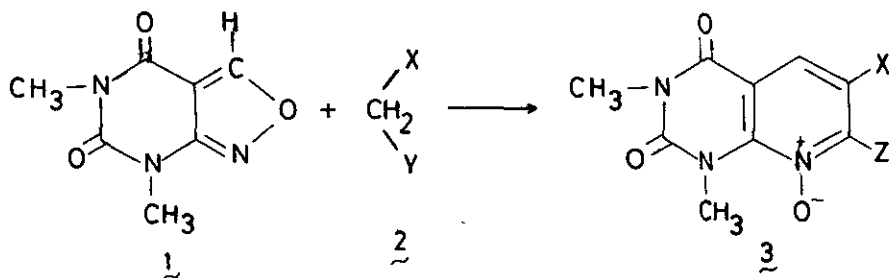


STUDIES ON PYRIMIDINE ANALOGUES: REACTION OF ISOXAZOLO-
(3,4-d)PYRIMIDINE WITH ACTIVE METHYLENE COMPOUNDS

Attaluri Siva Prasad, Jagir Singh Sandhu and Jogendra Nath Baruah*
Regional Research Laboratory, Jorhat, India

Abstract - 5,7-Dimethylisoxazolo[3,4-d]pyrimidine-
4,6(5H,7H)-dione is found to react with a variety of
active methylene compounds yielding novel pyrido[2,3-d]7-
pyrimidine-2,4(1H,3H)-dione oxides.

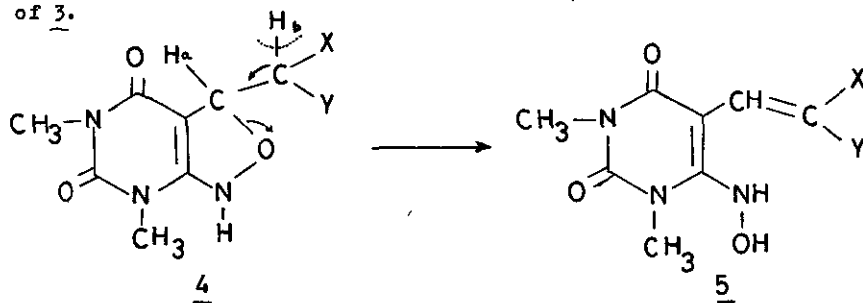
Anthranils have exceptionally low electron density at C-3 and therefore a large number of nucleophiles have been found to attack at this position of these molecules¹. In base-catalysed reactions deprotonation at C-3 has been assumed to be the first step, followed by rupture of isoxazole ring². In contrast it is also reported that C-3 proton could not be exchanged when triethylamine and D₂O were used³. Ethereal solution of diazomethane also did not methylate C-3 indicating that though this position is highly electron deficient the proton is not so much labile in character⁴. In this report we describe our results when a related system 1⁵ is reacted with various active methylene compounds 2 to give new pyrido[2,3-d]7pyrimidine-2,4(1H,3H)-dione oxides 3.



<u>2</u>	X	Y	<u>2</u>	X	Z
<u>a</u>	-CN	-CN	<u>a</u>	-CN	-NH ₂
<u>b</u>	-CO ₂ C ₂ H ₅	-CO ₂ C ₂ H ₅	<u>b</u>	-CO ₂ C ₂ H ₅	-OH
<u>c</u>	-CO ₂ C ₂ H ₅	-CN	<u>c</u>	-CO ₂ C ₂ H ₅	-NH ₂
<u>d</u>	-CONH ₂	-CN	<u>d</u>	-CONH ₂	-NH ₂

Equimolar quantities of 1 and 2 were refluxed for 2 h in absolute alcohol in the presence of a catalytic amount of triethylamine. After cooling the reaction mixture a white crystalline product was separated out which was filtered and recrystallised from absolute alcohol to give 3. The yields, melting points and elemental analysis are given in table I and spectral data in table II.

In the formation of the product 3 we propose similar mechanism as in the case of anthranils i.e. formation of intermediates 4 and 5 leading to the formation of 3.



In this case 4 is the result of direct attack of active methylene compounds (2a-d) at C-3 followed by rupture to 5 giving end product 3.

EXPERIMENTAL

A typical experimental procedure for the reaction described is as follows: a mixture of 5,7-dimethylisoxozolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, 1, (181 mg, 1 m mole) and malononitrile, 2a, (76 mg, 1 m mole) was refluxed for 2 h in 10 ml of absolute alcohol in the presence of catalytic amount of triethylamine and then cooled. The resultant white crystalline material separated was filtered and recrystallised from absolute alcohol to give 6-cyano-and 7-aminopyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione 8-oxide, 3a, (200 mg, 80% yield). In case of the reaction with diethyl malonate, 2b, ethyl cyanoacetate, 2c and cyanoacetamide, 2d, the clear reaction mixture after reflux was chilled to get the product.

Table I. Yields, melting points, elemental analysis of pyrido[2,3-d]7-pyrimidine-2,4(1H,3H)-dione oxides

Active methylene compound	Product	mp °C	Yield %	Molecular formula	Analysis %		
					C Found (Calculated)	H Found (Calculated)	N Found (Calculated)
2a Malono-nitrile	3a	272	80	C ₁₀ H ₉ N ₅ O ₃	48.40 (48.58)	3.61 (3.64)	22.23 (28.34)
2b Diethyl malonate	3b	205	60	C ₁₂ H ₁₃ N ₃ O ₆	48.62 (48.81)	4.39 (4.41)	14.12 (14.24)
2c Ethyl cyanoacetate	3c	203-204	60	C ₁₂ H ₁₄ N ₄ O ₅	48.79 (48.98)	4.72 (4.76)	18.88 (19.05)
2d Cyanoacetamide	3d	211-212	55	C ₁₀ H ₁₁ N ₅ O ₄	45.12 (45.28)	4.11 (4.15)	26.26 (26.41)

Table II. Ir, Mass and ¹H nmr data of compounds 3a-d

Compound	Ir (cm ⁻¹)	MS m/e	¹ H nmr δ
3a	3250, 2200, 1650, 1625, 970	247	3.38(s,3H), 4.07(s,3H), 7.832-8.427(m,2H), 8.9(s,1H)
3b	3450, 1675, 1650	295	1.4(t,3H), 3.3(s,3H), 3.66(s,3H), 4.3(q,2H), 8.66(s,1H)
3c	3250, 1675, 1650, 970	294	1.41(t,3H), 3.35(s,3H), 3.66(s,3H), 4.3(q,2H), 8.63(s,1H)
3d	3250, 1650, 1615, 970	265	2.84(s,3H), 3.44(s,3H), 7.4-8.0(b,4H), 8.26(s,1H)

Ir (KBr); ¹H nmr; 3a-c, 270 MHz⁶, 3d, 60 MHz; Solvent: 3a, TFA+CDCl₃, 3b-c, CDCl₃ and 3d, TFA

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