SOME REDUCTION PRODUCTS OF QUINAZOLINE AND SOME QUINAZOLINE ALKALOIDS

A DISSERTATION

Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
in the Faculty of Pure Science,
of Columbia University

BY

ELEANOR B. MARR

NEW YORK CITY
1935

TABLE OF CONTENTS

and third crops obtained by evaporation and subsequent cooling totaled 1.4 g. of crystals of M. P. 206-208° C. which were purified by recrystallization from ethyl alcohol and found to be identical with the product obtained by the sodium amalgam reduction. Probably the reason for only a part of the styryl hydrogenating was one of solubility, for it is very insoluble in cold alcohol and the reduction product is only moderately so.

2-Phenethyl-4-chloroquinazoline (II_6)

Ground 2 g. of 2-phenethyl-4-quinazolone, dried at 110° C., with 2 g. of phosphorous pentachloride and immediately transferred it to a flask through the reflux condenser which had been sealed on and added 20 cc. of phosphorous oxychloride. Heated the mixture in an oil bath at 115° C. 15 hours. A calcium chloride tube on the reflux was used to protect it from moisture in the air. The quinazolone gradually formed a clear yellow solution, which darkened somewhat before the end of the heating period. Cooled the solution, poured it into 600 g. of pulverized ice with stirring, immediately extracted with ether. The ether solution was washed once with dilute sodium carbonate and then 3 times with water and dried over calcium chloride. Upon distilling off the ether, 1.2 g. of a light yellow oil containing a few crystals were obtained. Treated the oil with cold petroleum ether which did not dissolve the crystals, filtered and washed the crystals and filter with petroleum ether. The crystals were a mixture of the starting material and its hydrochloride. The petroleum ether, upon evaporation, left 1.0 g. of a light yellow oil which gave a marked test for chlorine after a sample was fused with sodium. This substance was used without further purification.

2-Phenethyl-4-methoxyquinazoline (II_7)

The 1.0 g. of 2-phenethyl-4-chloroquinazoline was dissolved in 15 cc. of absolute methyl alcohol in a small Erlenmeyer flask and 10 cc. of absolute methyl alcohol in which 0.2 g. of sodium had dissolved were added. There was a marked precipitate when the two warm solutions were mixed. The flask was stoppered and allowed to stand at room temperature for 2.5 days. Filtered

out the sodium chloride and added 50 cc. of water to the filtrate which caused the ether to separate in small oily drops which crystallized to fine, slightly yellow needles. The yield was 0.75 g. of M. P. 58-59.5° C. The product was very soluble in cold ethyl and methyl alcohol, cold ethyl acetate and cold ligroin. It was recrystallized for analysis from dilute ethyl alcohol (1:1) and dried in vacuum over sulfuric acid to constant weight. The pure crystals are colorless and melt at 58.5-59.8° C. (corr.).

Analysis:

Calculated for $C_{17}H_{16}N_2O$, C = 77.23% H = 6.10%
Found, C = 77.09 H = 5.74

A 0.12 g. portion of this pure ether was heated under reflux for one-half hour with 10 cc. of concentrated hydrochloric acid. It went into solution within 5 minutes, then colorless crystals began to form. Cooled, diluted the mixture with water, filtered, washed and dried the crystals which were identical with 2-phenethyl-4-quinazolone.

Hydrocinnamic acid (III_1)

This was prepared by the Clemmensen reduction of cinnamic acid. Reid and Mitchell [51] mention this as a good method but give no details. Forty-two g. of granulated zinc were allowed to stand in 85 cc. of 5% mercuric chloride solution for one hour in an Erlenmeyer flask. The supernatant liquid was decanted and the amalgam washed once with water by decantation. Then 31 g. of cinnamic acid (M. P. 132-133° C.), and 20 cc. of concentrated hydrochloric acid diluted with 40 cc. of water were added and an adapter carrying a condenser and a mechanical stirrer attached. The mixture was heated under reflux and stirred for 8 hours. At intervals of 1 hour, six 10 cc. portions of concentrated hydrochloric acid were added through the condenser. A total of 80 cc. of concentrated acid was used. When the contents of the flask cooled, an oily layer floated. The mixture was decanted from the zinc amalgam which was washed twice with hot water. These were combined with the mixture of hydrocinnamic and its solution. When this cooled and stood, long colorless needles of hydrocinnamic formed. The crude acid was filtered by suction, washed with water and air dried. Yield was 30.1 g. of M. P.

45-48° C. Purified it by distilling in vacuum at 26 mm. The first fraction of 2.5 g. was not used in subsequent work and not all the material was distilled. The second fraction weighed 19.4 g. and solidified in long, slender, colorless needles which melted at 48-49° C. (corr.). The melting point given in the literature is 48-49° C.

Hydrocinnamoyl chloride (III_2)

Prepared as described by Mohr.[52] Placed 19.1 g. of hydrocinnamic acid in a round bottomed flask and attached a reflux condenser, cooled the flask in ice water and added 24 cc. of thionyl chloride through the condenser. Then warmed the mixture in a water bath at 40-50° C. until the evolution of gas stopped (2¾ hours) and cooled it to room temperature. The solution was poured into a Claisen flask and fractionally distilled in vacuum. The fraction boiling at 125-127.5° C. at 26 mm. weighed 19.3 g. and was an almost colorless liquid. Yield was 90% of the theoretical. Literature gives B. P. 122° C. at 25 mm.

N-Hydrocinnamoyl anthranilic acid (III_3)

13.5 g. of hydrocinnamoyl chloride (0.08M) dissolved in dry ether were added to 21.9 g. (0.16M) of anthranilic acid dissolved in dry ether. The flask was chilled in ice water while the solutions were being mixed. Anthranilic hydrochloride began to precipitate out immediately. The flask was stoppered and allowed to stand at room temperature for 36 hours with frequent shaking. The hydrochloride was filtered out and washed with ether. When the ether was distilled off, 18.4 g. of crude N-hydrocinnamoyl anthranilic acid were obtained which melted at 120-127° C. Recrystallization once from benzene produced 18.0 of light yellow crystals melting at 135-137° C. These are slender prisms soluble in alcohol, benzene, and ethyl acetate but insoluble in water and petroleum ether. The color was removed by treating the alcoholic solution with Norite, filtering and diluting the hot filtrate with water. When the dilute alcohol solution cooled, colorless crystals were obtained. These were purified for analysis by recrystallizing from benzene and from dilute alcohol (1:1). The sample for

analysis was dried to constant weight in a vacuum over sulfuric acid and sodium hydroxide; M. P. 138.7-139.7° C. (corr.).

Analysis:

Calculated from $C_{16}H_{15}NO_3$, C = 71.34% H = 5.62%
Found, C = 71.69 H = 5.59

N-Hydrocinnamoyl anthranil (III_4)

Four grams of N-hydrocinnamoyl anthranilic acid were added slowly to 15 cc. of acetic anhydride heated just to boiling and the resulting solution distilled down to ⅓ its original volume, as in the preparation of acetanthranil. This anil did not crystallize from acetic anhydride and was not isolated.

2-Phenethyl-4-quinazolone (III_5)

The acetic anhydride solution of N-hydrocinnamoyl anthranil, prepared above, was added slowly to 30 cc. of concentrated ammonium hydroxide solution (sp. gr. 0.9) heated just to boiling. After the anil was in solution, 2 cc. of a 10% potassium hydroxide solution were added and the boiling continued for 1 hour. Crystals began to appear in the hot solution at the end of 15 minutes. The mixture was cooled and the crystals filtered out and washed with water and dried. Obtained 2.9 g. of nearly colorless crystals, M. P. 205.5-207° C., which was 97% of the theoretical, calculated from N-hydrocinnamoyl anthranilic acid. Recrystallized for analysis from ethyl alcohol, from ethyl acetate and from dilute alcohol (1:1), and dried to constant weight at 105° C. The crystals were long, silky and colorless and melted at 208.5-209.5° C. (corr.). The mixed melting point with the 2-phenethyl-4-quinazolone obtained by reduction (M. P. 209.5-210.5°) was 209-210°.

Analysis:

Calculated for $C_{16}H_{14}N_2O_2$, C = 76.76% H = 5.64%
Found, C = 76.99 H = 5.68

2-(3′, 4′-Dimethoxystyryl)-4-quinazolone (IV_1)

Heated 8 g. of 2-methyl-4-quinazolone with 8.5 g. of veratraldehyde in a 125 cc. Erlenmeyer flask in an oil bath at 180-185° C.