spectrum very similar to that of 4-chloromethylpyridinium hydrochloride.

B. **N,C-Diacetyl Derivative 10.**—A 1.7-g (0.015 mole) sample of 4-pyridylacetonitrile was mixed with 7.5 g (0.075 mole) of acetic anhydride. Upon heating, the yellow-orange precipitate of the N-acetyl compound dissolved to give a clear solution. After 10 min the solution was cooled, whereupon a bright yellow material crystallized. This was removed by filtration and consisted of 1.8 g (62%) of 1-acetyl-4(acetylcyanomethylidene)-1,4-dihydropyridine (**10**), mp 210–225° dec. Recrystallization from chloroform gave the pure product as bright yellow blades: mp 225° dec; $\tilde{\nu}^{\mathrm{KBr}}$ (in cm^{-1}) 3100 (C–H), 2200 (C═CCN), 1760 ($R_3N^+COCH_3$), 1670 (C═CO$^-$), 1650 (C═C), 1600 (C═C); nmr (DMSO-d_6) (in ppm) singlets at 1.82, 2.08, 2.20 and 2.57 accounting for six protons (CH_3), a doublet at 6.80, and singlets at 7.85 and 8.30 accounting for four protons (ring H).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.69; H, 4.55; N, 13.84.

C. **C-Acetyl Derivative 11.**—In an attempt to recrystallize the N,C-diacetyl compound **10** from 1-butanol, the solution changed color upon heating and deposited a brown material which was subsequently recrystallized from water to yield 2-(4′-pyridyl)-3-hydroxy-2-butenonitrile (**11A**) and/or its tautomer 4-(acetylcyanomethylidene)-1,4-dihydropyridine (**11B**) as small, glistening, colorless crystals: mp 268–269°; $\tilde{\nu}^{\mathrm{KBr}}$ (in cm^{-1}) 2700 (acidic H), 2190 (C═CCN), 1630 (C═C–C═O), 1545 (pyridine); $\lambda_{\max}^{\mathrm{pH}\ 1}$ (ϵ) 227 mμ (11,000), 320 (16,000), 355 (8200); $\lambda_{\max}^{\mathrm{pH}\ 5}$ (ϵ) 233 mμ (15,400), 250 (shoulder), 356 (32,000); $\lambda_{\max}^{\mathrm{pH}\ 12}$ (ϵ) 225 mμ (13,800), 245 (shoulder), 316 (21,000); pK_A from spectrophotometric determination = 8.40 and 1.76; nmr (DMSO-d_6) (in ppm) three-proton singlet at 2.16 (CH_3C═), one-proton broad singlet at 3.29 (acidic H), four-proton unsymmetrical doublet at 7.9 (PyH_2, H_3, H_5, H_6).

Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.35; H, 4.58; N, 17.40.

This material is only slightly soluble in most organic solvents; dimethyl sulfoxide and dimethylformamide are among the better solvents. It is readily soluble in dilute, aqueous sodium hydroxide, and sodium carbonate as well as in dilute acid.

Knoevenagel Reaction with Acetaldehyde.—A mixture of 18 g (0.15 mole) of 2-pyridylacetonitrile, 6.6 g (0.15 mole) of freshly distilled acetaldehyde, 1.2 g of piperidine, 1.8 g of acetic acid, and 100 ml of benzene was placed in a flask equipped with a Dean–Stark tube. After refluxing for 45 min the theoretical amount of water had been collected, whereupon the reaction mixture was cooled and worked up to yield 16 g (74%) of 2-(2′-pyridyl)-2-butenonitrile (**6**) as a colorless liquid: bp 70–71° (0.25 mm); $\tilde{\nu}_{\max}^{\mathrm{liq}}$ (in cm^{-1}) 3100 (C–H), 2230 (C═CCN), 1630 (C═C), 1570 (pyridine); $\lambda_{\max}^{\mathrm{heptane}}$ (ϵ) 241 mμ (11,500), 275 (6100); nmr (CCl$_4$ in ppm) three-proton doublet (J = 7 cps) at 2.18 ($CHCH_3$), one-proton quartet (J = 7 cps) at 7.19 (═$CHCH_3$), three-proton multiplet at 7.35–7.80 (PyH_3, H_4, H_5), one-proton doublet at 8.45 (PyH_6).

Anal. Calcd for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43. Found: C, 75.21; H, 5.95; N, 19.06.

A 7.2-g (0.05 mole) sample of the above product was dissolved in 100 ml of ethanol, treated with 1 g of 10% palladium-on-charcoal catalyst, and subjected to hydrogenation at atmospheric pressure and room temperature. When the theoretical amount of hydrogen for 1 mole equiv had been absorbed (*ca.* 1.1 l.), the catalyst was removed by filtration and the solvent by evaporation, and the residue was distilled to give 6.5 g (88%) of 2-(2′-pyridyl)-butyronitrile (**7**) as a colorless liquid: bp 73–76° (0.5 mm); $\tilde{\nu}^{\mathrm{liq}}$ (in cm^{-1}) 3030 (C–H), 2260 (CN), 1585 (pyridine), 1565 (pyridine); nmr (CCl$_4$) (in ppm) three-proton triplet (J = 7.8 cps) at 1.07 (CH_2CH_3), two-proton pattern of overlapping triplets (J = 7.8 and 6.8 cps) at 2.06 ($CH\text{–}CH_2\text{-}CH_3$), one-proton triplet ($J$ = 6.8 cps) at 3.92 ($CH\text{–}CH_2$), three-proton multiplet at 7.1–7.9 (pyridine H_3, H_4, H_5), one-proton doublet at 8.52 (pyridine H_6).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.64; H, 6.83; N, 18.70.

Ethylation of C-Acetyl Derivative from 2-Pyridylacetonitrile.—A 3.2 g (0.02 mole) sample of 2-(2′-pyridyl)-3-hydroxy-2-butenonitrile (**3**) was dissolved in 20 ml of 1 *N* sodium hydroxide, and the solution was treated with 3.4 g (0.02 mole) of silver nitrate in 40 ml of water. The resulting silver salt was separated by filtration, washed with alcohol and ether, dried in a vacuum desiccator, and treated in ether suspension with 4.7 g (0.03 mole) of ethyl iodide. After removing the silver iodide by filtration, the solvent was evaporated, and the residue was recrystallized from petroleum ether (bp 63–69°) to give 2-(4′pyridyl)-3-ethoxy-2-butenonitrile (**5**) as pale yellow crystals: mp 81–82°; $\tilde{\nu}^{\mathrm{KBr}}$ (in cm^{-1}) 3040 (C–H), 2220 (C═CCN), 1630 (C═C), 1585 (pyridine), 1560 (pyridine); $\lambda_{\max}^{\mathrm{EtOH}}$ (ϵ), 265 mμ (12,200), 287 (14,400), 362 (1250); nmr (CDCl$_3$) (in ppm) three-proton triplet at 1.43 (CH_2CH_3), three-proton singlet at 2.51 (═CCH_3), two-proton quartet at 4.23 (CH_2CH_3), three-proton multiplet at 7.0–8.0 (PyH_3, H_4, H_5), one-proton singlet at 8.65 (PyH_6).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.91; H, 6.18; N, 14.96.

Methylation of C-Acetyl Derivative from 4-Pyridylacetonitrile.—A 1.6-g sample of 2-(4′-pyridyl)-3-hydroxy-2-butenonitrile (**11**) was treated as described above (methyl iodide in place of ethyl iodide) to produce 1-methyl-4-(acetylcyanomethylidene)-1,4-dihydropyridine (**12**) as pale yellow crystals after recrystallization from ethyl acetate: mp 216–217°; $\tilde{\nu}^{\mathrm{KBr}}$ (in cm^{-1}) 3100 (C–H), 2200 (C═C–CN), 1660 (C═C–C═O), 1600 (C═C); $\lambda_{\max}^{\mathrm{pH}\ 5\text{-}9}$ (ϵ) 235 mμ (15,400), 362 (35,000); $\lambda_{\max}^{\mathrm{pH}\ 1}$ (ϵ) 230 mμ (12,800), 362 (22,400); nmr (DMSO-d_6) (in ppm) three-proton singlet at 2.35 (CH_3C═O), three-proton singlet at 4.03 (CH_3N), four-proton doublet at 7.95 (ring H).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79. Found: C, 68.75; H, 5.79.

Registry No.—1, 2739-97-1; **2B,** 13427-04-8; **3A,** 13449-02-0; **3A** hydrochloride, 13427-05-9; **3B,** 13427-06-0; **3B** hydrochloride, 13441-16-2; **4A,** 13427-07-1; **4B,** 13444-35-4; **5,** 13427-08-2; **6,** 13427-09-3; **7,** 13427-10-6; **8,** 13121-99-8; **9a,** 13427-12-8; **9b,** 13427-13-9; **9c,** 13427-14-0; **10A,** 13444-36-5; **10A′,** 13427-15-1; **11A,** 13427-16-2; **11B,** 13427-17-3; **12,** 13427-18-4.

The Gattermann Reaction of 3,5-Dimethoxyphenylacetonitrile. A Synthesis of 6,8-Dioxyisoquinolines

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Treatment of 3,5-dimethoxyphenylacetonitrile with zinc cyanide and a hydrogen halide gave a 3-halo-6,8-dimethoxyisoquinoline. Structural confirmation of the products was obtained by hydrogenolysis to 6,8-dimethoxyisoquinoline, which was synthesized by an unambiguous route. Partial or complete demethylation of dimethoxyisoquinoline derivatives could be effected and a comparison of spectral data showed that 6,8-dihydroxyisoquinolines exist as hydroxy tautomers with no detectable contribution from quinolone forms.

During the course of synthetic studies directed toward mold metabolites of the isochromene group,[1] we have found that 3,5-dimethoxyphenylacetonitrile (**1**), when treated with zinc cyanide and either hydrogen chloride or hydrogen bromide under the usual conditions of the Gattermann reaction, affords a 3-halo-6,8-dimethoxy-

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[1] F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth and Co. Ltd., London, 1963, p 450; G. Büchi, J. D. White, and G. N. Wogan, *J. Am. Chem. Soc.*, **87**, 3484 (1965), and references cited.

TABLE I

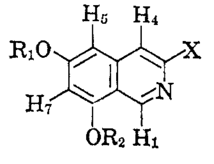
AROMATIC PROTON RESONANCES AND ULTRAVIOLET SPECTRA OF ISOQUINOLINE DERIVATIVES

	Chemical shift,[a] δ				Absorption maxima, mμ (extinction coefficient, ε)[b]
Compd	H_1	H_3	H_4	H_5 and H_7	
2	9.16 (s)	...	7.46 (s)	6.57 (s)	244 (55,200), 316 (4620), 324 (4920)
3	9.10 (s)	...	7.61 (s)	6.44 (s)	246 (55,600), 315 (4960), 324 (5260)
4	9.44 (s)	8.39[c] (d)	7.39[c] (d)	6.50[d] (q)	238 (51,500), 306 (5240), 319 (4920)
5	9.13 (s)	...	7.80 (s)	6.71 (s)	247 (38,600), 329 (3460)
6	9.05 (s)	...	7.88 (s)	6.69 (s)	248 (59,000), 330 (4840)
7	9.03 (s)	...	7.88 (s)	6.69 (s)	247 (51,050), 326 (5830)
8	9.40 (s)	8.35[c] (d)	8.05[c] (d)	6.88[d] (q)	240 (26,100), 325 (3060)

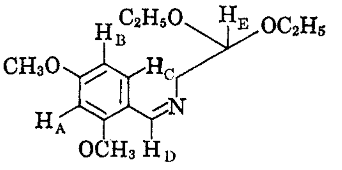
[a] Determined in deuteriochloroform (compounds **2–4**) and deuteriodimethyl sulfoxide solution (compounds **5–8**); chemical shifts are reported as ppm downfield from tetramethylsilane as internal standard; multiplicities are denoted by s (singlet), d (doublet), and q (quartet). [b] Determined in ethanol solution. [c] Part of an AB system, $J = 6$ cps. [d] Measured as the center of an AB system, $J = 2$ cps.

isoquinoline. A related observation was recently reported in a communication[2] describing the synthesis of 3-alkyl-6,8-dihydroxyisoquinolines by the Gattermann reaction of 3,5-dihydroxylbenzyl ketones. Isoquinolines bearing oxygenated substituents at both the 6 and 8 positions comprise an important group of degradation products from a variety of naturally occurring substances and might possibly serve as useful intermediates in the reconstitution of the natural materials.

The structures of isoquinolines **2** and **3** follow from their elemental analyses and mass spectra, which establish the empirical formulas as $C_{11}H_{10}NO_2X$ (X = Cl, Br), and from their ultraviolet spectra (Table I), which reveal the presence of an isoquinoline chromophore.[3] The nmr spectra showed that there were two nonequivalent methoxyl groups and four aromatic protons. The chemical shift of the singlet at lowest field (Table I) is in good agreement with that of the proton at the 1 position in isoquinolines[4] and the one-proton singlet at higher field can be identified with the proton at the 4 position. Hydrogenolysis of **2** or **3** over palladium on charcoal in ethanolic potassium hydroxide afforded 6,8-dimethoxyisoquinoline (**4**). The latter showed an AB quartet with chemical shifts of δ 8.39 and 7.39, corresponding to H_3 and H_4, respectively,[5] thus confirming that the halogen substituent had originally occupied the 3 position. The structure of the hydrogenolysis product was established unambiguously as **4** by comparison with 6,8-dimethoxyisoquinoline obtained by Pomeranz–Fritsch cyclization[6] of imino acetal **9**, prepared by condensation of 2-aminoacetaldehyde diethyl acetal with 2,4-dimethoxybenzaldehyde.



2, $R_1 = R_2 = CH_3$; X = Cl
3, $R_1 = R_2 = CH_3$; X = Br
4, $R_1 = R_2 = CH_3$; X = H_3
5, $R_1 = R_2 = H$; X = Cl
6, $R_1 = R_2 = H$; X = Br
7, $R_1 = H$; $R_2 = CH_3$; X = Br
8, $R_1 = R_2 = H$; X = H_3



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When the Gattermann reaction of **1** was carried out with ^{15}N-labeled zinc cyanide,[7] analysis of the product by mass spectrometry showed the theoretical amount of label present in the isoquinoline. The nitrogen atom of the isoquinoline nucleus is therefore derived from cyanide rather than the nitrile group of **1**. Other, more general aspects of the mechanism of formation of isoquinolines **2** and **3** remain uncertain, although several instances of cyclization of *ortho*-substituted phenylacetonitrile[8] and benzyl ketone[2,9] derivatives to yield isoquinolines and isocarbostyrils have recently been noted. Attempts to convert 3,4-dimethoxyphenylacetonitrile to an isoquinoline by treatment with zinc cyanide and hydrogen chloride were unsuccessful, the only isolable product after hydrolysis being 3,4-dimethoxyphenylacetamide.

Demethylation of **2**, **3**, and **4** could be effected under a variety of conditions, including treatment with hydriodic acid or boron tribromide in refluxing chloroform or benzene. Controlled reaction with hydriodic acid was found to yield isoquinolines selectively demethylated at the 6 position, while more prolonged exposure to acid cleanly afforded 6,8-dihydroxyisoquinolines.[10] Table I summarizes ultraviolet spectral data and chemical shifts of aromatic protons of isoquinolines **2–8**. The close correspondence of spectral characteristics between hydroxy- and methoxy-substituted derivatives leads to the conclusion that, in neutral solution, isoquinolone tautomers i and iii are

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[2] G. R. Birchall, M. N. Galbraith, and W. B. Whalley, *Chem. Commun.*, 474 (1966).

[3] A. I. Scott, "The Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 185.

[4] E. Vander Donckt, R. H. Martin, and F. Geerts-Evrard, *Tetrahedron*, **20**, 1495 (1964).

[5] The spectrum of isoquinoline (No. 520) given in the "Varian Catalog of NMR Spectra," Varian Associates, Palo Alto, Calif., has apparently been incorrectly interpreted. A singlet at δ 9.26 is assigned to H_3 and a doublet ($J = 6$ cps) at δ 8.52 to H_1. Arguments based on spin-spin coupling constants as well as chemical shift data[4] indicate that these assignments should be reversed (see J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 268).

[6] W. J. Gensler, *Org. Reactions*, **6**, 74 (1957).

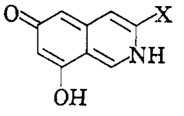
[7] Prepared from ^{15}N-labeled potassium cyanide (97%, Merck Sharp and Dohme of Canada) by a method analogous to that described from sodium cyanide.[14]

[8] F. Johnson and W. A. Nasutavicus, *J. Org. Chem.*, **27**, 3953 (1962); G. Simchen, *Angew. Chem.*, **78**, 674 (1966); T. Okano, S. Goya, and Y. Tsuda, *Yakugaku Zasshi*, **86**, 544 (1966) (*Chem. Abstr.*, **65**, 15319 (1966)).

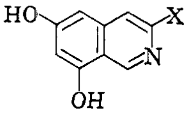
[9] W. T. Boyce and R. Levine, *J. Org. Chem.*, **31**, 3807 (1966).

[10] This result may most reasonably be attributed to a *peri* effect (V. Balasubramanian, *Chem. Rev.*, **66**, 567 (1966)).

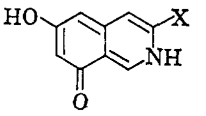
not present in significant amount and, in fact, these species were undetectable spectroscopically. This is in agreement with ultraviolet spectral measurements on 6-hydroxy- and 8-hydroxyisoquinolines[11] but differs from the interpretation put upon the spectra of aposclerotioramine and certain other 6,8-dihydroxyisoquinolines derived from sclerotiorin.[12]



i



ii



iii

Experimental Section[13]

3-Chloro-6,8-dimethoxyisoquinoline (2).—Dry hydrogen chloride was bubbled rapidly into a stirred suspension of 3.54 g (0.020 mole) of 2,5-dimethoxyphenylacetonitrile (1)[14] and 6.70 g (0.040 mole) of zinc cyanide in 40 ml of anhydrous ether at 0°. After 0.5–1 hr a viscous yellow oil separated. Water (50 ml) was added, cautiously at first, and the ether distilled off. The mixture was then refluxed for 0.5 hr. On cooling, a pale yellow crystalline precipitate separated which was collected and crystallized twice from aqueous ethanol to give colorless needles (2.39 g, 54%): mp 160–161°; infrared ν_{max} 1635, 1565, 1390, 1210, 1160, 1125, 862, 820, and 690 cm^{-1}. The mass spectrum showed intense peaks for the isotopic molecular ions at *m/e* 223 and 225 in the anticipated ratio (~3:1).[15] In addition to the signals listed in Table I, the nmr spectrum showed two three-proton singlets at δ 3.90 and 3.98.

Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; Cl, 15.85; N, 6.26. Found: C, 59.00; H, 4.35; Cl, 15.72; N, 6.16.

3-Chloro-6,8-dimethoxyisoquinoline-^{15}N was prepared in an analogous manner from 0.075 g of 1 and 0.125 g of zinc cyanide labeled with 97 atom % of ^{15}N. The product isolated showed parent peaks in the mass spectrum at *m/e* 224 and 226 (3:1) which indicated that the isoquinoline contained 94 ± 4% of ^{15}N.

3-Bromo-6,8-dimethoxyisoquinoline (3).—Dry hydrogen bromide was bubbled rapidly into a stirred suspension of 3.22 g (0.018 mole) of 1 and 7.10 g (0.042 mole) of zinc cyanide in 100 ml of anhydrous ether at 0°. A yellow precipitate formed after 0.5 hr. After 1 hr, 100 ml of water was cautiously added and the mixture stirred at room temperature for 2 hr. The ether was removed *in vacuo* and the aqueous phase was extracted with chloroform. The chloroform extract was washed with saturated salt solution, saturated sodium bicarbonate solution, and water, and dried over calcium chloride. Removal of solvent left a yellow, semicrystalline residue which was recrystallized from benzene–ligroin to give colorless plates (2.74 g, 57%): mp 159–160°; infrared ν_{max} 1635, 1565, 1410, 1210, 1160, 1125, 860, 825, and 675 cm^{-1}. The mass spectrum showed intense peaks for the molecular ions at *m/e* 267 and 269 in the anticipated ratio (1:1).[15] In addition to the signals due to the aromatic protons (Table I), the nmr spectrum showed two three-proton singlets at δ 3.89 and 3.95.

Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.28; H, 3.76; Br, 29.81; N, 5.23. Found: C, 49.17; H, 3.70; Br, 29.60; N, 5.45.

6,8-Dimethoxyisoquinoline (4). **A. By Hydrogenolysis.**—A solution of 0.640 g (2.86 mmoles) of 2 in 40 ml of 5% ethanolic potassium hydroxide was stirred under hydrogen at atmospheric pressure in the presence of 5% palladium on carbon at 50–55°. The rate of hydrogen uptake varied considerably over several runs and when hydrogen consumption stopped before the uptake of a full equivalent, an additional quantity of catalyst was added. The mixture was filtered and most of the ethanol removed from the filtrate *in vacuo*. The residue was diluted with water and extracted three times with ether. The ethereal solution was washed with 0.01 *N* hydrochloric acid and water and dried over magnesium sulfate. Removal of solvent gave a residue which was crystallized from ligroin, yielding colorless prisms (0.504 g, 93%): mp 124–125°; infrared ν_{max} 1635, 1575, 1450, 1400, 1210, 1200, 1155, 1130, 1030, 852, and 829 cm^{-1}. The mass spectrum of 4 showed a strong peak for the molecular ion at *m/e* 189. The nmr spectrum showed the expected two three-proton singlets for the methoxyl groups at δ 3.89 and 3.95.

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.35; H, 5.86; N, 7.17.

Hydrogenolysis of 0.827 g (3.09 mmoles) of 3 under similar conditions gave 0.555 g (95%) of 4, identical by mixture melting point and infrared spectral comparison with the material obtained from 2.

B. By Pomeranz–Fritsch Cyclization.—A mixture of 3.60 g (0.022 mole) of 2,4-dimethoxybenzaldehyde and 3.48 g (0.026 mole) of 2-aminoacetaldehyde diethyl acetal[16] in 50 ml of benzene was refluxed for 2 hr. Solvent was removed *in vacuo*, leaving 6.14 g (99%) of crude 2,4-dimethoxybenzalamino acetal 9 (infrared ν_{max} 1635, 1600, 1575, 1500, 1260, 1200, 1155, 1115, 1060, 1035, and 830 cm^{-1}); the nmr spectrum showed a triplet (J = 7 cps, 6 H), at δ 1.19, a singlet (2 OCH_3) at 3.78, a complex pattern at 3.30–3.85 (2 OCH_2 and 1 $=NCH_2$), a triplet (J = 5 cps, H_E) at 4.77, a multiplet (H_A and H_B) at 6.45, a doublet (J = 8 cps, H_C) at 7.90, and a singlet (H_D) at 8.60.

The crude benzalaminoacetal 9 (2.84 g, 0.01 mole) was added slowly to 20 ml of 75% sulfuric acid stirred at 0° under nitrogen. The mixture was stirred at 0° for 3 hr after addition was complete and for a further 3 hr at room temperature. The dark reaction mixture was diluted with 100 ml of water and extracted with ether. Chromatography of the ether extract on neutral alumina, eluting with hexane–benzene mixtures, gave, from the early fractions, a residue which could be recrystallized from benzene–ligroin to yield 6,8-dimethoxyisoquinoline (4, 0.142 g, 7.5%), mp 125–126°. The identity of this material with that obtained by procedure A above was established by mixture melting point and infrared spectral comparison. Later fractions of the eluate from the chromatogram yielded substantial amounts of 2,4-dimethoxybenzaldehyde.

3-Chloro-6,8-dihydroxyisoquinoline (5).—A mixture of 0.412 g (1.85 mmoles) of 2 in 15 ml of 57% hydriodic acid was refluxed for 1.5 hr. The dimethoxy compound dissolved initially and the product crystallized on cooling at the end of the reflux period. After collection by filtration through a sintered-glass funnel, the product was recrystallized from water to give colorless needles (0.297 g, 82.5%): mp 242–243° dec; infrared ν_{max} 3400 (br), 1640, 1590, 1565, 1475, 1390, 1175, 1115, 1100, 943, 888, 860, 791, and 678 cm^{-1}.

Anal. Calcd for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; Cl, 18.12; N, 7.16. Found: C, 55.11; H, 2.98; Cl, 17.76; N, 7.27.

3-Bromo-6,8-dihydroxyisoquinoline (6).—Prepared from 3 in a manner analogous to that described for 5, this compound was obtained as a colorless, microcrystalline solid from water in 78% yield: dec pt 258–263°; infrared ν_{max} 3300 (br), 1645, 1595, 1565, 1390, 1340, 1275, 1160, 1105, 1000, 931, 868, and 832 cm^{-1}.

Anal. Calcd for $C_9H_6BrNO_2$: C, 45.03; H, 2.52; Br, 33.28; N, 5.83. Found: C, 44.84; H, 2.43; Br, 32.89; N, 5.53.

3-Bromo-6-hydroxy-8-methoxyisoquinoline (7).—A mixture of 0.510 g (1.71 mmoles) of 3 in 15 ml of 57% hydriodic acid was refluxed for 0.25 hr. On cooling, 7 separated out and was collected and recrystallized from aqueous ethanol to give colorless needles (0.282 g, 58%): mp 247–249° dec; infrared ν_{max} 3200 (br), 1625, 1570, 1400, 1200, 1165, 1125, 880, and 852 cm^{-1}. The mass spectrum showed the anticipated isotopic molecular ion peaks at *m/e* 253 and 255 (1:1)[15] and the nmr spectrum showed a singlet (3 H) at δ 4.00 for the methoxyl group at the 8 position.

Anal. Calcd for $C_{10}H_8BrNO_2$: C, 50.45; H, 3.38; Br, 33.46; N, 5.88. Found: C, 50.22; H, 3.46; Br, 33.14; N, 5.60.

6,8-Dihydroxyisoquinoline (8).—Prepared from 4 in a manner analogous to that described for 5, 8 was obtained as a colorless, microcrystalline solid from water in 64% yield: dec pt 253–257°;

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[11] K. Nakanishi, M. Ohashi, S. Kumasaki, and H. Koike, *Bull. Chem. Soc. Japan*, **34**, 534 (1961); S. F. Mason, *J. Chem. Soc.*, 5010 (1957).

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infrared ν_{max} 3300 (br), 1625, 1575, 1545, 1440, 1400, 1300, 1265, 1175, 860, 830, 781, and 749 cm^{-1}.

Anal. Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.94; H, 4.34; N, 8.78.

Registry No.—**1**, 13388-75-5; **2**, 13388-76-6; **3**, 13388-77-7; **4**, 13388-78-8; **5**, 13388-79-9; **6**, 13388-80-2; **7**, 13388-81-3; **8**, 13388-82-4; **9**, 13388-83-5.

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Diphenylcarbinyl Derivatives. I. Solvolysis of Some Monosubstituted Benzhydryl Chlorides

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Rates of solvolyses of various monosubstituted benzhydryl chlorides, including *p*-CH_3O, *m*-CH_3O, *p*-CH_3, *m*-CH_3, H, *p*-F, *m*-F, *p*-Cl, *m*-Cl, *p*-Br, *m*-Br, *p*-CN, *m*-CN, *p*-NO_2, and *m*-NO_2, are studied at 25.0° in methanol, in ethanol, and in 2-propanol. Rate data are correlated linearly with σ^+ values; ρ values are found to be rather constant in the three solvents examined.

The Hammett ρ–σ relationship[2] has been studied extensively in recent years[3] and provides a quantitative approach to the correlation between the structure and reactivity of organic compounds. As a result, it is clearly established that the strongly electron-demanding reactions, termed *electrophilic side chain reaction*,[4] are correlated more nicely with σ^+ values[3,4] than with Hammett σ values.[2,5] The solvolysis of benzhydryl chlorides is such an electrophilic side-chain reaction and has been studied by several workers,[6-23] but varieties of the substituents are rather limited and one sided. It is thus our purpose to investigate the solvolytic reactivities of benzhydryl chlorides substituted by a wide variety of substituents.

Results and Discussion

Most benzhydrols are prepared by the sodium borohydride reduction of corresponding benzophenones; chlorides are prepared by the reaction of carbinols with hydrogen chloride. Dry hydrogen chloride is introduced into a solution of benzhydrol in purified methylene dichloride in the presence of Drierite; after drying the solution by the addition of fresh Drierite, the solvent is removed under the reduced pressure. In this manner, benzhydryl chloride is obtained in a satisfactory purity for the kinetic study; the rate constant obtained by solvolyzing the chloride thus prepared is found to be in excellent agreement with that given by the purified chloride (see Experimental Section). Cyano- and nitrobenzhydryl chloride are prepared by the reaction of carbinol with thionyl chloride; the resulting chloride is purified by distillation under reduced pressure. The rates of solvolysis are mostly determined at 25.0°; in the case of certain chlorides, which are extremely reactive or unreactive, extrapolations are made to obtain the rate constants at 25.0°. The results are summarized in Table I.

A plot of the rate data in ethanol, except *p*-methoxy, *vs.* the Brown σ^{+} [3c,4] gives a good straight line with the correlation coefficient 0.998 and the standard deviation 0.099 (Figure 1). The *p*-methoxy derivative is omitted for the treatment because the point deviates from the regression line; the deviation might be primarily due to the experimental uncertainty caused by numbers of the extrapolations made both in the present study and in the solvolysis of phenyldimethylcarbinyl chloride in 90 vol % acetone, from which the σ^+ values have been evaluated.[3c,4] Another reason for the deviation could be the difference in the reaction system between the present study (secondary system) and the solvolysis of phenyldimethylcarbinyl chlorides (tertiary system).

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