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SYNTHESIS OF 2- AND 6-ARYLAMINOPYRIMIDINEDIONES

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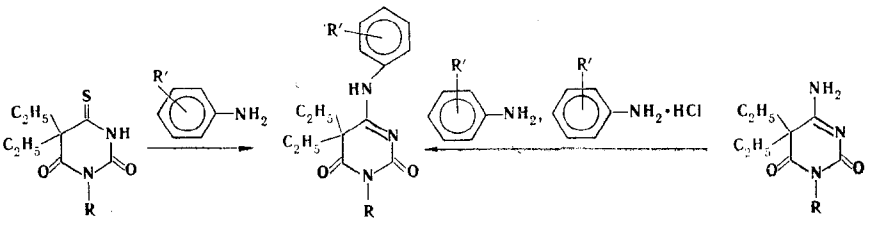
Methods for the synthesis of 6-arylamino-5,5-diethyl-3H,5H-pyrimidine-2,4-diones from the corresponding 6-thioxo and 6-amino derivatives were developed. The isomeric 2-arylamino-5,5-diethyl-1H,5H-pyrimidine-4,6-diones were obtained by the reaction of 2-mercapto- and 2-methylthio-1H,5H-pyrimidine-4,6-diones with substituted anilines. The ionization constants of the compounds obtained were determined.

In contrast to the substituted (at the amino group) 5,5-dialkyl-2-amino-1H,5H-pyrimidine-4,6-diones, for the preparation of which several rather general methods are known [1-4], little study has been devoted to the synthesis of the isomeric 6-amino derivatives. Only the preparation of 3-methyl-6-methylamino-5,5-diethyl-3H,5H-pyrimidine-2,4-dione by methylation of the corresponding 6-amino derivative has been described [5]. However, this method cannot be regarded as convenient from a preparative point of view, since methylation proceeds ambiguously to give a mixture of isomeric 6-imino-1,3-dimethyl-1H,3H,5H- and 3-methyl-6-methylamino-1H,5H-pyrimidine-2,4-diones [6]. The aim of the present research was to develop methods for the synthesis of 6-arylamino derivatives of 3H,5H-pyrimidine-2,4-dione (III). For this, we investigated the reaction of 6-thioxo-5,5-diethyl-1H,3H,5H-pyrimidine-2,4-diones (I) with aromatic amines. We found that heating thioxo derivatives I with excess aromatic amine at 160-180°C for 6-20 h without a solvent leads to 6-arylamino-1H,3H-pyrimidine-2,4-diones (III) in good yields (Table 1).

Thioxo derivatives I are relatively difficult to obtain. We therefore attempted to obtain III by transamination under the conditions described for 2-amino derivatives of 5,5-dialkyl-1H,5H-pyrimidine-4,6-diones [7]. We established that heating equimolar amounts of the arylamine, the arylamine hydrochloride, and II at 170-180°C leads to the corresponding 6-arylamino-substituted derivatives III. However, the yields and reaction times depend substantially on the presence of a substituent attached to the N_3 atom. Thus in the case of IIb the reaction with various arylamines under the selected conditions takes place in 1-2 h, and the yields amount to 80-90%. However, in the absence of a substituent (IIa) the reaction time increases considerably, and the yields are reduced to 30%.



I, IIa, R=H; b R=CH_3; IIIa-e, R=H; a R′=H; b R′=*p*-Cl; c R′=*p*-CH_3; d R′=*m*-CH_3; e R′=*p*-CH_3O; IIIf-h R=CH_3; f R′=H; g R′=*m*-Cl; h R′=*p*-Cl

Compounds III are white, high-melting, crystalline substances. Absorption bands corresponding to the vibrations of NH and C=O groups at 3200 and 1700 cm^{-1} are present in their IR spectra. The PMR spectra contain signals of protons of aryl and alkyl substituents. The mass

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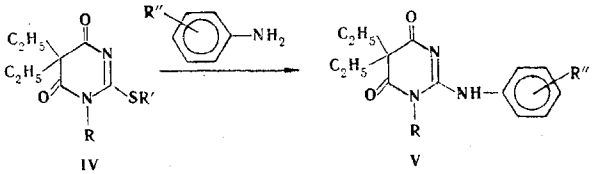
TABLE 1. 6-Arylamino-5,5-diethyl-3H,5H-pyrimidine-2,4-diones

Compound	mp, deg C	IR spectrum, cm^{-1}		Found, %			Empirical formula	Calculated, %			pK_a	Yield, % (method)
		NH	C=O, C=N, C=C	C	H	N		C	H	N		
IIIa	236—238	3285, 3120, 3070	1724, 1675, 1608, 1545	64,5	7,0	16,5	$C_{14}H_{17}N_3O_2$	64,9	6,6	16,2	10,32	79 (A)
IIIb	214—215	3300, 3200, 3140, 3070	1716, 1676, 1620, 1600, 1570, 1547	57,2	5,8	14,4	$C_{14}H_{16}ClN_3O_2$	57,2	5,5	14,3	10,04	64 (A)
IIIc	238—240	3308, 3180; 3063	1715, 1675, 1620, 1582, 1539, 1517	65,5	7,1	15,5	$C_{15}H_{19}N_3O_2$	65,9	7,0	15,4	10,47	83 (A)
IIId	209—210	3282, 3165, 3120, 3020	1727, 1650, 1618, 1603, 1525	65,8	7,2	—	$C_{15}H_{19}N_3O_2$	65,9	7,0	—	10,32	71 (A)
IIIe	207—209	3312	1717, 1670, 1602, 1571, 1535, 1516	62,2	6,7	14,8	$C_{15}H_{19}N_3O_3$	62,3	6,6	14,5	10,49	91 (A)
IIIf	157—158	3238, 3070	1731, 1710, 1675, 1650, 1608, 1575, 1542	65,8	7,4	15,2	$C_{15}H_{19}N_3O_2$	65,9	7,0	15,4	11,80	79 (B)
IIIg	165—166	3311, 3210, 3150, 3101, 3074	1713, 1647, 1624, 1603, 1575, 1547	59,0	6,0	13,3	$C_{15}H_{18}ClN_3O_2$	58,5	5,9	13,7	10,81	89 (B)
IIIh	169—170	3310, 3215	1711, 1655, 1612, 1601, 1577, 1550	58,6	6,0	13,9	$C_{15}H_{18}ClN_3O_2$	58,5	5,9	13,7	11,24	85 (B)

spectra contain molecular-ion peaks corresponding to the calculated values, and the subsequent fragmentation is similar to the fragmentation of the similarly constructed I and II [6, 8, 9]. To confirm the structure of III, in which a substituent is bonded to the exocyclic amino group, we subjected them to acidic hydrolysis. In all cases the hydrolysis product was either 5,5-diethylbarbituric acid (for R = H) or 1-methyl-5,5-diethylbarbituric acid (for R = CH_3). This constitutes evidence that the Dimroth rearrangement that takes place in the alkylation of amino derivatives II [6] does not occur in the preparation of pyrimidinediones III.

It is known that barbituric acid has a rather high acidity (pK_a 4.05)[10], whereas the acidities of its 5,5-diethyl derivatives are considerably lower [pK_a 7.96 for 5,5-diethylbarbituric acid (veronal) and pK_a 8.39 for **N-methylveronal] [10]**. From this point of view it seemed of interest to measure the ionization constants of our new 6-arylaminobarbituric acids and the corresponding isomeric 2-arylaminobarbituric acids (Tables 1 and 2).* Compounds V were syntheiszed by amination of the corresponding 2-mercapto (R = H, CH_3; R' = H) or 2-methylthio derivatives IV (R = R' = CH_3).



IV V

Va-f R=H; a R″=H; b R″=*m*-Cl; c R″=*p*-Cl; d R″=*m*-CH_3; e R″=*p*-CH_3; f R″=*p*-CH_3O; Vg-i R=CH_3; g R″=H; h R″=*p*-Cl; i R″=*p*-CH_3O

*A comparison of the pK_a values of IIIa-e and Va-f with the Hammett σ constants makes it possible to obtain the linear dependences

$$pK_a = 10{,}27 - 0{,}96\sigma \quad (r = 0{,}99;\ S = 0{,}04) \text{ for IIIa-e}$$

$$pK_a = 8{,}37 - 0{,}57\sigma \quad (r = 0{,}93;\ S = 0{,}064) \text{ for Va-f}$$

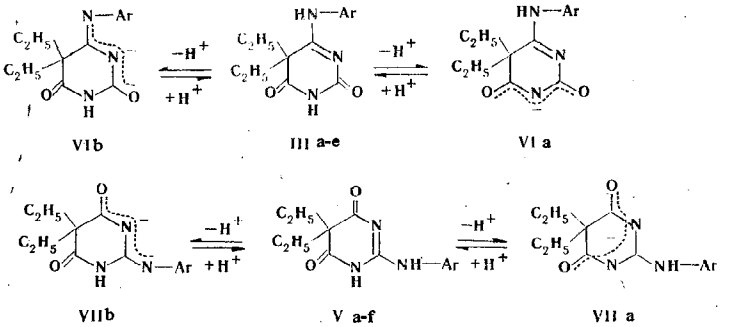
The correlation in the latter case, although it is appreciable, is less satisfactory than for the 6-arylamino derivatives.

TABLE 2. 2-Arylamino-5,5-diethyl-1H,5H-pyrimidine-4,6-diones

Compound	mp, degC	IR spectrum, cm^{-1}		Found, %			Empirical formula	Calc., %			pK_a	Yield, % (method)
		NH	C=O, C=N, C=C	C	H	N		C	H	N		
VIIa	252—254[a]	3180, 3030	1730, 1700, 1680, 1597, 1500								8,45	83 (A)
VIIb	230—232	3185, 3030	1730, 1680, 1657, 1574, 1516	57,0	6,0	14,2	$C_{14}H_{16}ClN_3O_2$	57,2	5,5	14,3	8,19	83 (A)
VIIc	280—283[b]	3175, 3032	1730, 1680, 1596, 1492								8,16	72 (A)
VIId	210—212	3300—3000	1734, 1658, 1608, 1598, 1582, 1527	65,8	7,3	15,1	$C_{15}H_{19}N_3O_2$	65,9	7,0	15,4	8,42	70 (A)
VIIe	239—241[c]	3190, 3030	1729, 1680, 1614, 1580, 1562, 1510								8,42	68 (A)
VIIf	239—240	3190, 3020	1725, 1682, 1586, 1512	62,2	6,6	14,8	$C_{15}H_{19}N_3O_3$	62,3	6,6	14,5	8,53	70 (A)
VIIg	100—101	3400, 3210, 3070	1726, 1685, 1654, 1597	66,1	7,1	15,4	$C_{15}H_{19}N_3O_2$	65,9	7,0	15,4	9,51	58 (C)
VIIh	130—132	3210	1722, 1679, 1648, 1591	58,8	6,0	13,4	$C_{15}H_{18}ClN_3O_2$	58,8	5,9	13,7	9,31	63 (C)
VIIi	102—103	3185, 3080	1724, 1680, 1610, 1510	63,4	7,0	—	$C_{16}H_{21}N_3O_3$	63,4	7,0	—	9,93	89 (C)

[a]This compound had mp 253°C [3]. [b]This compound had mp 276-277°C (AcOH) [1]. [c]This compound had mp 239-240°C [1].

2-Arylamino derivatives V (Table 2), which were obtained from both 2-mercapto and from 2-methylthio analogs, had identical IR spectra, did not depress one another's melting points, and upon acidic hydrolysis were converted to 5,5-diethyl- (Va-f) or 1-methyl-5,5-diethylbarbituric acids (Vg-i).



It is apparent from the ionization constants presented in the tables that IIIa-e and Va-f are rather weak acids. In order to ascertain the structure (VI or VII) of their anions we determined the pK_a values of methylated (at the ring nitrogen atom) derivatives IIIf-h and Vg-i.

We found that alkylation lowers the acidity by one to 1.5 orders of magnitude. This constitutes evidence that splitting out of a proton from the nitrogen atom of the pyrimidine ring plays the principal role in the ionization of aminopyrimidinediones IIIa-e and Va-f, i.e., the acid—base equilibrium is shifted significantly to favor anions VIa and VIIa. The higher acidities of 2-arylamino derivatives V may be due to the greater ease of delocalization of the charge along the system of O—C—N—C—N bonds in the anion that develops during deprotonation.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin-Elmer 577 spectrometer. The mass spectra were obtained with an MKh-1303 mass spectrometer with a system for direct introduction of the samples into the ion source at an ionizing voltage of 70 eV. The basicity constants were determined by potentiometric measurements of 50% solutions in alcohol at 25°C. The reproducibility was no less than 0.06 pK_a units. The course of the reactions and the purity of the compounds obtained were monitored by thin-layer

chromatography (TLC) on Silufol UV-254 plates in chloroform–methanol (10:1), benzene–ethyl acetate (3:1), and hexane–ethyl acetate (2:1) systems with development in UV light or by means of iodine vapors.

6-Amino-5,5-diethyl- and 6-amino-3-methyl-5,5-diethyl-3H,5H-pyrimidine-2,4-diones (IIa, b) were obtained by the method in [5]. 2-Mercapto-5,5-diethyl-1H,5H-pyrimidine-4,6-dione was synthesized by the method in [11], 2-mercapto-1-methyl-5,5-diethyl-1H,5H-pyrimidine-4,6-dione was obtained by the method in [12], and 1-methyl-2-methylthio-5,5-diethyl-1H,5H-pyrimidine-4,6-dione was prepared by the method in [14]. 6-Thioxo-5,5-diethyl-1H,3H,5H-pyrimidine-2,4-dione (Ia) was obtained by the method in [13].

3-Methyl-6-thioxo-5,5-diethyl-1H,3H,5H-pyrimidine-2,4-dione (Ib). This compound, with mp 139–140°C (benzene–hexane), was obtained in 51% yield by the method in [13]. IR spectrum: 3210 (NH); 1740, 1670 cm^{-1} (C=O, C=N). Found: C 50.4; H 6.8; N 12.9; S 14.7%; M 214 (by mass spectrometry). $C_9H_{14}N_2O_2S$. Calculated: C 50.5; H 6.6; N 13.1; S 15.0%; M 214.3.

6-Arylamino-5,5-diethyl-1H,3H-pyrimidine-2,4-diones (III). A) A mixture of the corresponding 6-thioxo-5,5-diethyl-1H,3H,5H-pyrimidine-2,4-dione I and 0.015 mole of the amine was heated without a solvent at 160–180°C for 6–20 h, after which the solid material was suspended in ether, the suspension was filtered, and the solid was recrystallized from benezene or aqueous ethanol.

B) A mixture of 0.01 mole of amino derivative II, 0.01 mole of the amine, and 0.01 mole of the amine hydrochloride was heated without a solvent at 170–180°C for 1–2 h, after which the solid material was suspended in water. The suspension was filtered, and the solid was washed with ether and recrystallized from benzene or aqueous ethanol.

The characteristics of the compounds obtained are presented in Table 1.

2-Arylamino-5,5-diethyl-1H,5H-pyrimidine-4,6-diones (V). C) A mixture of 0.01 mole of methylthio derivative IV and 0.015 mole of the corresponding amine was heated without a solvent at 160–180°C for 6–12 h, after which the solid material was suspended in ether. The suspension was filtered, and the solvent was recrystallized from benzene.

Compounds V were also obtained by method A from the corresponding 2-mercapto derivatives IV. The characteristics of the compounds obtained are presented in Table 2.

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