ANTIFUNGAL AGENTS. 3[1,2]. CHEMICAL MODIFICATION OF ANTIBIOTICS FROM *POLYANGIUM CELLULOSUM* VAR. *FULVUM* A DIVINYLCYCLOPROPANE-CYCLOHEPTADIENE REARRANGEMENT

DAVID T. CONNOR*, SYLVESTER KLUTCHKO and MAXIMILLIAN VON STRANDTMANN**

Warner-Lambert/Parke-Davis, Pharmaceutical Research Division
2800 Plymouth Road, Ann Arbor, Michigan 48106, U.S.A.

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The thermal rearrangement of antifungal antibiotic **1**, isolated from *Polyangium cellulosum* var. *fulvum*, to cycloheptadiene derivative **2** is described.

We recently described[1,2] the isolation and structure elucidation of two antifungal antibiotics from *Polyangium cellulosum* var. *fulvum*. The antibiotics were highly active against pathogenic fungi such as *Histoplasma capsulatum* and *Coccidioides immitis*. In a search for new antifungal antibiotics by chemical modification and to gain structural information, antibiotic **1**[1] was thermally rearranged to cycloheptadiene derivative **2** in diphenyl ether at 240°C. It is well known[3] that divinylcyclopropanes rearrange to cycloheptadienes and that *cis* divinylcyclopropanes rearrange at room temperature. Acid **1** is probably the most complex divinylcyclopropane to be transformed to the corresponding cycloheptadiene.

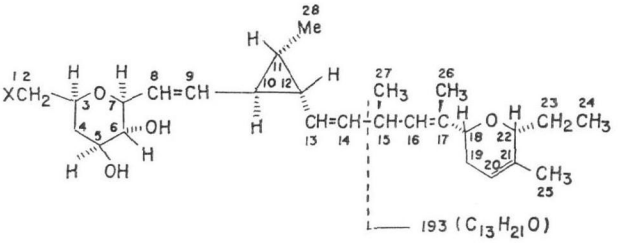
The rearrangement product, acid **2**, had greater TLC mobility than **1**, but gave a similar mass spectrum fragmentation pattern with a molecular ion at 474 ($C_{28}H_{42}O_6$). Acid **2** was converted to monomethyl ester **3**, diacetate **4** and triol **5**. In these reactions the behavior of **2** parallels that of **1**. The products (**3**, **4** and **5**) had greater TLC mobility than the corresponding products from **1**. Acid **2** and its derivatives showed a strong M−195 peak as well as a strong 193 peak, whereas **1** and its derivatives showed a strong 193 peak but a much weaker M−195 peak. This was the only major difference in the mass spectra of the two sets of compounds. The ^1H NMR spectrum of diacetate **4** showed several differences from that of the diacetate of **1**. In the ^1H NMR spectrum of **4** the vinyl protons at C_9, C_{10}, C_{12} and C_{13} were all crowded in the region δ 5.64~5.46, C_7H (no longer allylic) was at δ 3.44 (compared to 3.71), the bisallylic proton was at 3.25 compared to 3.04 ($C_{11}H$ in **2**, $C_{15}H$ in **1**) and 26-CH_3 was at 1.73 (compared to 1.64). A methyl group (27 or 28) at δ 1.01 in **1** shifted to between δ 0.94~0.84 in **4** and overlapped the triplet due to 24-CH_3. All these changes are consistent with the rearrangement of **1** to **2**.

Differences in the chemistry of **1** and **2** result from the fact that **1** contains the strained divinylcyclopropane system and **2** does not. Thus **1** and corresponding triol (**1a**) gave dihydro derivatives when reduced with lithium/liquid ammonia/ethanol and decahydro derivatives on catalytic reduction respectively, due to reductive cleavage of the cyclopropane ring. Triol **5** gave the expected octahydro product (**7**) on catalytic hydrogenation and was not reduced by lithium/liquid ammonia/ethanol.

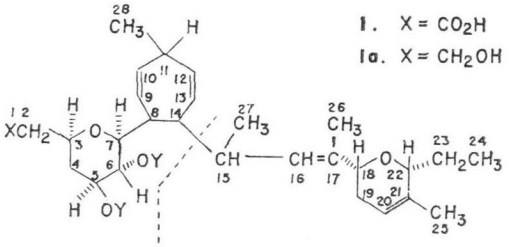
The rearrangement provided further evidence for the existance of the divinylcyclopropane system in **1** and indicated *trans* arrangement of the two vinyl groups on the cyclopropane ring. The structure

* To whom inquiries should be directed.
** Present address, ICI North America, Wilmington, Delaware.

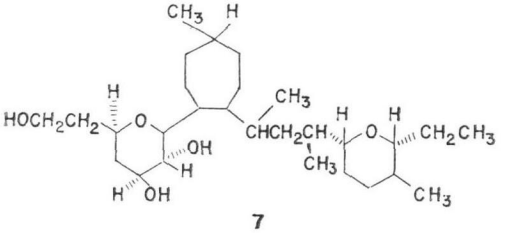
Scheme 1.



1. X = CO_2H
1a. X = CH_2OH



2. X = CO_2H, Y = H
3. X = CO_2CH_3, Y = H
4. X = CO_2H, Y = $COCH_3$
5. X = CH_2OH, Y = H
6. X = CH_2OCOCH_3, Y = $COCH_3$



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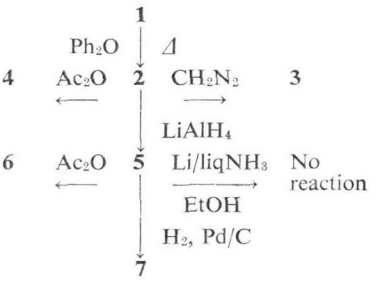
Scheme 2.



of **1** was eventually unequivocally established by single crystal X-ray analysis[1], confirming **2** as the structure of the rearrangement product.

The TLC mobility of **2** was compared to the mobilities of the compounds in the ethyl acetate extract of the fermentation broth. In contrast to certain seaweeds[4], in which divinylcyclopropanes and the corresponding cycloheptadienes occur together, no **2** was detected in the fermentation broth of *Polyangium cellulosum* var. *fulvum*. Also the expectation that the rearrangement would provide a new series of antifungal agents was not realized. Acid **2** was devoid of antifungal activity indicating activity strongly depends on the geometry provided by atoms 8 to 14 in **1**.

Experimental

^1H NMR spectra were run in $CDCl_3$ on a Varian HR-220 spectrometer with Me_4Si used as internal standard. Infrared spectra were recorded on a Perkin-Elmer 700 spectrometer. Mass spectra were obtained with an AEI MS-902 instrument. TLC was performed on silica gel plates (Quantum) using iodine vapor for visualization.

Rearrangement of **1** to Cycloheptadiene Derivative **2**

A solution of **1** (150 mg) in diphenyl ether (10 ml) was heated at 240 under nitrogen for 10 minutes. The reaction mixture was cooled and poured into petroleum ether (200 ml) to precipitate the product. The solvents were decanted to give the product as an off-white powder. The product was purified by preparative TLC with the solvent system ethyl acetate - cyclohexane (4: 1) to give **2** as a white amorphous powder (homogeneous by TLC) (73 mg, 48%). IR (film) 3600~3200 (OH), 2800~2400 (OH), 1720 cm^{-1} (CO); mass spectrum *m/e* (relative intensity) 474 (15), 456 (10), 445 (23), 297 (35), 279 (75), 193 (100).

Preparation of Ester **3**

Diazomethane in ether was added to a solution of **2** (5 mg) in methanol (2 ml) until TLC indicated the absence of **2** in the mixture. The solvents were evaporated to give **3** as a colorless oil (homo-

geneous by TLC), IR (film) 3600~3200 (OH), 1730 cm^{-1} (CO).

Preparation of Diacetate **4**

Acetic anhydride (0.5 ml) was added to a solution of **2** (50 mg) in pyridine (1.0 ml). The reaction mixture was allowed to stand at room temperature overnight. A few drops of water were added and the solvents were removed at reduced pressure to give a colorless oil (homogeneous by TLC) (55 mg, 93%); IR (film) 3600~3200 (OH), 2800~2400 (OH), 1745 (CO), 1720 cm^{-1} (CO); ^1H NMR δ 5.64~5.46 (m, 5, C_9H, $C_{10}H$, $C_{12}H$, $C_{13}H$, $C_{20}H$), 5.21 (m, 1, $C_{16}H$), 5.05~4.77 (m, 2, C_5H, C_6H), 4.05 (bs, 1, $C_{22}H$), 3.94 (m, 1, C_3H), 3.81 (dd, 1, $C_{18}H$), 3.44 (d, 1, C_7H), 3.25 (m, 1, $C_{11}H$), 2.68~2.41 (m, 2, C_2H), 2.01 (s, 3, CH_3CO), 2.00 (s, 3, CH_3CO), 1.73 (s, 3, 26-CH_3), 1.58 (s, 3, 25-CH_3), 1.09 (d, 3, CH_3-CH), 0.94~0.84 (m, 6, CH_3CH and CH_3CH_2); mass spectrum *m/e* (relative intensity) 558 (10), 529 (33), 463 (8), 365 (6), 363 (8), 305 (14), 303 (12), 245 (24), 193 (100). Found: M^+-29, 529.2780; $C_{30}H_{41}O_8$ requires 529.2801.

Preparation of Triol **5**

Lithium aluminum hydride (20 mg) was added to a solution of **2** (22 mg) in THF (5 ml). The reaction mixture was refluxed with stirring under nitrogen for 4 hours. The mixture was cooled in an ice-bath, and a few drops of water were added, followed by magnesium sulfate (50 mg). The inorganic solids were filtered off and washed with ethyl acetate. The filtrate and washings were evaporated to give a colorless gum. The product was purified by preparative TLC with the solvent system ethyl acetate - cyclohexane (4: 1) to give a colorless gum (homogeneous by TLC) (13 mg, 61%); IR (film) 3600~3200 cm^{-1} (OH); mass spectrum *m/e* (relative intensity) 460 (24), 442 (15), 431 (26), 297 (24), 277 (90), 265 (100), 247 (50), 193 (100). Found: M^+ 460.3142; $C_{28}H_{44}O_5$ requires 460.3189.

Preparation of Triacetate **6**

Triol **5** (10 mg) was acetylated by the method described above to give **6** as a colorless oil (homogeneous by TLC) (10 mg, 78%); IR (film) 1740 cm^{-1} (CO); mass spectrum *m/e* (relative intensity) 586 (8), 557 (20), 491 (6), 391 (6), 371 (3), 331 (3), 287 (35), 283 (16), 227 (25), 193 (100). Found: M^+-29, 557.3029; $C_{32}H_{45}O_8$ requires 557.3101.

Preparation of Octahydrotriol **7**

A solution of triol **5** (10 mg) in absolute ethanol (10 ml) was hydrogenated over 10% palladium on carbon at atmospheric pressure for 4 hours. The catalyst was filtered off and washed with ethanol. The filtrate and washings were evaporated to give a colorless oil (homogeneous by TLC) (5 mg, 49%); IR (film) 3600~3200 cm^{-1} (OH); mass spectrum *m/e* (relative intensity) 468 (3), 466 (4), 450 (8), 432 (2), 407 (3), 344 (8), 337 (37), 319 (11), 269 (6), 253 (10), 167 (40), 154 (50), 127 (100). Found: M^+ 468.3718; $C_{28}H_{52}O_5$ requires 468.3814.

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