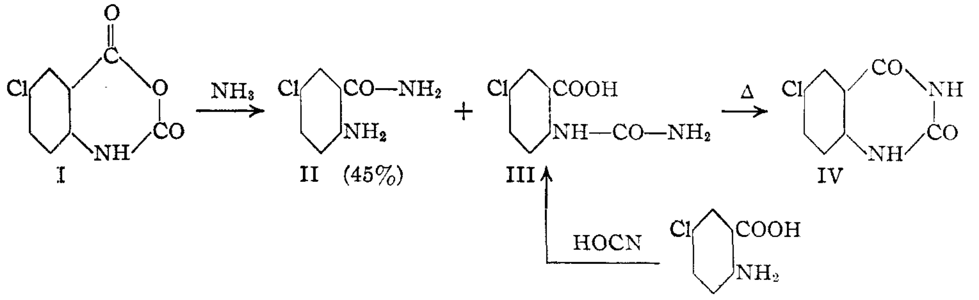
[Contribution from the Venable Chemical Laboratory of the University of North Carolina]

6-(and 7-)-Chloro-4-(1-diethylamino-4-pentylamino)-2-(*p*-methoxyphenyl)-quinazoline Dihydrochlorides

By R. L. McKee,[1] M. K. McKee and R. W. Bost

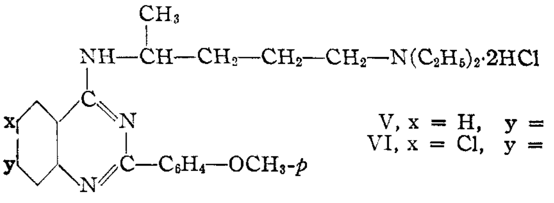
The initial intermediates of this series of reactions were 4-chloro-2-nitrobenzonitrile,[2] prepared in 60% yield from 4-chloro-2-nitroaniline according to the procedure of Bogert and Hand,[3] and 2-amino-5-chlorobenzamide.[4] The latter compound was prepared from 5-chloroanthranilic acid, which was converted into 7-chloroisatoic anhydride[3] (I) by the procedure of Heilbron, Kitchen, Parkes and Sutton,[5] action of ammonia on the anhydride formed the desired amino amide (II), together with 5-chloro-2-ureidobenzoic acid[6] (III). The latter was identified by synthesis and analysis, and its conversion into 6-chlorobenzoyleneurea (IV).



Although the reduction of 4-chloro-2-nitrobenzonitrile by iron and acetic acid results in concurrent hydrolysis to form 2-amino-4-chlorobenzamide,[7] it was found that stannous chloride at room temperature[3] results in a 73% yield of the desired 2-amino-4-chlorobenzonitrile.

The reaction of 2-amino-4-chlorobenzonitrile with *p*-anisoyl chloride in pyridine proceeded somewhat unexpectedly. In a molar ratio of 1:1, two compounds were isolated (in addition to unreacted aminochloronitrile), one melting at 216–217°, and one melting at 169–170°. Analyses indicated that the higher melting compound was a di-anisoyl derivative, while the lower melting compound was the expected mono-anisoyl product. In an amine acid-chloride ratio of 1:2, the above two products were found in about equal amounts, together with unreacted anisoyl chloride. Both of these products, together with a large amount of a mixture of the two, were found to hydrolyze and undergo ring closure in the presence of alkali and hydrogen peroxide[8] to form 7-chloro-2-(*p*-methoxyphenyl)-4-quinazolone.

This quinazolone was converted by phosphorus pentachloride[9] into the corresponding 4-chloroquinazoline, which without isolation was allowed to react with 1-diethylamino-4-aminopentane to form 7-chloro-4-(1-diethylamino-4-pentylamino)-2-(*p*-methoxyphenyl)-quinazoline dihydrochloride (V).



V, x = H, y = Cl
VI, x = Cl, y = H

2-Amino-5-chlorobenzamide (II) was allowed to react with *p*-anisoyl chloride, and the product was heated with alkali to effect ring closure[11] to 6-chloro-2-(*p*-methoxyphenyl)-4-quinazolone. This quinazolone was converted as in the case of the 7-chloro isomer, into 6-chloro-4-(1-diethylamino-4-pentylamino)-2-(*p*-methoxyphenyl)-quinazoline dihydrochloride (VI).

Experimental

2-Amino-4-chlorobenzonitrile.—4-Chloro-2-nitrobenzonitrile (54.5 g., 0.297 mole) was added slowly and with stirring to 220 g. (0.97 mole) of stannous chloride dissolved in 185 cc. of concentrated hydrochloric acid and 50 cc. of acetic acid, the temperature being kept between 25–30°. The mixture was allowed to stand at room temperature overnight, then thoroughly chilled and filtered. The precipitate was transferred to a beaker and made strongly alkaline (sodium hydroxide). The resulting precipitate was filtered and washed with water. After crystallization from benzene and petroleum ether, 33 g. (73% of the theoretical) of a white product melting at 161–162° was obtained.

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(1) The Wm. S. Merrell Co., Postdoctoral Fellow.

(2) Claus and Kurz, *J. prakt. Chem.*, [2] **37**, 196 (1888).

(3) Bogert and Hand, This Journal, **24**, 1031 (1902).

(4) Dorsch, *J. prakt. Chem.*, [2] **33**, 50 (1886).

(5) Heilbron, Kitchen, Parkes and Sutton, *J. Chem. Soc.*, **127**, 2171 (1925).

(6) Sheibley, *J. Org. Chem.*, **3**, 414 (1939), has proved that, contrary to the report of Dorsch (ref. 4), 5,7-dichloroisatoic anhydride is converted by ammonia into 6,8-dichlorobenzoyleneurea. In the light of this report and of our findings, it appears that the products obtained on cleavage of isatoic anhydrides may be chiefly influenced by substituents in the aromatic part of the molecule.

(7) Hunn, This Journal, **45**, 1024 (1923).

(8) Bogert and Hand, *ibid.*, **25**, 935 (1903).

(9) Marr and Bogert, *ibid.*, **57**, 729 (1935).

(10) Weddige, *J. prakt. Chem.*, [2] **36**, 143 (1887).

Anal. Calcd. for $C_7H_5ClN_2$: N, 18.44. Found: N, 18.34.

Reaction of 2-Amino-4-chlorobenzonitrile with *p*-Anisoyl Chloride. 7-Chloro-2-(*p*-methoxyphenyl)-4-quinazolone.—2-Amino-4-chlorobenzonitrile (17.5 g., 0.115 mole) was dissolved in 50 cc. of dry pyridine and 41.3 g. (0.24 mole) of *p*-anisoyl chloride was added dropwise with stirring and cooling (ice). This mixture was diluted with water to one liter, filtered and the filtrate discarded. The gummy precipitate was stirred up under 100 cc. of warm acetone, 50 cc. of 20% sodium hydroxide was stirred in and the mixture was immediately diluted to one liter, chilled and filtered. The filtrate, after adding acetic acid and sodium hydroxide until just alkaline to phenolphthalein, slowly deposited a white crystalline precipitate (the mono-anisoyl derivative) which was removed and recrystallized from alcohol to yield 4.5 g. of a product melting at 169–170°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: N, 9.77. Found: N, 9.78.

The solid residue from the treatment with acetone and alkali was refluxed under 75 cc. of acetone–50 cc. methyl alcohol, leaving a 6-g. residue melting at 210–215°; the filtrate gave on concentration and chilling 31 g. of material melting from 135 to 152°, assumed to be a mixture of anisoylation products.

The fraction melting at 210–215° was recrystallized from dioxane to a constant melting point of 216–217°.

Anal. Calcd. for $C_{23}H_{17}ClN_2O_4$: N, 6.67. Found: N, 6.59.

The above two compounds and the mixture were treated individually and in the same manner with alkali and hydrogen peroxide as follows: Each sample was refluxed for one hour in eight times its weight of 5% sodium hydroxide containing twice its weight of dioxane and twice its weight of 30% hydrogen peroxide. The resulting solutions were diluted with water, acidified with acetic acid, and made alkaline with ammonium hydroxide. The quinazolone precipitated and was filtered. Due to its insolubility, it was purified by refluxing under acetone, filtering hot, and washing with acetone. The materials obtained from all three sources were identical and consisted, when combined, of 19.7 g. (59% of the theoretical based on the 2-amino-4-chlorobenzonitrile) of a fine white powder melting at 310–312° (dec.).

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: N, 9.77. Found: N, 9.99, 9.71.

7-Chloro-4-(1-diethylamino-4-pentylamino)-2-(*p*-methoxyphenyl)-quinazoline Dihydrochloride (V).—The above quinazolone (10.5 g., 0.037 mole) and 7.6 g. (0.037 mole) of phosphorus pentachloride were refluxed in 50 cc. of freshly distilled phosphorus oxychloride for forty hours. Dry xylene (35 cc.) was added and 60 cc. of solvent was removed by distillation, after which 21 g. (0.13 mole) of 1-diethylamino-4-aminopentane was added and refluxed for four hours. This was then treated with 200 cc. of water containing 50 cc. of concentrated hydrochloric acid, and the small amount of xylene was separated from the aqueous layer while still hot and discarded. The acidic solution was warmed, treated with norite and chilled. The pasty white solid was filtered, dried and recrystallized to constant melting point from absolute alcohol and ether, giving 16.7 g. (91% yield based on the quinazolone) of a fine white powder melting at 233–235° with evolution of gas. This material was found to be quite water soluble but is precipitated by the addition of even a small amount of hydrochloric acid.

Anal. Calcd. for $C_{24}H_{31}ClN_4O{\cdot}2HCl$: N, 11.21; Cl^-, 14.19. Found: N, 11.00; Cl^-, 14.10.

Interaction of 7-Chloroisatoic Anhydride with Ammonia.—Twenty grams (0.109 mole) of 7-chloroisatoic anhydride[4] (I) was refluxed in 100 cc. of concentrated ammonium hydroxide for one hour, chilled and filtered. The solid was heated with acetone and filtered from a small residue (about 0.5 g. of material of unknown composition melting at 215°). From the acetone solution 2-amino-5-chlorobenzamide[4] (II) crystallized and, after recrystallization from hot water, melted at 169–171°. The yield was 8.5 g. (45% of the theoretical).

The aqueous ammoniacal filtrate from above was neutralized with dilute acetic acid, chilled, and the resulting white crystalline material was filtered and recrystallized from alcohol–water. Due to its appreciable water solubility, only 4.0 g. was obtained in a pure state after recrystallization. This material melts sharply at 184–185° and resolidifies immediatley, remelting again at 306–315°. The solubility and melting point behavior indicated that this material probably was 5-chloro-2-ureidobenzoic acid (III). This was confirmed by melting and mixed melting comparisons with the product obtained from 5-chloroanthranilic acid and potassium cyanate under the experimental conditions of Walther and Wlodlowski.[11]

Anal. Calcd. for $C_8H_7ClN_2O_3$: N, 13.06. Found: N, 12.73.

On heating the ureido acid (III) to 200° for ten minutes, the corresponding 6-chlorobenzoyleneurea (IV) was obtained. After recrystallization from alcohol, in which it is only sparingly soluble, it melts at 321–324°.

Anal. Calcd. Calcd. for $C_8H_5ClN_2O$: N, 14.25. Found: N, 14.23.

6-Chloro-2-(*p*-methoxyphenyl)-4-quinazolone.—2-Amino-5-chlorobenzamide (8.5 g., 0.050 mole) was dissolved in 25 cc. of dry pyridine, and 11 g. (0.064 mole) of *p*-anisoyl chloride was added slowly. After heating on a steam-bath for four hours, water was added together with sufficient hydrochloric acid to neutralize the pyridine, and the solid was filtered. This precipitate was suspended in 200 cc. of 5% sodium hydroxide and 25 cc. of dioxane and refluxed until solution was complete (about one hour). This solution was made acid with acetic acid and then alkaline with ammonium hydroxide, and the solid filtered and washed. Because of its sparingly soluble nature, purification was achieved by boiling under acetone, filtering hot and washing with hot acetone. The product thus obtained weighed 12 g. (84%) and melted without decomposition at 289–290°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: N, 9.77. Found: N, 9.99.

2-(*p*-Methoxyphenyl)-4-(1-diethylamino-4-pentylamino)-6-chloroquinazoline Dihydrochloride (VI).—Thirteen grams (0.045 mole) of the above quinazolone was refluxed with 9.4 g. (0.045 mole) of phosphorus pentachloride in 50 cc. of freshly distilled phosphorus oxychloride for twenty hours. After removal of 35 cc. of the solvent by distillation, 35 cc. of dry xylene was added, and the resulting solution was distilled as dry as possible under diminished pressure (water pump). To the residue, a mass of pale yellow crystals, 10.8 g. (0.068 mole) of 1-diethylamino-4-aminopentane was added and the mixture allowed to reflux for six hours. This product was steam distilled until its odor indicated that it was free of xylene, acidified (litmus) with hydrochloric acid, treated with norite while hot, and chilled. The precipitate was filtered, and the filtrate concentrated to about 700 cc. and chilled in an unsuccessful effort to obtain additional product.[12] The solution was made alkaline, and the free base was filtered, washed with water and dried. This was converted into the dihydrochloride (in benzene with dry hydrogen chloride) and combined with the material obtained above from the aqueous solution. Recrystallization was carried out from a mixture of methyl alcohol and acetone, resulting in the formation of 11 g. (57% of the theoretical) of a white powder melting with evolution of gas at 261–263°. (An additional 4.0 g. of material was isolated from the alcohol–acetone filtrates which melted at 256–259° with decomposition.)

Anal. Calcd. for $C_{24}H_{31}ClN_4O{\cdot}2HCl$: N, 11.21. Found: N, 11.22.

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[11] Walther and Wlodlowski, *J. prakt. Chem.*, [2] **59**, 273 (1899).

[12] At this point, the solution was very viscous when hot and turned to a jelly when chilled. Later work showed that a solution containing 1 g. of the dihydrochloride in as much as 70–75 cc. of water was rather viscous hot and tended to jell on cooling.

Acknowledgment.—The authors wish to express their appreciation to The Wm. S. Merrell Company through whose generous support this work was carried out.

Summary

1. 2-Nitro-4-chlorobenzonitrile has been reduced to the corresponding amino nitrile.
2. The cleavage of 5-chloroisatoic anhydride by ammonia has been more fully investigated.
3. From these intermediates, two new basically substituted quinazolines have been prepared.

CHAPEL HILL, NORTH CAROLINA

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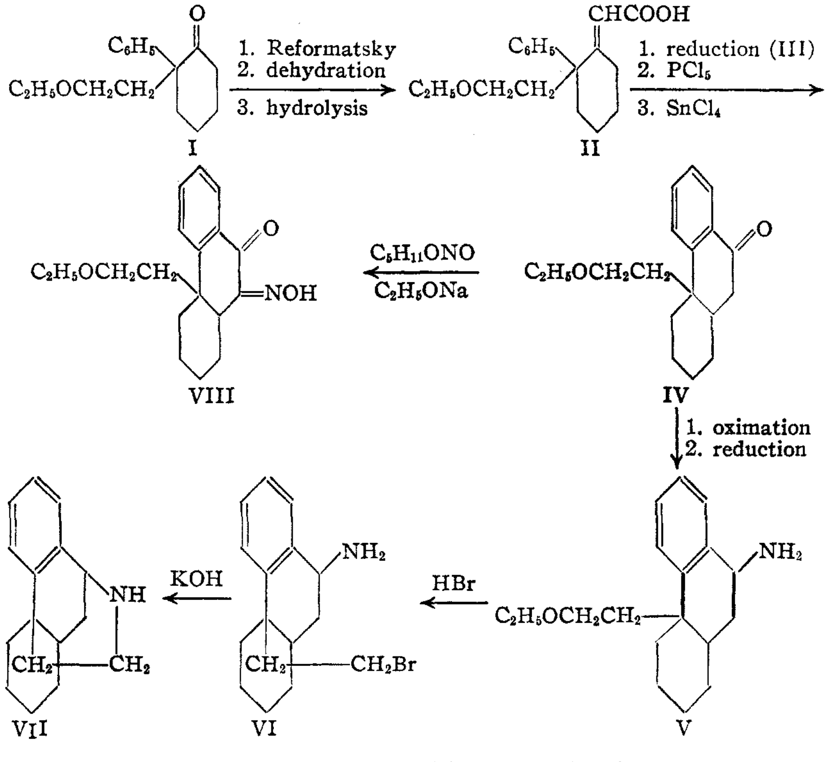
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Hydroaromatic Compounds Containing Angular Groups. III. 9,4a(2)-Iminoethanohydrophenanthrene Series[1]

BY MELVIN S. NEWMAN AND BARNEY J. MAGERLEIN[2]



The present work was undertaken with the object of exploring methods for the synthesis of heterocyclic compounds similar to those found in morphine and related alkaloids. Although this work is only partially completed, it seems worth while to present the results obtained to date. Evidence is given for the successful synthesis of 1,3,4,9,10,10a - hexahydro - 9,4a(2) - iminoethanophenanthrene,[3] although it was not isolated in a pure state. A lack of material prevented further work at this stage. We have also made some progress as indicated by formula VIII toward the synthesis of 1,3,4,9,10,10a-hexahydro-10,4a(2)-iminoethanophenanthrene which contains a ring system more nearly analogous to that of morphine.

The synthetic scheme follows closely along the lines previously developed[4] and is outlined in the chart.

The work was made difficult by the fact that none of the compounds was obtained in a crystalline form. For the most part they were fairly viscous oily mixtures of stereoisomers. In the case of ketones I and IV crystalline semicarbazones were obtained. A small amount of a crystalline oxime of IV was also isolated but the regenerated ketones failed to crystallize.

Accurate molecular models show that the ring closure involved in proceeding from VI to VII is possible with only two of the four possible inactive isomers of VI. Isomers incapable of cyclization might either polymerize or dehydrobrominate to yield a primary 12-vinylamine isomeric with the desired secondary amine, VII.

The monomolecular product we obtained in very small yield was not sufficient for further work. The analysis for carbon, hydrogen, and nitrogen agreed with the theoretical values for VII. However, a Van Slyke amino nitrogen determination[5]

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(1) The material herein presented was taken from the Ph.D. Thesis of Barney J. Magerlein, Ohio State University, June, 1946.

(2) The authors wish to take this opportunity to acknowledge with thanks a grant-in-aid from a special fund donated by the Ohio State University Research Foundation and administrated by the Graduate School.

(3) The nomenclature is consistent with that used by *Chemical Abstracts*. The parent substance is 9,4a(2)-iminoethanophenanthrene, a 2,4a-dihydrophenanthrene derivative. The number 9 comes first to indicate the position of the nitrogen linkage of the bridge.

(4) M. S. Newman and M. D. Farbman, THIS JOURNAL, **66**, 1550 (1944), article I, this series.

(5) We wish to thank Drs. D. D. Van Slyke and Paul B. Hamilton of the Rockefeller Institute for Medical Research for this analysis.