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

Chlorination of Some Alkylpyrazines[1]

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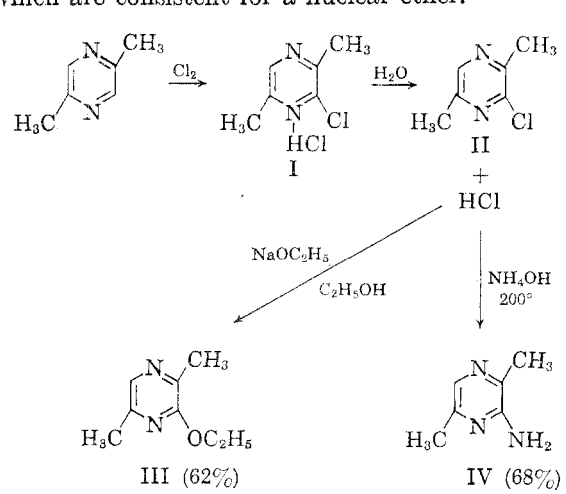
A reinvestigation of the reaction of 2,5-dimethylpyrazine in carbon tetrachloride solution with chlorine under ultraviolet light revealed that the product was 2-chloro-3,6-dimethylpyrazine (II) and that recourse to ultraviolet treatment was unnecessary. Treatment of 2-methylpyrazine with chlorine afforded a mixture of 2-chloro-3-methyl- (VII) and 2-chloro-5-methylpyrazine (VIII). In allowing 2,6-dimethylpyrazine to react with chlorine, it was found that ultraviolet radiation was essential and that the product was an unstable side chain halogenated compound, 2,6-bis(α-chloromethyl)pyrazine (XV). Alcoholysis converted XV to the bis ether XVI. Treating 2-methyl- and 2,5-dimethylpyrazine with one equivalent of *N*-chlorosuccinimide and a small quantity of benzoyl peroxide afforded unstable α-chloromethyl derivatives V and XI which were converted to the corresponding side chain ethers VI and XII.

While a general procedure for preparing 2-chloropyrazines from the corresponding hydroxypyrazines has been described in the literature,[4] it however seemed of interest to study the direct chlorination of various alkylpyrazines. This synthetic approach had been examined previously by C. Larson[5] who reported the preparation of a halogenated compound believed to be 2-(α-chloromethyl)-5-methylpyrazine (V), by treatment of 2,5-dimethylpyrazine with chlorine gas under the influence of ultraviolet radiation. Unexpectedly, however, the attempted ammonolysis and hydrolysis of this alleged α-chloromethylpyrazine were unsuccessful. It was found, however, that the chlorinated compound did react quite readily with sodium ethoxide in absolute ethanol to form the corresponding ether.

In analogy with α-chloromethyl- and α-bromomethylpyridine[6,7,8] which are strong lachrymators and skin irritants and also slowly polymerize on standing, similar properties could be expected from chloromethylpyrazines. However, the compound reported by Larson[5] was found to be quite stable and without offensive properties. These facts prompted a reinvestigation of the photo chlorination of 2,5-dimethylpyrazine.

Duplication of Larson's procedure[5] was accomplished by passing chlorine gas through a carbon tetrachloride solution of 2,5-dimethylpyrazine under the influence of ultraviolet radiation. As expected, an almost immediate reaction occurred with the formation of heavy white precipitate, the strongly exothermic reaction causing the solvent to boil. The precipitated material, with a neutralization equivalent of 169–171 was the hydrochloride salt I, indicating the addition of chlorine to the original molecule. Hydrolysis of I occurred readily in water, affording the free halogenated base as an insoluble oil, the aqueous solution becoming quite acidic.

The physical properties and stability of this oil indicated that nuclear rather than side chain chlorination had occurred and that the product was 2-chloro-3,6-dimethylpyrazine (II). The infrared absorption curves of both II and an authentic sample[4] were identical. Further verification was obtained by preparation of the identical amines as well as comparison of the hydrochloride salts of II. Finally, the oil by ethanolysis afforded a 62% yield of 2-ethoxy-3,6-dimethylpyrazine, whose infrared spectrum was identical with the ethoxy derivative prepared from authentic II. Both curves exhibited strong peaks at 1037 and 1172 cm.$^{-1}$ which are consistent for a nuclear ether.[9,10]



(1) Presented before the eleventh Meeting in Miniature of the Metropolitan Long Island Subsection of the New York Section, American Chemical Society, March 11, 1960.

(2) (a) The work here reported is based on a dissertation by Albert Hirschberg in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn, June 1960; (b) Du Pont Teaching Fellow, 1958–59; Texaco Research Fellow, 1959–60.

(3) To whom all inquiries should be addressed.

(4) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, 74, 1580 (1952).

(5) C. Larson, Doctoral Dissertation, Polytechnic Institute of Brooklyn, June 1949.

(6) J. Overhoff, J. Boeke, and A. Gorter, *Rec. trav. chim.*, 55, 293 (1936).

(7) F. Sorm and L. Sedevy, *Collection Czechoslov. Communs.*, 13, 288 (1948).

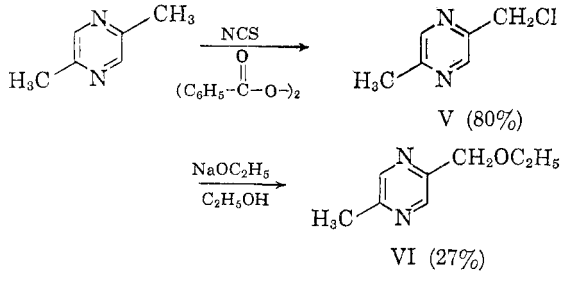
(8) M. Hasagawa, *Pharm. Bull. (Japan)*, 1, 293 (1953); *Chem. Abstr.*, 49, 8275 (1954).

(9) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1958, p. 115.

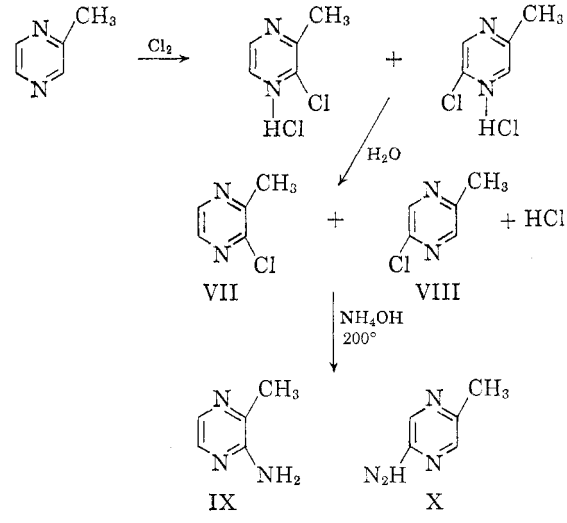
It was now apparent that the photochlorination of 2,5-dimethylpyrazine was not a free radical process since such a reaction course in analogy with the photochlorination of alkylbenzenes should have led to chlorination on the alkyl side chains.[11] Additional experiments, wherein the chlorination readily took place in the dark with comparable yields, further demonstrated the nonradical mechanism of this reaction.

The chlorination of 2,5-dimethylpyrazine was now studied under conditions favoring a free radical process.[12] Accordingly, 2,5-dimethylpyrazine was treated with an equivalent of *N*-chlorosuccinimide (NCS) and a catalytic amount of benzoyl peroxide and the resulting mixture was refluxed. This procedure afforded, upon work-up, 70–80% of a crude brownish oil, which could not be distilled, and which was highly lachrymatory and extremely irritating to the skin. Upon standing, the oil slowly polymerized to a dark brown tacky solid, which still retained the unpleasant properties of the original oil. It was therefore necessary when working with this material to use it immediately after the solvent had been removed.

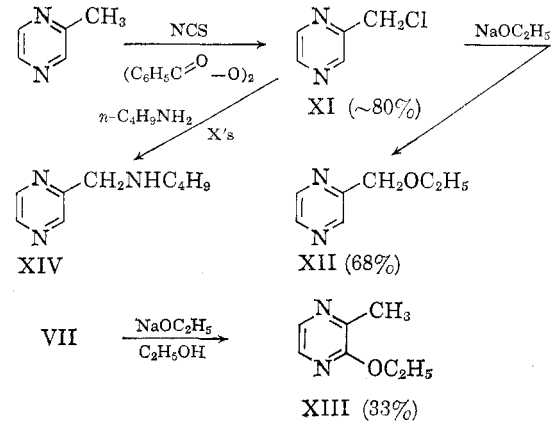
The general physical properties of the product led us to assume that 2-(α-chloromethyl)-5-methylpyrazine (V) had been formed. Attempts at preparing a picrate as well as a stable hydrochloride were unsuccessful. Ethanolysis, however, afforded a 27% yield of a stable, pungent oil presumably 2-methyl-5-pyrazinylmethyl ethyl ether (VI). This was confirmed by examination of the compound's infrared spectrum which indicated the presence of an aliphatic ether grouping due to a strong peak at 1122 cm.$^{-1}$ [9] The elemental analysis indicated that this compound was isomeric with the nuclear ether III previously prepared. These facts indicated that as expected, side chain halogenation had occurred and the following reaction scheme could be formulated



A parallel series of chlorinations were carred out using 2-methylpyrazine. Passage of chlorine through a carbon tetrachloride solution of 2-methylpyrazine, even in the dark, afforded a heavy white hydrochloride having a neutralization equivalent of 158–160. Hydrolysis of this hydrochloride in water afforded a heavy stable chlorinated oil, insoluble in the resulting aqueous acidic solution. Distillation of the oil afforded a 65% yield of stable compounds assumed to be a mixture of ring chlorinated methylpyrazines (VII and VIII). Repeated distillation having failed to bring about a good separation the oil was subjected to ammonolysis at 200° which yielded a solid mixture of amines which on fractional crystallization afforded 60% of 2-amino-3-methylpyrazine (IX) and 5% of 2-amino-5-methylpyrazine (X). The identity of both amines was demonstrated by comparison with authentic amines prepared independently.[4]



The treatment of 2-methylpyrazine with one equivalent of *N*-chlorosuccinimide using benzoyl peroxide as a catalyst afforded a highly unstable lachrymatory oil, presumably α-chloromethylpyrazine (XI). Ethanolysis of this oil using sodium ethoxide afforded a stable compound exhibiting a strong aliphatic ether peak at 1121 cm.$^{-1}$ in the infrared.[9] In addition, elemental analysis indicated the product to be pyrazinylmethyl ethyl ether (XII). For comparison purposes, the isomeric nuclear ether, 2-ethoxy-3-methylpyrazine (XIII), was prepared by ethanolysis of VII. The infrared



(10) N. B. Colthup, *J. Opt. Sci. Amer.*, 40, 397 (1950).
(11) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, 1956, p. 433.
(12) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, 1956, p. 429.

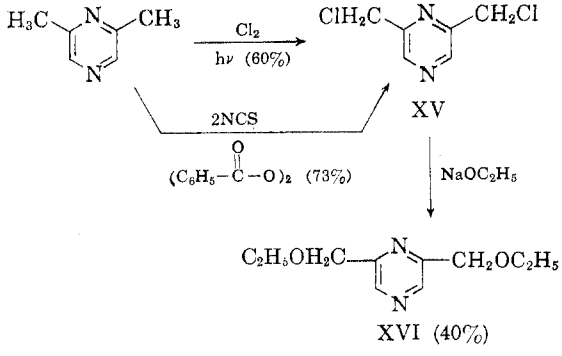
curve of this material exhibited two strong peaks at 1038 cm.$^{-1}$ and 1192 cm.$^{-1}$, indicative of an aromatic ether.[9,10]

While attempts to convert XI into the corresponding hydroxymethyl or aminomethyl derivative were unsuccessful, a higher amine derivative was obtained, however, by allowing the chloromethyl compound to react with excess *n*-butylamine. By this procedure, an oil was isolated whose infrared spectrum exhibited a medium peak at 3200 cm.$^{-1}$ indicative of a secondary amine.[9] Elemental analysis of both the oil and its phenyl isothiocyanate derivative indicated the secondary amine was pyrazinylmethyl-*n*-butylamine (XIV).

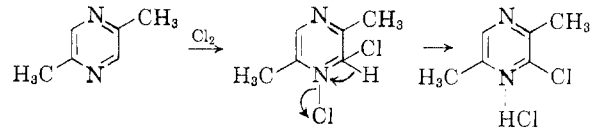
Chlorination of 2,6-dimethylpyrazine in carbon tetrachloride, in strong contrast to the 2- or 2,5 isomer, proceeded extremely slowly, as evidenced by the small amount of precipitate formed even after several hours. Strong illumination with ultraviolet light, on the other hand, apparently accelerated the reaction for within twenty minutes a heavy white precipitate appeared which surprisingly was found to be 2,6-dimethylpyrazine hydrochloride.

Evaporation of the carbon tetrachloride filtrate left a residual, lachrymatory oil, which polymerized on standing, and which could not be distilled. Ethanolysis of this product afforded a stable material exhibiting strong aliphatic ether peaks at 1104 cm.$^{-1}$ and 1122 cm.$^{-1}$ Elemental analysis showed the product to be the bis ether XVI, and hence that the oil obtained originally was 2,6-bis-α-chloromethylpyrazine (XV).

An independent synthesis of XV was accomplished by treating 2,6-dimethylpyrazine with two equivalents of *N*-chlorosuccinimide and a catalyst quantity of benzoyl peroxide in carbon tetrachloride solution. The unstable, lachrymatory oil obtained from this procedure was subjected to ethanolysis, affording the bis ether XVI.



In the absence of detailed mechanistic studies, the mechanism of the reaction between chlorine and 2-methyl- and 2,5-dimethylpyrazine must remain a matter of conjecture. While a free radical reaction seems to be ruled out, it seems on the other hand unlikely that the reaction proceeds *via* electrophilic substitution on the pyrazine nucleus because of the known resistance of pyrazine and its alkyl and aryl derivatives to this type of attack.[13] A possible reaction course might involve an addition of chlorine across the azomethine linkage of the pyrazine ring followed by a rearrangement forming the hydrochloride salt.



The mechanism of the reaction of 2,6-dimethylpyrazine with chlorine appears to be a free radical process due to its dependence on ultraviolet radiation and the formation of a side chain halogenated product. This marked contrast to the cases of 2-methyl- and 2,5-dimethylpyrazine is rather curious, however, since it is not clear why this particular isomer should show such a difference in reaction behavior.

Further work on this problem as well as chlorination reactions of other alkyl and arylpyrazines is being carried out and will be reported on in due course.

EXPERIMENTAL[14]

A. *2 Chloro-3,6-dimethylpyrazine* II. In 500 ml. of carbon tetrachloride 20.0 g. (0.185 mole) of 2,5-dimethylpyrazine was dissolved. Chlorine gas was bubbled in and within a few minutes the solution started to boil and a voluminous white precipitate formed. The passage of chlorine was continued for another 0.5 hr. and the precipitate was then collected, washed with two fresh 100-ml. portions of carbon tetrachloride, and dried in a vacuum desiccator. The dry powdery solid was added to 300 ml. of water whereupon a heavy oil separated at once, and collected at the bottom of the flask. This oily material was extracted completely from the aqueous solution with ether. The ether extracts were dried over magnesium sulfate and then concentrated on a steam bath. The oily residue was distilled through a 6-inch Vigreux column to yield 16.0 g. (61%) of 2-chloro-3,6-dimethylpyrazine (II), boiling at 112–114° (70 mm.), n_D^{25} 1.5247.

B. *Chlorination of methylpyrazine.* The procedure as outlined in A was applied to 2-methylpyrazine affording a 65% yield of an oily mixture of 2-chloro-3-methylpyrazine (VII) and 2-chloro-5-methylpyrazine (VIII).

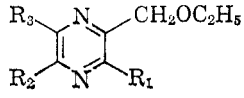
C. *Ammonolysis of the 2-chloro-3-methylpyrazine* (VII) *and 2-chloro-5-methylpyrazine* (VIII) *mixture.* A mixture of 2.56 g. (0.02 mole) of the mixture of the chlorinated isomers obtained from B and 80 ml. of 28% aqueous ammonia was heated in a stainless steel autoclave at 200° for 36 hr. The resulting solution was made strongly basic with sodium hydroxide at 0°, and then thoroughly extracted with ether. The ether extract was dried over sodium sulfate and then evaporated, yielding a solid residue which was recrystallized

(13) I. J. Krems and P. E. Spoerri, *Chem. Revs.*, 40, 328 (1947).

(14) All melting points are corrected. Infrared curves were taken using potassium bromide disks on a Perkin-Elmer Model 21 recording infrared spectrophotometer. Microanalyses were performed by Schwarzkopf Laboratories in New York or M. Manser, Basel, Switzerland. The syntheses of all chloropyrazines referred to in this section have been described in a previous publication or are given below.

TABLE I

PYRAZINYLMETHYL ETHYL ETHERS



	R_1	R_2	R_3	B.P./Mm.	n_D^t	t°	Yield,[a] %	N% Calcd.	N% Found
VI	H	H	H	110–112/53	1.4909	22	68	20.58	20.58
XII	H	CH_3	H	98–104/20	1.4869	28	27	18.41	18.59

[a] Yields based on assuming 100% purity of starting chloromethylpyrazines.

from ethanol to yield 1.30 g. (60%) of 2-amino-3-methylpyrazine melting at 166–167°.

Anal. Calcd. for $C_5H_7N_3$: N, 38.51. Found: N, 38.44.

The ethanol mother liquor was evaporated to dryness and the residue recrystallized from benzene affording 0.11 g. (5%) of 2-amino-5-methylpyrazine melting at 111–112° (lit.,[15] m.p. 116–118°).

Anal. Calcd. for $C_5H_7N_3$: N, 38.51. Found: N, 38.19.

D. *2-Amino-3,6-dimethylpyrazine* (IV). The ammonolysis procedure described in C was applied to 2.84 g. (0.02 mole) of 2-chloro-3,6-dimethylpyrazine (II). The residue was recrystallized from benzene affording 1.77 g. (68%) of IV as white prisms melting at 111–113° (lit.,[16] m.p. 112–113°).

E. *2-Ethoxy-3,6-dimethylpyrazine* (III). To 150 ml. of absolute ethanol was added 0.69 g. (0.03 mole) of sodium and 1.42 g. (0.01 mole) of 2-chloro-3,6-dimethylpyrazine (II) dissolved in 50 ml. of absolute ethanol. The resulting mixture was allowed to reflux for 10 hr. during which time a precipitate of sodium chloride formed. The mixture was cooled, filtered, and the residue of sodium chloride washed with several portions of absolute ethanol. The filtrate and washings were combined and 25 ml. of water added. The resulting solution was concentrated on a water bath and the residual oil was then extracted completely from the alkaline aqueous liquor with ether. The ether extracts were dried over magnesium sulfate and concentrated on a water bath. The residual oil was carefully distilled at 86–88°/20 mm. yielding 2.8 g. (62%) of the ethoxy compound III, n_D^{26} 1.4934.

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.16; H, 7.95; N, 18.41. Found: C, 63.38; H, 81.22 N, 18.16.

F. *2-Ethoxy-3-methylpyrazine* (XIII). The procedure as described in E was applied to 1.28 g. (0.01 mole) of 2-chloro-3-methylpyrazine (VII) affording 0.45 g. (33%) of the ethoxy compound XIII boiling at 88–90°/48 mm., n_D^{26} 1.4938.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.86; H, 7.30; N, 20.28. Found: C, 60.57; H, 7.47; N, 20.24.

G. *2-(α-Chloromethylpyrazines* (*Compounds* V *and* XI). Two 2-(α-chloromethyl)pyrazines were prepared by the reaction of *N*-chlorosuccinimide with an equimolar quantity of the corresponding alkyl pyrazine, using a catalytic amount of benzoyl peroxide. These α-chloromethyl derivatives could not be distilled and are unstable. They were therefore used immediately after isolation and converted to the corresponding pyrazinylmethyl ethyl ethers (procedures J and K). The obnoxious and toxic properties of these compounds makes it imperative that they be handled with extreme caution.

In 250 ml. of carbon tetrachloride was dissolved 0.10 mole of 2-methyl- or 2,5-dimethylpyrazine. To the solution was added 13.0 g. (0.10 mole) of *N*-chlorosuccinimide and 0.1 g. of benzoyl peroxide and the resulting mixture refluxed for 12 hr., cooled to 0°, and carefully filtered. The residue (mostly succinimide) was washed with two 50-ml. portions of carbon tetrachloride. The washings and filtrate were combined and evaporated under vacuum at room temperature. The residual oils were then used immediately for the preparation of the corresponding ethers. The yields of these crude oils ranged from 70 to 80% (assuming the oils to be pure).

H. *2,6-Bis(α-chloromethyl)pyrazine* (XV). 1. To 500 ml. of carbon tetrachloride was added 20 g. (0.185 mole) of 2,6-dimethylpyrazine. Chlorine gas was bubbled in while the flask was irradiated with ultraviolet radiation (Burdick—Type QA-250N). A heavy white precipitate formed almost immediately. The chlorination and irradiation continued for 2 hr., after which time the contents of the flask were carefully filtered and the residue of 2,6-dimethylpyrazine hydrochloride was washed with 100 ml. of fresh carbon tetrachloride. The filtrate and washings were combined and allowed to stand for 2 days in a hood to allow the excess chlorine to evaporate. The remaining carbon tetrachloride solution was then evaporated under reduced pressure leaving 10.82. g. of XV as a residual lachrymatory oil, which was used directly for the preparation of the corresponding ether XVI. A 31% conversion to the bischloromethyl derivative XV was obtained, based on 10.3 g. of free 2,6-dimethylpyrazine recovered from its hydrochloride. The yield was 60%, assuming the oil to be pure.

2. To 250 ml. of carbon tetrachloride was added 10 g. of (0.10 mole) of 2,6-dimethylpyrazine. To this solution was added 26 g. (0.20 mole) of *N*-chlorosuccinimide and 0.1 g. of benzoyl peroxide. The mixture was refluxed for 24 hr. and then worked up as described in G. The yield was 70 to 80%.

I. *Pyrazinylmethyl-n-butylamine* (XIV). To 120 ml. of freshly distilled *n*-butylamine was added 5.0 g. (0.039 mole) of α-chloromethylpyrazine (XI). The resulting mixture was allowed to reflux for 5 hr. and then evaporated under reduced pressure, at room temperature, leaving an oily residue behind. The residue was taken up in ether yielding a precipitate (butylamine hydrochloride) which was filtered off and washed with fresh ether. The ether washings and filtrate were combined, dried over sodium sulfate, and evaporated on a water bath. The residual oil was distilled through a 6-inch Vigreux column affording 4.89 g. (68%) of the secondary amine XIV boiling at 76–78°/0.5 mm., n_D^{22} 1.5089.

Anal. Calcd. for $C_9H_{15}N_3$: C, 65.42; H, 9.15; N, 25.06. Found: C, 65.16; H, 9.61; N, 25.43.

A phenyl isothiocyanate derivative was prepared according to the procedure of Shriner, Fuson, and Curtin,[17] m.p. 97.5–98.5°.

Anal. Calcd. for $C_{16}H_{20}N_4S$: C, 63.96; H, 6.71; N, 18.65; S, 10.67. Found: C, 64.11; H, 6.92; N, 18.40; S, 10.75.

J. *2-Pyrazinylmethyl ethyl ethers* (*Compounds* VI *and* XII). Two 2-pyrazinylmethyl ethyl ethers (VI and XII) were prepared from the corresponding 2-(α-chloromethyl)pyrazines (Compounds V and XI) by the Williamson synthesis

(15) J. Weilgard, M. Tishler, and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945).

(16) R. R. Joiner and P. E. Spoerri, *J. Am. Chem. Soc.*, **63**, 1929 (1941).

(17) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley & Sons, Inc., New York, 1956, p. 227.

using a 3*M* excess of sodium ethoxide in absolute ethanol as described in E. These two ethers are listed in Table I, together with the pertinent analytical and physical data.

K. *2,6-Bispyrazinylmethyl diethyl ether* (XVI). The procedure was the same as in E, in which 7.0 g. (0.036 mole) of 2,6-bis(α-chloromethyl)pyrazine (XV) was allowed to react with a 3*M* excess of sodium ethoxide in absolute ethanol. Work-up afforded 2.86 g. (37%) of the bis ether XVI which boiled at 130–133°/20 mm., n_D^{25} 1.4892.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.24; H, 8.25; N, 14.00.

Acknowledgment. The authors wish to express sincere thanks to Prof. F. M. Beringer and Dr. J. G. Lombardino for helpful discussions. The technical assistance of Mr. H. Talts and Mr. R. Parla is also gratefully acknowledged. We also wish to acknowledge the generous samples of alkylpyrazines used for this work supplied by the Wyandotte Chemicals Corp.

BROOKLYN 1, N. Y.

[CONTRIBUTION FROM THE RESEARCH DIVISION, WYANDOTTE CHEMICALS CORP.]

Chlorination of Alkylpyrazines[1]

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Methyl-, 2,5-dimethyl-, or 2,5-diethylpyrazine, when treated in carbon tetrachloride at 40° with excess chlorine, gave 2-chloro-3-methyl-, 3-chloro-2,5-dimethyl-, and 3-chloro-2,5-diethylpyrazine, respectively, in good yields. A nuclear chlorinated product under these mild conditions was unexpected. The chlorine atom of the alkylchloropyrazines was very reactive towards nucleophilic reagents. Replacement of the halogen was readily effected by reaction of the chloro compounds with alcohols, ammonia, aliphatic amines, and aqueous alkali to give ethers, amines, and hydroxy derivatives.

A chlorination study of alkylpyrazines was begun initially with the objective of preparing α-chloromethylpyrazine. When methylpyrazine in carbon tetrachloride was treated with an excess of elemental chlorine at room temperature and with irradiation from an incandescent lamp a monochloro product was obtained. One might expect a methyl substituted chloro derivative to form under these conditions but the chemical and physical properties of the product indicated that 2-chloro-3-methylpyrazine, a ring substituted compound, had formed instead. Light was later found to have no effect on the reaction. The reaction was applied to the chlorination of 2,5-dimethyl- and 2,5-diethylpyrazine and the products were also ring substituted alkylchloropyrazines.

In addition to the derivatives of the chloro compounds prepared in the course of their identification, several other amino and alkoxy compounds were prepared. When 2-chloro-3-methyl- or 3-chloro-2,5-dimethylpyrazine was heated in an autoclave at about 200° with aqueous ammonia, methylamine, dimethylamine, or ethanolamine the corresponding substituted amines were obtained. To prepare the pyrazyl ethers from 2-chloro-3-methylpyrazine the sodium alkoxides were usually employed. Later we found that simply refluxing a mixture of the chloropyrazine in alcohol with potassium hydroxide was sufficient to afford the corresponding ethers in good yield. By these methods ethers were made from allyl, *n*-butyl and myristyl alcohols and from ethylene glycol. Since ethylene glycol is bifunctional both possible ethers were obtained: the hydroxyethyl ether and the ethylene bispyrazyl ether. 3-Chloro-2,5-dimethylpyrazine presumably reacts in a similar fashion since the corresponding ethyl ether was made in good yield from the chloropyrazine, ethanol and potassium hydroxide.[2]

(1) Presented before the Division of Organic Chemistry at the 138th Meeting of the American Chemical Society, New York, N. Y., September, 1960.

EXPERIMENTAL[3]

2-Chloro-3-methylpyrazine. To 5.4 l. of carbon tetrachloride heated to 40° in a 12 l. flask equipped with stirrer, Dry Ice-acetone condenser and dropping funnel was added 142 g. (2 moles) of chlorine through a tube ending above the surface of the carbon tetrachloride. This was followed by 94 g. (1 mole) of methylpyrazine added within 5 min. Warming was necessary to maintain the temperature at 40° until an exothermic reaction took place and precipitation of 2-chloro-3-methylpyrazine hydrochloride occurred. Addition of reactants was repeated in this manner (with cooling when necessary) except that the ratio of chlorine to methylpyrazine was adjusted so that final total amounts, 937 g. (13.2 moles) of chlorine and 1128 g. (12 moles) of methylpyrazine, had been added in 6 hr.

After standing overnight the hydrochloride was removed by filtration and washed with carbon tetrachloride. The filter cake was slurried with 500 ml. of water and the mixture was neutralized with 1.2 l. of 35% aqueous sodium hydroxide while the temperature was kept below 40° by cooling. The 2-chloro-3-methylpyrazine precipitated as an oil. It was separated and distilled. Yield: 1029 g. (67%), b.p. 55–65°/15 mm., n_D^{25} 1.5262 (reported[4] b.p. 94–96°/65 mm. and n_D^{25} 1.5302). The compound was unreactive towards hot alcoholic silver nitrate.

3-Chloro-2,5-dimethylpyrazine. This chloro compound was prepared from 2,5-dimethylpyrazine as above. Yield: 87%, b.p. 64°/10 mm.–65°/12 mm., n_D^{25} 1.5237 (reported[4]

(2) H. Gainer, M.S. thesis, Polytechnic Institute of Brooklyn, 1951.

(3) All melting points are uncorrected.

(4) G. Karmas and P. E. Spoerri, *J. Am. Chem. Soc.*, 74, 1580 (1952).