Tetrahedron Letters No. 17, pp 1577 - 1580, 1973. Pergamon Press. Printed in Great Britain.

TRANSFORMATION OF TOXOFLAVIN INTO FERVENULIN VIA 1-DEMETHYLTOXOFLAVIN

Fumio Yoneda and Tomohisa Nagamatsu

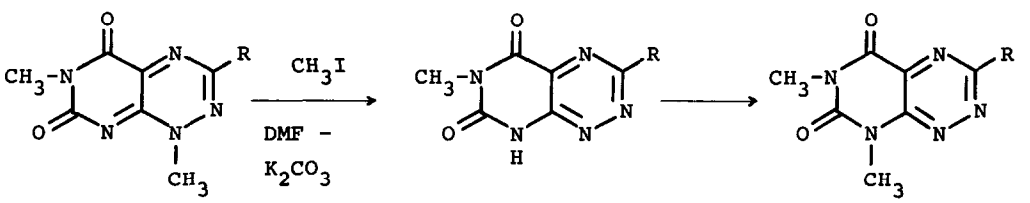
Faculty of Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan

(Received in Japan 6 February 1973; received in UK for publication 20 March 1973)

Toxoflavin (I) (1), one of the toxic principles produced by Pseudomonas cocovenenans (identical with xanthothricin (2) isolated from cultures of an organism similar to Streptomyces albus), is isomeric with fervenulin (II) (3-6) isolated from Streptomyces fervens n. sp. (identical with planomycin (7) isolated from Streptomyces rubrireticuli). Compounds I and II, together with 2-methylfervenulone (8), form an interesting class of antibiotics having pyrimido[5,4-e]-as-triazine as their basic ring system. The present paper describes the transformation of toxoflavin and its derivatives into fervenulin and its derivatives.

Heating I under reflux with methyl iodide in dimethylformamide containing anhydrous potassium carbonate for 2 hr, followed by concentration of the reaction mixture in vacuo and treatment of the residue with water, caused II to separate in 35% yield and in a good state of purity. The product was identical in all respects with an authentic sample (5) prepared by an alternative route. Similarly, heating other toxoflavin derivatives (1) with methyl iodide in dimethylformamide in the presence of potassium carbonate led to formation of the respective 3-substituted fervenulins (TABLE I).

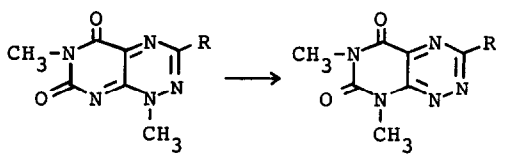
The reaction essentially involves the demethylation of the toxoflavins to



I (R = H) III II (R = H)

1-demethyltoxoflavins (8-demethylfervenulins) (III), then alkylation of the latters with methyl iodide. Both heating toxoflavins with excess methyl iodide in dimethylformamide in the absence of potassium carbonate, and heating toxoflavins alone in dimethylformamide in the presence of potassium carbonate yielded only the corresponding III in almost quantitative yields. On using dimethyl sulfoxide instead of dimethylformamide under similar conditions, the demethylation did not occur, but the starting material was recovered. The reaction was likewise not effected by ethanol or by water. Thus dimethylformamide proves to be an useful reagent for the demethylation of toxoflavins into III, and a number of III have actually been synthesized by refluxing 1 part of the corresponding toxoflavin in 5 parts of dimethylformamide for 30 min followed by dilution with water (TABLE II). It should be noted that III have previously been prepared by multiple step (9).

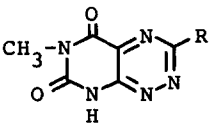
TABLE I Conversion of Toxoflavins (1) into Fervenulins (5)



R in Starting Materials and Products	Yield (%)
Hydrogen	35
Phenyl	52
4-Chlorophenyl	61
3,4-Dimethoxyphenyl	57
3-Pyridyl	66

Next, the alkylation of 3-phenyltoxoflavin, a member of toxoflavin derivatives, with several alcohols in the presence of diethyl azodicarboxylate and triphenylphosphine was carried out to obtain the respective homologs of 3-phenylfervenulin (TABLE III). This procedure is an application of the known alkylation of oxidation-reduction process (10). A typical example is as follows. Refluxing a mixture of 3-phenyltoxoflavin (0.5 g, 0.00196 mole) and ethylene

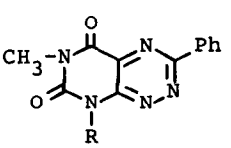
TABLE II Preparation of 1-Demethyltoxoflavins[a)]



3-Substituent (R)	M.p. (°C)	Yield (%)
Hydrogen	210 (dec.)	85
Methyl	247 (dec.)	89
Phenyl	>300	93
4-Chlorophenyl	>300	98
3,4-Dichlorophenyl	>300	98
3,4-Dimethoxyphenyl	>300	95
Styryl	>300	95
2-Pyridyl	>300	96
3-Pyridyl	>300	97
4-Pyridyl	>300	80
2-Thienyl	>300	88

a) All products were recrystallized from EtOH or DMF.

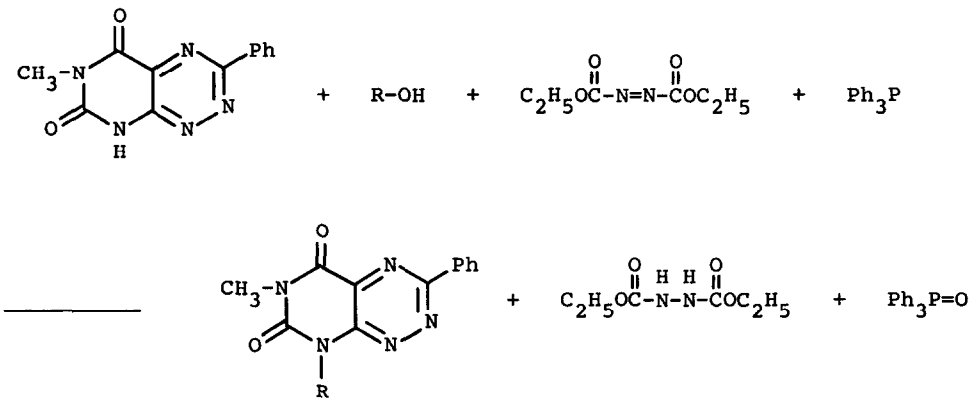
TABLE III Preparation of 1-Substituted 3-Methyl-6-phenyl-7-azalumazines[a)]



1-Substituent (R)	M.p. (°C)	Yield (%)
Methyl	276	51
Ethyl	223	60
n-Propyl	214	67
i-Propyl	226	76
Allyl	213	78
2-Hydroxyethyl	215	95

a) All products were recrystallized from EtOH

glycol (1.23 g, 0.0196 mole) in 40 ml of dioxane in the presence of diethyl azodicarboxylate (0.685 g, 0.00392 mole) and triphenyl phosphine (0.77 g, 0.00284 mole) for 3 hr, concentration of the reaction mixture in vacuo, and treatment of the residue with ethanol caused separation of 1-hydroxyethyl-3-methyl-6-phenyl-7-azalumazine, which was collected by filtration, washed with benzene, and recrystallized from ethanol to give pale yellow crystals.



REFERENCES

(1) F. Yoneda, K. Shinomura and S. Nishigaki, Tetrahedron Letters, 851 (1971) and references therein.

(2) R. A. Machlowitz, W. P. Fisher, B. S. McKey, A. A. Tytell and J. Charney Antibiotics and Chemotherapy, 259 (1954).

(3) G. D. Daves, R. K. Robins and C. C. Cheng, J. Org. Chem., 26, 5256 (1961).

(4) E. C. Taylor and F. Sowinski, J. Am. Chem. Soc., 90, 1374 (1968).

(5) F. Yoneda, M. Kanahori, K. Ogiwara and S. Nishigaki, J. Heterocyclic Chem., 7, 1443 (1970).

(6) G. Blankenhorn and W. Pfleiderer, Chem. Ber., 105, 3334 (1972).

(7) K. Tanabe, Y. Asahi, M. Nishikawa, T. Shima, Y. Kuwada, T. Nanzawa and K. Ogata, Takeda Kenkyusho Nempo, 22, 133 (1963); C. A., 60, 13242 (1963).

(8) E. C. Taylor and F. Sowinski, J. Am. Chem. Soc., 91, 2143 (1963).

(9) T. K. Liao, F. Baiocchi and C. C. Cheng, J. Org. Chem., 31, 900 (1966).

(10) O. Mitsunobu, M. Wada and T. Sano, J. Am. Chem. Soc., 91, 2143 (1969).