# HALOGENATION OF PHENACYLPYRIMIDINES

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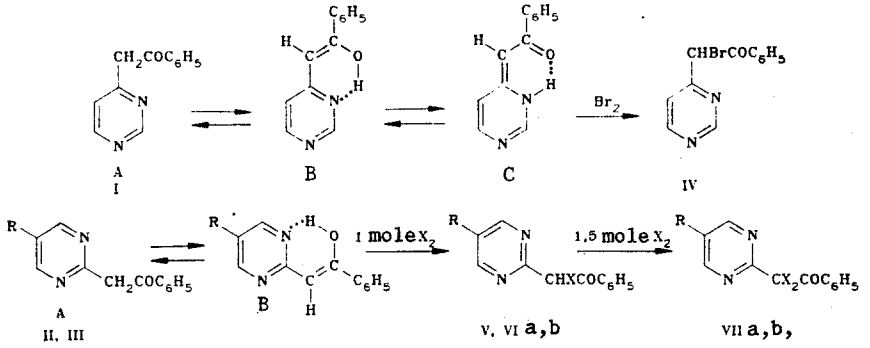
The action of bromine and chlorine of phenacylpyrimidines yields a series of α-mono- and α,α'-dihalophenacylpyrimidines. IR, UV and PMR spectroscopy showed that, in contrast to the starting compounds, the monohalo derivatives exist in the keto form.

In a further study of the chemical properties of carbonyl-containing azine derivatives [1], we investigated the halogenation of synthetically available phenacylpyrimidines I-III containing the phenacyl group at $C_{(2)}$ and $C_{(4)}$ in the pyrimidine ring.

As in the case of 4,6-diphenyl-2-phenacylpyrimidine [2], I-III are enolized in solution and as solids. The structure of the tautomeric forms A and B was indicated by IR, UV, and PMR spectroscopy. The existence of form C was demonstrated by $^{17}O$ and $^{14}N$ NMR spectroscopy for I [3]. For example, the content of the tautomeric forms A and (B + C) in deuterochloroform under equilibrium conditions was 50% A and 50% (B + C) for chloropyrimidine II, 40% A and 60% (B + C) for 5-phenyl derivative III and 30% A and 70% (B + C) for 4-phenacylpyrimidine (I) as indicated by PMR spectroscopy.




II, V R=Cl; III, VI, VII R=$C_6H_5$; V, VIa, VIIa X=Cl; VIb, VIIb X=Br

The halogenation of phenacylpyrimidines I-III is conveniently carried out by the action of halogens in acetic acid in the presence of sodium acetate. The action of one equivalent bromine on pyrimidines I and III at 20°C gives 70-80% yields of the α-bromo derivatives, namely, 2-bromo-2-(4-pyrimidinyl)-1-phenyl-1-ethanone (IV) and 2-bromo-2-(5-phenyl-2-pyrimidinyl)-1-phenyl-1-ethanone (VIb). Although the yields of the desired products IV and VIb are rather high, the reaction mixture always contains the starting compound such as III and a small amount of the dibromo derivative such as VIIb. This behavior may be related ot disproportionation of the monobromoketone as observed in the case of bromo derivatives of alkyl phenyl ketones [4].

The yields of the monochloro derivatives, 1-phenyl-2-chloro-2-(5-chloro-2-pyrimidinyl)-1-ethanone (V) and 1-phenyl-2-(5-phenyl-2-pyrimidinyl)-2-chloro-1-ethanone (VIa), obtained by the action of a saturated solution of chlorine in acetic acid on II and III in the presence of sodium acetate, are higher than for bromophenacylpyrimidines IV and VIb and reach 90-98%.

It is interesting that IR, UV and PMR spectroscopy indicates that monohalo derivatives IV-VI exist in keto form A both in the solid and in solution in $CDCl_3$, $CCl_4$, acetone and

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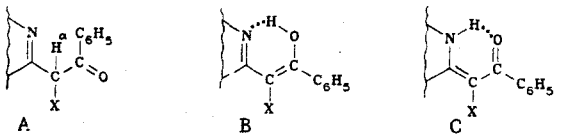
TABLE 1. Physicochemical Indices of I-IX

| Compound* | mp, °C (from ethanol) | UV spectrum, $\lambda_{max}$, nm (log ε) | PMR spectrum, δ, ppm | Found, % | | | | Chemical formula | Calculated, % | | | | Yield, (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | Br(Cl) | N | | C | H | Br(Cl) | N | |
| I | 93—95 | 243 (3,98), 350 (4,20), 362 (3,27) | 4,34 (s, 2H, α,α′-H)$^{A}$; 5,91 (s, 1H, α-H)$^{B+C}$; 6,84 (d, 1H, 5-H)$^{B+C}$; 7,31 (d, 1H, 5-H)$^{A}$; 7,36—8,10 (m, 5H, $C_6H_5$$^{A}$ and 5H, $C_6H_5$$^{B+C}$); 8,33 (d, 1H, 6-H)$^{B+C}$; 8,57 (d, 1H, 6-H)$^{A}$; 8,81 (s, 1H, 2-H)$^{B+C}$; 9,10 (s, 1H, 2-H)$^{A}$; 14,11 (br.d, 1H, OH)$^{B}$ | | | | | | | | | | 62 |
| II | 106—110 | 205 (4,20), 242 (3,96), 330 (4,23) | 4,61 (s, 2H, α,α′-H)$^{A}$; 6,31 (s, 1H, α-H)$^{B}$; 7,34—8,02 (m, 5H, $C_6H_5$$^{A}$ and 5H, $C_6H_5$$^{B}$); 8,49 (s, 2H, 4,6-H)$^{B}$; 8,61 (s, 2H, 4,6-H)$^{A}$; 13,32 (s, 1H, OH)$^{B}$ | 61,9 | 4,0 | (15,2) | 12,0 | $C_{12}H_9ClN_2O$ | 61,9 | 3,9 | (15,2) | 12,0 | 65 |
| III | 139—143 | 202 (4,45), 242 (3,96), 345 (4,40) | 4,67 (s, 2H, α,α′-H)$^{A}$; 6,41 (s, 1H, α-H)$^{B}$; 7,34—8,17 (m, 10H, $2C_6H_5$$^{A}$ and 10H, $2C_6H_5$$^{B}$); 8,81 (s, 2H, 4,6-H$^{B}$); 8,91 (s, 2H, 4,6-H$^{A}$); 14,04 (s, 1H, OH)$^{B}$ | | | | | | | | | | 69 |
| IV | 113—115 | 205 (4,20), 252 (4,32) | 6,31 (s, 1H, α-H); 7,27—7,64; 7,91—8,14 (m, 5H, $C_6H_5$); 7,74 (br.d, 1H, 5-H); 8,77 (br.d, 1H, 6-H); 9,11 (s, 1H, 2-H) | 51,9 | 3,0 | 28,6 | 9,8 | $C_{12}H_9BrN_2O$ | 51,9 | 3,2 | 28,9 | 10,1 | 70 |
| V | 65—67 | 207 (4,18), 250 (4,15) | 6,44 (s, 1H, α-H); 7,34—8,17 (m, 5H, $C_6H_5$); 8,69 (s, 2H, 4,6-H) | 51,8 | 3,0 | (27,5) | 10,6 | $C_{12}H_8Cl_2N_2O$ | 51,8 | 3,2 | (27,8) | 10,9 | 90 |
| VIa | 132—134 | 205 (4,48), 255 (4,44) | 6,45 (s, 1H, α-H); 7,28—7,52; 7,75—8,00 (m, 10H, $2C_6H_5$); 8,85 (s, 2H, 4,6-H) | 69,7 | 4,4 | (11,5) | 9,2 | $C_{18}H_{13}ClN_2O$ | 70,0 | 4,2 | (11,5) | 9,1 | 98 |
| VIb | 127—128,5 | 203 (4,54), 256 (4,46) | 6,62 (s, 1H, α-H); 7,29—8,15 (m, 10H, $2C_6H_5$); 8,85 (s, 2H, 4,6-H) | 61,3 | 3,7 | 22,3 | 7,9 | $C_{18}H_{13}BrN_2O$ | 61,2 | 3,7 | 22,6 | 7,9 | 80 |
| VIIa | 104—106 | 203 (4,34), 260 (4,39) | 7,30—7,90 (m, 10H, $2C_6H_5$); 8,92 (s, 2H, 4,6-H) | 63,1 | 3,5 | (20,5) | 8,4 | $C_{18}H_{12}Cl_2N_2O$ | 63,0 | 3,5 | (20,7) | 8,2 | 95 |
| VIIb | 128—129 | 203 (4,40), 264 (4,36) | 7,30—7,90 (m, 10H, $2C_6H_5$); 9,00 (s, 2H, 4,6-H) | 49,9 | 2,7 | 36,7 | 6,6 | $C_{18}H_{12}Br_2N_2O$ | 50,0 | 2,8 | 36,9 | 6,5 | 98 |
| VIII | 93—94 | 207 (4,27), 254 (4,20) | 6,49 (s, 1H, α-H); 7,19 (q, 1H, 5-H); 7,42 (d, 1H, 3-H); 7,45—7,71; 7,89—8,05 (m, 6H, 4-H and $C_6H_5$); 8,49 (m, 1H, 6-H) | | | | | | | | | | 95 |
| IX | 235—237 | 205 (4,53), 253 (4,43) | 7,45—8,05 (m, 10H, $2C_6H_5$); 9,35 (s, 2H, 4,6-H) | 74,7 | 4,1 | | 9,6 | $C_{18}H_{12}N_2O_2$ | 74,9 | 4,2 | | 9,7 | 70 |

*The A:(B + C) ratio is 3:7 for I, while the A:B ratio is 1:1 for II and 2:3 for III.

DMSO. The IR spectra of these compounds show a strong band at 1710 $cm^{-1}$ (C=O group in ketone A), while $\nu_{C=O\ldots H}$ does not exceed 1650 $cm^{-1}$ for ylidene structure C [5]. The $\nu_{C=O}$ values for N-substituted ylidene derivatives C also do not exceed 1640-1650 $cm^{-1}$ [6]. The PMR spectra of halophenacylpyrimidines IV-VI show signals for the α-hydrogen atoms at 6.3-6.6 ppm* and the hydrogen atoms of the pyrimidine and phenyl rings. The ratio of the integral intensities of these signals exactly corresponds to the existence of only the keto form. The UV spectra of IV-VI have maxima at 205 and 260 nm. The lack of absorption at longer wavelengths characteristic for enol B and ylidene form C [6, 7] also indicates the existence of monohalo derivatives only in the keto form.



A B C

The introduction of a bulky alkyl substituent in the α-position relative to the carbonyl group of 2-phenacylpyridine leads to its complete conversion to the keto form [8]. Branch [8] attributed the destabilization of the enol form to the steric hindrance between the alkyl group and the ortho-hydrogen atoms of the $C_6H_5$ group in the phenacyl fragment, which leads to the loss of coplanarity and decrease in the resonance stabilization of the enol due to conjugation with the phenyl group. The ketone structure of α-halophenacylpyrimidines IV-VI is probably largely a consequence of the same factors. The analogous properties are also seen for 2-(α-bromophenacyl)pyridine (VIII) [9] whose spectral characteristics are given in Table 1.

The introduction of a second halogen atom into monohaloketones VIa and VIb proceeds considerably more slowly and requires 1.5-2 equivalents of the halogenating agent. The yield of final products VIIa and VIIb in this case is 95%, while the halogenation of VIb as an anion usually employed for slightly enolized systems [10] leads to dibromoketone VIIb in only 60% yield.

Monohalo derivatives IV-VI and also dichloroketone VIIa are rather stable in 0.1 N hydrochloric acid and 0.4 N ethanolic NaOH at 20°C and upon heating at 80°C for 30 min. An exception is found for V and VIa which are no longer detected by thin-layer chromatography upon treatment by ethanolic alkali for 5-10 min at 20°C.

Dibromophenacylpyrimidine VIIb is converted upon heating at reflux in ethanol to 1-phenyl-2-(5-phenyl-2-pyrimidinyl)ethanedione (IX). Its structure is confirmed by elemental analysis and spectral indices (Table 1). The IR spectrum of IX has a strong band at 1720 $cm^{-1}$ for the carbonyl group of an α-diketone [5].

## EXPERIMENTAL

The IR spectra of these compounds were taken on a UR-20 spectrophotometer in KBr pellets. The PMR spectra were taken on a Varian A-56/60 spectrometer using HMDS as the internal standard in $CDCl_3$. The UV spectra were taken on a Specord UV-vis spectrophotometer in ethanol. The reactions were monitored and the purity of the compounds obtained was checked by thin-layer chromatography on Silufol UV-254 plates using chloroform as the eluent.

The syntheses of 5-phenyl-2-phenacylpyrimidine (III) and 4-phenacylpyrimidine (I) were described in our previous work [12]. A sample of 2-phenacyl-5-chloropyrimidine (II) was obtained from 2-methyl-5-chloropyrimidine [11] according to our previous procedure [2].

The physicochemical indices for pyrimidines I-VII and IX are given in Table 1.

Monohalo derivatives IV-VI. Solutions of 0.01 mole phenacylpyrimidine I-III and 1.65 g (0.02 mole) fused sodium acetate in 100 ml glacial acetic acid were prepared. A solution of 0.01 mole $Cl_2$ or $Br_2$ in 50 ml glacial acetic acid was added dropwise with stirring at 20°C over 30 min. The reaction mixture was stirred at 20°C for 1 h until the starting compound disappeared as indicated by thin-layer chromatography. Acetic acid was evaporated on a rotary evaporator at 40°C bath temperature. The oily residue was triturated with 50

*The chemical shifts of the α-H atoms are in good agreement with the shifts of substituted methylazines determined by an additive scheme.

ml petroleum ether. The precipitate formed was filtered off, washed with 20 ml saturated aq. $NaHCO_3$ and three 20-ml portions of water until the pH of the wash water was about 7, dried in a vacuum dessicator and recrystallized from ethanol to give 70-98% IV-VI (see Table 1).

2,2-Dibromo-2-(5-phenyl-2-pyrimidinyl)-1-phenyl-1-ethanone (VIIb) and 1-Phenyl-2-(5-phenyl-2-pyrimidinyl)-2,2-dichloro-1-ethanone (VIIa). A sample of 0.01 mole 5-phenyl-2-phenacylpyrimidine (III) and 3.28 g (0.04 mole) fused sodium acetate were dissolved in 100 ml glacial acetic acid. A solution fo 0.025 mole $Cl_2$ or $Br_2$ in 50 ml acetic acid was added dropwise at 20°C. The reaction mixture was stirred at 20°C for about 150 min and monitored by thin-layer chromatography and treated as described above to give 95-98% VIIa and VIIb.

Bromination of Pyrimidine VIb as the Sodium Salt. A sample of 0.35 g (1 mmole) VIb was dissolved in 35 ml monoglyme. Then, 0.03 g (1 mmole) of an 80% dispersion of NaH in paraffin oil (supplied by Merck) was added and the mixture was stirred until there was no further liberation of gas bubbles. A solution of 0.054 ml (1 mmole) $Br_2$ in 10 ml monoglyme was added dropwise and the mixture was stirred for 30 min at 20°C until the starting compound completely disappeared as indicated by thin-layer chromatography. Monoglyme was removed on a rotary evaporator at 30°C bath temperature. The oily residue was treated as described above for monhaloketones IV-VI to give 60% VIIb.

Stability of Pyrimidines IV-VI and VIIa in Acid and Basic Media. A. A sample of 1 mmole halophenacylpyrimidine IV-VI or VIIa was dissolved in 20 ml ethanol, 0.1 ml concentrated hydrochloric acid was added and the mixture was heated at reflux for 30 min. Ethanol was removed on a rotary evaporator at 30°C bath temperature and 5 ml water was added to the residue. The precipitate was filtered off, washed with 5 ml water and dried to give starting IV-VI or VIIa identified by thin-layer chromatography and melting point.

B. A sample of 1 ml 30% ethanolic NaOH was added to a solution of 1 mmole pyrimidine IV-VI or VIIa in 20 ml ethanol and maintained at 20°C. After 5-10 min, thin-layer chromatography indicates that monochlorophenacylpyrimidines V and VIa are completely converted to other compounds ($R_f$ 0.5, violet emission in UV light) which were not identified. Products IV, VIb and VIIb were maintained at 20°C in 0.4 N ethanolic NaOH for 1 h and then heated at reflux for 30 min. Ethanol was evaporated and the residue was treated as described in experiment A to give starting IV, VIb and VIIb identified by thin-layer chromatography and melting point.

1-Phenyl-2-(5-phenyl-2-pyrimidinyl)ethanedione (IX). A solution of 1.75 g pyrimidine VIIb in 200 ml ethanol was heated at reflux for 2 h. The solution was cooled and the crystalline precipitate (0.6 g) was filtered off and dried. An additional amount of IX was obtained from the filtrate upon evaporation. The yield was 70%.

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