Synthesis and Properties of 6-Benzyl Analogs of Toxoflavin

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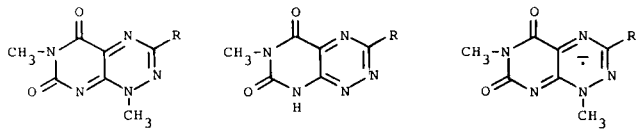
Previously, it was reported that the antibiotic toxoflavin and analogs (I) undergo demethylation with dimethylformamide to give the corresponding 1-demethyltoxoflavins (8-demethylfervenulins) (II) (1) and that during the reactions, the toxoflavin radical anions (III) are observed (2). The present paper describes the synthesis of the 6-benzyl analogs of toxoflavin and their demethylation reaction with dimethylformamide.

SCHEME I



I II III

Treatment of 3-benzyl-6-chlorouracil (3) with methylhydrazine in ethanol gave 3-benzyl-6-(1′-methylhydrazino)-uracil (IV), which was converted into the key intermediates, 3-benzyl-6-(benzylidene-1′-methylhydrazino)-uracils (V) by treatment with several aromatic aldehydes in ethanol (Table I). Stirring of V in acetic acid with equimolar sodium nitrite at 0° for 30 minutes, followed by dilution with ether gave the corresponding benzyl analogs of toxoflavin, 3-substituted 6-benzyl-1-methylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,1*H*)diones (VI) (Table II).

The structures of VI were established by microanalyses, by molecular weight determinations by mass spectrometry, and by the quite similar ir and uv spectra to those of the corresponding toxoflavins.

The behavior of VI toward dimethylformamide was also similar to that of toxoflavins. Namely, heating VI in dimethylformamide under reflux for 5 minutes led to the dark green solutions, in which esr signals were observed. After refluxing for 30 minutes, the reaction mixtures were cooled to separate the final products, 3-benzyl analogs of 1-demethyltoxoflavin (VII), in almost quantitative yields (Table III).

Figure I shows the radical observed during the reaction of 6-benzyl-1-methyl-3-phenylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,1*H*)dione (VIa) with dimethylformamide. The same esr spectrum was obtained by reaction of VIa with potassium *t*-butoxide in dimethylformamide. Therefore, the signal is undoubtedly the radical anion of VIa (VIa$^{\cdot-}$). The hyperfine structure consists of 10 lines with approximate intensity ratios 1:6:18:35:48:48:35:18:6:1, analogously to the toxoflavin radical anions. This spectrum can be explained by the synthesis based on the following coupling constants: $a_{N_1} \doteq a_{N_2} \doteq a_{N_4} \doteq a_{H(N_1\text{-}CH_3)} =$

TABLE I

Preparation of 3-Benzyl-6-(benzylidene-1′-methylhydrazino)uracils (V)

No	R	M.p., °C	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Va	Phenyl	195	85	$C_{19}H_{18}N_4O_2$	68.24	5.42	16.76	68.20	5.41	16.59
Vb	4-Chlorophenyl	243	95	$C_{19}H_{17}ClN_4O_2$	61.87	4.65		61.68	4.63	
Vc	3,4-Dichlorophenyl	195	96	$C_{19}H_{16}Cl_2N_4O_2$	56.59	3.99		56.44	3.97	
Vd	Styryl	150	82	$C_{21}H_{20}N_4O_2$	69.98	5.59	15.55	69.84	5.52	15.28
Ve	3-Pyridyl	118	75	$C_{18}H_{17}N_5O_2$	64.46	5.11	20.89	64.44	5.06	20.94
Vf	4-Pyridyl	(a)	70	$C_{18}H_{17}N_5O_2$						

(a) Used for next step without purification.

TABLE II

Preparation of 6-Benzyl Analogs of Toxoflavin (VI)

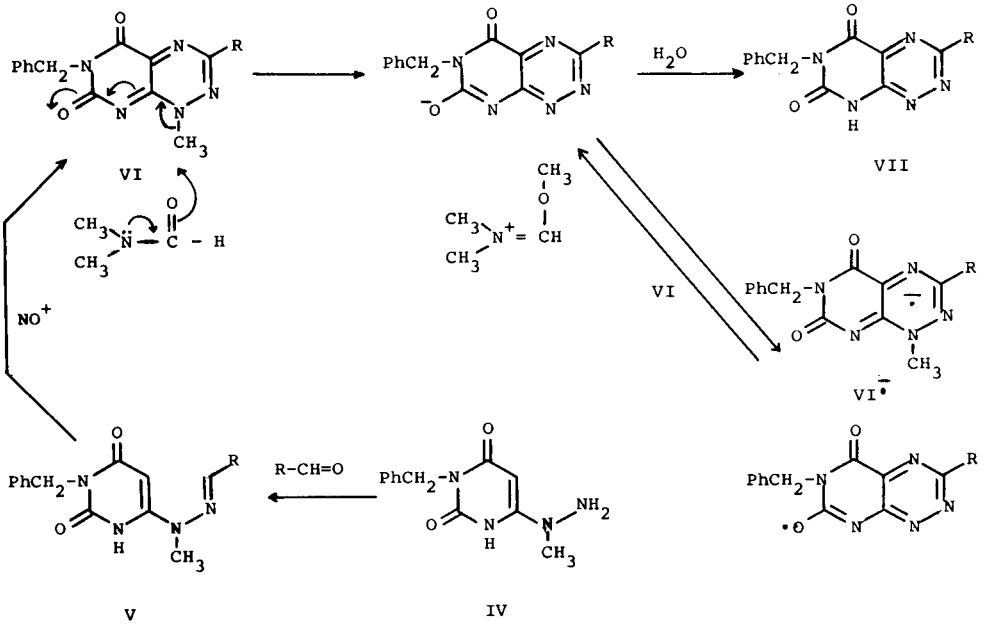
No	R	M.p., °C	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIa	Phenyl	223	69	$C_{19}H_{15}N_5O_2$	66.07	4.38	20.28	66.14	4.45	20.06
VIb	4-Chlorophenyl	175	71	$C_{19}H_{14}ClN_5O_2$	60.08	3.72	18.44	60.01	3.66	18.32
VIc	3,4-Dichlorophenyl	195	55	$C_{19}H_{13}Cl_2N_5O_2$	55.35	3.16	16.91	55.37	3.08	16.78
VId	Styryl	126	70	$C_{21}H_{17}N_5O_2$	67.91	4.61	18.86	67.82	4.43	18.87
VIe	3-Pyridyl	137	75	$C_{18}H_{14}N_6O_2$	62.42	4.07	24.27	62.09	3.89	24.06
VIf	4-Pyridyl	121	66	$C_{18}H_{14}N_6O_2$	62.42	4.07	24.27	62.30	3.91	24.16

TABLE III

Preparation of 6-Benzyl Analogs of 1-Demethyltoxoflavin (VII)

No	R	M.p., °C	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIIa	Phenyl	>300	100	$C_{18}H_{13}N_5O_2$	65.25	3.96	21.14	65.07	3.90	21.06
VIIb	4-Chlorophenyl	>300	100	$C_{18}H_{12}ClN_5O_2$	59.10	3.31		59.42	3.22	
VIIc	3,4-Dichlorophenyl	>300	92	$C_{18}H_{11}Cl_2N_5O_2$	54.02	2.77		53.89	2.73	
VIId	Styryl	>300	95	$C_{20}H_{15}N_5O_2$	67.22	4.23	19.60	67.14	4.19	19.29
VIIe	3-Pyridyl	>300	98	$C_{17}H_{12}N_6O_2$	61.44	3.64	25.29	61.45	3.54	25.07
VIIf	4-Pyridyl	>300	99	$C_{17}H_{12}N_6O_2$	61.44	3.64		61.23	3.71	

SCHEME II



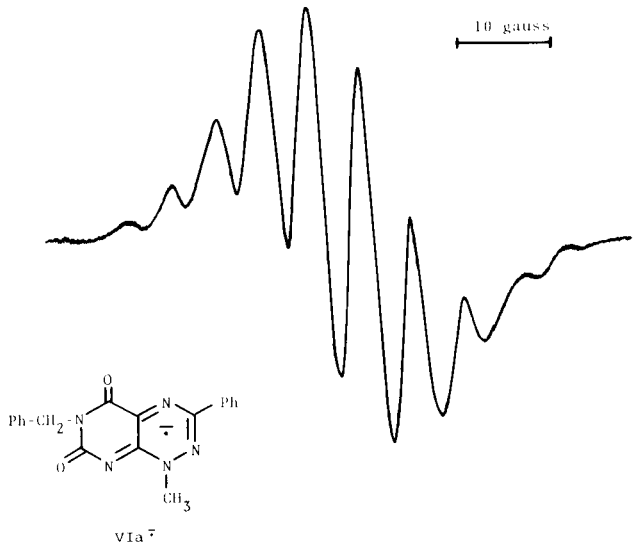


Figure 1

Figure 1. First derivative esr spectrum of 6-benzyl-1-methyl-3-phenylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,1*H*)-dione radical anion in dimethylformamide.

5.20 gauss. These facts suggest that the mechanism depicted in Scheme II is the most reasonable. This is the same essentially as the demethylation mechanism of toxoflavins themselves.

EXPERIMENTAL (4)

3-Benzyl-6-(benzylidene-1′-methylhydrazino)uracils (V); General Procedure.

To a stirred solution of 3-benzyl-6-(1′-methylhydrazino)uracil (IV) (0.01 mole) in ethanol (100-200 ml.) was added an aromatic aldehyde (0.015-0.02 mole) at room temperature. After stirring was continued for 2 hours, the product which separated was collected by filtration, dried and recrystallized from methanol to give colorless needles.

3-Substituted 6-Benzyl-1-methylpyrimido[5,4-*e*]-*as*-triazine-5,7-(6*H*,1*H*)dione (6-Benzyl Analogs of Toxoflavin) (VI); General Procedure.

To a solution of V (0.01 mole) in acetic acid (50 ml.) was added drop by drop saturated aqueous solution of equimolar sodium nitrite under stirring and cooling at 0°. After stirring for 30 minutes, the reaction mixture was diluted with water to separate yellow crystals, which were filtered and recrystallized from alcohol to give yellow needles.

3-Substituted 6-Benzylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)dione (6-Benzyl Analogs of 1-Demethyltoxoflavin) (VII); General Procedure.

A solution of 1 part of a 6-benzyl analog of toxoflavin (VI) in 5 parts of dimethylformamide was refluxed for 30 minutes, followed by cooling in a refrigerator, to separate the demethylated product. Recrystallization from dimethylformamide gave pale yellow prisms.

3-Benzyl-6-(1′-methylhydrazino)uracil (IV).

To a solution of 2.37 g. (0.01 mole) of 3-benzyl-6-chlorouracil in 100 ml. of absolute ethanol was added dropwise 2.30 g. (0.05 mole) of methylhydrazine under stirring. After heating on the hot plate to boiling, the solution was stirred at room temperature for 1 hour. The solvent and excess methylhydrazine were evaporated and the residue was recrystallized from ethanol to give 2.34 g. (95%) of colorless crystals, m.p. 166-168°.

Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.52; H, 5.73; N, 22.75. Found: C, 58.38; H, 5.71; N, 22.60.

REFERENCES

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(3) H. Goldner, G. Dietz, and E. Carstens, *Ann. Chem.*, **691**, 142 (1966).

(4) All melting points were determined on a Yanagimoto Micro-Melting Point Apparatus and are uncorrected.