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A NOVEL PHOTO-INDUCED METHYLATION OF PYRIMIDINES AND CONDENSED PYRIMIDINE COMPOUNDS

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We have found that irradiation of 4-hydroxypyrazolo[3,4-d]pyrimidine (I)$^{1)}$, Allopurinol*, by UV-light (a 60 W low-pressure mercury lamp) in methanol containing 2% hydrogen chloride (w/w) at room temperature for 6 hours afforded 4-hydroxy-6-methylpyrazolo[3,4-d]pyrimidine (II)$^{2)}$ in 67% yield.

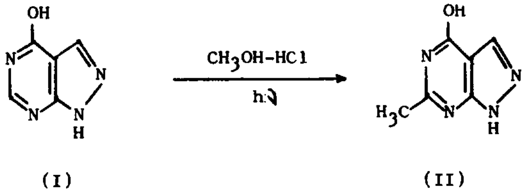

Chart 1

Similarly, 4-aminopyrazolo[3,4-d]pyrimidine$^{1)}$ furnished 4-amino-6-methylpyrazolo[3,4-d]pyrimidine (III)$^{3)}$ in 45% yield.

Other pyrazolo[3,4-d]pyrimidines and pyrimidines were also methylated as summarized in Table I.

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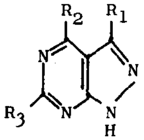
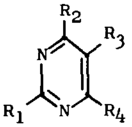
* Allopurinol or 4-hydroxypyrazolo[3,4-d]pyrimidine (I) is a potent xanthine oxidase inhibitor of clinical usefulness for the treatment of gout$^{4)}$.

TABLE 1

Photo-induced Methylation of Pyrazolo[3,4-d]pyrimidines and Pyrimidines

	Starting material					Product				
	R_1	R_2	R_3	R_4		R_1	R_2	R_3	R_4	Yield (%)
	H	OH	H	-	II[2]	H	OH	CH_3	-	67
	"	NH_2	"	-	III[3]	H	NH_2	"	-	45
	CH_3	"	"	-	IV	CH_3	"	"	-	56
	H	NH_2	CN	H	V[5]	CH_3	NH_2	CN	CH_3	60
	CH_3	"	"	"	V	"	"	"	"	86
	NH_2	"	"	"	VI	NH_2	"	"	"	57
	H	"	CH_2NH_2	"	VII[6]	CH_3	"	CH_2NH_2	"	52
	CH_3	"	"	"	VII	"	"	"	"	33

The structure of the product obtained was confirmed by the comparison of IR, UV, NMR and Mass spectra with authentic samples. With new compounds (IV, VI) the structure was established either by direct comparison with an authentic sample obtained by an unambiguous synthesis as shown in Chart 2, or by the NMR spectrum (IV: m.p. > 300°, C, 51.62; H, 5.73; N, 42.89. $C_7H_9N_5$ requires C, 51.52; H, 5.56; N, 42.92%; VI: hydrochloride, m.p. > 300°, C, 39.11; H, 4.44; N, 37.69. $C_6H_7N_5HCl$ requires C, 38.80; H, 4.34; N, 37.73%, NMR, 60 Mc. in D_2SO_4; CH_3 as singlet at 2.64 ppm, no annular proton observed).

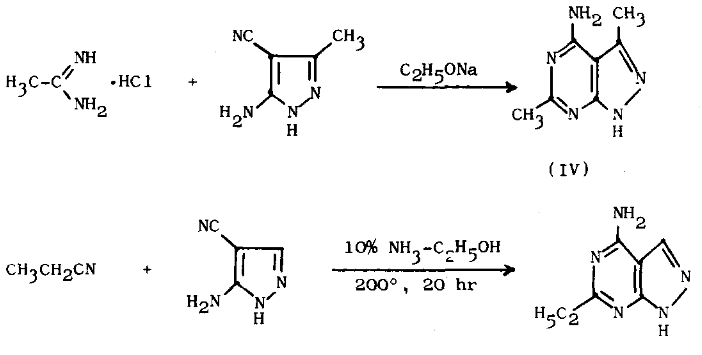


Chart 2

Other strong acids, i.e., sulfuric acid, chlorosulfonic acid and toluenesulfonic acid were also effective. Irradiation by a high-pressure mercury lamp or the sun-light were also proved to be effective for this alkylation reaction, but in lower yields.

When an ethanol solution of 4-aminopyrazolo[3,4-d]pyrimidine containing 2% hydrogen chloride (w/w) was irradiated at room temperature for 6 hours, 4-amino-6-ethylpyrazolo[3,4-d] pyrimidine (VIII: m.p. 257°, C, 51.00; H, 5.38; N, 42.79. $C_7H_9N_5$ requires C, 51.52; H, 5.56; N, 42.92%) was obtained in 41% yield. The structure of VIII was confirmed by direct comparison of IR spectrum with a sample obtained by the reaction shown in Chart 2.

The reaction provides a facile synthesis of C_2 (and/or C_4)-alkylpyrimidines and condensed alkylpyrimidines. The yields were best with HCl-methanol as alkylating agent and showed a tendency to decrease with higher alcohols. The present alkylation reaction was not feasible with purine bases.

Further work to clarify the scope, limitation and mechanism of this new photo-induced alkylation reaction is under progress.

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