lution, the potential drifted in a direction opposite to that noted by Oakes and Salisbury and entirely out of the range of any possible hydrogen-ion concentration. Indicator measurements showed that no significant change in Sörensen value had taken place in the solution. However, the electrode had turned bright. Occasionally, "abnormal" potentials, suggesting a change of about 0.05 Sörensen units, have been noted.

Since the method used in almost every case permits the rapid attainment of equilibrium, it might be assumed that the period of the experiment was in no case sufficient to have detected drifts. However, Oakes and Salisbury record a rate of drift which would at once have been detected in the author's apparatus.

With the suspicion that previous observations might have been clouded by a slow and undetected drift where Oakes and Salisbury encountered a rapid one, I have recently set up an outfit not designed for accurate control of liquid-junction potential differences but better adapted for observations over long periods than the shaking electrode vessel. Duplicate vessels were used, holding in one case an electrode of iridium gray on gold-plated platinum and in the other case two electrodes, one of platinum black on gold-plated platinum and the second of palladium black on rhotanium alloy. The drifts over 24 hours were within one millivolt. For the last 18 hours no drift amounting to more than 0.000,05 volt (the limit of the potentiometer's adjustment) was detected. No change in the Sörensen value of the solution was detected with indicators.

I am at a loss to account for the radical difference in my observations and those of Oakes and Salisbury, and must say that after several years' use by others phthalate has not to my knowledge fallen under suspicion in the manner noted by Oakes and Salisbury.

WASHINGTON, D. C. WM. MANSFIELD CLARK

Received Feb. 18, 1922

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

SYNTHESES IN THE CINCHONA SERIES. VII. 5,8-DIAMINODIHYDROQUININE AND 5,8-DIAMINO-6-METHOXYQUINOLINE AND THEIR CONVERSION INTO THE CORRESPONDING AMINOHYDROXY AND DIHYDROXY BASES[1]

BY WALTER A. JACOBS AND MICHAEL HEIDELBERGER

Received July 22, 1921

In a former communication[2] amino-azo dyes prepared from 5-aminodihydroquinine and the analogous 5-amino-6-methoxyquinoline were described. These substances were shown to be easily converted by acids into the corresponding hydroxyazo dyes. By reduction of 8-(*p*-sulfo-

[1] Presented at the Annual Meeting of the American Chemical Society, New York, September, 1921.

[2] THIS JOURNAL, **42**, 2278 (1920).

phenylazo)-dihydroquinine we have now prepared 5,8-diamino-dihydroquinine. The base itself is a yellow amorphous powder which crystallizes with great difficulty and rapidly undergoes alteration on exposure to light and air. Like 5-amino-quinoline, it dissolves in dilute acids to form red solutions and yields crystalline salts of which the vermilion tetrahydrobromide and the brown basic sulfate have been studied.

As in the parent amino-azo dyes, it was not surprising to find the amino group here also easily replaceable by hydroxyl. In fact, this occurs so readily that it was at first found difficult to select conditions for the isolation of the polyacid salts. Lability, however, was not confined to the amino group in Position 5, but was shown also by that in Position 8, for on long standing in the cold or on boiling with 1:1 hydrochloric acid 5,8-dihydroxy-dihydroquinine was formed. This substance was isolated as the beautifully crystalline red dihydrochloride which forms orange-red solutions. The instability of the free base prevented its isolation in crystalline form.

From numerous tests that were made, the impression was gained that the amino group in Position 5 was the more readily replaced and that 8-amino-5-hydroxy-dihydroquinine was formed as an intermediate product. Unfortunately, the isolation of this substance from the reaction mixture was rendered very difficult by its properties. We have, however, obtained indirect evidence of its formation by a parallel study of the effect of acids on diamino-methoxyquinoline as described below. 5-Hydroxy-8-amino-dihydroquinine was, however, obtained directly as a tin double salt by reduction of 5-hydroxy-8-phenylazo-dihydroquinine;[3] but the instability of the free aminophenol and the solubility of its simple salts prevented their isolation and study. Like the preceding compounds, solutions of the latter are orange-red.

By boiling diamino-dihydroquinine with conc. hydrobromic acid, which should demethylate as well as desaminate it, yellow needles of an easily soluble hydrobromide of what is probably the 5,6,8-trihydroxy dihydrobromide were obtained mixed with ammonium bromide, but other work intervened to prevent its further study. We hope to complete this study at a later date, as well as the alkylation of the di- and trihydroxy-dihydroquinines.

Parallel with the above studies, 5,8-diamino-6-methoxyquinoline was prepared from the corresponding sulfo-phenylazo dye. The latter was also converted into the 5-hydroxy-8-phenylazo dye, from which 8-amino-5-hydroxy-6-methoxyquinoline was obtained on reduction. On warming diamino-methoxyquinoline with 10% hydrochloric acid, it was possible to isolate as the main product of the reaction an amino hydroxy compound identical with that of known composition obtained from the above hy-

[3] Ref. 2, p. 2280.

droxyazo dye. From this it is evident that the amino group in Position 5 is more labile than that in Position 8.

Finally, by boiling the diamino compound with stronger hydrochloric acid both amino groups were replaced, with the production of 5,8-dihydroxy-6-methoxyquinoline.

The quinoline compounds proved to be more stable than the dihydroquinine derivatives and were readily obtained in crystalline form.

It was also of interest to determine whether the methoxy group in Position 6 contributed to the lability of these amino groups, since it had been already ascertained in our previous work with the amino-azo dyes that those obtained from 5-aminoquinoline itself were much more resistant to the action of acids than the 6-methoxy compounds. 5,8-Diaminoquinoline proved to be even more resistant than its parent azo dye, since boiling it for many hours with hydrochloric acid resulted in the cleavage of but a trace of ammonia. The substitution of Position 6 in these compounds is therefore a determining factor as regards the replaceability of the amino group by hydroxyl by the action of boiling acids.

A. Derivatives of Dihydroquinine

5,8-Diamino-dihydroquinine.—Sixteen g. of 5-amino-8-(*p*-sulfo-phenylazo)-dihydroquinine[4] were dissolved in 80 cc. of 50% acetic acid and treated with 16 g. of stannous chloride in 50 cc. of 1:1 hydrochloric acid. A gelatinous mass of the tin compound of the unreduced dye was first formed, and this was rapidly dissolved as it was stirred and the reduction proceeded. The mixture warmed considerably and changed to a deep brownish-red solution from which the yellow tin double salt of the diamino compound commenced to separate. The mixture was diluted with water and poured into ice and an excess of alkali, the diamino-dihydroquinine precipitating as yellow flocks. The collected precipitate was washed thoroughly with water, during which the exposed portion darkened perceptibly. Dried in a desiccator it formed a tan colored friable mass. The crude product was dissolved in a small volume of benzene, and the deep brown-olive solution cleared with bone black and filtered as quickly as possible. The deeply colored filtrate was treated with ligroin in amount sufficient to precipitate the product as a brown paste which rapidly hardened to a brittle mass. This was filtered quickly, washed with ligroin and dried in a desiccator containing paraffin, during which it lightened in color to a brown-yellow shade. The yield was 8 g. On exposure to light and air the base gradually darkened. All attempts to crystallize the amorphous substance have proved futile, except in one case in which we observed that during the collection of the base from the benzene and ligroin mixture, the mother liquor slowly deposited more of the substance which appeared under the microscope as minute yellow needles. These possessed all the properties of the former product with the exception of the melting point but, unfortunately, the amount was too small for analysis and its use as seeding material in attempts to crystallize the amorphous base was without result.

The amorphous base darkens above 90°, gradually shrinks together and melts from 125° to 140° with decomposition. The crystalline material, however, melted at 85 to 90° to a dark tar. The amorphous base is easily soluble in the usual organic solvents except ligroin, forming dark brownish-red solutions. In dilute acids it forms deep brown-red solutions which, on standing or more rapidly on heating, no longer give a

[4] Ref. 2, p. 2281.

precipitate of the base when treated with an excess of alkali, but yield solutions which smell strongly of ammonia.

Analyses. Calc. for $C_{20}H_{28}O_2N_4$: C, 67.40; H, 7.86; N, 15.71. Found: C, 68.00; H, 7.82; N, 15.59.

THE TETRAHYDROBROMIDE.—The amino-azo dye was also readily reduced to the diamino base as follows. Five and a half g. of the dye were dissolved in a mixture of 55 cc. of alcohol and 55 cc. of conc. ammonia, and the deep red solution was saturated with hydrogen sulfide. The color changed to a deep yellow-brown and, as the base did not separate, the mixture was poured into a separatory funnel, shaken with ether, and then without removing the ether an excess of ammonia was added and the mixture again shaken. This procedure removed free hydrogen sulfide and avoided the formation of pasty lumps of the base which are difficult to disintegrate and dissolve. After drying the ether extract and concentrating, the base was left as a dark syrup. On dissolving this in a small volume of cold water and sufficient cold hydrobromic acid to make the solution acid to congo red, the addition of sodium bromide accompanied by rubbing caused 5 g. of lustrous golden scales to separate. These were filtered off and washed with acetone, the color changing to an orange-red. A solution of the salt in 12 cc. of warm water was cooled and treated with sufficient strong hydrobromic acid to cause crystallization. The salt separated slowly as vermilion needles and prisms which were air-dried. It is easily soluble in water and in alcohol, forming deep red solutions. The analytical results were not all that could be desired, but with a substance so sensitive to the action of acids and so easily hydrolyzed we were unable to improve upon them.

Analyses. Calc. for $C_{20}H_{28}O_2N_4.4HBr$: N, 8.24; Br, 47.04. Found, air-dry: N, 8.00; Br, 49.29. Salt dried in desiccator over H_2SO_4: N, 8.47; Br, 41.80.

THE SULFATE.—The brown-red ether extract of the base obtained by the reduction of 16 g. of dye by either method was washed with water and then shaken out with 50 cc. of *N* acetic acid. The deep brown-red aqueous layer was filtered rapidly and treated with saturated ammonium sulfate solution. On rubbing, the sulfate crystallized as a yellow-brown powder consisting of microscopic 6-sided polyhedra, while the mother liquor retained dark impurities. The yield was excellent. The salt was washed with ice water and recrystallized in small portions by dissolving it in hot water and adding a little ammonium sulfate solution to the dark yellow-brown solution. When cooled and rubbed the solution deposited the salt as a brown powder consisting of globules or hexagonal crystals which darken rapidly and undergo decomposition. The anhydrous substance darkens above 160° and melts and decomposes at 220–225°.

Although the salt is obtained from an acid solution, it is rather surprising that, judged by analytical data, the substance is a basic sulfate.

In the analysis of the substance, water was determined by drying it over sulfuric acid at room temperature, and sulfur by the Carius method.

Analyses. Calc. for $(C_{20}H_{28}O_2N_4)_2.H_2SO_4.5H_2O$: H_2O, 10.00. Found: H_2O, 10.68. Calc. for $(C_{20}H_{28}O_2N_4)_2.H_2SO_4$: C, 59.22; H, 7.16; N, 13.82; S, 3.96. Found: C, 58.50; H, 7.21; N, 13.87; S, 4.35.

5-Hydroxy-8-amino-dihydroquinine (tin double salt).—Fourteen and a half g. of 5-hydroxy-8-phenylazo-dihydroquinine[3] were dissolved in 100 cc. of alcohol by the addition of a few cubic centimeters of acetic acid, warmed, shaken vigorously and treated as quickly as possible with a warm solution of 18 g. of stannous chloride in 100 cc. of 10% hydrochloric acid. The thick paste which first formed dissolved rapidly as the reduction proceeded, giving a deep red solution from which a good yield of the tin double salt of the aminophenol quickly separated as lustrous golden-yellow needles and leaflets. These were filtered, washed with 10% hydrochloric acid, and recrystallized from 50% acetic acid, from which the salt separated in the same form. The substance was dried in a

desiccator over sulfuric acid and sodium hydroxide. The salt darkens above 200°, but does not melt when heated to 280°. It is fairly soluble in water or dilute alcohol, especially on warming, yielding orange-red solutions. It is practically insoluble in alcohol or acetone. It dissolves in alkali, forming a clear, light brown solution which deposits light colored flocks on standing. Ferric chloride, added to the aqueous solution, gives a light green color changing to a deep emerald green when sodium acetate is added.

Analyses. Calc. for $C_{20}H_{27}O_3N_3.2HCl.SnCl_4$: C, 34.74; H, 4.24; N, 6.08. Found: C, 35.55; H, 4.47; N, 6.13.

When an aqueous suspension of the tin double salt was decomposed with hydrogen sulfide the filtrate consisted of a red solution of the aminophenol hydrochloride. Attempts made to obtain the crystalline salt failed since this proved too soluble for isolation, and manipulation was rendered difficult by the ease with which the amino group was replaced by hydroxyl under the influence of acid. In a number of instances, in which the solution stood for a long time in the refrigerator, a well-defined hydrochloride crystallized, but analysis showed this salt to be the dihydrochloride of dihydroxy-dihydroquinine. Likewise all attempts to obtain the free base were unsuccessful because of its instability.

5,8-Dihydroxy-dihydroquinine Dihydrochloride.—Diamino-dihydroquinine obtained from 24 g. of the *p*-sulfo-phenylazo dye was boiled with 5 parts of 1:1 hydrochloric acid for 3 hours, and the resulting deep red solution concentrated to smaller volume and chilled, rosets of red silky needles soon filling the liquid. The salt, washed with 10% hydrochloric acid, was recrystallized from this solvent and formed rosets of vermilion needles which were collected, washed with 10% hydrochloric acid, and air-dried. The yield was 5.5 g. The salt is easily soluble in water or alcohol, forming an orange-red solution. It is less soluble in dil. hydrochloric acid or in salt solution, and insoluble in acetone. When anhydrous, it decomposes at 208–211°. Sodium carbonate and dil. aqueous ammonia added to its solution precipitate the free base as yellow amorphous flocks which rapidly turn green on exposure to air and finally become brown. It is soluble in alkali and excess of ammonia to form brown solutions which gradually deepen in color. Ferric chloride gives a light brown color which changes to a brown-olive when sodium acetate is added. The addition of hydrobromic acid or sodium bromide to the solution of the salt causes the separation of the hydrobromide as rosets of flat, red needles.

The salt was also obtained when acid solutions of amino-hydroxy-dihydroquinine were allowed to stand for a long time.

Analyses. Calc. for $C_{20}H_{26}O_4N_2.2HCl.4H_2O$: H_2O, 14.31. Found: H_2O, 15.10. Calc. for $C_{20}H_{26}O_4N_2.2HCl$: N, 6.49; Cl, 16.43. Found: N, 6.57; Cl, 16.25.

Because of the instability of the free base we have been unable to obtain it in crystalline form.

B. Quinoline Derivatives

5-Amino-6-methoxy-8-(*p*-sulfo-phenylazo)quinoline.—Diazotized sulfanilic acid was coupled in the usual way with 5-amino-6-methoxyquinoline[5] in dil. acetic acid containing sufficient sodium acetate to act as buffer. A deep purple solution formed, accompanied by a tar which crystallized when alcohol was added. When dissolved in 50% alcohol with the aid of ammonia, and heated, re-acidifying the solution with acetic acid, the acid separated as flat, brown, microscopic needles which did not melt when heated to 295°. It is almost insoluble in the usual neutral solvents. The solution in dil. alkali is orange-red, and purple in dil. acids, while in conc. sulfuric acid it gives a red solution which appears purple in thin layers.

[5] Ref. 2, p. 2285.

Analysis. Calc. for $C_{10}H_{14}O_4N_4S$: N, 15.63. Found: N, 16.04.

5,8-Diamino-6-methoxyquinoline.—Thirty-two g. of the sulfo-phenylazo dye dissolved in 300 cc. of 10% ammonia were saturated with hydrogen sulfide. Decolorization occurred rapidly, with deposition of crystals of the deep olive-brown diamino base. The mixture was made distinctly ammoniacal, filtered, and washed with water. The yield was 15 g. Extraction of the mother liquor with ether gave an additional gram. Recrystallization from toluene with the addition of bone black gave lustrous golden leaflets which are fairly stable when pure, but gradually turn olive colored when moist, due to oxidation. When rapidly heated, the base darkens above 155°, sinters, and then melts at 163–164° to form a dark tar. It is appreciably soluble in acetone and chloroform, especially on warming, and in hot alcohol, benzene or toluene, and only sparingly soluble in ether, to form yellow solutions which darken to a brown-olive color on standing. The solution in dil. acid is a reddish-orange, resembling the corresponding dihydroquinine derivative, and in conc. sulfuric acid the color is a faint yellow. A concentrated solution in 10% hydrochloric acid deposits delicate yellow needles of the polyhydrochloride on chilling. The solution in dil. acetic acid turns a light green when treated with ferric chloride, changing to a deep emerald green when sodium acetate is added.

Analysis. Calc. for $C_{10}H_{11}ON_3$: N, 22.22. Found: N, 22.34.

8-Amino-5-hydroxy-6-methoxyquinoline.—Three g. of diamino-6-methoxyquinoline were dissolved in 30 cc. of 10% hydrochloric acid, warmed for 30 minutes on the water-bath, then diluted with water, and boiled free from air. The solution was chilled and neutralized with a considerable excess of sodium acetate solution. When rubbed the solution yielded 2 g. of the aminophenol as a yellow powder which quickly turned to an olive color on the surface because of oxidation. It was recrystallized by dissolving it in a considerable amount of hot toluene, filtering rapidly, cooling, and again filtering rapidly from green amorphous flocks which had separated. On scratching, the yellow filtrate yielded aggregates of yellow microscopic leaflets or stout crystals which darkened to an olive color when exposed to the air. It darkened above 130° and slowly melted to a dark mass at 180–182° with preliminary sintering. It is appreciably soluble in methyl alcohol, acetone, and ether, and in hot benzene or toluene. It crystallizes from hot alcohol as stout microscopic crystals and dissolves in dil. acids with the formation of an orange-red solution. Addition of ferric chloride to a solution, followed by sodium acetate, gave a deep emerald-green color. The solution in alkali, at first yellow in color, changes almost instantly to green.

Analysis. Calc. for $C_{10}H_{10}O_2N_2$: N, 14.73. Found: N, 14.60.

This compound proved to be identical with the substance obtained as follows. Fourteen g. of 5-hydroxy-6-methoxy-8-phenylazoquinoline, described below, were dissolved in 140 cc. of 10% ammonia, and hydrogen sulfide was passed in until the deep purple liquid changed to a brown, with deposition of glistening crystals of the 8-amino-5-hydroxy-6-methoxyquinoline. The yield was 6 g. Recrystallization from toluene, as previously described, gave a yellow substance which agreed in all properties with the aminophenol described above. This was confirmed by a mixed melting point determination.

Analysis. Calc. for $C_{10}H_{10}O_2N_2$: N, 14.73. Found: N, 14.63.

5-Hydroxy-6-methoxy-8-(*p*-sulfo-phenylazo)quinoline.—Because of the insolubility of the amino-azo dye described above, its conversion into the hydroxyazo dye could not be accomplished conveniently in alcoholic solution as in previous instances but was carried out as follows. Sixteen g. of the amino-azo dye were suspended in 160 cc. of hot glacial acetic acid and then 160 cc. of hot 1:1 hydrochloric acid were added. As the deep purple paste of the hydrochloride which formed was heated on the water-bath it gradually dissolved, and after 10 minutes the solution turned a deep orange-red

and deposited the hydroxyazo dye almost quantitatively. Redissolved in hot 50% alcohol with the aid of ammonia and re-acidified with hydrochloric acid it formed a purple powder which appeared under the microscope as rosets of brown platelets. It is practically insoluble in neutral solvents and does not melt when heated to 290°.

Analyses. Calc. for $C_{16}H_{13}O_5N_3S.H_2O$: H_2O, 4.77. Found: H_2O, 5.51. Calc. for $C_{16}H_{13}O_5N_3S$: N, 11.68. Found: N, 11.78.

5,8-Dihydroxy-6-methoxyquinoline.—When 5 g. of diamino-methoxyquinoline were boiled for 3 hours in 1:1 hydrochloric acid and then chilled, red-brown crystals of the dihydroxy hydrochloride slowly separated. This salt was washed with the acid, dissolved in water, and treated with an excess of sodium acetate. On rubbing, 3 g. of the base quickly separated as yellow microscopic prisms which became purple on exposure. It was recrystallized from about 40 parts of alcohol and then from toluene, forming lustrous yellow leaflets and needles melting at 195–197° with slight preliminary softening and darkening. It is sparingly soluble in the cold in methyl and ethyl alcohols and in acetone, but more readily soluble if the solvent is warmed. It dissolves in dil. acids with the formation of a brown-orange colored solution and in conc. sulfuric acid with an orange-yellow color. The solution in alkali is brown and the shade deepens on standing, while an alcoholic solution gives an olive color with ferric chloride.

Analyses. Calc. for $C_{10}H_9O_3N$: C, 62.80; H, 4.71; N, 7.33. Found: C, 62.90; H, 4.72; N, 7.81.

Action of Acids on 5,8-Diaminoquinoline.—Two and a half g. of diaminoquinoline were boiled 3 hours with 1:1 hydrochloric acid, a portion of the hydrochloride remaining undissolved throughout. From the collected salt almost all of the base was recovered unchanged. When the mother liquor was rendered alkaline, it showed the presence of a trace of hydroxy compound by the deposition of green flocks, but the odor of ammonia was scarcely detectable on boiling.

Summary

Like the amino groups in the amino azo dyes derived from 5-amino-dihydroquinine and 5-amino-6-methoxyquinoline, those in the 5,8-diamino-compounds obtained from the dyes by reduction are easily replaceable by hydroxyl. A number of the intermediate and end products of this transformation are described.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

SYNTHESES IN THE CINCHONA SERIES. VIII. THE HYDROGENATION OF DIHYDROCINCHONINE, CINCHONINE AND DIHYDROQUININE[1]

BY WALTER A. JACOBS AND MICHAEL HEIDELBERGER

Received July 22, 1921

The hydrogenation of the cinchona alkaloids has been studied by many workers in the past. Since the attempts of others by different methods had yielded substances of indefinite character, Konek von Norwall,[2] and Lippmann and Fleissner[3] applied the Ladenburg method of reduction

[1] Presented at the Annual Meeting of the American Chemical Society, New York, September, 1921.

[2] von Norwall, *Monatsh.*, **16**, 630 (1895).

[3] Lippmann and Fleissner, *ibid.*, **16**, 321 (1895); *Ber.*, **28**, 1637 (1895); **29**, 801 (1896).