Hydrolysis of Isocyanate III. A 0.98-g (5.2 mmole) sample of III was dissolved in 30 ml of acetone, and 1 ml of water was added. The solution was allowed to stand at 20°C for 18 h, after which the solvent was removed by vacuum distillation to give 0.84 g (99%) of I with mp 218-221°C (from ethanol); no melting-point depression was observed for a mixture of this product with a genuine sample.

Hydrolysis of Isocyanate IV. Hydrolysis was carried out with 1.33 g (5 mmole) of IV in 50 ml of acetone, as in the hydrolysis of III. Workup gave 1.2 g (100%) of II with mp 217-219°C (from ethanol); no melting-point depression was observed for a mixture of this product with a genuine sample.

5-Substituted 4,6-Dichloro-2-pyrimidinylcarbamic Acid Esters (V-VIII). A solution of 0.01 mole of methanol (or 2-naphthol) in 30 ml of absolute benzene was added to a solution of 0.01 mole of III or IV in 50 ml of absolute benzene, and the mixture was allowed to stand overnight. The solvent was removed by vacuum distillation, and the residue was purified by recrystallization. Workup gave acicular crystals of V, VI, and VIII and prisms of VII.

N'-Substituted N-(4,6-Dichloro-5-Substituted 2-Pyrimidinyl)urea (IX-XII). A 0.01-mole sample of the corresponding amine in 30 ml of absolute benzene was added to 0.01 mole of III or IV in 50 ml of absolute benzene, and the mixture was allowed to stand at 20°C for 18 h. The precipitate was removed by filtration, and the benzene filtrate was evaporated to dryness. The residue was combined with the precipitate and recrystallized to give IX and XII as lamellar crystals, X as needles, and XI as long prisms.

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4-(o-CARBOXYPHENYLAMINO)PYRIMIDINES

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UDC 547.853.7'855

2-Chloro-4-(o-carboxyphenylamino)pyrimidines were synthesized by reaction of 2,4-dichloropyrimidines with anthranilic acid in aqueous media in the presence of hydrochloric acid. A number of their derivatives – 2-hydroxy-, 2-methoxy-, and 2-amino-4-(o-carboxyphenylamino)pyrimidines – were obtained.

Pyrimidine derivatives that contain an o-carboxyphenylamino group are of interest as potential physiologically active substances [1, 2]. In this connection the preparation of new compounds of this series and the study of their properties are of importance.

In the present paper we describe 4-(o-carboxyphenylamino)pyrimidines (IIa-g) obtained by the reaction of 2,4-dichloropyrimidines (Ia-g) with anthranilic acid:

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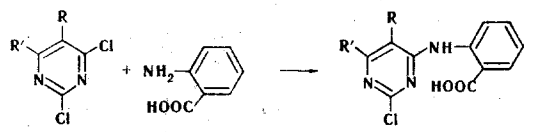
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1252-1254, September, 1977. Original article submitted December 20, 1976.

0009-3122/77/1309-1009$07.50

TABLE 1. 4-(o-Carboxyphenylamino)pyrimidines

Compound	R	R^1	R^2	mp, °C (dec.)	Found, % Cl	Found, % N	Empirical formula	Calc., % Cl	Calc., % N	λ, nm (log ε) (in methanol)	Yield, %
IIa	Cl	H	H	220	14,2	16,9	$C_{11}H_8ClN_3O_2$	14,2	16,8	240 (4,15), 286 (4,11), 326 (4,19)	78
IIb	Cl	H	CH_3	290—292	13,3	16,1	$C_{12}H_{10}ClN_3O_2$	13,4	16,0	236 (4,21), 294 (4,31), 319 (4,32)	87
IIc	Cl	F	H	280—283	13,3	15,4	$C_{11}H_7ClFN_3O_2$	13,2	15,7	239 (4,16), 298 (4,12), 326 (4,28)	70
IId	Cl	H	COOH	150	11,7	13,7	$C_{12}H_8ClN_3O_4$	12,1	14,3	251 (3,93), 272 (3,73), 338 (3,70)	65
IIe	Cl	CH_3	H	204—205	13,6	15,9	$C_{12}H_{10}ClN_3O_2$	13,4	16,0	211 (4,21), 295 (4,13), 325 (4,22)	82
IIf	Cl	Br	H	233—235	21,5*	13,1	$C_{11}H_7BrClN_3O_2$	21,7*	12,8	216 (4,20), 285 (4,00), 326 (4,09)	63
IIg	Cl	Br	CH_3	192	20,5*	12,1	$C_{12}H_9BrClN_3O_2$	20,8*	12,2	215 (4,21), 285 (3,99), 323 (4,08)	71
IIIa	NH_2	H	H	263—264	—	24,0	$C_{11}H_{10}N_4O_2$	—	24,3	265 (3,22), 314 (3,58)	65
IIIb	OH	H	H	250	12,8	15,4	$C_{11}H_9N_3O_3 \cdot HCl$	13,3	15,7	230 (4,30), 320 (4,31)	50
IIIc	OCH_3	H	H	290	—	17,0	$C_{12}H_{11}N_3O_3$	—	17,1	236 (4,09), 295 (4,11), 323 (4,13)	81

* The sum of the Cl and Br.



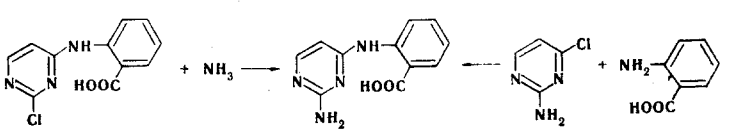
Ia-g IIa-g

I, IIa R=R¹=H; b R=H, R¹=CH₃; c R=F, R¹=H; d R=H, R′=COOH; e R=CH₃, R¹=H; f R=Br, R¹=H; g R=Br, R′=CH₃

Compounds IIa-g are obtained in good yields by reaction of the starting components in equimolar amounts in aqueous media in the presence of traces of hydrochloric acid. The reaction takes place at room temperature or when the components are heated briefly to 50°C.

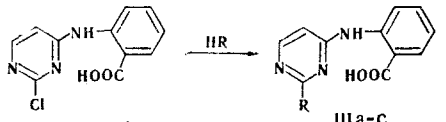
Under the conditions indicated above, substitution by the o-carboxyphenylamino group takes place primarily at 4-C of the pyrimidine ring.

The structure of 2-chloro-4-(o-carboxyphenylamino)pyrimidine was proved by conversion to 2-amino-4-(o-carboxyphenylamino)pyrimidine (IIIa) by the action of ammonia and by comparison with IIIa obtained from 2-amino-4-chloropyrimidine and anthranilic acid (no melting-point depression was observed for a mixture of the two products, and they had identical thin-layer chromatograms and UV spectra):



IIa IIIa

The chlorine atom in 2-chloro-4-(o-carboxyphenylamino)pyrimidine was replaced by hydroxy, methoxy, and amino groups by reaction with the corresponding nucleophilic agents via the following scheme:



IIIa R = NH_2; b R = OH; c R = OCH_3 IIIa-c

This sort of substitution takes place under more severe conditions, since an o-carboxyphenylamino group in the 4 position of the pyrimidine ring lowers the lability of a chlorine atom in the 2 position. The synthesized compounds have antiphlogistic activity.

EXPERIMENTAL

Starting Ia-g were obtained by chlorination of the corresponding hydroxy derivatives of pyrimidine by known methods [3, 4].

The UV spectra of the compounds were obtained with an SF-4 spectrophotometer. Thin-layer chromatography was carried out on Silufol UV-254 plates in an ammonia–ethanol system (1 : 10).

2-Chloro-4-(o-carboxyphenylamino)pyrimidine (IIa). A mixture of 1 g (6.7 mmole) of 2,4-dichloropyrimidine and 0.92 g (6.7 mmole) of anthranilic acid in 15 ml of water containing 0.1 ml of concentrated hydrochloric acid was heated with stirring at 50°C in a reactor for 15 min. Stirring was continued at room temperature for 1 h. The starting compounds dissolved initially, after which the resulting precipitate, which was 2-chloro-4-(o-carboxyphenylamino)pyrimidine, was removed by filtration and recrystallized from alcohol.

Compounds IIb-g and IIIa were similarly obtained.

2-Amino-4-(o-carboxyphenylamino)pyrimidine (IIIa). A mixture of 1.15 g (5 mmole) of 2-chloro-4-(o-carboxyphenylamino)pyrimidine and 4 ml of a 7% alcohol solution of ammonia was heated in a sealed tube at 120°C for 3 h and at 180°C for 2 h, after which it was evaporated to dryness, and the residue was recrystallized from dimethylformamide to give a product with R_f 0.72.

2-Hydroxy-4-(o-carboxyphenylamino)pyrimidine (IIIb). A 1-g (4 mmole) sample of 2-chloro-4-(o-carboxyphenylamino)pyrimidine was dissolved in 10 ml of 10% HCl, and the solution was refluxed for 2 h. The solvent was then evaporated, and the residual colorless crystalline product was purified by reprecipitation from ammonia solution by the addition of acetic acid and recrystallization from aqueous alcohol.

2-Methoxy-4-(o-carboxyphenylamino)pyrimidine (IIIc). A solution of sodium methoxide [0.23 g (0.01 mole) of sodium metal in 10 ml of absolute methanol] was added dropwise in the course of 30 min to a solution of 2.49 g (0.01 mole) of 2-chloro-4-(o-carboxyphenylamino)pyrimidine in 20 ml of absolute methanol, and the mixture was refluxed at 70°C for 4 h. It was then cooled, and the resulting precipitate was removed by filtration. The solvent was removed from the filtrate by vacuum distillation, and the residue was dried and recrystallized from alcohol.

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