[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE SEARCH FOR SUPERIOR DRUGS FOR TROPICAL DISEASES. I. DERIVATIVES OF QUININALDEHYDE AND 6,7-DIMETHOXYCINCHONINALDEHYDE

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The search for such drugs has led to the extensive investigations of derivatives of quinoline, particularly methoxyquinolines. Quinoline aldehydes, when available, are convenient compounds for the introduction of substituents in the quinoline nucleus. Such aldehydes can be prepared when alkyl groups are present in the 2- or 4-position by their oxidation with selenium dioxide and a few aldehydes have been prepared by this method. Quininaldehyde was synthesized by Monti (15), cinchoninaldehyde and quininaldehyde by Kwartler and Lindwall (8), and 8-nitrocinchoninaldehyde by Johnson and Hamilton (16). Kaplan (7) studied the action of freshly prepared and aged selenium dioxide. Burger and Modlin (17), and Glenn and Bailey (18), found that alkyl groups in the 3- or 8- positions were not oxidized by selenium dioxide. They were thus able to prepare 3,8-dimethyl, 5-nitro-3,8-dimethyl, 8-ethyl, and 3-methyl-8-ethyl quininaldehydes from the corresponding alkylquinolines.

Researches having indicated that the work on compounds with substituents in the 4-position of the quinoline nucleus is worthy of extension (1, 2, 3, 4), the present article reports condensation reactions of quininaldehyde and 6,7-dimethoxycinchoninaldehyde. Previous condensations of quinoline-4-aldehydes reported in the literature are the reactions of cinchoninaldehyde with acetophenone, nitromethane (8), methylmagnesium iodide (16), 2-methoxy-4-methyl-8-aminoquinoline (19), *alpha*-diethylamino-*delta*-aminopentane (5), lepidine, quinaldine, sulfanilamide (20), and the reaction of 8-nitrocinchoninaldehyde with nitroethane (16).

6-Methoxylepidine (I), prepared according to the method of Mikhailov (6), as improved upon by Ainley and King (2), was oxidized by means of freshly prepared selenium dioxide (8) to give (II), which in turn was condensed with nitromethane and nitroethane to the *alpha*-nitrocarbinols (III), following essentially the same procedure used by Kwartler and Lindwall (8) to condense cinchoninaldehyde with nitromethane. Repeated attempts to reduce the nitroethane condensation product to the corresponding carbinolamine (IV) by hydrogen in the presence of Raney nickel in absolute alcohol failed. When the solution was acidified with acetic acid, however, the reduction product was stabilized and the carbinolamine was obtained, although attempts to purify the compound led to decomposition. Similar difficulties in the reduction of nitrocarbinols were encountered by Gakenheimer and Hartung (9) who also suggested the successful method used above for reducing such compounds. The acetylsulfonamide (V)

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and the sulfonamide (VI) derivatives of (IV) were made by the action of acetylsulfanilyl chloride and subsequent hydrolysis.

6,7-Dimethoxylepidine (VII) was synthesized by the Mikhailov (6) method and oxidized by selenium dioxide to 6,7-dimethoxycinchoninaldehyde (VIII), which was then condensed with nitroethane to give the *alpha*-nitrocarbinol (IX).

During the course of this investigation, 6-methoxylepidine and 6,7-dimethoxyquinoline were hydrogenated to the corresponding 1,2,3,4-tetrahydro derivatives, and treatment with acetylsulfanilyl chloride produced the acetylsulfanilamides. Of these two sulfanilamides the latter has been subjected to pharmacological tests and the results will be reported elsewhere.

By the action of methyl iodide on (XI) the N-methyl compound (XII) and the N-dimethylquinolinium iodide (XIV) were obtained.

Work in the 6,7-dimethoxyquinoline field was suspended when the findings of Schönhöfer (10) and of Frisch and Bogert (12) showed that the introduction of the methoxyl group in the 7-position of the quinoline nucleus reduced the antimalarial activity of such compounds. Further studies on the condensation of quininaldehyde and cinchoninaldehyde with nitroalkanes and amines are being carried out in these laboratories and will be communicated later.

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EXPERIMENTAL

All melting points are corrected for exposed thermometer stem.

Quininaldehyde (II). Sixty-eight grams of freshly distilled 6-methoxylepidine dissolved in 450 ml. of xylene was heated to 130° in a three-neck flask equipped with a Hershberg stirrer (11) and an air condenser, and 45 g. of selenium dioxide was added in small amounts over a period of one-half hour, the condenser being removed before each addition to allow the water which had been formed to distil off. Stirring and heating at 130–135° were then continued for one hour. The solution was filtered, washed with potassium carbonate solution and water, and the xylene was distilled off under reduced pressure. The pure aldehyde was obtained by extracting the residue with boiling Skelly D solvent and chilling the extract; yield, 41 g. (56%); m.p. 95°. When a water solution of the aldehyde was evaporated on the steam-bath, long, soft, pale yellow needles filled the beaker above the solution. These melted at 97–97.5°. Previously reported m.p. 96–98° (from toluene); yield, 52% (8).

alpha-(6-Methoxyquinolyl-4)-beta-nitropropanol (III). To 10 g. of (II) dissolved in 40 ml. of absolute alcohol and cooled in an ice-water bath, was added 12 ml. of nitroethane and 50 drops of fresly distilled diethylamine. The mixture was seeded with a crystal of the condensation product, since unless crystallization started promptly, the yield fell off considerably. The solution was allowed to stand for two days at room temperature and then chilled and filtered. The product was washed once with cold ethanol and several times with ether until it was white. Cautious addition of water to the alcoholic filtrate yielded a second crop; yield, 10.5 g. (75%); m.p. 149.5–150.5° (when placed in the melting point bath at 140°).

Anal. Calc'd for $C_{13}H_{14}N_2O$: C, 59.5; H, 5.4.
Found: C, 59.9; H, 5.7.

alpha-(6-Methoxyquinolyl-4)-beta-nitroethanol. In a similar manner (II) was condensed with nitromethane. The yield was 75%, and recrystallization from methyl alcohol produced white needles, m.p. 148–149°.

Anal. Calc'd for $C_{12}H_{12}N_2O_4$: C, 58.1; H, 4.9.
Found: C, 58.3; H, 4.8.

FLOW SHEET

I = R—Me

II = R—CHO

III = R—CH(OH)CHMeNO$_2$

IV = R—CH(OH)CHMeNH$_2$

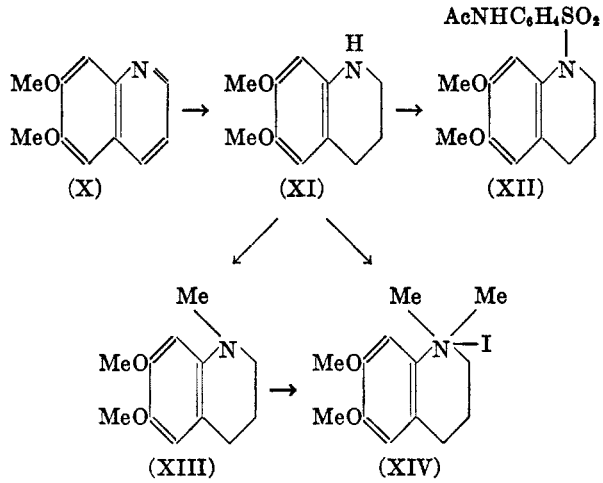
V = R—CH(OH)CHMeNHSO$_2$C$_6$H$_4$NHAc

VI = R—CH(OH)CHMeNHSO$_2$C$_6$H$_4$NH$_2$

VII = R′—Me

VIII = R′—CHO

IX = R′—CH(OH)CHMeNO$_2$



alpha-(6-Methoxyquinolyl-4)-beta-acetylsulfanilamidopropanol (V). Five and eight-tenths grams of (III) was dissolved in 14 ml. of acetic acid and 30 ml. of absolute alcohol and reduced under 30 lbs. pressure by hydrogen in the presence of 1 g. of Raney nickel. Occasional heating to 60° accelerated the process. When no more hydrogen was absorbed, the solution was filtered and the solvents were distilled off under reduced pressure at room temperature. The residue was dissolved in water, neutralized with potassium carbonate, and refluxed with 5 g. of acetylsulfanilyl chloride in acetone-aqueous potassium carbonate

solution for one and one-half hours. Most of the acetone was then evaporated, water was added, and the crystalline precipitate filtered out; yield, 4 g. It was recrystallized from ethanol-water in the form of extremely thin white plates, m.p. 216.5–217° (decomp.).

Anal. Calc'd for $C_{21}H_{23}N_3O_5S$: C, 58.7; H, 5.4.

Found: C, 59.2; H, 5.5.

alpha-(6-Methoxyquinolyl-4)-beta-sulfanilamidopropanol (VI). Two grams of (V) was refluxed with 25 ml. of 10% hydrochloric acid for two hours, diluted with water, and neutralized with sodium bicarbonate. A gummy precipitate formed which crystallized on standing a short time. The solid was boneblacked and recrystallized from 80% ethanol; yield, 1.6 g. (83%); long white needles, m.p. 210–210.5°.

Anal. Calc'd for $C_{19}H_{21}N_3O_4S$: C, 58.9; H, 5.5.

Found: C, 59.0; H, 5.5.

6-Methoxy-1,2,3,4-tetrahydrolepidine. Thirteen grams of 6-methoxylepidine was hydrogenated under 2800 lbs. pressure at 240° in the presence of 2 g. of copper chromite catalyst (14) without the use of any solvent. The catalyst was filtered, washed with alcohol, and the filtrate fractionated; yield, 11.5 g. (86%); b.p. 114–115°/0.5 mm.

Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.6; H, 8.5.

Found: C, 75.0; H, 8.5.

1-Acetylsulfanilyl-6-methoxy-1,2,3,4-tetrahydrolepidine. Eleven grams of the above was refluxed with 16 g. of acetylsulfanilyl chloride in acetone-aqueous sodium bicarbonate for one hour and the mixture was then poured into water and filtered; yield, 20 g. (86%). Recrystallization from alcohol-water gave a white solid which melted at 173–174°.

Anal. Calc'd for $C_{19}H_{22}N_2O_4S$: N, 7.5.

Found: N, 7.8.

2-Chloro-6,7-dimethoxylepidine. Sixty-four grams of 2-hydroxy-6,7-dimethoxylepidine, prepared according to the method of Frisch and Bogert (12) from 4-aminoveratrole, was refluxed with 170 ml. of phosphorus oxychloride for three hours. The excess of oxychloride was removed by distillation under reduced pressure. The crude product was stirred with two liters of water, dissolved by warming, filtered, and the filtrate made alkaline by the addition of ammonium hydroxide; yield, 64.5 g. (92%). Recrystallization from hot ethanol by the addition of water, gave white needles, m.p. 172.5–173°.

Anal. Calc'd for $C_{12}H_{12}ClNO_2$: C, 60.6; H, 5.1.

Found: C, 61.0; H, 5.3.

6,7-Dimethoxylepidine (VII). A mixture of 25 g. of 2-chloro-6,7-dimethoxylepidine, 180 ml. of glacial acetic acid, 8 g. of anhydrous sodium acetate, and 2 g. of Pd-C catalyst, was shaken under 40 lbs. pressure with hydrogen at 65–70°. When the theoretical amount of hydrogen had been absorbed, the mixture was filtered and the acetic acid removed under reduced pressure. The residue was made alkaline with potassium hydroxide, extracted with ether, and the extract dried over magnesium sulfate. On evaporation of the ether, 20 g. (94%) of a light solid was obtained. Recrystallization from ether gave white thin plates, m.p. 112–112.5°.

Anal. Calc'd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.5.

Found: C, 71.15; H, 6.6.

The *picrate* formed immediately when alcoholic solutions of (VII) and picric acid were mixed. It recrystallized from hot ethanol in the form of flat needle-like prisms, m.p. 247–247.5° (decomp.).

Anal. Calc'd for $C_{18}H_{16}N_4O_9$: C, 50.0; H, 3.7.

Found: C, 50.3; H, 3.9.

6,7-Dimethoxycinchoninaldehyde (VIII). Five grams of (VII) was oxidized with 3.1 g. of selenium dioxide in 75 ml. of dioxane. After refluxing for four hours, the mixture was filtered and the dioxane evaporated under reduced pressure. The residue was extracted with hot water and the extract bone-blacked. The aqueous solution was evaporated to a small volume, made just alkaline with sodium carbonate, and extracted three times with ether. The ether extract was dried over magnesium sulfate and the ether removed by

evaporation; yield, 3.7 g. (71%). Two recrystallizations from ethanol gave soft, long needles, m.p. 171–171.5°.

Anal. Calc'd for $C_{12}H_{11}NO_3$: C, 66.3; H, 5.1; N, 6.45.
Found: C, 66.6; H, 5.4; N, 6.6.

alpha-(6,7-Dimethoxyquinolyl-4)-beta-nitropropanol (IX). To 6 g. of (VIII) dissolved in 200 ml. of absolute alcohol and cooled in an ice-water bath was added 7.5 ml. of nitroethane and 45 drops of freshly distilled diethylamine. A crop of crystals appeared in a short time when the solution was allowed to stand at room temperature. After two days the mixture was filtered; yield, 6.4 g. (79%). Recrystallization from ethanol gave small white needles, m.p. 177–177.5°.

Anal. Calc'd for $C_{14}H_{16}N_2O_5$: C, 57.5; H, 5.5; N, 9.6.
Found: C, 57.6; H, 5.4; N, 9.3.

6,7-Dimethoxy-1,2,3,4-tetrahydroquinoline (XI). Forty-six grams of 6,7-dimethoxyquinoline (X), prepared from 4-aminoveratrole according to the method of Frisch and Bogert (13) was dissolved in cyclohexane-absolute alcohol, mixed with 4 g. of copper chromite catalyst (14), and hydrogenated under 2900 pounds pressure at 200°. The catalyst was filtered off, the solvents evaporated, and the residue fractionated. The distillate solidified on standing; yield, 41 g. (87%). A sample recrystallized by dissolving it in the minimum quantity of benzene and diluting with a large volume of Skelly B solvent, melted at 45–45.5°.

Anal. Calc'd for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8.
Found: C, 68.7; H, 8.1.

1-Acetylsulfanilyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (XII). Three grams of (XI) was refluxed with 4 g. of acetylsulfanilyl chloride in acetone-aqueous sodium bicarbonate for one hour and the mixture was poured into water and filtered; yield, 5 g. (82%). A sample was purified by dissolving it in ethanol, boneblacking, and adding water. The crystals appeared as bipyramids with hexagonal bases, m.p. 181–181.5°, and exhibited dimorphism. When dissolved in ethanol, containing a small amount of water and kept at steam-bath temperature, needles appeared, m.p. 192–193°. These could be reconverted to the bipyramids by dissolving them in ethanol, evaporating to a small volume, and precipitating rapidly by the addition of cold water. When the lower-melting form was kept in the melting point apparatus just above its melting point, it solidified and then melted at the higher melting point when the temperature was raised.

Anal. Calc'd for $C_{19}H_{22}N_2O_5$: C, 58.4; H, 5.7.
Found: C, 58.5; H, 5.9.

A small amount of (XII) remaining from the biochemical tests was refluxed with 10% HCl, a few drops of ethanol being added to prevent foaming and creeping. The solution was neutralized, filtered, and the precipitate was boneblacked in ethanol. Addition of water yielded white crystals of the deacetylated compound, m.p. 166–167°.

1-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (XIII). Twenty-one grams of methyl iodide was added to 28 g. of (XI). A vigorous reaction took place, the mixture boiling so violently that cooling was necessary. A slight excess of methyl iodide was added and the mixture was allowed to stand overnight in the refrigerator. It was dissolved in hot water, stirred with 20 ml. of 20% sodium hydroxide solution, and extracted with ether. The ether extract was washed with small portions of water and dried over potassium hydroxide. The solvent was removed by evaporation and the residue was fractionated; b.p. 135–136°/1 mm.; yield, 17 g. (57%).

Anal. Calc'd for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.1.
Found: C, 69.5; H, 8.2.

1,1-Dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinolinium iodide (XIV). A voluminous precipitate was present in the water layer obtained from the ether extraction of (XIII). It dissolved on warming and formed long white prisms on cooling. Recrystallization from 90% ethanol, yielded 10 g. (20%) of (XIV), m.p. 216.5–217.5° (decomp.).

Anal. Calc'd for $C_{13}H_{21}INO_2$: C, 44.6; H, 6.0.
Found: C, 44.9; H, 6.0.

SUMMARY

1. Quininaldehyde was condensed with nitromethane and nitroethane and the product was reduced to the corresponding carbinol amine. From the latter the acetylsulfanilamide and sulfanilamide derivatives were prepared.

2. 6-Methoxylepidine was hydrogenated to the corresponding 1,2,3,4-tetrahydrolepidine, from which the acetylsulfanilamide was prepared.

3. 6,7-Dimethoxylepidine was synthesized and oxidized to 6,7-dimethoxycinchoninaldehyde, which was condensed with nitroethane.

4. 6,7-Dimethoxyquinoline was hydrogenated to the corresponding 1,2,3,4-tetrahydroquinoline, from which the acetylsulfanilamide, sulfanilamide, N-methyl, and N-dimethyl iodide derivatives were prepared.

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