ARYLAMINATION OF CHLOROQUINOLINES

S. I. Burmistrov and V. S. Litvinov

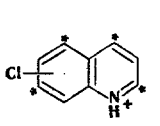
UDC 542.958.3+547.831.4-6

The first representatives of arylaminoquinolines with arylamino groups in the benzene ring were synthesized by arylamination of the corresponding chloroquinolines. A catalytic effect of arylamine hydrochlorides on the replacement of chlorine in the benzene ring of the chloroquinolines was observed.

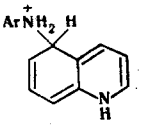
It is known that chlorine atoms in the 2 or 4 positions of the quinoline ring are readily replaced by amino or arylamino groups. Thus 4-phenylamino-2-methylquinoline was synthesized by reaction of equimolar amounts of 4-chloro-2-methylquinoline with aniline at 190°C [1]. However, a chlorine atom in a benzene ring of the quinoline system is not replaced by an arylamino group under the indicated conditions: the chlorine atoms prove to be just as inert in nucleophilic substitution reactions as the halogen atoms in halobenzenes. Thus 7-chloro (bromo)quinoline reacts with alkylamines only at 250-290° [2].

We have previously observed a catalytic effect of arylamine salts on the replacement of chlorine in 3-chlorindazoles [3], but 5-chloro- and 5,7-dichloroindazole proved to be inert under similar conditios. It was found that some benzene-ring-substituted chloroquinolines also react with arylamines in the presence of the hydrochlorides at a rate adequate for preparative purposes at 200-210° [4]. Thus 8-phenylaminoquinoline is obtained in good yields from 8-chloroquinoline and aniline in the presence of aniline hydrochloride. It should be noted that the liquid compound obtained by reaction of equimolar amounts of 8-hydroxyquinoline with aniline in the presence of catalytic amounts of iodine, which was previously described by Buu-Hoi [5] as 8-phenylaminoquinoline, was found to be different from the crystalline 8-phenylaminoquinoline that we synthesized from 8-chloroquinoline. When we reproduced the synthesis by the Buu-Hoi method, we isolated a substance identical to that synthesized from 8-chloroquinoline in low yield.

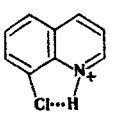
The catalytic effect of the hydrochloride salts is undoubtedly due to the fact that the chloroquinolinium cation (I), which is more electrophilic than free chloroquinoline, is formed in adequate concentrations in the reaction mixture. According to the Vesly—Jakes quinogen rule [6], in the quinolinium cation the halogen atoms in the quinogen positions relative to the positively charged center, viz., the nitrogen atom — the 4,2,7, and 5 positions, labeled with asterisks, in the order of decreasing electrophilicity — should undergo nucleophilic attack more readily, inasmuch as the addition of a nucleophile to the indicated positions leads to the formation of a quinoid complex (II) with the charge on the nitrogen atom of the nucleophile.



I



II



III

F. É. Dzerzhinskii Dnepropetrovsk Chemical-Engineering Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 661-664, May, 1976. Original article submitted April 21, 1975.

Both 8- and 5-chlorquinoline react with arylamines at approximately identical rates. Moreover, 5-chloro-8-phenylaminoquinoline is obtained in the reaction of 5,8-dichloroquinoline with aniline, i.e., the chlorine atom in the 8 position primarily undergoes substitution. The structure of the product of arylamination of 5,8-dichloroquinoline with aniline was proved by conversion to the acetyl derivative, which proved to be identical to the product of chlorination of 8-(N-acetylphenylamino)quinoline. The ease of replacement of the chlorine atom in the 8 position in 8-chloro- and 5,8-dichloroquinoline is unexpected, since the addition of a nucleophile to the 8 carbon atom cannot lead to the formation of an intermediate quinoid complex of the II type. Similarly, the chlorine atom in the 8 position is replaced in the case of 6,8-dichloroquinoline.

We suppose that the relatively high reactivity of the chlorine atom in the 8 position is due to the formation of a hydrogen bond between the chlorine atom in the 8-chloroquinolium cation (III) and the proton attached to nitrogen; this facilitates direct detachment of a chloride ion during attack by a nucleophile.

The arylaminoquinolines synthesized by the indicated reactions were light-yellow or intensely crystalline substances. Their solutions in organic solvents have a light-yellow color with an intensely blue fluorescence. Deepening of the color is observed when they are converted to salts; thus 8-phenylaminoquinoline hydrochloride forms red crystals, but aqueous solutions are orange. The maximum in the UV spectrum of the base is found at 245 nm, whereas solutions of the hydrochloride have an absorption maximum at 375 nm. The IR spectra of the synthesized compounds are presented in Table 1. It follows from the data presented in Table 1 that arylaminoquinolines without methyl groups in the 2 position have three absorption bands in the region of vibrations of the N-N bonds: one band of medium intensity is found at 3335-3360 cm^{-1}, and less intense bands are observed at 3460-3470 and 3200-3230 cm^{-1}. In the spectrum of 8-phenylamino-2-methylquinoline absorption bands at 3200-3220 and 3460 cm^{-1} are absent, and there is only one absorption band at 3360 cm^{-1}; this attests to the absence of intermolecular hydrogen bonds formed through the endocyclic nitrogen atom. The appearance of three absorption bands in the spectra of arylaminoquinolines with a nitrogen atom that is not shielded by a methyl group distinguishes them substantially from secondary aromatic amines, which have one intense absorption band at 3350-3500 cm^{-1}. This difference should be explained by the fact that the arylaminoquinolines contain a more basic endocyclic nitrogen atom that forms intramolecular and intermolecular hydrogen bonds with the amino group of the arylamine residue. The absence of absorption bands at 3460 and 3360 cm^{-1} in the IR spectrum of 5-phenylamino-8-hydroxyquinoline is undoubtedly associated with the formation of hydrogen bonds between the hydroxyl group and the heterocyclic nitrogen atom, which leads to a broad absorption band at 2500-3200 cm^{-1}. The inertness of the chlorine in 5-chloro- and 5,7-dichloroindazoles [3] should be explained by the fact that the halgoens in these compounds are in nonquinogenic positions relative to the positive center (the protonated nitrogen atom).

TABLE 1. IR Spectra of Arylaminoquinolines

Compound	Wave numbers of the maxima, cm^{-1}
8-Phenylaminoquinoline (IV)	3460 (s)*, 3350 (vs), 3220; 3040 (w), 1625 (vs), 1545, 1495 (vs), 1460 (w), 1440 (s), 1320 (s), 1300 (s), 1280 (s), 1207, 1180, 1145 (w), 1130 (w), 1075 (w), 1050 (w), 985 (vs), 830 (vs), 810 (s), 760 (vs), 740 (w), 670, 565, 540, 525
6-Chloro-8-phenylaminoquinoline (V)	3470, 3360 (vs), 3220, 1630 (vs), 1480 (vs), 1390, 1325 (vs), 1295 (vs), 1180 (vs), 1100, 1000, 890, 870, 850, 820, 790, 775, 675, 580, 505
5-Chloro-8-phenylaminoquinoline (VI)	3465, 3335 (s), 3220 (w), 1625 (vs), 1600 (vs), 1540, 1480, 1410 (w), 1390 (w), 1320 (s), 1290 (s), 1280 (s), 1180 (vs), 1130 (w), 1095, 1055 (w), 990, 890, 870, 850, 820, 790, 765, 667, 575
8-Phenylamino-2-methylquinoline (VII)	3360 (vs), 3050, 2920 (w), 1600 (vs), 1590 (vs), 1570 (vs), 1550 (vs), 1500 (vs), 1435 (vs), 1385 (vs), 1345 (vs), 1305 (vs), 1250, 1240, 1170, 1140 (w), 1080, 1065, 840, 830, 820 (s), 795 (vs), 745 (vs), 700 (vs), 590 (s), 510 (vs)
5-Phenylamino-8-hydroxyquinoline (VIII)	3200—3060 (br), 1595, 1500 (vs), 1480, 1415 (vs), 1385 (vs), 1290 (vs), 1280 (vs), 1250 (vs), 1215 (vs), 1175, 1155 (w), 1110, 1080 (w), 905 (w), 820 (s), 795 (vs), 750 (vs), 720 (s).

*The intensities of the bands are indicated in parentheses after the wave numbers: vs is very strong, s is strong, and w is weak. All of the other bands are of medium intensity.

TABLE 2. Arylaminoquinolines

Compound	mp, °C	Empirical formula	N, %		Yield, %
			found	calc.	
IV	121—122	$C_{15}H_{12}N_2$	12,7	12,7	80
V	176—177	$C_{15}H_{11}ClN_2$	10,8	11,0	72
VI	163—164	$C_{15}H_{11}ClN_2$	10,8	11,0	71
VII	58,5—60	$C_{16}H_{14}N_2$	11,8	11,9	70
VIII	73—74	$C_{15}H_{12}N_2O$	11,4	11,9	65
IX	82—83	$C_{16}H_{13}ClN_2O$	9,7	9,9	13

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of aqueous alcohol solutions of the compounds were recorded with an SF-4A spectrophotometer.

5-Chloro-8-phenylaminoquinoline (VI). A mixture of 1.5 g (16 mmole) of aniline, 5.9 g (30 mmole) of 5,8-dichloroquinoline, and 1.9 g (16 mmole) of aniline hydrochloride was heated in a flask equipped with a reflux condenser at 200-210° for 10 h. At the end of the reaction the mixture was treated with alkali, and the unchanged aniline and the 5,8-dichloroquinoline were removed by steam distillation. The insoluble solid was removed by filtration and converted to the hydrochloride (light-brown needles with mp 227-228°) for purification. Treatment of an alcohol solution of the hydrochloride with a dilute alkali solution gave 3.6 g (71%) of the free base as yellowish needles with mp 163-164°. The base was subjected to diazo coupling on paper with a p-nitrobenzenediazonium salt, and an intensely yellow coloration was observed in pyridine vapors; this coloration changed to orange in hydrogen chloride vapors. 8-Phenylaminoquinoline also underwent similar diazo coupling.

Acetylation of 5-chloro-8-phenylaminoquinoline with refluxing acetic anhydride gave pale-yellow crystals of the acetyl derivative, with mp 86-86.5° (from alcohol), which was identical to the product of chlorination of 8-(N-acetylphenylamino)quinoline. The results of the analyses and data on the melting points of the other arylaminoquinolines are presented in Table 2. 8-Phenylaminoquinoline (IV), 6-chloro-8-phenylaminoquinoline (V), 5-phenylamino-8-hydroxyquinoline (VIII), 5-chloro-8(p-methoxyphenylamino)quinoline (IX), and 8-phenylamino-2-methylquinoline (VII) were obtained, respectively, from 8-chlorquinoline, 6,8-dichloroquinoline, 5-chloro-8-hydroxyquinoline, and 8-chloro-2-methylquinoline via a similar method.

LITERATURE CITED

1. M. Conrad and G. Limpach, Ber., 20, 953 (1887).
2. L. Bradford, T. J. Elliott, and F. M. Rowe, J. Chem. Soc., No. 4, 437 (1947).
3. S. I. Burmistrov and V. S. Belykh, Khim. Geterotsikl. Soedin., No. 2, 249 (1973).
4. S. I. Burmistrov and V. S. Litvinov, USSR Author's Certificate No. 327195: Byul. Izobr., No. 5, 69 (1972).
5. N. P. Buu-Hoi, J. Chem. Soc., 4346 (1952).
6. V. Vesely and M. Jakes, Bull. Soc. Chim. France, Ser., 4, 33, 954 (1923).