17-dihydrouleine (**11**) as a yellow-brown oil (3.1 mg, 0.9%): ^{1}H-nmr, ($CDCl_3$) δ 0.95 (5H, m, 18-H_3, 19-H_2), 1.65 (3H, s, 17-H_3), 2.28 (3H, s, 5-H_3), 4.27 (1H, br d, J=2Hz, 21-H), 7.10–7.60 (4H, m, 4 x Ar-H), and 9.40 (1H, br s, N-H); ms, *m/z* 284 (M^+, 59%), 266 (7), 237 (14), 228 (15), 227 (58), 224 (12), 223 (35), 222 (37), 213 (12), 211 (14), 210 (31), 209 (69), 208 (19), 201 (15), 198 (17), 197 (19), 196 (25), 195 (12), 194 (29), 185 (15), 184 (18), 183 (31), 182 (19), 181 (16), and 180 (29). The sample was identical to **11**, prepared from uleine (**4**) by $LiAlH_4$ reduction (14).

METABOLITES OF *Penicillium adametzi*.—The four metabolites isolated from extracts of *P. chrysogenum* cultures were also identified by tlc in the alkaloid extract of *P. adametzi* cultures.

ISOLATION OF *Streptomyces rimosus* METABOLITES.—The alkaloid extract from the *S. rimosus* cultures was chromatographed over a column of Silica gel-60 (50 g, 1.5 x 85 cm) packed in ethyl acetate. Elution was commenced with ethyl acetate, followed by ethyl acetate-isopropanol-ammonium hydroxide mixtures (90:10:1–30:10:1) of increasing polarity, and finally methanol. Nineteen fractions (125 ml per fraction) were collected. Thin-layer chromatographic comparison of the fractions indicated that alkaloids were present in fractions 9–15.

Preparative tlc of fractions 9 and 10 (30:10:1) from the column on Silica gel-60 F_{254} with ethyl acetate-isopropanol-ammonium hydroxide (20:20:1) as developing solvent afforded uleine (**4**) (R_f 0.65) and three alkaloidal constituents (R_f 0.49, 0.41, 0.23). Further preparative tlc of the band at R_f 0.49 in the same solvent system afforded des-*N*-methyluleine (**8**) as a yellow-brown amorphous gum (8.2 mg, 2.3%): ^{1}H-nmr, ($CDCl_3$) δ 0.86 (5H, m, 18-H_3, 19-H_2), 4.42 (1H, br d, J=2.4 Hz, 21-H), 5.00 (1H, s, 17-H), 5.30 (1H, s, 17-H) and 7.00–7.60 (4H, m, 4 x Ar-H); ms, *m/z* 252 (M^+, 100%), 251 (29), 237 (18), 236 (10), 235 (11), 224 (37), 223 (73), 222 (26), 210 (20), 209 (52), 208 (36), 207 (21), 206 (30), 196 (20), 195 (72), 194 (65), 193 (28), 192 (16), 191 (11), 183 (15), 182 (23), 181 (28), and 180 (62).

Further preparative tlc of the band at R_f 0.41 in the same solvent system afforded (16*R*)-16-hydroxy-16,17-dihydrouleine (**10**) as an amorphous yellow-brown gum (2.9 mg, 0.8%), identical (^{1}H-nmr, ms) with a sample prepared from uleine (**4**) by $LiAlH_4$ reduction (14).

Further preparative tlc of the band at R_f 0.23 in the same solvent afforded (4*S*)-uleine-N_b-oxide (**9**) as an amorphous yellow-brown gum (5.5 mg, 1.6%), identical (^{1}H-nmr, ms) with a sample prepared from uleine (**4**) by chemical oxidation (13).

Preparative tlc of fraction 11 (30:10:1) in the same solvent system afforded a main band R_f 0.26, identified as (16*S*)-16-hydroxy-16,17-dihydrouleine (**11**), a yellow-brown oil (3.2 mg, 0.9%), possessing spectral (^{1}H-nmr, ms) properties identical to a sample prepared from uleine (**4**) by $LiAlH_4$ reduction (14).

METABOLITES OF *Streptomyces purpurescens*.—The four metabolites isolated from extracts of *S. rimosus* were also identified by tlc in the alkaloid extract of *S. purpurescens* cultures.

STRUCTURE DETERMINATION OF THE METABOLITES.—Fourteen organisms from our collection were selected for their potential to transform uleine (**4**). Nine of these organisms, *Aspergillus niger*, *Beauveria bassiana*, *Streptomyces bambergiensis*, *S. ederensis*, *S. erythreus*, *S. geysiriensis*, *S. griseus* forma *farinosus*, *S. paucisporogenes*, and *S. platensis*, produced only (4*S*)-uleine-N_b-oxide (**9**) as a metabolite. *Rhizoctonia solani* alone did not metabolize uleine (**4**). Four organism *Penicillium adametzi*, *P. chrysogenum*, *Streptomyces purpurescens* and *S. rimosus* afforded **9** and other metabolites which were investigated through preparative transformations.

Low yields of the isolated metabolites reported are due in part to substantial losses during the purification process, resulting from permanent adherence to the chromatographic adsorbents.

(4*S*)-Uleine-N_b-oxide (**9**) was identified in all cases by direct comparison with synthetic **9** by tlc, and by mass and proton nmr spectroscopy.

The mass spectrum of the second metabolite isolated from the *Penicillium chrysogenum* fermentation displayed a molecular ion at *m/z* 282, with a substantial loss of 16 amu suggesting that it, too, might be an N_b-oxide of uleine. From the proton nmr spectrum, the isolate showed a number of distinct differences compared with the spectrum of **9**. Chemical reduction with ferrous sulfate of this isolate afforded uleine (**4**), identical to the natural product by its tlc and mass spectrum, thereby establishing it to be an uleine-N_b-oxide.

The configuration at position 4 (N_b) in the two *N*-oxide derivatives was assigned on the basis of their proton nmr spectra. In the minor N_b-oxide the proton at C–21 was observed as a multiplet at δ 5.10, 0.64 ppm downfield of the corresponding signal in the major product. Since 21–H is equatorial, this is consistent with a more deshielding, equatorial oxygen in the former compound and an axial oxygen in the latter. The chemical shift of 5-H_3, the *N*-methyl group, is also of some significance. Examination of Dreiding models suggests that an equatorial methyl group is spatially proximate to the indole nucleus and might be expected, like 18-H_3, to experience shielding due to the ring current. Indeed, the *N*-methyl group of the major N_b-oxide resonates 0.27 ppm upfield of the corresponding group in the minor isomer. Thus the major N_b-oxide isomer and the synthetic N_b-oxide produced by chemical transformation is assigned the (4*S*)-configuration (N-methyl group equatorial), and the minor N_b-oxide produced by microbial transformation is assigned the (4*R*)-configuration.

The two C–16 stereoisomers of 16-hydroxy-16,17-dihydrouleine were compared directly (tlc, and mass and proton nmr spectroscopy) with the products from the $LiAlH_4$ reduction of uleine (**4**) (14). Stereochemistry in these products had been established by examination of their carbon-13 nmr spectra (14).

The *Streptomyces rimosus* and *S. purpurescens* fermentations did not produce any of the (4*R*)-uleine-N_b-oxide isomer which had been produced by the *Penicillium* species, but they did produce the (4*S*)-isomer **9** and the two 16-hydroxy-16,17-dihydro isomers **10** and **11**. However, a new metabolite was produced showing an intense molecular ion at *m/z* 252, fourteen mass units less than **4** and consistent with a molecular formula $C_{17}H_{20}N_2$. The fragmentation was quite similar with that of uleine. Except for the absence of the *N*-methyl singlet (δ 2.29) in uleine and a slight downfield shift of 21-H, the proton nmr spectrum of the metabolite was very similar to that of **4**. On this basis the metabolite was assigned the structure des-*N*-methyluleine (**8**).

DISCUSSION

Microbial transformation of uleine has thus far failed to yield the metabolites required for use in a biomimetic synthesis of ellipticine (**1**). However, several interesting metabolites were isolated and fully characterized, namely the two N_b-oxides **7** and **9**, and the two 16-hydroxy-16,17-dihydro derivatives **10** and **11** produced by the two *Penicillium* species, and the des-*N*-methyl uleine (**8**) produced by the *Streptomyces* species. Several other organisms metabolized uleine to the (4*S*)-N_b-oxide (**9**).

Microbial *N*-demethylation and production of the 16-hydroxy-16,17-dihydrouleine derivatives were not exceptional (15,16). However, we believe this to be the first report of a microbial *N*-oxidation producing an *N*-oxide not also produced by chemical synthesis.

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