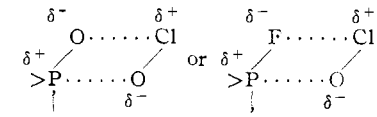
wards[15] has been able to correlate many rate data of the nucleophilic displacement type by assigning numerical values to nucleophiles based upon their electrode potentials (E_n) and basicities to protons (H). The values for hypochlorite ion, using Edwards' equations,[15] along with those of the hydroxide ion and the thiosulfate ion are shown below.

Ion	E_n	H
OH^-	1.65	17.48
$S_2O_3^=$	2.52	3.60
OCl^-	2.01	9.14

The relative importance of the two parameters will depend upon the compound under attack. For example, displacements on carbon compounds are very rapid with compounds of high E_n values, whereas the basicity factor appears to be more important in displacements on hydrogen.[15] It has been found in independent experiments that the thiosulfate ion, a material with a high E_n value and a powerful nucleophile toward carbon,[16] does not accelerate the hydrolysis rate of Sarin. It has also been established from studies of the hydrolysis of diisopropyl phosphorofluoridate[17] that the effectiveness of a nucleophile in this reaction was related to its basicity. Thus it might be conjectured that for displacements on phosphorus, the rate will be more correlatable with the nucleophile's ability to accept protons. Yet hydroxyl ion, which is more basic than hypochlorite ion by eight powers of ten, has a bimolecular rate constant (calculated from the data in footnote (1)) of only three to four times that of the hypochlorite ion. It would thus appear that the basicity alone of hypochlorite ion cannot be used to explain its activity.

It is proposed that the enhanced reactivity of the hypochlorite ion is due to a bifunctional attack,[18] the oxygen of the hypochlorite attacking the phosphorus atom and the positive chlorine attacking the phosphoryl oxygen (or the fluorine) thereby inducing polarization and aiding in displacement.

The transition state is depicted as



The effective van der Waals radii and the bond lengths[19] of the participating groups are such as to make such a postulation plausible, and spectral studies on various organic phosphorus compounds indicate the phosphoryl group is subject to polarization.[20]

(15) J. O. Edwards, THIS JOURNAL, **76**, 1540 (1954).
(16) P. D. Bartlett and G. Small, *ibid.*, **72**, 4867 (1950).
(17) M. Kilpatrick and M. L. Kilpatrick, *J. Phys. Colloid Chem.*, **53**, 1371 (1949).
(18) See *e.g.*, C. G. Swain and J. F. Brown, THIS JOURNAL, **74**, 2538 (1952); J. Epstein, D. H. Rosenblatt and M. M. Demek, *ibid.*, **78**, 341 (1956).
(19) L. Pauling, "Nature of the Chemical Bond," 2nd Edition, Cornell University Press, Ithaca, N. Y., 1945, p. 164, 189.
(20) J. V. Bell, J. Heisler, H. Tannenbaum and J. Goldenson, THIS JOURNAL, **76**, 5185 (1954); G. F. Svatos and J. Goldenson, Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Feb. 27–March 2, 1956.

ARMY CHEMICAL CENTER, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Displacements and Nuclear Substitutions on Hydroxypyrazines

BY GEORGE KARMAS[1] AND PAUL E. SPOERRI

RECEIVED MARCH 15, 1956

A variety of 2-hydroxypyrazines has been brominated and phenylated, and three have been nitrated. It has been found that halogens and nitro groups *ortho* to hydroxyl are easily displaced by acidic reagents, and such reactions afford convenient syntheses of dihalo- and dihydroxypyrazines.

I. Nitration.—In 1953, we reported that 2-hydroxy-5,6-diphenylpyrazine is readily nitrated in the 3-position under mild conditions and that 2-hydroxy-3,6-diphenylpyrazine undergoes random nitration under a variety of strongly acidic conditions.[2] Since then we have found that briefly boiling an acetic acid solution of equivalent amounts of nitric acid and the 3,6-diphenyl isomer leads to a 75% yield of the 2-hydroxy-5-nitro-3,6-diphenylpyrazine.

When one equivalent of nitric acid is added to a solution of 2-hydroxy-3-phenylpyrazine, the nitrate of this pyrazine soon crystallizes. This salt is stable in air but is hydrolyzed in water. Boiling in water does not effect nitration, but if the salt is briefly boiled in acetic acid, 2-hydroxy-3-phenyl-5-nitropyrazine is formed. Presumably, in hot acetic acid, dissociation of the nitrate is a relatively slow, temperature-dependent process which is followed by very rapid nitration of the nucleus.

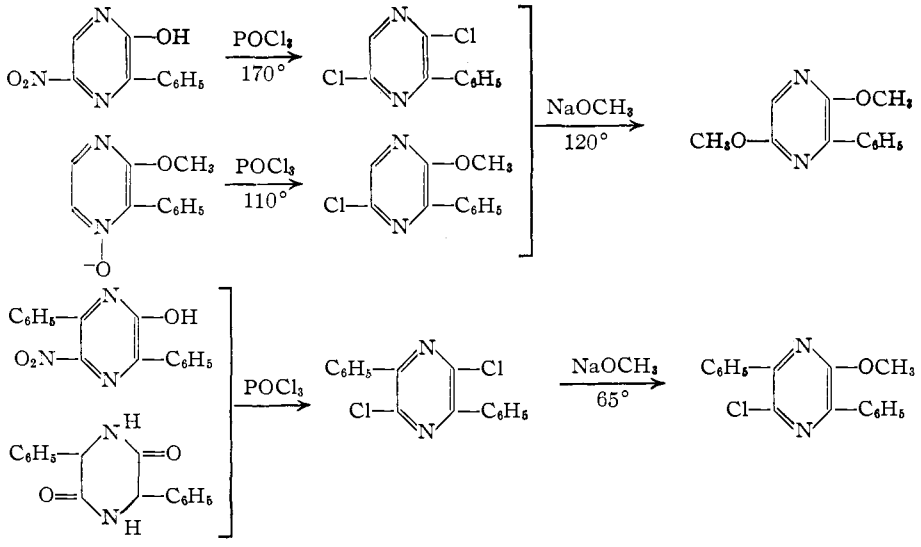
The nitrates of the diphenylhydroxypyrazines, which are weaker bases, could not be isolated, and so it may not yet be assumed that they are intermediates as in the nitration of 2-hydroxy-3-phenylpyrazine.

Structures of the 5-nitropyrazines were proved by conversion to ethers which had alternatively been synthesized by independent methods to be described below and based in part on the elegant conversion of N-oxides to chloropyrazines as reported by Newbold and Spring.[3]

No conditions have been found for the nitration of alkylhydroxypyrazines. These reacted with nitric acid in hot acetic acid, but no pyrazinoid products could be isolated.

II. Bromination.—*para*-Substitution in 2-hydroxy-3,6-diphenylpyrazine and 2-hydroxy-3-(*sec*-

(1) Ortho Pharmaceutical Corporation, Raritan, New Jersey.
(2) G. Karmas and P. E. Spoerri, THIS JOURNAL, **75**, 5517 (1953).
(3) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1183 (1947).



butyl)-6-isobutylpyrazine has been reported to occur with bromine in acetic acid,[4] but this procedure was unsatisfactory when applied to simpler hydroxypyrazines.

An essential feature of our successful bromination of alkylated hydroxypyrazines was the presence of a stronger base (pyridine) as hydrogen bromide acceptor. In its absence the yields of bromohydroxypyrazines were very low. The technique developed for bromination of 2-hydroxy-3,6(and 5,6)-disubstituted pyrazines and 2-hydroxy-3-phenylpyrazine was to add one equivalent of bromine in acetic acid to a cold solution of the pyrazine plus two equivalents of pyridine in acetic acid. Dilution of the reaction mixture with water precipitated the 3- or 5-bromohydroxypyrazines.

Because 2-hydroxy-3-*mono*alkylpyrazines were rapidly destroyed by the combination of bromine, acetic acid and excess pyridine, they had to be brominated under much milder conditions. One equivalent of pyridine–bromine complex in chloroform was added slowly to a very cold (−25°) solution of the hydroxypyrazine in chloroform. The yields of 2-hydroxy-3-alkyl-5-bromopyrazines were not good, but other techniques of bromination yielded no pyrazinoid products at all.

As expected, 2-hydroxy-3,5-dimethylpyrazine, which has no free *ortho* or *para* position, gave no bromopyrazine by either procedure. The starting material was destroyed in preference to substitution at the electron-poor 6-position.

The chemical behavior of the bromohydroxypyrazines, as discussed below, left no doubt as to the correctness of the assigned structures. Table I summarizes the brominations.

(4) F. S. Spring, *et al.*, *J. Chem. Soc.*, 910 (1949); 4870 (1952).

III. Phenylation.—A well-known reaction of 2-hydroxypyrazines is diazonium coupling at the 5(*para*)-position[5] in neutral or mildly alkaline solution. We have found that when phenyldiazonium chloride is added to hydroxypyrazines in *molar* aqueous sodium hydroxide, phenylation of the

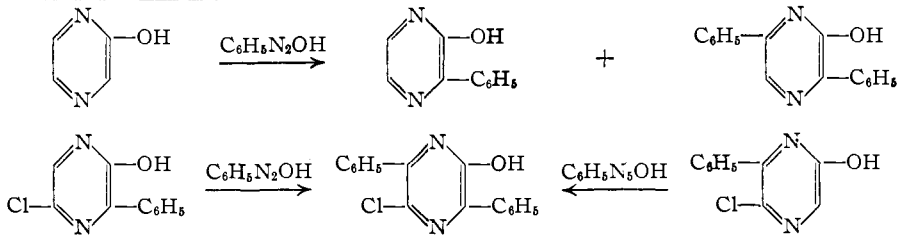
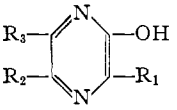


TABLE I

BROMOHYDROXYPYRAZINES



Cpd.	R_1	R_2	R_3	Procedure[a]	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found
I	CH_3	Br	H	A	20	185–187[b]	14.82	14.58
II	C_2H_5	Br	H	A	12	125–126	13.80	13.70
III	*i*-C_3H_7	Br	H	A	42	119–121	12.90	12.62
IV	C_6H_5	Br	H	B	64	192–193	11.16	10.90
V	CH_3	Br	CH_3	B	55	237–239[b]	13.80	13.67
VI	C_2H_5	Br	CH_3	B	38	179–180	12.90	12.95
VII	C_6H_5	Br	CH_3	B′	57	270–271	10.57	10.52
VIII	Br	CH_3	CH_3	B	61	227–228[b]	13.80	13.76
IX	Br	C_6H_5	C_6H_5	B′	53	223–224[b]	8.56	8.25
X	Br	Cl	C_6H_5	B′	87	210–211	9.82	9.50

[a] Details of these procedures are presented in the Experimental section. [b] Decomposed on melting.

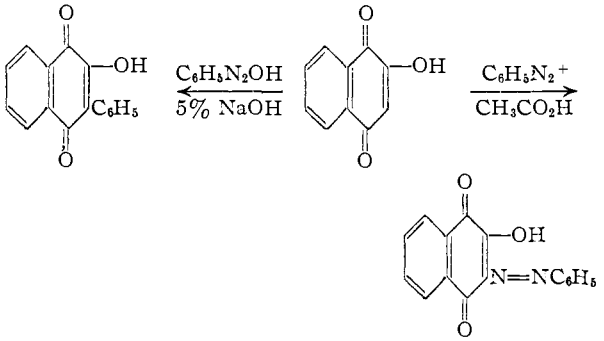
nucleus occurs, with evolution of nitrogen. In this apparently general reaction substitution occurs preferentially at a free 3-position but may also occur at positions 5 and 6 if these also originally bore hydrogen. The following examples are illustrative, and others are detailed in the Experimental section. 2-Hydroxy-3-*alkyl*pyrazines were not phenylated in sodium hydrozide, but neither did they yield the 5-phenylazo derivatives which are formed in sodium carbonate solution.

Phenylazohydroxypyrazines are apparently not intermediates in the phenylation reaction, for the

(5) E. Princevalle, *Gazz. chim. ital.*, **60**, 298 (1930).

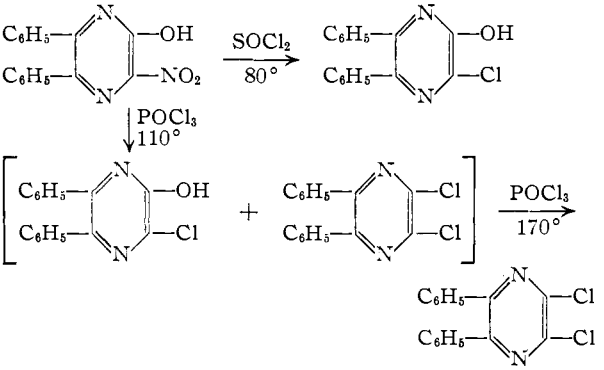
only action of aqueous sodium hydroxide on 2-hydroxy-3-phenylazo-5,6-dimethylpyrazine was partial destruction of the compound with no formation of the 3-phenyl analog. A free radical process is obviously suggested by the multipositional nature of this substitution and by the fact that a deep orange to red color develops immediately on mixing of the reagents, this soon being followed by brisk evolution of nitrogen.

A strikingly similar example of substitution by either phenyl or phenylazo, depending on *p*H of the medium, has been reported to occur with 2-hydroxy-1,4-naphthoquinone[6]



IV. Reactions of Phenylnitrohydroxypyrazines.—These compounds are sufficiently acidic to dissolve in aqueous sodium bicarbonate and are stable in strong alkali. They do not react with dimethyl sulfate in alkaline solution or with sodium ethoxide and ethyl iodide in hot ethanol.

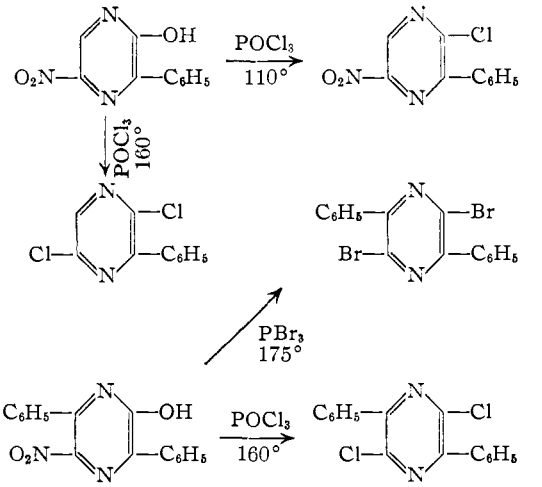
In strongly acidic media displacements of the nitro group occur. Attempted preparations of 2-chloro-3-nitro-5,6-diphenylpyrazine failed because heating of the hydroxypyrazine with phosphorus oxychloride or thionyl chloride resulted in displacement of the nitro group by chlorine, with evolution of nitrogen oxides



The same starting material was quantitatively converted to 2,3-dihydroxy-5,6-diphenylpyrazine on refluxing in an aqueous hydrochloric acid–acetic acid solution. However, aqueous *sulfuric acid*–acetic acid cleaved the molecule to benzil.[2]

The *p*-nitro group in 2-hydroxy-3-phenyl-5-nitropyrazine and 2-hydroxy-5-nitro-3,6-diphenylpyrazine was far more resistant to acidic displacement than was the *o*-nitro. A chloronitro derivative could be formed from the first of these, and double displacements occurred only at high temperatures

(6) O. Neunhoeffer and J. Weise, *Ber.*, **71**, 2703 (1938).



There was no study of mechanisms, but it seems likely that pyrazinium cations and their tautomeric carbonium ions are intermediates in each of these reactions.

V. Reactions of Bromohydroxypyrazines.—Halogen in these compounds was extremely inert toward nucleophilic displacement by strong bases, as might be expected for a bromophenol but, surprisingly, in the *o*-bromohydroxypyrazines it was rapidly displaced by hydroxyl on heating in hydrobromic acid or aqueous sulfuric acid–acetic acid. This proved to be an excellent synthesis of 2,3-dihydroxy-5,6-dimethyl-(and diphenyl)-pyrazine.

2-Hydroxy-5-bromo-3,6-diphenylpyrazine was stable in hydrobromic acid. Since it was known from other experiments (forthcoming publication) that *p*-dihydroxypyrazines are unstable in acid, the reaction of other *p*-bromohydroxypyrazines with aqueous acid was not investigated.

The bromohydroxypyrazines were most useful as precursors to the dihalides. When they were heated in a large excess of phosphorus oxychloride, good yields of the 2,3- or 2,5-dichloropyrazines invariably were isolated because displacement of bromine by chlorine occurred readily.

Only the diphenylbromohydroxypyrazines could be converted to the dibromides by refluxing in phosphorus tribromide. However, a useful indirect synthesis of dibromides was based on the facile halogen displacements which occur in either direction

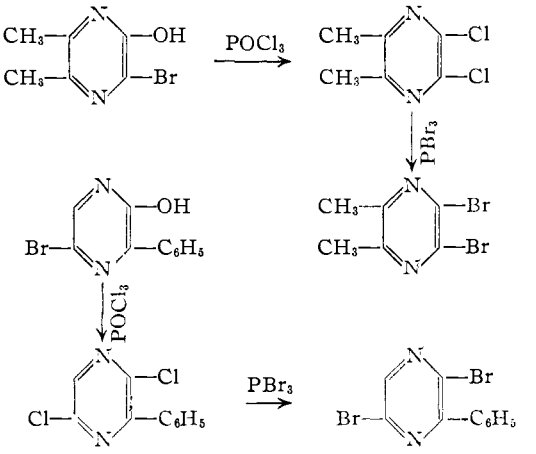
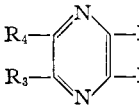


TABLE II

DIHALOPYRAZINES



R_1 and R_2 = Cl or Br

or R_1 and R_3 = Cl or Br

Cpd.	R_1	R_2	R_3	R_4	Type of starting material	Yield, %	M.p., °C.	Bromine, % Calcd.	Bromine, % Found
XI	Br	Br	CH_3	CH_3	Dichloride	68	87–88	60.00	59.87
XII	Br	Br	C_6H_5	C_6H_5	Bromohydroxy	53	212–214	40.92	41.17
XIII	Br	C_6H_5	Br	H	Dichloride	63	71-72	50.90	50.78
XIV	Br	C_6H_5	Br	C_6H_5	Bromohydroxy	75	197–198	40.92	40.57
								Chlorine, % Calcd.	Chlorine, % Found
XV	Cl	Cl	CH_3	CH_3	Dihydroxy	95	80–81	40.03	39.62
					Bromohydroxy	84			
XVI[a]	Cl	CH_3	Cl	CH_3	Bromohydroxy	74	72–73	...	...
XVII	Cl	C_6H_5	Cl	H	Nitrohydroxy	92	59–60	31.50	31.41
					Bromohydroxy	77			
XVIII	Cl	Cl	C_6H_5	C_6H_5	Nitrohydroxy	73	182-183	23.38	23.29
					Chlorohydroxy	68			
XIX[b]	Cl	C_6H_5	Cl	C_6H_5	Bromohydroxy	80	159–160	...	...

[a] Previously prepared from the di-N-oxide (ref. 3). [b] Previously prepared from *dl*-phenylglycine anhydride (ref. 4).

The syntheses of dibromopyrazines and dichloropyrazines are summarized in Table II.

Experimental

I. Nitrations. A. 2-Hydroxy-5-nitro-3,6-diphenylpyrazine.—A solution of 10.0 g. (0.04 mole) of 2-hydroxy-3,6-diphenylpyrazine in 800 ml. of boiling acetic acid was cooled with stirring to 85°, and 2.5 ml. of 18 *N* nitric acid in 30 ml. of acetic acid was added in one portion. This solution was then refluxed with stirring for 10 minutes and poured into 3000 ml. of water. The yellow solid was filtered off and boiled for 10 minutes with 40 g. of potassium bicarbonate in 1500 ml. of water. After filtration while hot the bicarbonate solution was poured with stirring into 1000 ml. of 5% hydrochloric acid. The reprecipitated nitro compound was filtered off, washed with water and dried at 80°. Recrystallization from acetone gave 8.9 g. (75%) of small yellow granules, m.p. 274–276° dec.

Anal. Calcd. for $C_{16}H_{11}N_3O_3$: N, 14.33. Found: N, 14.32.

B. **2-Hydroxy-3-phenylpyrazine Nitrate and 2-Hydroxy-3-phenyl-5-nitropyrazine.**—Six ml. of 18 *N* nitric acid in 15 ml. of acetic acid was added in one portion to a solution of 16.3 g. (0.095 mole) of 2-hydroxy-3-phenylpyrazine in 160 ml. of acetic acid. After 2 hr. at 25° the peach prisms (17.2 g. of the nitrate) were filtered off and the filtrate was concentrated at 30–35° under vacuum to a volume of 30 ml. This concentrate deposited 2.4 g. more of the salt for a total of 19.4 g. (87%) of air-dried nitrate which had m.p. 123–125° dec.

Anal. Calcd. for $C_{10}H_9N_3O_4$: N, 17.88. Found: N, 17.20.

To 100 ml. of boiling acetic acid was added over a period of 5 minutes 2.4 g. (0.01 mole) of 2-hydroxy-3-phenylpyrazine nitrate in 0.5-g. portions. After an additional five minutes of boiling, the acetic acid solution was evaporated under vacuum and the residue was recrystallized from acetone to give 1.5 g. (68%) of 2-hydroxy-3-phenyl-5-nitropyrazine as large yellow prisms, m.p. 254–256°.

Anal. Calcd. for $C_{10}H_7N_3O_3$: N, 19.37. Found: N, 19.12.

II. Nuclear Brominations.—The hydroxypyrazines which were brominated have previously been described,[7,8] except for 2-hydroxy-5-chloro-6-phenylpyrazine, for which the synthesis is given below. Two general procedures and a variant were used and are referred to as A, B and B′ in Table I.

A. Compounds I, II and III.—A solution of 0.10 mole of the appropriate 2-hydroxy-3-alkylpyrazine in 150 ml. of chloroform was vigorously stirred at −25° while a cold (0°) solution of 8.1 ml. (0.10 mole) of pyridine and 5.1 ml. (0.10 mole) of bromine in 80 ml. of chloroform was added over a period of 15 minutes. The mixture was warmed to −5°, 180 ml. of 4% hydrochloric acid was added and stirring while cooling in ice was continued until all the solid had dissolved. After separation of the chloroform layer, the aqueous phase was further extracted with three 100-ml. portions of chloroform, and the combined extracts were dried with magnesium sulfate and evaporated to dryness. Compound I was then recrystallized from 90 ml. of acetone and compounds II and III from 150 ml. of isoöctane.

B. **Compounds IV, V, VI and VIII.**—A solution of 0.05 mole of the appropriate hydroxypyrazine and 10 ml. (0.124 mole) of pyridine in 20 ml. of acetic acid was vigorously stirred at 10° while 2.5 ml. (0.05 mole) of bromine in 12 ml. of acetic acid was added over a period of 15 minutes. Then 100 ml. of 5% hydrochloric acid was added and after chilling at 0° the crystalline bromohydroxypyrazine was filtered off, washed with ice-water and dried in air. Compound IV was recrystallized from 75 ml. of acetone and VI from 60 ml. of toluene. Compounds V and VIII were of high purity as isolated, but small portions were easily recrystallized from toluene.

B′. **Compounds VII, IX and X** were prepared as described in procedure B except that the hydroxypyrazine and the pyridine were first dissolved in 150 ml. of acetic acid and the bromination mixture was finally diluted with 1500 ml. of water to precipitate the product. All were recrystallized from 300 ml. of ethanol.

III. Nuclear Phenylations. A. 2-Hydroxy-3-phenylpyrazine and 2-Hydroxy-3,6-diphenylpyrazine.—A phenyldiazonium chloride solution, from 8.0 g. (0.086 mole) of aniline plus 90 ml. of 6% hydrochloric acid and 6.0 g. (0.088 mole) of sodium nitrite in 15 ml. of water, was added in one portion to an ice-cold solution of 4.2 g. (0.043 mole) of 2-hydroxypyrazine in 350 ml. of 5% aqueous sodium hydroxide layered with 10 ml. of butanol (anti-foam). After standing at 20° for 30 minutes, the mixture was concentrated at 45° under vacuum to a volume of 350 ml., cooled to 30° and decanted from the tar. The alkaline solution was neutralized with carbon dioxide to *p*H 7, thus precipitating an orange solid which was recrystallized from pyridine and identified by mixed m.p. (292–293°) as 2-hydroxy-3,6-diphenylpyrazine (0.4 g., 4%). The neutral aqueous filtrate was evaporated to dryness and the residue was leached with 170 ml. of hot methanol. After filtration the methanol extract was evaporated to dryness and the residue was boiled with 600 ml. of water and then filtered at 50°. Concentration of the filtrate to 50 ml. resulted in crystallization of a brown solid which was recrystallized from 30 ml. of acetone to give 3.5 g. (47%) of 2-hydroxy-3-phenylpyrazine, identical with an authentic specimen.

B. **2-Hydroxy-3-phenyl-5-methylpyrazine and 2-Hydroxy-3,6-diphenyl-5-methylpyrazine.**—A phenyldiazonium chloride solution (0.086 mole as prepared in A) was added to an ice-cold solution of 4.0 g. (0.036 mole) of 2-hydroxy-5-

(7) R. G. Jones, THIS JOURNAL, **71**, 78 (1949).

(8) G. Karmas and P. E. Spoerri, *ibid.*, **74**, 1580 (1952).

methylpyrazine in 350 ml. of 5% sodium hydroxide. After 1 hr. at 5° and 12 hr. at 20°, the mixture was warmed to 80° to coagulate tar, cooled to 50° and decanted from the tar. The alkaline solution was neutralized with carbon dioxide, heated to boiling and filtered to isolate a red solid which was recrystallized from 60 ml. of ethanol and then from 50 ml. of butyl acetate to give 1.3 g. (14%) of buff flakes, m.p. 229–231°, identified by analysis and general properties as 2-hydroxy-3,6-diphenyl-5-methylpyrazine.

Anal. Calcd. for $C_{17}H_{14}N_2O$: N, 10.68. Found: N, 10.65.

The neutral aqueous filtrate was concentrated to 120 ml. and the precipitated solid was filtered off and recrystallized from 100 ml. of heptane to give 1.4 g. (20%) of buff needles which melted at 152–154°, solidified and remelted at 160–161°. This was 2-hydroxy-3-phenyl-5-methylpyrazine—a mixture with an authentic specimen showed the same behavior on melting.

Anal. Calcd. for $C_{11}H_{10}N_2O$: N, 15.07. Found: N, 15.01.

C. 2-Hydroxy-3-phenyl-6-methylpyrazine and 2-Hydroxy-3,5-diphenyl-6-methylpyrazine.—A phenyldiazonium chloride solution (0.086 mole as prepared in A) was added to an ice-cold solution of 5.0 g. (0.045 mole) of 2-hydroxy-6-methylpyrazine in 350 ml. of 5% sodium hydroxide. After 1 hr. at 5° and 3 hr. at 20°, the mixture was concentrated to 300 ml., decanted from tar, acidified with acetic acid and chilled at 0°. The solids were filtered off, boiled 15 minutes in one liter of water and the suspension filtered while hot to isolate a red-brown solid. This was recrystallized from 100 ml. of acetone, then from 35 ml. of butanol and again from 20 ml. of butanol to give 0.25 g. (2%) of small orange prisms, m.p. 277–279°, identified by physical properties and analysis as 2-hydroxy-3,5-diphenyl-6-methylpyrazine.

Anal. Calcd. for $C_{17}H_{14}N_2O$: N, 10.68. Found: N, 11.01.

The aqueous filtrate from isolation of the diphenyl compound was evaporated to dryness, and the residue was recrystallized from 35 ml. of ethanol and then from 40 ml. of ethyl acetate to give 1.5 g. (18%) of yellow prisms, m.p. 206–208°. This was assigned the structure 2-hydroxy-3-phenyl-6-methylpyrazine by analysis and because it differs from the known 5-phenyl-6-methyl isomer of m.p. 254°.[9]

Anal. Calcd. for $C_{11}H_{10}N_2O$: N, 15.07. Found: N, 14.84.

D. 2-Hydroxy-3-phenyl-5,6-dimethylpyrazine.—A phenyldiazonium chloride solution (0.086 mole as prepared in A) was added to an ice-cold solution of 5.3 g. (0.043 mole) of 2-hydroxy-5,6-dimethylpyrazine in 500 ml. of 5% sodium hydroxide. After 2 hr. at 0°, 10 ml. of butanol was added to the frothy mixture, and it was concentrated to 200 ml. The orange solution was filtered with Super-Cel and the clear filtrate was acidified with hydrochloric acid, chilled to 5° and filtered to isolate a brown solid. This was recrystallized from 150 ml. of butanol and again from 80 ml. of butanol to give 3.9 g. (45%) of buff needles, m.p. 242-243°, identical with 2-hydroxy-3-phenyl-5,6-dimethylpyrazine prepared in another manner.[7]

E. 2-Hydroxy-3,5,6-triphenylpyrazine.—This phenylation, yielding 75% of 2-hydroxy-3,5,6-triphenylpyrazine, was described in our previous publication.[10]

F. 2-Hydroxy-3,6-diphenyl-5-chloropyrazine.—A solution of phenyldiazonium chloride (0.011 mole) was added to an ice-cold solution of 1.0 g. (0.0053 mole) of 2-hydroxy-3-phenyl-5-chloropyrazine in 50 ml. of 7% sodium hydroxide. After 1 hr. at 20° the mixture was warmed to 80°, cooled to 35° and filtered with Super-Cel. Acidification of the filtrate with hydrochloric acid precipitated a yellow solid which was recrystallized from 50 ml. of acetone to give 0.6 g. (40%) of 2-hydroxy-5-chloro-3,6-diphenylpyrazine, m.p. 260–261°.

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: Cl, 12.54. Found: Cl, 12.41.

Phenylation of 1.0 g. of 2-hydroxy-5-chloro-6-phenylpyrazine exactly as described for its isomer gave 0.9 g. (60%) of the same product, m.p. 260–261°.

IV. Dihalopyrazines.—The yields, melting points and analytical data for compounds of this type are summarized in Table II. All reactions with phosphorus oxychloride were performed by first boiling the compounds gently in an open pressure tube until all solid had dissolved and then sealing the tube before heating at high temperature.

A. 2,3-Dichloro-5,6-dimethylpyrazine (XV).—(1) 2-Hydroxy-3-bromo-5,6-dimethylpyrazine (0.05 mole) was heated in 40 ml. of phosphorus oxychloride for 7 hr. at 170°. After hydrolyzing this solution on ice and treating with aqueous ammonia until alkaline, the dichloride was extracted with three 100-ml. portions of ether and subsequently was purified by distillation (b.p. 122–123° at 15 mm.), followed by recrystallization from 40 ml. of hexane. (2) 2,3-Dihydroxy-5,6-dimethylpyrazine (0.03 mole) was heated in 20 ml. of phosphorus oxychloride for 18 hr. at 160°. The dichloride was isolated as described above and was pure after distillation.

B. 2,5-Dichloro-3,6-dimethylpyrazine (XVI).—2-Hydroxy-5-bromo-3,6-dimethylpyrazine (0.02 mole) was heated in 30 ml. of phosphorus oxychloride for 6 hr. at 170°. The dichloride was isolated in the same manner as the 2,3-isomer and was recrystallized from 12 ml. of pentane.

C. 2,5-Dichloro-3-phenylpyrazine (XVII).—(1) 2-Hydroxy-3-phenyl-5-nitropyrazine (0.03 mole) was heated in 35 ml. of phosphorus oxychloride for 6 hr. at 170°. After hydrolyzing this solution on ice, the dichloride was extracted with two 100-ml. portions of ether and subsequently was purified by distillation (b.p. 115–116° at 0.3 mm.). (2) 2-Hydroxy-3-phenyl-5-bromopyrazine (0.03 mole) was heated in 35 ml. of phosphorus oxychloride for 6 hr. at 190°. The dichloride was isolated as before and was recrystallized from 20 ml. of isoöctane.

D. 2,3-Dichloro-5,6-diphenylpyrazine (XVIII).—(1) 2-Hydroxy-3-nitro-5,6-diphenylpyrazine (0.0068 mole) was heated in 12 ml. of phosphorus oxychloride for 7 hr. at 170°. After hydrolysis of this solution on ice the dichloride was extracted with two 100-ml. portions of chloroform, and the residue from evaporation of this solvent was recrystallized from 15 ml. of acetone. (2) 2-Hydroxy-3-chloro-5,6-diphenylpyrazine (0.0068 mole) was heated in 20 ml. of phosphorus oxychloride for 40 hr. at 170° to form the same dichloride, isolated as before.

E. 2,5-Dichloro-3,6-diphenylpyrazine (XIX).—2-Hydroxy-5-bromo-3,6-diphenylpyrazine (0.01 mole) was heated in 30 ml. of phosphorus oxychloride for 60 hr. at 180°. The dichloride was isolated as described for its 2,3-isomer and was recrystallized from 30 ml. of isoöctane to yield a product identical with that obtained from the reaction of *dl*-phenylglycine anhydride with phosphorus oxychloride.[4]

F. 2,3-Dibromo-5,6-dimethylpyrazine (XI).—2-Hydroxy-3-bromo-5,6-dimethylpyrazine (0.10 mole) was heated in 35 ml. of phosphorus oxychloride for 16 hr. at 175°. The crude reaction product was isolated as described in A and was distilled (b.p. 120–145° at 20 mm.) to give 28.4 g. of yellow solid. This was refluxed with 70 ml. of phosphorus tribromide for 17 hr., and this solution was cooled to 25° and hydrolyzed on 1200 g. of ice. The dibromide was extracted with two 150-ml. portions of ether and was purified by distillation (b.p. 140–150° at 20 mm.) followed by recrystallization from 60 ml. of heptane, yielding 18.0 g. (68%) of large white granules.

G. 2,3-Dibromo-5,6-diphenylpyrazine (XII).—A mixture of 5.0 g. (0.0153 mole) of 2-hydroxy-3-bromo-5,6-diphenylpyrazine and 35 ml. of phosphorus tribromide was refluxed for 35 hr., cooled to 25° and hydrolyzed on 500 g. of ice. The dibromide was extracted with two 100-ml. portions of chloroform, and the extracts were washed with 300 ml. of 1% sodium hydroxide and then evaporated to dryness. Recrystallization of the chloroform residue from 200 ml. of acetone afforded small cream prisms of the pure dibromide.

H. 2,5-Dibromo-3,6-diphenylpyrazine (XIV).—A mixture of 10.0 g. (0.03 mole) of 2-hydroxy-5-bromo-3,6-diphenylpyrazine and 50 ml. of phosphorus tribromide was refluxed for 60 hr., and then the crude dibromide was isolated as described above for its 2,3-isomer. It was recrystallized by dissolving the chloroform residue in 25 ml. of hot toluene and diluting the solution with 20 ml. of heptane, thus yielding 9.0 g. (75%) of the pure dibromide.

I. 2,5-Dibromo-3-phenylpyrazine (XIII).—2-Hydroxy-3-phenyl-5-bromopyrazine (0.072 mole) was heated in 40 ml. of phosphorus oxychloride for 17 hr. at 170°. After hydrolysis of this solution on ice the crude product was extracted with ether and distilled (b.p. 115-125° at 0.3 mm.).

(9) J. A. Tota and R. C. Elderfield, *J. Org. Chem.*, **7**, 317 (1942).

(10) G. Karmas and P. E. Spoerri, THIS JOURNAL, **78**, 2141 (1956).

The solid distillate was refluxed in 50 ml. of phosphorus tribromide for 4 hr., and, after cooling, the solution was hydrolyzed on 800 g. of ice. The product was extracted with two 100-ml. portions of ether and the ether residue was recrystallized from 60 ml. of isoöctane to give pale yellow needles of the dibromide.

V. 2,3-Dihydroxypyrazines. A. 2,3-Dihydroxy-5,6-dimethylpyrazine.—A mixture of 7.0 g. (0.0344 mole) of 2-hydroxy-3-bromo-5,6-dimethylpyrazine and 70 ml. of 48% hydrobromic acid was refluxed for 15 minutes, and then it was evaporated to dryness under vacuum. The solid residue was dried in air and recrystallized from ethanol to give 4.4 g. (91%) of pale pink prisms which did not melt up to 340°.

Anal. Calcd. for $C_6H_8N_2O_2$: N, 20.00. Found: N, 19.95.

B. **2,3-Dihydroxy-5,6-diphenylpyrazine.**—(1) A mixture of 4.0 g. (0.0136 mole) of 2-hydroxy-3-nitro-5,6-diphenylpyrazine, 60 ml. of acetic acid and 60 ml. of 6 *N* hydrochloric acid was refluxed for 1 hr. and then poured into 400 ml. of water. The pale yellow solid was filtered off, dissolved in 500 ml. of warm (80°) 1% sodium hydroxide and reprecipitated by neutralizing with carbon dioxide. The yield was 3.4 g. (94%) of small white granules which did not melt up to 340°.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: N, 10.60; C, 72.67; H, 4.58. Found: N, 10.59; C, 72.44; H, 4.56.

(2) A mixture of 2-hydroxy-3-bromo-5,6-diphenylpyrazine and 35 ml. of 48% hydrobromic acid was refluxed for 2 hr. and then evaporated to dryness under vacuum. Purification as in (1) gave 0.8 g. (93%) of the dihydroxy compound.

VI. Miscellaneous. A. 2-Chloro-5-methoxy-3,6-diphenylpyrazine.—A mixture of 3.3 g. (0.011 mole) of 2,5-dichloro-3,6-diphenylpyrazine, 100 ml. of xylene and 280 ml. of 5% methanolic sodium methoxide was refluxed for 3 hr., concentrated under vacuum to 100 ml. and poured into 300 ml. of benzene. The residue from evaporation of the benzene–xylene solution was recrystallized from 20 ml. of ethanol to give 2.8 g. (87%) of cream prisms, m.p. 108–109°.

Anal. Calcd. for $C_{17}H_{13}N_2OCl$: Cl, 11.97. Found: Cl, 11.91.

B. **2-Hydroxy-3-chloro-5,6-diphenylpyrazine.**—A mixture of 3.0 g. (0.01 mole) of 2-hydroxy-3-nitro-5,6-diphenylpyrazine and 30 ml. of thionyl chloride was refluxed for 30 minutes and then evaporated to a tacky residue. This was dissolved in 500 ml. of warm (45°) 2% sodium hydroxide, and the solution was filtered and neutralized with carbon dioxide. The precipitated solid was recrystallized from 75 ml. of ethanol to give 1.9 g. (66%) of pale yellow needles, m.p. 229–231° dec.

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: Cl, 12.54. Found: Cl, 12.56.

C. **2-Chloro-3-phenyl-5-nitropyrazine.**—A mixture of 4.0 g. (0.0184 mole) of 2-hydroxy-3-phenyl-5-nitropyrazine and 50 ml. of phosphorus oxychloride was refluxed for 5 days and then evaporated under vacuum. The residue was hydrolyzed on 400 g. of ice, and this mixture was made neutral with potassium bicarbonate and 10 g. more of the latter was added. The chloride was extracted with two 150-ml. portions of ether and the residue after evaporation was recrystallized from 35 ml. of heptane to give 1.1 g. (25%) of peach prisms, m.p. 89–91°.

Anal. Calcd. for $C_{10}H_6ClN_2O_2$: Cl, 15.07. Found: Cl, 14.93.

Acidification of the bicarbonate solution precipitated 2.8 g. (70%) of the starting material.

D. **2-Hydroxy-3-phenylazo-5,6-dimethylpyrazine.**—A phenyldiazonium chloride solution (0.05 mole) was added in one portion to an ice-cold solution of 5.0 g. (0.044 mole) of 2-hydroxy-5,6-dimethylpyrazine and 15 g. of sodium carbonate in 400 ml. of water. After 20 minutes at 0° the mixture was filtered and the red solid was dried in air. This azo compound decomposed on heating in anhydrous solvents, and so it was recrystallized from a hot mixture of 150 ml. of acetone, 70 ml. of water and 20 ml. of methanol to give large red prisms (a hydrate) which, on drying over phosphorus pentoxide, were converted to 6.1 g. (63%) of a microcrystalline dust which chars below 100°.

Anal. Calcd. for $C_{12}H_{12}N_4O$: N, 24.54. Found: N, 24.25.

E. **2,5-Dimethoxy-3-phenylpyrazine.**—A mixture of 4.5 g. (0.02 mole of 2,5-dichloro-3-phenylpyrazine and 35 ml. of 20% methanolic sodium methoxide was heated in a sealed tube at 120° for 15 hr., and then the tube contents were washed with methanol into 400 ml. of water. The product was extracted with two 100-ml. portions of pentane, and the pentane residue was distilled to give 9.2 g. (63%) of yellow oil, b.p. 107–108° at 0.1 mm., $n^{18}D$ 1.6137.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: N, 12.97. Found: N, 12.86.

F. **2-Chloro-3-phenylpyrazine.**—A mixture of 30 g. (0.174 mole) of 2-hydroxy-3-phenylpyrazine and 100 ml. of phosphorus oxychloride was refluxed with stirring for 2 hr. and then concentrated under vacuum. After hydrolysis of the residue on ice and neutralization with sodium hydroxide, the product was extracted with two 200-ml. portions of ether. Distillation of the ether residue gave 27.4 g. (83%) of colorless solid, b.p. 92–93° at 0.3 mm., m.p. 66–67° after recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_7ClN_2$: Cl, 18.63. Found: Cl, 18.54.

G. **2-Methoxy-3-phenylpyrazine.**—A mixture of 25.0 g. (0.13) mole of the chloride obtained in F and 200 ml. of 5% methanolic sodium methoxide was refluxed for 3 hr. and poured into 1200 ml. of water. The product was extracted with two 350-ml. portions of pentane and the pentane residue was distilled to give 23.8 g. (97%) of colorless oil, b.p. 143–145° at 14 mm., $n^{20}D$ 1.6195.

Anal. Calcd. for $C_{11}H_{10}N_2O$: N, 15.06. Found: N, 15.09.

H. **2-Methoxy-3-phenylpyrazine-4-oxide.**—A mixture of 23.8 g. (0.128 mole) of 2-methoxy-3-phenylpyrazine, 150 ml. of acetic acid and 200 ml. of 30% aqueous hydrogen peroxide was heated at 55° for 20 hr. and poured onto 2000 g. of ice. This mixture was made alkaline with 50% sodium hydroxide and the N-oxide was extracted with three 300-ml. portions of chloroform. The chloroform residue was recrystallized from an acetone–hexane mixture to give 25.2 g. (97%) of white granules, m.p. 94–96°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: N, 13.87. Found: N, 13.76.

I. **2-Methoxy-3-phenyl-5-chloropyrazine.**—A mixture of 2.5 g. (0.0124 mole) of the N-oxide obtained in H and 15 ml. of phosphorus oxychloride was refluxed for 15 minutes and then hydrolyzed on 200 g. of ice. The product was extracted with two 100-ml. portions of ether and the extract washed with 50 ml. of 2% sodium hydroxide. Distillation of the ether residue gave 2.4 g. (88%) of pale yellow oil, b.p. 111–113° at 0.3 mm., $n^{20}D$ 1.6324.

Anal. Calcd. for $C_{11}H_9ClN_2O$: N, 12.71. Found: N, 12.80.

J. **2-Hydroxy-3-phenyl-5-chloropyrazine.**—A mixture of 7.0 g. (0.032 mole) of 2-methoxy-3-phenyl-5-chloropyrazine, 50 ml. of acetic acid and 50 ml. of 12.5 *N* hydrochloric acid was refluxed for 2 hr. and concentrated under vacuum. Recrystallization of the solid residue from methanol gave 5.6 g. (85%) of pale yellow flakes, m.p. 174–176°.

Anal. Calcd. for $C_{10}H_7ClN_2O$: N, 13.58. Found: N, 13.22.

Heated at 170° for 6 hr. with phosphorus oxychloride, this compound gave authentic 2,5-dichloro-3-phenylpyrazine, m.p. 57–58°.

K. **2-Chloro-3-phenyl-5-methoxypyrazine.**—A mixture of 10.0 g. (0.0445 mole) of 2,5-dichloro-3-phenylpyrazine and 400 ml. of 4% methanolic sodium methoxide was refluxed for 2 hr., boiled down to 150 ml. and poured into 600 ml. of water. The product was extracted with two 200-ml. portions of pentane, and the pentane residue was distilled (b.p. 110–120° at 0.3 mm.) to give a mixture of the two isomeric methoxychloro-3-phenylpyrazines. This yellow oil was crystallized from 25 ml. of pentane to give 5.8 g. (59%) of white prisms, m.p. 73–74°.

Anal. Calcd. for $C_{11}H_9ClN_2O$: Cl, 16.07. Found: Cl, 16.20.

The mother liquor contains the liquid isomer described in I.

L. **2-Hydroxy-5-chloro-6-phenylpyrazine.**—Five grams (0.023 mole) of 2-chloro-3-phenyl-5-methoxypyrazine was cleaved as described in J, and the crude solid product was re-

crystallized from water to give 3.8 g. (81%) of buff needles, m.p. 142–144°.

Anal. Calcd. for $C_{10}H_7ClN_2O$: N, 13.58. Found: N, 13.40.

With phosphorus oxychloride this compound gives 2,5-dichloro-3-phenylpyrazine (m.p. 57–58°), as does its isomer in J.

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RARITAN, NEW JERSEY

[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

Hexamethylene-1,6-bis-*t*-amines in Which Part of the Six Carbon Chain is also Part of a Six-membered Ring

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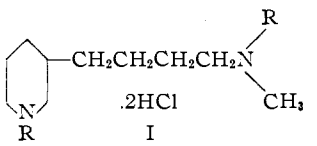
A series of hexamethylene-1,6-bis-*t*-amine hydrochlorides in which part of the six-carbon chain is part of a six-membered ring has been prepared. These compounds were tested as hypotensives and ganglionic blocking agents and some were as effective orally as hexamethonium chloride in anesthetized cats.

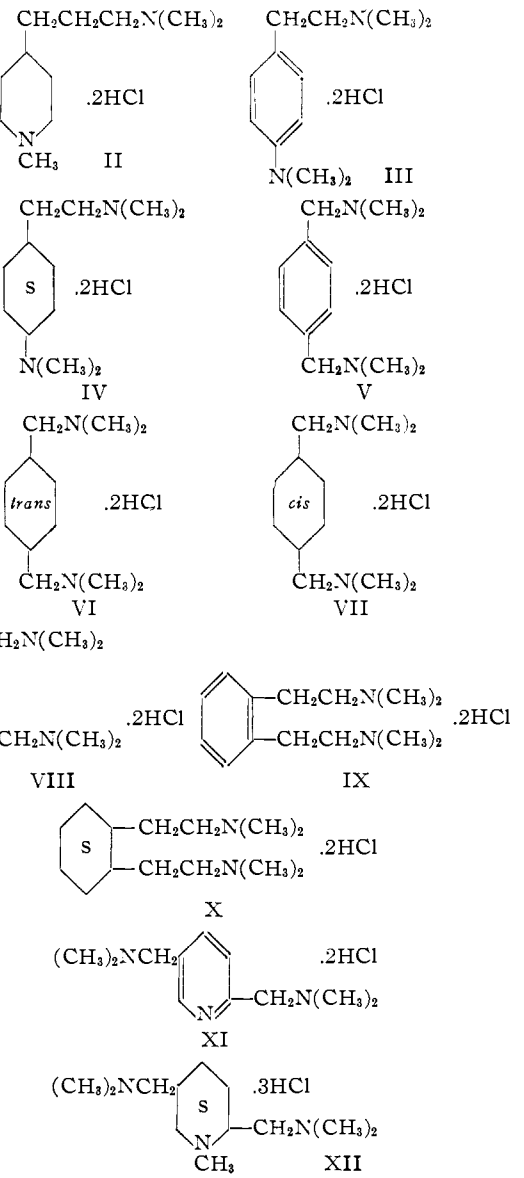
Norton and Phillips[1,2] reported that compounds of the structure I possess potent ganglionic blocking activity. It is apparent that this is a hexamethylenediamine in which part of the six-carbon chain is also part of a six-membered ring. It was decided to prepare a series of analogous compounds in which various parts of the six-carbon chain are also part of a six-membered ring. The preparation of this series of compounds constitutes the subject matter of this communication.



I

In the compounds that were prepared (II–XII) the six-membered ring was variously benzene, cyclohexane, pyridine and piperidine.

Compound II was prepared by two separate routes: (1) 1-Methyl-4-(γ-chloropropyl)-piperidine has been prepared by Ruddy and Bishop[3] by thionyl chloride treatment of 1-methyl-4-(γ-hydroxypropyl)-piperidine, which was made[4] by catalytic reduction of 4-(γ-hydroxypropyl)-pyridine followed by methylation by heating with a mixture of formic acid and formaldehyde. The intermediate 1-methyl-4-(γ-hydroxypropyl)-piperidine has now been prepared by an alternate procedure. 4-(γ-Hydroxypropyl)-pyridine was converted to its methobromide quaternary, and hydrogenated in ethanol over platinum to give the desired methyl-piperidylpropanol. 1-Methyl-4-(γ-chloropropyl)-piperidine hydrochloride on treatment with an excess of dimethylamine in benzene gave a moderate yield of II which was somewhat difficult to purify. (2) 4-(γ-Hydroxypropyl)-pyridine[5] was oxidized with acidic potassium permanganate, by the procedure previously described for oxidizing 2-(γ-hy-



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(2) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).
(3) A. W. Ruddy and H. W. Bishop, *ibid.*, **74**, 1919 (1952).
(4) R. R. Burtner and J. M. Brown, *ibid.*, **69**, 630 (1947).
(5) Reilly Tar and Chemical Corporation.