solved in 10 ml. of glacial acetic acid and shaken under hydrogen at atmospheric pressure in presence of 10 ml. of Adams' platinum oxide catalyst for 2 hr., when absorption ceased. The catalyst was filtered off, the solution evaporated to dryness, treated with alkali, and extracted with methylene dichloride. After removal of the solvent, the residual oil was dissolved in 2 ml. of ether and absorbed on a 30-g. column of Woelm alumina (basic, grade 1). The following fractions were eluted: (*i*) 100 ml. of pentane gave 23 mg. of forerun; (*ii*) 400 ml. of pentane with 5% ether gave 175 mg. of the crude base XI; (*iii*) pentane containing increasing amounts of ether, then ether, and finally methanol gave 340 mg. of crude carbinol XXII.

The crude base gave on distillation an almost colorless, viscous oil, b.p. 113° (bath, 0.15 mm.), n_D^{22} 1.5095, $[\alpha]_D^{24}$ −37.2° (*c* 0.8, ethanol). Infrared absorption showed the "*trans*-quinolizidine band" at 3.57 and 3.61 μ.

Anal. Calcd. for $C_{15}H_{28}N_2$: C, 76.21; H, 11.94; N, 11.85. Found: C, 76.71; H, 11.71; N, 11.63.

The *dipicrate* was prepared in ethanol-acetone mixture and recrystallized from boiling water: m.p. 112–113° with shrinking at 108.5°.

Anal. Calcd. for $C_{27}H_{34}N_8O_{14}$: C, 46.68; H, 4.93. Found: C, 46.43; H, 5.07.

The *dimethiodide* was formed at room temperature in acetone solution, then recrystallized from ethanol as clusters of prisms, m.p. 284–286°.

Anal. Calcd. for $C_{17}H_{34}I_2N_2$: C, 39.24; H, 6.59; I, 48.78. Found: C, 39.54; H, 6.87; I, 48.82.

Acknowledgment. The author is grateful to Mr. Joseph Grodsky and Mr. Charles N. Harper for elemental analyses and infrared spectra, and to Mr. Norman Spiere for rotations and assistance with some of the chromatographic separations.

RARITAN, N. J.

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

Synthesis of Substituted Pyrazines. I. 2-Substituted 3-Methylpyrazines[1,2]

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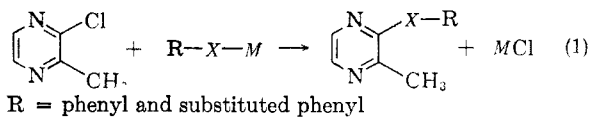
A variety of 2-substituted 3-methylpyrazines, where the substituents are certain phenoxy, thiophenoxy, anilino, and silyl radicals, was obtained in high yields with nucleophilic displacement reactions upon 2-chloro-3-methylpyrazine by the appropriate sodium phenoxide, sodium thiophenoxide, and aniline reagents, and by a magnesium coupling reaction with a chlorosilane, respectively. The action of sodium amide in liquid ammonia upon 2-chloro-3-methylpyrazine produced a dimeric coupling product, 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine. The reaction of sodium diphenylamine with 2-chloro-3-methylpyrazine gave various products depending on the conditions of the reaction.

As part of an extensive program for the preparation of various substituted pyrazines, the synthesis of certain 2-substituted-3-methylpyrazines has been investigated. The general route adopted for the synthesis of these compounds involved reactions by different reagents on the chlorine site of 2-chloro-3-methylpyrazine.[3]

The simple compound, chloropyrazine, has previously been reported to be susceptible to nucleophilic displacement reactions by hydroxyl, alkoxy, and amino groups[4] to give the corresponding hydroxy, ethoxy, and aminopyrazines. Similarly, the related compound, 2-chloro-3-methylpyrazine, has recently been found to undergo reactions with certain aliphatic amines and alcohols.[3] These reactions appeared to be relatively straightforward, with no unexpected complications or difficulties reported. In our investigation, involving a wide scope of nucleophilic displacement reagents, we have confirmed the reactivity of the chlorine in the latter compound. However, it was found that the reaction was not always simple, in that where strongly basic reagents were used competing reactions between the methyl and the chlorine site occurred, giving rise to more complex products.

It is the purpose of this paper to provide a preliminary definition of the scope of displacement and condensation reactions of 2-chloro-3-methylpyrazine, and to lay a foundation for the further inquiry into other derivatives of this highly interesting system. It was of specific interest in the present study to determine whether different and bulkier nucleophilic reagents would react at the chlorine site adjacent to the methyl group. To this end, a variety of aromatic nucleophilic displacement reagents were interacted with 2-chloro-3-methylpyrazine to give high yields of the desired products (see Table I). The general equation (1) illustrates these reactions.



R = phenyl and substituted phenyl

X = O, S, N, N, and Si (CH3)2

M = H, Na and Cl (with Mg)

(1) Presented in part at the 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960.

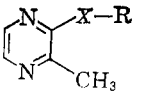
(2) This investigation was conducted under contract with Materials Central, Wright Air Development Division, Dayton, Ohio.

(3) H. Gainer, M. Kokorudz, and W. K. Langdon, *J. Org. Chem.*, 26, 2360 (1961).

(4) A. E. Erickson and P. E. Spoerri, *J. Am. Chem. Soc.*, 68, 853 (1946).

TABLE I

2-SUBSTITUTED 3-METHYLPYRAZINES



Compound	X	R	Yield,[18] %	M.P.[18] or B.P./Mm.		C, %	H, %	N, %	Other, %
I-1	O	C_6H_5—	62	90/0.5	Calcd.:	70.95	5.41	15.05	
					Found:	71.13	4.91	15.24	
						71.08	4.96	15.17	
I-2	O	*m*-(CH_3)C_6H_4—	85	67–68	Calcd.:	71.97	6.04	13.99	
					Found:	72.00	5.94	13.96	
I-3	O	*p*-(CH_3)C_6H_4—	70	101/0.3	Calcd.:	71.97	6.04	13.99	
					Found:	71.26	5.74	14.34	
I-4	O	*o*-(C_6H_5)C_6H_4—	58	134/0.1	Calcd.:	77.84	5.38	10.68	
					Found:	77.37	5.25	11.17	
I-5	O	*m*-(HO)C_6H_4—	86	176–177	Calcd.:	65.33	4.98	13.86	
					Found:	65.40	4.96	13.84	
II-1	S	C_6H_5—	83	70–71	Calcd.:	65.31	4.98	13.85	15.85[a]
					Found:	65.13	5.13	13.93	15.77[a]
II-2	S	*x*-(CH_3)C_6H_4—	90	128–131/0.8	Calcd.:	66.63	5.59	12.95	14.83[a]
					Found:	66.58	5.81	12.79	14.92[a]
						66.39	5.79	12.84	15.01[a]
II-3	S	*x,x'*-(CH_3)$_2C_6H_3$—	80	120/0.1	Calcd.:	67.79	6.13	12.17	13.92[a]
					Found:	68.08	6.16	12.06	14.05[a]
						68.11	6.04	12.11	13.89[a]
II-4	S	*p*-(*t*-C_4H_9)C_6H_4—	71	90.5–91.5	Calcd.:	69.79	7.02	10.85	12.41[a]
					Found:	69.58	6.91	10.94	12.37[a]
						69.64	6.98	10.82	12.40[a]
III-1	H | N	C_6H_5—	84	78–79[b]	Calcd.:	71.33	5.99	22.69	
					Found:	71.51	5.91	22.56	
				92–93[c]		71.08	5.96	23.26	
III-2	H | N	*m*-(Br)C_6H_4—	83	78–79	Calcd.:	50.02	3.82	15.91	30.26[d]
					Found:	50.05	3.99	15.93	30.19[d]
III-3	H | N	*m*-(CF_3)C_6H_4—	43	131.5–133.0	Calcd.:	56.91	3.98	16.59	22.51[e]
					Found:	56.95	3.89	16.53	22.47[e]
III-4	H | N	*o*-(CH_3O)C_6H_4—	63	81–82	Calcd.:	66.92	6.09	19.52	
					Found:	67.58	6.10	19.33	
						67.44	5.90	19.44	
III-5	H | N	*p*-(CH_3O)C_6H_5—	Quantitative	106–107	Calcd.:	66.92	6.09	19.52	
					Found:	67.17	6.07	19.67	
						67.17	5.83	19.73	
III-6	CH_3 | N	C_6H_5—	50[f] (41)[g]	85–86/0.07	Calcd.:	72.33	6.57	21.09	
					Found:	72.25	6.36	21.44	
						72.30	6.30	21.37	
III-7	C_6H_5 | N	C_6H_5—	15[h]	118	Calcd.:	78.13	5.79	16.08	
					Found:	77.98	5.74	16.31	
						77.89	5.70	16.34	
IV-1	CH_3 | Si | CH_3	C_6H_5—	29	81/0.03	Calcd.:	68.37	7.06	12.27	12.30[i]
					Found:	68.11	7.11	12.32	12.22[i]
						68.42	7.16	12.40	12.29[i]

[a] Values for sulfur. [b] Melting point of product initially isolated and recrystallized from an ether–petroleum ether mixture. [c] Melting point of product after prolonged standing in recrystallization solvent or after purification by elution chromatography with acid washed alumina. This isomerization phenonenon will be dealt with in greater detail in a subsequent publication. [d] Values for bromine. [e] Values for fluorine. [f] Yield from reaction with temperature up to 218° and six-hour reaction time. [g] Yield from reaction with temperature up to 200° and five-hour reaction time. [h] Yield from reaction carried out entirely at the reflux temperature of the tetrahydrofuran mixture. [i] Values for silicon.

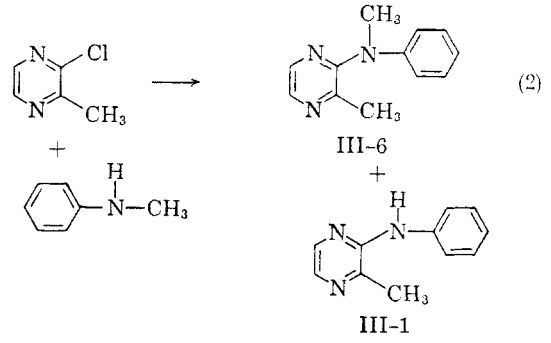
The reaction of sodium phenoxide with 2-chloro-3-methylpyrazine in phenol was found to proceed slowly at 90–105°, affording only 4% of 2-phenoxy-3-methylpyrazine after a twenty-six-hour reaction period. When the reaction was repeated at a higher temperature range, 130–140°, the yield was increased to 62%. Similar reactions were performed using the higher temperature conditions with a

number of substituted phenols. The results of these reactions are shown in Table I (compounds I-1 through I-5). The relatively high melting point (176–177°) of the resorcinol product is noteworthy. The hydroxyl group of 2-(*m*-hydroxyphenoxy)-3-methylpyrazine is apparently not free but in chelated form, as indicated by the infrared spectrum of this compound. The spectrum contains no free hydroxyl bands[5a] in the 3650–3590-cm.$^{-1}$ region but does contain chelated hydroxyl bands[5b] in the 3200–2500-cm.$^{-1}$ region.

The stronger nucleophilic displacement reagent,[6] sodium thiophenolate, was found to react more readily than the phenoxides with 2-chloro-3-methylpyrazine under even milder conditions. Refluxing of an ethanol solution of these reagents for twenty hours gave an 83% yield of 2-phenylmercapto-3-methylpyrazine. Similar reactions with other sodium thiophenolates gave corresponding products in high yields as shown in Table I (compounds II-1 through II-4). None of the possible side product, 2-ethoxy-3-methylpyrazine, that could arise from a competing reaction with ethoxide ion was isolated in any of these experiments. These results are in accord with the reported stronger nucleophilicity of thiophenolate ion as compared to the ethoxide ion.[7]

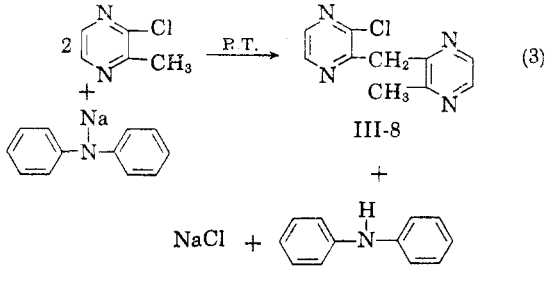
Aniline and a number of substituted anilines were found to react with 2-chloro-3-methylpyrazine to give good yields of 2-anilino-3-methylpyrazines when a mixture of these reagents was heated at reflux temperature for short periods of time. The course of the reaction was followed by the increase in the reflux temperature of the mixture. The results of these reactions are shown in Table I (compounds III-1 –III-5). It can be seen that good-to-excellent yields were obtained in these reactions without resorting to the conversion of the anilines to their metal derivatives as in the case of the phenols and thiophenols. This behavior is not in accord with the known weaker nucleophilic strength of aniline compared to thiophenolate and phenoxide ion.[6] The high reactivity of the anilines found in the present study might possibly be attributed to the higher temperatures (over 200°) at which these reactions were performed. All of the reactions were performed using an excess of the aniline as solvent. When the reaction with aniline was first performed using excess 2-chloro-3-methylpyrazine as the solvent, a volatile amine hydrochloride salt was liberated and the reaction mixture solidified upon cooling into a black brittle glass.

The procedure found to be successful with the primary aromatic amines was attempted with a representative secondary alkylaryl amine, *N*-methylaniline. When this compound was heated with 2-chloro-3-methylpyrazine, the reflux temperature of the mixture rose gradually with intermittent leveling off. Isolated from this reaction was 50% of the desired product, 2-(*N*-methylanilino)-3-methylpyrazine (III-6), and 37% of an unexpected degradation product, 2-anilino-3-methylpyrazine (III-1) (Equation 2). Formation of the side product apparently occurred because of reaction or work-up conditions, as no significant contamination of the starting *N*-methylaniline with aniline could be detected by infrared spectroscopy. The reaction was repeated under slightly modified conditions (shorter time and lower temperature) and provided a lower yield (41%) of the desired product, but also gave a lower proportion of the side product (19%). These results suggest that the drastic reaction conditions, and not the work-up, were responsible for the side reaction.



(2)

The representative diaryl secondary amine, diphenylamine, failed to react with 2-chloro-3-methylpyrazine when a mixture of these compounds was refluxed for twenty-four hours. An attempt was, therefore, made to prepare 2-(*N*,*N*-diphenylamino)-3-methylpyrazine (III-7) by the interaction of 2-chloro-3-methylpyrazine with sodium diphenylamine, prepared by the action of sodium hydride upon diphenylamine. The intended reaction was not straightforward, however, and yielded various products depending upon the conditions. The interaction of these reagents at room temperature for twenty-four hours gave only recovered diphenylamine and a self-coupling product of 2-chloro-3-methylpyrazine, 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine (III-8) (Equation 3).



(3)

(5) (a) L. J. Bellamy, "Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 85; (b) *Ibid.*, p. 90.

(6) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, 49, 273 (1951).

(7) J. F. Bunnett and W. D. Merritt, Jr., *J. Am. Chem. Soc.*, 79, 5967 (1957).

TABLE II

NMR SPECTRA[a]

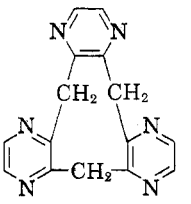
Compound	Ring C—H	Methinyl C—H	Methylene C—H	Methyl C—H	$Si(CH_3)_4$ C—H
Toluene	—	—	—	7.66[b]	10.0
Diphenylmethane	—	—	6.08[b]	—	10.0
Bis-*p*-tolylmethane	—	—	6.19[b]	—	10.0
Bis-*p*-tolylethane	—	—	5.81[b]	—	10.0
Triphenylmethane	—	4.42[c]	—	—	10.0
Methylpyrazine	1.68	—	—	7.48	10.0
2-Chloro-3-(3-methyl-2-pyrazyl-methyl)pyrazine	1.50	—	5.55	7.42	10.0
Tri(methylpyrazine)	1.65 1.78	3.82	—	7.52 7.62	10.0

[a] The positions of appearance of peaks are noted in terms of dimensionless units compared to the hydrogen peak for tetramethylsilane as an internal reference having an arbitrary shift of 10. [b] These values reported by Tiers.[10] [c] This value obtained by conversion of data by Chamberlain[11] to Tiers[10] tau scale.

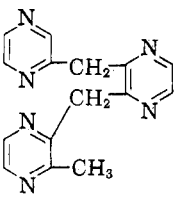
The self-coupling reaction presumably occurred by metalation of the methyl site of 2-chloro-3-methylpyrazine, followed by the reaction of the metalated compound with another mole of 2-chloro-2-methyl-pyrazine. Analogy for the metalation reaction can be found in the metalation of the simpler compound, methylpyrazine, with alkali amides in liquid ammonia.[8,9]

When this reaction was performed by interacting the reagents at room temperature and then refluxing the mixture for twenty-four hours, some of the desired product, 2-(*N*,*N*-diphenylamino)-3-methylpyrazine (III-7), along with a "tri(methylpyrazine)" (III-9) were isolated. This reaction was carried out once more, this time completely at the reflux temperature of the mixture. The last reaction yielded 15% of 2-(*N*,*N*-diphenylamino)-3-methylpyrazine, 4% of 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine, 1% of "tri(methylpyrazine)," and 69% of recovered diphenylamine. This series of reactions indicates that with a strong base, competing reactions can occur at the chlorine and the methyl sites of 2-chloro-3-methylpyrazine. The metalation reaction at the methyl site seems to be favored at lower temperatures; whereas, at higher temperatures the displacement reaction at the chlorine site becomes significant.

The NMR spectra of the trimer and the self-coupling product, 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine, are compared with the spectra of methylpyrazine and other reference compounds in Table II. The NMR spectrum of 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine is consistent with the assigned structure. The spectrum of the "tri(methylpyrazine)," however, seems to exclude the possible simple cyclic (III-9A) and the open chain (III-9B) structures. There is no peak in the region expected for a compound having a methylene radical. The indicated presence of a methinyl



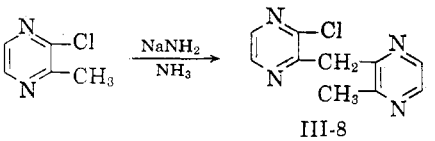
III-9A



III-9B

group, two different kinds of methyl radicals and two different types of ring hydrogens suggests an entirely different structure for this compound. Further work on the structure elucidation of this product is currently in progress and will be reported on at a later date.

The observed formation of a "tri(methylpyrazine)" from the interaction of sodium diphenylamine with 2-chloro-3-methylpyrazine prompted the investigation of the effect of another strong base. When 2-chloro-3-methylpyrazine was treated with sodium amide in liquid ammonia, only the mono-coupling product, 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine, was obtained in a 70% yield.



III-8

The recently reported[12] synthesis of 2- and 4-silylpyridines by a magnesium coupling reaction between a chlorosilane and the appropriate bromopyridine suggested the investigation of a similar route for the preparation of 2-silyl-3-methylpyrazines. The first attempted magnesium coupling reaction between 2-chloro-3-methylpyrazine and phenyldimethylchlorosilane gave a complicated product mixture. The products from this reaction were found to be crude 2-phenyldimethylsilyl-3-

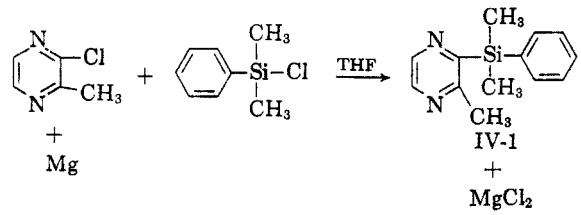
(8) J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5157 (1959).

(9) J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5666 (1959).

(10) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(11) N. F. Chamberlain, *Anal. Chem.*, **31**, 65 (1959).

(12) R. P. Anderson and M. M. Sprung, WADC Technical Report 59-61, June 1959.



methylpyrazine (19%) contaminated with 1,3-diphenyltetramethyldisiloxane and phenyldimethylsilanol (50%). The side products are believed to arise from the hydrolysis of unchanged phenyldimethylchlorosilane during the aqueous work-up. This reaction was repeated using an anhydrous work-up procedure to avoid undesirable side products and gave a 29% yield of 2-phenyldimethylsilyl-3-methylpyrazine along with a 47% recovery of 2-chloro-3-methylpyrazine.

The above reactions are believed to be illustrative of the variety of reagents which can readily displace the chlorine from 2-chloro-3-methylpyrazine. It is interesting to note that even in the case of a bulky reagent such as sodium *o*-phenylphenoxide, which might have been expected to be sterically hindered in the displacement of the chlorine adjacent to the methyl group, a relatively good yield (58%) of the desired product (I-4) was obtained. Further work is in progress on the preparation of additional 2-substituted-3-methylpyrazines and on various other substituted pyrazines and will be reported in subsequent publications.

EXPERIMENTAL[13]

2-Phenoxy-3-methylpyrazines. The following procedure for the preparation of 2-phenoxy-3-methylpyrazine (I-1) is representative of the procedures employed for the preparation of compounds I-1 through I-5 in Table I.

Sodium phenoxide (0.1 mole) was prepared by dissolving 2.3 g. (0.1 mole) of sodium metal in 100 ml. of phenol kept under an anhydrous nitrogen atmosphere at 50–80°. To the stirred solution was then added 12.9 g. (0.1 mole) of 2-chloro-3-methylpyrazine at 73–78°. The reaction mixture was then heated to 90° and held at 90–105° for 26 hr. The reaction mixture was then cooled, treated with excess 50% aqueous sodium hydroxide to convert all the phenol to its sodium salt, and extracted with chloroform. The combined chloroform extracts were distilled giving 8.8 g. (68%) of recovered 2-chloro-3-methylpyrazine, b.p. 38–41° at 3.5 mm. and 1.0 g. of product, b.p. 103–104° at 1.5 mm. The higher-boiling product was separated by vapor phase chromatography into two fractions which were identified by their infrared spectra. Phenol was found to be the minor constituent and the major portion was 2-phenoxy-3-methylpyrazine (4% yield), identical to the product from the experiment below which was identified by elemental analysis.

The above experiment was repeated using a higher reaction temperature of 130–140° for 24 hr. Work-up of the reaction, as above, gave 11.5 g. (62%) of 2-phenoxy-3-methylpyrazine, b.p. 93–96° at 0.8 mm. The product was purified by redistillation, b.p. 90° at 0.5 mm.

(13) All melting points and boiling points are uncorrected. Elemental analyses were by Spang Microanalytical Laboratory, Ann Arbor, Mich. Yields in Table I are based on crude products; the physical constants (melting point or boiling point) are on analytical samples.

2-Arylmercapto-3-methylpyrazines. The following procedure for the preparation of 2-phenylmercapto-3-methylpyrazine (II-1) illustrates the procedures employed for the preparation of compounds II-1 through II-4 in Table I.

Sodium ethoxide (0.1 mole) was prepared by dissolving 2.3 g. (0.1 mole) of sodium in 100 ml. of absolute ethanol. To the solution, under a nitrogen atmosphere, was added 11.0 g. (0.1 mole) of thiophenol[14] followed by 12.9 g. (0.1 mole) of 2-chloro-3-methylpyrazine at room temperature. Heat was applied to bring the mixture to reflux and refluxing was maintained for 20 hr. The resulting mixture was then filtered to obtain 5.8 g. of solid sodium chloride. The ethanol was removed from the filtrate by evaporation at reduced pressure leaving 15.6 g. (83%) of crude white crystalline 2-phenylmercapto-3-methylpyrazine, m.p. 68–69°. The product was purified by recrystallization from an ethanol-water mixture, m.p. 70–71°.

2-Arylamino-3-methylpyrazines. The following procedure for the preparation of 2-anilino-3-methylpyrazine (III-1) is representative of the procedure employed for the preparation of compounds III-1 through III-5 in Table I.

A mixture of 30 ml. (approximately 0.3 mole) of aniline[15] and 15.9 g. (0.123 mole) of 2-chloro-3-methylpyrazine was heated gradually from room temperature to 207° over a 1-hr. period. The resulting dark liquid mixture was poured into 200 ml. of water, neutralized with sodium carbonate, and made strongly basic with sodium hydroxide, then extracted with chloroform. Distillation of the extract gave 19.1 g. (84%) of crude 2-anilino-3-methylpyrazine, b.p. 121–127° at 0.20–0.15 mm. The product which solidified upon standing was purified by recrystallization from an ether–petroleum ether (b.p. 60–90°) mixture, m.p. 78–79°.

After standing in the recrystallization solvent for several days or upon purification by elution chromatography using Merck acid-washed alumina this same product gave a different melting point, 92–93°, when recrystallized from petroleum ether.

2-(N-Methylanilino)-3-methylpyrazine (III-6). A mixture of 33.0 g. (0.3 mole) of *N*-methylaniline and 13.5 g. (0.1 mole) of 2-chloro-3-methylpyrazine was heated to its reflux temperature (approximately 170°). Heating was continued for 6 hr. longer as the temperature rose intermittently to 218°. The mixture was allowed to cool to room temperature and then poured into water, neutralized with sodium carbonate, made strongly basic with sodium hydroxide, saturated with sodium chloride, and extracted with chloroform. The dried chloroform extract was distilled at reduced pressure to give 9.9 g. (49.5%) of crude 2-(*N*-methylanilino)-3-methylpyrazine, b.p. 87–96° at 0.03–0.08 mm. and 6.9 g. (37.0%) of 2-anilino-3-methylpyrazine, b.p. 95–116° at 0.05–0.03 mm. The desired product was purified by redistillation, b.p. 85–86° at 0.07 mm., n_D^{25} 1.6142.

The crude 2-anilino-3-methylpyrazine solidified on standing, m.p. 67–90°. This material was purified by recrystallization from an ether-petroleum ether mixture, m.p. 91–93°, and was identified by a mixed melting point with an authentic sample.

The above reaction was repeated employing less drastic conditions. The same proportions of reagents were used but the reaction mixture was heated only up to 200° over a 5-hr. period. Obtained from this reaction were 8.2 g. (41.2%) of crude 2-(*N*-methylanilino)-3-methylpyrazine, b.p. 80–97° at 0.1 mm., n_D^{25} 1.6129–1.6160, and 3.6 g. (19%) of crude 2-anilino-3-methylpyrazine, b.p. 103° at 0.1 mm.

(14) The thiophenols employed in the preparation of this group of compounds were generously supplied by Pitt-Consol Chemical Co., Newark, N. J. The thiocresol and thioxylenol are mixed isomers.

(15) Two of the substituted anilines employed in the preparation of this group of compounds were courtesy samples supplied by the following manufacturers: *m*-trifluoromethylaniline, Gamma Corp., Great Meadows, N. J.; *o*-anisidine, Koppers Co., Inc., Lock Haven, Pa.

2-(N,N-Diphenylamino)-3-methylpyrazine (III-7). (a) An attempt was first made to prepare this compound by the standard procedure for the preparation of 2-arylamino-3-methylpyrazines described above. Diphenylamine, 16.9 g. (0.1 mole), and 25 g. (0.2 mole) of 2-chloro-3-methylpyrazine were refluxed for 24 hr. at 186–187°. The mixture was cooled, made strongly basic with 12 g. of sodium hydroxide dissolved in 100 ml. of water and extracted with chloroform. Distillation of the chloroform extract gave 22.8 g. (91%) of recovered 2-chloro-3-methylpyrazine, b.p. 61–65° at 14 mm., and a residue of 15.8 g. (93%) of recovered diphenylamine, m.p. 46–54°.

(b) The second attempt to prepare this compound was performed using sodio diphenylamine. Sodium hydride, 5.2 g. of 52% dispersion in mineral oil, (0.11 mole) dissolved in 75 ml. of tetrahydrofuran was treated with 16.9 g. (0.1 mole) of diphenylamine and the mixture was refluxed for approximately 2 hr. During the refluxing, approximately the stoichiometric volume of hydrogen gas, 2.3 l., was liberated. The gas evolved somewhat abruptly after what appeared to be an induction period. To the resulting mixture was added 12.9 g. (0.1 mole) of 2-chloro-3-methylpyrazine over a 1-hr. period at 50–68°, the reflux temperature of the mixture. The color of the mixture changed from pale green to blood-red upon the addition of the 2-chloro-3-methylpyrazine and grew dark with elapsed time. Refluxing was continued for 23 hr. and then the mixture was cooled to room temperature, hydrolyzed with 10 ml. of ethanol, poured on ice, and extracted with chloroform. The chloroform extract was distilled giving 13.6 g. (80%) of recovered diphenylamine, b.p. 110–111° at 0.8 mm., m.p. 52–53° alone and when mixed with an authentic sample, and 3.5 g. of a higher boiling fraction, boiling from 152° at 0.7 mm. to 177° at 0.27 mm., along with 6.1 g. of nondistillable residue. A yellow liquid was decanted from the solidified higher boiling fraction and purified by microdistillation at an air bath temperature of 104–148° at 1.2–0.8 mm. Elemental analysis of this fraction along with its infrared spectrum shows it to have a high hydrocarbon content, presumably starting mineral oil.

Anal. Calcd. for C_nH_{2n}: C, 85.63; H, 14.37. Found: C, 85.27; H, 13.29; N, 1.10; Cl, 0.00.

A sample of the remaining solid was recrystallized from an ether–petroleum ether mixture to obtain a purified sample of tri(methylpyrazine) (III-9), m.p. 156–157°.

Anal. Calcd. for $C_{15}H_{14}N_6$: C, 64.72; H, 5.07; N, 30.20; mol. wt., 278. Found: C, 64.72, 64.81; H, 4.49, 5.03; N, 30.11, 30.14; mol. wt., 299, 286.

From the mother liquor of the above recrystallization a small quantity of the expected product 2-(*N,N*-diphenylamino)-3-methylpyrazine was isolated and purified by recrystallization from petroleum ether, m.p. 118°.

Anal. Calcd. for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 77.98, 77.89; H, 5.74, 5.70; N, 16.31, 16.34.

(c) The above reaction was repeated using identical quantities of reagents and similar conditions, the only difference being that all of the operations were performed at the reflux temperature of the reaction mixture. The product mixture was separated by elution chromatography to give 3.9 g. (15%) of crude 2-(*N,N*-diphenylamino)-3-methylpyrazine, 1.1 g. (4%) of 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine (III-8), and 0.3 g. (1%) of tri(methylpyrazine), all identified by their infrared spectra, along with 11.6 g. (69%) of recovered diphenylamine.

2-Chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine (III-8). (a) *Interaction of 2-chloro-3-methylpyrazine with sodium diphenylamine at room temperature.* A 5.2-g. quantity of 52% sodium hydride (0.11 mole) dispersion in mineral oil in 75 ml. of tetrahydrofuran heated to reflux with stirring was treated with 16.9 g. (0.1 mole) of diphenylamine dissolved in 25 ml. of tetrahydrofuran over an 80-min. period. When the addition was completed, stirring and refluxing was continued for an additional 10 min. when the hydrogen evolution had essentially stopped. The amount of hydrogen liberated was 2230 ml., approximately 0.1 mole. The mixture was then allowed to cool to room temperature over a 1-hr. period. At this point, 12.9 g. (0.1 mole) of 2-chloro-3-methylpyrazine was added over a 12-min. period. The addition was accompanied by a change to a red color in the mixture and by some evolution of heat. The temperature was maintained at below 36° during the addition with an ice bath. Stirring was continued at room temperature for 20 hr. and then the reaction was quenched by adding 10 ml. of absolute ethanol. The mixture was stirred for 10 min. longer, poured onto ice and the aqueous mixture saturated with sodium chloride and extracted with chloroform. The extract was dried and the solvent evaporated at reduced pressure. The residue, on cooling, yielded 3.5 g. of crude 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine, m.p. 108–114°, identified by a mixed melting point of a purified sample, m.p. 115–117°, with an authentic sample and by its infrared spectrum. The remaining filtrate was concentrated by evaporation at reduced pressure and subjected to prolonged cooling to give 8.6 g. of a discolored low-melting crystalline solid. More 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine was isolated from this fraction but no yield could be calculated for this product because of some accidental loss during the isolation by recrystallization.

(b) *Interaction of 2-chloro-3-methylpyrazine with sodium amide in liquid ammonia.* Sodium amide (0.2 mole) was prepared by dissolving 4.6 g. (0.2 mole) of sodium in approximately 100 ml. of liquid ammonia containing a catalytic quantity of ferric nitrate.

To the gray dispersion of sodium amide in liquid ammonia was then added 12.9 g. (0.1 mole) of 2-chloro-3-methylpyrazine. Upon adding the first drop, the mixture turned blood red and became very dark after the addition was complete in 15 min. The mixture was stirred for 4 hr. and then the reaction was quenched by the addition of 13 g. of solid ammonium chloride. The ammonia was displaced by adding 100 ml. of ether and warming the mixture with a water bath. The resulting mixture was dumped onto ice, left standing overnight, and then filtered giving 4.5 g. of dark solid. An additional 1.0 g. of solid was obtained from the filtrate, after making it basic with sodium hydroxide and salting out with sodium chloride, and 2.0 g. more of solid was obtained from a chloroform extract of the filtrate. Purification of these solids by recrystallization from ether gave materials melting at 114–116° which did not show a depression upon mixed melting point with each other. The combined weight of crude 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine was 7.5 g. (70%). A sample of the product was further purified by recrystallization from ether, m.p. 116–117°.

Anal. Calcd. for $C_{10}H_{10}N_4Cl$: C, 54.18; H, 4.55; N, 25.28; Cl, 16.07. Found: C, 54.29, 54.33; H, 4.09, 4.11; N, 25.37, 25.26; Cl, 15.93.

2-Phenyldimethylsilyl-3-methylpyrazine (IV-1). (a) Magnesium, 2.7 g. (0.11 mole), was placed in 60 ml. of tetrahydrofuran to which was added 5 drops of methyl iodide. The mixture was heated gently until it became slightly cloudy (approximately 35°) and then 20.5 g. (0.11 mole) of phenyldimethylchlorosilane was added rapidly. A sample of 12.9 g. (0.1 mole) of 2-chloro-3-methylpyrazine in 20 ml. of tetrahydrofuran was then added over a 1-hr. period as the temperature was maintained at 40–42° with a cooling bath. Stirring was continued at this temperature for an additional 2 hr. and then the mixture was stored in the refrigerator overnight at −5°. The unchanged magnesium, 0.35 g., was separated and the dark brown liquid at 0° was treated with water and then saturated sodium carbonate solution until the precipitation of magnesium carbonate was complete. The mixture was filtered, washed with benzene, and the precipitation and separation procedure repeated on the aqueous phase. The combined benzene washes and extracts were dried over sodium sulfate and distilled under reduced pressure. The first fraction, 9.0 g. (50%), b.p. 49.5–51.5° at 0.2 mm., n_D^{25} 1.5122, was identified by its infrared spectrum and elemental analysis as crude phenyldimethylsilanol.

Anal. Calcd. for $C_8H_{12}SiO$: C, 63.10; H, 7.94; Si, 18.45; N,

0.00. Found: C, 62.65, 62.68; H, 7.37, 7.41; Si, 19.23, 19.30; N, 1.33, 1.41.

The second fraction, 4.3 g. (19%), b.p. 94–98° at 0.28 mm., n_D^{25} 1.5470, was identified by its infrared spectrum and elemental analysis as crude 2-phenyldimethylsilyl-3-methylpyrazine containing some 1,3-diphenyltetramethyldisiloxane.

Anal. Calcd. for $C_{13}H_{16}N_2Si$: C, 68.37; H, 7.06; N, 12.27; Si, 12.30. Found: C, 66.85, 67.04; H, 7.05, 7.13; N, 9.14, 9.23; Si, 14.31, 14.42.

(b) The above reaction was repeated on the same scale using identical conditions except that only a 1-hr. rather than 2-hr. reaction time was used in the present experiment. In this reaction the tetrahydrofuran was freshly distilled from lithium aluminum hydride before use. The work-up procedure was modified to exclude water in an effort to prevent the formation of the 1,3-diphenyltetramethyldisiloxane side product. The reaction mixture was treated with 200 ml. of benzene to precipitate magnesium chloride and filtered. The clear dark red filtrate was distilled at reduced pressure to give 6.0 g. (46.5%) of recovered crude 2-chloro-3-methylpyrazine, b.p. 28–35° at 1.6–1.0 mm., and 6.4 g. (29%) of crude 2-phenyldimethylsilyl-3-methylpyrazine, b.p. 102–108° at 0.5–0.7 mm. The crude desired product was redistilled to give 6.0 g. (27%) of pure 2-phenyldimethylsilyl-3-methylpyrazine, b.p. 81° at 0.030 to 0.025 mm., n_D^{25} 1.5486.

Anal. Calcd. for $C_{13}H_{16}N_2Si$: C, 68.37; H, 7.06; N, 12.27; Si, 12.30. Found: C, 68.11, 68.42; H, 7.11, 7.16; N, 12.32, 12.40; Si, 12.22, 12.29.

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Synthesis of Possible Cancer Chemotherapeutic Compounds Based on Enzyme Approach. I. Hemisulfur Mustard and Its Esters[1]

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Hemisulfur mustard, 2-chloro-2′-hydroxydiethyl sulfide (I), has been prepared from sodiomercaptoethanol and ethylene chloride. The stability of I is measured by the use of 4-(*p*-nitrobenzyl)pyridine (NBP). Direct acylation of I with acid chlorides yields its corresponding esters. Alternatively, these esters may be prepared by first addition of mercaptoethanol to vinyl esters or direct monoacylation of thiodiglycol, followed by chlorination of the thiodiglycol monoesters thus produced. The synthesis of these new esters generates interest in the preparation of possible chemotherapeutic compounds based on enzymatic approach.

The reaction of *p*-toluenesulfonyl chloride and mercaptoethanol has been found to yield 2-chloro-2′-*p*-toluenesulfonyldiethyl sulfide (II), ditolyl sulfone (III), *p*-thiocresol (IV), and other polysulfide compounds. The anomaly in this reaction can be accounted for in part by the strong reducing power of mercaptoethanol.

In the design and synthesis of possible chemotherapeutic agents for cancer, Seligman and his associates have proposed[2] an interesting rationale based on the difference in the distribution of enzymes in normal and neo-plastic tissue. Thus, the tumor rich in a specific hydrolytic enzyme might liberate the toxic moiety that had been incorporated in a less toxic compound after hydrolysis. Conversely, if a tumor is known to be deficient in a specific enzyme, toxic compounds that could easily be detoxified by such enzymatic hydrolysis in normal cells should then be synthesized. The present series of synthetic work has been initiated to take advantage of the observation that carcinomas are particularly deficient in esterase.[3,4]

Hemisulfur mustard, or 2-chloro-2′-hydroxydiethyl sulfide (I), has been of interest to cancer chemotherapy not only because of its known beneficial effect[5–7] to ascites tumor, but also because of the absence of bone marrow effect, in contrast to the well-known alkylating agent nitrogen mustard. The synthesis of the esters of I was therefore undertaken with the expectation that the beneficial hematopoietic effect would be retained and that the difference in toxicity of the esters and the parent compound might provide a basis for taking advantage of the above mentioned rationale.

Even though it is known that hemisulfur mus-

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