[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Nitration of Lepidine and 2-Chlorolepidine

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In the course of an investigation of quinoline derivatives of potential antimalarial activity, certain aminolepidines were prepared from the corresponding nitro compounds.[2] It was found that the nitration of 2-chlorolepidine yielded two isomeric mono nitro derivatives in a ratio of 1:6. The isomer formed in smaller amount was identified as 6-nitro-2-chlorolepidine, while the major reaction product was postulated to be 5-nitro-2-chlorolepidine. The 8-position was ruled out for the nitro group because the chloro-2-hydroxy- and chloro-2-chlorolepidine prepared from our nitro product differed from the 8-chloro-2-hydroxy- and the 2,8-dichlorolepidine, respectively, as reported by Kermack and Muir.[3] The data furnished by the British authors did not seem to call for re-investigation since their preparation of 8-chloro-2-hydroxylepidine from *o*-chloroacetoacetanilide, and the melting point of their product, had been confirmed by Monti and Cirelli.[4]

Shortly after the publication of our experiments, Johnson and Hamilton[5] reported that the compound obtained by cyclization of *o*-chloroacetoacetanilide could also be prepared from the major nitration product of 2-chlorolepidine. The melting point of their product checked that of the compound which we had regarded as 5-chloro-2-hydroxylepidine. Likewise, the melting point of the 2,8-dichlorolepidine of Johnson and Hamilton did not agree with that observed by Kermack and Muir for their dichloro compound, but with that of the substance to which we had assigned the structure of 2,5-dichlorolepidine.

In the nitration of lepidine the nitro group enters position 8 since the corresponding aminolepidine can be derived from 8-nitro-2-chlorolepidine by reduction.[5a]

We repeated Johnson and Hamilton's ring closure using commercial *o*-chloroacetoacetanilide, and corroborated the results of these authors. A mixture melting point of the 8-chloro-2-hydroxylepidine obtained by this procedure exhibited no depression with a sample of our chloro-2-hydroxylepidine, and thereby established the structure of our nitro derivative as 8-nitro-2-chlorolepidine.

The position of the nitro group has now been confirmed by degradation to a well-known nitroquinoline. For this purpose, 8-nitrolepidine was converted to 8-nitroquinoline-4-aldehyde by the method of Koenigs,[6] and the aldehyde was oxidized to 8-nitrocinchoninic acid. This acid was decarboxylated to 8-nitroquinoline, which was identified by mixture melting point with a sample prepared from *o*-nitroaniline by the Skraup synthesis. Moreover, 5-nitrocinchoninic acid prepared by nitration of cinchoninic acid[7] depressed the melting point of our 8-nitroquinoline-4-carboxylic acid.

It seemed probable that Kermack and Muir, and Monti and Cirelli, had obtained the isomeric 8-chloro-4-hydroxyquinaldine in their ring closures. A support was given to this assumption by recent studies of Jacini,[8] who showed that in the preparation of acetoacetanilide derivatives by the method of Fierz-David and Ziegler,[9] elimination of one molecule of water rather than of ethanol may occur with the formation of ethyl β-arylaminocrotonates. This method had been used by Monti in the synthesis of compounds interpreted by her as 2-hydroxylepidine derivatives.

8-Chloro-4-hydroxyquinaldine as described by Hughes and Lions[10] melts at 220°. We repeated the synthesis of these investigators, and obtained a compound melting at 229–230°. Chlorination of this derivative yielded 4,8-dichloroquinaldine; the structure of this compound was proved by degradation to quinaldine. The dichloro derivative reacted with piperidine to furnish 8-chloro-4-piperidinoquinaldine; with sodium methoxide it yielded 8-chloro-4-methoxyquinaldine. The melting points of these compounds are listed in the following table and compared with those of the supposedly isomeric lepidine derivatives of Kermack and Muir.

(1) Eli Lilly Research Fellow, 1940–1942.
(2) Krahler and Burger, THIS JOURNAL, **63**, 2367 (1941).
(3) Kermack and Muir, *J. Chem. Soc.*, 300 (1933).
(4) Monti and Cirelli, *Gazz. chim. ital.*, **66**, 723 (1936).
(5) (a) Johnson and Hamilton, THIS JOURNAL, **63**, 2864 (1941); (b) **63**, 2867 (1941).
(6) Koenigs, *Ber.*, **31**, 2364 (1898).
(7) Koenigs and Lossow, *ibid.*, **32**, 717 (1899).
(8) Jacini, *Gazz. chim. ital.*, **71**, 53 (1941).
(9) Fierz-David and Ziegler, *Helv. Chim. Acta*, **11**, 776 (1928).
(10) Hughes and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 458 (1938); *Chem. Abs.*, **33**, 611 (1939).

Derivatives of quinaldine	M. p., °C.	Kermack and Muir's postulated derivatives of lepidine	M. p., °C.
8-Chloro-4-hydroxy-	229–230	8-Chloro-2-hydroxy-	230
4,8-Dichloro-	87–88	2,8-Dichloro-	87–88
8-Chloro-4-piperidino--picrate	124–125 161–163	8-Chloro-2-piperidino--picrate	125–126 159
8-Chloro-4-methoxy-	122–124	8-Chloro-2-methoxy-	122

Only 2-hydroxylepidine could be isolated from the reaction mixture when 2-chlorolepidine was oxidized with selenium dioxide. Bromination of 2-chlorolepidine yielded small amounts of 4-(dibromomethyl)-2-hydroxylepidine; this compound could not be hydrolyzed to 2-hydroxyquinoline-4-aldehyde.

In an experiment designed to synthesize 2-lepidylmalonic acid, sodium diethyl malonate was condensed with 2-chlorolepidine in carefully dried ethanol solution. The reaction product was found to be 2-ethoxylepidine instead; sodium ethoxide had competed with sodium diethylmalonate in the condensation.

Experimental

8-Nitroquinoline-4-aldehyde.—Several attempts were made to oxidize 8-nitrolepidine to the aldehyde with selenium dioxide according to the direction of Johnson and Hamilton,[5a] but more reproducible results were obtained by the method of Koenigs.[6] Bromination of 8-nitrolepidine gave 8-nitro-4-(dibromomethyl)-quinoline in 89% yield, m. p. 111.5–112.5°. The hydrolysis of the dibromomethyl group was effected by dissolving equal parts of the compound and of silver nitrate in five parts of 60% acetic acid and heating the mixture on a steam-bath for four hours. A small amount of hydrochloric acid was added to complete the precipitation of silver halides. The solution was filtered, made alkaline with solid sodium carbonate, and the precipitated aldehyde was isolated. The yield of crude colorless product of m. p. 163–173° was 97%; the compound could be used in the following oxidation without further purification.

8-Nitroquinoline-4-carboxylic Acid.—One and seven-tenths grams of the crude aldehyde, dissolved in 50 cc. of acetone, was oxidized by dropwise addition of 17.75 cc. of a 5% potassium permanganate solution at 40°. The precipitated manganese dioxide was brought into solution by adding some water saturated with sulfur dioxide, the acetone boiled off, and the volume of the solution maintained constant by dilution with water. 8-Nitrocinchoninic acid crystallized as glittering yellow needles, m. p. 253–254° (dec.). The yield was 1.3 g. (71%).

Anal. Calcd. for $C_{10}H_6N_2O_4$: N, 12.84. Found: N, 12.55.

8-Nitroquinoline.—Three-tenths gram of 8-nitrocinchoninic acid, mixed with an equal amount of copper bronze, was heated gently at 100 mm. pressure until the rapid decarboxylation had subsided. The reaction product was distilled out under 20 mm. pressure, and the oily distillate crystallized on cooling. Sublimation at 70° and 2 mm. yielded yellow crystals, m. p. 86–89°. A mixture melting point with an authentic sample of 8-nitroquinoline (m. p. 88–90°) showed no depression.

Attempted Preparation of 2-Chloroquinoline-4-aldehyde.—To a boiling solution of 2.2 g. of 2-chlorolepidine and 4.4 g. of anhydrous sodium acetate in 35 cc. of glacial acetic acid was added a solution of 4.2 g. of bromine in 20 cc. of glacial acetic acid. Decolorization occurred after thirty minutes of boiling. The solution was cooled, poured into ice-water, and the precipitated solid extracted four times with ether. The insoluble material was recrystallized from boiling ethanol. The almost colorless needles melted at 307–308° (dec.), the yield was 0.5 g. (12%). The compound proved to be 4-(dibromomethyl)-2-hydroxyquinoline.

Anal. Calcd. for $C_{10}H_7Br_2NO$: C, 37.86; H, 2.23. Found: C, 38.06; H, 2.65.

Hydrolysis to 2-hydroxyquinoline-4-aldehyde was unsuccessful. This is in accord with the observation[5a] that 2-hydroxy-4-(bromomethyl)-quinoline resists hydrolysis when refluxed with 80% acetic acid.

The oily residue from the combined ether extracts of the high-melting 2-hydroxy-4-(dibromomethyl)-quinoline was hydrolyzed with silver nitrate in acetic acid solution. The oily reaction product gave a pronounced aldehyde test but did not crystallize and yielded no crystalline derivatives.

8-Chloro-4-hydroxyquinaldine.—Ten grams of *o*-chloroaniline was dissolved in 10 g. of ethyl acetoacetate, one drop of 17% hydrochloric acid was added, and the mixture was allowed to stand over sulfuric acid in an evacuated desiccator for twenty-four hours. The oily yellow ethyl β-(*o*-chlorophenyl)-aminocrotonate was dropped with stirring into 100 cc. of dry paraffin oil preheated to 240°. When all the ester had been added, the temperature was maintained at 240° for five minutes. The clear yellow solution was allowed to cool; crystallization set in at 150°. The mixture was diluted with ligroin, the product was filtered and recrystallized from dilute ethanol. The colorless crystals melted at 229–230°; the yield was 4.4 g. (29%).

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.17. Found: C, 62.10; H, 4.79.

4,8-Dichloroquinaldine.—A mixture of 1.4 g. of 8-chloro-4-hydroxyquinaldine and 5 cc. of phosphorus oxychloride was heated on a steam-bath until all the material had gone into solution. This chlorination proceeded more rapidly than the corresponding reaction with 2-hydroxylepidine. The mixture was poured into ice-water and made ammoniacal. An oily precipitate appeared, and solidified on scratching. Recrystallization from dilute methanol, and sublimation at 70° and 2 mm. yielded 1.3 g. (85%) of colorless needles, m. p. 87–88°.

Anal. Calcd. for $C_{10}H_7Cl_2N$: C, 56.63; H, 3.33. Found: C, 56.62; H, 4.30.

One-half gram of the dichloro compound was mixed with 3 g. of zinc dust, and heated slowly in a small distilling flask. A few drops of a clear oil distilled from the mixture. The picrate, prepared from the distillate and recrystallized from boiling ethanol, appeared as yellow needles, m. p. 188–190° (dec.). A mixture melting point with quinaldine picrate (m. p. 192–194°) showed no depression.

8-Chloro-4-piperidinoquinaldine.—A mixture of 0.6 g. of 4,8-dichloroquinaldine and 5 cc. of piperidine was re-

fluxed for four hours, poured into water, the precipitated piperidino derivative was filtered and recrystallized three times from dilute methanol. The compound appeared as lustrous colorless plates; m. p. 124–125°.

Anal. Calcd. for $C_{15}H_{17}ClN_2$: C, 69.09; H, 6.57. Found: C, 69.26; H, 7.41.[11]

The **picrate** crystallized from ethanol as yellow needles, m. p. 161–163°.

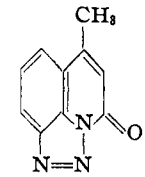
8-Chloro-4-methoxyquinaldine.—A solution of 0.043 g. of sodium in 2 cc. of methanol was added to a solution of 0.4 g. of 4,8-dichloroquinaldine in 30 cc. of methanol, and the mixture was refluxed for twelve hours. The reaction product was precipitated as an almost colorless solid by dilution with water, and purified by fractional sublimation at 90° and 3 mm. The small colorless plates melted at 122–124°.

Anal. Calcd. for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85. Found: C, 64.30; H, 5.39.

2-Chlorolepidine and Sodium Diethyl Malonate.—A solution of 9 g. of diethyl malonate in 10 cc. of absolute ethanol was refluxed with a solution of 1.3 g. of sodium in 30 cc. of absolute ethanol for five minutes; 10 g. of 2-chlorolepidine in 10 cc. of absolute ethanol was added, and the mixture boiled for fifty hours. The separated sodium chloride was filtered, 7.6 g. of potassium hydroxide was added, and the alkaline mixture refluxed for four hours to complete hydrolysis of the ester. Neutralization with dilute acetic acid precipitated an oil which crystallized on cooling. It was recrystallized from dilute alcohol and appeared as colorless needles, m. p. 49–50°. Analysis showed it to be 2-ethoxylepidine.[12]

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00. Found: C, 76.33; H, 6.91.

2-Oxo-4-methylquinoline-1,8-diazoimide.—The method of preparation of this diazoimide which we had interpreted[2] as 5-hydroxy-3-pyrido-[4,3,2-*de*]-cinnoline, has now been improved. A hot solution of 8-amino-2-hydroxylepidine



in 21 cc. of 10% hydrochloric acid was cooled, and the suspension of the finely divided hydrochloride was diazotized with sodium nitrite solution. The diazoimide separated as a brown amorphous precipitate. It was filtered, suspended in hot water, and the mixture heated on a steam-bath for one hour. The tan solid was filtered; the yield was 1.0 g. (47.5%); m. p. 236–237.5° (dec.).

The diazoimide could be recrystallized from boiling ethanol without decomposition, in contrast to other diazoimides (aryl azides)[13] which decompose under these conditions with the loss of one molecule of nitrogen. However, when our diazoimide was boiled in ethanol solution with "darco" a strong odor of acetaldehyde was noted, and 2-hydroxylepidine crystallized on dilution with water. It was identified by a melting point and a mixture melting point with an authentic sample.

Summary

1. The structure of the lepidine derivatives substituted in position 8 prepared by Johnson and Hamilton has been confirmed. These compounds are identical with those previously interpreted by us as the isomeric 5-substituted derivatives of lepidine.

2. The compound described by us as 5-hydroxy-3-pyrido-[4,3,2-*de*]-cinnoline is therefore 2-oxo-4-methylquinoline-1,8-diazoimide.

3. The 8-chloro derivatives of lepidine reported by Kermack and Muir apparently are 8-chloro derivatives of quinaldine.

(11) The values for hydrogen for our quinaldine derivatives ran high due to weather conditions. The daily test microanalyses of known compounds showed the same tendency.

(12) Knorr, *Ann.*, **236**, 69 (1886).

(13) Sah and Wen-Hou Yin, *Rec. trav. chim.*, **59**, 238 (1940).

CHARLOTTESVILLE, VA. RECEIVED JUNE 24, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of Phenolic Glycosides

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In the course of work in this Laboratory on derivatives of tetrahydrocannabinol, we had occasion to attempt the preparation of the glucoside. The method of Helferich and Schmitz-Hillebrecht,[2] employing zinc chloride or *p*-toluenesulfonic acid as catalyst in a fused mixture of phenol and sugar pentaacetate, was first used. It was not possible in the case of the difficultly accessible phenol, tetrahydrocannabinol, to use the large excess ordinarily employed in this procedure, and poor results were obtained when equimolar quantities of the reactants were used.

On the other hand, we found that tetrahydrocannabinol and a number of other phenols condense smoothly with fully acetylated sugars in benzene solution in the presence of moist phosphorus oxychloride, giving high yields of acetyl-

(1) We are indebted to Smith, Kline and French Laboratories, and one of us (T. H. B.) to the Julius Rosenwald Fund for generous grants to support this work.

(2) Helferich and Schmitz-Hillebrecht, *Ber.*, **66**, 378 (1933).