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SYNTHESIS OF 6-AMINO-2-(*p*-AMINOPHENYL)-4-PHENYLQUINAZOLINE

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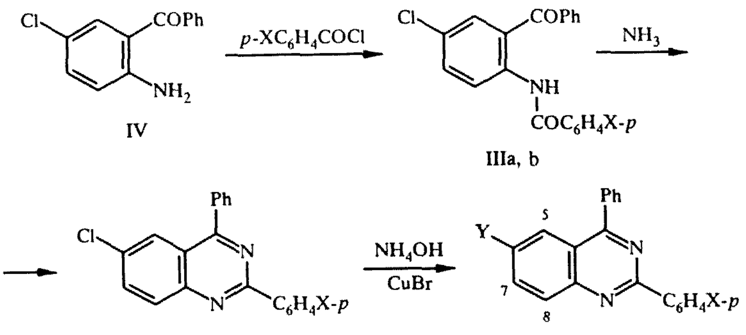
A study was carried out on the amination of 6-chloro-2-arylquinazolines. The reaction of p-*chlorophenyl- and* p-*nitrophenyl derivatives gives a mixture of mono- and diamination products with predominance of the monoamino products. The desired diamine was also obtained in the reduction of 6-amino-2-(*p-*nitrophenyl)-quinazoline.*

Heteroaromatic diamines hold considerable interest as starting reagents in the production of heat-resistant and high-strength polymer materials [1]. Lindeman et al. [2] have reported the synthesis of 6-amino-2-(*p*-aminophenyl)-4-phenylquinazoline (Ia) by the reduction of the corresponding dinitro derivative, while Ponomarev et al. [3] used this compound for the preparation of polynaphthoylenimidoquinazoline, a rigid-chain heterocyclic polymer. In a continuation of work on the synthesis of substituted diazine diamino monomers and their use in the preparation of high-strength, heat-resistant polyimides [4], we carried out an alternative synthesis of Ia as an analog of the well-known monomer, 5-amino-2-(*p*-aminophenyl)-benzimidazole [5].

In the present study of the synthesis of 6-amino-2-aryl-4-phenylquinazolines Ia and Ib, we investigated the amination of the corresponding 6-chloro-2-aryl-4-phenylquinazolines IIa and IIb under conditions used previously for various pyrimidine derivatives [6]. The amination of dichloride IIa in a solution of ammonia in dioxane in the presence of CuBr at 200°C over 33 h (see Experiment 1, Table 1) led to the desired product Ia along with the starting reagent as well as a 2:3 mixture of isomeric aminochloroquinazolines Ic and Id as indicated by PMR spectroscopy. The structures of isomers Ic and Id were established by PMR spectroscopy through comparison of the chemical shifts of the signals for 5-H and 7-H in Ia-Ic ($Y = NH_2$), Id ($Y = Cl$), IIa, and IIb and the chemical shifts of the m-H_{Ar} signals in Ia and Id ($R = NH_2$), Ic, and IIa ($R = Cl$).



Ia $X = Y = NH_2$; b $X = NO_2$, $Y = NH_2$; c $X = Cl$, $Y = NH_2$; d $X = NH_2$, $Y = Cl$;
II, III a $X = Cl$, b $X = NO_2$

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TABLE 1. Results of the Amination of Chloroquinazolines

Experiment	Starting compound	Reaction time, h	Major reaction mixture components, %*			
			starting compound	Ia	Ib	Ic + Id
1	IIa	33	15	25	—	55
2	IIa	48	6	50	—	32
3	IIb	33	28	5	60	—
4	IIb	48	16	7	65	—
5	Ic + Id	48	—	60	—	25

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*After separation of the reaction mixture on an alumina column.

More prolonged amination of dichloroquinazoline IIa (48 h, Experiment 2, Table 1) doubles the yield of desired diamine Ia. The content of monoamines Ic and Id is markedly reduced although the ratio of these products remains virtually unchanged. This invariability indicates lower nucleophilic lability of the halide at $C_{(6)}$ of the quinazoline system than for the chlorine atoms in the aryl substituent [7]. We should also note that amination of a mixture of aminochloroquinazolines Ic and Id under these conditions (Experiment 5, Table 1) did not lead to their complete conversion to diamine Ia.

The amination of nitrochloroquinazoline IIb under these conditions over 33 h leads to the expected 6-amino-2-(*p*-nitrophenyl)-4-phenylquinazoline (Ib), the starting compound, and a small amount of diamino derivative Ia. An increase in the amination time has no significant effect on the reaction product ratio (Experiments 3 and 4, Table 1). The formation of Ia indicates the possibility of the nucleophilic substitution even of the nitro group in the aromatic ring.

Desired diaminoquinazoline Ia was obtained in the hydrogenation of nitrophenylquinazoline Ib over Pd/C. However, the difficulty of replacing the chlorine atom by an amino group in chloroquinazolines makes this method of preparing diamine Ia from chloro derivatives II, Ic, and Id quite unsuitable.

Starting chloroquinazolines IIa and IIb were obtained by the Bischler cyclization reaction of the corresponding aroylaminobenzophenones IIIa and IIIb in ethanol saturated with ammonia, which permits a significant increase in the yield of the indicated compounds synthesized previously by other methods [8-10].

EXPERIMENTAL

The PMR spectra of the synthesized compounds were taken on Bruker SF-200 (Ib, Ic, Id, and IIb) and Bruker WP200 SY spectrometers in DMSO-d_6 using the solvent signal at 2.50 ppm as the internal standard. The IR spectra were taken for KBr pellets on a Specord M-80 spectrometer. The mass spectra were taken on a Finnigan MAT-8200 spectrometer. The physicochemical and spectral characteristics of the compounds are given in Table 2.

The elemental analysis data for C, H, Cl, and N correspond to the calculated values.

2-Amino-5-chlorobenzophenone (IV) was obtained in 85% yield by the hydrogenation of 3-phenyl-5-chlorobenzisoxazole in ethyl acetate over 10% Pd/C, mp 97-98°C (from petroleum ether) (98-100°C [11]).

2-(*p*-Chlorobenzoyl)-5-chlorobenzophenone (IIIa, $C_{20}H_{13}Cl_2NO_2$). A mixture of 3.5 g (0.015 mole) *p*-chlorobenzoyl chloride and 1.3 g (0.017 mole) pyrimidine in 15 ml benzene was heated at reflux for 4 h. Benzene was evaporated. The residue was washed with saturated aqueous $NaHCO_3$ and then water and crystallized from ethanol to give 4.6 g (83%) benzophenone IIIa, mp 146-148°C. IR spectrum: 1625 (COPh), 1680 (COAr), 3230 cm^{-1} (NH).

2-(*p*-Nitrobenzoyl)amino-5-chlorobenzophenone (IIIb, $C_{20}H_{13}ClN_2O_4$) was obtained analogously to IIIa from benzophenone IV and *p*-nitrobenzoyl chloride. At the end of the reaction, 20 ml water was added. The precipitated was filtered off, washed with benzene, saturated aqueous $NaHCO_3$, and water, and crystallized from ethanol–DMF to give 3.8 g (67%) benzonitrophenone IIIb, mp 158-159°C. IR spectrum: 1345, 1525 (NO_2), 1620 (COPh), 1680 (COAr), 3230 cm^{-1} (NH).

4-Phenyl-6-chloro-2-(*p*-chlorophenyl)quinazoline (IIa). A sample of 0.4 g (1.08 mmole) benzophenone IIIa in 4 ml ethanol containing 0.2 g ammonia was maintained in a sealed ampule for 4.5 h at 150°C. The precipitate was filtered off and crystallized from dioxane to give 0.37 g (98%) IIa.

TABLE 2. Characteristics of Substituted Quinazolines I-II

Compound	Chemical formula	mp, °C (lit. mp)	M^+	PMR spectra, chemical shifts, δ, ppm, coupling constants (J), Hz							
				Het			Ar		Ph		NH_2*3 (2H, s)
				5-H (1H, d)	7-H (1H, d.d)	8-H (1H, d)	o-H (2H, d)	m-H (2H, d)	o-H (2H, m)	m-H + p-H (3H, m)	
				(J_{57})	(J_{78})		(J_{OM})				
Ia	$C_{20}H_{16}N_4$	257...259, (250 [2])	312	6,96 (2,0)	7,34 (8,8)	7,73 (8,8)	8,19 (8,8)	6,64 (8,8)	7,75	7,62...7,59	5,74, 5,50
Ib	$C_{20}H_{14}N_4O_2$	253...255	342	7,04 (2,7)	7,24 (9,0)	7,90 (9,0)	8,35 (9,0)	8,70 (9,0)	7,81	7,65...7,61	6,11
Ic	$C_{20}H_{14}ClN_3$	165...170*	331	7,03 (2,5)	7,43 (9,0)	*2 (9,0)	8,49 (8,5)	7,55 (8,5)	*2	7,70...7,60	5,67
Id	$C_{20}H_{14}ClN_3$	165...170*	331	*2	*2 (9,0)	8,02 (9,0)	8,29 (9,0)	6,69 (9,0)	*2	7,70...7,60	5,90
IIa	$C_{20}H_{12}Cl_2N_2$	205...206, (202...205 [8])	350	8,04 (2,5)	8,09 (9,0)	8,20 (9,0)	8,60 (9,0)	7,65 (9,0)	7,91	7,72...7,68	—
IIb	$C_{20}H_{12}ClN_3O_2$	234...236, (222...224 [9])	361	8,01 (2,5)	8,13 (9,0)	8,26 (9,0)	8,44 (9,0)	8,83 (9,0)	7,96...7,91	7,72...7,68	—

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*Mp of a 2:3 mixture of Ic and Id.

*2Signal overlapped by the signals of the *m*- and *p*-H of the phenyl group.

*3Signals of the protons of the NH_2 group in the Het and/or Ar group.

2-(*p*-Nitrophenyl)-4-phenyl-6-chloroquinazoline (IIb) was obtained from benzophenone IIIb by analogy to IIa in 93% yield.

Amination of Chloroquinazolines. A mixture of 0.018 mole chloroquinazoline, 80 ml dioxane, 80 ml concentrated NH_4OH, and 0.7 g CuBr was maintained in an autoclave at 200°C for several hours. After cooling, a three-fold volume of water was added. The precipitate was filtered off and subjected to chromatography on a 20×500-mm alumina column, eluting with petroleum ether, 1:1, 1:4, and 1:8 petroleum ether–dioxane. The separated products were crystallized from dioxane–petroleum ether (Ia) or aqueous ethanol (Ib-Id) and sublimed in vacuum. The results of the individual experiments are given in Table 1.

6-Amino-2-(*p*-aminophenyl)-4-phenylquinazoline (Ia). A. Amination of IIa according to the procedure described above gave Ia, identical to the sample prepared by the reduction of 6-nitro-2-(*p*-nitrophenyl)-4-phenylquinazoline, mp 294-296°C (according to the method of Lindeman et al. [2]) as indicated by thin-layer chromatography, melting point, and IR spectroscopy.

B. A sample of Ib in 40 ml dioxane was hydrogenated under atmospheric pressure in the presence of 50 ml 4% Pd/C until hydrogen was no longer taken up. The catalyst was separated and the filtrate was evaporated to give 0.17 g (92%) Ia, mp 247-253°C. The product was crystallized from dioxane–petroleum ether to give 0.11 g (61%) quinazoline Ia, mp 257-259°C identical to the product synthesized by procedure A in its thin-layer chromatography, melting point, IR spectroscopy, and mass spectrometry.

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