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PYRIMIDINES.

72.* SYNTHESIS AND SOME PROPERTIES OF 5-AMINO-2-R-4,6-DIPHENYLPYRIMIDINES AND THE PRODUCTS OF THEIR TRANSFORMATIONS

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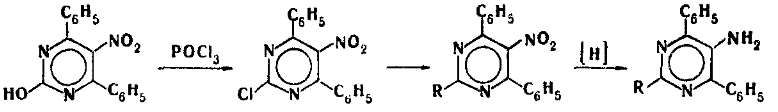
The corresponding 5-aminopyrimidines were obtained by reduction of 2-substituted 5-nitro-4,6-diphenylpyrimidines, and reactions involving the amino group were studied. A Schiff base was obtained, and acetylation and diazotization reactions were carried out. The corresponding diazonium salts were converted to 2-dimethylamino-5-hydroxy-4,6-diphenylpyrimidine and 5-azido-2-methoxy-4,6-diphenylpyrimidine. 2-Methoxy-4-phenyl-5H-pyrimido[5,4-b]indole was obtained by photocyclization of the latter.

Very little study has been devoted to the relatively difficult-to-obtain sterically hindered heterocyclic amines. In the pyrimidine series only 2-substituted 5-amino-4,6-dimethylpyrimidines and their derivatives involving the amino group are known [2, 3].

We have previously obtained 5-amino-2-hydroxy-4,6-diphenylpyrimidine [4]. We assumed that the latter could serve as the starting compound for the synthesis of 5-amino-2-R-4,6-diphenylpyrimidine. However, this method for the production of 5-aminopyrimidines proved to be unsuitable because of the difficulty encountered in converting the corresponding 2-hydroxypyrimidine to 2-chloro-5-amino-4,6-diphenylpyrimidine. It is known [4] that 5-nitro-2-hydroxy-4,6-diphenylpyrimidine reacts with phosphorus oxychloride to give 2-chloro-5-nitro-4,6-diphenylpyrimidine in good yield. We used the latter to obtain substituted 5-aminopyrimidines that are analogs of sterically hindered anilines.

Compounds IIa-d were obtained from 2-chloro-5-nitro-4,6-diphenylpyrimidine, in which the chlorine is readily replaced by a methoxy group or a substituted amino group by the action of sodium methoxide or an alcohol solution of the amine.

The corresponding 5-aminopyrimidines (IIIa, b, e) were obtained in good yields by reduction of I and IIa, b with stannous chloride in hydrochloric acid [5]. To avoid possible complications in the reduction of IId that are associated with hydrolysis of the methoxy group [6] we carried out the reduction of IId to IIId by the action of iron in acetic acid (with heating) [7]. Other 5-nitropyrimidines can also be reduced under these conditions; this was verified in the case of the reduction of I to IIIe.



I   II a-d   III a, b, d, e

II, III a $R=N(CH_3)_2$; b $R=N(C_2H_5)_2$; II c $R=NHCH_3$; II, III d $R=OCH_3$; III e $R=Cl$

The properties of the resulting 5-aminopyrimidines III, the amino group of which is shielded by two adjacent phenyl groups and the basicities of which are reduced because of the acceptor properties of the pyrimidine ring, were studied.

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*See [1] for Communication 71.

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TABLE 1. Characteristics of II-VIII

Compound	mp, °C (from alcohol)	UV spectrum, λ_{max}, nm (log ε)	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIa	164—166	256 (4,51), 352 (3,72)	67,8	4,8	17,6	$C_{18}H_{16}N_4O_2$	67,5	5,0	17,5	90
IIb	175—177	256 (4,46), 352 (3,68)	68,5	5,8	15,9	$C_{20}H_{20}N_4O_2$	68,9	5,8	16,1	86
IIc	200—202	254 (4,34), 333 (3,60)	66,3	4,6	18,0	$C_{17}H_{14}N_4O_2$	66,5	4,6	18,3	80
IId	134—135	253 (4,24), 299 (4,20)	66,7	4,2	13,8	$C_{17}H_{12}N_3O_3$	66,4	4,3	13,7	90
IIIa	130—132	230 (4,33), 241 (4,34)	74,4	6,4	19,4	$C_{18}H_{18}N_3$	74,4	6,2	19,3	80
IIIb	128—130	395 (3,79), 229 (4,31), 246 (4,43), 400 (3,70)	75,4	7,0	17,6	$C_{20}H_{24}N_4$	75,1	7,0	17,4	75
IIId[a]	Oil[b]	235 (4,20), 364 (3,96)	—	—	—	$C_{17}H_{15}N_3O$	—	—	—	85
IIIe	141,5—143	238 (3,30), 358 (3,00)	68,6	4,4	15,0	$C_{16}H_{12}N_3Cl$	68,3	4,3	14,9	80
IV	222—223,5	246 (4,15), 293 (4,07)	71,2	5,2	13,5	$C_{19}H_{17}N_3O_2$	71,4	5,4	13,2	70
V	147—149	256 (4,47), 338 (4,18)	79,0	5,4	11,6	$C_{24}H_{19}N_3O$	78,9	5,2	11,6	70
VI	123—125	224 (4,46), 256 (4,42), 375 (3,96)	74,3	6,1	14,6	$C_{18}H_{17}N_3O$	74,2	5,9	14,4	55
VII[c]	73—75	255 (4,32), 330 (3,81)	67,2	4,5	—	$C_{17}H_{13}N_5O$	67,3	4,3	—	50
VIII	235—237	247 (4,28), 270 (4,15), 314 (4,30), 390 (4,00)	74,0	4,6	15,3	$C_{17}H_{13}N_3O$	74,2	4,8	15,3	35

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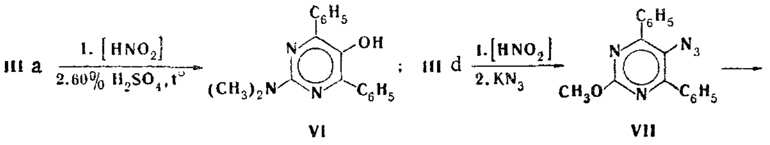
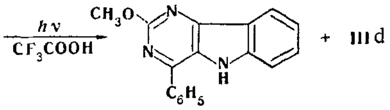
[a] The empirical formulas were determined by mass spectrometry with an MS-902 mass spectrometer. [b] From alcohol. [c] The results of analysis for nitrogen were 1.5% too low. The mass spectrum does not contain a molecular-ion peak but does contain a peak with mass 275.1062 [(M–28)].

Compound IIId was converted to 5-acetamido-2-methoxy-4,6-diphenylpyrimidine (IV) by heating with acetic anhydride; 5-benzylideneamino-2-methoxy-4,6-diphenylpyrimidine (V) is formed with benzaldehyde in acetic acid.

It is known [8] that the diazotization of 5-aminopyrimidines proceeds successfully in the case of 4,6-dimethyl derivatives [3] or when a strong electron-donor group is present in one of these positions [9]. We assumed that aminopyrimidines III that have electron-donor substituents (OCH_3 and NR_2) in position 2 would also undergo diazotization. In fact, IIIa and IIId are converted to diazonium salts by the action of sodium nitrite in concentrated sulfuric acid. Suspensions of the diazonium salts obtained are relatively stable at room temperature. 2-Dimethylamino-5-hydroxy-4,6-diphenylpyrimidine (VI), which is an analog of sterically hindered phenols, was obtained by diazotization of IIIa and subsequent refluxing of the diazonium salt with 60% sulfuric acid. The phenolic character of VI is confirmed by a positive reaction with ferric chloride and comparison of the UV spectra of VI in neutral and alkaline solutions: The strong bathochromic shift of the absorption maximum as compared with the absorption maximum observed for a neutral solution that is characteristic for phenols is observed in alkaline solution (see the experimental section).

5-Azido-2-methoxy-4,6-diphenylpyrimidine (VII) was synthesized from IIId by conversion of IIId to a diazonium salt and the subsequent action of potassium azide.





VIII

It is known that the photolysis of 5-azido-2-methoxy-4-phenylpyrimidine leads to a pyrimidoindole system [10]. A mixture of five substances, the principal components of which are 2-methoxy-4-phenyl-5H-pyrimido[5,4-b]indole (VIII) and aminopyrimidine IIId, is formed when azide VII is irradiated in trifluoroacetic acid (in Pyrex with a DRSh-500 lamp).

Thus the properties of 2-substituted 5-amino-4,6-diphenylpyrimidines are similar to a considerable degree to the properties of aromatic amines and make it possible to obtain the interesting but little-studied 5-hydroxy- and 5-azido-4,6-diphenylpyrimidines.

The structures of the compounds obtained were proved by the results of elementary analysis and the spectral (IR, UV, mass, and PMR) data (Table 1).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in alcohol were recorded with a Unicam SP-700 C spectrophotometer. The PMR spectra were recorded with a Varian A56/60A spectrometer with hexamethyldisiloxane as the internal standard. The individuality of the compounds obtained was confirmed by chromatography on Silufol UV-254 plates; the plates were developed in UV light. The yields, melting points, results of elementary analysis, and the characteristics of the UV spectra are presented in Table 1.

2-Dimethylamino-5-nitro-4,6-diphenylpyrimidine (IIa). A 0.13-g (0.41 mmole) sample of 2-chloro-5-nitro-4,6-diphenylpyrimidine (I) was dissolved in 20 ml of alcohol by heating, 0.16 ml (3.3 mmole) of a 33% aqueous solution of dimethylamine was added with stirring to the the warm solution, and the mixture was allowed to stand overnight. The resulting precipitate was removed by filtration and washed with water and alcohol to give 0.1 g of IIa. IR spectrum: 1360 and 1515 cm^{-1} (NO_2).

Similarly, 0.25 g of 2-diethylamino-5-nitro-4,6-diphenylpyrimidine (IIb) was obtained from I and diethylamine. IR spectrum: 1350 and 1515 cm^{-1} (NO_2).

Similarly, 0.13 g of 2-methylamino-5-nitro-4,6-diphenylpyrimidine (IIc) was obtained from I and a 25% aqueous solution of methylamine. IR spectrum: 3280 and 3440 cm^{-1} (N—H).

5-Nitro-2-methoxy-4,6-diphenylpyrimidine (IId). A solution of sodium methoxide obtained from 0.012 g (0.5 mg-atom) of sodium and 5 ml of absolute methanol was added to a solution of 0.16 g (0.5 mmole) of I in 25 ml of absolute methanol, and the mixture was refluxed for 4 h. It was then concentrated in vacuo to half its original volume, cooled, and poured into a twofold volume of water. The precipitate was removed by filtration, washed with water, and dried to give 0.15 g of IId. IR spectrum: 1350 and 1540 cm^{-1} (NO_2). PMR spectrum (CCl_4): 7.41-7.83 (10H, m, C_6H_5) and 4.01 ppm (3H, s, O—CH_3).

5-Amino-2-diethylamino-4,6-diphenylpyrimidine (IIIb). A mixture of 0.25 g (0.7 mmole) of IIb, 0.68 g (3 mmole) of stannous chloride, 2 ml of concentrated HCl, and 3 ml of alcohol was refluxed for 5 h, after which it was cooled and neutralized with 10% NaOH solution. The bright-yellow precipitate was removed by filtration, washed with water, and dried in a desiccator over KOH. The residue (0.6 g), which contained a tin salt, was extracted in a Soxhlet apparatus with light petroleum ether for 3 h. Removal of the petroleum ether by distillation gave 0.17 g of bright-yellow needles of IIIb, which were insoluble in ordinary organic solvents but soluble in dimethyl sulfoxide (DMSO) and dimethylformamide (DMF). IR spectrum: 3340 and 3420 cm^{-1} (NH_2).

Similarly, 0.17 g of 5-amino-2-dimethylamino-4,6-diphenylpyrimidine (IIIa) was obtained from IIa. IR spectrum: 3320 and 3410 cm^{-1} (NH_2).

Similarly, 0.08 g of 2-chloro-5-amino-4,6-diphenylpyrimidine (IIIe) was obtained from I. IR spectrum: 3360 and 3440 cm^{-1} (NH_2).

Amide IIIe was also obtained by refluxing (for 3 h) a mixture of 0.31 g (1 mmole) of I, 0.2 g (35 mg-atom) of iron, 5 ml of acetic acid, and 25 ml of alcohol. The mixture was poured into 100 ml of cold water, and the resulting precipitate was removed by filtration and washed with water and alcohol to give 0.22 g of IIIe.

5-Amino-2-methoxy-4,6-diphenylpyrimidine (IIId). A mixture of 3.27 g (0.012 mole) of IId, 2.2 g (0.39 g-atom) of iron, and 270 ml of acetic acid was refluxed with stirring for 2.5 h. At the end of the reaction, 100 ml of acetic acid was removed by distillation, and the residual mixture was poured into 400 ml of cold water. The product was extracted with chloroform (three 150-ml portions). The chloroform was removed by vacuum distillation to give 2.5 g of IIId in the form of a viscous yellow oil. IR spectrum ($CHCl_3$): 3430 cm^{-1} (NH_2). PMR spectrum ($CDCl_3$): 8.91-9.55 (10H, m, C_6H_5), 3.88 (3H, s, $O-CH_3$), and 3.65 ppm (2H, s, NH_2). Found: M 277.1218. $C_{17}H_{15}N_3O$. Calculated: M 277.

5-Acetamido-2-methoxy-4,6-diphenylpyrimidine (IV). A mixture of 0.27 g (1 mmole) of IIId and 10 ml of acetic anhydride was heated at 100°C for 1.5 h, after which it was cooled and poured into water, and the resulting aqueous mixture was allowed to stand overnight. The precipitate was removed by filtration and washed with water and alcohol to give 0.21 g of IV. IR spectrum: 1690 (C=O); 3250, 3440 cm^{-1} (NH).

5-Benzylideneamino-2-methoxy-4,6-diphenylpyrimidine (V). A mixture of 0.14 g (0.5 mmole) of IIId, 0.07 ml (0.6 mmole) of benzaldehyde, and 5 ml of acetic acid was refluxed for 2 h, after which it was cooled and poured into water. The precipitate was removed by filtration and washed with water and alcohol to give 0.12 g of V. The IR spectrum did not contain absorption bands of stretching vibrations of the NH_2 group.

2-Dimethylamino-5-hydroxy-4,6-diphenylpyrimidine (VI). A mixture of 2.64 g (9 mmole) of IIIa, 8 g of ice, and 2.5 ml of concentrated H_2SO_4 was triturated with cooling, and a solution of 0.69 g (10 mmole) of $NaNO_2$ in 1.8 ml of water was then added to the bright-yellow suspension. The resulting gray-green paste of the diazonium salt was added to 12 ml of hot 60% H_2SO_4, and the mixture was refluxed for 15 min until nitrogen evolution ceased. It was then cooled and poured into water, and the bright-yellow precipitate was removed by filtration, washed with 6% Na_4OH and water, and dried in a desiccator over P_2O_5. The reaction product was dissolved in chloroform and chromatographed with a column filled with KSK silica gel (elution with chloroform) to give 1.43 g of VI. IR spectrum (CCl_4): 3560 cm^{-1} (OH). UV spectrum, λ_{max} (log ε) (alcohol): 256 (4.42) and 275 nm (3.96); in 0.1 N KOH (alcohol): 245 (4.34) and 434 nm (3.03). Pyrimidine VI was quite soluble in ether, chloroform, and carbon tetrachloride but less soluble in alcohol.

5-Azido-2-methoxy-4,6-diphenylpyrimidine (VII). A solution of 0.07 g (1 mmole) of $NaNO_2$ in 0.18 ml of water was added with thorough cooling and triturating with a glass rod to a mixture of 0.28 g (1 mmole) of IIId, 1 g of ice, and 0.2 ml of concentrated H_2SO_4. After 10 min, a solution of 0.08 g (1 mmole) of KN_3 in 0.3 ml of water was added, and the mixture was stirred for 30 min until nitrogen evolution ceased. Workup gave 0.3 g of a bright-yellow product consisting, according to TLC data, of four substances, including starting amine IIId. The mixture was separated preparatively on Silufol UV-254 (15 by 15 cm) by elution with methylene chloride to give 0.15 g of IIId and 0.12 g of VII. IR spectrum of VII: 2140 cm^{-1} (N_3).

2-Methoxy-4-phenyl-5H-pyrimido[5,4-b]indole (VIII). A 0.18-g (0.59 mmole) sample of VII was irradiated in 25 ml of trifluoroacetic acid at 20°C for 6 h (in Pyrex with a DRSh-500 lamp), after which the solvent was removed in vacuo at room temperature, and the residue was diluted with 10 ml of water. The aqueous mixture was neutralized with 10% $NaHCO_3$, and the resinous product was washed with water by decantation and dried in vacuo to give 0.13 g of a yellow-brown powder containing five substances (according to TLC data). The mixture was separated on a plate with silica gel by elution with chloroform to give 0.5 g of IIId and 0.057 g of VIII. IR spectrum: 3250 cm^{-1} (NH).

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