REACTION OF 5-ACETONYL-6-CHLOROPYRIMIDINES WITH HYDRAZINES AND DIAMINES

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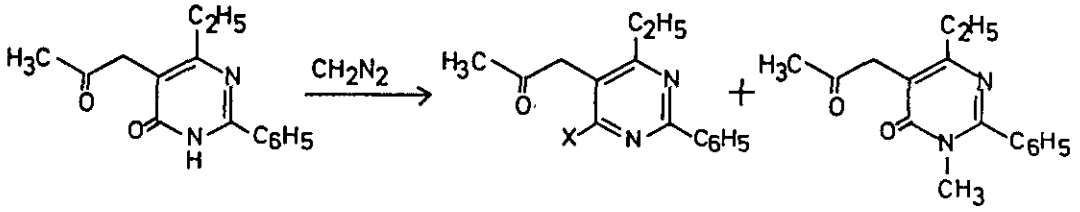
The reaction of 5-acetonyl-6-chloro-4-ethyl-2-phenylpyrimidine (4) with hydrazines yields dihydropyrimido-[4,5-c]pyridazines, while 1,2-diamines give pyrrolo-[2,3-d]pyrimidines and no pyrimido[4,5-e]-1,4-diazocines. Only 1,2-dimethylaminoethane reacts with 4 to give the pyrimido[4,5-e]-1,4-diazocine-system.

In former papers,[1] we reported the reaction of α-(alkoxyalkyliden)-$\Delta^{\beta,\gamma}$-butenolides with amidines, which leads[2] to 5-acetonyl-6-pyrimidones 1. We hoped to determine whether those acetonylpyrimidones 1 might be useful for the preparation of condensed heterocyclic substances and in this report wish to describe their reactions with hydrazines and diamines. For this purpose the weak reactivity of the lactam group of pyrimidone 1 must be increased by changing it into a more reactive function, as has been shown for similar reactions.[3] The pyrimidone 1 was allowed to

react with diazomethane to give its 6-methoxy derivative 2 (mp 122°; ν max ($CHCl_3$) 1720 cm^{-1}(CO)).

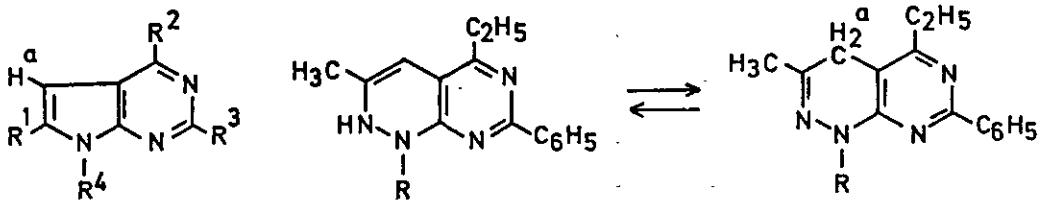
In ether, N-methylation also occurred to produce 3 (mp 99°; ν max ($CHCl_3$) 1720, 1650 cm^{-1}), in addition to the desired O-methylation. The ratio of 2 to 3 was determined by NMR spectroscopy to be 1:1.



1 2 (X=OCH_3) 3

4 (X=Cl)

Further reactions of the 6-methoxypyrimidine 2 with hydrazine in ethanolic solution under reflux did, however, show that the reactivity of this product had even been too low for a substitution at position 6. Consequently the pyrimidone 1 was chlorinated with $POCl_3$ to yield the more reactive 6-chloro-pyrimidine 4 (mp 93°; ν max ($CHCl_3$) 1730 cm^{-1}(CO)). Similar derivatives had already been transformed with amines[2] and hydrazines[4], whereby primary amines yield pyrrolo[2,3-d]pyrimidines 5 and hydrazines yield dihydropyrimido[4,5-c]pyridazines 6 and/or 7.



5 6 7

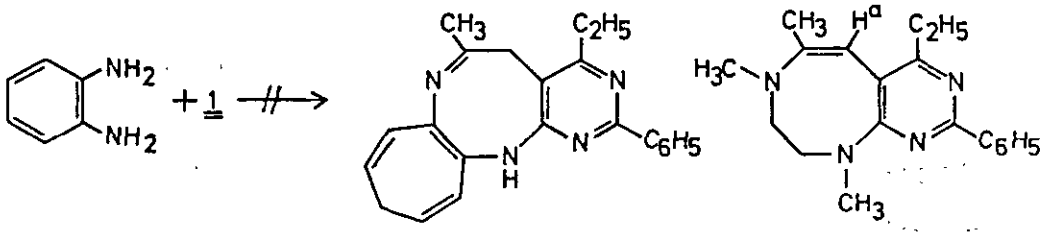
In the latter case, two tautomeric products 6 and 7 are possible, but nmr and ir spectra show that predominantly form 7 is formed. The nmr spectrum ($CDCl_3$) shows a sharp singlet at τ 6.6 - 6.7 for the CH_2^a protons. In the ir spectrum no N-H bands were seen, which points to form 7.

Table 1: Characteristic data of the pyrrolo[2,3-d]pyrimidines 7a-c nmr ($CDCl_3$, τ-value); ir ($CHCl_3$, cm^{-1})

	R	mp	CH_2^a	R	CH_3	ν_{NH}
7a	H	154°	6.67 s	1.60 s+	8.02	3400
7b	CH_3	110°	6.70 s	6.48 s	8.06	---
7c	C_6H_5	137°	6.58 s	2.70 m	7.97	---

+exchangeable with D_2O

If instead of hydrazines, diamines of the type o-phenylendiamine are allowed to react, the synthesis of pyrimido[4,5-e]diazocines 8 is possible in addition to the formation of pyrrolo[2,3-d]-pyrimidines 5.



8 9

By reacting 4 with aromatic and aliphatic diamines such as o-phenylendiamine, 4,5-dimethylphenylendiamine, 1,2-diamino-naphthalene, -cyclohexane, -propane and -ethane or 1,3-diamino-propane, only the pyrrolo derivatives 5 are formed.

Table 2: Characteristic data of the pyrrolo[2,3-d]pyrimidines 5a-g ($R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = C_6H_5$); nmr ($CDCl_3$, τ-values).

Substituent R^4		mp	H^a	$R^1=CH_3$	NH_2
5a	o-Aminophenyl	142°	3.63	7.80	6.45
5b	2-Amino-4,5-dimethylphenyl	202°	3.67	7.73	6.70
5c	2-Amino-1-naphthyl	190°	3.55	7.93	6.40
5d	2-Aminocyclohexyl	+	3.72	7.50	8.05
5e	2-Aminopropyl	+	3.82	7.64	8.80
5f	2-Aminoethyl	+	3.81	7.58	8.72
5g	3-Aminopropyl	+	3.86	7.62	8.47
		+ viscous oil			

Nmr spectra of the substances 5a-g show only a sharp singlet at τ 3.60 for the methine proton H^a and at τ 7.80 for the CH_3 protons. The free amino group of R^4, which hat not reacted, gives a signal at τ 6.4 - 8.4, typical for N-H protons, which disappears after shaking with D_2O. If these products 5a-g are acetylated with acetic anhydride, only one acetyl group is introduced and the nmr spectra of those compounds show a shift

of the remaining amide NH proton to $\tau<0$. All these data and observations support the supposed pyrrolo-structure 5a-g.

The above results demonstrate that the formation of a pyrrole ring only occurs if primary diamines react with 4. The formation of a diazocine ring should be possible if secondary diamines react with the 6-chloropyrimidine 4. After refluxing 4 with N,N'-dimethylethylendiamine in dioxane for 4 hours, we isolated an oily substance for which we propose the structure 9 on the basis of the spectroscopic data. There are no NH or carbonyl bands in ir ($CHCl_3$) and in nmr ($CDCl_3$) the methine proton H^a at τ 4.35 appears as a characteristic signal; both N-CH_3 groups appear as singlets at τ 6.80 or τ 7.40 and the CH_3^b protons appear at τ 8.20. The mass spectrum of 9 shows a clear molecular ion peak M^+ at m/e 308 (calcd. 308). Evidently the diazonine is very sensitive to hydrolysis because if it stands for a long time, it will hydrolyze with ring opening to 5-acetonyl-4-ethyl-2-phenyl-6-(N-2-methylaminoethyl-N-methylamino)pyrimidine as proved by ir, nmr and mass spectra.

REFERENCES

1 H. Wolfers, U. Kraatz and F. Korte, Chem. Ber., 106, 874 (1973).

2 E. Bisagni, J.P. Marquet and J. Andre-Luisfert, Bull. Soc. chim., France, 1969, 803.

3 A. Attar, H. Wamhoff and F. Korte, Chem. Ber., 106, 3524 (1973).

4 E. Bisagni, J.P. Marquet and J. Andre-Luisfert, Bull. Soc. chim., France, 1972, 1483.

Received, 30th October, 1974