

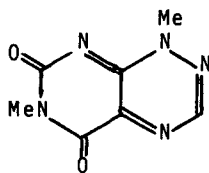
A NOVEL METHOXYLATION DURING OXIDATION OF SIMPLE
DIHYDROPYRIMIDO[5,4-*e*]-*as*-TRIAZINES

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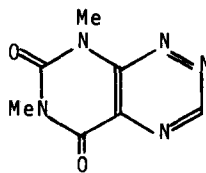
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The discovery and synthesis of the antibiotics toxoflavin⁽¹⁾(I) and fervenulin⁽²⁾(II), has stimulated interest in the chemistry of the pyrimido[5,4-*e*]-*as*-triazines of potential value as antibiotics or antifolates. We report a novel oxidative methoxylation of 1,2-dihydro-3-methylpyrimido[5,4-*e*]-*as*-triazine (IV; R=Me, R'=H), its isomer (IV; R=H, R'=Me) and its homologue (IV; R=R'=Me); and we suggest a rational course for this reaction.



(I)



(II)

The 1,2-dihydropyrimido[5,4-*e*]-*as*-triazines (IV) were conveniently synthesised by reductive cyclisation of the corresponding derivatives (III). Treatment of 4-hydrazino-5-nitropyrimidine⁽³⁾ with triethyl orthoformate gave 4-*β*-ethoxymethylenehydrazino-5-nitropyrimidine (III; R=R'=H), m.p. 151⁰, which was hydrogenated in ethanol over 5% palladised charcoal to 1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (IV; R=R'=H), m.p. ‡ 350⁰ [m/e 135; τ in (CD₃)₂SO: 3.61* (doublet, *J*=3 c.p.s., 3-H), 3.08 (5-H), 2.25 (7-H), 1.92[†](-NH-), and 1.20[†](-NH-)], characterised as its *picrate*, m.p. 197⁰.

* Doublet collapses to singlet with D₂O.

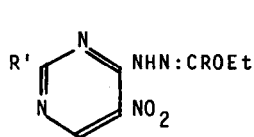
† Broad signal collapses with D₂O.

4- β -(α -Ethoxyethylidene)hydrazino-5-nitropyrimidine (III; R=Me; R'=H), m.p. 137⁰, was made similarly using triethyl orthoacetate and subsequently reductively cyclised to 1,2-dihydro-3-methylpyrimido[5,4-e]-as-triazine (IV; R=Me; R'=H), m.p. †350⁰ [m/e 149; τ in (CD₃)₂S₀: 8.44 (3-Me), 3.10 (5-H), 2.27 (7-H), 1.83[†](-NH-), and 1.20[†](-NH-)], with picrate, m.p. 205⁰. 4-Methoxy-2-methyl-5-nitropyrimidine, m.p. 48⁰, was prepared by silver oxide oxidation of 4-hydrazino-6-methoxy-2-methyl-5-nitropyrimidine. cf.(4) Aminolysis with hydrazine hydrate gave 4-hydrazino-2-methyl-5-nitropyrimidine, m.p. 152⁰ (confirmed in structure by silver oxide oxidation to the known⁽⁵⁾ 2-methyl-5-nitropyrimidine) and subsequent treatment with orthoesters as above gave 4- β -ethoxymethylenehydrazino-2-methyl-5-nitropyrimidine (III; R=H, R'=Me), m.p. 119⁰, and its 4- β -(α -ethoxyethylidene)hydrazino-homologue (III; R=R'=Me), m.p. 129⁰. Reductive cyclisation of these gave respectively 1,2-dihydro-7-methylpyrimido[5,4-e]-as-triazine (IV; R=H, R'=Me), m.p. †350⁰ [m/e 149; τ in (CD₃)₂S₀: 7.99 (7-Me), 3.74^{*} (doublet, $J=3$ c.p.s., 3-H), 3.30 (5-H), 2.12[†](-NH-), and 1.41[†](-NH-)], with picrate, m.p. 199⁰, and 1,2-dihydro-3,7-dimethylpyrimido[5,4-e]-as-triazine (IV; R=R'=Me), m.p. †350⁰ [m/e 163; τ in (CD₃)₂S₀: 8.46 (3-Me), 7.93 (7-Me), 3.10 (5-H), 1.86[†](-NH-), and 1.19[†](-NH-)] with picrate, m.p. 194⁰.

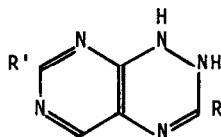
Oxidation of the dihydro compound (IV; R=Me, R'=H) with silver oxide in methanol at room temperature produced 5-methoxy-3-methylpyrimido[5,4-e]-as-triazine (V; R=R''=Me; R'=H), m.p. 169⁰ [m/e 177; τ in CDCl₃:6.77 (3-Me), 5.68 (5-OMe), and 0.92 (2-H); ν_{\max} (Nujol mull) 1135 cm.⁻¹ (-OMe)]. The isomeric dihydro compound (IV; R=H, R'=Me) similarly gave 5-methoxy-7-methylpyrimido[5,4-e]-as-triazine (V; R=H, R'=R''=Me), m.p. 110⁰ [m/e 177; τ in CDCl₃:7.10 (7-Me), 5.68 (5-OMe), and -0.11 (3-H)]; the dimethyl compound (IV; R=R'=Me) gave 5-methoxy-3,7-dimethylpyrimido[5,4-e]-as-triazine (V; R=R'=R''=Me), m.p. 189⁰ [m/e 191, τ in CDCl₃:7.14 (7-Me), 6.80 (3-Me), and 5.69 (5-OMe)].

† Broad signal collapses with D₂O.

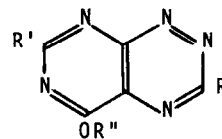
* Doublet collapses to singlet with D₂O.



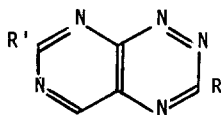
(III)



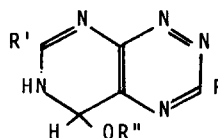
(IV)



(V)



(VI)



(VII)

The formation of the methoxy derivative (V; $R=R''=Me$, $R'=H$) may be rationalised by assuming that the initial product in the oxidation of (IV; $R=Me$, $R'=H$) is 3-methylpyrimido[5,4-*e*]-*as*-triazine (VI; $R=Me$, $R'=H$). If subsequent covalent addition of methanol were to take place across the 5,6-bond, the adduct (VII; $R=R''=Me$, $R'=H$) might then be oxidised to the observed product (V; $R=R''=Me$, $R'=H$). Such addition of methanol would be likely, since the system (VI; $R=Me$, $R'=H$) is analogous to a pteridine bearing a nitro group at the 7-position, and pteridines monosubstituted with a strongly electron-withdrawing group have recently been shown⁽⁶⁾ to form stable isolable covalent adducts with water and alcohol.

In support of this reaction sequence for the oxidative methoxylation, we have found that oxidation of the dihydro compound (IV; $R=Me$, $R'=H$) with silver oxide in dry tetrahydrofuran, followed by filtration directly into methanol, gave *5,6-dihydro-5-methoxy-3-methylpyrimido[5,4-*e*]-*as*-triazine* (VII; $R=R''=Me$, $R'=H$), m.p. 214° (dec.) [m/e 179.0819; τ in $(CD_3)_2SO$: 7.25 (3-Me), 6.77 (5-OMe), 4.25 (5-H), and 2.23 (2-H); ν_{max} . (Nujol mull) 3215 (-NH-), 1065 cm^{-1} (-OMe)]. Replacement of methanol by ethanol gave *5-ethoxy-5,6-dihydro-3-methylpyrimido[5,4-*e*]-*as*-triazine* (VII; $R=Me$, $R'=H$, $R''=Et$), m.p. 114° (dec.) [m/e 193.0950; τ in $(CD_3)_2SO$: 8.94 (triplet, $J=7$ c.p.s.), 6.41 (quartet, $J=7$ c.p.s.) (5-OEt), 7.25

(3-Me), 4.20 (5-H) and 2.25 (7-H); ν_{\max} . (Nujol mull) 3210 (-NH-), 1058 cm^{-1} (-OEt)]. Although oxidation of the adduct (VII; R=R''=Me, R'=H) was unsuccessful in tetrahydrofuran, it was oxidised to the heteroaromatic compound (V; R=R''=Me, R'=H) with silver oxide in methanol. An attempt to prepare 5-ethoxy-3-methylpyrimido[5,4-*e*]-*as*-triazine (V; R=Me, R'=H, R''=Et) by oxidation of the ethanol adduct (VII; R=Me, R'=H, R''=Et) with silver oxide in *methanol* gave the methoxy compound (V; R=R''=Me, R'=H), possibly as a result of fast conversion of the ethanol adduct into the methanol adduct, followed by a relatively slow oxidation. The oxidation of the 1,2-dihydro derivatives (IV) in aprotic media is being investigated.

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