REACTION OF 4,6-DIMETHYLPYRIMIDINE WITH CHLORIDES OF AROMATIC CARBOXYLIC ACIDS

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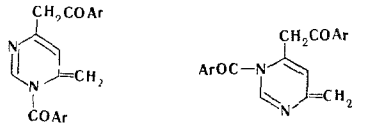
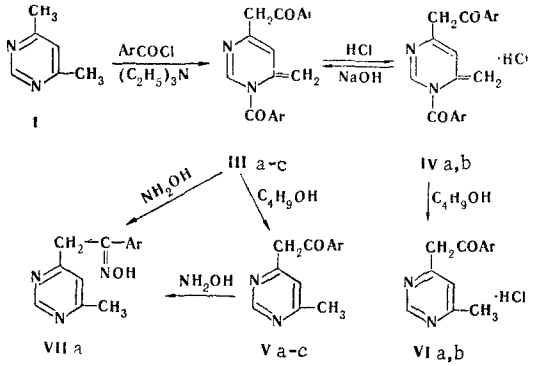
The reaction of methyl groups with acyl chlorides is described for the first time in the pyrimidine series. The corresponding ketones – 6-methyl-4-phenacylpyrimidines – have been obtained from 4,6-dimethylpyrimidine and chlorides or aromatic carboxylic acids. A possible mechanism of the reaction is discussed.

It is known that activated methyl groups in pyrimidine and some other nitrogen-containing heterocyclic compounds react with diazonium salts and with aromatic aldehydes.



We have begun a study of the reaction of methylpyrimidines with chlorides of carboxylic and sulfonic acids. 4,6-Dimethylpyrimidine (I) reacts with aromatic carbonyl chlorides (II) in the presence of triethylamine to form N-acyl-6-methylene-4-phenacylpyrimidines (III). Two possible structures for compounds (III) are given above. The former is used in the reaction scheme given below. It is impossible to determine the structure of the N-acyl compounds (III) by chemical and the usual spectroscopic methods. Only (IIIc) could be isolated in the form of the free base from the corresponding reaction mixture after the elimination of the triethylamine salt and the distillation of the solvent. The bases (IIIa and b) were isolated from the purified hydrochlorides (IVa and b) by treatment with caustic soda solution (Tables 1 and 2).

When the bases (III) and their hydrochlorides (IV) were heated in butanol, the acyl group was split off from the amide nitrogen atom as a result of alcoholysis. This was confirmed by the fact that the hydrochlorides (IV) reacted in a few minutes (acid catalysis), while several hours' boiling was required for the conversion of compounds (III). It is known that N-acyl groups in substituted pyridines and quinolines are readily hydrolyzed [1,2].



Ar = C_6H_5; b Ar = p-ClC_6H_4; c Ar = p-$CH_3OC_6H_4$; IIIa + NH_4 ⟶ Va + $C_6H_5CONH_2$.

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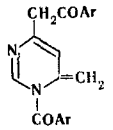
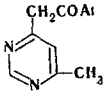
TABLE 1. N-Acyl-6-methylene-4-phenacylpyrimidines (III) and Their Hydrochlorides (IV)



Comp.	Ar	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	Cl	N	C	H	Cl	N	
IIIa	C_6H_5	83—84	$C_{20}H_{16}N_2O_2$	75,3	5,0		8,9	75,9	5,1		8,8	78
IIIb	p-ClC_6H_4	115	$C_{18}H_{14}Cl_2N_2O_2$	62,3	3,7	18,8		62,4	3,7	18,4		84
IIIc	p-OCH_3	148—150	$C_{22}H_{20}N_2O_4$	69,6	5,4		7,2	70,2	5,3		7,4	24
IVa	C_6H_5	175	$C_{20}H_{16}N_2O_2 \cdot HCl$			9,8	7,8			10,1	7,9	46
IVb	p-ClC_6H_4	152	$C_{18}H_{14}Cl_2N_2O_2 \cdot HCl$			24,8	6,5			25,1	6,6	40

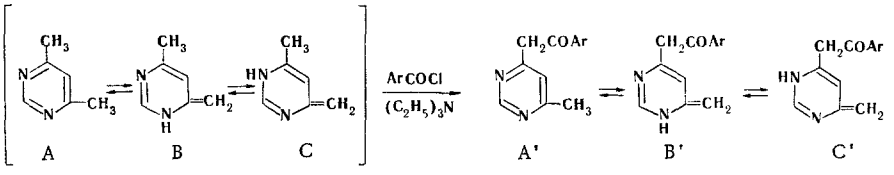
TABLE 2. 6-Methyl-4-phenacylpyrimidines (V) and Their Hydrochlorides (VI)



Comp.	Ar	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	Cl	N	C	H	Cl	N	
Va	C_6H_5	66—68[a]	$C_{13}H_{12}N_2O$	73,6	5,7			73,6	5,7			84,0
Vb	p-ClC_6H_4	100—102[b]	$C_{13}H_{11}ClN_2O$			14,7	11,3			14,7	11,0	80,0
Vc	p-$OCH_3C_6H_4$	105—106	$C_{14}H_{14}N_2O_2$	69,2	5,8			69,4	5,8			71,5
VIa	C_6H_5	203—205	$C_{13}H_{12}N_2O \cdot HCl$			14,3	11,4			14,3	11,3	93,0
VIb	p-ClC_6H_4	249—250	$C_{13}H_{11}ClN_2O \cdot HCl$			25,3				25,0		80,0

[a]From petroleum ether. [b]From heptane.

The presence of an N-acyl grouping in the ketones (III) is also confirmed by the fact that when ammonia was passed into a solution of (IIIa) in petroleum ether, benzamide was isolated quantitatively and (Va) was obtained. The structure of the 6-methyl-4-phenacylpyridines (V) was also shown by the preparation of the oxime (VII) from the ketone (Va). This oxime was also obtained from (IIIa), since the amide group is readily hydrolyzed under the standard conditions for obtaining oximes.



Evidently, in the first stage of the reaction there is a nucleophilic attack by the acyl halides on the tautomeric form A or the corresponding carbanion, since in this form the methyl group is in conjugation with both nitrogen atoms and the detachment of a proton from a methyl group of an enamine in the tautomeric forms B and C is less likely. In the second stage of the reaction the acylation of one of the tautomeric forms B' and C' takes place.

In the IR spectrum of each of compounds (III) there is an absorption band in the 1640-cm^{-1} region that is characteristic for the $C=CH_2$ group and an absorption band at 1440 cm^{-1} characteristic for the CH_2CO group. In the spectrum of each of compounds (V) there are bands in the 2950-2975-cm^{-1} region that are characteristic for the CH_3 group.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrophotometer in tablets with KBr.

Hydrochlorides of N-Acyl-6-methylene-4-phenacylpyrimidines (IVa,b). A mixture of 0.01 mole of a pyrimidine (I), 0.02 mole of an acyl chloride (II), and 0.02 mole of triethylamine in 20 ml of absolute benzene was boiled for 2 h. After cooling, the precipitate of triethylamine hydrochloride was filtered off

(yield about 65%). The filtrate was evaporated to dryness and the residue was treated with methanol. The hydrogen chloride liberated in the alcoholysis of the acid chloride (II) that had not reacted formed an oily precipitate of the corresponding hydrochloride (IV), which was treated with ether and filtered off. [If hydrogen chloride were passed into the reaction mixture to isolate the (IV), a mixture of compounds of undetermined structure would be obtained.] After crystallization from a mixture of chloroform and ether, compounds (IV) were obtained in the form of colorless crystals (Table 1).

N-Acyl-6-methylene-4-phenacylpyrimidines (IIIa,b). The free bases (III) were obtained by diluting solutions of the corresponding hydrochlorides (IV) with caustic soda solution. The precipitates were filtered off and washed with water. Colorless crystalline substances after crystallization from aqueous methanol (Table 1).

N-p-Anisoyl-4-(p-methoxyphenacyl)-6-methylenepyrimidine (IIIc). A mixture of 1 g (0.01 mole) of 4,6-dimethylpyrimidine, 2 g (0.02 mole) of triethylamine, and 3.4 g (0.02 mole) of p-anisoyl chloride in 20 ml of anhydrous benzene was boiled for 2 h. The precipitate of triethylamine hydrochloride was filtered off and the filtrate was evaporated to dryness. The residue – a dark brown oil – was repeatedly extracted with petroleum ether. Evaporation of the petroleum ether yielded 0.9 g of compound (IIIc), which was purified by crystallization from ether (Table 1).

Hydrochlorides of the 6-Methyl-4-phenacylpyrimidines (VIa,b). A hydrochloride (IV) (0.003 mole) was boiled in 5 ml of butanol for 30 min.* After cooling, the precipitate was filtered off and washed with butanol (Table 2).

6-Methyl-4-phenacylpyrimidines (Va,b). The bases (Va,b) were obtained from their hydrochlorides as in the preparation of (IIIa,b).

4-(p-Methoxyphenacyl)-6-methylpyrimidines (Vc). A mixture of 0.35 g (0.001 mole) of (IIIc) and 10 ml of butanol was boiled for 14 h.* The butanol was evaporated off and the residue was repeatedly extracted with heptane. Distillation of the heptane yielded 0.15 g of (Vc) (Table 2).

Reaction of the N-Acyl-6-methylene-4-phenacylpyrimidine (IIIa) with Ammonia. Dry ammonia was passed into a boiling solution of 0.1 g (0.003 mmole) of (IIIa) in 10 ml of petroleum ether (70-100°C). Benzamide (0.03 g; 99%) deposited (identified by a mixed melting point). After the petroleum ether had been distilled off, 0.05 g (98%) of (Va) was obtained: its melting point was identical with that of the (Va) obtained from the hydrochloride (VIa).

The oxime of 6-methyl-4-phenacylpyrimidine (VII) was obtained by the usual method from (Va). mp 96-97°C (from petroleum ether). Found, %: C 68.7; H 5.4; N 18.2. $C_{13}H_{13}N_3O$. Calculated, %: C 68.7; H 5.8; N 18.5.

LITERATURE CITED

1. E. Klingsberg, Pyridine and Its Derivatives, Interscience (1960).
2. W. E. McEwen, R. H. Terss, and J. W. Elliott, J. Amer. Chem. Soc., 74, 3605 (1952).

*The completeness of the hydrolysis was followed by TLC [Al_2O_3 of activity grade II; benzene–methanol (10:1); spots revealed in UV].