upon cooling in a Dry Ice and acetone bath. The oil distilled at 120–122° (0.25 mm.) and upon redistillation, b.p. 78° (0.09 mm.), 16.0 g. (80%) of the light yellow pyridotriazole, m.p. 34–35°, was obtained.

Anal. Calcd. for $C_6H_5N_3$: C, 60.49; H, 4.23; N, 35.28. Found: C, 59.93; H, 4.33; N, 34.99.

The azine of isoquinoline-3-aldehyde was isolated in 17% yield upon oxidation of the corresponding hydrazone with silver oxide. It was recrystallized from pyridine from which it separated as orange needles, m.p. 248–251°. The remainder of the product from the oxidation was an intractable tar.

Anal. Calcd. for $C_{10}H_{14}N_4$: C, 77.42; H, 4.55; N, 18.05. Found: C, 77.43; H, 4.88; N, 17.54.

In a similar oxidation of the hydrazone of quinoline-2-aldehyde it was necessary to heat the reaction mixture at reflux temperature for 18 hours. The solid product, 5,6-benzopyridotriazole, was obtained in 65% yield and was recrystallized from *n*-hexane from which it separated as colorless leaflets, m.p. 81°.

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 71.23; H, 4.29; N, 24.73.

The oxidation of the hydrazone of α-benzoylpyridine with silver oxide also was carried out in refluxing ether for 15 hours. The product, 1-phenylpyridotriazole, was obtained in 83% yield and recrystallized from *n*-hexane as long silky colorless needles, m.p. 113–115°.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.73; H, 4.99; N, 21.46.

The oxidation of the dihydrazone of α-pyridil was carried out in pyridine for one hour at 70°. The product, 1,1′-dipyridotriazole was obtained in 57% yield and was recrystallized from ethyl acetate from which it separated as colorless needles, m.p. 272–274° dec.

Anal. Calcd. for $C_{12}H_8N_6$: C, 61.01; H, 3.41; N, 35.60. Found: C, 61.09; H, 3.61; N, 35.96.

α-Pyridylmethylamine.—Apparatus and procedure for reduction with lithium aluminum hydride by normal addition was followed.[18] A solution of 20 g. (0.19 mole) of α-cyanopyridine in 75 ml. of anhydrous ether was added slowly to a vigorously stirred suspension of 10 g. of lithium aluminum hydride in 25 ml. of anhydrous ether at such a rate that reflux was maintained. The reaction mixture was held at reflux temperature for an additional three hours, cooled, cautiously diluted with 45 ml. of aqueous ethanol, treated with 75 ml. of 40% sodium hydroxide solution and separated by filtration. Ether extracts of both the precipitate and filtrate were combined, dried and concentrated *in vacuo*. Distillation of the brown oil residue afforded a light yellow oil, b.p. 96–98° (14 mm.). Upon redistillation, b.p. 81°[19] (12 mm.) and 70–72° (11 mm.), 10.5 g. (55%) of α-pyridylmethylamine was obtained; picrate m.p. 159–160° dec. (lit.[19] 162), oxalate m.p. 166–167° (lit.[19] 167°).

Upon diazotization of the amine under either normal conditions, in which sodium nitrite and aqueous hydrochloric acid were used, or under anhydrous conditions in which isoamyl nitrite and absolute alcohol were used, a brown oil was obtained which gave a picrate from ethanol. Upon recrystallization from ethanol the picrate, m.p. 178–181° dec. after turning green at about 175°, was obtained as an unidentified yellow powder.

Anal. Calcd. for $C_6H_8N_2O_2 \cdot C_6H_3N_3O_7$: C, 39.03; H, 3.00; N, 18.97. Found: C, 38.81; H, 2.91; N, 18.50.

Preparation of Pyridoöxadiazolone.—The reaction between phosgene and 2-aminopyridine-N-oxide[20] was carried out in an apparatus described by Shriner, Horne and Cox.[21] To 50 ml. of chloroform saturated with phosgene, 0.400 g. (0.0036 mole) of 2-aminopyridine-N-oxide in 25 ml. of chloroform was added dropwise. An oil separated which gradually crystallized. Excess solvent was removed *in vacuo* and the solid residue was recrystallized from a mixture of ethyl acetate and hexane from which the product separated as light yellow needles, m.p. 185–187° dec.

Anal. Calcd. for $C_6H_4N_2O_2$: C, 52.94; H, 2.96; N, 20.59. Found: C, 52.46; H, 3.39; N, 20.32.

A small amount of residue insoluble in ethyl acetate and hexane was not identified.

(18) R. F. Nystrom and W. G. Brown. THIS JOURNAL, **69**, 1197 (1947); **70**, 3738 (1948).

(19) R. Graf. G. Parathoner and M. Tatzel. *J. prakt. Chem.*, **146**, 88 (1936); L. C. Craig and R. M. Hixon. THIS JOURNAL, **53**, 436 (1931).

(20) R. Adams and S. Miyano. *ibid.*, **76**, 2785 (1954).

(21) R. L. Shriner, W. H. Horne and R. F. B. Cox. *Org. Syntheses*. Coll. Vol. II. John Wiley and Sons, Inc., New York, N. Y., 1947, p. 453.

NEW ORLEANS, LOUISIANA

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

Nucleophilic Displacements on Difunctional Pyrazines

BY GEORGE KARMAS[1] AND PAUL E. SPOERRI

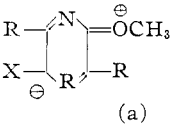
RECEIVED SEPTEMBER 13, 1956

The action of sodium alkoxides and cuprous cyanide on dihalopyrazines and halopyrazyl ethers has been studied with particular attention to the effect of ether groups on the halogen reactivity. Cleavage of pyrazine diethers by sodium methoxide has been developed as a method of preparing *o*- and *p*-dihydroxypyrazines and hydroxypyrazyl ethers.

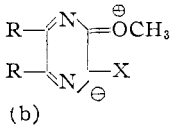
In a previous publication[2] we described the synthesis of *o*- and *p*-dihalopyrazines and now we wish to report on some novel aspects of the chemistry of these dihalides and their simple derivatives, the halopyrazyl ethers and the diethers.

Spring and co-workers reported that only one chlorine atom is readily displaced when a *p*-dichloropyrazine is refluxed in excess ethanolic sodium ethoxide and that temperatures of 120–130° are required for displacement of the second halogen by this very strong base.[3] Other examples of this diminished second halogen reactivity have been described by us,[2] and it seems to be a general property of this class of compounds. It seems likely that this is due to the substantial contribution of a resonance form such as (a) in which a second nucleophilic attack is discouraged by electrostatic repulsion.

We have observed that *o*-dihalopyrazines give high yields of diethers when refluxed in excess methanolic sodium methoxide. Apparently the



(a)



(b)

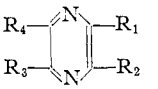
(1) Ortho Pharmaceutical Corporation, Raritan, N. J.

(2) G. Karmas and P. E. Spoerri. THIS JOURNAL, **78**, 4071 (1956).

(3) R. A. Baxter, G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1859 (1948).

TABLE I

PYRAZINE DIETHERS AND HALOPYRAZYL ETHERS



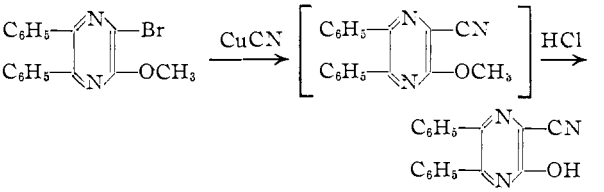
R_1	R_2	R_3	R_4	Yield, %	M.p., °C.	B.p. °C.	Mm.	Nitrogen, % Calcd.	Found
CH_3O	CH_3O	H	H	48	.....	108–110	50	20.00	19.92
CH_3O	CH_3O	CH_3	CH_3	80	62–63	105–110	15	16.67	16.49
CH_3O	CH_3	CH_3O	CH_3	57	63–65	103–104	14	16.67	16.59
CH_3O	C_6H_5	C_4H_9O	H	95	.....	137–140	0.3	10.84	10.71
CH_3O	CH_3O	C_6H_5	C_6H_5	76	140–141	.....	..	9.58	9.27
CH_3O	C_6H_5	CH_3O	C_6H_5	75	146–147	.....	..	9.58	9.66
								Br or Cl, % Calcd.	Found
Br	CH_3O	CH_3	CH_3	83	74–75	125–127	14	36.78	36.81
Br	CH_3O	C_6H_5	C_6H_5	86	182–183	.....	..	23.42	23.13
Br	C_6H_5	CH_3O	C_6H_5	90	137–138	.....	..	23.42	23.30
Br	C_6H_5	C_2H_5O	C_6H_5	79	100–101	.....	..	22.50	22.62
Cl	C_6H_5	C_2H_5O	C_6H_5	80	102–103	.....	..	11.42	11.37

resonance form (b) is of less significance than the corresponding *para* form. However, its contribution cannot be negligible in view of the fact that 2-bromo-3-methoxy-5,6-dimethyl-(and diphenyl)-pyrazine is formed in 83–85% yield on prolonged refluxing of the 2,3-dibromides in *one* equivalent of methanolic sodium methoxide. This order of yield of recrystallized products can only be ascribed to a definitely diminished reactivity for the second bromine atom. Table I presents a summary of those pyrazyl diethers and halopyrazyl ethers which we have not described in the previous publication.[2]

Nucleophilic displacements on only one *m*-dihalide, 2,6-dibromopyrazine, have been studied, and in this case it was observed that both bromine atoms were readily displaced in an excess of refluxing ethanolic sodium ethoxide.[4] Since 2-bromo-6-ethoxypyrazine was not sought nor isolated, there is no information on comparative halogen reactivity in the *meta* structure.

The facile displacement of halogen by cyanide that we have described for monobromopyrazines[5] was not observed with *o*- or *p*-dibromopyrazines. Complex tarry mixtures were always formed when the dibromides were heated with cuprous cyanide in γ-picoline. Only in the case of 2,5-dibromo-3,6-diphenylpyrazine was the 2,5-dinitrile detected, through its hydrolysis to 2-hydroxy-5-carboxy-3,6-diphenylpyrazine, a known reaction of the authentic dinitrile.[6] The dinitriles are obviously very easily polymerized by cuprous salts. This behavior also was observed by Schaaf and Spoerri[4] who finally achieved a 9% yield of 2,6-dicyanopyrazine by subliming this product (plus the bromonitrile) from a mixture of 2,6-dibromopyrazine with solid cuprous cyanide and cupric sulfate.

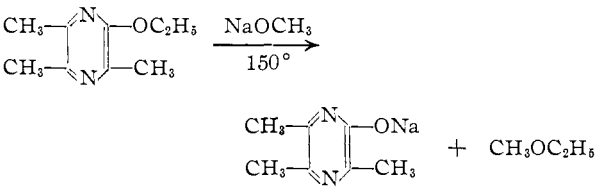
When 2-bromo-3-methoxy-5,6-diphenylpyrazine was heated with cuprous cyanide in γ-picoline, displacement of bromine occurred, but the product isolated was the corresponding 2-cyano-3-hydroxy derivative. It seems likely that cleavage of the methoxyl group occurred during the working-up, for it was necessary to use hydrochloric acid to destroy the cuprous salt complexes with the pyrazine base.



Attempts to verify this assumption through isolations avoiding all acid were unsuccessful because these complexes could not otherwise be broken.

2-Cyano-3-hydroxy-5,6-diphenylpyrazine was, like its 2-nitro analog,[7] soluble in aqueous sodium bicarbonate. Its structure was proved by hydrolysis to the carboxylic acid which lost carbon dioxide on melting and formed the known 2-hydroxy-5,6-diphenylpyrazine.[8]

The cleavage of alkaryl ethers by nucleophilic reagents is a known reaction and has been reviewed recently,[9] but no such reaction of pyrazyl ethers has been reported previously. We have found that methanolic sodium methoxide at elevated temperatures cleaves pyrazyl ethers by nucleophilic displacement of the alkoxy carbon. Such a

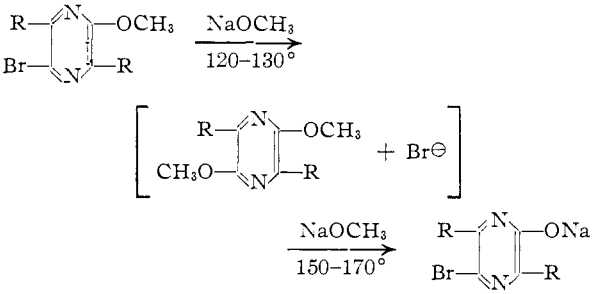


procedure offers no advantage over mineral acid cleavage for the simple monoethers, but it is possible to control the reaction so that diethers may yield hydroxypyrazyl ethers or dihydroxypyrazines.

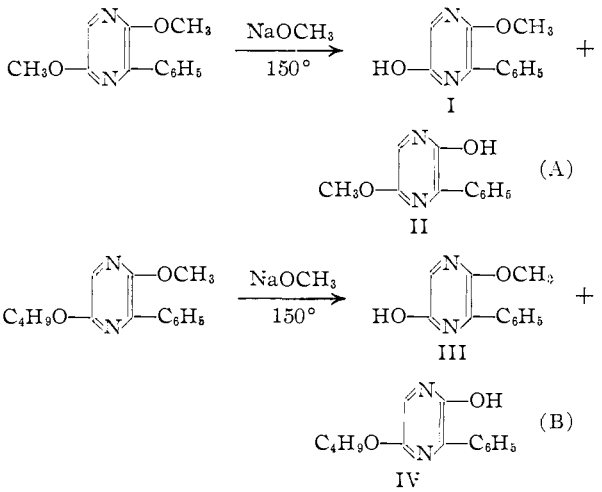
It has been mentioned that *p*-diether formation requires heating of the dihalide (or haloether) in excess methanolic sodium methoxide at 120–130°. Higher temperatures yield mixtures of phenolic products which contain halogen, and it seems that

(4) K. H. Schaaf and P. E. Spoerri. THIS JOURNAL, **71**, 2043 (1949).
(5) G. Karmas and P. E. Spoerri. *ibid.*, **78**, 2141 (1956).
(6) G. Gastaldi. *Gazz. chim. ital.*, **51**, I. 233 (1921).
(7) G. Karmas and P. E. Spoerri, THIS JOURNAL, **75**, 5517 (1953).
(8) R. G. Jones. *ibid.*, **71**. 78 (1949).
(9) R. L. Burwell, Jr., *Chem. Revs.*, **54**. 660 (1954).

under these conditions the halide ion can also effect nucleophilic displacement

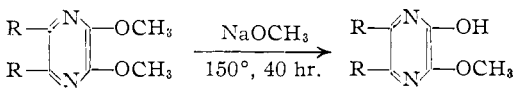


In the absence of halogen, *i.e.*, starting with a pure *p*-diether, the cleaving action of a five-to-tenfold excess of base can largely be confined to one methoxyl group if the temperature does not exceed 150°. An interesting study was the cleavage of two similar unsymmetrical diethers according to the scheme

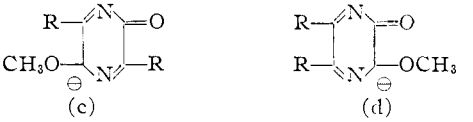


There was no specificity of cleavage due to steric hindrance by the phenyl group. Although no quantitative separation of the products of either reaction could be effected, the less soluble product from each reaction was purified easily and for both A and B this was the same substance (of m.p. 208–209°) to which must be assigned the structure 2-methoxy-3-phenyl-5-hydroxypyrazine (I and III).

Both ether groups in *o*-dimethoxypyrazines are cleaved by a large excess of methanolic sodium methoxide at 150–180°, but when the proportion of base is reduced to 1.2 molecular equivalents, the *o*-hydroxypyrazyl ethers are obtained in 70% yield.

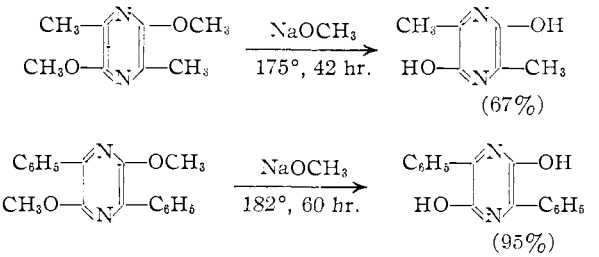


It is apparent that, as discussed for the dihalides, the second ether group has lower reactivity with regard to nucleophilic attack, presumably due to a large contribution from the anionic resonance form (c) and a significant, but lesser, contribution from the form (d)



As previously stated, a large excess of methanolic sodium methoxide at high temperature cleaves *o*-diethers to *o*-dihydroxypyrazines, but it is more convenient synthetically to prepare the latter through acidic displacement reactions as described in an earlier publication.[2]

No *p*-dihydroxypyrazine has previously been described, although a wide variety of conventional procedures was tried in attempted syntheses of 2,5-dihydroxy-3,6-dimethylpyrazine.[3] Nucleophilic cleavage with sodium methoxide finally yielded two compounds of this type



As proof of structure, each compound was converted to the corresponding known 2,5-dichloride[10,11] by heating with phosphorus oxychloride.

2,5-Dihydroxy-3,6-diphenylpyrazine was stable under alkaline and mildly acidic conditions but was destroyed by concentrated mineral acid. It could be obtained in no better than an 11% yield by refluxing the diether in 48% hydrobromic acid for a few minutes—prolonged refluxing completely destroyed the product. 2,5-Dihydroxy-3,6-dimethylpyrazine was stable in alkali but very sensitive to weak aqueous acids and could even be destroyed by carbonic acid (carbon dioxide bubbled through an aqueous suspension), apparently by a hydrolytic fission of the pyrazine nucleus.

Several attempts at synthesizing less highly-substituted *p*-dihydroxypyrazines failed. Although 2,5-dimethoxy-3-phenyl-(and ethyl)-pyrazine obviously reacted with methanolic sodium methoxide at 170–180°, no products identifiable as dihydroxy*mono*alkylpyrazines could be isolated, and it was concluded that such compounds must be far less stable than the dialkyl types.

Experimental

The syntheses of all halopyrazines referred to in this section have been described in previous publications[2-5] or are given below. Most of the analytical data, melting points and yields appear in Tables I and II.

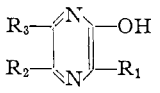
A. 2,3-Dibromopyrazine.—A mixture of 16.6 g. (0.10 mole) of 2-bromopyrazine, 5.7 ml. (0.11 mole) of bromine, 0.1 ml. of phosphorus tribromide and 5 mg. of anhydrous ferrous bromide was heated at 95° for 3 hr., and then the solid mass was hydrolyzed on 200 g. of ice layered with 100 ml. of ether. The dried (magnesium sulfate) ether extract was concentrated and the residue was distilled under vacuum. The portion which boiled at 90–110° (14 mm.) was recrystallized from 10 ml. of methanol, chilled at −10°, to give 5.5 g. of large white prisms, m.p. 57–58°. A second

(10) J. J. Gallagher, G. T. Newbold, F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 910 (1949).

(11) R. A. Baxter and F. S. Spring, *ibid.*, 2586 (1949).

TABLE II

HYDROXYPYRAZYL ETHERS



R_1	R_2	R_3	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found
CH_3O	CH_3	CH_3	71	234–235	18.16	17.95
CH_3	CH_3O	CH_3	63	180–181	18.16	18.03
CH_3O	C_6H_5	C_6H_5	71	266–268	10.07	10.12
C_6H_5	CH_3O	C_6H_5	74	194–196	10.07	9.95
C_6H_5	C_4H_9O	H	31	(Oil)	11.47	11.97
H	CH_3O	C_6H_5	26	208–209	13.87	13.51

crop, m.p. 56–58°, which crystallized from the mother liquor at −30° brought the yield to 7.7 g. (32%). A melting point of 59–61° is reported for 2,3-dibromopyrazine, isolated in unspecified yield from the products of the vapor phase bromination of 2-bromopyrazine.[12]

B. **2-Bromo-3-methoxy-5,6-dimethylpyrazine.**—To a solution of 0.44 g. (0.019 mole) of sodium in 60 ml. of anhydrous methanol was added 5.0 g. (0.019 mole) of 2,3-dibromo-5,6-dimethylpyrazine in 40 ml. of methanol and the mixture was refluxed for 6 hr. and then poured into 600 ml. of water. The methoxybromide was extracted with two 100-ml. portions of pentane and was subsequently distilled (b.p. 125–127° at 14 mm.) and recrystallized from 12 ml. of pentane. The yield, in two crops, was 3.4 g. of large white prisms and each crop melted at 74–75°.

C. **2-Bromo-3-methoxy-5,6-diphenylpyrazine.**—A solution of 3.2 g. (0.0082 mole) of 2,3-dibromo-5,6-diphenylpyrazine in 150 ml. of dry benzene was added to a solution of 0.20 g. (0.0087 mole) of sodium in 300 ml. of anhydrous methanol, and the mixture was refluxed for 30 hr. and then was evaporated to dryness under vacuum. The residue was leached with water and the insoluble solid was recrystallized from 50 ml. of acetone to give 2.4 g. of small white prisms, m.p. 182–183°.

D. **2-Bromo-5-methoxy-3,6-diphenylpyrazine, 2-Bromo-5-ethoxy-3,6-diphenylpyrazine and 2-Chloro-5-ethoxy-3,6-diphenylpyrazine.**—A mixture of 0.0128 mole of 2,5-dibromo-(or dichloro)-3,6-diphenylpyrazine and 2.3 g. (0.1 mole) of sodium in 160 ml. of anhydrous methanol (or ethanol) was refluxed for 6 hr. and then poured into 700 ml. of water. The insoluble solids were recrystallized from ethanol to give the pure 2-halo-5-alkoxy-3,6-diphenylpyrazines.

E. **2,3-Dimethoxypyrazine.**—A mixture of 7.5 g. (0.0136 mole) of 2,3-dibromopyrazine and 4.6 g. (0.2 mole) of sodium in 200 ml. of methanol was refluxed for 10 hr. and then 150 ml. of the methanol was distilled off through a short packed column. The residue was poured into 300 ml. of water and the diether was extracted with two 100-ml. portions of ether. After drying and concentration through a packed column, the ether residue was distilled (simple Claisen flask) to give 2.1 g. of colorless oil, b.p. 108–110° (50 mm.), $n^{18}D$ 1.5133.

F. **2,3-Dimethoxy-5,6-dimethylpyrazine.**—Five grams (0.0282 mole) of 2,3-dichloro-5,6-dimethylpyrazine was etherified with a tenfold excess of methanolic sodium methoxide as described in E. The product was a white solid which distilled at 105–110° (15 mm.) and was recrystallized from hexane to give 3.8 g. of large white prisms.

G. **2,3-Dimethoxy-5,6-diphenylpyrazine.**—Three grams (0.01 mole) of 2,3-dichloro-5,6-diphenylpyrazine was refluxed for 12 hr. in a solution of 2.3 g. (0.1 mole) of sodium in 200 ml. of methanol, and then the mixture was poured into 700 ml. of water. The insoluble solid was recrystallized from ethanol to give 2.2 g. of small cream flakes.

H. **2,5-Dimethoxy-3,6-dimethylpyrazine.**—A mixture of 2.4 g. (0.0136 mole) of 2,5-dichloro-3,6-dimethylpyrazine and 35 ml. (0.13 mole) of 20% methanolic sodium methoxide was heated in a sealed tube at 120° for 18 hr. The tube contents were washed with methanol into 300 ml. of water, and the diether was extracted with pentane. It was a white solid which distilled at 103–104° (14 mm.), and was recrystallized from a small volume of pentane.

I. **2,5-Dimethoxy-3,6-diphenylpyrazine.**—A mixture of 3.0 g. (0.01 mole) of 2-chloro-5-methoxy-3,6-diphenylpyrazine and 30 ml. (0.11 mole) of 20% methanolic sodium methoxide was heated in a sealed tube at 135° for 20 hr. The tube contents were washed with methanol into 300 ml. of water, and the product was extracted with two 150-ml. portions of chloroform. After it had been washed with 2% aqueous sodium hydroxide, the chloroform solution was evaporated to dryness and the residue was recrystallized from 40 ml. of butanol to give yellow needles of the diether.

J. **2-Methoxy-3-phenyl-5-butoxypyrazine.**—Eight grams (0.037 mole) of 2-methoxy-3-phenyl-5-chloropyrazine was added to a solution of 3.0 g. (0.13 mole) of sodium in 180 ml. of anhydrous butanol, and the mixture was refluxed for 22 hr. and then poured into 200 ml. of water plus 200 ml. of benzene. After vigorous shaking the benzene–butanol solution was dried (magnesium sulfate) and concentrated under vacuum and the residue was distilled to give the diether as a mobile yellow oil, b.p. 137–140° (0.3 mm.), $n^{20}D$ 1.5608.

K. **2-Hydroxy-3-methoxy-5,6-dimethylpyrazine and 2-Hydroxy-3-methoxy-5,6-diphenylpyrazine.**—A mixture of 0.025 mole of 2,3-dimethoxy-5,6-dimethylpyrazine and 1.6 g. (0.029 mole) of sodium methoxide in 50 ml. of anhydrous methanol was heated in a sealed tube at 150–155° for 40 hr. The tube contents were washed with methanol into 300 ml. of water and this alkaline solution was evaporated to a volume of 100 ml., and then it was acidified with hydrochloric acid and chilled at 0°. The insoluble solid was recrystallized from 300 ml. of acetone to give long white prisms of 2-hydroxy-3-methoxy-5,6-dimethylpyrazine. The same procedure was applied to 2,3-dimethoxy-5,6-diphenylpyrazine and the resulting hydroxymethoxydiphenylpyrazine was recrystallized from 200 ml. of acetone.

L. **2-Hydroxy-5-methoxy-3,6-dimethylpyrazine.**—A mixture of 3.3 g. (0.0196 mole) of 2,5-dimethoxy-3,6-dimethylpyrazine and 20 ml. (0.074 mole) of 20% methanolic sodium methoxide was heated in a sealed tube at 150° for 24 hr. The tube contents were washed with methanol into 300 ml. of water, and this solution was neutralized with carbon dioxide, and then it was extracted with three 65-ml. portions of chloroform. The residue, after evaporation of chloroform, was recrystallized from 150 ml. of acetone to give long white needles of the hydroxypyrazyl ether.

M. **2-Hydroxy-5-methoxy-3,6-diphenylpyrazine.**—A mixture of 2.4 g. (0.008 mole) of 2,5-dimethoxy-3,6-diphenylpyrazine and 27 ml. (0.10 mole) of 20% methanolic sodium methoxide was heated in a sealed tube at 150° for 20 hr. and then washed into 600 ml. of warm (60°) water. This solution was neutralized with carbon dioxide and the precipitated solid was filtered off and dried in air. It was dissolved in 50 ml. of warm (50°) toluene and filtered, and then the filtrate was evaporated to dryness, and the residue was recrystallized from 25 ml. of acetone to give small yellow prisms of the hydroxypyrazyl ether.

N. **Alkaline Cleavage of 2-Methoxy-3-phenyl-5-butoxypyrazine.**—A mixture of 9.0 g. (0.035 mole) of the diether (see J, above) and 54 ml. (0.20 mole) of 20% methanolic sodium methoxide was heated in a sealed tube at 150° for 12 hr. and then washed into 600 ml. of 1% aqueous sodium hydroxide. This solution was washed twice with ether, and then it was neutralized with carbon dioxide, and the tacky precipitate was taken up in chloroform. After evaporation of the chloroform, the residue was dissolved in 15 ml. of hot heptane. A yellow solid slowly crystallized, and after four days at 23° this was filtered off and recrystallized from ethyl acetate and then from 20 ml. of acetone to give 0.5 g. (7%) of **2-hydroxy-5-methoxy-6-phenylpyrazine**, m.p. 205–207°. The first heptane mother liquor was concentrated and the residue was distilled to give 2.6 g. (31%) of **2-hydroxy-3-phenyl-5-butoxypyrazine** as a very viscous oil of b.p. 135–140° (0.01 mm.).

O. **Alkaline Cleavage of 2,5-Dimethoxy-3-phenylpyrazine.**—A mixture of 9.0 g. (0.042 mole) of the diether and 37 ml. (0.135 mole) of 20% methanolic sodium methoxide was heated in a sealed tube at 150° for 18 hr. and then washed into 400 ml. of 1% aqueous sodium hydroxide. This solution was washed twice with ether, and then it was neutralized with carbon dioxide to precipitate an orange solid which was filtered off and dried in air. This was dissolved in 300 ml. of warm acetone and filtered, and the filtrate was boiled down to a volume of 40 ml. Yellow flakes of m.p. 204–207° crystallized at 0°, and these were again recrystallized from 40 ml. of acetone to give 2.2 g. (26%) of **2-hydroxy-5-methoxy-6-phenylpyrazine**, m.p. 208–209°. A mixture with the solid product described in N melted at

(12) A. A. Miller, U. S. Patent 2,573,268 (1951).

207–208°. The more soluble product from the cleavage, 2-hydroxy-3-phenyl-5-methoxypyrazine, could not be freed of its isomer by recrystallization.

P. 2,3-Dihydroxypyrazine.—A mixture of 2.0 g. (0.014 mole) of 2,3-dimethoxypyrazine and 60 ml. of 42% hydrobromic acid was refluxed for 15 minutes, and then it was evaporated to dryness under vacuum. The solid residue was recrystallized from 250 ml. of water to give 1.3 g. (81%) of the dihydroxypyrazine as light gray flat prisms which did not melt below 320°. This compound also has been prepared in 50% yield by acid hydrolysis of 1,2-di-(N⁴-acetylsulfanilyl)-pyrazine.[13]

Anal. Calcd. for $C_4H_4N_2O_2$: N, 25.00. Found: N, 25.16.

Q. 2,5-Dihydroxy-3,6-dimethylpyrazine.—A mixture of 1.8 g. (0.0107 mole) of 2,5-dimethoxy-3,6-dimethylpyrazine and 25 ml. (0.093 mole) of 20% methanolic sodium methoxide was heated in a sealed tube at 175° for 40 hr. and then poured into 180 ml. of warm (60°) water. After the yellow solid had dissolved, the solution was cooled to 25°, filtered and acidified with 8.0 ml. of acetic acid to precipitate the dihydroxy compound, which was filtered off immediately. This was dried in air and recrystallized by extraction from a Soxhlet thimble with methanol. The yield was 1.0 g. (67%) of small yellow granules which did not melt below 320°.

Anal. Calcd. for $C_6H_8N_2O_2$: N, 20.00; C, 51.46; H, 5.76. Found: N, 19.81; C, 51.54; H, 5.75.

If the alkaline solution of cleavage products was neutralized by bubbling carbon dioxide through it for several hours, the dihydroxy compound was precipitated and then slowly redissolved to form a golden yellow *neutral* solution. When heated with phosphorus oxychloride at 170° for 12 hr., the dihydroxypyrazine gave 2,5-dichloro-3,6-dimethylpyrazine, identical with an authentic specimen.[3]

R. 2,5-Dihydroxy-3,6-diphenylpyrazine. 1.—A mixture of 1.0 g. (0.0034 mole) of 2,5-dimethoxy-3,6-diphenylpyrazine and 20 ml. (0.074 mole) of 20% methanolic sodium methoxide was heated in a sealed tube at 182° for 60 hr. and then poured into 180 ml. of water. After warming to 80° to dissolve the yellow solid, the solution was cooled to 40°, filtered, and the filtrate was neutralized with carbon dioxide to precipitate the dihydroxy compound. This was recrystallized by dissolving it in 750 ml. of hot acetone and rapidly boiling the solution down to a volume of 50 ml. The yield was 0.85 g. (94%) of bronze-colored flakes, m.p. 295–300° dec.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: N, 10.69. Found: N, 10.39.

When heated with phosphorus oxychloride at 180° for 40 hr., this gave 2,5-dichloro-3,6-diphenylpyrazine, identical with an authentic specimen.[10]

2.—A mixture of 1.0 g. of 2,5-dimethoxy-3,6-diphenylpyrazine, 50 ml. of acetic acid and 50 ml. of 42% hydrobromic acid was refluxed for 15 minutes and then concentrated under vacuum. The residue was dissolved in warm 1% aqueous sodium hydroxide, and the yellow solution was filtered and neutralized with carbon dioxide. After recrystallization from acetone as described above, the yield of bronze flakes was 0.1 g. (11%), m.p. 295–300° dec.

S. 2-Hydroxy-5-carboxy-3,6-diphenylpyrazine.—A mixture of 4.0 g. (0.01 mole) of 2,5-dibromo-3,6-diphenylpyrazine and 16 g. of cuprous cyanide in 60 ml. of dry γ-picoline was refluxed for 7 hr. and then poured into 1000 ml. of 4 *N* hydrochloric acid. To this was added 500 ml. of chloroform, and the mixture was warmed to 40° and stirred mechanically for 10 minutes and then filtered. The chloroform phase was concentrated and the tarry residue was distilled to give 2.5 g. of pasty distillate which boiled at 170–220° (0.01 mm.). No pure product could be obtained from this mixture by recrystallization and so it was hydrolyzed by refluxing for 9 days in 100 ml. of ethanol containing 16 g. of potassium hydroxide. Water (500 ml.) was added to the clear solution, and then it was neutralized with carbon dioxide, filtered, and the filtrate was acidified with hydrochloric acid to precipitate a yellow solid. This was recrystallized from acetic acid to give 1.0 g. (33%) of yellow prisms, m.p. 264–265° with evolution of carbon dioxide and resolidification followed by a m.p. of 292–294°. This is the behavior of 2-hydroxy-5-carboxy-3,6-diphenylpyrazine, described by Gastaldi,[6] which decarboxylates to form 2-hydroxy-3,6-diphenylpyrazine.

T. 2-Hydroxy-3-cyano-5,6-diphenylpyrazine.—Two grams (0.0059 mole) of 2-bromo-3-methoxy-5,6-diphenylpyrazine was refluxed with 1.5 g. (0.017 mole) of cuprous cyanide in 40 ml. of dry γ-picoline for 3 hr., and then the hot solution was poured with stirring into a mixture of 500 ml. of cold 3 *N* hydrochloric acid and 100 ml. of chloroform. After 15 minutes of mechanical stirring the solid was filtered off, washing well with 100 ml. more chloroform. The chloroform portion of the filtrate was evaporated to dryness, and the residue was recrystallized from 25 ml. of ethanol to give 1.3 g. (72%) of long yellow prisms, m.p. 230–232°.

Anal. Calcd. for $C_{17}H_{11}N_3O$: N, 15.39. Found: N, 15.09.

U. 2-Hydroxy-3-carboxy-5,6-diphenylpyrazine.—One gram (0.0037 mole) of 2-hydroxy-3-cyano-5,6-diphenylpyrazine was refluxed for 7 hr. in 50 ml. of 15% aqueous potassium hydroxide, and then the yellow solution was diluted with 200 ml. of water, acidified with hydrochloric acid and extracted with two 120-ml. portions of chloroform. After evaporation of the chloroform extracts, the residue was recrystallized from ethanol to give 0.7 g. (65%) of yellow granules. This hydroxy-acid melted at 225–227°, with evolution of carbon dioxide, to form 2-hydroxy-5,6-diphenylpyrazine,[8] m.p. 239–240°.

Anal. Calcd. for $C_{17}H_{12}N_2O_3$: N, 9.58. Found: N, 9.56.

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RARITAN, NEW JERSEY

(13) F. G. McDonald and R. C. Ellingson. THIS JOURNAL, **69**, 1036 (1947).

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

On the Structure of an Intermediate in the Biological Demethylation of Lanosterol

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A new intermediate in the biological demethylation of lanosterol to cholesterol is described. It is isolated by chromatography of the non-saponifiable fraction of liver and intestinal tissue of rats which had been injected with C^{14}-acetate. Evidence is presented that the intermediate contains a *gem*-dimethyl substituent at C_4, a double bond between C_{24} and C_{25} and an inert nuclear double bond. On enzymatic conversion to cholesterol it yields two moles of CO_2. These properties suggest that the intermediate is a 4,4-dimethylcholestadienol.

Introduction

In a recent report,[1] we have described briefly the isolation of a new intermediate in the biological synthesis of cholesterol. Its source was the non-saponifiable fraction of liver and intestinal tissue from rats which had received C^{14}-acetate by injec-

(1) P. B. Schneider, R. B. Clayton and K. Bloch. *J. Biol. Chem.*, in press.