then was added in small portions. During addition, the temperature rose to 130° and the mixture turned dark brown. When all the sodium had reacted, the mixture was cooled to 55° and one mole (157.1 g.) of 2,3-dichlorodioxane was added dropwise. After this addition, the mixture was heated to 55–60° for five hours and then filtered. Distillation of the dark filtrate at 20 mm. yielded 787 g. of unreacted diethylene glycol and 269 g. of residue as a black oil. This residue was filtered to remove suspended solids and the filtrate distilled, yielding 115.5 g. (39%) of amber oil, b.p. 214–224° (2 mm.), $n^{25}D$ 1.4730.

Anal. Calcd. for $C_{12}H_{24}O_8$: OH, 11.5; mol. wt., 296. Found: OH, 11.1; mol. wt., 277.

Hydroxyl value was determined by acetylation of a sample with acetic anhydride, and titration of the liberated acid with a standard base.

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The Synthesis of 4-Hydroxy-6-quinaldine Carbohydrazide[1,2]

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The antituberculous activity of isonicotinic acid hydrazide and its related compounds[3] coupled with the knowledge that 4-hydroxyquinoline and 4-hydroxy-3-quinolinecarboxylic acid shows mild tuberculostatic activity[4] prompted a study of the influence of an acid hydrazino group in the 6-position of the quinaldine nucleus. For this purpose, 4-hydroxy-6-quinaldine carbohydrazide was prepared.

6-Cyano-4-methoxyquinaldine was obtained using a modification of the Sandmeyer synthesis[5] by treating the neutralized diazonium salt solution of 6-amino-4-methoxyquinaldine with cuprous cyanide. The cyano compound, like many other aromatic nitriles, was resistant to hydrolysis. The ordinary procedures, such as refluxing with concentrated sulfuric acid and absolute ethanol or reaction with methanol and dry hydrogen chloride, failed to effect the conversion of the nitrile into the corresponding acid ester. Refluxing with 90% sulfuric acid for 2 hours and subsequent treatment with sodium nitrite[6] yielded a mixture from which the desired product could not be isolated. The hydrolysis was accomplished by heating with 15% potassium hydroxide in glycerol at 150–170° for 9 hours. A concomitant demethylation occurred. Comparison of the ultraviolet absorption spectra revealed a closer structural resemblance of the acid to 4-hydroxyquinoline than to 4-methylquinoline.[7] The spectrum of 6-cyano-4-methoxyquinaldine shows a marked similarity to that of 4-methoxyquinoline but differs from the spectrum of the acid or its ester. The observed demethylation may be explained on the basis of an electron deficiency at C_4 of the quinoline ring which facilitates the nucleophilic substitution by the OH group.

The reactivity of the C_4-position toward nucleophilic reagents is evident from the amination reactions of 4,7-dichloroquinoline[8] and 4,6-dichloroquinaldine[9] in which it is reported that only the chlorine in the 4-position was replaced by the amino group.

The unusually high melting point (above 300°) of 4-hydroxy-6-quinaldinecarboxylic acid together with its insolubility in non-polar solvents suggested the probable existence of the acid in the form of a zwitterion. Unfortunately, the insolubility of the compound in dioxane precluded the measurement of its dipole moment. The acid reacted with ferric chloride to give a very faintly brownish-yellow color in aqueous solution, behaving much like carbostyril in this respect.

4-Hydroxy-6-quinaldine carbohydrazide was tested against *Mycobacterium tuberculosis* H37Rv according to the method of Fisher[10] and was found to be inactive.[11] The intermediates, when screened for their antibacterial activity, failed to inhibit the visible growth of *Escherichia coli*, *Micrococcus pyogenes* var. *aureus*, *Bacillus megatherium* and *Pseudomonas aeruginosa* at the concentration of 0.2 mg. per ml.

Experimental[12]

6-Cyano-4-methoxyquinaldine.—The nitrile was prepared from the corresponding amino derivative[13] by the procedure of Clarke and Read.[5] After the reaction was complete the solution was extracted successively with 100-ml. portions of chloroform. A small amount of alcohol was effective in overcoming the persistent emulsion which formed during the extraction. The combined chloroform extract was washed, dried over anhydrous sodium sulfate and concentrated to a volume of 30 to 50 ml. by distillation. Addition of petroleum ether precipitated the nitrile as buff-colored solid. The crude compound was decolorized with Darco and recrystallized from 50% ethanol to give 12 g. (60%) of product melting at 162–165° (uncor.).

6-Cyano-4-methoxyquinaldine was found to be very soluble in chloroform, ethanol and methanol, soluble in ether, sparingly soluble in benzene, and insoluble in cold water. The analytically pure compound, obtained by recrystallization from 75% methanol, appeared as colorless thin hairs which melted at 172–173°; $\lambda\lambda_{max}^{EtOH}$: 321.5 mμ (log ε 3.30), 294 (3.92), 287.5 (3.92), 238 (4.89); $\lambda\lambda_{min}^{EtOH}$: 319 (3.25), 256 (3.54).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09. Found: C, 72.92; H, 5.54.

Hydrolysis of 6-Cyano-4-methoxyquinaldine.—Fifteen grams (0.076 mole) of 6-cyano-4-methoxyquinaldine was

(1) Abstracted from a thesis submitted by C. T. Peng in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Chemistry, June, 1953.

(2) Presented in summary under the heading, "The Synthesis of Some 6-Substituted Amido Derivatives of 4-Aminoquinaldine and a Study of Their *in Vitro* Antibacterial Activity" before the Division of Medicinal Chemistry at the 123rd National Meeting of the American Chemical Society at Los Angeles, Calif., March, 1953.

(3) W. M. Benson, P. L. Stefko and M. D. Roe, *Am. Rev. Tuberc.*, **65**, 375 (1952); J. Bernstein, W. A. Lott, B. A. Steinberg and H. L. Yale, *ibid.*, **65**, 357 (1952); W. Steeken and E. Wolinsky, *ibid.*, **65**, 365 (1952).

(4) *Summary Tables of Biological Tests* (National Research Council, Washington, D. C.), **2**, 315 (CBC No. 503,567 (22)) (1950); **3**, 64 (CBC No. 503,568) (1951).

(5) H. T. Clarke and R. R. Read, *Org. Syntheses*, **4**, 69 (1925).

(6) K. Lehmstedt and E. Wirth, *Ber.*, **61**, 2047 (1928).

(7) The absorption characteristics of 4-hydroxy- and 4-methoxyquinolines used here for comparison were taken from J. M. Hearn, R. A. Morton and J. C. E. Simpson, *J. Chem. Soc.*, 3318 (1951).

(8) R. C. Elderfield, W. J. Gensler, O. Birstein, F. J. Kreysa, J. T. Maynard and J. Galbreath, THIS JOURNAL, **68**, 1250 (1946).

(9) R. Royer, *J. Chem. Soc.*, 1806 (1949).

(10) M. W. Fisher, *Am. Rev. Tuberc.*, **57**, 58(1948); M. W. Fisher, W. F. Kirchheimer and A. R. Hess, *J. Bact.*, **62**, 319 (1951).

(11) The test was performed by Miss Grace Gardner of the Antibiotics Laboratory, University of California College of Pharmacy.

(12) Analyses are by the Microanalytical Division of the Department of Chemistry, University of California, Berkeley.

(13) Prepared from the acetyl derivative (M. G. Pratt and S. Archer, THIS JOURNAL, **70**, 4065 (1948)) by hydrolysis.

suspended in 150 ml. of glycerol containing 23 g. of potassium hydroxide in a flask equipped with stirrer. The flask was immersed in an oil-bath kept at 150–170° for 9 hours. The cooled solution was diluted with an equal volume of water, boiled with a little Darco and then filtered. Acidification of the solution with 30 ml. of glacial acetic acid liberated the free acid as colorless thin needles which melted above 300°. The yield was 13.5 g. (88%).

The acid was insoluble in chloroform, benzene and dioxane, slightly soluble in dilute alcohol, and very soluble in dilute sodium hydroxide or ammonia. The acid was first purified by reprecipitation with acetic acid from a dilute ammonia solution and then by dilution of an alcohol solution with water; $\lambda\lambda_{max}^{EtOH}$: 330.5 mμ (log ε 4.07), 318 (4.05), 248–251 (4.40), 244 (4.42), 228–233 (4.47), 223 (4.48); $\lambda\lambda_{min}^{EtOH}$: 324 (3.99), 270 (3.26), 239 (4.40).

Anal. Calcd. for $C_{11}H_9NO_3$: neut. equiv., 203; methoxyl, 0. Calcd. for $C_{12}H_{11}NO_3$: neut. equiv., 217; methoxyl, 14.28. Found: neut. equiv., 204; methoxyl, 0.35.

Ethyl 4-Hydroxy-6-quinaldinecarboxylate.—Ten grams of the above purified, oven-dried acid was refluxed with 50 ml. of purified thionyl chloride and 50 ml. of dry thiophene-free benzene for 2 hours. Excess thionyl chloride and benzene were removed under reduced pressure at 60° and the residue was refluxed for 2 hours with 60 ml. of absolute alcohol. The excess ethanol was removed by distillation and the residue treated with ice-water and ammonia. The crude ester was recrystallized from dilute alcohol to yield 9 g. (79%) of a light tan crystalline product, m.p. 240–245° (uncor.). The compound recrystallized from dioxane as colorless thin plates, m.p. 267-268°; $\lambda\lambda_{max}^{EtOH}$: 331 mμ (log ε 4.08), 320 (4.04), 257.5 (4.38), 250 (4.38), 225 (4.54); $\lambda\lambda_{min}^{EtOH}$: 325 (4.04), 271 (3.37), 254 (4.36), 245 (4.34).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.51; H, 5.67. Found: C, 67.40; H, 5.88.

4-Hydroxy-6-quinaldine Carbohydrazide.—Seven grams of the ester was added to a mixture of 5 ml. of 85% hydrazine hydrate, 3 ml. of ethanol and 3 ml. of water and the mixture refluxed in an oil-bath at 110° for 6 hours. After chilling the solution, 6.5 g. of the hydrazide was obtained by filtration. An aqueous solution of the crude product was decolorized with Norite and filtered. On cooling, the acid hydrazide separated from the solution as colorless plates with a m.p. above 300°. Further crystallization from water in the absence of decolorizing charcoal caused slight discoloration of the compound. The acid hydrazide was slightly soluble in alcohol but insoluble in dioxane or benzene.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.11. Found: C, 60.76; H, 5.20.

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Rearrangement of 3-Chloro-3-ethylpentane During Acid-catalyzed Alkylation

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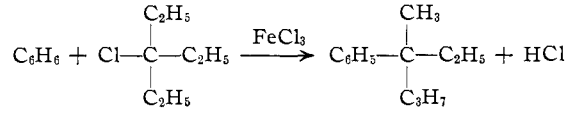
The extent of rearrangement during acid-catalyzed alkylation depends upon the activity of the catalyst and the structure of the alkylating agent.[1] An example of a large variation in the extent of rearrangement brought about by small changes in the structure of the alkylating agent has been observed in our laboratory. Benzene was alkylated with two tertiary chlorides; one rearranged but very slightly and the other completely.

Benzene was first alkylated under mild conditions by 2-chloro-2-methylpentane with ferric chloride catalyst; this catalyst has been recommended for cases where rearrangement is to be avoided.[2] The product was largely the expected, unrearranged isomer, 2-methyl-2-phenylpentane, contaminated with 1–2% of 3-methyl-3-phenylpentane and, unexpectedly, with 1–2% of the secondary isomer, 2-phenylhexane.

Benzene was also alkylated under the same conditions by 3-chloro-3-ethylpentane with ferric chloride catalyst. In sharp contrast to the above results the product was completely rearranged.



The yield was 90–95% 3-methyl-3-phenylhexane contaminated with an isomeric phenylheptane, tentatively identified as 2,3-dimethyl-2-phenylpentane. Because the expected product 3-ethyl-3-phenylpentane was not isomerized to 3-methyl-3-phenylhexane by ferric chloride in benzene, rearrangement must have occurred before or during alkylation.

Conceivably, rearrangement could have taken place during the preparation of the chloride from 3-ethyl-3-pentanol.[3] The chloride has been prepared previously, but no proof of structure has been attempted.[4–8] Hydrolysis of the chloride gave good first-order rate constants, which indicated that the material was not a mixture[8] but did not preclude total rearrangement to 3-chloro-3-methylhexane. To settle this point the chloride was examined by mass spectrometer. The spectrum was consistent with the 3-chloro-3-ethylpentane structure and clearly inconsistent with that of 3-chloro-3-methylhexane. Hence no rearrangement had occurred during the preparation of the chloride.

TABLE I

PARTIAL MASS SPECTRA OF ISOMERIC ALCOHOLS AND CHLORIDES

Spectra corrected for normally occurring C^{13}, Cl^{37} and H

	3-Ethyl-3-pentanol	3-Methyl-3-hexanol	3-Chloro-3-ethylpentane	3-Chloro-3-methylhexane
	Relative intensities[a]			
Parent	0.0	0.0	0.3	0.0
Parent less methyl	0.0	14.6	0.0	2.2
Parent less ethyl	100.0	100.0	100.0	100.0
Parent less propyl	1.1	150.1	6.5	154.3

[a] Values of 100.0 assigned to relative intensity at parent mass less ethyl.

Isomerization must have taken place during the alkylation. An analogous skeletal rearrangement of 3-ethylpentane to, among other things, 3-

(1) C. C. Price, "Organic Reactions," Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1946, p. 4.

(2) M. Inatome, K. W. Greenlee, J. M. Derfer and C. E. Boord, THIS JOURNAL, **74**, 292 (1952).

(3) For examples of rearrangements, see H. C. Brown and R. B. Kornblum, *ibid.*, **76**, 4511 (1954).

(4) E. Schriner, *J. prakt. Chem.*, [2] **82**, 294 (1910).

(5) F. C. Whitmore and D. E. Badertscher, THIS JOURNAL, **55**, 1559 (1933).

(6) O. R. Quayle, K. Owen and E. M. Beavers, *ibid.*, **61**, 3107 (1939).

(7) J. Shorter and C. Hinshelwood, *J. Chem. Soc.*, 2412 (1949).

(8) H. C. Brown and R. S. Fletcher, THIS JOURNAL, **71**, 1845 (1949).