$n^{27}D$ 1.5315. Analysis was acceptable for 2-(1′-methylallyl)-6-methoxyphenol.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.13; H, 7.92. Found: C, 74.39; H, 8.17.

This material gives a ferric chloride phenol test and decolorized permanganate readily.

A solution of 0.6 g. of this phenol and 1.2 g. of 3,5-dinitrobenzoyl chloride in 10 ml. of pyridine was kept at reflux for 5 hours, cooled and poured into 200 ml. of cold 5% sulfuric acid. The resulting oil was taken up in ether and washed with water, 5% sodium hydroxide and then with water. Evaporation of the dried ether gave a semi-solid. Recrystallization from ethanol gave a solid, m.p. 127–128°. This analyzed correctly for the 3,5-dinitrobenzoate of 2-(1′-methylallyl)-6-methoxyphenol.

Anal. Calcd. for $C_{12}H_{10}N_2O_7$: C, 58.06; H, 4.33. Found: C, 57.90; H, 4.37.

Ozonolysis for 15 minutes of 0.682 g. of the phenol showed 78% of the expected methylene group using the above described method which showed 81% of the methylene group of eugenol.

A solution of 0.75 g. of the phenol in 5 ml. of 20% sodium hydroxide was stirred vigorously with 15 ml. of dimethyl sulfate for 25 minutes. An additional 1.5 ml. of dimethyl sulfate and 5 ml. of 50% sodium hydroxide was added and stirring was continued for 2 hours. After heating gently a few minutes, the reaction mixture was extracted with ether. The ether, after drying, left 0.75 g. of residual oil. This was shaken with 20 ml. of 20° sodium hydroxide and 4.5 g. of potassium permanganate in 50 ml. of hot water. The solution turned green. The reaction mixture was filtered. The filtrate, which still had MnO_2 in it, was acidified and extracted with ether. The dried ether on evaporation left 0.3 g. of residue. This was taken up in 4 *N* sodium hydroxide and washed with ether. Acidification, extraction with ether and evaporation of the ether left a solid which was recrystallized from water with the aid of Darco G-60. The product melted at 120–120.5°. The melting point of *o*-veratric acid is reported as 122°.[24]

The alkaline and water washings of the ether solution of the original reaction mixture were combined, acidified, extracted with ether, and the ether layer dried over magnesium sulfate. Fractional distillation gave 16.2 g., $n^{23}D$ 1.5429, distilling at 93° (17 mm.), 2.2 g., $n^{23}D$ 1.5350, distilling at 110–135° (17 mm.) and 1 g. of residue.

The refractive index of the first fraction compared well with that of our guaiacol, $n^{24}D$ 1.5426. The 3,5-dinitrobenzoate prepared according to Phillips and Keenan[25] melted at 135–136° and did not depress the melting point of an authentic sample. The picrate melted at 86–88° as did the picrate of authentic guaiacol.

The second fraction gave a 3,5-dinitrobenzoate which did not depress the melting point of the 3,5-dinitrobenzoate obtained from the fraction identified as 2-(1′-methylallyl)-6-methoxyphenol.

(24) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **105**, 2376 (1914).

(25) M. Phillips and G. L. Keenan, THIS JOURNAL, **53**, 1924 (1931).

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Syntheses in the 5,8-Dihydroxyquinaldine Series

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RECEIVED NOVEMBER 8, 1952

A number of 5,8-dimethoxyquinaldine derivatives have been synthesized from 2,6-nitro- and amino-substituted derivatives of hydroquinone dimethyl ether. Some aspects of their reactions have been studied, and 4-(β-diethylaminoethylamino)-5,8-dihydroxyquinaldine has been prepared for biological tests.

Only few derivatives of 5,8-dihydroxyquinoline have become known which contain functional groups associated with special physiological properties. For example, no dialkylaminoalkylaminoquinoline carrying hydroxyl groups in positions 5 and 8 has been described, in spite of the possible significance of such substitutions for the Schönhöfer theory of antimalarial action of aminoquinolines.[1] This study contributes to the chemistry of compounds in this series.

As starting materials for our syntheses, 2,6-dinitrohydroquinone (I)[2] was prepared in excellent yield from its 4-monoacetate (II)[3] by acid-catalyzed methanolysis. It was methylated with diazomethane in ether–methanol solution; the resulting 1,4-dimethoxy-2,6-dinitrobenzene (m.p. 109–111°) (III) proved to be different from the 2,3-dinitro isomer (m.p. 177°) or the 2,5-dinitro isomer (m.p. 202°).[4] One of the two nitro groups of III was reduced selectively with stannous chloride in ethanolic hydrogen chloride; the widely used monoreduction of dinitrobenzene derivatives with ammonium sulfide[5] was not applicable to this case because of the instability of III in alkaline medium. In addition to 2,5-dimethoxy-3-nitroaniline (IV), a small amount of an *x*-chloro-2,5-dimethoxy-3-nitroaniline was obtained as a by-product in the stannous chloride reduction.

The amine (IV) was acetylated with acetic anhydride in the presence of triethylamine and the 2,5-dimethoxy-3-nitroacetanilide (V) was hydrogenated to 3-acetamido-2,5-dimethoxyaniline (VI). We were unable to convert IV to 2,5-dimethoxy-3-nitrophenol by the diazo reaction, perhaps because of the mobility of the methoxyl group in this series[6] or of the enhanced coupling ability of *m*-alkoxy substituted phenols.[7] Even the diazotization of 2,5-dimethoxyaniline carried out as a simplified model experiment gave only a 25% yield of 2,5-dimethoxyphenol.[8]

3-Acetamido-2,5-dimethoxyaniline (VI) was condensed with ethyl acetoacetate and the resulting β-(2,5-dimethoxy-3-acetamidoanilino)-crotonate was cyclized to 4-hydroxy-5,8-dimethoxy-7-acetamidoquinaldine (VII) in boiling diphenyl ether. Neither

(1) F. Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).

(2) F. Kehrmann, M. Sandoz and R. Monnier, *Helv. Chim. Acta*, **4**, 941 (1921).

(3) R. Nietzki, *Ann.*, **215**, 143 (1882).

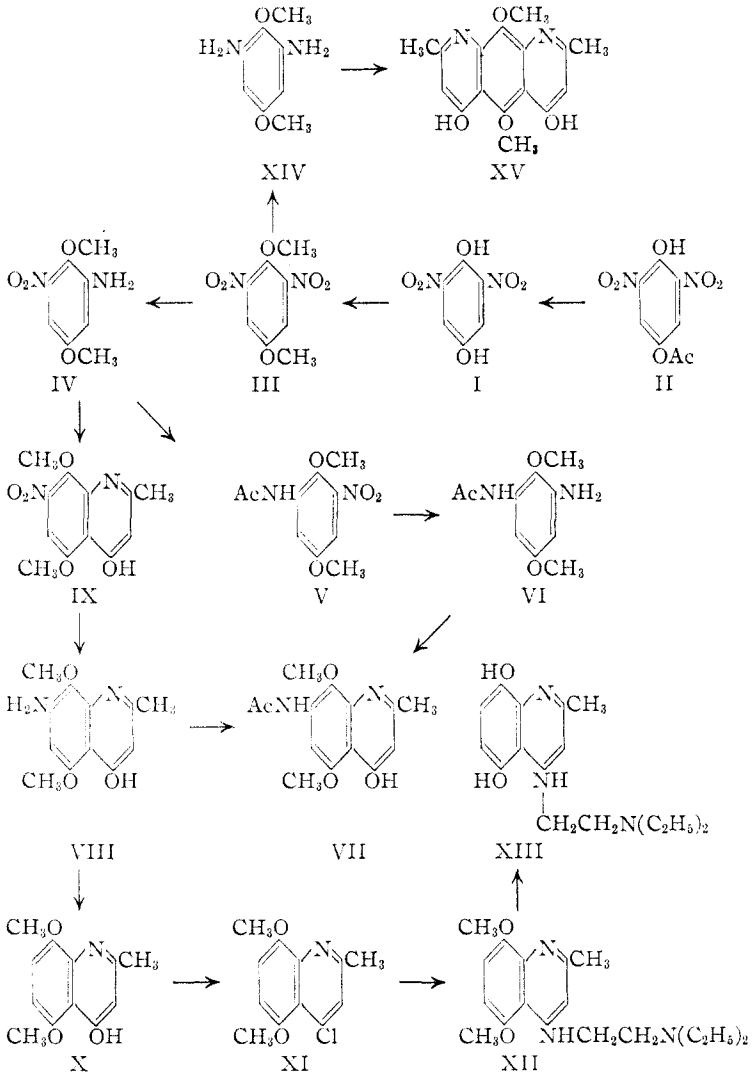
(4) R. Nietzki and F. Rechberg, *Ber.*, **23**, 1211 (1890).

(5) *Cf.* F. H. Curd and A. Robertson, *J. Chem. Soc.*, 437 (1933).

(6) N. Kornblum, in "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1946, pp. 274–275.

(7) L. F. Fieser, in Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1945, pp. 195, 197.

(8) 2,5-Dimethoxyphenol had been prepared previously only by the equivocal reduction of apione or dibromoapione with sodium and alcohol [G. Ciamician and P. Silber, *Ber.*, **24**, 2608 (1891)].



alkaline nor acid hydrolysis of the acetamido group of VII proceeded satisfactorily, but we obtained 4-hydroxy-5,8-dimethoxy-7-aminoquinaldine (VIII) by another route. A Conrad–Limpach reaction with 2,5-dimethoxy-3-nitroaniline (IV) gave 4-hydroxy-5,8-dimethoxy-7-nitroquinaldine (IX) in an over-all yield of 53%, and this nitro compound was reduced almost quantitatively to VIII. As far as we know this is the first example of a Conrad–Limpach reaction leading to a 7-nitroquinoline derivative although a few 7-nitro compounds have been obtained by the Skraup method in poor yields.[9,10]

Diazotization of the amine VIII proceeded normally as demonstrated by coupling of the diazonium salt with β-naphthol. However, we could not effect hydrolysis of the diazonium salt under a variety of conditions; when the diazo solution was warmed with methanol to 50° for several minutes deamination occurred and 4-hydroxy-5,8-dimethoxyquinaldine (X) was obtained. This compound was identical with a sample prepared by an authentic method.[11] X was converted with phosphorus oxychloride to 4-chloro-5,8-dimethoxyquinaldine (XI) which when heated with β-diethylaminoethylamine furnished 4-(β-diethylaminoethylamino)-5,8-dimethoxyquinaldine (XII). Demethylation to 4-(β-diethylaminoethylamino) - 5,8 - dihydroxyquinaldine (XIII) was accomplished by refluxing with hydrobromic acid.

The dihydrobromide of XIII did not show significant activity in *lophurae* malaria in the chick at 0.25% diet concentration. In doses as low as 15 or 25 mg./kg. intraperitoneally in guinea pigs, it exhibited a significant protective action against histamine-induced bronchospasm. Intravenous administration to dogs or cats demonstrated moderate hypotensive properties apparently due to local vasodilation or a reduced heart rate.[12]

1,4-Dimethoxy-2,6-diaminobenzene (XIV) was prepared by hydrogenation of the dinitro compound (III) using Raney nickel catalyst. The 1,4-dimethoxy-2,6-diacetamidobenzene prepared from XIV was found to be identical with the diacetyl derivative obtained from 3-acetamido-2,5-dimethoxyaniline (VI). A bilateral Conrad–Limpach reaction with XIV gave diethyl β,β′-(2,5-dimethoxy-1,3-phenylenediamino)-dicrotonate which was cyclized to 2,8-dimethyl-4,6-dihydroxy-5,10-dimethoxypyrido[3,2-*g*]quinoline (XV).

Experimental[13]

2,5-Dimethoxyphenol.—A solution of 10 g. (0.065 mole) of 2,5-dimethoxyaniline in sulfuric acid was diazotized at 0–2°, and the diazo solution was dropped into hot 10% sulfuric acid and steam distilled. Benzene extraction of the distillate furnished 3.3 g. of an oil which was fractionated. After a forerun of hydroquinone dimethyl ether, 13% of an almost colorless liquid was collected, b.p. 87–89° (0.7 mm.), $n^{25}D$ 1.5430.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.57; H, 6.53.

The 3,5-dinitrobenzoate, prepared by the Schotten-Baumann method, crystallized from dilute ethanol as orange crystals, m.p. 129.5–131°.

Anal. Calcd. for $C_{15}H_{12}N_2O_8$: N, 8.05. Found: N, 7.90.

2,6-Dinitrohydroquinone (I).—2,6-Dinitrohydroquinone-4-acetate (II) was prepared from 1,4-diacetoxybenzene by the direction of Kehrmann and Klopfenstein.[14] A solution of 477 g. (1.97 moles) of II in 4 l. of methanol containing 10 ml. of concentrated hydrochloric acid was refluxed for two hours, and the volume of the mixture was then reduced slowly to 500 ml. by distillation. The remainder of the solvent was stripped *in vacuo*, and the remaining deep-orange solid was recrystallized from toluene. The yield of yellow crystals melting at 132–136°[2,3] was 374 g. (95%).

1,4-Dimethoxy-2,6-dinitrobenzene (III).—A solution of 68 g. (0.34 mole) of 2,6-dinitrohydroquinone in 300 ml. of ether and 300 ml. of methanol was dropped slowly into a cooled solution of 46 g. (1.1 moles) of diazomethane in 2 l. of

(9) L. Kochanska and B. Bobranski, *Ber.*, **69**, 1807 (1936).

(10) L. Bradford, T. J. Elliot and F. M. Rowe, *J. Chem. Soc.*, 437 (1947).

(11) C. E. Kaslow and R. D. Stayner, THIS JOURNAL, **70**, 3350 (1948).

(12) Grateful acknowledgment is made to Parke, Davis and Co. for the antimalarial tests, and to Smith, Kline and French Laboratories for pharmacodynamic screening.

(13) All melting points are corrected.

(14) F. Kehrmann and W. Klopfenstein, *Helv. Chim. Acta*, **6**, 952 (1923).

ether. After standing overnight, the mixture was worked up and the reaction product recrystallized from ethanol with the aid of Darco. The yield of cream-colored needles of m.p. 109–111° was 68 g. (88%).

Anal. Calcd. for $C_8H_8N_2O_6$: C, 42.11; H, 3.53. Found: C, 42.25; H, 3.58.

2,5-Dimethoxy-3-nitroaniline (IV).—A solution of 355 g. (1.57 moles) of stannous chloride dihydrate in 2.4 l. of saturated ethanolic hydrogen chloride was added to a suspension of 120 g. (0.525 mole) of 1,4-dimethoxy-2,6-dinitrobenzene with cooling under an atmosphere of nitrogen. The heterogeneous mixture was refluxed for one hour, allowed to stand for 12 hours, cooled and filtered. The precipitate consisted of a stannic chloride complex of the reaction product. It was washed with benzene and decomposed with 10% sodium hydroxide solution. The crude nitroamine was filtered and recrystallized from benzene–isoöctane. The yield of bright-orange platelets, m.p. 87.5–89.5°, was 40.6 g. (39%).

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09. Found: C, 48.52; H, 4.83.

By concentrating the filtrate of the stannic chloride complex and rendering the solution strongly alkaline, a yellow oil was obtained which was extracted into benzene. It precipitated as a yellow solid on addition of isoöctane and was recrystallized from dilute methanol. It melted at 116.5–118.5° and represented an ***x*-chloro-2,5-dimethoxy-3-nitroaniline.**

Anal. Calcd. for $C_8H_7ClN_2O_4$: C, 41.30; H, 3.90; N, 12.04. Found: C, 41.34; H, 3.62; N, 11.70.

2,5-Dimethoxy-3-nitroacetanilide (V).—A solution of 24 g. (0.12 mole) of 2,5-dimethoxy-3-nitroaniline in 60 ml. of dry benzene was treated with 12 ml. (0.13 mole) of acetic anhydride and two drops of triethylamine, and heated to boiling for one minute. The cooled reaction mixture deposited lemon-yellow crystals which were recrystallized from dilute ethanol. The yield was 24 g. (83.5%), m.p. 137–139°.

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: N, 11.66. Found: N, 11.56.

3-Acetamido-2,5-dimethoxyaniline (VI).—A solution of 24 g. (0.10 mole) of 3-acetamido-2,5-dimethoxynitrobenzene in 350 ml. of ethyl acetate and 200 ml. of ethanol was hydrogenated in the presence of 5 g. of Raney nickel catalyst. The amino compound crystallized from isoöctane–benzene as colorless crystals, m.p. 95–97°. The yield was 19.3 g. (92%).

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.15; H, 6.90; N, 13.55.

The hydrochloride crystallized from methanol–ethyl acetate as colorless crystals, m.p. 222° (after slow decomposition from 175° on).

Anal. Calcd. for $C_{10}H_{15}ClN_2O_3$: C, 48.70; H, 6.13. Found: C, 49.33; H, 6.25.

Ethyl β-(2,5-Dimethoxy-3-acetamidoanilino)-crotonate.—A mixture of 7.4 g. (0.035 mole) of 2-acetamido-6-amino-1,4-dimethoxybenzene, 10 g. (0.077 mole) of ethyl acetoacetate and one drop of 20% hydrochloric acid was allowed to stand in a desiccator over sulfuric acid overnight. The residual light-brown solid was recrystallized from benzene–isoöctane to give 10.8 g. (96%) of colorless material, m.p. 120.5–122.5°.

Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 60.00, 59.91; H, 6.88, 6.69; N, 8.70.

4-Hydroxy-5,8-dimethoxy-7-acetamidoquinaldine (VII).—A solution of 10 g. (0.031 mole) of the crotonate just described in 75 ml. of warm diphenyl ether was dropped into 200 ml. of refluxing diphenyl ether with slow stirring over a period of six minutes. After refluxing another 15 minutes the solution was cooled and crystallization of the product was completed by addition of petroleum ether. It was recrystallized numerous times from dilute ethanol, m.p. 245–265° (dec.). The yield of colorless material was 6.3 g. (74%).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.92; H, 6.09; N, 9.94.

Ethyl β-(2,5-Dimethoxy-3-nitroanilino)-crotonate.—This compound was prepared from 2-amino-6-nitro-1,4-dimethoxybenzene by directions analogous to those described above. The yield was 84%. The lemon-yellow product crystallized from methanol, m.p. 88–90°.

Anal. Calcd. for $C_{14}H_{18}N_2O_6$: N, 9.03. Found: N, 9.21.

4-Hydroxy-5,8-dimethoxy-7-nitroquinaldine (IX).—A Conrad–Limpach cyclization of the crotonate just described in diphenyl ether gave a 63% yield of canary-yellow crystals, m.p. 245–247° (dec.), after purification from methanol.

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.58. Found: C, 54.47; H, 4.45.

4-Hydroxy-5,8-dimethoxy-7-aminoquinaldine (VIII).—Hydrogenation of the nitroquinaldine derivative IX in ethanol with Raney nickel catalyst under atmospheric pressure gave 96% of a colorless product which crystallized from methanol, m.p. 266–267° (dec., inserted in bath at 261°).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02. Found: C, 61.63; H, 5.84.

The N-acetyl derivative melted at 245–265° (dec.). A mixture with compound VII had the same melting point range.

4-Hydroxy-5,8-dimethoxyquinaldine (X).—A suspension of 1 g. of the amine VIII in 20 ml. of methanol and 3 ml. of concentrated hydrochloric acid was diazotized with a 25% solution of 0.5 g. of sodium nitrite at 0°. After 15 minutes the temperature was raised to 50° and maintained for several minutes until a drop of the solution no longer gave a purple color with β-naphthol. Evaporation to dryness under reduced pressure gave 0.5 g. of a pale tan **hydrochloride**, m.p. 217° (dec.).

Anal. Calcd. for $C_{12}H_{14}ClNO_3$: C, 56.36; H, 5.52. Found: C, 56.28; H, 5.57.

A mixture with a hydrochloride prepared from an authentic sample of 4-hydroxy-5,8-dimethoxyquinaldine[1] showed no melting point depression.

4-Chloro-5,8-dimethoxyquinaldine (XI).—A mixture of 9.5 g. (0.043 mole) of 4-hydroxy-5,8-dimethoxyquinaldine and 40 ml. of phosphorus oxychloride was refluxed for three hours. The excess phosphorus oxychloride was removed under reduced pressure and the resulting black material was decomposed with ice and allowed to stand eight hours. When the mixture was made alkaline a yellow precipitate separated. It was recrystallized from dilute ethanol to give 7.0 g. (69%) of colorless product which turned yellow in the air and melted at 122–123°.

Anal. Calcd. for $C_{12}H_{12}ClNO_2$: C, 60.63; H, 5.09. Found: C, 60.66; H, 5.27.

4-(β-Diethylaminoethylamino)-5,8-dimethoxyquinaldine (XII).—A mixture of 6.7 g. (0.028 mole) of 4-chloro-5,8-dimethoxyquinaldine and 20 ml. of β-diethylaminoethylamine was heated in a sealed tube at 160–170° for six hours. The dark-amber material was washed with dilute alkali and extracted with benzene; the benzene and most of the remaining diethylaminoethylamine were distilled off and the residual black, viscous oil solidified after washing with water. Its hydrobromide, prepared in an ether solution weighed 3.0 g. (22%). Recrystallization from ethanol containing a little ether gave light cream-colored crystals melting at 214°.

Anal. Calcd. for $C_{18}H_{29}Br_2N_3O_2$: C, 45.11; H, 6.10; Br, 33.35. Found: C, 44.71, 44.94; H, 6.07, 6.23; Br, 33.15.

4-(β-Diethylaminoethylamino)-5,8-dihydroxyquinaldine (XIII).—A solution of 1.6 g. of the dimethoxyquinaldine XII in 20 ml. of 48% hydrobromic acid was refluxed for nine hours in an atmosphere of nitrogen, and the hydrobromic acid was removed under reduced pressure in a desiccator. The cream-colored mass was washed with ether and recrystallized from methanol–ethyl acetate. The yield of almost colorless, hygroscopic crystals of the dihydrobromide was 1.0 g. (67%), m.p. above 275° (dec.).

Anal. Calcd. for $C_{16}H_{25}Br_2N_3O_2$: C, 42.59; H, 5.59; Br, 35.42. Found: C, 43.01; H, 5.58; Br, 34.85.

4-Chloro-5,8-dimethoxy-7-nitroquinaldine.—This compound was prepared from IX by refluxing with a tenfold excess of phosphorus oxychloride for 11 hours. It appeared as yellow crystals from ethanol, m.p. 154.5–156.5°.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_4$: C, 50.98; H, 3.92. Found: C, 50.96; H, 3.95.

2,6-Diamino-1,4-dimethoxybenzene (XIV).—A solution of 20 g. (0.088 mole) of 2,6-dinitro-1,4-dimethoxybenzene (III) in a mixture of ethanol and ethyl acetate was hydrogenated using Raney nickel catalyst. The mixture was worked up and the sirupy product was distilled at 133–138°

(0.7–0.9 mm.). The yield was 12 g. (81%). The colorless diamine solidified on standing and was recrystallized from benzene–petroleum ether, m.p. 69–72.5°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19. Found: C, 57.38; H, 6.95.

The 2,6-diacetyl derivative crystallized from ethyl acetate as silky white needles melting at 194.5–196.5°.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39. Found: C, 57.42; H, 6.12.

The diacetate of 2,6-diaminohydroquinone dimethyl ether was also prepared by acetylating 2-acetamido-6-amino-1,4-dimethoxybenzene (VI). Comparison of the two diacetates showed that they were identical.

2,8-Dimethyl-4,6-dihydroxy-5,10-dimethoxypyrido[3,2g]-quinoline (XV).—The condensation of 9.5 g. (0.056 mole) of 2,6-diamino-1,4-dimethoxybenzene with 20 g. (0.015 mole) of ethyl acetoacetate was carried out as described in the preparation of ethyl β-(2,5-dimethoxy-3-acetamidoanilino)-crotonate. After recrystallization from isoöctane, 16 g. (73%) of colorless crystals of **diethyl 2,5-dimethoxy-1,3-phenylenediaminodicrotonate** melting at 81.5–83.5° was obtained.

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: N, 7.14. Found: N, 7.34, 7.35.

A bilateral Conrad–Limpach synthesis using diphenyl ether and the dicrotonate yielded 61% of a rather insoluble material which could be converted to an orange **dihydrochloride** in hot hydrochloric acid. The salt was recrystallized from acidified water and melted at 290° (dec.).

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2O_4$: C, 51.48; H, 4.86; N, 7.51. Found: C, 52.81; H, 4.98; N, 7.40.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, DAVIS]

The Stereochemistry of the Four α-Amino-β,γ-dihydroxybutyric Acids

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The four α-amino-β,γ-dihydroxybutyric acids are described. The configuration of each (relative to D-glyceraldehyde) was assigned by preparation and reactions of the oxazolines of the lactones.

Starting with DL-glyceraldehyde, Fischer and Feldmann[2] first prepared α-amino-β,γ-dihydroxybutyric acid by the Strecker synthesis. Soon after Fischer and Baer[3a] reported a convenient synthesis of acetone D-glyceraldehyde (by glycol cleavage of 1,2,5,6-diacetone-D-mannitol), Fischer and Feldmann[3b] repeated the amino acid synthesis using the D-aldehyde. With D-glyceraldehyde the number of expected products is reduced from four to the diastereoisomers I and II. The product they isolated had $[\alpha]^{20}D$ −13.74°. Niemann and Nichols[4] repeated the synthesis several years later and isolated two products, one having $[\alpha]D$ −13.7° and the other $[\alpha]D$ +16.0°. Interest in the compound stemmed from the claim of Klenk and Diebold[5] that they obtained α-amino-β,γ-dihydroxybutyric acid having $[\alpha]D$ −33.4° by oxidative cleavage of sphingosine. The results of Niemann and Nichols showed clearly that the compound from sphingosine was not one of the α-amino-β,γ-dihydroxybutyric acids.

Niemann and Nichols assigned the *threo* configuration to the levorotatory amino acid and the *erythro* configuration to the dextrorotatory amino acid. Their evidence was based on enzymatic reactions which are specific for the group of amino acids assigned the L-configuration and for the group assigned the D-configuration, rotation changes upon the addition of H^+,[6] and formation of N-benzoyl lactone from one amino acid and N-benzoyl acid from the other. The results on benzoylation were those they predicted from scale models of the *n*-benzoyl derivatives of the two diastereoisomers.[7]

Recent evidence on the steric course of oxazoline formation suggested a different approach to the configuration from that used by Niemann and Nichols. Reactions leading to oxazolines should establish with reasonable certainty the configuration[8] of the two amino acids prepared from D-glyceralde-

(1) E. I. du Pont de Nemours, Niagara Falls, N. Y.

(2) H. O. L. Fischer and L. Feldmann, *Ber.*, **65**, 1211 (1932).

(3) (a) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **17**, 622 (1934); (b) H. O. L. Fischer and L. Feldmann, *ibid.*, **19**, 532 (1936).

(4) C. Niemann and P. L. Nichols, *J. Biol. Chem.*, **143**, 191 (1942).

(5) E. Klenk and W. Diebold, *Z. physiol. Chem.*, **198**, 25 (1931).

(6) (a) G. W. Clough, *J. Chem. Soc.*, **107**, 1509 (1915); **113**, 526 (1918); (b) O. Lutz and B. Jirgensons, *Ber.*, **63**, 448 (1930); **64**, 1221 (1931).

(7) The product obtained when the *erythro* acid (II) as benzoylated and the solution acidified is the N-benzoyl-free acid as Niemann and Nichols reported. Upon recrystallization of the benzoyl acid, crystals which proved to be the N-benozyl lactone slowly formed in the filtrate. The same N-benzoyl lactone is formed when the *erythro* lactone (III) is benzoylated in sodium carbonate solution. While the reactions described in this paper confirm the assignment of configuration of the two acids I and II by Niemann and Nichols, we do not consider our results on the preparation of the N-benzoyl derivatives evidence for assignment of configuration.

(8) One of our initial objectives was to convert one of the diastereoisomers to a naturally occurring amino acid by a method which did not involve a displacement at the optical center carrying the amino group. Thus, if the configuration of the optical carrying the amino group is known relative to the β-hydroxy optical center, a direct means of relating configuration of amino acids and carbohydrates is available. Shortly after these studies were undertaken two significant papers[9] relating configuration appeared. Wolfrom, *et al.*,[9a] reduced C_1 of D-glucosamine to methyl and, after glycol cleavage of the acetylamine, oxidized C_3 to carboxyl to give N-acetylalanine which had the same rotation as the N-acetyl derivative of the naturally occurring amino acid. The configuration of C_2 relative to C_5 in glucosamine had previously been established.[10] Shoemaker, *et al.*,[9b] confirmed by crystal structure analysis, the *threo* structure of L-threonine previously assigned by Meyer and Rose.[11] The β optical center of natural threonine has the same configuration as D-glyceraldehyde.[11]

These observations permit us to assign the configuration of the α-amino-β,γ-dihydroxybutyric acids relative to both carbohydrates and amino acids. Compound I has the same configuration at each optical center as natural threonine. In naming the amino acids and their derivatives the β-carbon will be referred to D-glyceraldehyde. Thus I is the D-*threo* acid (the same as Niemann and Nichols[4]) and IV is the L-*erythro* acid. This should not be confused with the above designation for threonine where the subscript s refers to serine.

(9) (a) M. L. Wolfrom, R. U. Lemieux and S. M. Olin, THIS JOURNAL, **71**, 2870 (1949); (b) D. P. Shoemaker, J. Donohue, V. Schomaker and R. B. Corey, *ibid.*, **72**, 2328 (1950).

(10) (a) W. N. Haworth, W. H. G. Lake and S. Peat, *J. Chem. Soc.*, 271 (1939); (b) W. O. Cutler and S. Peat, *ibid.*, 782 (1939).

(11) C. E. Meyer and W. C. Rose, *J. Biol. Chem.*, **115**, 721 (1936).