[CONTRIBUTION FROM NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

Condensation Reactions of Quinoline Aldehydes

BY CHARLES E. KWARTLER[1] AND H. G. LINDWALL

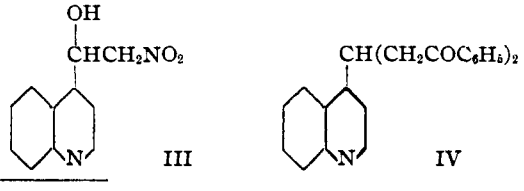
It has been found that lepidine and 6-methoxylepidine yield the corresponding quinoline-4-aldehydes when subjected to oxidation through the action of selenium dioxide. Their behavior with that oxidizing agent is analogous to that of quinaldine, which, as has been reported, is converted to quinoline-2-aldehyde.[2]

Quinoline-4-aldehyde (I) was isolated from its reaction mixture by steam distillation as the hydrate, which loses water upon being recrystallized from absolute toluene, or after long standing in a vacuum desiccator over sulfuric acid. Compound I reduces Tollens' reagent, and forms a sodium bisulfite addition product slowly; it has been characterized by oxime formation and by the preparation of its *p*-nitrophenylhydrazone.

It was found that 6-methoxyquinoline-4-aldehyde (II) does not steam distil; it was isolated directly from the reaction mixture as the free aldehyde. Even after crystallization from water no hydrate was obtained. Compound II reduces Tollens' reagent, and forms an oxime. The corresponding cinchoninic acid is a by-product in the preparation of both I and II.

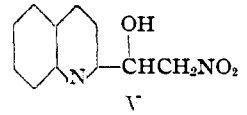
Quinoline-4-aldehyde hydrate melts at 84–84.5°, and the free aldehyde (I) at 51–53°. Neither of these melting points agrees with that (101–102°) reported by Koenigs[3] for the oxidation product of apocinchene, for which he suggested the quinoline-4-aldehyde structure.

Quinoline-4-aldehyde hydrate (I) condenses with nitromethane, yielding β-hydroxy-β-(quinolyl-4)-α-nitroethane (III). This reaction is catalyzed by diethylamine. Condensation of acetophenone with I takes place in the presence of sodium hydroxide; the product is diacetophenonyl-lepidine (IV). Compound IV forms a dioxime with hydroxylamine.

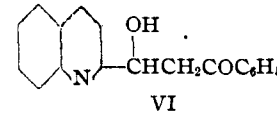


III IV

Quinoline-2-aldehyde hydrate reacts with "active-methylene" compounds somewhat more readily than does I. Nitromethane, in the presence of diethylamine, condenses to yield β-hydroxy-β-(quinolyl-2)-α-nitroethane (V). Acetophenone likewise yields an aldol-like product, (VI) β-hydroxy-β-(quinolyl-2)-ethyl phenyl ketone, when either diethylamine or sodium hydroxide is used as the catalyst.

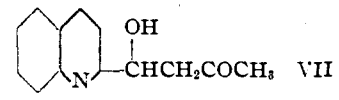


V

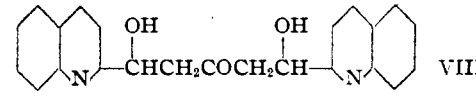


VI

The action of acetone with quinoline-2-aldehyde hydrate also has been studied. Two products result, depending upon the conditions (described in the Experimental part) under which the reactions are carried out. These condensation products are of the aldol type, 4-hydroxy-4-(quinolyl-2)-butanone-2 (VII) and 1,5-dihydroxy-1,5-bis-(quinolyl-2)-pentanone-3 (VIII).



VII



VIII

This research is being continued with the study of further condensation reactions, and their products, especially in the case of quinoline-4-aldehyde and its 6-methoxy derivative.

Experimental Part

Hydrate of Quinoline-4-aldehyde (I).—4-Methylquinoline (4 g.) was dissolved in 60 cc. of xylene, and the solution was held at 135° with constant stirring. Selenium dioxide (4.5 g.) was added in small portions over the period of one-half hour, after which the mixture was held at 135° for one hour. As selenium formed the mixture gradually became dark red. Upon cooling, crystals of cinchoninic acid separated; this and selenium were removed by filtration. The filtrate was steam distilled and the aldehyde collected separately after the xylene had distilled. The hydrate of I was filtered from the distillate after standing overnight, and more was obtained from the ether extract of the dis-

(1) From the dissertation presented by Charles E. Kwartler to the Faculty of the Graduate School of New York University in candidacy for the degree of Doctor of Philosophy.

(2) Monti, *Atti accad. Lincei*, **18**, 505 (1933); Henze, *Ber.*, **67**, 750 (1934).

(3) Koenigs, *J. prakt. Chem.*, **61**, 23 (1900).

tillate; yield, 61%, of small plates, m. p. 84–84.5°, soluble in water, toluene, xylene, ether, ethyl alcohol.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.57; H, 5.15; N, 8.00; mol. wt., 175. Found: C, 68.77, 68.89; H, 5.02, 5.03; N, 7.86, 7.71; mol. wt., 174, 174.

Quinoline-4-aldehyde (I).—The hydrate of I formed I after three weeks in a vacuum desiccator, or upon recrystallization from absolute toluene as colorless needles, m. p. 51–53°; these are soluble in ether, butyl alcohol, toluene, xylene. Compound I gives a positive reaction with Tollens' reagent, and forms a sodium bisulfite addition product slowly.

Anal. Calcd. for $C_{10}H_7NO$: N, 8.92. Found: N, 8.93.

Cinchoninic Acid.—4-Methylquinoline with larger amounts of selenium dioxide, and with longer heating of the mixture than described above for the preparation of I, is oxidized to cinchoninic acid in excellent yields.

***p*-Nitrophenylhydrazone of I.**—Yellow rectangular prisms from ethyl alcohol, m. p. 261–262°. Slightly soluble in warm carbon tetrachloride.

Anal. Calcd. for $C_{16}H_{12}O_2N_4$: N, 19.18. Found: N, 19.16.

Oxime of I.—White needles from methyl alcohol, m. p. 181–182°; yield, 88%.

Anal. Calcd. for $C_{10}H_8ON_2$: N, 16.28. Found: N, 16.33, 16.41.

6-Methoxyquinoline-4-aldehyde (II).—Compound II was prepared by the oxidation of 6-methoxy-4-methylquinoline in a manner identical with that employed for the preparation of the hydrate of I. Upon attempted steam distillation of the reaction mixture it was found that none of II would distil, and it was isolated from the residual material after steam distillation of the xylene. No hydrate was obtained even after crystallization from water: needles, m. p. 96–98°, from toluene; soluble in water, ethyl alcohol, xylene; reduces Tollens' reagent; yield, 52%.

Anal. Calcd. for $C_{11}H_9NO_2$: N, 7.49. Found: N, 7.49.

Oxime of II. Needles from ethyl alcohol; m. p. 214–216°; soluble in toluene.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: N, 13.86. Found: N, 13.81.

Oxime of Quinoline-2-aldehyde.—Fine white needles from 80% ethyl alcohol. The melting point of this compound, 188–190°, prepared by the action of hydroxylamine with quinoline-2-aldehyde, is in agreement with that reported by Pfitzinger,[4] who prepared this oxime by another method.

2',4' - Dinitrophenylhydrazone of Quinoline - 2 - aldehyde.—Yellow needles were obtained by diluting the ethyl alcohol solution of the crude product with water to incipient crystallization and allowing the mixture to stand, m. p. 251–253°.

Anal. Calcd. for $C_{16}H_{14}O_4N_8$: N, 20.59. Found: N, 20.77.

β - Hydroxy - β - (quinolyl - 4) - α - nitroethane (III).—A mixture of 0.3 g. of nitromethane, 0.5 cc. of absolute alcohol and 2 drops of diethylamine was cooled in ice and to it was added 0.32 g. of the hydrate of I. The reaction mixture was held at room temperature for one day, and then the alcohol was allowed to evaporate partially. Compound III separated as small plates, soluble in toluene, acetic acid and ethyl alcohol; recrystallized from ethyl alcohol, m. p. 133–136°; yield 78%.

Anal. Calcd. for $C_{11}H_{10}O_3N_2$: N, 12.84. Found: N, 12.50.

β - Hydroxy - β - (quinolyl - 2) - α - nitroethane (V).—A mixture was prepared of quinoline-2-aldehyde hydrate (0.43 g.) and 2 drops of diethylamine; to this was added 0.34 g. of nitromethane and 0.5 cc. of absolute ethyl alcohol. The reaction mixture became warm. Upon cooling, V separated as long white needles from ethyl alcohol; m. p. 110–113°; soluble in ethyl alcohol, isopropyl alcohol and acetic acid; yield 81%.

Anal. Calcd. for $C_{11}H_{10}O_3N_2$: N, 12.84. Found: N, 12.54.

Diacetophenonyl-lepidine (IV).—To a mixture of 6 cc. of 10% sodium hydroxide and 15 cc. of 95% ethyl alcohol were added 0.35 g. of acetophenone, 0.25 g. of the hydrate of I, and some small chips of ice. The temperature of the reaction mixture was allowed to rise to that of the room, and after one-half hour IV began to separate as white needles. Recrystallized by the slow dilution of the ethyl alcohol solution with water; yield 87%; m. p. 144–146°. Slight variations in the conditions for condensation resulted in other products which have not been studied.

Anal. Calcd. for $C_{26}H_{21}O_2N$: N, 3.69. Found: N, 3.52, 3.74.

Dioxime of IV.—Colorless needles from a methyl alcohol and dioxane mixture; m. p. 204–205°.

Anal. Calcd. for $C_{26}H_{23}O_2N_3$: N, 10.27. Found: N, 10.39.

β-Hydroxy-β-(quinolyl-2)-ethyl Phenyl Ketone (VI). Method A.—To a 10% solution of sodium hydroxide (15 cc.) were added 8 cc. of 95% ethyl alcohol, 0.2 g. of acetophenone, 0.2 g. of quinoline-2-aldehyde hydrate and a few chips of ice. Soon a light yellow solid (VI) separated and was recrystallized by the careful addition of water to its alcohol solution as pale yellow needles, m. p. 114–116°; yield 78%. **Method B.**—A solution of 0.12 g. of quinoline-2-aldehyde hydrate and 0.12 g. of acetophenone in 8 cc. of absolute ethyl alcohol was cooled in ice, and to it was added 2 drops of diethylamine. After four days water was added, and VI precipitated; purified as above in method A; yield 77%.

Anal. Calcd. for $C_{18}H_{15}O_2N$: N, 5.05. Found: N, 4.94, 4.99, 5.04.

4 - Hydroxy - 4 - (quinolyl - 2) - butanone - 2 (VII).—To a solution consisting of 12 cc. of 10% aqueous sodium hydroxide and 10 cc. of 95% ethyl alcohol were added 0.11 g. of quinoline-2-aldehyde hydrate, 0.15 g. of acetone and a few small chips of ice. Turbidity resulted after a few minutes of shaking, and soon VII separated in 68% yield. It was recrystallized from ethyl alcohol; m. p. 164–167°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: N, 6.51. Found: N, 6.64.

1,5-Dihydroxy-1,5-bis-(quinolyl-2)-pentanone-3 (VIII).—A mixture was prepared consisting of 0.4 cc. of ace-

(4) Pfitzinger, *J. prakt. Chem.*, **66**, 264 (1902).

tone, 0.9 cc. of 95% ethyl alcohol and 4 drops of diethylamine; to this was added 0.31 g. of quinoline-2-aldehyde hydrate. The reaction mixture was allowed to remain at room temperature for two days, and at the end of that time crystals of VIII had separated: soluble in benzene, xylene, butyl alcohol; recrystallized from xylene; m. p. 208–210°; yield 32%.

Anal. Calcd. for $C_{28}H_{20}O_3N_2$: N, 7.53. Found: N, 7.60.

Summary

Lepidine and 6-methoxylepidine are oxidized by selenium dioxide to quinoline-4-aldehyde and 6-methoxyquinoline-4-aldehyde, respectively. Quinoline-4-aldehyde condenses with nitromethane to give a product of the aldol type, while acetophenone yields diacetophenonyl-lepidine. Quinoline-2-aldehyde, previously described, forms aldol-like products with acetone, acetophenone and nitromethane.

UNIVERSITY HEIGHTS
NEW YORK, N. Y.

RECEIVED JANUARY 18, 1937

[CONTRIBUTION FROM PRIVATE LABORATORIES, AND RESEARCH LABORATORIES, MERCK AND COMPANY, INC.]

Studies of Crystalline Vitamin B_1. XV. C-Methylated 6-Amino- and 6-Oxypyrimidines

BY ROBERT R. WILLIAMS, A. E. RUEHLE AND JACOB FINKELSTEIN

For purposes of comparison with the pyrimidine cleavage products of vitamin B_1 (Aneurin), we have prepared 6-amino- and 6-oxypyrimidine and all of the possible mono- and di-C-methyl derivatives and have observed the ultraviolet absorption of each. 5-ethyl-6-aminopyrimidine is also included. The literature references indicate the methods of preparation of certain known compounds.[1] Some known compounds were obtained by new methods: *e. g.*, 4-methyl-6-oxy- and 5-methyl-6-oxypyrimidines were obtained by oxidizing the 2-thio derivatives with hydrogen peroxide.[2] 2,5-Dimethyl-6-oxypyrimidine resulted from condensing sodioformylpropionic ester with acetamidine and the oxy derivative was converted in the conventional way to the amino. The preparative operations were not carried out repeatedly so the reported yields in general are probably not optimal.

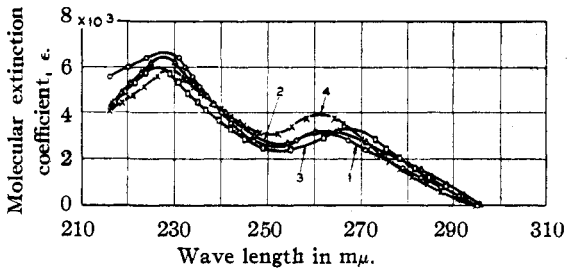


Fig. 1.—1. 6-Oxypyrimidine. 2. 4-Methyl-6-oxypyrimidine. 3. 2-Methyl-6-oxypyrimidine. 4. 5-Methyl-6-oxypyrimidine.

Discussion of Results

Curves of ultraviolet absorption in water solution for the series of 6-oxypyrimidines are shown in Figs. 1, 2 and 3. A great similarity of character is observed throughout, all the compounds exhibiting absorption in two bands which vary somewhat in frequency and slightly in intensity according to the number and position of substituent alkyls. Curves of this character are observed also in other oxy compounds in which one hydrogen of a substituent methyl group is replaced by ethoxy, halogen or sulfonic group as will develop in later papers.

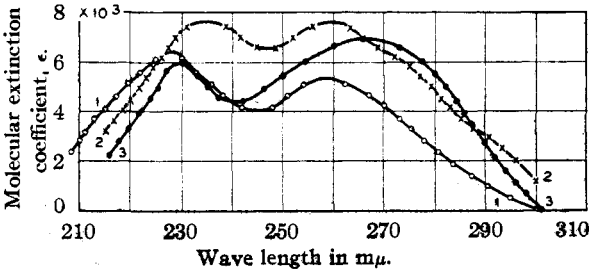


Fig. 2.—1. 2,4-Dimethyl-6-oxypyrimidine. 2. 4,5-Dimethyl-6-oxypyrimidine. 3. 2,5-Dimethyl-6-oxypyrimidine.

The 6-amino series shows a kindred absorption in water solution (Figs. 4 and 5), but the curves are less homogeneous in type than in the oxy series. The amino compounds show a striking

(1) (a) 6-Oxypyrimidine—Wheeler, *J. Biol. Chem.*, **3**, 287 (1907); (b) 6-aminopyrimidine—Buttner, *Ber.*, **36**, 2232 (1903); (c) 2-methyl-6-oxy- and 2-methyl-6-aminopyrimidine—Gabriel, *ibid.*, **37**, 3638 (1904); (d) 5-ethyl-6-aminopyrimidine—v. Merkatz, *ibid.*, **52**, 871 (1919); (e) 2,4-dimethyl-6-oxypyrimidine—Wollner, *J. prakt. Chem.*, [2] **29**, 132 (1884); (f) 2,4-dimethyl-6-aminopyrimidine—v. Meyer, *ibid.*, [2] **27**, 152 (1883).

(2) Wheeler and McFarland, *Am. Chem. J.*, **42**, 105 (1909).