and 4-chloro-5,7-dibromoquinoline and their condensation with a primary–tertiary diamine are described.

Nitration of 4,7-dichloroquinoline yields the 8-nitro derivative which was converted to 4,7,8-trichloroquinoline.

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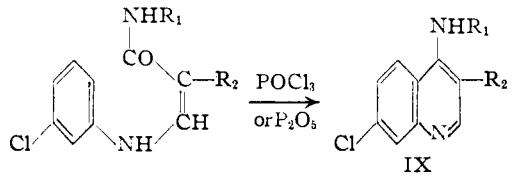
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Synthesis of Substituted 4-Aminoquinolines[1]

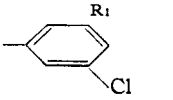
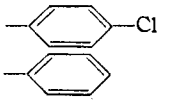
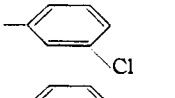
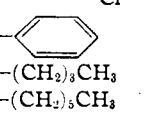
BY CHARLES C. PRICE[2] AND VIRGIL BOEKELHEIDE

A number of 4-aminoquinoline derivatives, especially those with a 7-chlorine atom, have been found to possess marked antimalarial activity.[3,4] The usual procedure for their preparation involves treatment of the requisite 4-chloroquinoline with the proper diamine side-chain. The synthesis of 4-hydroxyquinolines, necessary as intermediates in this type of preparation, has been discussed in a recent series of papers from this Laboratory.[5]

The present investigation was undertaken to find a general method of synthesis of the quinoline nucleus which would directly introduce an amino or a substituted amino group at the 4-position of the quinoline nucleus. This has been accomplished successfully by the cyclodehydration of a number of β-anilinoacrylamides according to the following scheme.

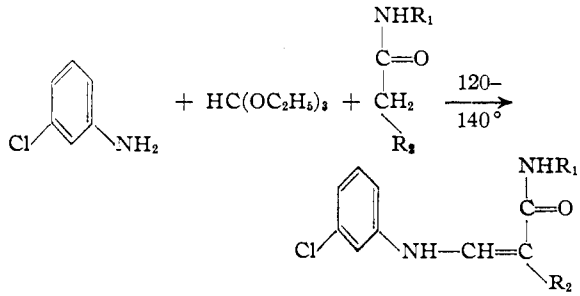


IX

	R1	R2
I,		—$COOC_2H_5$
II,		—$COOC_2H_5$
III,		—CN
IV,		—CN
V,	$-(CH_2)_3CH_3$	—CN
VI,	$-(CH_2)_5CH_3$	—CN
VII,	$-(CH_2)_2CN$	—CN
VIII,	$-(CH_2)_5CN$	—CN

Although this method of ring closure has been widely used in the synthesis of isoquinolines,[6] and was also used by Drozdov[7] in the synthesis of atabrine, it has apparently never been applied to the synthesis of quinolines before. Since the quinolines desired were those with a halogen in the 7-position, the reaction was studied only with β-*m*-chloroanilinoacrylamides. Undoubtedly the reaction could be extended to other β-arylaminoacrylamides.

A desirable feature of this method of preparing quinolines is the ready availability of the β-arylaminoacrylamides. Claisen[8] discovered that aniline would react with ethoxymethylenemalonic ester to give β-anilino-α-carbethoxyacrylic ester. Band[9] had previously shown that β-anilino-α-carbethoxyacrylic ester would react with another molecule of aniline to give β-anilino-α-carbethoxyacrylanilide. Unfortunately, this reaction is suitable only when it is desired that the amide group be the same as the amino group on the β-carbon atom. Otherwise a mixture of products results. It was found, however, that the desired β-*m*-chloroanilinoacrylamides could be obtained by suitably modifying the above reaction. This was done by first preparing the proper amide of an acid having an adjacent active methylene group and by then allowing this amide to react directly with ethyl orthoformate and *m*-chloroaniline.[5c] This method proved to be very satisfactory and is illustrated below.



The use of β-*m*-chloroanilinoacrylamides made it necessary to establish the structure of the quinoline produced by this reaction. If cyclization occurred *para* to the chlorine already present in the benzene ring, the resulting quinoline would

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

(2) Present address, University of Notre Dame, Notre Dame, Indiana

(3) (a) Andersag, Breitner and Jung (to Winthrop Chemical Co.), U. S. Patent 2,233,970; *C. A.*, **35**, 3771 (1941); (b) (to I. G. Farbenindustrie, German Patent 683,692; *C. A.*, **36**, 4973 (1942).

(4) Iensch, *Z. angew. Chem.*, **50**, 891 (1937).

(5) (a) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946); (b) Price, Leonard and Herbrandson, *ibid.*, **68**, 1251 (1946); (c) Snyder and Jones, *ibid.*, **68**, 1253 (1946); (d) Price and Roberts, *ibid.*, **68**, 1255 (1946); (e) Price, Leonard and Reitsema, *ibid.*, **68**, 1256 (1946); (f) Leonard, Herbrandson and van Heyningen, *ibid.*, **68**, 1279 (1946).

(6) Kindler and Peschke, *Arch. Pharm.*, **272**, 236 (1934).

(7) Drozdov, *J. Gen. Chem.* (U. S. S. R.), **8**, 1192 (1938).

(8) Claisen, *Ann.*, **297**, 77 (1897).

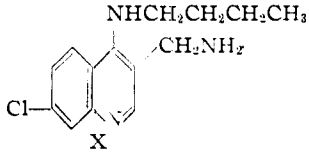
(9) Band, *ibid.*, **285**, 145 (1895).

have the structure, IX, as written above. On the other hand, the ring closure might possibly occur *ortho* to the chlorine present in the benzene ring and then the resulting quinoline would have the chlorine atom in the 5-position. Since in every case only one product was isolated, it must be assumed that cyclization occurred in one direction, or, if both isomers are formed, one isomer was formed in such small amounts that it was lost in the isolation of the product.

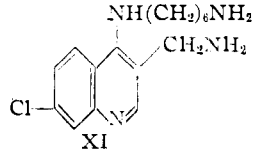
Cyclizations of I and III were shown to produce quinolines with the chlorine atom in the 7-position as represented by IX as follows. Cyclization of I gave ethyl 4-*m*-chloroanilino-7-chloro-3-quinolinecarboxylate (IX, R = *m*-ClC_6H_4, R_2 = $COOC_2H_5$). This was hydrolyzed to give 4-*m*-chloroanilino-7-chloro-3-quinolinecarboxylic acid (IX, R_2 = COOH) which was decarboxylated to give 4-*m*-chloroanilino-7-chloroquinoline. The structure of the latter was established by comparison with an authentic sample obtained from the reaction of 4,7-dichloroquinoline with *m*-chloroaniline. Likewise, the cyclization of III with phosphorus pentoxide gave 4-*m*-chloroanilino-7-chloro-3-quinolinecarbonitrile (IX, R_2 = CN) which was hydrolyzed to give 4-*m*-chloroanilino-7-chloro-3-quinolinecarboxylic acid identical with that prepared from the ester above.

The cyclization of III and IV by the use of phosphorus oxychloride did not give the 3-quinolinecarbonitriles, but gave instead the corresponding imidoethers. Apparently, the 3-quinolinecarbonitriles were converted to the corresponding imidochlorides under the conditions used in the cyclization, which were transformed to the iminoethers on treatment with alcohol and ether in the usual manner for working up the products. The structure of the iminoether (IX, R_1 = *m*-ClC_6H_4, R_2 = $C(=NH)OC_2H_5$) was confirmed by analysis and by hydrolysis to the corresponding acid.

Reduction of the 3-quinolinecarbonitriles formed by cyclization of V, VI and VIII could be carried out using Raney nickel catalyst to give the corresponding 3-aminomethylquinolines. Thus, 4-*n*-butylamino-7-chloro-3-quinolinecarbonitrile was hydrogenated to 3-aminomethyl-4-*n*-butylamino-7-chloroquinoline (X). Likewise, 7-chloro-4-(5-cyanopentylamino)-3-quinolinecarbonitrile was hydrogenated to 4-(6-aminohexylamino)-3-aminomethyl-7-chloroquinoline (XI).



X



XI

Most of the results of this investigation are summarized in Tables I and II. The preparation of β-*m*-chloroanilinoacrylamides (Table I) was carried out in very good yields. Losses of material occurred mainly during the purification of the product. The cyclization of the β-*m*-chloroanilinoacrylamides (Table II) gave fair yields of the corresponding quinolines in most cases. The preparation of 4-arylaminoquinoline (examples 1 to 5 in Table II) was accomplished in better yield when the cyclization was carried out using phosphorus oxychloride than when phosphorus pentoxide was used. On the other hand, the preparation of 4-alkylaminoquinolines was successful only when the cyclization was carried out using phosphorus pentoxide.

The preparation of 4-alkylaminoquinolines in which the alkyl group contained an amino substituent failed entirely. Thus the cyclization of β-*m*-chloroanilino-α-cyano-N-(4-diethylamino-1-methylbutyl)-acrylamide to 7-chloro-4-(4-diethylamino-1-methylbutylamino)-3-quinolinecarbonitrile was attempted repeatedly without success. Likewise, the one attempted cyclization of the cyanoamide (VII) gave only a tarry product. The cyclization of the cyanoamide (VIII) was tried a number of times but the yield of 7-chloro-4-(5-cyanopentylamino)-3-quinolinecarbonitrile never exceeded 12%.

Two of the compounds, 4-*n*-butylamino-7-chloro-3-quinolinecarbonitrile (SN-12,345)[10] and 3-aminomethyl-4-*n*-butylamino-7-chloroquinoline (SN-12,265) were tested for activity against avian malaria and were both found to be inactive in the maximum dose tolerated.

A number of unsuccessful schemes for the direct synthesis of 4-aminoquinolines were investigated. For example, the Schiff base from *o*-aminobenzonitrile and acetaldehyde was treated with lithium diethylamide in the hope that a cyclization would occur similar to that of dinitriles carried out by Ziegler.[11] However, this reaction failed to give 4-aminoquinoline, probably due to the rapid polymerization of the Schiff base.

Another scheme was to effect ring closure between an aromatic nucleus and a nitrile group. It was thought that such a cyclization might be accomplished under the conditions of the Hoesch reaction. When the reaction was attempted with β-anilino-α-chloropropionitrile or with β-arylamino-α-cyanoacrylonitriles, it was entirely unsuccessful.

Experimental[12]

The Preparation of β-*m*-Chloroanilinoacrylamides.—The results of these experiments are given in Table I. The general procedure employed was as follows. Ethyl cyanoacetate (0.25 mole) and the proper amine (0.25 mole) were placed in a Claisen flask, and the mixture was heated until sufficient alcohol (14 ml., 0.25 mole) had distilled to show that the amide formation was complete. The temperature required to effect amide formation varied from 125° for aliphatic amines to 180° for aryl amines. Then, to the crude amide which was not allowed to cool

(10) The Survey Number, designated SN-, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

(11) Ziegler, *Ann.*, **504**, 94 (1933).

(12) All melting points corrected. Analyses by Miss Theta Spoor and Miss Lillian Hruda.

TABLE I

SUBSTITUTED β-*m*-CHLOROANILINOACRYLAMIDES

β-*m*-Chloroanilinoacryl amides	Yield, %	M. p., °C.	Molecular formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
α-Carbethoxy-*m*-chloroanilide	90	114	$C_{18}H_{16}O_3N_2Cl_2$	57.00	57.21	4.22	4.32
α-Carbethoxy-*p*-chloroanilide	72	143–144	$C_{18}H_{16}O_3N_2Cl_2$	57.00	57.16	4.22	4.28
α-Cyano-*m*-chloroanilide	78	164–166	$C_{16}H_{11}ON_3Cl_2$	57.85	58.15	3.34	3.40
α-Cyanoanilide	65	138–140	$C_{16}H_{12}ON_3Cl$	64.54	64.56	4.04	4.05
α-Cyano-N-*n*-butyl	91	99–100	$C_{14}H_{16}N_3OCl$	60.54	60.67	5.77	5.85
α-Cyano-N-*n*-hexyl	87	90–92	$C_{16}H_{20}ON_3Cl$	62.84	62.96	6.55	6.75
α-Cyano-N-(2-cyanoethyl)-amide	95	201–202	$C_{13}H_{11}ON_4Cl$	56.83	56.36	4.01	4.06
α-Cyano-N-(5-cyanopentyl)-amide	80	110–111	$C_{16}H_{17}ON_4Cl$	60.66	60.65	5.41	5.35

TABLE II

SUBSTITUTED 4-AMINO-7-CHLOROQUINOLINES

7-Chloroquinolines	Yield, %[a]	M. p., °C.	Molecular formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
4-*m*-Chloroanilino-3-carbethoxy[b]	A57 B21	121–123	$C_{18}H_{14}O_2N_2Cl_2$	59.83	59.79	3.88	3.95
4-*p*-Chloroanilino-3-carbethoxy	A65	143–144	$C_{18}H_{14}O_2N_2Cl_2$	59.83	59.76	3.88	3.96
4-*m*-Chloroanilino-3-cyano[c]	B25	290–295	$C_{16}H_9N_3Cl_2$	61.20	62.29	2.88	2.69
4-*m*-Chloroanilino-3-carboximino ether (as the hydrochloride)[d]	A45	278–280	$C_{18}H_{15}ON_3Cl_3 \cdot HCl$	54.47	54.24	4.03	3.96
4-Anilino-3-carboximino-methyl ether[e]	A48	163–164	$C_{17}H_{14}ON_3Cl$	65.50	65.82	4.50	4.53
4-*n*-Butylamino-3-cyano	B65	146–147	$C_{14}H_{14}N_3Cl$	64.75	64.75	5.39	5.43
4-*n*-Hexylamino-3-cyano	B50	133–134	$C_{16}H_{18}N_3Cl$	66.82	67.20	6.31	6.44
4-(5-Cyanopentyl)-3-cyano	B12	160–161	$C_{16}H_9N_3Cl_2$	64.31	64.40	5.06	5.25

[a] A. Cyclization was carried out using $POCl_3$. B. Cyclization was carried out using P_2O_5. [b] The *hydrochloride* melted at 260°. *Anal.* Calcd. for $C_{18}H_{14}O_2N_2Cl_2 \cdot HCl$: C, 54.35; H, 3.80. Found: C, 54.50; H, 3.71. The dipicrate melted at 215°. *Anal.* Calcd. for $C_{18}H_{14}O_2N_2Cl_2 \cdot 2C_6H_3O_7N_3$: C, 48.82; H, 2.88. Found: C, 49.07; H, 2.91. [c] This compound was highly insoluble and very difficult to purify. Its structure was established by the fact that it could be hydrolyzed with methanolic potassium hydroxide to give 4-*m*-chloroanilino-7-chloro-3-quinolinecarboxylic acid. [d] This compound was hydrolyzed to 4-*m*-chloroanilino-7-chloro-3-quinolinecarboxylic acid by treatment with 10% sodium hydroxide. [e] This compound was also analyzed for nitrogen. *Anal.* Calcd. for $C_{17}H_{14}ON_3Cl$: N, 13.49. Found: N, 13.54.

more than necessary, there was added *m*-chloroaniline (0.25 mole) and ethyl orthoformate (0.25 mole). The resulting mixture was heated at 120 to 140° until sufficient alcohol (42 ml., 0.75 mole) had distilled to show that the reaction was complete. The contents of the flask were poured into a beaker and allowed to cool. The solid product thus obtained was purified by crystallization from ethanol. All of the β-*m*-chloroanilinoacrylamides were obtained as white, fluffy needles.

The preparation of β-*m*-chloroanilino-α-carbethoxyacrylo-*p*-chloroanilide differed from the above procedure in that carbethoxyaceto-*p*-chloroanilide[13] was first prepared and then treated directly with *m*-chloroaniline and ethyl orthoformate.

The preparation of β-*m*-chloroanilino-α-carbethoxyacrylo-*m*-chloroanilide was carried out by merely heating *m*-chloroaniline (0.50 mole) with ethoxymethylenemalonic ester (0.25 mole) at 110° for one-half hour.

The Preparation of Substituted 4-Amino-7-chloroquinolines.—The preparation of substituted 4-amino-7-chloroquinolines was carried out by treating the proper β-*m*-chloroanilinoacrylamide with either phosphorus oxychloride in boiling benzene (method A) or phosphorus pentoxide in boiling xylene (method B). The results of these experiments are given in Table II. The general procedure is outlined below.

(a) **Method A.**—Phosphorus oxychloride (0.2 mole) was added to a solution of the proper β-*m*-chloroanilinoacrylamide (0.1 mole) in 400 ml. of dry benzene (thiophene-free). The solution was then gently boiled for six to ten hours. As the reaction proceeded the solution turned a dark red and the hydrochloride salt of the product began to precipitate. At the conclusion of the reaction the benzene and the excess phosphorus oxychloride were removed *in vacuo*. The red gummy residue was then treated with 50 ml. of ethyl or methyl alcohol and warmed until all of the residue dissolved. The yellow granular hydrochlorides usually separated when the alcohol solution was cooled and the precipitation was completed by adding an excess of ether. The hydrochloride was then removed by filtration, washed with ether and dried. Usually, the quinoline hydrochlorides were converted to the free base by warming them with aqueous potassium carbonate for fifteen minutes. The free quinoline bases could be purified by crystallization from either alcohol or benzene. All of the quinolines obtained in this way were light yellow solids.

An attempt to apply this method to the preparation of 4-alkylamino-7-chloroquinolines produced only tarry products.

(b) **Method B.**—Phosphorus pentoxide[14] (100 g.) was added to a solution of the proper β-*m*-chloroanilinoacrylamide (0.1 mole) in purified technical xylene (500 ml.). The mixture was boiled under reflux with good stirring for four to six hours. As the reactions proceeded the phosphorus pentoxide darkened and became lumpy. At the conclusion of the reaction the mixture was cooled and the solid material was removed by filtration. The solid product on the filter was washed several times with benzene to remove as much neutral organic material as possible. The residue was then dropped onto chopped ice (300 g.) to decompose the excess phosphorus pentoxide. The insoluble phosphate salt of the quinoline separated and was removed by filtration. The crude phosphate was then converted to the free quinoline base by warming with 10

(13) Chattaway and Mason, *J. Chem. Soc.*, **97**, 341 (1910).

(14) For this reaction it is best that the phosphorus pentoxide be as finely divided as possible. The highest yields were obtained using phosphorus pentoxide supplied by the J. T. Baker Chemical Co., Phillipsburg, New Jersey.

N sodium hydroxide (200 ml.). The free quinoline base was removed by filtration, dried and crystallized from a minimum amount of benzene. All of the quinolines obtained in this way were light yellow solids with the exception of 4-*m*-chloroanilino-7-chloro-3-quinolinecarbonitrile, which was brick red in color.

4-*m*-Chloroanilino-7-chloro-3-quinolinecarboxylic Acid.—Ethyl 4-*m*-chloroanilino-7-chloro-3-quinolinecaroxylate, XI, (4.0 g.) was dissolved in 25% methanolic potassium hydroxide solution (30 ml.). The solution was allowed to stand for several hours and then the methanol was removed *in vacuo*. The residue was dissolved in water, filtered and acidified. The acid which precipitated was removed by filtration and dried. There was obtained 3.5 g. (95%) of a yellow powder, m. p. 266°, dec. The acid was insoluble in all of the common solvents and it was difficult to purify a sample for analysis.

Anal. Calcd. for $C_{16}H_{10}O_2N_2Cl_2$: C, 57.60; H, 3.03. Found: C, 56.74; H, 3.29.

4-*m*-Chloroanilino-7-chloroquinoline.—Two grams of 4-*m*-chloroanilino-7-chloro-3-quinolinecarboxylic acid was heated in a test-tube at the temperature necessary to melt the acid. When evolution of carbon dioxide had ceased, the tube was cooled and the resulting solid was removed. Crystallization of this solid from ethanol yielded 1.5 g. (86%) of large white shining plates, m. p. 223–225°.

Anal. Calcd. for $C_{15}H_{10}N_2Cl_2$: C, 62.28; H, 3.46. Found: C, 62.31; H, 3.56.

4-*m*-Chloroanilino-7-chloroquinoline was also prepared by the method of Banks.[15] A few drops of hydrochloric acid were added to a mixture of 4,7-dichloroquinoline (2.0 g.) and *m*-chloroaniline (1.3 g.) in water (100 ml.) and the mixture was heated to a gentle boil. Within a few minutes the hydrochloride salt of the product began to precipitate. The reaction mixture was heated for an additional ten minutes before the hydrochloride salt was removed by filtration. The free quinoline base was then obtained by warming the hydrochloride with 10% sodium hydroxide. Crystallization of the free quinoline from ethanol yielded 2.8 g. of large white shining plates, m. p. 223–5°. When a sample of this product was mixed with the sample above, the mixture showed the same melting point.

3-Aminomethyl-4-*n*-butylamino-7-chloroquinoline (X).—Raney nickel catalyst (3 g.) was added to a solution of 4-*n*-butylamino-7-chloro-3-quinolinecarbonitrile (19.0 g.) in 10% alcoholic ammonia (300 ml.). The mixture was shaken under a pressure of hydrogen of one-half atmosphere until the expected quantity of hydrogen was absorbed. The catalyst was then removed by filtration and the solvent was removed *in vacuo*. There was thus obtained 19.0 g. (99%) of a light yellow solid, m. p. 110–112°. Crystallization of the crude product from benzene gave light yellow needles, m. p. 114–115°.

Anal. Calcd. for $C_{14}H_{18}N_3Cl$: C, 63.76; H, 6.88. Found: C, 63.95; H, 7.06.

A sample of 3-aminomethyl-4-*n*-butylamino-7-chloroquinoline (SN-12,265) was dissolved in three equivalents of acid and back-titrated with standard base electrometrically. The curve which was obtained indicated the following pK values; $pK_{a_1} = 7.35$; $pK_{a_2} = 9.00$. These values are in agreement with those obtained with other tribasic quinolines,[16] so that the lack of activity of this compound cannot be ascribed to improper base strength.

4-(6-Aminohexylamino)-3-aminomethyl-7-chloroquinoline XI.—Raney nickel catalyst (0.5 g.) was added to a solution of 7-chloro-4-(5-cyanopentylamino)-3-quinolinecarbonitrile (1.0 g.) in 10% alcoholic ammonia (20 ml.). The mixture was shaken under a pressure of one-half an atmosphere of hydrogen until the expected quantity of hydrogen had been absorbed. The catalyst was then removed by filtration and the solvent was removed *in vacuo*. The light brown oil which remained was treated directly with picric acid in ethanol. The dipicrate was crystallized from aqueous ethanol as yellow needles, m. p. 163–164°.

Anal. Calcd. for $C_{16}H_{23}N_4Cl \cdot 2C_6H_3O_7N_3$: C, 44.00; H, 3.83. Found: C, 44.63; H, 4.00.

N-(4-Diethylamino-1-methylbutyl)-cyanoacetamide.—Ethyl cyanoacetate (28.0 g., 0.25 mole) and 4-amino-1-diethylaminopentane (40.0 g., 0.25 mole) were heated together at 150° until the required amount of alcohol (14 ml.) had distilled. The product was then distilled under reduced pressure. There was obtained 30.0 g. (54%) of a water-white oil; b. p. 165–170° (2 mm.); $n^{23}D$ 1.4748.

Anal. Calcd. for $C_{12}H_{23}ON_3$: C, 64.00; H, 10.22. Found: C, 63.85; H, 10.35.

Attempted Preparation of 7-Chloro-4-(4-diethylamino-1-methyl-butylamino)-3-quinolinecarbonitrile.—A mixture of N-(4-diethylamino-1-methylbutyl)-cyanoacetamide (56.2 g., 0.25 mole), *m*-chloroaniline (31.8 g., 0.25 mole) and ethyl orthoformate (37.0 g., 0.25 mole) was heated together until the required quantity of alcohol (42 ml., 0.75 mole) had distilled. When the product was cooled, a thick red oil was obtained. This oil did not solidify and it decomposed when distillation under high vacuum was attempted. Therefore, the crude product was treated directly according to the procedures for cyclization. Both methods A and B were tried. In each case the product was a thick red oil which could not be converted to a solid derivative and which decomposed when distillation was attempted.

Attempted Cyclization of the Schiff Base.—Freshly distilled acetaldehyde (9.0 g., 0.2 mole) was added to a solution of *o*-aminobenzonitrile[17] (24.0 g., 0.2 mole) in dry ether (150 ml.). The dark red solution of the Schiff base was dried, cooled to 10° and a solution of lithium diethylamine (prepared by treating 15 g. of phenyllithium in 50 ml. of ether with 14 g. of dry diethylamine) was added slowly with stirring. The reaction mixture was stirred at 10° for two hours and was then decomposed with water. Separation of the ether layer and removal of the ether left a thick red oil. No identifiable material could be obtained from the oil.

Attempted Ring Closure of a Nitrile Group with the Aromatic Nucleus.—Zinc chloride (8 g.) was added to a solution of β-anilino-α-chloropropionitrile[18] (9.0 g., 0.05 mole) in ether (150 ml.). The mixture was stirred for three hours while dry hydrogen chloride gas was passed in. Precipitation of the hydrochloride occurred. When the ether was removed and the residue was made basic the β-anilino-α-chloropropionitrile was recovered.

The experiment was repeated several times with other solvents. When sufficient dioxane was used precipitation of the hydrochloride salt did not occur but here again the β-anilino-α-chloropropionitrile was recovered almost completely.

The experiments were also repeated using β-anilino-α-cyanoacrylonitrile and β-*m*-chloroanilino-α-cyanoacrylonitrile, respectively, in place of β-anilino-α-chloropropionitrile. In no case was there any evidence of reaction other than salt formation.

β-Anilino-α-cyanoacrylonitrile.—The preparation of β-anilino-α-cyanoacrylonitrile was carried out by allowing aniline to react with ethoxymethylenemalononitrile. The product was obtained as a white powder which, after crystallization from ethanol, melted at 245°.

Anal. Calcd. for $C_{10}H_7N_3$: C, 71.00; H, 4.14, Found: C, 70.99; H, 4.19.

β-*m*-Chloroanilino-α-cyanoacrylonitrile.—This compound was similarly obtained as a white powder which, after crystallization from alcohol, melted at 198–199°.

Anal. Calcd. for $C_{10}H_6N_3Cl$: C, 59.00; H, 2.98. Found: C, 58.92; H, 3.06.

Summary

By the cyclodehydration of various β-arylam-

(15) Banks, THIS JOURNAL, **66**, 1127 (1944).

(16) By private communication from Dr. J. Logan Irvin, Johns Hopkins University.

(17) Bogert and Hand, THIS JOURNAL, **24**, 1035 (1902).

(18) McElvain, *ibid.*, **49**, 2864 (1927).

inoacrylamides with phosphorus oxychloride or phosphorus pentoxide a number of substituted 4-amino-7-chloroquinolines have been prepared.

The substituted β-*m*-chloroanilinoacrylamides were prepared by treating the amide of an acid having an adjacent active methylene group with an aryl amine and ethyl orthoformate.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of Certain Simple 4-Aminoquinoline Derivatives[1]

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Quinoline derivatives containing a primary amine group in the 4-position have, as a general rule, been prepared in the past from the corresponding quinoline-4-carboxylic acids by either the Hofmann or Curtius degradations. The ready availability of derivatives of 4-chloroquinoline[2] suggests that the amino derivatives might be prepared more conveniently by replacement of the 4-chlorine atom. Whereas 4-chloroquinoline and its derivatives react readily with primary aliphatic amines,[3] the chlorine atom has now been found to be remarkably inert toward reaction with ammonia. Thus when 4,7-dichloroquinoline was heated with anhydrous ammonia at 170° for three hours, it was recovered quantitatively; at 230–240° for five hours, extensive decomposition occurred. When it was fused with potassium phthalimide at 170° or when it was heated with sodamide in dioxane at 100° for twelve hours, recovery of unreacted material was also quantitative. However, reaction of 4,7-dichloroquinoline with ammonia in the presence of phenol by a modification of the procedure of Andersag, Breitner and Jung[4] furnished 4-amino-7-chloroquinoline readily. In a similar fashion, 4-amino-6-methoxyquinoline was prepared.

When 4,7-dichloroquinoline was subjected to the action of dimethylamine in phenol under conditions which led to ammoniation, no reaction occurred and the material was recovered quantitatively. Use of a higher temperature and pressure for the reaction with dimethylamine resulted in replacement of both chlorine atoms with the formation of 4,7-bis-dimethylaminoquinoline.

4-Amino-7-chloroquinoline has also been prepared by the general method of Backeberg[5] by reduction of 7-chloroquinoline-4-phenylhydrazine, and 4-amino-6-methoxyquinoline has been prepared by an improvement of the Hofmann degradation of quininic acid amide as given by Hirsch.[6]

Reaction of 4,7-dichloroquinoline with ethanolamine to yield 4-(β-hydroxyethyl)-7-chloroquinoline and conversion of the latter to 4-(β-chloroethyl)-7-chloroquinoline and 4-(β-bromoethyl)-7-chloroquinoline have been described briefly in the patent literature.[4] In connection with other work we have had occasion to prepare these substances and the opportunity is now taken to record their preparation and properties.

Experimental[7,8]

4-Amino-7-chloroquinoline: (a) **From 7-Chloroquinoline-4-phenylhydrazine.**—The hydrazine was prepared in 43% yield exactly according to Backeberg[5] from 4,7-dichloroquinoline. It was reduced directly, after one recrystallization from water, with zinc dust and hydrochloric acid according to Backeberg,[5] yielding 42% of 4-amino-7-chloroquinoline melting at 150–152.5° after recrystallization from benzene (carbon).

Anal. Calcd. for $C_9H_7ClN_2$: C, 60.5; H, 3.9. Found: C, 60.9; H, 4.0.

(b) **By Ammoniation of 4,7-Dichloroquinoline.**—A mixture of 66 g. of 4,7-dichloroquinoline and 300 g. of phenol was heated in an oil-bath to 170° in a three-necked flask equipped with a stirrer, reflux condenser, thermometer and gas inlet tube. Dry ammonia was then passed through the mixture at 170–175° for six hours. At the start a solid separated which went into solution as the reaction proceeded. The cooled solution was poured into 10% sodium hydroxide solution, yielding crude 4-amino-7-chloroquinoline as a tan solid. Solid carbon dioxide was added to the solution of the crude material in moist ether (1 liter) until no further precipitation of the amine carbonate occurred. The carbonate was filtered and dissolved in hot 10% hydrochloric acid from which the hydrochloride separated on cooling. This was decomposed with 10% sodium hydroxide yielding 52% of 4-amino-7-chloroquinoline melting at 150–151°.

4-Amino-6-methoxyquinoline (a).—This was prepared by exactly the same procedure as was used for the synthesis of 4-amino-7-chloroquinoline. The substance melted at 119–120° after recrystallization from benzene and showed no depression in melting point when mixed with a sample prepared by degradation of quininic acid.

(b) **From Quininic Acid Amide.**—The procedure of Hirsch[6] has been improved by the use of dioxane as solvent. To a well-stirred mixture of 25 g. of quininic acid amide (m. p. 197°), 104 ml. of pure dioxane, 5 g. of sodium hydroxide and 50 ml. of water at 25–30° was added dropwise a solution of 20.5 g. of bromine in 25.6 g. of sodium hydroxide and 120 ml. of water. Stirring was continued for fifteen minutes, when solution was substantially complete. The mixture was then heated at 85° for an hour. The two-phase mixture was concentrated to about one-fourth its volume, cooled in ice and the precipitate filtered off. The crude tan product was crystallized from water, yielding 68% of 4-amino-6-methoxyquinoline melt-

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

(2) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(3) Steck, Hallock and Holland, *ibid.*, **68**, 129, 132 (1946); Surrey and Hammer, *ibid.*, **68**, 113 (1946), where a good review of previous work is found.

(4) Andersag, Breitner and Jung, U. S. Patent 2,233,970, *C. A.*, **35**, 3771 (1941).

(5) Backeberg, *J. Chem. Soc.*, 1083 (1938).

(6) Hirsch, *Monatsh.*, **17**, 327 (1896).

(7) All melting points are corrected.

(8) Microanalyses by Mr. William Saschek and Miss Lois May.