SYNTHESIS OF AMINO DERIVATIVES OF QUINOLINE AND 5,6-BENZOQUINOLINE

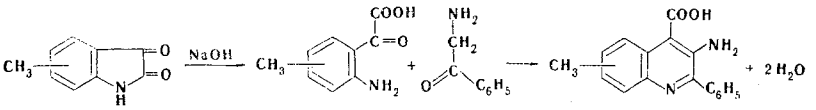
B. I. Ardashev, A. S. Zarif'yan, and G. G. Glukhovets

UDC 547.831.6'832.5.07

3-Aminocinchophen and 2-phenyl-3-aminoquinolines were synthesized by the reaction of isatin and 5-, 6-, and 7-methylisatins with ω-aminoacetophenone in alkaline media. A number of 3-amino-5,6-benzoquinoline derivatives were obtained by the condensation of azomethines from aromatic aldehydes and β-naphthylamine with ω-aminoacetophenone.

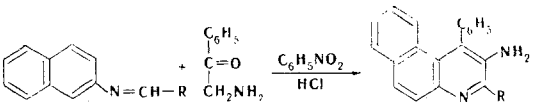
Reduction of nitroquinolines [1,2] and replacement of a halogen or hydroxyl group by an amino group or a substituted amino group [3,4] are the principal methods for preparing 3-aminoquinolines.

We have synthesized 3-aminocinchophen (2-phenyl-3-aminoquinoline-4-carboxylic acid) and 2-phenyl-3-aminoquinoline derivatives by condensation of isatin and its methyl-substituted derivatives with ω-aminoacetophenone in alkaline media [5].



The decarboxylation of the resulting 3-aminocinchophen derivatives in the presence of phosphoric acid [6] gives 2-phenyl-3-aminoquinolines. The Nimentowski reaction [7, 8] was used to obtain 1-oxo-5-phenyl-2H-pyrimido[4,5-c]quinoline, which can be converted to 1-chloro derivatives and other 1-substituted (in the pyrimidine ring) compounds [9].

We have also developed a convenient method for the preparation of 3-amino-5,6-benzoquinolines (see Table 1) by the reaction of azomethines – β-naphthylamine derivatives – with ω-aminoacetophenone. The condensation was carried out in alcohol in the presence of nitrobenzene and concentrated sulfuric acid:



The structures of the compounds obtained were confirmed by IR spectroscopy and qualitative reactions for the NH_2 and COOH groups (benzoylation, synthesis of esters, the Nimentowski reaction, etc.).

EXPERIMENTAL

The methylisatins were obtained by the method in [10].

2-Phenyl-3-aminoquinoline-4-carboxylic Acid (I). A mixture of 1.5 g (10 mmole) of isatin, 12 ml of alcohol, 2 ml of 33% sodium hydroxide solution, and 1.2 g (10 mmole) of ω-aminoacetophenone was heated at 95° on an air bath for 6-8 h. The solvent was removed by distillation until the temperature of the mixture reached 100°. The reaction product was cooled, 14 ml of water was added, and the mixture was stirred thoroughly and filtered. The filtrate was acidified carefully with 50% acetic acid. After several

Novocherkassk Polytechnic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 525-526, April, 1972. Original article submitted February 22, 1971.

TABLE 1. Properties of Amino Derivatives of Quinoline and 5,6-Benzoquinoline

Comp.	Name	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
				C	H	C	H	
I	2-Phenyl-3-aminoquinoline-4-carboxylic acid (3-aminocinchophen)	180—181	$C_{16}H_{12}N_2O_2$	72,6	4,6	72,7	4,5	83
II	2-Phenyl-3-amino-5-methylquinoline-4-carboxylic acid	105—106	$C_{17}H_{14}N_2O_2$	73,4	5,6	73,4	5,8	65
III	2-Phenyl-3-amino-6-methylquinoline-4-carboxylic acid	194—195	$C_{17}H_{14}N_2O_2$	73,3	5,8	73,4	5,8	60
IV	2-Phenyl-3-amino-7-methylquinoline-4-carboxylic acid	157—158	$C_{17}H_{14}N_2O_2$	73,3	5,6	73,4	5,8	50
V	2-Phenyl-3-aminoquinoline	121—122	$C_{15}H_{12}N_2$	81,8	5,3	81,8	5,4	55
VI	2-Phenyl-3-amino-5-methylquinoline	145—146	$C_{16}H_{14}N_2$	82,0	5,9	82,1	6,0	60
VII	2-Phenyl-3-amino-6-methylquinoline	183—184	$C_{16}H_{14}N_2$	81,9	5,8	82,1	6,0	62
VIII	2-Phenyl-3-amino-7-methylquinoline	175—176	$C_{16}H_{14}N_2$	82,0	5,9	82,1	6,0	70
IX	2-(2-Thienyl)-3-amino-4-phenyl-5,6-benzoquinoline	163—164	$C_{23}H_{16}N_2S$	78,5	4,5	78,4	4,5	56
X	2-(5-Nitro-2-thienyl)-3-amino-4-phenyl-5,6-benzoquinoline	287—288	$C_{23}H_{15}N_3O_2S$	72,6	4,0	72,4	3,9	36
XI	2-(4-Bromo-2-thienyl)-3-amino-4-phenyl-5,6-benzoquinoline	170—171	$C_{23}H_{15}BrN_2S$	64,7	3,6	64,6	3,5	53
XII	2,4-Diphenyl-3-amino-5,6-benzoquinoline	166—167	$C_{25}H_{18}N_2$	86,8	5,4	86,7	5,2	75
XIII	2-(o-Methoxyphenyl)-3-amino-4-phenyl-5,6-benzoquinoline	173—174	$C_{26}H_{20}N_2O$	84,0	5,2	84,0	5,1	50
XIV	2-(2-Hydroxynaphthyl)-3-amino-4-phenyl-5,6-benzoquinoline	121—122	$C_{29}H_{20}N_2O$	84,6	4,9	84,5	4,8	60

minutes, a yellow crystalline precipitate formed and was recrystallized from acetic acid to give 83% of a product with mp 180-181° that was quite soluble in acetone and insoluble in alcohol.

Compounds II-IV (see Table 1) were similarly obtained.

2-Phenyl-3-aminoquinoline (V). A mixture of 0.5 g (2 mmole) of acid I and 3 ml of phosphoric acid (sp. gr. 1.75) was heated on an oil bath to 170° for 30 min, and the temperature was slowly raised to 210°. After 1 h, the mixture was cooled, stirred, and diluted with 15 ml of water. The mixture was filtered, and the filtrate was made alkaline with ammonia. The tacky reaction product was separated and dissolved in 10 N hydrochloric acid. The solution was treated with ammonia, and the precipitate was dissolved in methanol. Water was added to the warm solution to isolate a small amount of a resinous product. The solution was filtered, and crystallization was induced by the addition of water to give 55% of a product with mp 121-122°.

Compounds VI-VIII (see Table 1) were similarly obtained.

2-(2-Thienyl)-3-amino-4-phenyl-5,6-benzoquinoline (IX). A solution of 1.5 g (6 mmole) of N-(2-thienylidene)-2-naphthylamine, 1.2 g (10 mmole) of ω-aminoacetophenone, 1.2 g (10 mmole) of nitrobenzene, and 0.3 ml of concentrated hydrochloric acid in 10 ml of alcohol was heated on a water bath for 50 min. The mixture was allowed to stand until the following day until a precipitate formed. The precipitate was removed by filtration, washed with alcoholic ammonia, filtered again, and recrystallized from dimethylformamide to give 56% of a product with mp 163-164°.

Compounds X-XIV (see Table 1) were similarly obtained.

1-Oxo-5-phenyl-2H-pyrimido[4,5-c]quinoline. A 0.7-g (0.5 mmole) sample of acid I was heated with excess (0.8 g) formamide at 145-150° for 4 h. The reaction product was removed by filtration and recrystallized from cyclohexanone to give 57% of a product with mp 295-296°. The product was insoluble in water, alcohol, benzene, toluene, and dimethylformamide and soluble in acetone. Found: C 71.3; H 4.2%. $C_{17}H_{11}N_3O$. Calculated: C 71.1; H 4.0%.

LITERATURE CITED

1. G. R. Clemo and G. A. Swan, J. Chem. Soc., 867 (1945).
2. N. S. Kozlov, 5,6-Benzoquinolines [in Russian], Minsk (1970), p. 89.
3. G. Renshaw and H. Friedman, J. Am. Chem. Soc., 61, 3320 (1939).
4. A. Kuhn and W. Westphal, Ber., 73, 1107 (1940).

5. H. John and E. Pietsch, J. Pr. Chem., 143, 245 (1935).
6. V. A. Petrow, M. V. Stack, and W. R. Wragg, J. Chem. Soc., 316 (1943).
7. M. M. Endicott, E. Wick, and M. L. Mercury, J. Am. Chem. Soc., 68, 1299 (1946).
8. K. H. Meyer and H. Wagner, J. Org. Chem., 8, 239 (1943).
9. R. Elderfield (editor), Heterocyclic Compounds, Wiley (1961).
10. Organic Synthesis [Russian translation], Vol. 1, Inostr. Lit., Moscow (1949), p. 216.