[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICINAL RESEARCH]

Some Derivatives of Alkylene-Bridged 5,6-Dihydroxyquinoline[1a]

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An enhancement of antimalarial activity by modification of the quinoline nucleus in the pamaquine type occurs when a second RO– group is substituted in the 5-position.[1b,2] This paper deals with the synthesis of related compounds containing the 5,6-methylenedioxy-, 5,6-ethylenedioxy- and 5,6-isopropylidenedioxy groups. Compounds of this type have been proposed during the malaria research program,[3] but apparently no report of their successful preparation has been published; the preparation of 6,7-methylenedioxyquinoline by the reaction of 6-aminopiperonal and methazonic acid has been described.[4]

The preparation of the alkylene bridged 5,6-dihydroxyquinoline prototypes is illustrated by the series of reactions involved in the synthesis of 5,6-ethylenedioxy-8-(isopropylaminoamylamino)-quinoline: resorcinol → 1,4-benzodioxane → 4-nitro-1,4-benzodioxane → 4-amino-1,4-benzodioxane → 4-acetamido-1,4-benzodioxane → 5-nitro-4-acetamido-1,4-benzodioxane → 5-nitro-4-amino-1,4-benzodioxane → 5,6-ethylenedioxy-8-nitroquinoline.

Along with 5,6-ethylenedioxy-8-nitroquinoline, as a by-product of the 60-second Skraup reaction,[2,5] there was obtained 5,6-dihydroxy-8-nitroquinoline. The formation of 5-hydroxy-6-methoxy-8-nitroquinoline during a 90-second Skraup reaction with 4-acetamino-5-nitroveratrole has been reported.[2]

5,6-Methylenedioxy-8-aminoquinoline could not be condensed with isopropylaminoamyl chloride hydrochloride or 1-isopropylamino-4-bromopentane hydrobromide under the usual conditions.[6,7] However, a condensation with diethylaminopropyl chloride was eventually effected by using sodamide as the condensing agent,[8] a method originally described by Eisleb[9] for introducing the dialkylaminoethyl group into active methylene compounds and later extended by Dewar[10] for the dialkylaminoalkylation of substituted anilines.

It was not possible to convert 5-nitro-4-acetamido-1,2-isopropylidenedioxybenzene to the corresponding quinoline derivative by the various Skraup methods.[11,12] This could be attributed to the lability of the isopropylidenedioxy grouping since none of the starting material was recovered.

Pharmacological Studies.[13]—In two series of Test G-1[1b] against *Plasmodium lophurae* in the duckling, 5,6-ethylenedioxy-8-(isopropylaminoamylamino)-quinoline gave Q-values of 60 and 80; against *Plasmodium cathemerium* the same compound gave Q-values of 60 and 80. In one series of tests against *Plasmodium lophurae* 5,6-methylenedioxy-8-(diethylaminopropylamino)-quinoline gave a Q-value of 30.

Experimental Part[13a]

1,2-Methylenedioxybenzene[14] and **4-nitro-1,2-methylene-dioxybenzene**[15] were prepared according to the literature methods.

4-Acetamido-1,2-methylenedioxybenzene has been described previously[15] but was prepared for the first time via a catalytic reduction of the nitro compound. A mixture of 16.7 g. (0.1 mole) of 4-nitro-1,2-methylenedioxybenzene, 0.3 g. of 5% palladium on charcoal and 150 ml. of absolute ethanol was shaken at room temperature under 50 pounds pressure of hydrogen. Reduction was complete in about twenty minutes. Five runs were carried out in this manner, combined, filtered free of catalyst and the alcohol removed under reduced pressure. The oily residue crystallized when treated with 150 ml. of acetic anhydride. Acetylation was completed by an additional one hour of heating on the steam-bath. The crystalline 4-acetamido-1,2-methylenedioxybenzene separated out on cooling. After filtering and washing with water the solid weighed 60 g. (67% yield), m. p. 135–136° (lit.[15] 135°).

5-Nitro-4-acetamido-1,2-methylenedioxybenzene was prepared according to the method of Jones and Robinson.[16]

5-Nitro-4-amino-1,2-methylenedioxybenzene has been prepared[15] but no experimental details were given. In the present work the preparation was carried out as follows: a mixture of 121 g. (0.54 mole) of the 5-nitro-4-acetamido-1,2-methylenedioxybenzene, 363 ml. of absolute ethanol and 726 ml. of concd. hydrochloric acid was refluxed and stirred for one-half hour, then poured into one liter of water. The solution was made alkaline with concd. ammonia and the precipitated solid was filtered, washed with water and air-dried. A quantitative yield of 5-nitro-4-amino-1,2-methylenedioxybenzene was obtained, 98 g., m. p. 194–195° (lit.[15] 198°).

5,6-Methylenedioxy-8-nitroquinoline.—Method B[12] was followed except that the operating temperature was 60–70°. The yield from a 0.1 mole run was 11 g. (50%), m. p. 191–192°.

Anal. Calcd. for $C_{10}H_6N_2O_4$: C, 55.05; H, 2.75; N, 12.84. Found: C, 54.97; H, 2.69; N, 13.08.

(1a) Presented before the Division of Medicinal Chemistry, 113th Meeting, American Chemical Society, Chicago, Ill., April 19–23, 1948.

(1b) F. Y. Wiselogle, "Survey of Antimalarial Drugs, 1941–1945." Vol. II, Part II, J. W. Edwards, Ann Arbor, Michigan, 1946, pp. 1231–1233.

(2) Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).

(3) Private communication from F. Y. Wiselogle.

(4) Clemo and Swan, *J. Chem. Soc.*, 867 (1945).

(5) Drake, *et al.*, THIS JOURNAL, **68**, 1536 (1946).

(6) Drake, *et al.*, *ibid.*, **68**, 1529 (1946).

(7) Elderfield, *et al.*, *ibid.*, **68**, 1524 (1946).

(8) This method will be reported in detail by Dr. J. T. Sheehan in a forthcoming publication from these laboratories.

(9) Eisleb, *Ber.*, **74**, 1433 (1941).

(10) Dewar, *ibid.*, 619 (1944).

(11) Yale, THIS JOURNAL, **69**, 1230 (1947).

(12) Yale and Bernstein, *ibid.*, **70**, 254 (1948).

(13) The pharmacological studies were carried out by the Division of Pharmacology, Squibb Institute for Medical Research.

(13a) All melting points are uncorrected.

(14) Shorygin, Simanovskaya and Bogdanova, *J. Gen. Chem., U. S. S. R.*, **8**, 975 (1938); *C. A.*, **33**, 3777 (1939).

(15) Perkin, Robinson and Thomas, *J. Chem. Soc.*, **95**, 1979 (1909).

(16) Jones and Robinson, *J. Chem. Soc.*, **111**, 903 (1917).

5,6-Methylenedioxy-8-aminoquinoline.—A suspension of 10.9 g. (0.05 mole) of 5,6-methylenedioxy-8-nitroquinoline and 10 g. of 5% palladium on charcoal in 130 ml. of ethyl acetate was hydrogenated at room temperature and 50 pounds pressure of hydrogen. The product isolated in the usual manner weighed 6.0 g. (63% yield), m. p. 116–117°.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.25; N, 14.89. Found: C, 63.56; H, 4.25; N, 14.86.

5,6-Methylenedioxy-8-(3-diethylaminopropylamino)-quinoline.—Four grams of sodamide wet with toluene was added to a solution of 15 g. (0.08 mole) of 5,6-methylenedioxy-8-aminoquinoline, 12.4 g. (0.083 mole) of diethylaminopropyl chloride and 75 ml. of distilled toluene. The mixture was heated in an oil-bath to 70° and kept at this temperature for half an hour during which time there was a constant evolution of ammonia. The bath temperature was then raised to 115° over a period of half an hour and maintained at this temperature for five hours, when the evolution of ammonia had ceased. After cooling to room temperature, 8 g. of unreacted starting material crystallized out and was recovered by filtration. The toluene solution was washed with water and then extracted four times with 75-ml. portions of 5% acetic acid. The combined acid extracts were washed with three 25-ml. portions of ether, then made alkaline with sodium hydroxide and the free oily base extracted with three 100-ml. portions of ether. The combined ether extracts were washed with water and dried over anhydrous potassium carbonate. The ether was evaporated and the residue fractionated. The fraction boiling at 198–200° (1.4 mm.), 5.0 g., (20% yield) was collected. Allowing for the recovered starting material, the yield was 44%.

Anal. Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.77; H, 7.64; H, 13.95. Found: C, 67.33; H, 7.62; N, 14.27.

5,6-Methylenedioxy-8-(3-diethylaminopropylamino)-quinoline Monohydriodide.—Five grams (0.0166 mole) of the free base was dissolved in 30 ml. of 4% acetic acid and treated with a solution of 3 g. of potassium iodide in 10 ml. of water. The product separated cleanly and was recrystallized from alcohol–ether; yield, 6 g. (84.3% yield) of a bright yellow crystalline solid, m. p. 154–155°.

Anal. Calcd. for $C_{17}H_{23}N_3O_2 \cdot HI$: C, 47.56; H, 5.59; N, 9.79. Found: C, 47.68; H, 5.54; N, 9.86.

5,6-Methylenedioxy-8-(3-diethylaminopropylamino)-quinoline Dihydriodide.—The dihydriodide was prepared by dissolving the base in anhydrous ether and adding a slight excess (5%) over the calculated amount of 57% hydriodic acid. The product obtained in this manner, even after several recrystallizations from alcohol, was discolored and somewhat unstable so that satisfactory analyses could not be obtained. The compound melted at 158–159°.

Anal. Calcd. for $C_{17}H_{23}N_3O_2 \cdot 2HI$: C, 36.63; H, 4.48; N, 7.54. Found: C, 37.57; H, 4.96; N, 7.66.

Attempted Condensations with 5,6-Methylenedioxy-8-aminoquinoline.—Utilizing procedures which were successful in condensing other 8-aminoquinolines, a number of attempts were made to condense isopropylaminoamyl chloride hydrochloride and 1-isopropylamino-4-bromopentane hydrobromide with 5,6-methylenedioxy-8-aminoquinoline, but without success.

1,4-Benzodioxane was prepared according to the method of Ghosh[17] and was converted to **4-nitro-1,4-benzodioxane** according to the directions of Vorländer.[18] **4-Amino-1,4-benzodioxane** was not isolated but was converted directly to the 4-acetamidobenzodioxane,[19] as described above for the methylene compound.

5-Nitro-4-acetamido-1,4-benzodioxane was prepared according to the method of Jones and Robinson[16] for the methylene compound; yield, 92%, m. p. 179°.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.20; N, 11.76. Found: C, 50.26; H, 4.38; N, 11.78.

5-Nitro-4-amino-1,4-benzodioxane.—The hydrolysis of the above derivative was effected as described above for the methylene derivative; yield 96%, m. p. 150–151°.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.97; H, 4.11; N, 14.28. Found: C, 48.57; H, 4.03; N, 14.64.

5,6-Ethylenedioxy-8-nitroquinoline. (a) **The Sixty-Second Skraup.**—A procedure essentially that employed by Elderfield[2] was used. Our procedure is described in detail because of certain changes which facilitate the mechanical operations involved. Into a beaker set in an oil-bath and equipped with a mechanical stirrer and two long-stemmed separatory funnels which extended to the bottom of the beaker, was placed a mixture of 12 g. (0.055 mole) of 5-nitro-4-acetamido-1,4-benzodioxane, 7 g. (0.031 mole) of arsenic pentoxide and 40 ml. of *high-test* glycerol. One funnel contained 15 ml. of concd. sulfuric oxide and the other 150 ml. of ice-water.

The oil-bath was heated to 150° while the mixture was stirred vigorously. The flame was removed and all the sulfuric acid was added below the surface of the mixture. An immediate exothermic reaction occurred and was allowed to continue for exactly sixty seconds. The oil-bath was removed and the water added all at once below the surface of the reaction mixture. The reaction mixture was filtered to remove any unreacted starting material and the filtrate made strongly alkaline with 200 ml. of 20% sodium hydroxide. The precipitate was filtered off, washed with water and redissolved in 40 ml. of 5% hydrochloric acid. From the above alkaline filtrate after adjusting to *p*H 4 there was obtained 4 g. of crude **5,6-dihydroxy-8-nitroquinoline** (see below). The acid solution containing the product was made alkaline with 11 ml. of concd. ammonia and the solid filtered off and dried. After crystallization from acetone there was obtained 5 g. (42%) of 5,6-ethylenedioxy-8-nitroquinoline, m. p. 158–159°.

Anal. Calcd. for $C_{11}H_8N_2O_4$: C, 56.89; H, 3.44; N, 12.06. Found: C, 56.93; H, 3.63; N, 12.18.

5,6-Dihydroxy-8-nitroquinoline was recrystallized from boiling water, even though the solubility is only about 0.5 g. per liter. No other suitable solvent could be found. From water the compound forms purple needles which do not melt up to 300°.

Anal. Calcd. for $C_9H_6N_2O_4$: C, 52.43; H, 2.91; N, 13.59. Found: C, 52.95; H, 3.24; N, 13.66.

(b) **With Acrolein (Method A).**[12]—Yield, 36%.

(c) **With Acrolein** (see procedure above for methylenedioxy derivative), yield 53%.

5,6-Ethylenedioxy-8-aminoquinoline.—A suspension of 14.7 g. of 5,6-ethylenedioxy-8-nitroquinoline, 100 ml. of ethyl acetate and 2.5 g. of 5% Pd on charcoal was reduced catalytically at room temperature and 45 pounds pressure of hydrogen. The product was recrystallized from 75 ml. of 95% ethanol; yield 8.5 g. (66%), m. p. 73–74°, b. p. 144° (0.3 mm.) (oil-bath at 204–208°).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.95; N, 13.86. Found: C, 65.48; H, 4.77; N, 14.03.

5,6-Ethylenedioxy-8-(isopropylaminoamylamino)-quinoline Monohydrochloride and Monophosphate.—The condensation was carried out under the conditions described for SN 13,276[6] using 23.5 g. (0.165 mole) of the nucleus, 16.8 g. (0.084 mole) of isopropylaminoamyl chloride hydrochloride and 21 ml. of water. The monohydrochloride crystallized from hot water, m. p. 125–126°, 24.3 g., 79.0% yield.

Anal. Calcd. for $C_{19}H_{28}N_3O_2Cl$: N, 11.50; Cl, 9.71. Found: N, 11.29; Cl, 9.85.

The monohydrochloride was converted to the monophosphate in the usual manner,[6] the yield 23.5 g. (65.4%) of a bright yellow crystalline product, m. p. 216–218°.

Anal. Calcd. for $C_{19}H_{30}N_3O_6P$: N, 9.84; P, 7.26. Found: N, 9.60; P, 7.20.

1,2-Isopropylidenedioxybenzene and **4-nitro-1,2-isopropylidenedioxybenzene** were prepared according to the literature methods.[20]

(17) Ghosh, *J. Chem. Soc.*, **107**, 1588 (1915).

(18) Vorländer, *Ann.*, **280**, 206 (1894).

(19) Moureau, *Ann. chim.*, [7] **18**, 100 (1899).

(20) Slooff, *Rec. trav. chim.*, **54**, 995 (1935).

4-Acetamido-1,2-isopropylidenedioxybenzene was prepared as described for the corresponding methylene- and ethylenedioxy- compounds. A small portion of the product was purified for analysis, m. p. 107–108°, after recrystallization from a mixture of ethyl acetate and hexane.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.73; H, 6.28; N, 6.76. Found: C, 63.60; H, 5.99; N, 6.67.

5-Nitro-4-acetamido-1,2-isopropylidenedioxybenzene was obtained in the manner described for the corresponding methylene- and ethylenedioxy- compounds, m. p. 162–163° after recrystallization from 95% ethanol. The yield, based on the 4-nitro-1,2-isopropylidenedioxybenzene, was 85%.

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.35; H, 4.77; N, 11.12. Found: C, 52.28; H, 4.87; N, 11.32.

5-Nitro-4-amino-1,2-isopropylidenedioxybenzene was prepared by the hydrolysis of the corresponding acetamido compound in the same manner as described for the methylene- and ethylenedioxy- compounds. Employing 45 g. (0.18 mole) of 5-nitro-4-acetamido-1,2-isopropylidenedioxybenzene and 350 ml. of 1.3 *N* ethanolic hydrochloric acid there was obtained 30 g. (80% yield) of product, m. p. 123.5–124.5°, after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.79; N, 13.33. Found: C, 51.35; H, 5.07; N, 13.38.

Attempted preparation of **5,6-isopropylidenedioxy-8-nitroquinoline**: (a) Method A, with acrolein.—Carried out in the usual manner there was obtained no acid-soluble material. The principal product was a black acid insoluble gum, which was somewhat soluble in boiling ethanol, giving a red solid which did not melt up to 250°.

(b) Method B, with phosphoric acid at 25° and 40°; none of the desired quinoline compound was obtained.

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Summary

The preparation of several prototype alkylene bridged 5,6-dihydroxyquinoline compounds is described. The compounds have shown fairly high activity against *Plasmodium lophurae* and *Plasmodium cathemerium* in the duckling.

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Alkylation of Thiophene with Olefins

BY PHILIP D. CAESAR[1]

The direct alkylation of thiophene with olefins and alcohols in the presence of alumina–silica type catalysts and of 100% phosphoric acid was reported by Kutz and Corson.[2] In contrast to their observations, it has been found in this Laboratory that thiophene can be alkylated with olefins under suitable conditions in the presence of sulfuric acid, aluminum chloride, or boron trifluoride–diethyl ether complex without excessive decomposition or resinification of the thiophene. Other suitable alkylation catalysts were found to be fluoacids of boron trifluoride with water, ethyl acetate, ethyl alcohol and acetic acid. The olefinic alkylating agents employed were isobutylene, trimethylethylene, 1-pentene, diisobutylene, 1-octene and 1-hexadecene.

There are two primary factors which determine the selection of the catalyst. One is the reactivity of the olefinic alkylating agent and the other is the relative proportion of mono- and dialkylthiophene desired. If a reactive olefin such as isobutylene, trimethylethylene or diisobutylene is used, any of the catalysts described above, with the possible exception of aluminum chloride and concentrated sulfuric acid, will give satisfactory yields of the corresponding alkylthiophenes at moderate temperatures and atmospheric pressure (see Table I). The alkylation of thiophene with the relatively unreactive, straight chain olefins such as 1-pentene, 1-octene or 1-hexadecene, takes place most satisfactorily in the presence of strong catalysts such as 90–96% sulfuric acid or boron trifluoride–water complex.

TABLE I

CATALYTIC ALKYLATION OF THIOPHENE WITH OLEFINS: MOLE RATIO OF REACTANTS = 1.0

Olefin form.	g.	Catalyst form.	g.	Time, hr.	Temp.,[b] °C.	Product,[d] % yield mono.[e]	di.[e]
i-C_4H_8	116	75% H_2SO_4	15	3	67	61	30
i-C_4H_8	116[a]	75% H_2SO_4	15	4	67	56	41
i-C_4H_8	26	90% H_2SO_4	42	1	−10	<20	<20
i-C_4H_8	24	60% H_2SO_4	42	1	82	0	0
i-C_4H_8	117	$H_3BO_2F_2$	10	3	62	66	31
i-C_4H_8	110	BF_3–ether	10	3	62	25	59
i-C_4H_8	110[a]	BF_3–ether	10	4	62	12	77
i-C_4H_8	50	$AlCl_3$	3	2	70	<10	..
i-C_5H_{10}	70	75% H_2SO_4	15	2	67	62	14
i-C_5H_{10}	140	$H_3BO_2F_2$	20	3	62	75	14
i-C_5H_{10}	140	BF_3–ether	20	3	67	16	68
(*i*-C_4H_8)$_2$	1120	80% H_2SO_4	120	4	35	82	7
(*i*-C_4H_8)$_2$	1680[a]	BF_3–ether	100	4	35	25	54
(*i*-C_4H_8)$_2$	55	$AlCl_3$	1	5	47[c]	25	52
1-C_5H_{10}	76	BF_3–ether	25	2	137	16	64
1-C_8H_{16}	56	96% H_2SO_4	15	5	100	43	<20
1-C_8H_{16}	112	BF_3·H_2O	80	2	75	28	<72
1-$C_{16}H_{32}$	224	BF_3·H_2O	80	2	75	10	< 8

[a] Mole ratio of olefin to thiophene is 2. [b] Range of 5°. [c] Temperature rose from 25–70°. [d] Crude product; see Table II for final distillation. [e] Yield based on total theoretical conversion of thiophene to mono- and dialkylthiophenes, respectively.

If a high ratio of mono- to dialkylthiophene be desired, sulfuric acid (70–80% concentration) or dihydroxyfluoboric acid should be given primary

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(2) Kutz and Corson, THIS JOURNAL, **68**, 1477 (1946).