Tetrahedron Letters No.13, pp. 851-854, 1971. Pergamon Press. Printed in Great Britain.

A CONVENIENT SYNTHESIS OF TOXOFLAVINS AND TOXOFLAVIN-N-OXIDES

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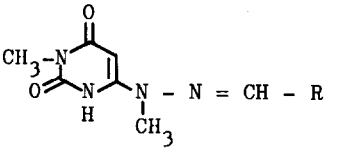
(Received in Japan 14 December 1970; received in UK for publication 9 March 1971)

The structure of toxoflavin, an antibiotic isolated from Pseudomonas cocovenenans, was determined by total synthesis in 1961 (1). The antibiotic xanthothricin (2) from a member of the genus Streptomyces was confirmed as being identical with toxoflavin (3). This communication describes a convenient synthesis of toxoflavins and some toxoflavin-4-oxides.

Stirring of 3-methyl-6-(1'-methylhydrazino)-uracil (I) (4) in acetic acid with equimolar 37% formaldehyde under cooling at 5° for ca 15 min gave the hydrazone, which was in situ treated with equimolar sodium nitrite (saturated aqueous solution) for 20 min. Dilution of the reaction mixture with ether gave a mixture of toxoflavin (II) and its 4-oxide (III), m.p. 215° (dec.), in 40 and 25% yield respectively, which were separated by preparative thin-layer chromatography [Silica Gel G acc. to Stahl, $CHCl_3$-MeOH (9:1)]. II was in all respects identical with an authentic sample (4). The structure of III was assigned by elemental analysis, satisfactory spectral data, especially the presence of a strong parent ion (m/e 209) and a remarkable M-16 ion in its mass spectrum, and also a speculative mechanism of the formation. The assigned structure was confirmed with the formation of II by its mild reduction in methanol using benzenethiol at room temperature, the latter being converted into phenyl disulfide (see Scheme). III, and IV and V (vide infra) are the first representatives of the azapteridine-N-oxide system. II was also obtained in moderate yield by treatment of the hydrazone in ethanol-acetic acid (3:2) with equimolar isoamyl nitrite at 20° for 30 min. In this case, however, III could not be detected.

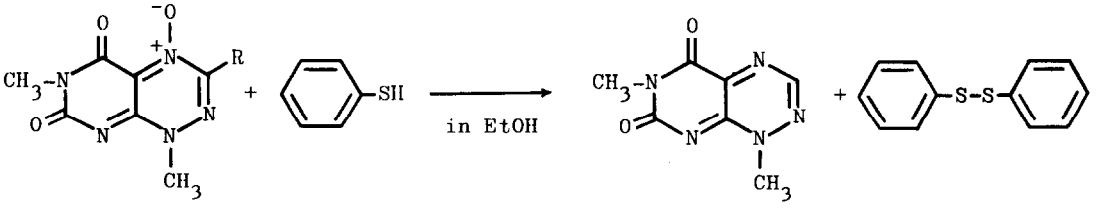
TABLE I

Preparation of The Hydrazones of 3-Methyl-6-(1'-methylhydrazino)-uracil



Aldehyde	R in Product[a)]	M.p. (°C)	Yield (%)
Acetaldehyde	Methyl	182-183	92
Benzaldehyde	Phenyl	237-238	93
p-Chlorobenzaldehyde	p-Chlorophenyl	192-193	76
3,4-Dichlorobenzaldehyde	3,4-Dichlorophenyl	260-261	84
Veratraldehyde	3,4-Dimethoxyphenyl	211-212	87
Cinnamaldehyde	Styryl	249-251	88
Picolinaldehyde	2-Pyridyl	248-249	89
Nicotinaldehyde	3-Pyridyl	216-218	85
Isonicotinaldehyde	4-Pyridiyl	268-270	90
Thiophene-2-aldehyde	2-Thienyl	229-230	74

a) All compounds were recrystallized from EtOH.



(III) R = H

(IV) R = C_6H_4Cl (p)

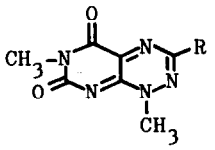
(V) R = $C_6H_3Cl_2$ (3,4)

(II) toxoflavin

Scheme

TABLE II

Preparation of Toxoflavin and Its Derivatives[a)]



3-Substituent (R)	Procedure	M.p. (°C)	Yield (%)
Hydrogen (4)	$NaNO_2$ in AcOH, 5°, 20 min	172	40
	Isoamyl nitrite in EtOH+AcOH (3:2), 20°, 30 min		35
Methyl (4)	$NaNO_2$ in AcOH, 5°, 20 min	180-181	53
Phenyl	$NaNO_2$ in AcOH, 5°, 20 min	197	65
3,4-Dimethoxyphenyl	$NaNO_2$ in AcOH, 5°, 20 min	229	67
Styryl	Isoamyl nitrite in EtOH, 80°, 30 min	210-213	67
2-Pyridyl	$NaNO_2$ in AcOH, 5°, 20 min	210	74
3-Pyridyl	$NaNO_2$ in AcOH, 5°, 20 min	205 (dec.)	59
4-Pyridyl	$NaNO_2$ in AcOH, 5°, 20 min	209 (dec.)	35
2-Thienyl	Isoamyl nitrite in EtOH+trace of HCl, 45°, 30 min	233	57

a) All products were recrystallized from MeOH or EtOH. Satisfactory analytical and spectral data were obtained for all the products.

Similarly, I and other several aldehydes yielded the corresponding stable hydrazones (TABLE I), which were treated with the nitrosating agents described above under similar conditions to give the respective 3-substituted toxoflavins in satisfactory yields (TABLE II). The reaction can naturally be performed in a single step without isolation of the hydrazones to give the almost same yields of the products. It is known that under nitrosation conditions some 5-nitroso-6-substituted-amino (or -hydrazino)-uracils undergo simultaneous cyclization (5,6); this also appears to be the case in the above nitrosative cyclization. It should be noted that nitrosation of p-chloro- and 3,4-dichlorobenzaldehyde hydrazones by sodium nitrite in acetic acid did not give the corresponding toxoflavins but 3-(p-chlorophenyl- (IV), m.p. 207°, and 3-(3,4-dichlorophenyl)-toxoflavin-4-oxide (V), m.p. 222°, as the sole products, in 38 and 45% yield respectively. Searches into the reaction conditions to get the toxoflavins themselves or to get other toxoflavin-4-oxides are continuously being made.

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