*HETEROCYCLES, Vol 3, No. 3, 1975*

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

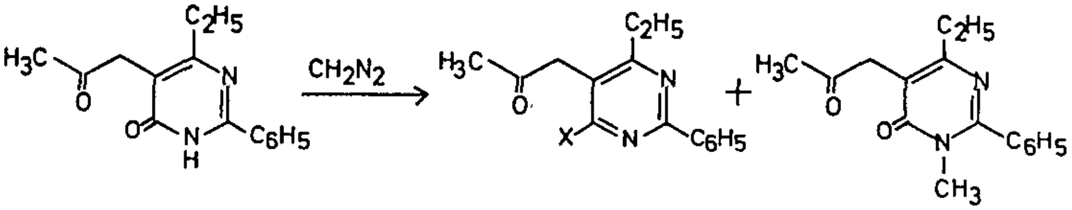
Heinz Wolfers, Udo Kraatz and Friedhelm Korte[+]

Institut für Ökologische Chemie der TU München
und Institut für Ökologische Chemie der Gesell-
schaft für Strahlen- und Umweltforschung mbH
München, D-805 Freising-Weihenstephan, Am Löwentor.

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.

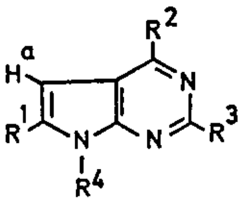
In former papers,[1] we reported the reaction of $\alpha$-(alkoxyalkyliden)-$\Delta^{\beta,\gamma}$-butenolides with amidines, which leads[2] to 5-acetonyl-6-pyrimidones 1. We hoped to determine whether those acetonylpyrimidones 1 might be useful for the preparation of condensed heterocyclic substances 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°; $\nu$max ($CHCl_3$) 1720 $cm^{-1}$(CO)).

In ether, N-methylation also occurred to produce 3 (mp 99°; $\nu$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=$OCH_3$) 4 (X=Cl) 3

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-chloropyrimidine 4 (mp 93°; $\nu$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.



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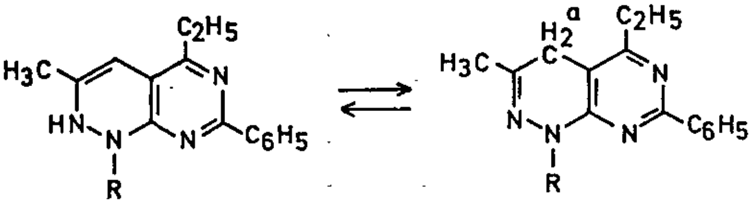


6 7

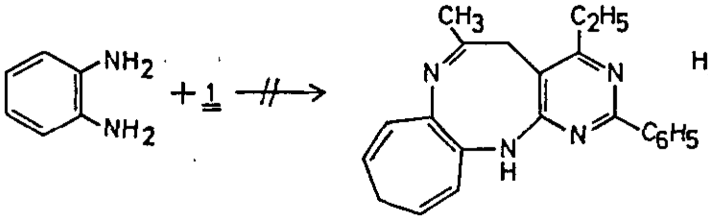
In the latter case, two tautomeric products 6 and 7 are possible, but nmr and ir spectra show that predominantly form 7 is formed. The nmr spectrum ($CDCl_3$) shows a sharp singlet at $\tau$ 6.6 - 6.7 for the $CH_2^a$ protons. In the ir spectrum no N-H bands were seen, which points to form 7.

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

| | R | mp | $CH_2^a$ | R | $CH_3$ | $\nu_{NH}$ |
|---|---|---|---|---|---|---|
| 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.



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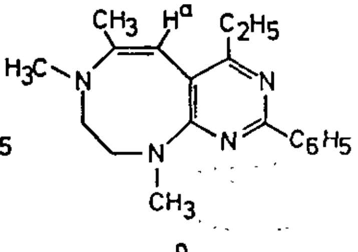

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By reacting 4 with aromatic and aliphatic diamines such as o-phenylendiamine, 4,5-dimethylphenylendiamine, 1,2-diaminonaphthalene, -cyclohexane, -propane and -ethane or 1,3-diaminopropane, only the pyrrolo derivatives 5 are formed.

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 ($CDCl_3$, $\tau$-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 $\tau$ 3.60 for the methine proton $H^a$ and at $\tau$ 7.80 for the $CH_3$ protons. The free amino group of $R^4$, which hat not reacted, gives a signal at $\tau$ 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 $\tau$ 4.35 appears as a characteristic signal; both $N\text{-}CH_3$ groups appear as singlets at $\tau$ 6.80 or $\tau$ 7.40 and the $CH_3^b$ protons appear at $\tau$ 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