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PYRIMIDINES. 69.* SYNTHESES BASED ON ACETYLPYRIMIDINES. DIPYRIMIDINYLS AND PYRIMIDINE ANALOGS OF CHALCONE

M. A. Mikhaleva, V. V. Gulevich, I. I. Naumenko, and V. P. Mamaev

UDC 547.855:543.422.4

Substituted pyrimidinyl styryl ketones were obtained by condensation of 4-methyl-2-phenyl-5-acetylpyrimidine with aromatic aldehydes, and their conformations in KBr and in solution in $CHCl_3$ were examined. 4',5-Dipyrimidinyl derivatives were obtained by cyclization of the pyrimidinyl styryl ketones with benzamine. The isomeric trioxo-4',5- and -4,6'-dipyrimidinyls were obtained by reaction of 5- and 6-acetyluracils with benzalbisurea.

Interest in 4,4'- and 4,5'-dipyrimidinyl derivatives has arisen in connection with their formation as the principal products in the photolysis of frozen aqueous solutions of uracil, cytosine, etc. [2, 3]. The methods that have been developed for the synthesis of dipyrimidinyls pertain for the most part to symmetrical derivatives — 2,2'- or 5,5'-dipyrimidinyls [4]. A number of methods for the synthesis of 4,5'-dipyrimidinyls from 4-methylpyrimidine [5, 6], by photolysis of uracil and cytosine [7, 8], through pyrimidinyllithium compounds [9] and by condensation of aminomethylene derivatives of acetylpyrimidines [2, 10] have been recently published.

Continuing our study of the synthesis of pyrimidine derivatives from substituted acetophenones [11], we attempted to use acetylpyrimidines for the synthesis of dipyrimidinyl derivatives.

Using the readily accessible 4-methyl-2-phenyl-5-acetylpyrimidine (I) as the starting compound, we tried to subject it to condensation with benzalbisurea in CH_3COOH or n-butanol—HCl [11]; however, the expected 4,5'-dipyrimidinyl (II) was not detected among the reaction products. Protonation of pyrimidine I probably occurs in acidic media, and electrophilic substitution by the ureidobenzyl cation at the acetyl group does not take place.

Another possible method for the synthesis of 4,5'-dipyrimidinyls from ketones is through the corresponding chalcone analogs [12, 13]. The pyrimidine analogs of chalcone

*See [1] for Communication 68.

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 678-683, May, 1979. Original article submitted August 7, 1978.

0009-3122/79/1505-0551$07.50

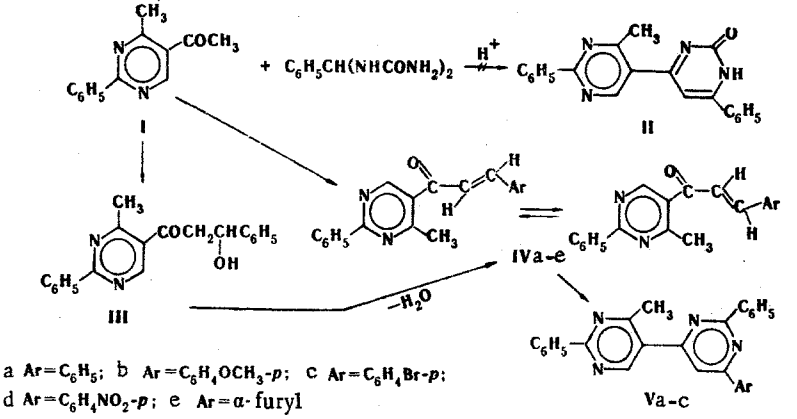
TABLE 1. α,β-Unsaturated Pyrimidinyl Ketones

Compound	mp, °C (from alcohol)	λ_{max}, nm (lg ε)	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IVa	104—106	206 (4,48), 228 (4,23), 310 (4,51)	79,0	5.2	9,4	$C_{20}H_{16}N_2O$	80,0	5,4	9,3	77
IVb	125—132	205 (4,34), 243 (4,15), 291 (4,25), 345 (4,43)	76,1	5,6	8,5	$C_{21}H_{18}N_2O_2$	76,3	5,5	8,5	70
IVc	122—123	206 (4,45), 228 i (4,25), 317 (4,50)	63,6	4,0	7,4	$C_{20}H_{15}BrN_2O$	63,3	4,0	7,4	53
IVd	—*	204 (4,35), 219 i (4,16), 302 (4,37)	—	—	—	$C_{20}H_{15}N_3O_3$†	—	—	—	46
IVe	92—93‡	205 (4,22), 248 i (4,06), 294 (4,23), 342 (4,49)	74,2	5,1	9,7	$C_{18}H_{14}N_2O_2$	74,5	4,9	9,7	65

*This compound melted slowly at 120-130°C, after which it solidified and melted again at 165-175°C. †This is the calculated empirical formula from the established molecular weight of 345.1112. ‡This compound solidified and melted again at 101°C.

have not been described in the literature, and we undertook the synthesis of α,β-unsaturated ketones from 5-acetylpyrimidine I and aromatic aldehydes.

It is known that chalcone analogs are readily formed from acetylpyridines in alkaline media [14]. The condensation of acetylpyrimidine I with benzaldehyde in an aqueous alkaline



medium did not go to completion at room temperature [13]. Two compounds were isolated along with starting I. The IR spectrum of one of these compounds contained the band of a C=O group at 1685 cm^{-1}, which differs slightly from the position of the band in the spectrum of the starting ketone, and the band of an OH group at 3600 cm^{-1}. The UV spectrum of this compound virtually coincided with the UV spectrum of ketone I. The 4-methyl-2-phenyl-5-pyrimidinyl β-hydroxy-β-phenylethyl ketone structure (III) proposed on the basis of the spectral data was confirmed by the results of elementary analysis and by the determination of the molecular weight.

The structure of a chalcone analog — 4-methyl-2-phenyl-5-pyrimidinyl styryl ketone (IVa) — was proposed for the second compound, which has a characteristic shift of the $\nu C=O$ band in the IR spectrum to the low-frequency region and a bathochromic shift in the UV spectrum. The yield of styryl ketone IVa increased and its isolation from the reaction mixture was simplified when the reaction was carried out at a higher temperature and particularly in solution in methanol. α,β-Unsaturated ketones IVb-e were obtained in good yields under the same conditions (Table 1).

It is known that α,β-unsaturated ketones exist in the form of s-cis and s-trans conformers [15]. These conformations can be distinguished from the position and relative intensities of the C=O and C=C stretching vibrations in the IR spectra. It is noted in the literature that these relationships are not always observed for heterocyclic analogs of chalcone; in particular, drawing together of the bands in the s-cis conformation and an increase in the intensity of the $\nu C=C$ band due to conjugation with the aromatic ring are pos-

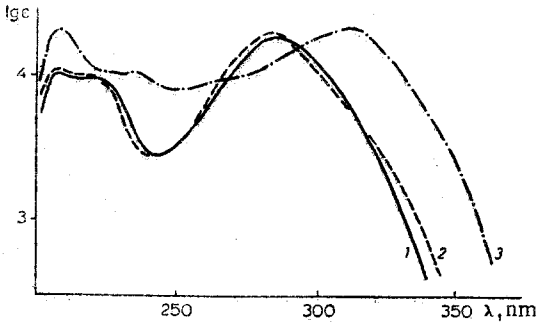


Fig. 1

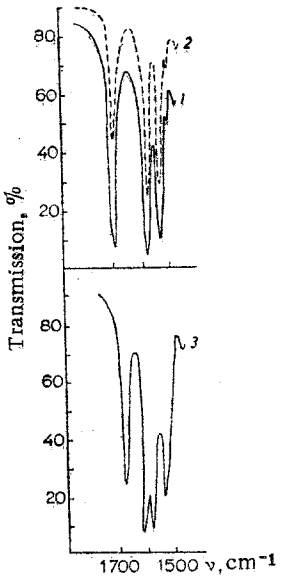


Fig. 2

Fig. 1. UV spectra: 1) acetylpyrimidine I; 2) hydroxy ketone III; 3) styryl ketone IVa.

Fig. 2. IR spectra (in KBr): 1) acetylpyrimidine I; 2) hydroxy ketone III; 3) styryl ketone IVa.

TABLE 2. IR Spectra of α,β-Unsaturated Ketones of 4-Methyl-2-phenylpyrimidine

Compound	KBr (s-cis)			$CHCl_3$ (s-cis⇌s-trans)		
	$\nu_{C=C}$	$\nu_{C=O}$	$\nu_{C=O}$ to $\nu_{C=C}$ intensity ratio*	$\nu_{C=C}$	$\nu_{C=O}$	$\nu_{C=O}$ to $\nu_{C=C}$ intensity ratio*
IVa	1607	1666	1	1600 1622	1668 1642	0,6 3
IVb	1608	1661	~1	— 1637	— 1664	 0,5
IVc	1596	1661	1,1	1604 1623	1667 1655	0,9 2
IVd	1608	1669	~1	1612 1635	1671 1651	1,2 50
IVe	1600 1621	1660	0,5	1600 1622	1665 1643	0,6 0,8

*The ratio of the areas was determined by cutting out the peaks and weighing them.

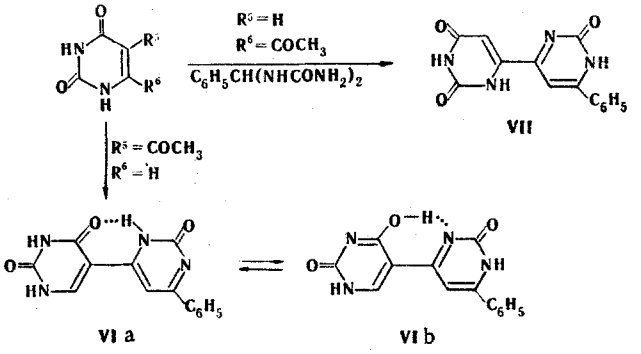
sible [16, 17]. In the general case the intensity of the $\nu_{C=C}$ band is, as a rule, higher than (or close to) that of the $\nu_{C=O}$ band for the s-cis conformation in the case of a greater distance between them than for the s-trans conformer vis-à-vis an inverted intensity ratio. A distinct boundary between the $\nu_{C=C}$ and $\nu_{C=O}$ bands exists in the IR spectra of ketones IV (Fig. 2), and this makes it possible to determine their conformations. It is apparent from the data from the IR spectra (Table 2) that the compounds obtained, as might have been expected [15], exist in the s-cis conformation in KBr. A low-intensity $\nu_{C=C}$ band at 1621 cm^{-1}, which makes it possible to assume the presence of the s-trans conformer, is observed only for IVe. The corresponding $\nu_{C=O}$ band does not show up, evidently because of its low intensity. The appearance of a doublet of bands of both carbonyl absorption and of the C=C bond is observed in the IR spectra in the case of $CHCl_3$ solutions (Fig. 2 and Table 2) for all of the ketones; this is apparently due to the existence of the s-cis ⇄ s-trans conformational equilibrium [16]. Only one $\nu_{C=O}$ band, which, on the basis of the data in [16], we assume to be due to the s-trans conformation, is present in the spectrum of ketone IVb.

It is not possible to use the PMR spectra for the determination of the relative orientations of the substituents attached to the C=C bond (the cis and trans isomers) in view of

the superimposition of the signals of the protons of two phenyl rings on the signals of the protons attached to the double bond. However, the presence of a band of medium or strong intensity in the IR spectra at 980-990 cm^{-1}, which is characteristic for the out-of-plane deformation vibrations of a trans-vinylene group [18], makes it possible to identify ketones IV as the trans isomers.

In the case of styryl ketones IVa-c we investigated the possibility of their use in the synthesis of dipyrimidinyl derivatives. Condensation in an acidic medium with benzaldehyde and urea [12] was unsuccessful, while the corresponding 4',5-dipyrimidinyls (V) were obtained in the case of condensation with benzamidine in alcoholic alkali [13].

We assumed that the acetylpyrimidines that are less basic than acetylpyrimidine I might undergo reaction with benzalbisurea under the conditions in [11]. We used 5-acetyl- and 6-acetyluracils as compounds of this sort. In the condensation of the latter with benzalbisurea in n-butanol—HCl the reaction actually took place at the CH_3 group of the acetyl group with subsequent cyclization to trioxo-4',5- and 4',6-dipyrimidinyls VI and VII. They are high-melting compounds and are very slightly soluble in ordinary organic solvents. In contrast to isomer VII, the existence of tautomeric forms VIa and VIb is possible in the case of trioxodipyrimidinyl VI, owing to the formation of a chelate ring with an intramolecular hydrogen bond.



EXPERIMENTAL

The IR spectra of the α,β-unsaturated ketones in KBr pellets (c 0.25% and in solution in $CHCl_3$ (c 5%) were recorded with a Specord IR-75 spectrometer. The IR spectra of solutions of the remaining compounds in $CHCl_3$ were recorded with a UR-10 spectrometer. The UV spectra of ethanol solutions were recorded with a Specord spectrophotometer. The PMR spectra were recorded with Varian A56/60A and Bruker WP-80 spectrometers with hexamethyldisiloxane as the internal standard. The molecular weights were determined with an MS 902 high-resolution mass spectrometer.

4-Methyl-2-phenyl-5-acetylpyrimidine (I). This compound, with mp 103-103.5°C (literature mp 107°C), was obtained in 37% yield by the method in [19]. IR spectrum: 1575 (aromatic ring C=C) and 1690 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 2.59 (s, 3H, acetyl group CH_3), 2.78 (s, 3H, 4-CH_3), 7.49-7.67 (m, 3H, m,p-H_{arom}), 8.51-8.71 (m, 2H, o-H_{arom}), and 9.12 ppm (2, 1H, pyrimidine ring 6-H).

2-Phenyl-4-methyl-5-pyrimidinyl β-Hydroxy-β-phenylethyl Ketone (III) and 2-Phenyl-4-methyl-5-pyrimidinyl Styryl Ketone (IVa). A) A solution of 0.28 g (7 mmole) of NaOH in 3 ml of water was added to a suspension of 2 g (9.6 mmole) of acetylpyrimidine I and 1.2 ml (11.2 mmole) of benzaldehyde in 60 ml of water, and the mixture was stirred at room temperature. It was then extracted with $CHCl_3$, and the extract was dried with $MgSO_4$ and evaporated. The residue was chromatographed on plates with KSK silica gel in a benzene—chloroform—alcohol system (20:20:1). Workup of the first zone gave 0.1 g of hydroxy ketone III with R_f 0.30 and mp 121-123°C (from alcohol). Found: N 8.8%; M 318.1366. $C_{20}H_{18}N_2O_2$. Calculated: N 8.8%; M 318.1368. The second zone contained starting ketone I, and workup of the third zone gave 0.1 g of styryl ketone IVa with R_f 0.70. PMR spectrum ($CDCl_3$): 2.75 (s, 3H, CH_3), 7.35-8.50 (m, 12H, H_{arom} and —CH=CH—), and 9.00 ppm (s, 1H, pyrimidine ring 6-H).

B) The styryl ketone was obtained in 57% yield when the reaction was carried out at 40-50°C for 7 h.

C) A total of 6 ml of 10% KOH solution was added to a solution of 2.1 g (0.01 mole) of ketone I and 1.05 ml (0.01 mole) of benzaldehyde in 50 ml of methanol, and a yellow precipitate formed in the flask after a few minutes. The mixture was allowed to stand overnight, and the precipitate was removed by filtration and washed with water and alcohol. The yield of styryl ketone IVa was 2.3 g (77%).

4-Methyl-2-phenyl-5-pyrimidinyl p-methoxystyryl ketone (IVb) and the corresponding p-bromostyryl ketone (IVc), p-nitrostyryl ketone (IVd), and β-(α-furyl)vinyl ketone (IVe) were obtained by method C from acetylpyrimidine I and the appropriate aldehydes (Table 1).

4-Methyl-2,2',6'-triphenyl-5,4'-dipyrimidinyl (Va). A 1-g (3.3 mmole) sample of styryl ketone IVa and 0.26 g (1.65 mmole) of benzamidine hydrochloride were added to a solution of 0.4 g (7.1 mmole) of KOH in 15 ml of alcohol, and the mixture was refluxed for 3 h. It was then cooled, and a precipitate formed. The mixture was allowed to stand overnight, after which the precipitate was removed by filtration, washed with water, and recrystallized from alcohol to give 0.11 g (20%) of dipyrimidinyl Va with mp 148-152°C. PMR spectrum ($CDCl_3$): 2.90 (s, 3H, CH_3), 7.75 (s, 1H, pyrimidine ring 5-H), 7.30-7.52 (m, 9H, H_{arom}), 8.17-8.66 (m, 6H, o-H_{arom}), and 9.09 ppm (s, 1H, pyrimidine ring 6-H). Found: N 13.9%; M 400. $C_{27}H_{20}N_4$. Calculated: N 14.0%; M 400.

4-Methyl-2,2'-diphenyl-6'-(p-methoxyphenyl)-4',5-dipyrimidinyl (Vb). A 0.7-g (2.1 mmole) sample of styryl ketone IVb and 0.165 g (1.05 mmole) of benzamidine hydrochloride were added to a solution of 0.28 g (4 mmole) of KOH in 10 ml of alcohol, and the mixture was refluxed for 2 h. It was then cooled, and the precipitate was removed by filtration and dissolved in ether. The ether solution was filtered, the ether was evaporated from the filtrate, and the residue was recrystallized from alcohol to give 0.11 g (24%) of dipyrimidinyl Vb with mp 163-164°C. Found: C 78.3; H 5.0; N 13.1%; M 430. $C_{28}H_{22}N_4O$. Calculated: C 78.1; H 5.1; N 13.0%; M 430.

4-Methyl-2,2'-diphenyl-6'-(p-bromophenyl)-4',5-dipyrimidinyl (Vc). A 0.092-g (0.59 mmole) sample of benzamidine hydrochloride and 0.45 g (1.18 mmole) of styryl ketone IVc were added to a solution of 0.13 g (2.36 mmole) of KOH in 6 ml of alcohol, and the mixture was refluxed for 3 h. It was then cooled, and the precipitate was removed by filtration, washed with alcohol, and dissolved in 10 ml of ether. The ether solution was filtered, and the ether was evaporated to give 0.2 g (70%) of dipyrimidinyl Vc with mp 155-160°C (from alcohol). Found: M 478.0793. The empirical formula $C_{27}H_{19}BrN_4$ was calculated from this molecular weight.

2,2',4-Trioxo-6'-phenyl-1,1',2,2',3,4-hexahydro-4',5-dipyrimidinyl (VI). An 18.6-g (0.12 mole) sample of 5-acetyluracil and 24.9 g (0.24 mole) of benzalbisurea were added to a solution of 9.0 g (0.25 mole) of dry HCl in 380 ml of absolute n-butanol, and the mixture was refluxed for 6 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with 10% $NaHCO_3$ solution, water, alcohol, and ether to give 37.5 g (72%) of dipyrimidinyl VI with mp > 360°C. PMR spectrum (d_6-DMSO): 7.36-7.85 (m, 3H, H_{arom}), 7.64 (s, 1H, pyrimidine ring 5'-H), 7.74-8.09 (m, 2H, o-H_{arom}), and 8.49 ppm (s, 1H, pyrimidine ring 6-H), and 11.66 ppm (broad, N–H). Found: C 58.1; H 3.8; N 19.4%; M 282. $C_{14}H_{10}N_4O_3 \cdot 0.5H_2O$. Calculated: C 58.0; H 3.8; N 19.3%; M 282 + 9.

2,2',4-Trioxo-6'-phenyl-1,1',2,2',3,4-hexahydro-4',6-dipyrimidinyl (VII). This compound was similarly obtained from 0.28 g (1.8 mmole) of 6-acetyluracil [20], 0.75 g (3.6 mmole) of benzalbisurea, and 5.9 ml of absolute n-butanol in the presence of 0.14 g of dry HCl. The yield of product with mp > 360°C was 0.20 g (55%). Found: M 282.0174. The empirical formula $C_{14}H_{10}N_4O_3$ was calculated from this molecular weight. PMR spectrum (d_6-DMSO): 7.28-7.55 (m, 3H, H_{arom}), 7.68 (s, 1H, pyrimidine ring 5-H), 7.76-8.06 (m, 2H, o-H_{arom}), 8.55 (s, 1H, pyrimidine ring 5-H), and 11.65 ppm (broad, 3H, N–H).

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QUINAZOLINES. 13.* SOME REACTIONS OF 2,3-POLYMETHYLENE-3,4-DIHYDRO-4-QUINAZOLONES WITH ELECTROPHILIC REAGENTS

É. Oripov, Kh. M. Shakhidoyatov,
Ch. Sh. Kadyrov, and N. D. Abdullaev

UDC 547.856.1

2,3-Polymethylene-3,4-dihydro-4-quinazolones react with bromine and sulfur trioxide to give complexes involving the nitrogen atom, while bromination in acidic media and Vilsmeier—Haack formylation lead to replacement of the hydrogen atoms of the carbon atom in the α position. Their nitration and chlorosulfonation give 6-nitro- and 6-chlorosulfonyl-2,3-polymethylene-3,4-dihydro-4-quinazolones. Some of the chemical transformations of the synthesized compounds were studied.

We have previously developed a method for the synthesis of 2,3-polymethylene-3,4-dihydro-4-quinazolones (I) and quinazolines [2].

Continuing our systematic studies of quinazolines [3, 4] in order to synthesize pesticides we have studied several electrophilic substitution reactions of I: bromination, reaction with sulfur trioxide, chlorosulfonation, and Vilsmeier—Haack formulation.

It is known that in the nitration of quinazoline and 4-quinazolone the nitro group enters the 6 position of the aromatic ring [5, 6]. There are no other data available with regard to this problem.

The direction of bromination of 2,3-poly(tri-, tetra-, and penta-)methylene-3,4-dihydro-4-quinazolones (Ia-c) and their 6-nitro derivatives (IIa-c) depends on the conditions: Perbromides IIIa-c and IVa-c, respectively, were obtained from I and II in various solvents (chloroform, glacial acetic acid, concentrated H_2SO_4, and 80% methanol) in the cold in the presence of catalysts (iron filings of mixture of iron filings and iodine, as well as alumi-

*See [1] for Communication 12.

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 684-691, May, 1979. Original article submitted April 11, 1978.

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