Tetrahedron Letters No. 45, pp 4271 - 4274, 1971. Pergamon Press. Printed in Great Britain.

A NOVEL SYNTHESIS OF PYRIMIDOPTERIDINE-10-OXIDES

Yoshifumi Maki, Magoichi Sako[a] and Edward C. Taylor[b]

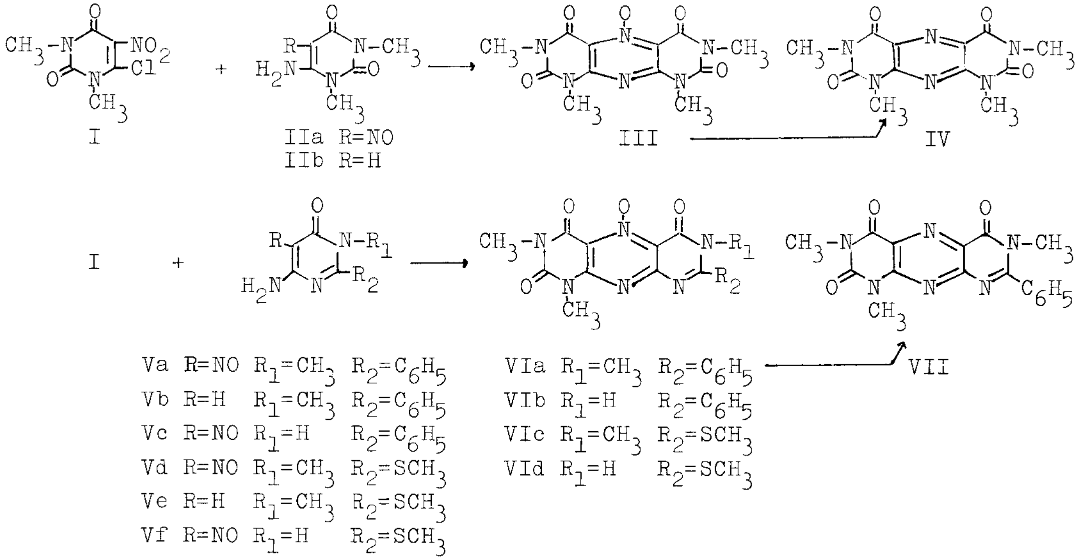
a) Gifu College of Pharmacy, Mitahora, Gifu, Japan

b) Department of Chemistry, Princeton University,
Princeton, N.J., U.S.A.

(Received in Japan 13 September 1971; received in UK for publication 6 October 1971)

Recent works[1)2)] have demonstrated the unusual lability of a 5-nitro grouping on the uracil ring toward elimination. We have exploited its remarkable chemical nature for a one-step synthesis of pyrazolo(3,4-d)pyrimidines[3)].

In the further study on the reactivity of the nitro group, we found a novel, widely applicable synthetic route to pyrimidopteridine-10-oxides, (III) and (VI), which are useful intermediates for the preparation of pyrazine- and pteridine-N-oxides. To our best knowledge, this type of thermal N-oxide formation has not been described previously.



Scheme 1

The general procedure is as follows: A mixture of 1,3-dimethyl-5-nitro-6-chlorouracil(I)[4](1 mole) and 6-aminouracils(IIa,b) or 6-amino-4(3H)-pyrimidinones(Va~f)(1 mole) in DMF was heated at reflux for 0.5-1 hr. During the course of the reaction, the color of the reaction mixture was changed from red to yellow. In the reaction of (I) with nitroso compounds, (IIa) and (Va,c,d, f), the liberation of nitrous acid was detected. After standing at room temperature, the reaction mixture deposited the solid mass which was recrystallized to give pure pyrimidopteridine-10-oxides, (III) and (VIa d). Physical properties and synthetic data of (III) and (VIa~d) are listed in the Table below.

Table Physical and synthetic data of pyrimidopteridine-10-oxides

Reactant	Reaction time[a] (hr)	Pyrimidopteridine-10-oxide	Solvent[b]	mp (°C)	Yield (%)
IIa	0.5	III	DMF	350	90
IIb	1	III	DMF	350	50
Va	0.5	VIa	DMF-Et_2O	290	80
Vb	1	VIa	DMF-Et_2O	290	70
Vc	0.5	VIb	DMF-Et_2O	350	55
Vd	0.5	VIc	DMF-Et_2O	282	90
Ve	1	VIc	DMF-Et_2O	282	75
Vf	0.5	VId	DMF-Et_2O	350	35

a) All reactions were carried out in DMF.

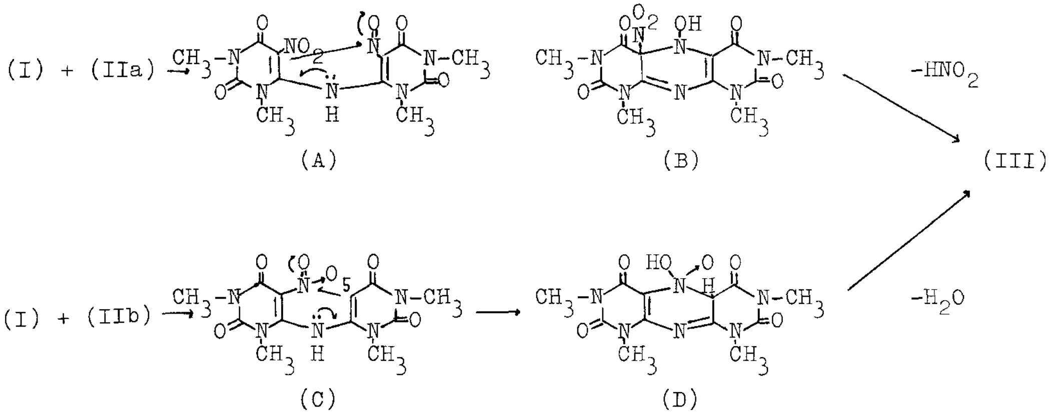
b) Solvent for recrystallization.

1,3,6,8-tetramethyl-2,4,5,7(1H,3H,6H,8H)-pyrimido(5,4-g)pteridinetetrone-10-oxide(III) was identical in every respect with a sample prepared by lead tetraacetate oxidation of (IIa)[5][6]. Deoxygenation of (III) with sodium hydrosulfite gave (IV), identical with an authentic sample[7]. A similar treatment of 2-phenyl-3,6,8-trimethyl-4,5,7(3H,6H,8H)-pyrimido(5,4-g)pteridinetrione-10-oxide(VIa) resulted in the formation of (VII), which was synthesized independently by heating a mixture of (IIb) and (Va) without solvent.

In general, the reaction of (I) with 5-nitroso-6-aminopyrimidinones takes place more readily than that with 6-aminopyrimidinones. For example, while the reaction of (I + IIa → III) completes within 0.5 hr, the reaction of (I + IIb →

III) requires prolonged heating up to about 1 hr. The product (III) in the latter reaction was often contaminated with (IV), whose formation can be ascribed to deoxygenation of the initially formed (III). In fact, the deoxygenation occurs efficiently by heating (III) in DMF.

We tentatively propose the following plausible mechanisms for the above thermal N-oxide formation. (For reactions of (I) with (IIa,b), see Scheme 2.)



Scheme 2

The reaction of (I) with (IIb) appears to consist of the formation of an intermediate(C), the nucleophilic attack on the nitro-nitrogen atom by an electron rich carbon (C_5) of the uracil ring and the elimination of water from the resulting cyclic intermediate (D) to give (III).

The formation of N-oxide via the base- or acid-catalysed reaction of a nitro group with an aliphatic (stabilized) carbanion, a reactive aromatic ring, or an amino group has been extensively studied.8)9)10) However, there has been only an example suggesting the N-oxide formation in the thermal cyclization between an aromatic ring and a nitro group: When heated with sand at high temperature, 2-nitrodiphenylamine yields phenazine, but a possible intermediate phenazine-N-oxide has not been isolated.11)

In the reaction of (I) with (IIa), a nitroso group rather than a nitro group in an intermediate (A) appears to be the origin of the N-oxide grouping in (III). (See (A) in Scheme 1.) Elimination of the mobile nitro group as nitrous acid from an imtermediate (B) leads to the formation of (III).

Recently, cyclization of 6-arylamino-5-nitrosouracils to alloxazine-N-oxides has been reported.12) The reaction, however, involves apparently the oxidative dehydration which is in contrast with the thermal elimination of nitrous acid in our reaction.

We are currently extending our studies on the scope of this most interesting reaction.

The uracil ring of pyrimidopteridine-N-oxides, (III) and (VI), undergoes facile hydrolysis to give pteridine- and pyrazine-N-oxides. This new synthetic route leading to both the N-oxides will be reported in a separated paper.

References and Footnotes

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