Acknowledgments.—The authors are grateful to Parke Davis and Company for arranging for the biological tests, the results of which will be reported in detail elsewhere. In addition to the general results mentioned previously, the following data include some of the intermediates examined for antimalarial activity in avian infections: 4-chloro-6-methoxy-2-phenylquinoline, 2-(2′-methoxyphenyl)-quinoline hydrochloride, 6-methoxy-2-(4′-chlorophenyl)-quinoline, 6-methoxy-2-(4′-chlorophenyl)-quinoline-N-oxide, 4-chloro-6-methoxy-2-(4′-chlorophenyl)-quinoline, 6-methoxy-2-(3′-chlorophenyl)-quinoline, 6-methoxy-2-(3′-chlorophenyl)-quinoline-N-oxide, and 4-chloro-6-methoxy-2-(3′-chlorophenyl)-quinoline were inactive; and 4-chloro-2-(2′-methoxyphenyl)-quinoline was of doubtful activity.

Summary

Four α-aryl-γ-chloroquinolines have been conveniently prepared through a three-step sequence of reactions involving: (1) RLi addition to the anil linkage; (2) N-oxide formation of the anil addition product; and (3) halogenation of the latter with phosphorus oxychloride. Condensation of these variously substituted γ-chloroquinolines with 1-diethylamino-4-aminopentane resulted in a series of compounds having essentially the functional groups of the more highly fused atabrine.

Antimalarial activity in avian malaria was shown by 6-methoxy-2-(3′-chlorophenyl)-4-[(α-methyl - δ - diethylaminobutyl) - amino] - quinoline, and by the isomeric (4′-chlorophenyl) compound. The presence of chlorine is not a necessary condition for activity, for 6-methoxy-2-(phenyl) - 4 - [(α - methyl - δ - diethylaminobutyl) - amine]-quinoline is also active. However, the position of the methoxy group (in the chlorine-free type) is important, because 2-(2′-methoxyphenyl) - 4 - [(α - methyl - δ - diethylaminobutyl)-amino-quinoline, unlike the 6-methoxy isomer, is inactive.

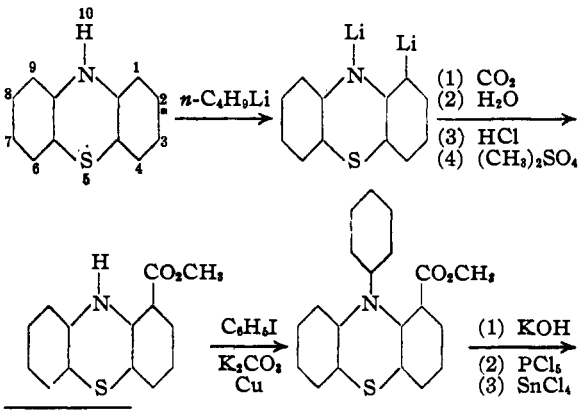
AMES, IOWA RECEIVED JANUARY 3, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Metalation of Phenothiazine[1]

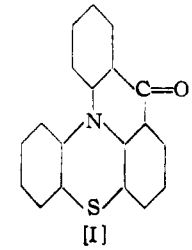
BY HENRY GILMAN, DAVID A. SHIRLEY AND PAUL R. VAN ESS

Phenothiazine is mono-metalated by *n*-butyllithium to give an RLi compound which, subsequent to carbonation, yields a mono-carboxylic acid. On the basis of earlier studies on metalations,[2] it appeared probable that metalation occurred in the 1- or the 4-position. After some unsuccessful attempts to prepare 1-carboxyphenothiazine by ring closure reactions, the acid obtained by metalation was shown to have the carboxyl group in the 1-position by the following indirect proof.



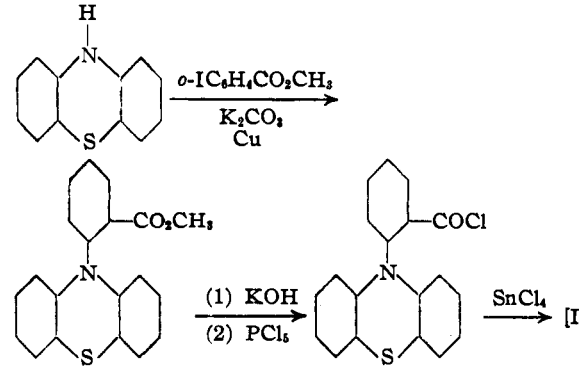
(1) Paper LIV in the series: "The Relative Reactivities of Organometallic Compounds"; the preceding paper is in THIS JOURNAL, 65, 1729 (1943).

(2) See p. 536 of Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943.



[I]

The identity of 9-quino(3,2,1-kl)phenothiazinone [I] prepared by the above sequence of reactions was established by comparison with the product obtained by the following transformations



The metalation of phenothiazine by *n*-butyllithium in the 1-position is of interest for two reasons. First, all previously described nuclear

substitution reactions of phenothiazine take place in the 3-position, or para to the nitrogen. This is an additional[2] illustration of the applicability of metalation in making available positions otherwise inaccessible by the more common nuclear substitution reactions. Second, in view of a subsequent observation, one might have expected metalation to be ortho to sulfur rather than ortho to nitrogen. In a reaction[3] in which molar equivalents of N-ethylcarbazole and dibenzothiophene were allowed to compete for one molar equivalent of *n*-butyllithium, the dibenzothiophene was metalated exclusively.

It should be mentioned that exceptions to the rule of metalation by *n*-butyllithium of an ortho-position to a hetero element are methyl phenyl sulfide,[4a] triphenylamine,[4b] and the closely related triphenylarsine[4c] and triphenylphosphine.[4d]

Experimental

Metalation of Phenothiazine.—To 800 ml. of an ethereal solution of *n*-butyllithium, prepared from 104 g. (0.76 mole) of *n*-butyl bromide and 20 g. (2.9 g. atoms) of lithium was added slowly with stirring 40 g. (0.20 mole) of phenothiazine.[5] The mixture was stirred at room temperature under an atmosphere of dry nitrogen for twenty hours, and then allowed to stand an additional fifteen hours before pouring jetwise on a slurry of ether and excess crushed solid carbon dioxide. The mixture was allowed to stand until all solid carbon dioxide had disappeared, and was then hydrolyzed by the addition of excess water. The aqueous layer was separated, and the aqueous extracts were acidified with hydrochloric acid to precipitate 32 g. of crude acid. This solid was dissolved in a minimal amount of 10% sodium hydroxide solution, and then 40% sodium hydroxide was added until precipitation of the sodium salt was complete. This sodium salt was filtered off, dissolved in water, and the solution acidified with hydrochloric acid to precipitate 25 g. (52%) of pure 1-carboxyphenothiazine which melted at 264–264.5°. The compound can be crystallized from 70% ethanol.

Anal. Calcd. for $C_{13}H_9O_2NS$: N, 5.76. Found: N, 6.01.

The 1-carbomethoxyphenothiazine, melting at 113–113.5°, was obtained in a 32% yield by the action of dimethyl sulfate on an alkaline solution of the acid.

1-Carbomethoxy-10-phenylphenothiazine.—Four grams (0.016 mole) of 1-carbomethoxyphenothiazine, 100 g. of iodobenzene, 20 g. of finely ground anhydrous potassium carbonate, and 2.5 g. of copper bronze were stirred and refluxed for twelve hours. The mixture was filtered hot, and the filtrate was steam distilled to remove unreacted iodobenzene. The residue from steam distillation was recrystallized twice from petroleum ether (b. p. 80–110°) to give 3.2 g. (60%) of 1-carbomethoxy-10-phenylphenothiazine melting at 123.5–124.5°.

Anal. Calcd. for $C_{20}H_{15}O_2NS$: N, 4.20. Found: N, 4.40.

9-Quino(3,2,1-*kl*)phenothiazinone.[6]—To a suspension of 1.5 g. (0.0047 mole) of 1-carboxy-10-phenylphenothiazine in 60 ml. of dry xylene was added 1.4 g. (0.0067 mole) of phosphorus pentachloride, and the mixture was stirred at room temperature for ten minutes to give a clear yellow-brown solution. The solution was cooled in an ice-bath, and a solution of 6.25 g. (0.024 mole) of anhydrous stannic chloride in 20 ml. of xylene was added dropwise to the stirred solution over a period of ten minutes. The stirring was continued for forty-five minutes after the addition had been completed. The dark red mixture was hydrolyzed by the dropwise addition of 25 ml. of cold concentrated hydrochloric acid followed by 30 ml. of water. The yellow xylene layer was separated, washed with dilute sodium carbonate solution to remove acid, and evaporated to dryness to yield a yellow solid. This solid was recrystallized from a mixture of benzene–petroleum ether (b. p. 80–110°) to give 1.2 g. (85%) of bright yellow-green minute crystals. The ketone melted at 218–219°.

Anal. Calcd. for $C_{19}H_{11}ONS$: N, 4.64; mol. wt., 301. Found: N, 4.55; mol. wt. (benzene, cryoscopic), 300.

10-(2′-Carbomethoxy)-phenylphenothiazine.—A mixture of 13.2 g. (0.05 mole) of methyl *o*-iodobenzoate, 10 g. (0.05 mole) of phenothiazine, 6 ml. of nitrobenzene, 7.5 g. of potassium carbonate, 85 ml. of xylene, and 0.2 g. of copper bronze was stirred and refluxed for fourteen hours. The mixture was filtered hot and washed with boiling xylene. Upon cooling, green crystals were precipitated from the xylene solution. Recrystallization from xylene gave 7.0 g. (42%) of light green prisms melting at 143–144°.

Anal. Calcd. for $C_{20}H_{15}O_2NS$: N, 4.20. Found: N, 4.32.

10-(2′-Carboxy)-phenylphenothiazine.—A suspension of 6.5 g. (0.020 mole) of 10-(2′-carbomethoxy)-phenylphenothiazine in 125 ml. of 15% aqueous potassium hydroxide was refluxed for five hours. The resulting solution was diluted with water and acidified with hydrochloric acid to give a quantitative yield of acidic product melting at 209–210°. One recrystallization from glacial acetic acid gave red-yellow plates melting at 214–215°.

Anal. Calcd. for $C_{19}H_{13}O_2NS$: N, 4.38; neut. equiv., 319. Found: N, 4.60; neut. equiv., 320 and 313.

Ring Closure of 10-(2′-Carboxy)-phenylphenothiazine to 9-Quino(3,2,1-*kl*)phenothiazinone.—One and five-tenths grams (0.0047 mole) of 10-(2′-carboxy)-phenylphenothiazine was treated with phosphorus pentachloride and anhydrous stannic chloride in xylene by the procedure described previously. The product weighed 0.85 g. (60%) and melted at 219°. A mixed m. p. with the compound obtained from the metalation-acid showed no depression.

Attempted Ring Closures. [A] 2-Carboethoxydiphenylamine.—This reaction involved heating 2-carboethoxydiphenylamine with sulfur as a means of preparing 1-carboethoxyphenothiazine. First, 2-carboxydiphenylamine was prepared in 86% yield in essential accordance with the directions of Ullmann and Dieterle.[7] The negative results of Schroeter and Eisleb[8] in the attempted esterification of the acid may have been due to an insufficient time of reaction. A solution of 40 g. (0.188 mole) of 2-carboxydiphenylamine in 200 ml. of absolute ethanol was saturated with hydrogen chloride and refluxed for two hours. The solution was cooled and again saturated. The mixture was allowed to stand fourteen hours and then was refluxed for an additional five hours, during which a slow stream of hydrogen chloride was passed over the surface. The oil obtained after pouring on ice was extracted with 10% sodium carbonate solution, and then with a saturated calcium chloride solution. After drying over sodium sulfate, the ester was distilled at 184–187° (6 mm.). The yield of yellow oil was 33 g. (80%), and 5 g. of acid was recovered.

Anal. Calcd. for $C_{15}H_{15}O_2N$: N, 5.81. Found: N, 6.07.

A small quantity of the oil was hydrolyzed by alcoholic potassium hydroxide to give 2-carboxydiphenylamine (mixed m. p.).

A solution of 4.26 g. (0.02 mole) of 2-carboxydiphenyl-

(3) Unpublished studies by C. G. Stuckwisch.

(4) (a) Gilman and Webb, THIS JOURNAL, **62**, 987 (1940); (b) Gilman and Brown, *ibid.*, **62**, 3208 (1940); (c) Gilman and Stuckwisch, *ibid.*, **63**, 3532 (1941); (d) G. E. Brown, Doctoral Dissertation, Iowa State College (1941).

(5) Knoevenagel, *J. prakt. Chem.*, **89**, 1 (1913).

(6) This nomenclature was recommended by Drs. E. J. Crane and L. T. Capell,

(7) Ullmann and Dieterle, *Ann.*, **355**, 322 (1907).

(8) Schroeter and Eisleb, *ibid.*, **367**, 144 (1909).

amine, 1.28 g. (0.04 g. atom) of sulfur, and 0.04 g. of iodine in 20 ml. of *o*-dichlorobenzene was refluxed at 180° for fifteen minutes. The acid is unstable under these conditions for carbon dioxide as well as hydrogen sulfide was evolved. The reaction mixture yielded 2.2 g. of the acid.

In another experiment, 4.82 g. (0.02 mole) of 2-carboethoxydiphenylamine and 1.28 g. of sulfur was heated without solvent in a bath at 285–300°. Hydrogen sulfide was evolved slowly at first, and then the odor of ethyl mercaptan was quite pronounced. Heating was discontinued after two hours, when the evolution of gas had ceased. The products isolated were 1.5 g. of the ester initially used, 0.2 g. of phenothiazine, but no phenothiazine-ester. The phenothiazine is probably formed as a consequence of pyrolysis of the ester, or decarboxylation of the acid (formed by cleavage of the ester) to give diphenylamine which then reacts with sulfur in the usual manner.

[B] Coupling Reactions with 2,2'-Diaminodiphenyl Disulfide.—One of these coupling reactions was patterned after the method used by Kehrmann and Nossenko[9] for the preparation of 1-nitrophenothiazine. A solution of 2,2'-diaminodiphenyl disulfide,[10] 2-bromo-3-nitrobenzoic acid,[11] and of sodium acetate in ethanol was refluxed for twenty-four hours. The diamine and acid were recovered.

A second coupling reaction was a modification of a procedure by Ullmann and Hoz.[12] A mixture of 2,2'-diaminodiphenyl disulfide, potassium *o*-chlorobenzoate, sodium acetate, amyl alcohol, and a trace of copper bronze was refluxed for two hours. The diamine and *o*-chlorobenzoic acid were recovered.

Summary

Phenothiazine is metalated by *n*-butyllithium in the 1-position or ortho to the nitrogen. The structure of the 1-carboxyphenothiazine, obtained by carbonation of the metalation product, was established indirectly by cyclization reactions.

(9) Kehrmann and Nossenko, *Ber.*, **46**, 2809 (1913).

(10) Teppema and Sebrell, THIS JOURNAL, **49**, 1751 (1927).

(11) Culhane, "Organic Syntheses," Coll. Vol. I, 125 (1941).

(12) Ullmann and Hoz, *Ann.*, **355**, 352 (1907).

AMES, IOWA RECEIVED JANUARY 17, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY NO. 296]

A Large-Scale Preparation of D-Altrose. D-Altrose Oxime and its Rate of Mutarotation[1]

BY ROBERT C. HOCKETT AND LEONARD B. CHANDLER[2]

In 1926, Kunz and Hudson,[3] by the action of aluminum chloride on a chloroform solution of octaäcetyl β-lactose, obtained the "acetochloro" derivative of a new disaccharide which they named neolactose, and which was proved to be a D-galactosyl-D-altrose. Richtmyer and Hudson[4] later improved this preparation by using phosphorus pentachloride along with aluminum chloride, isolated crystalline neolactose and a number of its derivatives, and showed how crystalline D-altrose may be obtained from the disaccharide despite the tendency of this hexose to form an anhydride when it is treated with hydrochloric acid.

When a sample of D-altrose was needed in this Laboratory, we undertook to repeat the preparation described by these authors, both on a much increased scale and with the introduction of short-cuts to eliminate a number of manipulations.

The chief modification was as follows: "α-aceto-chloroneolactose" formed from octaäcetyl lactose but not isolated, was subjected directly to hydrolysis by hydrochloric acid in a water–acetone solution under such conditions as to (1) hydrolyze the chlorine, (2) to remove the acetate groups, and (3) to break the disaccharide link all in a single operation yielding a mixture containing hydrochloric acid, acetic acid, glucose, galactose, altrose and altrosan. Hydrochloric acid was removed with lead carbonate followed by silver carbonate, metallic ions by hydrogen sulfide, acetic acid by distillation, and glucose and galactose by yeast fermentation. Finally, altrose and altrosan were recovered as D-altrose dibenzyl mercaptal as described by Richtmyer and Hudson.[4] From this derivative the crystalline sugar was obtained without seed, as described by Richtmyer and Hudson.[4]

The over-all yield from one kilogram of D-lactose monohydrate was 18 g. of crystalline D-altrose or 3.7% of the theoretical. A more efficient method of preparation of this sugar from α-methyl-D-glucoside was subsequently described by Richtmyer and Hudson.[5]

The oxime of D-altrose and measurements of the rate of mutarotation of this derivative in aqueous solution are described for the first time.

We wish to thank Doctors Hudson and Richtmyer, with whom we made arrangements in connection with this work.

Experimental

D-Altrose Oxime.—Two grams (0.0111 mole) of crystalline altrose was treated with 0.0282 mole of hydroxylamine in methanol at room temperature overnight. After a brief warming on the steam-bath, the solution was concentrated to a colorless sirup (diminished pressure) which was dissolved in a minimum volume of dry methanol. Absolute ethanol was added to turbidity and the solution soon deposited 1.7 g. of fine prisms. Recrystallized by dissolving in 10 cc. of water, filtering, concentrating to a sirup and repeating the process described above, the compound was obtained with a maximum melting point of 143–144° and a

(1) This paper is taken from a thesis submitted by Leonard B. Chandler to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in October, 1939.

(2) Present address: Nylon Division, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

(3) Kunz and Hudson, THIS JOURNAL, **48**, 1978, 2435 (1926).

(4) Richtmyer and Hudson, *ibid.*, **57**, 1716 (1935).

(5) Richtmyer and Hudson, *ibid.*, **63**, 1729 (1941).