solution of 30% H_2O_2 (0.76 g, 6.7 mmol) in glacial AcOH (5 ml) was added. The reaction mixture was stirred overnight, and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed twice with H_2O and once with 5% $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated to dryness to give 1.50 g of a yellow foam. Tlc showed the presence of three components, none of which was starting material. The crude product was chromatographed over silica gel (60 g) using a linear 100% benzene → 100% EtOAc gradient. The fractions were pooled according to purity as determined by tlc. The major component (0.900 g) was crystallized from acetone–ether yielding 0.620 g (38%) of (*S*)-sulfoxide: mp 176–178° dec; uv_{max} (EtOH) 216 mμ (ε 3000), 264 (sh), 268 (9350), 273 (sh); ir ($CHCl_3$) 1790, 1730, 1680, and 1040 cm^{-1}; nmr (DMSO-d_6) δ 2.13 (3 H, s), 3.74, 3.96 (2 H, t, J = 19 Hz), 4.70 (2 H, s), 5.04 (1 H, d, J = 5 Hz), 5.05, 5.17 (2 H, t, J = 12 Hz), 6.04 (1 H, q, J = 5, 10 Hz), 6.8–7.5 (5 H, m), 8.18 (1 H, d, J = 10 Hz).

Anal. Calcd for $C_{18}H_{17}Cl_3N_2O_6S$: C, 43.61; H, 3.46; Cl, 21.46; N, 5.81; S, 6.47. Found: C, 44.23; H, 4.02; Cl, 21.63; N, 5.65; S, 6.55.

A second component crystallized from acetone to give the (*R*)-sulfoxide (0.090 g, 0.5%) as prisms: mp 186–187°; uv_{max} (EtOH) quartet 217, 263 (sh), 267, and 274 (sh) mμ; ir ($CHCl_3$) 1780, 1730, 1630, and 1040 cm^{-1}; nmr (DMSO-d_6) δ 2.19 (3 H, d), 3.75, 4.19 (2 H, q, J = 16.5 Hz), 4.63 (2 H, s), 4.78 (1 H, d, J = 5 Hz), 5.08 (2 H, s), 5.65 (1 H, q, J = 5, 8 Hz), 6.8–7.5 (5 H, m), 9.32 (1 H, d, J = 8 Hz).

Anal. Found: C, 43.66; H, 3.66; Cl, 21.39; N, 5.70; S, 6.38.

Reducing Agent without External Activation. Phosphorus Trichloride.—(*S*)-2,2,2-Trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (2.00 g, 4.03 mmol) was dissolved in CH_2Cl_2 (100 ml) containing PCl_3 (3.2 g, 22 mmol). The solution was heated under reflux for 2.5 hr. After cooling to room temperature, the reaction was neutralized with a saturated solution of aqueous $NaHCO_3$, washed with H_2O, and dried over $MgSO_4$. Removal of solvent *in vacuo* yielded 1.65 g (85%) of reduced material, which crystallized from hot *i*-PrOH, mp 115–117°. The nmr, ir, and uv spectra and elemental analysis of the product were identical with those of an authentic sample of 2,2,2-trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate.

Cationic Reducing Agent. Stannous Chloride.—(*S*)-2,2,2-Trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate 1-oxide (2.0 g, 3.7 mmol) was dissolved in CH_3CN (15 ml) and DMF (6 ml) and stirred at 0°. Stannous chloride (624 mg, 4.04 mmol) and AcCl (1.2 g, 1.54 mmol) were added. This mixture was stirred at 0° for 1 hr and then at room temperature for an additional hour. The CH_3CN was removed *in vacuo;* the residue was poured into H_2O and extracted into EtOAc. The organic solution was washed with 3% HCl solution, 5% $NaHCO_3$ solution, and then with H_2O. After drying over Na_2SO_4, the solvent was removed to give 1.9 g (98%) of product which crystallized from hot *i*-PrOH, mp 120–122°, and was identical in all respects with authentic 2,2,2-trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate.

Registry No.—2,2,2-Trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate, 24647-47-0; 2,2,2-trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate, 5317-29-3; *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate 1-oxide (*S*), 24647-49-2; *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate 1-oxide (*R*), 24647-50-5; *p*-methoxybenzyl 3-acetoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide, 24670-41-5; *t*-butyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide, 24647-51-6; 2,2,2-trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (*S*), 24689-52-9; 2,2,2-trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (*R*), 24689-53-0.

Acknowledgment.—We thank Mr. C. Ashbrook, Mr. T. Goodson, Miss F. Jose, Mrs. G. Mattick, and Mr. R. Vasileff for their technical assistance.

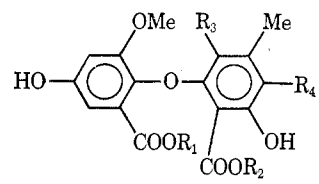
A Novel Diaryl Ether, LL-V125α, from a Fungus of the Order Sphaeropsidales

W. J. McGahren, W. W. Andres, and M. P. Kunstmann

Lederle Laboratories, a Division of American Cyanamid Company, Pearl River, New York 10965

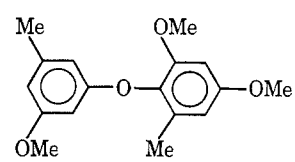
Received December 29, 1969

Diaryl ethers have been isolated from plants[1] and sea sponges.[2] To our knowledge the only microbial metabolite of this type isolated so far is asterric acid, I.[3] The closely related compounds, erdin hydrate, II, and geodin hydrate, III, have been obtained by chemical conversion of natural products[4] and the elaboration of III by mutants of *Aspergillus terreus* has been demonstrated.[5] Diphenyl ethers have been obtained as



I, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$
II, $R_1 = R_2 = R_3 = R_4 = H$
III, $R_1 = CH_3$; $R_2 = H$; $R_3 = R_4 = Cl$

breakdown products from *Lichen depsidones*[6,7] and, in particular, one such compound was characterized as the trimethyl ether of alectol, IV. We have isolated



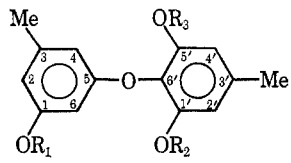
IV

the novel metabolite, 5′-methoxy-5,6′-oxydi-*m*-cresol (V), from a fungus of the order Sphaeropsidales (Lederle culture V125). By *in vitro* testing V had weak antifungal activity.

Compound V has the formula $C_{15}H_{16}O_4$ (*m/e* 260). The nmr spectrum of V in $CDCl_3$ shows sharp, three-proton singlets at δ 2.05 and 2.20 (2 CH_3, aromatic) and 3.75 (OCH_3, aromatic), two broad one-proton exchangeable singlets at 5.20 and 4.57 (2 H, phenolic),

(1) P. Bernfeld, "Biogenesis of Natural Compounds," Pergamon Press, The Macmillan Co., New York, N. Y., 1963, p 626.
(2) P. R. Burkholder, M. Guez, and G. M. Sharma, American Society of Pharmacognosy, Tenth Annual Meeting, Aug 18–22, 1969, School of Pharmacy, Oregon State University, Corvallis, Ore.
(3) R. F. Curtis, C. H. Hassall, C. W. Jones, and T. W. Williams, *J. Chem. Soc.*, 4838 (1960).
(4) C. T. Calam, A. E. Clutterbuck, A. E. Oxford, and H. Raistrick, *Biochem. J.*, **41**, 458 (1947).
(5) R. F. Curtis, P. C. Harries, C. H. Hassall, and J. D. Levi, *ibid.*, **90**, 43 (1964).
(6) Y. Asahina and F. Fugikawa, *Ber.*, **67**, 163 (1934).
(7) Y. Asahina and S. Shibata, "Chemistry of Lichen Substances," Japan Society for the Promotion of Science, Ueno, Tokyo, 1954, p 118.

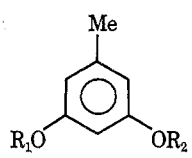
and a multiplet (5 H, aromatic) at 6.28. The dimethyl and diethyl ethers VI and VII were prepared in addition to the diacetate derivative VIII. The nmr



V, $R_1 = R_2 = H$; $R_3 = CH_3$
VI, $R_1 = R_2 = R_3 = CH_3$
VII, $R_1 = R_2 = C_2H_5$; $R_3 = CH_3$
VIII, $R_1 = R_2 = COCH_3$; $R_3 = CH_3$
IX, $R_1 = R_2 = R_3 = H$

spectrum of the dimethyl ether VI showed aromatic methoxy groups at δ 3.75 and 3.84 and, hence, one of the newly formed methoxy groups is in the same chemical environment as the one already present on the parent compound.

Reagents frequently used to cleave ethers such as sodium in liquid ammonia[8-10] or in refluxing pyridine[11] left V mostly unaltered. Procedures such as refluxing with hydriodic acid and phenol or fusion with KOH, both of which cleave IV,[6,7] merely split the methoxy groups of V to give IX. Treatment of VI with sodium in liquid ammonia gave small amounts of the mono and dimethyl ethers (X and XI) of orcinol (XII). However, similar treatment of the diethyl ether VII gave ~80% yields of the ethyl and methyl ethyl ethers XIII and XIV of orcinol. Clearly, then, V consists of or-



X, $R_1 = H$; $R_2 = CH_3$
XI, $R_1 = CH_3$; $R_2 = CH_3$
XII, $R_1 = R_2 = H$
XIII, $R_1 = C_2H_5$; $R_2 = H$
XIV, $R_1 = C_2H_5$; $R_2 = CH_3$

cinol, XII, connected through one of its oxygen atoms to its own monomethyl ether (X). A number of facts show that the bond with the second orcinol moiety is formed at the position *para* to the methyl group thus establishing V as the structure of the metabolite. This structure satisfies the condition that upon formation of the dimethyl ether the newly formed methoxy group at the 1′ position is in the same chemical environment as the original group at 5′. If the connecting bond were formed at either of the positions *ortho* to the methyl group, the dimethyl ether from both compounds would be identical with the alectol material (IV). Since VI failed to give a quinone under oxidative conditions which produce 2-methyl-6-methoxy-1,4-benzoquinone from IV and since the aryl ether linkage of VI was stable to conditions which cleaved IV, both of the latter modes of attachment are eliminated.

(8) P. A. Sartoretto and F. J. Sowa, *J. Amer. Chem. Soc.*, **59**, 603 (1937).
(9) C. D. Hurd and G. L. Oliver, *ibid.*, **81**, 2795 (1959).
(10) E. J. Strojny, *J. Org. Chem.*, **31**, 1662 (1966).
(11) V. Prey, *Ber.*, **76**, 156 (1943).

Experimental Section[12]

Fermentation and Isolation.—About 300 l. of medium consisting of 3% glucose, 0.2% NH_4OAc, 0.1% Na_2SO_4, 0.75% K_2HPO_4, 0.03% KCl, 0.01% $Mg(OAc)_2 \cdot 4H_2O$, 0.002% $FeCl_3 \cdot 6H_2O$, and 0.1% Yeastamine 95 (A. E. Staley Manufacturing Co., Decator, Ill.) with pH adjusted to 6.5 were inoculated with 12 l. of a 48-hr vegative suspension of Lederle culture V125 grown on a medium consisting of 2% Edamine (Sheffield Chemical Co., Norwich, N. Y.), 2% glucose, and 0.5% corn steep liquor (pH adjusted to 6.5). Fermentation proceeded for 140 hr at 28° using 1/2 v/v/min aeration and under mechanical stirring at 300 rpm. The pH of the harvest mash was 5.0. The broth was clarified by filtration with diatomaceous earth and the beer was extracted with equal volume of $CHCl_3$. The concentrated extract ~50 g was passed over a kilogram of acid-washed Davison 62 grade silica gel using the solvent 2% ether in CH_2Cl_2. The sixth–tenth holdback volumes yielded an oil which did not crystallize from dry solvents. The material did crystallize as the hemihydrate from $CHCl_3$–hexane to give 23 g of off-white crystals: mp 121.5–122.5°; λ_{max} (MeOH) 225 nm (ϵ 21,500) (sh), 275 (5100) and 282 (5400); λ_{max} (methanolic NaOH) 235 nm (ϵ 18,800) (sh) and 290 (5650).

Anal. Calcd for $C_{15}H_{16}O_4 \cdot 0.5H_2O$: C, 66.91; H, 6.22. Found: C, 67.14; H, 5.90 (*m/e* 260).

Derivatives of V.—The diacetate VIII was made using pyridine–acetic anhydride. The pure material was obtained by eluting with $CH_3COOC_2H_5$–hexane from silica gel: mp 75–76°; λ_{max} (MeOH) 225 nm (ϵ 19,600) (sh) and 277 (3440).

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.92. Found: C, 66.33; H, 5.92.

Surprisingly, starting material only was isolated following treatment of V with CH_2N_2. Using $(CH_3)_2SO_4$ and 4 *N* NaOH, VI was prepared: mp 91–92°; λ_{max} (MeOH) 227 nm (ϵ 20,200) (sh), 272 (4900) and 282 (5300).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.77; H, 6.83.

The diethyl ether VII was prepared using $(C_2H_5)_2SO_4$ and 4 *N* NaOH to get a colorless oil which could be distilled at 150° (70 μ): λ_{max} (MeOH) 225 nm (ϵ 22,400) (sh), 277 (5050) and 282 (5400).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 77.12; H, 7.65. Found: C, 77.01; H, 7.46.

Reactions of V and VI.—An attempt to cleave 1.3 g (5 mmol) of V by fusion with KOH[6] gave 0.90 g of oil following silica gel chromatography. The material was purified further by partition chromatography over diatomaceous earth using the system hexane–$CH_3COOC_2H_5$–CH_3OH–H_2O (80/20/15/6). The tenth–twelfth holdback volumes yielded 500 mg of colorless oil which spectral data showed to be IX: λ_{max} (MeOH) 220 nm (ϵ 21,900) (sh), 272 (4500) and 278 (4900); δ ($CDCl_3$) 2.02 (3 H, singlet), 2.19 (3 H, singlet), 6.27 (5 H, mulitplet), 7.73 (1 H, broad exchangeable singlet) and 8.53 (2 H, broad exchangeable singlet).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 67.67; H, 5.94.

About 1.3 g (5 mmol) of VI and 3.5 g of phenol were refluxed in 30 ml of 57% HI for 4.5 hr. Work-up of the reaction mixture gave a 65% yield of XI.

Attempted oxidation of VI in acetic acid using saturated $K_2Cr_2O_7$ solution[6] gave only starting material.

Cleavage of Aryl Ether Linkages of VI and VII.—The sodium in liquid ammonia method used to cleave thalicarpine[13] failed to split V.

When VI was subjected to the same procedure, a small yield (20%) of an oil was obtained. The oil could be distilled at 90° (70 μ) to get crystals; mp 62–63°, which proved to be X: λ_{max} (MeOH) 222 nm (ϵ 7250) (sh), 272 (1380) and 280 (1380).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.20; H, 7.17.

(12) Melting points were taken in capillary tubes and are uncorrected. Nmr spectra were recorded on a Varian A-60 instrument with trimethylsilane as internal standard. The uv spectra were made using a Cary 60 recording spectrophotometer and the mass spectrum was run on an AE-I MS9 direct inlet mass spectrometer. Purity of compounds was determined on precoated thin layer chromatography plates of silica gel F-254 (0.25 mm) obtainable from Brinkmann Instruments, Westbury, N. Y. Systems varied from 5 to 100% $CH_3COOC_2H_5$ in hexane.

(13) S. M. Kupchan and N. Yokohama, *J. Amer. Chem. Soc.*, **86**, 2177 (1964).

This material was identical with authentic X prepared by standard methods.[14]

In a repeat of this experiment using a longer reaction time only a small yield (about 15%) of a colorless oil was recovered which could be distilled at 75° under 80 μ. Spectral data showed the oil to be XI: δ (CCl_4) 2.25 (3 H, singlet), 3.70 (6 H, singlet) and 6.19 (3 H, broad singlet).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.13; H, 7.88.

When 1.0 g (~3 mmol) of VII was treated with sodium in liquid ammonia, an ether extract yielded 470 mg of a light yellow oil which was purified over 62 grade Davison silica gel (2% $CH_3COOC_2H_5$ in hexane) to get 380 mg of a colorless oil. This oil could be distilled at 80° (100 μ). Spectral data showed the oil to be XIV: λ_{max} (MeOH) 223 nm (ε 7500) (sh), 273 (1600) and 280 (1660); δ (CCl_4) 1.35 (3 H, triplet J = 7 Hz), 2.23 (3 H, singlet), 3.70 (3 H, singlet), 3.90 (2 H, quartet, J = 7 Hz) and 6.15 (3 H, singlet).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.31; H, 8.47.

Work-up of the reaction mixture on the acid side yielded by ether extraction 370 mg of an oil which was purified by partition chromatography over 120 g of diatomaceous earth using heptane saturated with MeOH. The third and fourth holdback volumes gave 300 mg of an oil which upon distillation at 90° (100 μ) gave crystals, mp 52–53°, which proved to be XIII: λ_{max} (MeOH) 225 nm (ε 8360) (sh), 275 (1670) and 282 (1670); δ (CCl_4) 1.32 (3 H, triplet J = 7–8 Hz), 2.17 (3 H, singlet), 3.83 (2 H, quartet, J = 7–8 Hz), 5.90 (1 H, broad exchangeable singlet) and 6.08 (3 H, singlet).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.72; H, 7.83.

Hence, it may be noted that the ease of ether cleavage in V, VI, and VII is increased significantly as R_2 goes from H to CH_3 to C_2H_5.

Registry No.—V, 24741-92-2; VI, 24741-93-3; VII, 24741-94-4; VIII, 24741-95-5; IX, 24741-96-6; X, 3209-13-0; XI, 4179-19-5; XIII, 24741-99-9; XIV, 24742-00-5.

Acknowledgment.—We wish to thank Dr. P. Shu and associates for large-scale fermentation and processing, Mr. L. Brancone and staff for elemental analyses, Mr. W. Fulmor and associates for spectral data, and Dr. H. Tresner for culture isolation and classification.

(14) H. Walbaum and A. Rosenthal, *Ber.*, **67**, 770 (1924).

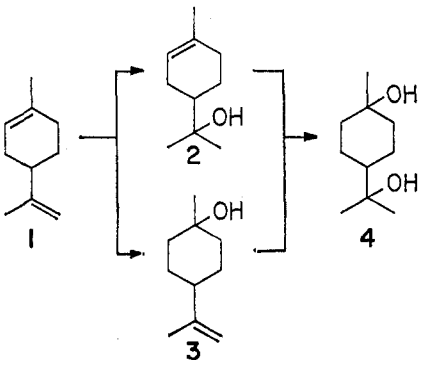
Photochemistry of Cycloalkenes. VII. Limonene[1]

PAUL J. KROPP

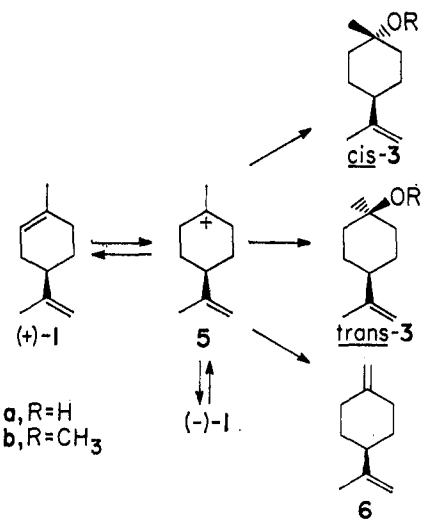
The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received January 19, 1970

Recent studies have shown that photosensitized irradiation of cyclohexenes and -heptenes in hydroxylic solvents results in a light-initiated protonation of the olefin.[2,3] Since this behavior is specifically limited to six- and seven-membered-ring olefins, photoprotonation should afford the unique synthetic advantage of permitting the selective protonation of a cyclohexene or -heptene moiety of a complex molecule in the presence of other double bonds contained in either a larger ring or an acyclic environment.[2] This synthetic capability has now been demonstrated in the case of the diene limonene (**1**).



Acid-catalyzed hydration of limonene affords a mixture of products, including α- (**2**) and β-terpineol (**3**) and terpin (**4**), resulting from competing protonation of both double bonds.[4] In one case in which selective reaction was observed, attack occurred at the C_8–C_9 double bond to afford α-terpineol (**2**).[5] By contrast it has now been found that xylene-sensitized irradiation of (+)-limonene [(+)-**1**] in aqueous solution affords a 1.2:1 mixture of *cis*- and *trans*-β-terpineol (**3a**), respectively, as well as a small amount of the exocyclic isomer **6** with no detectable formation of the C_8–C_9 addition products α-terpineol (**2**) or terpin (**4**). Likewise, irradiation in methanolic solution affords a 1.6:1 mixture of the corresponding methyl ethers *cis*- and *trans*-**3b** as the only detectable addition products. Thus photoprotonation affords a powerful method of effecting reaction selectively at the C_1–C_2 position of limonene and, by analogy, inducing selective protonation of any cyclohexene or -heptene chromophore in the presence of an acyclic, exocyclic, or larger ring cyclic olefin.



It is of further interest to note that the recovered unreacted limonene was found to have undergone extensive racemization (84%) as would be expected for

(1) Part VI: P. J. Kropp and H. J. Krauss, *J. Amer. Chem. Soc.*, **91**, 7466 (1969).

(2) P. J. Kropp and H. J. Krauss, *ibid.*, **89**, 5199 (1967).

(3) J. A. Marshall, *Accounts Chem. Res.*, **2**, 33 (1969), and references cited therein.

(4) For a recent review of the chemistry of limonene, see J. Verghese, *Perfum. Essent. Oil Rec.*, **59**, 439 (1968).

(5) L. Kuczynski and H. Kuczynski, *Rocz. Chem.*, **25**, 432 (1951).