Communications to the Editor

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SYNTHESIS AND PROPERTIES OF A NEW CLASS OF PYRIDODIPYRIMIDINES, 8-ALKOXYPYRIDO[2,3-d:6,5-d']DIPYRIMIDINE-2,4,6(3H,10H,7H)-TRIONES

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A new class of pyridodipyrimidines, 8-alkoxypyrido[2,3-d:6,5-d']-dipyrimidine-2,4,6(3H,10H,7H)-triones (2) were synthesized by the reaction of 6-alkylamino-3-methyluracils (1) with appropriate trialkyl orhtoformates in dimethylformamide and their structures were unambiguously established by the X-ray diffraction analysis of 2f.

KEYWORDS——— pyrido[2,3-d:6,5-d']dipyrimidine; 6-alkylamino-3-methyluracil; triethyl orthoformate; trimethyl orthoformate; O-alkylation; X-ray diffraction analysis

The 10-substituted pyrido[2,3-d:6,5-d']dipyrimidines (3) are interesting compounds because of their demonstrated strong oxidizing ability.[1] They were synthesized by the condensation of the corresponding 6-chloro-5-formyluracils with appropriate 6-substituted-aminopyrimidines.[1] Here we wish to report a new simple synthesis of 8-alkoxypyrido[2,3-d:6,5-d']dipyrimidine-2,4,6(3H,10H,7H)-triones (2) which belong to unexplored class of pyridodipyrimidines. For this appropriate 6-alkylaminouracils are treated with trialkyl orthoformates in dimethylformamide.

For example, the refluxing of 3-methyl-6-n-propylaminouracil (1c) (1 g, 5.46 mmol) with triethyl orthoformate (16.2 g, 109 mmol) in dimethylformamide (10 ml) at 150°C for 7 h, followed by concentration of the reaction mixture under reduced pressure and recrystallization of the residue from ethanol, afforded 8-ethoxy-3,7-dimethyl-10-n-propylpyrido[2,3-d:6,5-d']dipyrimidine-2,4,6(3H,10H,7H)-trione (2f). Other pyridodipyrimidines (2a–e and 2g,h) were similarly prepared by heating 1 with appropriate trialkyl orthoformates in dimethylformamide under the same conditions (Chart 1) (Table I). These 8-alkoxypyridodipyrimidines (2) were also obtained by the reaction of 10-alkyl-3,7-dimethylpyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(3H,10H,7H,9H)-tetrones (3) with appropriate trialkyl orthoformates. Thus, the refluxing of the compounds 3 (3 mmol) with appropriate trialkyl orthoformates (60 mmol) in dimethylformamide (8 ml) at 150°C for 5 h gave the corresponding pyridodipyrimidines (2).

The structures of 2a–h were determined initially by elemental analyses and spectral data including mass spectrometry, and particularly, by the presence of the characteristic C-5 proton at δ 9.72 - 9.79 in ^{1}H-NMR spectra. However, this did not exclude the possibility of 2 possessing 9-alkyl- and 6-alkoxy-type structures. Therefore, the structures of 2 were finally determined by X-ray crystallographic

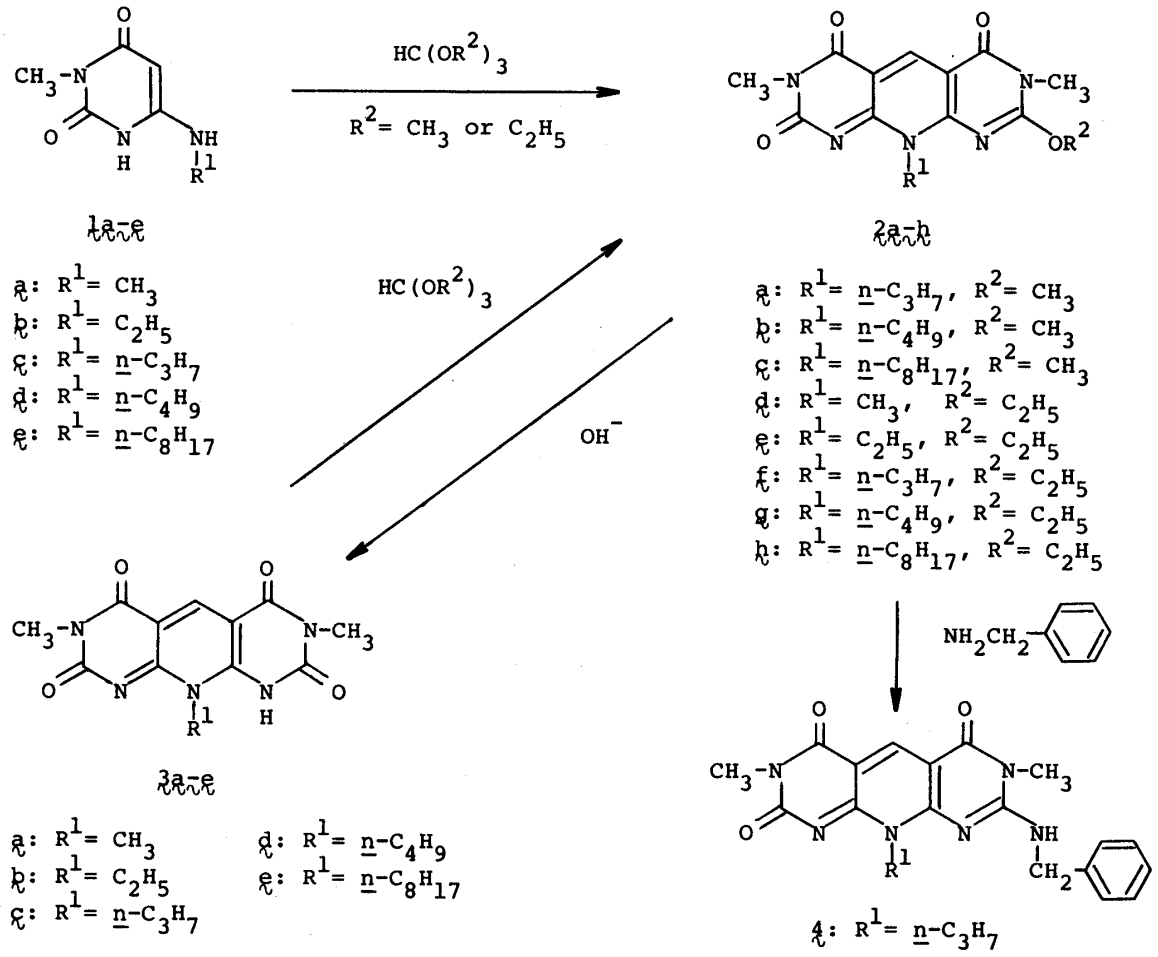

Chart 1

Table I. 8-Alkoxy-3,7,10-trisubstituted-pyrido[2,3-d:6,5-d']dipyrimidine-2,4,6-(3H,10H,7H)-triones (2a-h)

starting material	product[a]	mp (°C)[b]	Yield (%)[c]	Appearance	^{1}H-NMR δ[ppm][d]
1c (3c)	2a	191	68 (65)	yellow needles	9.72
1d (3d)	2b	230	72 (68)	yellow needles	9.79
1e (3e)	2c	138	70 (65)	yellow needles	9.78
1a (3a)	2d	253	71 (67)	yellow needles	9.77
1b (3b)	2e	257	76 (72)	yellow needles	9.73
1c (3c)	2f	231	68 (65)	pale yellow prisms	9.79
1d (3d)	2g	183	59 (57)	pale yellow powder	9.75
1e (3e)	2h	147	47 (50)	yellow powder	9.75

a) All compounds gave satisfactory microanalyses.
b) These compounds were recrystallized from ethanol.
c) The yields in parentheses are yields of the reactions of compounds 3a-e with trialkyl orthoformates.
d) These values are chemical shifts at the C-5 protons of the compounds 2a-h (CF_3CO_2H / TMS).

analysis of compound 2f (R[1]= n-C_3H_7, R[2]= C_2H_5) (Fig. 1).

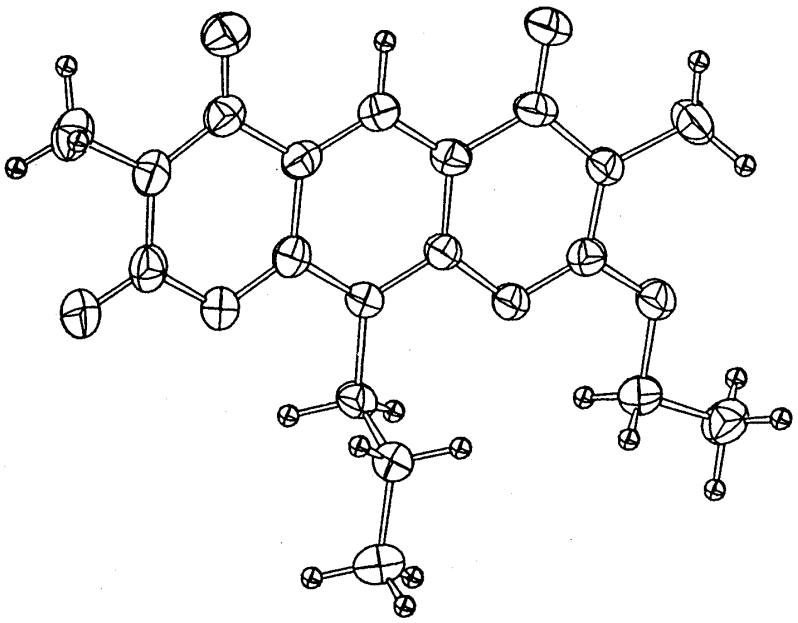

Fig. 1. Molecular Structure of 2f

Crystal Data

Crystal System	monoclinic
Cell Dimentions	a = 13.147(4)Å
	b = 15.338(3)Å
	c = 8.207(2)Å
	β = 102.94(2)°
Cell Volume	1612.9(7)Å
Space Group	$p2_1/n$
Number of Formula Units in the Unit Cell	Z = 4
Calculated Density	1.422 g/cm^3

The final R value was 0.058 for 1752 observed reflections.

The synthesis of compounds 2 is rationalized by the initial formation[2] of pyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(3H,10H,7H,9H)-tetrones (3), followed by the O-alkylation with trialkyl orhtoformate. The O-alkylation is considered to be initiated by the formation of oxygen-stabilized carbonium ions from trialkyl orthoformates by the action of the acidic proton of 3, as indicated in Chart 2. It is known that alkyl and aryl ethers can be prepared using triethyl orthoformate in a few cases.[3] To best of our knowledge, however, this is the first example of the O-alkylation of the pyrimidine moiety.

The 8-alkoxypyridodipyrimidines (2) are stable against conc. hydrochloric acid but unstable with alcoholic potassium hydroxyde, and are readily hydrolyzed to yield the corresponding pyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(3H,10H,7H,9H)-

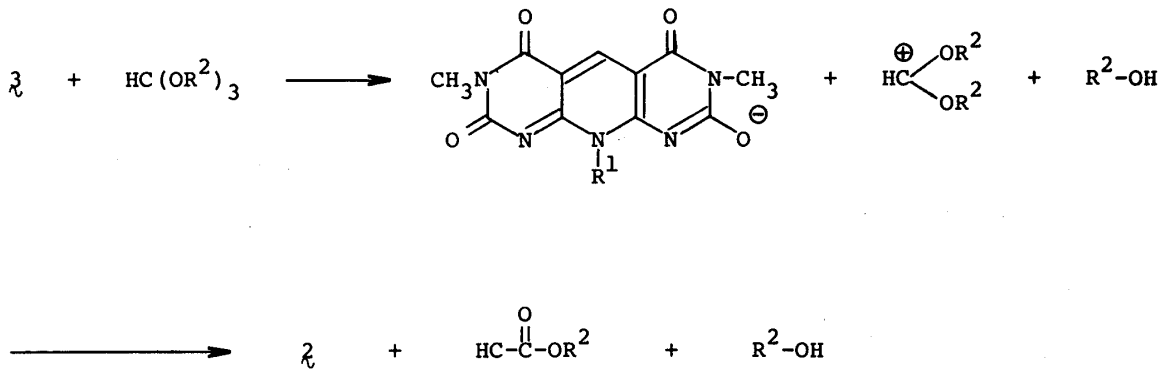

Chart 2

tetrones (3).[1] Namely, stirring of compound 2f (0.2 g, 0.58 mmol) with potassium hydroxyde (0.1 g) in ethanol (5 ml) at room temperature for 20 min, followed by acidification of the mixture with glacial acetic acid, afforded the corresponding dealkylated compound 3c in quantitative yield. Similarly, the treatment of 2f (0.3 g, 0.87 mmol) with benzylamine (0.19 g, 1.77 mmol) in dimethylformamide (4 ml) under refluxing at 160°C for 2 h gave the 8-benzylamino-3,7-dimethyl-10-n-propylpyrido[2,3-d:6,5-d']dipyrimidine-2,4,6(3H,10H,7H)-trione (4), mp> 330°C (77% yield). In this way, the compounds 2 are also useful as starting materials for several pyridodipyrimidine derivatives.

In relation to our studies on the biomimetic oxidation mediated by 5-deazaflavins and analogues,[1,4,5] it was found that the 8-alkoxypyridodipyrimidines (2) have strong ability and remarkable autorecycling toward oxidation of alcohols, which will be published in the full account of this paper.

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