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

Cyclic Aminoalkylamino Derivatives of Lepidine

BY STANLEY E. KRAHLER[1] AND ALFRED BURGER

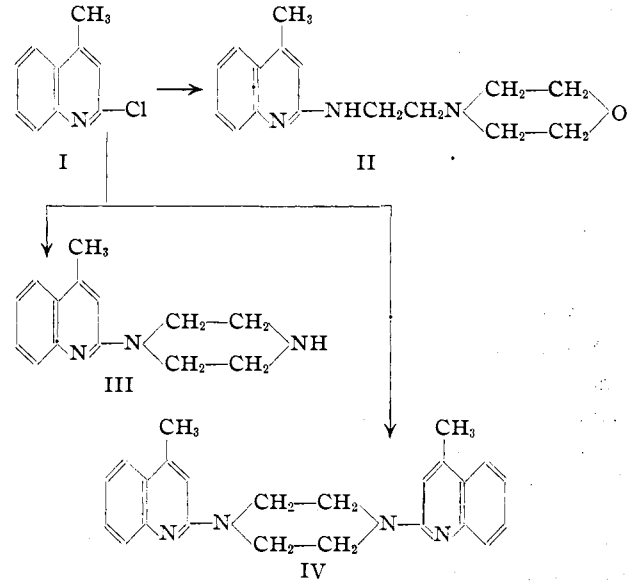
Certain aliphatic diamines exhibit a noticeable antiplasmodial action, and this effect may be increased considerably in favorable cases by attaching one of the two amino groups to an aromatic or heterocyclic nucleus. A large number of systematic variations of this principle has culminated in the syntheses of plasmoquine and atabrine, and these in turn have caused extended investigations of analogous compounds which should shed some light on possible relations between chemical structure and chemotherapeutic action.

A working program of this Laboratory calls for the systematic search for potential chemotherapeutic, especially protozoacidal, agents based on newer and easily available heterocyclic starting materials.[2] This communication reports the preparation, and structural proof, of some new substitution products of lepidine which may be obtained readily from commercial 2-hydroxy-4-methylquinoline,[3] and describes the introduction of piperazine and N-β-aminoethylmorpholine[3] side-chains into some of these derivatives.

2-Chlorolepidine (I) was condensed with N-β-aminoethylmorpholine to yield N-β-(2-lepidylamino)-ethylmorpholine (II), and an excess of piperazine reacted in like manner to give 1-(2-lepidyl)-piperazine (III). When equimolar quantities of 2-chlorolepidine and piperazine were heated at 130–140°, 1,4-(2,2′-dilepidyl)-piperazine (IV) was formed. These diamine side-chains were introduced in order to increase the basicity of the heterocyclic nucleus, because such an increase had been correlated in some cases with a rise in antimalarial action. This purpose was partly defeated in our compounds since the basicity of amino groups directly attached to the quinoline system in position-2 is weakened by the tendency for a tautomeric shift of their hydrogen to the nitrogen atom in the quinoline nucleus. Thus, the substituted α-amino groups in some of our compounds are not even capable of forming stable salts with mineral acids. In order to counteract this partial loss of basicity, the introduction of amino groups into the benzenoid nucleus was contemplated, and the corresponding nitro derivatives were prepared as a starting point.

6-Nitro-2-chlorolepidine (V) can be prepared from 6-nitro-2-hydroxylepidine by the action of phosphorus halides,[4] but the product obtained by this procedure cannot be purified easily. The nitration of 2-chlorolepidine was therefore studied with the hope of avoiding the formation of tars and colored by-products which accompany the 6-nitro derivative prepared by the Balaban method. Only 10% of 6-nitro-2-chlorolepidine was obtained in the nitration, while the main reaction product consisted of another nitro-2-chlorolepidine (VI) which could be separated easily by fractional crystallization. The nitro group in this compound could occupy positions 3, 5, 7, or 8, and the structure of our compound was established as 5-nitro-2-chlorolepidine by the following evidence.

Selective reduction of the nitro group gave an



amino-2-chlorolepidine (VII) melting at 102.5–103° while 7-amino-2-chlorolepidine[5] melts at 142–143°. Exchange of the amino group with a chlorine atom by the Sandmeyer reaction furnished a dichlorolepidine (VIII), melting at 105–

(1) Eli Lilly and Company Fellow.

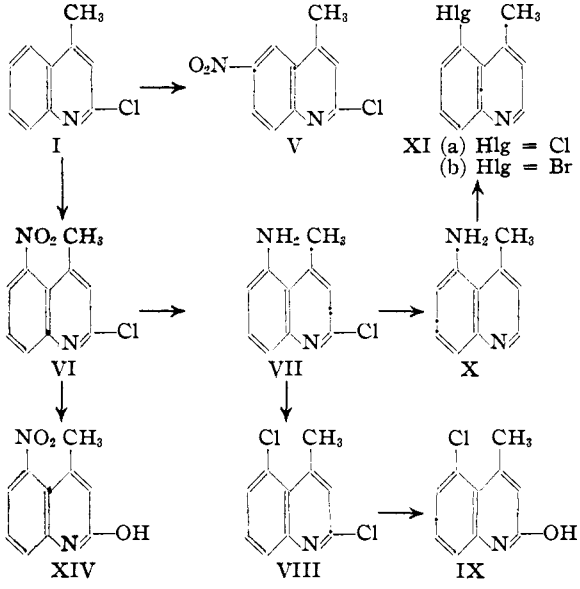
(2) (a) Burger and Modlin, THIS JOURNAL, **62**, 1079 (1940); (b) Modlin and Burger, *ibid.*, **63**, 1115 (1941).

(3) "Fine Chemicals," Carbide and Carbon Chemicals Corp., New York, N. Y., 1939.

(4) Balaban, *J. Chem. Soc.*, 2346 (1930).

(5) Besthorn and Byvanck, *Ber.*, **31**, 796 (1898).

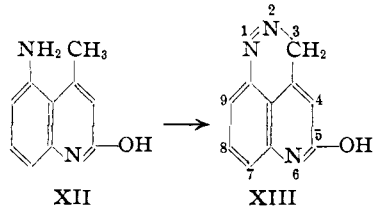
106°, which differed from 2,7-dichlorolepidine (m. p. 97–98°)[6] and 2,8-dichlorolepidine (m. p. 87–88°).[7] Moreover, the 7- and 8-positions were ruled out because the properties of the chloro-2-hydroxylepidine (IX) prepared by acid hydrolysis of the dichlorolepidine VIII disagreed with those of 2-hydroxy-7-chloro-[6] and 2-hydroxy-8-chlorolepidine,[7] respectively. In order to decide between positions 3 and 5 for the substituents in our series, the aminochlorolepidine VII was dehalogenated by hydrogenation with Raney nickel in the presence of one mole of potassium hydroxide, and the resulting aminolepidine X was converted to the chloro- and bromolepidines (XI a and b) by the Sandmeyer reaction. The melting points of these compounds differed from those of 3-chloro- and 3-bromolepidine,[8] respectively, thus placing the halogen atom in XI in position-5.



Nitration of N-β-(2-lepidylamino)-ethylmorpholine (II) furnished N-β-[2-(6-nitrolepidylamino)]-ethylmorpholine, and by the same treatment a nitro group could be introduced into position-6 of 1-(2-lepidyl)-piperazine. The structure of these nitro compounds was established by condensing 6-nitro-2-chlorolepidine with N-β-aminoethylmorpholine, and piperazine, respectively, and comparing the resulting nitro derivatives with those obtained by nitration. The properties of the respective compounds prepared by either method showed complete agreement. 5-Nitro-2-chlorolepidine (VI) was also condensed with the two cyclic diamines, and yielded N-β-[2-(5-nitrolepidylamino)]-ethylmorpholine, and 1,4-[2,2′-di-(5,5′-nitrolepidyl)]-piperazine, respectively.

Catalytic hydrogenation of N-β-[2-(6-nitrolepidylamino)]-ethylmorpholine in ethanol solution in the presence of Raney nickel gave N-β-[2-(6-aminolepidylamino)]-ethylmorpholine in satisfactory yield.

A vigorous evolution of nitrogen was observed when a strongly acid solution of diazotized 5-aminolepidine was heated, but no well-defined phenolic derivative has been isolated as yet from the reaction mixture. On the other hand, no nitrogen was evolved from the heated solution of 2-hydroxylepidine-5-diazonium chloride, but a colorless reaction product containing three atoms of nitrogen precipitated out on cooling. It appears that coupling has taken place across the peri-positions, and the compound is assigned the formula of a 5-hydroxy-3-pyrido[4,3,2,-*de*]-cinnoline (XIII).



The formation of pyridazine derivatives from compounds containing an active methylene group δ to a diazonium salt group has been observed before; Richter[9] prepared hydroxycinnoline carboxylic acid from *o*-aminophenylpropiolic acid apparently through β-(*o*-aminophenyl)-ketopropionic acid under similar conditions.

2-Lepidyl-N-β-aminoethylmorpholine dihydrochloride has been tested in the Warburg apparatus with duck's erythrocytes infected with *Plasmodium lophurae* by Dr. K. K. Chen of the Lilly Research Laboratories. It did not show much inhibition of oxygen consumption by these parasites, and it is thus unlikely that it has much antimalarial activity.

Experimental Part

2-Chlorolepidine[10] **(I).**—One hundred grams of 2-hydroxylepidine was mixed well with 110 g. of phosphorus oxychloride. The mixture was heated at 70–80° until it liquefied completely and then poured into 2 liters of ice water. It was made alkaline with sodium carbonate, the

(6) German Patent 556,324, *C. A.*, **26**, 5573 (1932).
(7) Kermack and Muir, *J. Chem. Soc.*, 300 (1933).
(8) Magnanini, *Ber.*, **20**, 2608 (1887); Pictet and Misner, *ibid.*, **45**, 1800 (1912).
(9) Richter, *ibid.*, **16**, 677 (1883).
(10) Knorr, *Ann.*, **236**, 69 (1886); Mikhailov, *J. Gen. Chem.* (U. S. S. R.). **6**, 511 (1936).

precipitate filtered and recrystallized from dilute ethanol with the aid of Norit; m. p. 58°; the yield was 95%.[11]

Lepidine.—A solution of 20 g. of 2-chlorolepidine and 6.3 g. of potassium hydroxide in 150 cc. of ethanol absorbed one mole of hydrogen in the presence of 3 g. of Raney nickel catalyst[12] in sixteen hours. The catalyst was filtered, the solvent removed, and the residue was extracted with ether and washed with water. The dried ether extract was evaporated, and the crude lepidine purified by distillation. The boiling point was 126° under 40 mm. pressure, the yield 94%.

N-β-(2-Lepidylamino)-ethylmorpholine (II).—A mixture of 2 g. of 2-chlorolepidine and 2 cc. of N-β-aminoethylmorpholine was heated at 150° for four hours, the yellow resin was extracted with dilute hydrochloric acid, and the solution made alkaline. The oily base was extracted into ether, and the **dihydrochloride** precipitated with ethanolic hydrogen chloride. Recrystallization from ethanol gave short colorless needles, m. p. 272–273°.

Anal. Calcd. for $C_{16}H_{23}Cl_2N_3O$: C, 55.82; H, 6.73. Found: C, 55.60; H, 6.97.

1-(2-Lepidyl)-piperazine (III).—Patterned after the method of Kermack and Smith,[13] 10 g. of 2-chlorolepidine was heated with 40 g. of piperazine at 130–140° for three hours. The crude product was extracted with 3% hydrochloric acid, and the small amount of insoluble dilepidylpiperazine filtered. By neutralizing the filtrate with ammonium hydroxide and allowing the solution to stand, it was possible to isolate 1-(2-lepidyl)-piperazine **hydrochloride** which settled out after some time. It crystallized from absolute ethanol as colorless needles, m. p. 265–267° (dec.).

Anal. Calcd. for $C_{14}H_{18}ClN_3$: C, 63.74; H, 6.88. Found: C, 63.74; H, 7.19.

The base, obtained from the salt with sodium hydroxide solution and extraction with ether, was oily. The **trihydrochloride,** prepared with ethanolic hydrogen chloride, crystallized as fine needles, m. p. 285.5–286°.

Anal. Calcd. for $C_{14}H_{20}Cl_3N_3$: C, 49.94; H, 5.99. Found: C, 50.22; H, 6.55.

1,4-(2,2'-Dilepidyl)-piperazine (IV).—(*Cf.* footnote 13.) A mixture of 7 g. of 2-chlorolepidine and 7 g. of piperazine hexahydrate was heated at 130–140° for three hours. The solid reaction product was suspended in ammoniacal water, filtered, and recrystallized from boiling pyridine. It appeared as greenish-yellow needles, m. p. 236.5–237°. The yield was 6.5 g. (90%).

Anal. Calcd. for $C_{24}H_{24}N_4$: C, 78.23; H, 6.57. Found: C, 78.12; H, 6.40.

The **dinitrate** crystallized from dilute nitric acid as a yellow crystal powder, m. p. 183–186° (dec.).

Anal. Calcd. for $C_{24}H_{26}N_6O_6$: C, 58.29; H, 5.30. Found: C, 58.51; H, 5.53.

1-[2-(6-Nitrolepidyl)]-piperazine.—(a) One gram of 1-(2-lepidyl)-piperazine (III) was dissolved in 10 cc. of fuming nitric acid (d. 1.5) at 0°. The solution was kept at this temperature for one hour, poured into ice water, and made ammoniacal. A yellow solid separated, and was purified by recrystallization from methanol. It crystallized as yellow needles, m. p. 211.5–212.5°.

(b) A mixture of 0.5 g. of 6-nitro-2-chlorolepidine (V) and 4 g. of piperazine was heated at 150–160° for two hours, extracted with 3% hydrochloric acid, the solution was filtered to remove a small amount of di-(6-nitrolepidyl)-piperazine, and the filtrate was made alkaline with ammonium hydroxide. The yellow precipitate was filtered and recrystallized from ethanol. The resulting short yellow needles melted at 211.5–212.5°.

Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 60.83; H, 6.09; N, 21.55.

A mixture melting point with the product obtained by method (a) showed no depression.

N-β-[2-(6-Nitrolepidylamino)]-ethylmorpholine.—(a) One gram of N-β-(2-lepidylamino)-ethylmorpholine dihydrochloride was dissolved in 10 cc. of fuming nitric acid (d. 1.5) at 0°. After allowing the mixture to stand at this temperature for three hours, it was worked up as described for the nitration of compound III (experiment *a*). The nitro derivative exhibited dimorphism and showed two melting points, 144–145°, and 156.5–157°. The lower melting form could be converted into the higher melting one by seeding an ethanol solution with a crystal of a sample melting at 156.5–157°.

(b) Five-tenths gram of 6-nitro-2-chlorolepidine was condensed with 4 cc. of N-β-aminoethylmorpholine at 140° for four hours. The yellow liquid was dissolved in dilute hydrochloric acid, the heated solution was made ammoniacal, the yellow precipitate was filtered and recrystallized from ethanol. It melted at 158–158.5°. A mixture melting point with the higher melting form of a sample obtained by method *a* showed no depression.

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 60.74; H, 6.37. Found: C, 60.28; H, 6.45.

The mononitrate crystallized from ethanol as long yellow needles, m. p. 216.5–220.5° (dec.).

Anal. Calcd. for $C_{16}H_{21}N_5O_6$: C, 50.65; H, 5.58. Found: C, 50.47; H, 5.73.

N-β-[2-(6-Aminolepidylamino)]-ethylmorpholine.—One gram of N-β-[2-(6-nitrolepidylamino)]-ethylmorpholine, dissolved in 50 ml. of ethanol, absorbed one mole of hydrogen in the presence of Raney nickel in thirty minutes. The catalyst was filtered, the solution concentrated to 10 cc., and the hydrochloride was precipitated by addition of ethanolic hydrogen chloride and ether. The base was liberated from the salt with a saturated sodium carbonate solution and extracted into ether. It crystallized on slow evaporation of this solvent and was purified by sublimation at 120° and 1 mm. The pale yellow needles melted at 145–145.5° and were fairly soluble in water.

Anal. Calcd. for $C_{16}H_{22}N_4O$: C, 67.10; H, 7.74. Found: C, 67.21; H, 8.16.

Nitration of 2-Chlorolepidine.—2-Chlorolepidine was nitrated in a manner analogous to that used by Fischer and Gutmann[14] with 2-chloroquinoline. Fifteen grams of 2-chlorolepidine was dissolved at 0° in a mixture of 50 cc. of fuming nitric acid (d. 1.5) and 50 cc. of concentrated sulfuric acid. The solution was heated on a steam-bath for fifteen minutes and then poured into 2 liters of ice water.

(11) The optimal conditions were worked out by Mr. J. E. Wheeler.

(12) Whitmore and Revukas, THIS JOURNAL, **62**, 1691 (1940).

(13) Kermack and Smith, *J. Chem. Soc.*, 1356 (1930).

(14) Fischer and Gutmann, *J. prakt. Chem.*, **98**, 378 (1916).

The solid mixture of nitro derivatives separated in 79% yield and was filtered, dried and dissolved in 500 cc. of ethanol. The solution was allowed to cool to 55° and filtered. 6-Nitro-2-chlorolepidine (V) melting at 211–213° was thus obtained in a yield of 1.9 g. (10%). Recrystallization from ethanol rendered long colorless needles, m. p. 213.5–214°. A mixture melting point with a sample prepared by the method of Balaban,[4] and purified by high-vacuum sublimation to m. p. 214–215°, showed no depression.

The ethanolic filtrate was cooled in ice, and 10.4 g. of 5-nitro-2-chlorolepidine (VI) crystallized out. It was recrystallized from ethanol and appeared as colorless needles, m. p. 133–134°.

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 53.95: H, 3.17. Found: C, 54.08; H, 3.67.

Another 2 g. of VI was obtained by fractional crystallization of the mother liquors, making the total yield 66%.

5-Amino-2-chlorolepidine (VII).—Following the procedure of Capps and Hamilton[15] for the reduction of nitrochloroquinoline derivatives, 1 g. of 5-nitro-2-chloroquinoline (VI) was hydrogenated in hot ethanol solution (35 cc.) in the presence of Raney nickel catalyst. Three moles of hydrogen was absorbed in twenty minutes, the catalyst was filtered, and the solution concentrated to 10 cc. The amine crystallized on addition of water as light brown crystals. The yield was 0.8 g. (92%). Recrystallization from dilute ethanol gave short rhombohedra, m. p. 102.5–103°.

Anal. Calcd. for $C_{10}H_9ClN_2$: C, 62.34; H, 4.71. Found: C, 62.52; H, 5.15.

2,5-Dichlorolepidine (VIII).—One gram of 5-amino-2-chlorolepidine (VII), dissolved in 50 cc. of 17% hydrochloric acid, was diazotized at 0°, and the solution was poured into a solution of 3 g. of cuprous chloride in 50 cc. of concentrated hydrochloric acid at 60°, heated to boiling,[16] and poured into 150 cc. of ice water. A white solid separated; it was purified by sublimation at 100° and 1 mm., and melted at 104.5–105°. An additional small amount of dichlorolepidine was precipitated from the acid filtrate with ammonium hydroxide.

Anal. Calcd. for $C_{10}H_7Cl_2N$: C, 56.63; H, 3.33. Found: C, 56.29; H, 3.58.

5-Chloro-2-hydroxylepidine (IX).—Five-tenths gram of 2,5-dichlorolepidine (VIII) was boiled with 30 cc. of concentrated hydrochloric acid for two hours, the solution was poured into ice water, and the hydroxy compound crystallized out. For purification, it was recrystallized from ethanol, and sublimed at 200° and 1 mm. It crystallized as short colorless needles, m. p. 213.5–214.5°.

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.16. Found: C, 62.28; H, 4.62.

5-Amino-2-hydroxylepidine (XII).—One gram of 5-amino-2-chlorolepidine (VII) was refluxed with 30 cc. of concentrated hydrochloric acid for two hours, the solution was poured into ice water, made ammoniacal, and the yellowish precipitate was filtered. Sublimation at 230° and 1 mm. gave yellow crystals, m. p. 294° (dec.).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.79. Found: C, 69.26; H, 6.20.

(15) Capps and Hamilton, THIS JOURNAL, **60**, 2104 (1938).

(16) Dikshoorn, *Rec. trav. chim.*, **48**, 550 (1929).

5-Hydroxy-3-pyrido[4,3,2-*de*]-cinnoline (XIII).—A solution of 1.5 g. of 5-amino-2-hydroxylepidine (XII) in 150 cc. of 17% hydrochloric acid was diazotized at 0°. The white precipitate obtained during the diazotization was only partly soluble in the hot 50% sulfuric acid into which the solution was poured. No evolution of nitrogen was observed on boiling, and the white precipitate settled out on cooling. It was soluble in hot sodium hydroxide solution but showed no ferric chloride test. Crystallization from ethanol gave colorless needles. m. p. 235.5–236°.

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.66; H, 4.61; N, 22.44.

5-Aminolepidine (X).—One gram of 5-amino-2-chlorolepidine (VII) dissolved in 30 cc. of ethanol containing 0.3 g. (1 mole) of potassium hydroxide absorbed one mole of hydrogen in the presence of Raney nickel. The catalyst was filtered, and the **hydrochloride** of the amine precipitated by addition of ethanolic hydrogen chloride and ether. Recrystallization from ethanol–ether furnished yellow needles, m. p. 285–289° (dec.). The yield was 61%.

Anal. Calcd. for $C_{10}H_{11}ClN_2$: C, 61.70; H, 5.70. Found: C, 61.21; H, 6.22.

The base was liberated by addition of sodium carbonate solution and purified by sublimation at 90° and 1 mm. The pale-yellow crystals melted at 82.5–83.5°.

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37. Found: C, 75.47; H, 6.50.

5-Chlorolepidine (XIa).—5-Aminolepidine was subjected to a Sandmeyer reaction analogous to that described in the preparation of VIII. The base was liberated from the acid solution with ammonium hydroxide and extracted into ether. Distillation at 1 mm. pressure and recrystallization from dilute methanol yielded colorless needles, m. p. 106.5°. The yield was 59%.

Anal. Calcd. for $C_{10}H_8ClN$: C, 67.61; H, 4.54. Found: C, 67.71; H. 5.17.

5-Bromolepidine (XIb).—A Sandmeyer reaction with 5-aminolepidine analogous to that described in the preceding experiment, and using a 48% hydrobromic acid solution of cuprous bromide, yielded colorless needles which were purified by sublimation at 110° and 1 mm., and crystallization from methanol. The yield was 72%, m. p. 112.5–113.5°.

Anal. Calcd. for $C_{10}H_8BrN$: C, 54.08; H, 3.63. Found: C, 53.76; H, 3.68.

5-Nitro-2-hydroxylepidine (XIV).—One gram of 5-nitro-2-chlorolepidine (VI) was refluxed with 30 cc. of concentrated hydrochloric acid for two hours, the solution poured into ice water, the yellow precipitate filtered and crystallized from ethanol; yellow prisms, m. p. 197–198°.

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95. Found: C, 58.61; H, 4.27.

N-β-[2-(5-Nitrolepidylamino)]-ethylmorpholine.—One gram of 5-nitro-2-chlorolepidine (VI) was heated with 2 cc. of N-β-aminoethylmorpholine at 100° for five hours, the solution was poured into alkaline water, and extracted with ether. The ether extract was washed with water, dried, and ethanolic hydrogen chloride was added. The oily hydrochloride crystallized on treatment with acetone and was recrystallized from ethanol–ether. It appeared as almost colorless needles, m. p. 246–247° (dec.).

Anal. Calcd. for $C_{16}H_{22}Cl_2N_4O_3$: C, 49.36; H, 5.70. Found: C, 48.95; H, 6.58.

1,4-[2,2'-Di(5,5'-nitrolepidyl)]-piperazine.—Two grams of 5-nitro-2-chlorolepidine was heated with 2 g. of piperazine hexahydrate at 140–150° for three hours. The solid orange reaction product was extracted with dilute hydrochloric acid, the filtered solution was made ammoniacal, and the orange precipitate filtered. Recrystallization from 10 cc. of boiling pyridine gave orange needles, m. p. 320° (dec.).

Anal. Calcd. for $C_{24}H_{22}N_6O_4$: C, 62.87; H, 4.84. Found: C, 62.93; H, 5.26.

Summary

The nitration of 2-chlorolepidine has been studied, and the structures of the resulting derivatives have been established as 5-nitro- and 6-nitro-2-chlorolepidine, respectively. A route to lepidine derivatives substituted in position-5 has thereby been opened.

2-Chlorolepidine and its nitro derivatives have been condensed with piperazine and N-β-aminoethylmorpholine, and some of the condensation products have been tested for their antimalarial action.

2-Hydroxylepidine-5-diazonium chloride has been found to cyclize with the formation of 5-hydroxy-3-pyrido[4,3,2,-*de*]-cinnoline.

A simplified preparation of lepidine from 2-hydroxylepidine has been reported.

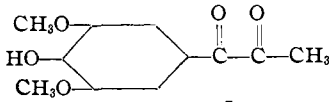
CHARLOTTESVILLE, VIRGINIA RECEIVED JULY 3, 1941

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LIII. Isolation of Vanilloyl and Syringoyl Methyl Ketones from Ethanolysis Products of Maple Wood

BY MARSHALL KULKA, W. LINCOLN HAWKINS AND HAROLD HIBBERT

In a preliminary communication[1] it was indicated that the syringyl dicarbonyl component, obtained from the bisulfite-soluble fraction of maple ethanolysis oils, was syringoyl methyl ketone (I), its identity being established through its mono- and disemicarbazones. The analogous guaiacyl derivative, vanilloyl methyl ketone (II), also was isolated in the form of the same derivatives, along with vanillin, from the bisulfite-soluble fraction of spruce ethanolysis oils.[2]



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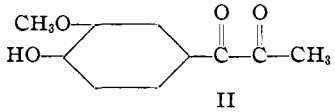

II

In this latter communication, it was shown that the amounts of vanillin and vanilloyl methyl ketone varied in different ethanolysis experiments, the former actually being absent in certain runs, and this fact led to the belief that vanillin might be a secondary product of the ethanolysis reaction, probably resulting from an oxidative cleavage.

In an earlier investigation of the bisulfite-soluble fraction of maple ethanolysis oils, Pyle, Brickman and Hibbert[3] isolated, in addition to derivatives of the diketones (I and II), also vanillin and syringaldehyde. While these aldehydic components were identified by comparison with authentic samples, and were present as relatively large amounts (*ca.* 20%) of the distilled bisulfite-soluble fraction, the results were based on a single ethanolysis extraction.

The bisulfite-soluble ethanolysis oils from maple wood have now been reinvestigated in order to effect the quantitative separation and isolation of the diketones as such, to establish the identity of syringoyl methyl ketone, and to determine possible variations in the amounts of aldehydic components present.

Separation of the Diketones.—A quantitative separation of the two diketone components in the distilled bisulfite-soluble fraction of crude oils has been accomplished by conversion into their nickel glyoxime salts (III), through treatment with hydroxylamine sulfate in the presence of nickel chloride, as applied previously to analogous compounds.[4]

(1) Brickman, Pyle, Hawkins and Hibbert, THIS JOURNAL, **62**, 986 (1940).

(2) Brickman, Hawkins and Hibbert, *ibid.*, **62**, 2149 (1940).

(3) Pyle, Brickman and Hibbert, *ibid.*, **61**, 2198 (1939).

(4) Diehl, "The Applications of the Dioximes to Analytical Chemistry," the G. Frederick Smith Chemical Co., Columbus, Ohio, 1940; Prill, Fabricius and Hammer, Iowa State College of Agriculture Research Bulletin 268, Dec., 1939; Johlin, THIS JOURNAL, **37**, 892 (1915).