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PYRIMIDINES.

LXI.* SYNTHESIS OF N-PYRIMIDINYLANTHRANILIC ACIDS AND 2,4-DIARYLPYRIMIDO[2,1-b]QUINAZOL-6-ONES

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N-(4,6-Diarylpyrimidinyl)anthranilic acids, obtained by condensation of the appropriate 2-chloropyrimidines with anthranilic acid, are converted to 2,4-diarylpyrimido[2,1-b]quinazol-6-ones when they are treated with acetic anhydride.

The number of studies devoted to the synthesis of physiologically active anthranilic acid derivatives has increased in recent years [2-4]. A great deal of attention is being paid to the synthesis of N-heteroaryl-substituted anthranilic acids, including pyrimidine derivatives [4-6]. On the other hand, it is known that the introduction of aryl substituents in pyrimidine and quinazoline derivatives in some cases leads to new physiologically active compounds, the action of which differs from that of their unsubstituted or alkyl-substituted analogs [7, 8]. We therefore undertook the synthesis of pyrimidinylanthranilic acids with aryl substituents in the 4 and 6 positions of the pyrimidine ring by means of the readily accessible 2-oxo-4,6-diarylpyrimidines as the starting compounds [9].

2-(o-Carboxyphenylamino)-4,6-diarylpyrimidines (IIIa-f) were obtained in good yields when 2-chloro-4,6-diarylpyrimidines (IIa-f), obtained by the usual method from 2-oxo derivatives of pyrimidine (Ia-f), were fused with anthranilic acid or when the starting components were refluxed in alcohol for a long time. Similarly, 2-(o-carboxyphenylamino)-4-phenyl-5,6-dihydrobenzo[h]quinazoline (IV) was isolated from 2-chloro-4-phenyl-5,6-dihydrobenzo[h]quinazoline.

Compounds III are stable crystalline substances. However, intramolecular cyclization with splitting out of a water molecule to give 2,4-diarylpyrimido[2,1-b]quinazol-6-ones (Va-d) occurs when they are heated briefly in acetic anhydride. Similar behavior has also been previously noted for other N-pyrimidinylanthranilic acids [10, 11].

*See [1] for communication LX.

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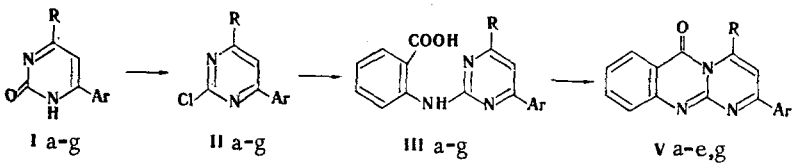
TABLE 1. PMR Spectra of Pyrimido[2,1-b]quinazol-6-ones (Va-d,g)*

Compound	H^3	H^7	H^9	H^{10}	Ar^2	R^1
Va	7,04 s	8,11 d	7,79t	7,85 d	H_o 8,25 $H_{m,p}$7,52—7,22	7,52—7,22
Vb	6,94s	8,09 d	7,75 t	7,78 d	H_o 8,18 H_m6,87	H_o 7,25 H_m6,89
Vc	6,93s	8,07 d	7,74 t	7,79 d	H_o 8,17 H_m6,87	7,65—7,21
Vd†	6,97 s	8,02 d	7,69t	7,73 d	H_o 8,23 H_m7,01	7,35—7,10
Vg	7,30 d ($J_{3,4}$=7,5 Hz.)	8,33 d	7,79 t	7,86 d	H_o 8,24 $H_{m,p}$7,56—7,38	9,08 d ($J_{3,4}$=7,5 Hz)

*The solvent was $CDCl_3$, and the integral intensity ratios were in agreement with the assignments. The H^8 signal is superimposed on the CH_{arom} signals at 7.10-7.50 ppm; accurate assignment was made only for Vg (δ_{H^8} = 7.40 ppm). Found: $J_{7,8}$ = 9 and $J_{9,10}$ = 8 Hz.

†The signals of the C_6H_5 group of the substituent attached to 2-C ($C_6H_4OC_6H_5$) coincide with the signal of R^4 (C_6H_5).

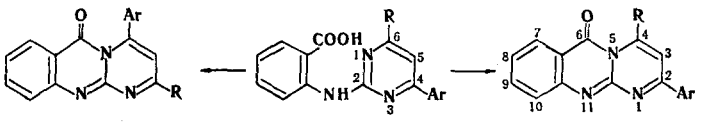


I—III, V a R=C_6H_5, Ar=C_6H_5; b R=$C_6H_4OCH_3$-*p*, Ar=$C_6H_4OCH_3$-*p*; c R=C_6H_5, Ar=$C_6H_4OCH_3$-*p*; d R=C_6H_5, Ar=$C_6H_4OC_6H_5$-*p*; e R=C_6H_5, Ar=$C_6H_4NO_2$-*p*; I—III f R=$C_6H_4OCH_3$-*p*, Ar=$C_6H_4NO_2$-*p*; I—III, V g R=H, Ar=C_6H_5

In contrast to the colorless or weakly colored pyrimidinylanthranilic acids III, cyclization products V have intense colors; a characteristic absorption maximum appears in the UV spectra of these compounds at about 415 nm.

In contrast to diarylpyrimidines, we were unable to isolate an N-pyrimidinylanthranilic acid (IIIg) in the condensation of 2-chloro-4-phenylpyrimidine (IIg) with anthranilic acid because of its tendency to undergo cyclization. The reaction product in this case was pyrimidoquinazolone Vg.

The cyclization of unsymmetrically substituted pyrimidines IIIc-g could proceed at either of the two nitrogen atoms of the pyrimidine ring, since the π-electron densities on the nitrogen atoms in III differ only slightly (for example, N^1 1.253 and N^3 1.252 in IIIc). However, judging from the chromatographic data, the compounds obtained in this study are individual compounds; this was also confirmed by the PMR spectral data.



It might have been supposed that the somewhat higher basicity of the N^1 atom as compared with N^3 in IIIg and the considerably lower steric hindrance during the intramolecular cyclization of this compound at N^1 should lead to the formation of isomer A, i.e., 2-phenylpyrimido-[2,1-b]quinazol-6-one (Vg). However, the question of the structure of Vg and of diaryl derivatives V has remained an open one.

*The calculations were made by L. N. Shchegoleva by the Hückel MO method.

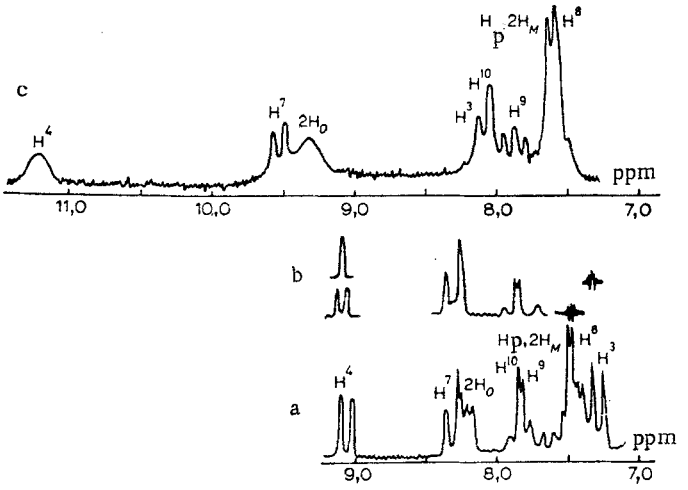


Fig. 1. PMR spectrum of 2-phenylpyrimido[2,1-b]quinazol-6-one (Vg): a) in $CDCl_3$; b) double resonance spectrum; c) spectrum in the presence of the $Eu(DPM)_3$ shift reagent.

We used the PMR spectra of V (Table 1) to prove their structures. The assignment of the signals was made on the basis of an analysis of the intensities, the splitting, and, in the case of monophenyl derivative Vg, double resonance data (Fig. 1). In the spectrum of this compound the two protons of the pyrimidine portion of the molecule (H^3 and H^4) give signals at 9.08 (H^4) and 7.30 ppm (H^3) (doublets with $J_{3,4}$ = 7.5 Hz). Because of the anisotropic effect of the C=O group, the H^7 signal is shifted to weak field and has a chemical shift of 8.33 ppm ($J_{7,8}$ = 9 Hz, $J_{7,9}$ = 1.5 Hz). The H^8 signal is found at 7.38-7.56 ppm and coincides with the signal of the $H_{m,n}$ protons of the phenyl substituent. The correctness of this assignment was confirmed by perturbation by a strong radiofrequency field of the signals in the indicated region, which led to coalescence to singlets of the H^7 and H_o (phenyl group) signals. The H^9 and H^{10} signals resonate at, respectively, 7.79 and 7.86 ppm; they represent an AB system $J_{9,10}$ = 8 Hz) in the double resonance spectrum (Fig. 1b). We made the selection of the position of the substituent (the C_6H_5 group) on the basis of the spectra of Vg recorded in the presence of the $Eu(DPM)_3$ shift reagent.

On the basis of the literature data on the effect of $Eu(DPM)_3$ on the proton shifts in the spectra of nitrogen-containing heterocycles [12] having several types of nitrogen and oxygen atoms [13], it might have been expected that complexing in Vg would occur primarily at the C=O group. In this case the character of the changes in the chemical shifts of the protons if the C_6H_5 group is located in the 2 position should correspond to the sequence $H^4 \approx H^7 > H^3$, H^8, etc.; however, if the C_6H_5 group is in the 4 position, the sequence should be different — $H_o \approx H^7 > H^3$, $H^8 > H^2$, etc.

When the shift reagent is added (Fig. 1c), the greatest shift is observed for two signals — H^4 and H^7; a smaller shift is observed for the H^3 and H_o signals, and the signals of the remaining protons are shifted only slightly. Thus on the basis of the spectral data obtained it may be assumed that Vg is formed in the cyclization of N-(4-phenylpyrimidinyl)anthranilic acid (IIIg).

Having established the position of the phenyl substituent in Vg we also made a thorough analysis of the PMR spectra of the other V. In the spectrum of Vg it is apparent that H_o resonates at weaker field than H_m and H_p (Table 1). The difference in the spectral behavior of the protons of both Ar groups is appreciable when an Ar substituent is introduced in the 4 position of the pyrimidoquinazolone (Va and Vb). Thus in Vb the Ar^4 protons (o, m, and p) resonate over a narrow range (7.22-7.52 ppm), whereas the Ar^2 protons behave like the C_6H_5 protons in Vg. The signals of the $H^2{}_o$ protons in the spectrum of Vb lie at weaker field than the signals of the $H^4{}_o$ protons. We used these data for the determination of the position of the anisyl and phenoxyphenyl groups (in Vc and Vd, Table 1). All of the protons of the C_6H_5 group in Vc resonate at 7.21-7.65 ppm, whereas the signals of the protons of the anisyl group (H_o and H_m) lie at 8.17 and 6.87 ppm; this indicates that the C_6H_5 group is in the 4 position and that the anisyl group is in the 2 position of the condensed system.

TABLE 2. 2-Chloro-4,6-diarylpyrimidines (IIb-f)

Comp.	Time, h	mp, °C	Found, %				Empirical formula	Calc., %				UV spectra, λ_{max}, nm (log ε)
			C	H	Cl	N		C	H	Cl	N	
IIb	3	187—189[a]	—	—	10,9	—	$C_{18}H_{15}ClN_2O_2$	—	—	10,9	—	270 (4,24), 298 (4,33), 330 (4,53)
IIc	7	135—136[b]	—	—	12,1	—	$C_{17}H_{13}ClN_2O$	—	—	11,9	—	262 (4,24), 284 (4,19), 324 (4,40)
IId	3	112—114[c]	74,3	4,0	9,9	7,8	$C_{22}H_{15}ClN_2O$	73,6	4,2	9,9	7,8	260 (4,29), 290 (4,23), 320 (4,43)
IIe	6	204—205[b]	61,5	3,3	11,3	13,7	$C_{16}H_{10}ClN_3O_2$	61,5	3,3	11,4	13,5	261 (4,29), 294 (4,26), 316 (4,32)
IIf	13	211—213[d]	—	—	10,4	12,1	$C_{17}H_{12}ClN_3O_3$	—	—	10,4	12,3	

a) From decalin. b) From benzene—alcohol. c) From alcohol. d) From dioxane.

Consequently, on the basis of the PMR spectra, Vc and Vd should be, respectively, 2-(p-methoxyphenyl)-4-phenylpyrimido[2,1-b]quinazol-6-one and 2-(p-phenoxyphenyl)-4-phenylpyrimido-[2,1-b]quinazol-6-one. Because of its low solubility, the structure of Vd could not be elucidated.

We obtained confirmation of the correctness of the choice of the positions of the C_6H_5 and $C_6H_4OCH_3$ groups in Vc from the PMR spectra by recording the ^{15}N NMR spectrum of specially synthesized $^{15}N^1$-2-(p-methoxyphenyl)-4-phenylpyrimido[2,1-b]quinazol-6-one (Vc-$^{15}N^1$) [14]. Only one signal of the ^{15}N atom at δ 91 ppm was observed in the spectrum of this compound, this is in agreement with the pyrimidoquinazolone structure with ^{15}N in the 1 position (compared with δ ^{15}N 63 ppm for pyridine and 90 ppm for quinazoline [15]). The signal of the $^{15}N^5$ atom for the Vc-$^{15}N^5$ isomer should have been found at about 200 ppm (δ 209 ppm for ^{15}N-2-pyridone [15]).

The pyrimidoquinazolones V are quite basic, readily form hydrochlorides, are unstable in acidic solutions, and are converted to starting anthranilic acids III.

According to our preliminary data, the synthesized pyrimidinylanthranilic acids display analgetic and high antistaphylococcus activity.

EXPERIMENTAL*

The UV spectra of ethanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with Varian 56/60 A and HA-100 spectrometers with hexamethyldisiloxane as the internal standard. The ^{15}N NMR spectrum was recorded with a Bruker Physik AG SXP 4-100 spectrometer with an $H^{15}NO_3$ external standard. The molecular weights were determined with an MS 902 spectrometer. The individuality of the compounds was verified by means of thin-layer chromatography (TLC) on Silufol UV-254.

The synthesis of the starting compounds has been described: Ib,c,e [9], Id [16], IIa [18], IIg [17], 2-chloro-4-phenyl-5,6-dihydrobenzo[h]quinazoline [19], and $^{15}N^1$-2-(p-methoxyphenyl)-4-phenylpyrimido[2,1-b]quinazol-6-one [14].

2-Oxo-4-(p-methoxyphenyl)-6-(p-nitrophenyl)-1,2-dihydropyrimidine (If). This compound, with mp 325-328° (from dioxane—DMF), was obtained in 50% yield by the method used to prepare Ic [9] by condensation of p-nitroacetophenone with p-methoxybenzalbisurea. Found, %: N 13.2. $C_{17}H_{13}N_3O_4$. Calculated, %: N 13.0.

2-Chloro-4,6-diarylpyrimidines (IIb,c,d,e). These compounds were obtained in 50-70% yields in analogy with the synthesis of IIa [18] by refluxing the appropriate dihydropyrimidines I with phosphorus oxychloride. The reaction times, melting points, results of elementary analysis, and UV spectra of the compounds are presented in Table 2.

2-Chloro-4-(p-methoxyphenyl)-6-(p-nitrophenyl)pyrimidine (IIf). A mixture of 1.0 g (0.003 mole) of 2-oxopyrimidine (If), 50 ml of $POCl_3$, and 5 g of PCl_5 was refluxed for 13 h, after which the excess $POCl_3$ was removed by vacuum distillation, and the residue was decomposed with ice water. The IIf was extracted with chloroform, the extract was dried with

*With the participation of A. I. Shadrina.

TABLE 3. 2-(o-Carboxyphenylamino)-4-R-6-arylaminopyrimidines (IIIa-g)*

Compound	mp, °C †	Found, %			Empirical formula	Calc., %			UV spectra, λ_{max}, nm (log ε)	Yield, %
		C	H	N		C	H	N		
IIIa	288—295	75,0	4,6	11,6	$C_{23}H_{17}N_3O_2$	75,2	4,7	11,4	203 (4,63), 227 (4,47), 280 (4,53), 328 (4,13)	80
IIIb	247—249	70,4	5,0	9,9	$C_{25}H_{21}N_3O_4$	70,2	4,9	9,8	208 (4,67), 222 sh (4,62), 290 (4,69)	55
IIIc	234—236	72,2	4,8	10,5	$C_{24}H_{19}N_3O_3$	72,5	4,8	10,6	252 (4,36), 294 (4,56), 360 (3,62)	90
IIId	232—234	74,3	4,8	9,2	$C_{29}H_{21}N_3O_3 \cdot 0,5H_2O$	74,4	4,7	9,0	253 (4,43), 294 (4,64), 360 (3,83)	70
IIIe	305—307	63,9	4,3	13,3	$C_{23}H_{16}N_4O_4 \cdot 0,5H_2O$	64,2	4,2	13,0	206 (4,77), 288 (4,59), 395 (3,45)	75
IIIf	294—296	64,5	4,3	12,5	$C_{24}H_{18}N_4O_5$	65,2	4,1	12,7	204 (4,59), 286 (4,58)	65

*We were unable to isolate IIIg in pure form because of its facile cyclization to Vg.
†Compounds IIIa,c,d,e were recrystallized from acetic acid, and IIIb,f were recrystallized from alcohol—dioxane.

TABLE 4. 2-Aryl-4-R-pyrimido[2,1-b]quinazol-6-ones (Va-e,g)

Comp.	mp, °C*	Found, %			Empirical formula†	Calc., %			UV spectra λ_{max}, nm (log ε)	Yield, %
		C	H	N		C	H	N		
Va	249—251	79,2	4,4	12,1	$C_{23}H_{15}N_3O$	79,1	4,3	12,0	233 (4,57), 290 (4,57), 370 (3,90), 417 (3,86)	70
Vb	197—200	72,9	5,0	9,8	$C_{25}H_{19}N_3O_3$	73,3	4,7	10,3	231 (4,52), 282 (4,13), 348 (4,54), 416 (3,90)	60
Vc	234—235	76,4	4,7	11,5	$C_{24}H_{17}N_3O_2$	76,0	4,5	11,1	232 (4,58), 275 (4,24), 344 (3,63), 416 (3,90)	70
Vd	211—214	76,4	4,3	9,0	$C_{29}H_{19}N_3O_2 \cdot H_2O$	76,0	4,6	9,1	232 (4,54), 272 (4,25), 342 (4,56), 419 (3,77)	46
Ve	324—327	68,7	3,6	14,1	$C_{23}H_{14}N_4O_3 \cdot 0,5H_2O$	68,5	3,7	13,9	—	
Vg	190—192	74,9	4,0	15,1	$C_{17}H_{11}N_3O$	74,7	4,0	15,4	222 (4,44), 238 sh (4,32), 294 (4,41), 343 (3,88), 360 (3,88)	46

*Recrystallized from isopropyl alcohol—$CHCl_3$.
†Molecular weights (by mass spectrometry): Va 349, Vc 379, Vd 441, and Ve 394.

$MgSO_4$, and the solvent was removed by vacuum distillation. The residue was recrystallized from dioxane to give 4 g (50%) of IIf (Table 2).

2-(o-Carboxyphenylamino)-4,6-Diarylpyrimidines (IIIa-g). The chloropyrimidines (10 mmole) were used with 11 mmole of anthranilic acid at 140-160° for 1-2 h, after which the mixture was cooled and triturated thoroughly with $NaHCO_3$ solution. The solid material was removed by filtration, washed with water, and refluxed with 20 ml of glacial acetic acid. The precipitate was removed by filtration to give IIIa-g (Table 3).

2-(o-Carboxyphenylamino)-4-phenyl-5,6-dihydrobenzo[h]quinazoline (IV). This compound, with mp 227-230° (acetic acid), was obtained in 80% yield from 2-chloro-4-phenyl-5,6-dihydrobenzo[h]quinazoline and anthranilic acid by the method used to prepare III. UV spectrum, λ_{max} (log ε): 209 (4.63) and 284 nm (4.52). Found, %: C 76.6; H 4.9; N 10.9. $C_{25}H_{19}N_3O_2$. Calculated, %: C 76.3; H 4.9; N 10.9.

2,4-Diarylpyrimido[2,1-b]quinazol-6-ones (Va-f). Compound III (70 mmole) was refluxed in 50 ml of acetic anhydride until it dissolved (3-15 min). The color of the solution changed from yellow to bright-orange. The precipitate was removed by filtration to give Va-f (Table 4).

2-Phenylpyrimido[2,1-b]quinazol-6-one (Vg). A mixture of 0.7 g (3.7 mmole) of IIg and 0.6 g (4.3 mmole) of anthranilic acid was fused at 110-140° for 10 min, after which it was

cooled and dissolved in chloroform. The solution was washed with $NaHCO_3$ solution, and the chloroform was evaporated to give Vg with mp 190-192° (from isopropyl alcohol—chloroform) in 46% yield (Table 4).

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