A New Method for the Transformation of Toxoflavins to Fervenulins

Fumio Yoneda and Tomohisa Nagamatsu*

Faculty of Pharmaceutical Sciences, Kumamoto University,
Oe-honmachi, Kumamoto 862, Japan

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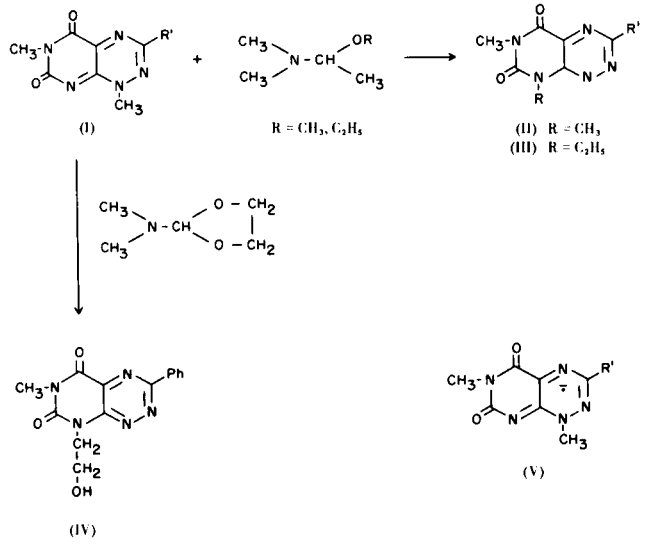
A recent investigation in this laboratory has shown that treatment of toxoflavin and its derivatives with methyl iodide in dimethylformamide containing anhydrous potassium carbonate resulted in the formation of fervenulin and its derivatives (1). The reaction essentially involved the demethylation of the toxoflavins to 1-demethyltoxoflavins, then methylation of the latter compounds with methyl iodide. A possible reaction mechanism has been proposed for this novel demethylation with dimethylformamide (2). The present paper describes a new convenient method for the transformation of toxoflavin derivatives into fervenulin derivatives.

Scheme I



A suspension of 1 part of the toxoflavins (I) (3) in 10 parts of dimethylformamide dimethyl acetal (4) was stirred under gentle reflux for 30 minutes and then the reaction mixture was cooled for a few hours. The crystals thus separated were collected by filtration and washed with ether to give the corresponding fervenulins (II) (5,6) in high yields and in a good state of purity (see Table I).

Similarly, the heating of I with dimethylformamide diethyl acetal (4,8) led to the formation of the 8-ethyl homologs of fervenulins, 6-substituted 1-ethyl-3-methyl-7-azalumazines (III). These compounds were identified by comparison with authentic samples prepared by the ethylation of the corresponding 1-demethyltoxoflavins (1) with ethyl iodide in the presence of potassium carbonate in dimethylformamide.

Next, the heating of 3-phenyltoxoflavin with dimethylformamide ethylene acetal (2-dimethylamino-1,3-dioxolane) (8) under mild reflux followed by concentration and dilution with ethanol caused the separation of 1-(2-hydroxyethyl)-3-methyl-6-phenyl-7-azalumazine (IV), which was in all respects identical with the authentic sample prepared by the hydroxyethylation of 1-demethyl-3-phenyltoxoflavin (1).

Furthermore, we have observed the respective transient radicals by esr measurements during the reactions described above. Radical formation is characterized by a color change of the reaction mixtures to dark green, which slowly disappeared. These radicals have been shown to be identical with the toxoflavin radical anions (V) which have already been analyzed (2).

A possible reaction mechanism involves a nucleophilic attack of the dimethylformamide acetals on I to displace the respective 1-demethyltoxoflavin anions, which are alkylated at position 8 with the acetals to give the corresponding fervenulin derivatives. On the other hand, the transient formation of V would be due to the electron transfer to I from the 1-demethyltoxoflavin anions as good reducing agents.

An another plausible explanation of the mechanism would be the alkylation (quaternization) of I at position 8 by the dimethylformamide acetals. It is possible that quaternization at *N*-8 takes place with simultaneous loss of the *N*-1 methyl group to give rise to the thermodynamically more stable fervenulin derivatives.

EXPERIMENTAL (9)

Transformation of Toxoflavins (I) into Fervenulins (II).

General Procedure.

A mixture of 0.5 g. of the toxoflavin derivative in 5 ml. of dimethylformamide dimethyl acetal was stirred under mild reflux for 30 minutes and then cooled in a refrigerator for 2-3 hours. The crystals thus separated were collected by filtration.

TABLE I

Conversion of Toxoflavins (3) into Fervenulins (5,6)

Starting Material (M.p., °C)	Product (M.p., °C)	Yield (%)
Toxoflavin (172)	Fervenulin (175)	69
3-Phenyltoxoflavin (197)	3-Phenylfervenulin (270)	90
3-(4-Chlorophenyl)toxoflavin (207)	3-(4-Chlorophenyl)fervenulin (280)	89
3-(4-Methoxyphenyl)toxoflavin (244) (a)	3-(4-Methoxyphenyl)fervenulin (268) (d)	79
3-(3,4-Dimethoxyphenyl)toxoflavin (229)	3-(3,4-Dimethoxyphenyl)fervenulin (305)	75
3-(3,4-Methylenedioxyphenyl)toxoflavin (265) (b)	3-(3,4-Methylenedioxyphenyl)fervenulin (274)	85
3-(4-Dimethylaminophenyl)toxoflavin (>300) (c)	3-(4-Dimethylaminophenyl)fervenulin (>300)	83
3-(3-Pyridyl)toxoflavin (205)	3-(3-Pyridyl)fervenulin (213)	85
3-(4-Pyridyl)toxoflavin (209)	3-(4-Pyridyl)fervenulin (262)	70

(a) *Anal.* Calcd. for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.38; N, 23.40. Found: C, 56.04; H, 4.35; N, 23.26. (b) *Anal.* Calcd. for $C_{14}H_{11}N_5O_4$: C, 53.67; H, 3.54; N, 22.36. Found: C, 53.70; H, 3.61; N, 22.29. (c) *Anal.* Calcd. for $C_{15}H_{16}N_6O_2$: C, 57.68; H, 5.16; N, 26.91. Found: C, 57.44; H, 5.08; N, 26.73. (d) *Anal.* Calcd. for $C_{14}H_{13}N_5O_3$: C, 56.18; H, 4.38; N, 23.40. Found: C, 56.22; H, 4.37; N, 23.37.

TABLE II

6-Substituted 1-Ethyl-3-methyl-7-azalumazines

Substituent	M.p., °C	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Phenyl	228	62	$C_{14}H_{13}N_5O_2$	59.35	4.63	24.72	59.31	4.70	24.50
p-Chlorophenyl	255	60	$C_{14}H_{12}ClN_5O_2$	52.92	3.81	22.04	52.87	3.77	22.24
p-Dimethylaminophenyl	258	52	$C_{16}H_{18}N_6O_2$	58.88	5.56	25.75	58.99	5.35	25.49
3,4-Methylenedioxyphenyl	238	63	$C_{15}H_{13}N_5O_4$	55.04	4.00	21.40	55.03	3.73	21.22

The filtrate was evaporated *in vacuo* leaving more crystals. The combined crystals were washed with ether and recrystallized from ethanol to give a fervenulin derivative, which was in all respects identical with an authentic sample formed by the known reaction of 6-amino-1,3-dimethyl-5-nitrosouracil and the corresponding aldehyde hydrazone (5).

Transformation of Toxoflavins (I) into 8-Ethyl Homologs of Fervenulins (III).

General Procedure.

A mixture of 0.5 g. of the toxoflavin derivative in 5 ml. of dimethylformamide diethyl acetal was heated under mild reflux for 1 hour and then the reaction mixture was evaporated *in vacuo*. The resulting residue was recrystallized from ethanol to give the corresponding 8-ethyl homolog of fervenulin, 1-ethyl-3-methyl-7-azalumazine derivative (see Table II).

Ethylation of 1-Demethyltoxoflavins with Ethyl Iodide.

General Procedure.

A mixture of 0.5 g. of a 1-demethyltoxoflavin derivative, 1 g. of ethyl iodide and 0.5 g. of potassium carbonate in 15 ml. of dimethylformamide was refluxed under stirring for 2-3 hours. After evaporation of the solvent, the residue was diluted with 50 ml. of water and the crystals which separated were recrystallized from ethanol to give the corresponding 1-ethyl-3-methyl-7-azalumazine in a high yield.

1-(2-Hydroxyethyl)-3-methyl-6-phenyl-7-azalumazine (IV).

A mixture of 0.5 g. (0.0019 mole) of 3-phenyltoxoflavin in 5 ml. of dimethylformamide ethylene acetal was refluxed for 2 hours. After evaporation of the acetal, the residue was recrystallized from ethanol to give 0.4 g. (72%) of yellow crystals, m.p. 209°, which was in all respects identical with an authentic sample (1); mass spectrum m/e: 299 (M^+).

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