filtered quickly to remove silicates, and the filtrate cooled to 5°. The product slowly separated as a yellow curdy precipitate which quickly turned blue-green on exposure to the air. This material was filtered with suction and washed with water and ethanol to obtain 0.63 g. (82%) of a pale bluish green solid, with no definite melting point (decomposed gradually above 200°). For analysis a sample was recrystallized from water to obtain bluish needles, gradual decomposition above 200°. The sample was dried at 100° *in vacuo* for 48 hr. before analysis.

Anal. Calcd. for $C_{13}H_{14}N_2O_3 \cdot H_2O$: C, 59.07; H, 6.10; N, 10.60. Found: C, 59.04; H, 6.14; N, 10.64.

The analysis did not change significantly upon drying the sample at 140° at 0.05 mm. for 24 hr.

This compound gave negative tests with *p*-dimethylaminobenzaldehyde or potassium iodate,[10] indicating a lack of free 1 or 3 positions. The ultraviolet spectra was typical of a 3-acetylindolizine (peaks at 372, 264, and 226 mμ). The infrared spectrum (Nujol mull) was compatible with structure X.[13]

3-Acetyl-1-indolizinealanine (X) formed a sparingly soluble *monohydrochloride* when treated with 10% hydrochloric acid at room temperature. This salt was extremely difficult to purify, however, readily decomposing to deep blue solutions when dissolved in water. The best sample was obtained by dissolving in warm water, adding 2 drops of 2*N* hydrochloric acid, and then adding several volumes of acetone to precipitate bluish prisms, m.p. 265–267° dec. (cap.).

Anal. Calcd. for $C_{13}H_{15}ClN_2O_3$: Cl, 12.54; N, 9.91. Found: Cl, 12.23; N, 9.44.

The presence of the intact indolizine ring system in X was also shown by conversion to the known compound, *1,3-dinitroindolizine*.[6] A suspension of 0.50 g. of 3-acetyl-1-indolizinealanine (X) in 5 ml. of glacial acetic acid was treated cautiously with 3 ml. of concd. nitric acid (sp. gr. 1.42). The clear, dark yellow solution was heated on the steam bath for 1 hr., evaporated *in vacuo* until most of the acetic acid was removed, and then treated with 7 ml. of water. The bright yellow precipitate (0.1 g.) was isolated by suction filtration and washed with water. Recrystallization of this material (m.p. 230–231°) from Methyl Cellosolve gave yellow leaflets, m.p. 232–233°. A mixed melting point with an authentic sample of 1,3-dinitroindolizine[5] (m.p. 234–235°) was undepressed. Scholtz[6] reported m.p. 229° for this material.

1-Indolizinealanine (XI). 3-Acetyl-1-indolizinealanine (X) (11.4 g.; 0.0432 mole) was mixed with 115 ml. of 10% hydrochloric acid and heated under reflux for 20 hr. (nitrogen atmosphere). The deep blue solution was cooled, neutralized to *p*H 8–9 with ammonium hydroxide with cooling, and evaporated the solution (now dark yellow) to a small volume *in vacuo*. After chilling to 5°, the pale yellow solid was isolated by suction filtration and washed thoroughly with ice water to remove ammonium chloride. The solid thus obtained weighed 6.41 g. (72.9%), m.p. (cap.) 233–235° (dec.). This material was very difficult to handle, since it quickly turned deep bluish green upon exposure to the air and light. Attempts to recrystallize the material from water gave only blue solutions from which the amino acid was difficult to recover.

This compound is best characterized and purified as the *dihydrochloride* salt. Two-tenths gram was dissolved in a minimum quantity of warm water and 10 drops of concentrated hydrochloric acid added. The deep green solution was treated with 6 volumes of absolute ethanol, and the precipitated solid purified by reprecipitation from dilute hydrochloric acid with ethanol. The dihydrochloride was thus obtained as bluish green prisms, m.p. (cap.) 240–243° dec.

Anal. Calcd. for $C_{11}H_{14}Cl_2N_2O_2$: C, 47.66; H, 5.09; Cl, 25.58. Found: C, 47.41; H, 5.14; Cl, 25.28.

Compound XI gave strongly positive tests with both acidic *p*-dimethylaminobenzaldehyde and potassium iodate, indicating an unsubstituted 1 or 3 position.[10] The ultraviolet spectrum was typical of that of a simple alkyl-substituted indolizine,[3] showing maxima at 296, 285, and 233 mμ in neutral or basic solutions, with a shift in acid to maxima at 307 and 235 mμ with strong end absorption. The infrared spectrum (Nujol mull) was that of a typical α-amino acid.

Acknowledgment. The authors are indebted to Mr. E. F. Shelberg and his staff for the microanalyses, to Mr. F. Chadde for the ultraviolet absorption spectra, and to Mr. W. Washburn and his staff for the infrared absorption spectra.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Chemistry of Pyrazine and Its Derivatives. IV. The Alkylation and Arylation of Methylpyrazine[1]

JOHN D. BEHUN[2] AND ROBERT LEVINE

Received February 24, 1961

Methylpyrazine has been alkylated at its side chain with a series of alkyl halides and benzyl chloride and arylated with bromobenzene using the sodium amide-liquid ammonia method. It has also been alkylated with benzyl alcohol using potassium hydroxide as the condensing agent. The alkylpyrazines have been reduced to 2-alkylpiperazines, which have been converted to the corresponding bis(benzenesulfonamides).

In the earlier papers in this series, we reported that pyrazylmethylsodium, prepared from methylpyrazine and sodium amide in liquid ammonia, can be acylated with a series of esters to give a variety of pyrazylmethyl ketones,[3] $PzCH_2COR$, and condensed with several aldehydes and ketones to give the corresponding pyrazylmethylcarbinols, $PzCH_2C(OH)RR'$.[4]

(1) This work was performed under Contract No. AT-(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(2) This paper is based on part of the thesis presented by J. D. Behun to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

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

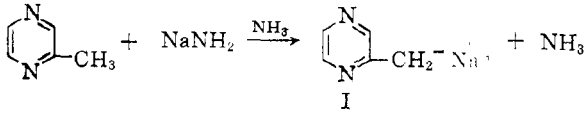
TABLE I

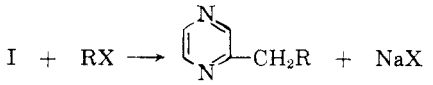
ALKYL PYRAZINES, $C_4H_3N_2CH_2R$, BY ALKYLATING METHYLPYRAZINE WITH ALKYL HALIDES, RX

R	Yield, %	B.P.	Mm.	n_D^{25}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_2H_5	78.7	172–174		1.4909	$C_7H_{10}N_2$	68.52	68.09	8.22	8.40
n-C_3H_7	71.7	90–92	20	1.4822	$C_8H_{12}N_2$	70.53	70.31	8.88	8.74
i-C_3H_7	77.6	67–70	10	1.4849	$C_8H_{12}N_2$	70.53	70.52	8.88	8.82
n-C_4H_9	78.5	94–96	11	1.4855	$C_9H_{14}N_2$	71.96	72.36	9.39	9.36
i-C_4H_9	81.0	90–93	12	1.4843	$C_9H_{14}N_2$	71.96	72.23	9.39	9.34
n-C_5H_{11}	68.0	104–106	12	1.4838	$C_{10}H_{16}N_2$	73.11	73.50	9.82	9.90
$CH_2CH_2N(CH_3)_2$[a]	44.2	80–82	2	1.4968	$C_9H_{15}N_3$	65.42	65.68	9.15	9.45
$C_6H_5CH_2$[a]	57.0[b]	118–121	2	1.5673	$C_{12}H_{12}N_2$	78.22	78.66	6.57	6.62

[a] The alkyl halide is a chloride. In all other cases bromides were used. [b] In addition 23% of the dialkylated product, 2-(1,3-diphenyl-2-propyl)pyrazine, b.p. 180–184° at 2 mm. and m.p. 65.2–66.2° (from petroleum ether, b.p. 60–70°), was obtained. *Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61. Found: C, 83.22; H, 6.63.

In the present paper we report the results of a study of the alkylation and phenylation of pyrazylmethylsodium. The over-all reactions are shown in the following scheme.





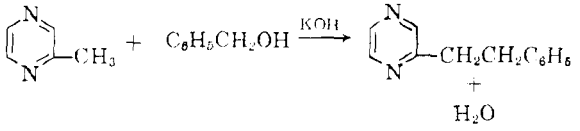
I + RX → + NaX

II

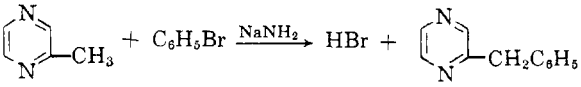
R = alkyl or phenyl

The results are found in Table I. It may be seen that good yields, 44–81% of monoalkylated products were obtained in all cases. In order to minimize the formation of dialkylated materials, an excess of pyrazylmethylsodium over alkyl halide was employed. Thus, a 2:2:1 molar ratio of methylpyrazine–sodium amide–halide was used. In spite of these conditions, small amounts of higher boiling materials, presumably the dialkylated products, were produced in some reactions. Only in the alkylation of pyrazylmethylsodium with benzyl chloride was enough higher boiling material obtained in a sufficiently high state or purity so that it could be subjected to elemental analysis.

As Abramoff and Sprinzak[5] reported the alkylation of the isomeric picolines with benzyl alcohol, it was of interest to determine whether methylpyrazine could be alkylated by a similar procedure. Thus, a 41.5% yield of 2-phenethylpyrazine[6] was obtained from the interaction of methylpyrazine with benzyl alcohol using potassium hydroxide as the condensing agent. By the sodium amide–liquid ammonia method (Table I), methylpyrazine was alkylated with benzyl chloride to give a mixture of 2-phenethylpyrazine (57%) and 2-(1,3-diphenyl-2-propyl)pyrazine (23%).



Pyrazylmethylsodium was also phenylated[7] by reaction with benzyne, in liquid ammonia, to give a 53% yield of benzylpyrazine.



Apparently only one of the compounds listed in Table I, viz., *n*-butylpyrazine, was prepared previously. Thus, Klein and Spoerri[8] treated the difficultly obtainable pyrazine with *n*-butyllithium in ether at −20° and obtained a 10.4% yield of *n*-butylpyrazine as compared with the 71.7% yield which was obtained in the present study by the alkylation of the commercially available methylpyrazine with *n*-propyl bromide. Therefore, the present method appears to be the best which is currently available for the synthesis of 2-alkylpyrazines.

Attempts to prepare picrates, cresolates and styphnates of the alkylated pyrazines failed. However, all the monoalkylated products could be reduced readily to the corresponding piperazines, III, by means of sodium in alcohol or by low pressure hydrogenation over palladium on charcoal (Table II). With the exception of 2-phenethylpiperazine, all the piperazines were very hygroscopic materials which were converted to their stable bisbenzene-

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

(5) M. Abramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 4090 (1956).

(6) This reaction was performed by J. D. Behun at Wyandotte Chemicals Corp., Wyandotte, Mich.

(7) Apparently the bromobenzene is dehydrohalogenated to benzyne, which then reacts with the anion of methylpyrazine. This experiment was performed by Dr. W. W. Leake. For related work on the use of benzyne as a synthetic intermediate, see (a) W. W. Leake and R. Levine, *J. Am. Chem. Soc.*, **81**, 1169 (1959). (b) W. W. Leake and R. Levine, *J. Am. Chem. Soc.*, **81**, 1627 (1959).

(8) B. Klein and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 2949 (1951).

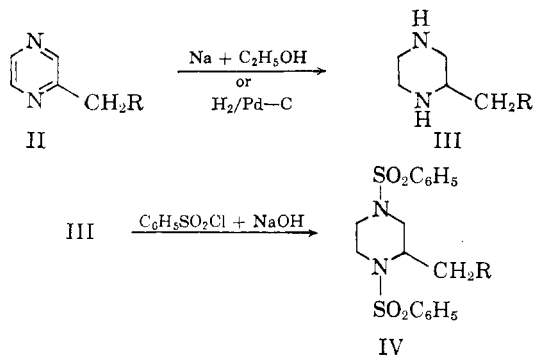
TABLE II

2-ALKYLPIPERAZINES, $C_4H_9N_2CH_2R$-2 AND THEIR BIS(BENZENESULFONAMIDES)

R	Yield, %	Method	B.P.	Mm.	Bis(benzenesulfonamides) M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_2H_5	61.3	A[a]	122–124	90	128.4–129.2[b]	$C_{19}H_{24}N_2O_4S_2$	55.86	55.95	5.92	5.73
n-C_3H_7	62.0	B[c]	90–93	15	120.0–120.6	$C_{20}H_{26}N_2O_4S_2$	56.85	56.64	6.21	5.80
i-C_3H_7	66.3	B	82–84	6	155.6–156.0	$C_{20}H_{26}N_2O_4S_2$	56.85	56.85	6.21	5.80
n-C_4H_9	86.1	A	115–118	12	93.8–94.8	$C_{21}H_{28}N_2O_4S_2$	57.77	57.92	6.46	6.51
i-C_4H_9	82.0	A	96–100	12	123.4–124.0	$C_{21}H_{28}N_2O_4S_2$	57.77	57.79	6.46	6.46
n-C_5H_{11}	83.0	B	95–98	6	97.2–97.8	$C_{22}H_{30}N_2O_4S_2$	58.64	58.91	6.71	6.83
$CH_2CH_2N(CH_3)_2$	69.0	A	103–107	3	123.2–124.0	$C_{21}H_{29}N_3O_4S_2$	55.86	56.05	6.47	6.16
$C_6H_5CH_2$	47.8	A	120–124 101.2–101.8 (m.p.)[d]	1.5	148.6–149.6	$C_{24}H_{26}N_2O_4S_2$	61.39	61.46	5.37	5.29

[a] Prepared from the corresponding pyrazine by sodium in ethanol reduction. [b] All the bis(benzenesulfonamides) were recrystallized from an ethanol-water mixture. [c] Prepared from the corresponding pyrazine by reduction with hydrogen over a palladium on charcoal catalyst. [d] Recrystallized from petroleum ether (b.p. 60–70°). *Anal.* Calcd. for $C_{12}H_{18}N_2$: C, 76.37; H, 9.53. Found: C, 76.00; H, 9.23.

sulfonamides, IV, by the Hinsberg reaction.[9] The nonhygroscopic 2-phenethylpiperazine was readily recrystallized and identified as such.



EXPERIMENTAL[10]

In this section the syntheses of four compounds are described: a typical alkylpyrazine, a typical 2-alkylpiperazine, benzylpyrazine, and 2-phenylethylpyrazine.

Preparation of n-butylpyrazine and 2-n-butylpiperazine. To 0.4 mole of sodium amide[11] in 400 ml. of anhydrous liquid ammonia contained in a 1-l., three neck, round bottom flask, equipped with a stirrer, Dry Ice condenser and dropping funnel, was added 37.6 g. (0.4 mole) of methylpyrazine. The blood-red solution of pyrazylmethylsodium which resulted was stirred for 0.5 hr. to ensure complete conversion of the methylpyrazine to its anion. Then, n-propyl bromide (24.6 g., 0.2 mole), diluted with an equal volume of anhydrous ether, was added over a 20-min. period and the mixture was stirred for an additional hour. The reaction was quenched by the addition of 25 g. of solid ammonium chloride. The Dry Ice condenser was replaced by a water-cooled condenser and the ammonia was replaced by ether. The mixture was heated on a steam bath until the ether started to reflux. The resulting solution was poured onto ice, was made strongly acidic with concentrated hydrochloric acid and was extracted with several portions of ether. The aqueous phase was made basic with sodium hydroxide and was extracted with several portions of chloroform.

Distillation of the chloroform and ether extracts gave 19.5 g. (71.7%) of n-butylpyrazine, b.p. 90–92° at 20 mm. A tarry, non-distillable residue (4.0 g.) remained in the distillation flask.

n-Butylpyrazine (6.8 g., 0.05 mole), dissolved in 150 ml. of 95% ethanol, was treated with hydrogen over a palladium on charcoal catalyst in a Parr hydrogenator at 3–4 atm. and gave on distillation 4.4 g. (62.0%) of 2-n-butylpiperazine, b.p. 90–93° at 15 mm. The bisbenzenesulfonamide of this hygroscopic compound was formed in essentially quantitative yield and melted at 120.0–120.6° after recrystallization from an ethanol-water mixture.

In those reactions where the alkylpyrazine was reduced to the 2-alkylpiperazine by sodium in alcohol the following procedure was used. The alkylpyrazine (0.04 mole) was dissolved in 200 ml. of absolute ethanol. Sodium (0.4 mole, 9.2 g.) was added in the form of small cubes over a 1-hr. period and the mixture was stirred an additional half-hour. The mixture was poured onto ice, was extracted with chloroform, and was processed in the regular manner.

Preparation of benzylpyrazine. Using the Two Flask Method, which was described previously[12] for the phenylation of other active hydrogen compounds, the interaction of sodium amide (1.0 mole), methylpyrazine (0.5 mole, 47.0 g.) and bromobenzene (0.25 mole, 39.3 g.) gave 22.4 g. (52.5%) of benzylpyrazine, b.p. 107–108° at 1.3 mm. and 6.0 g. (19.5%) of what may be benzhydrylpyrazine (b.p. 172–175° at 1.3 mm., m.p. 106–107° from 95% ethanol) although this compound did not give a satisfactory analysis.

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.99. Found: C, 77.52; H, 6.03.

Preparation of 2-phenethylpyrazine. Methylpyrazine (10 ml.), benzyl alcohol (110 ml.) and potassium hydroxide (11.2 g.) were placed in a 250-ml., one neck, round bottom flask and the mixture was refluxed for 24 hr. The reaction mixture was allowed to cool to room temperature, 200 ml. of water was added, and the mixture was extracted with several portions of chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate, the solvent was removed at atmospheric pressure and the residue was distilled to give 8.1 g. (41.5%) of 2-phenethylpyrazine, b.p. 110–117° at 2 mm.; 2.5 g. (10.3%) of what is probably predominantly 2-(1,3-diphenyl-2-propyl)pyrazine, b.p. 170–

(9) S. M. McElvain, *Characterization of Organic Compounds*, Macmillan, New York, 1953, p. 174.

(10) The methylpyrazine used in this study was supplied through the courtesy of Wyandotte Chemicals Corp.

(11) S. R. Harris and R. Levine, *J. Am. Chem. Soc.*, **70**, 3360 (1948).

(12) See ref. 7a.

200° at 2 mm. and 1.0 g. of tarry residue. On redistillation, the 2-phenethyl-pyrazine boiled at 118–121° at 2 mm. A sample of this material was reduced by treatment with sodium in ethanol to 2-phenethylpiperazine, m.p. 101–102° after recrystallization from petroleum ether (b.p. 60–70°) (see Table II).

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT, AGRICULTURAL DIVISION, AMERICAN CYANAMID CO.

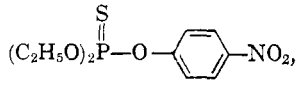
Synthesis of Pyridazinyl-Substituted Phosphorothioate Esters

SHIRLEY DU BREUIL

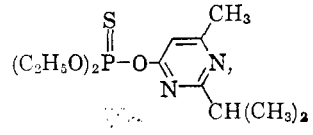
Received January 4, 1960

A series of insecticidally active dialkyl pyridazinyl phosphates and phosphorothioates was prepared by the reaction of the appropriate phosphorochloridate with hydroxypyridazinones.

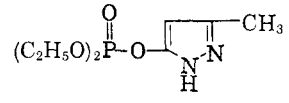
Since the introduction of parathion,



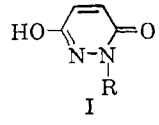
as a potent broad-spectrum insecticide, there have appeared a variety of other phosphate insecticides prepared from compounds containing an acidic or enolizable hydrogen atom. Of particular interest have been derivatives of nitrogen-containing heterocycles such as Diazinon[1] *O,O*-diethyl *O*-(2-isopropyl-6-methyl-4-pyrimidyl) phosphorothioate;[1a]



and Pyrazoxon[1] diethyl 3-methyl-5-pyrazolyl phosphate,[2]

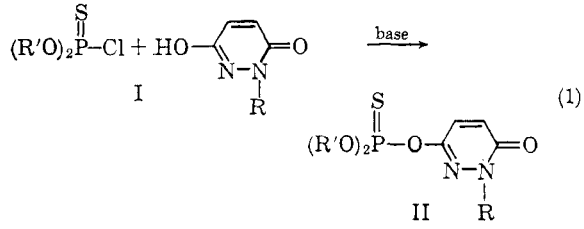


In our laboratories, interest has centered on the derivatives of 6-hydroxy-3(2*H*)-pyridazinone, more commonly known as maleic hydrazide (I, R = H):



I

I(R = H) is a difficultly soluble, high melting monobasic acid which has pK_a 7.6 in 90% ethanol (5.7 in water[3]). Substitution at the (2*H*) position by alkyl or aryl groups does not affect the acidity appreciably, but the solubility in organic solvents is improved. As expected, these compounds react similarly to phenols with *O,O*-dialkyl phosphorochloridothioates (equation 1):



(1)

The products obtained are usually crystalline solids, soluble in organic solvents other than the paraffinic hydrocarbons, and essentially insoluble in water. When R = H, the phosphorothioates are weakly acidic (pK_a 10–11 in 90% ethanol), and they may be recovered in fair yield upon acidification of an alkaline solution.

Generally the *O,O*-dialkyl *O*-pyridazinyl phosphorothioates (II) were prepared according to equation 1, using anhydrous sodium carbonate as the base in *N,N*-dimethylformamide (DMF) or 1-methyl-2-pyrrolidone (NMP). In some cases the preformed sodium salts of I were used, and, in fact, these were preferred for those pyridazinones having pK_a values of 8.5 or higher in 90% ethanol. Reactions conducted in acetone, methyl isobutyl ketone, or toluene were not successful, possibly due to the extreme insolubility of the starting heterocycles. Dioxane and tetrahydrofuran appeared to dissolve small amounts of maleic hydrazide, but the desired products were not isolated from reactions conducted in these solvents. Reactions utilizing *O,O*-dimethyl phosphorochloridothioate (equation 1, R′ = CH_3), were conducted in water with an equivalent of potassium or sodium hydroxide, since in dimethylformamide or 1-methyl-2-pyrrdidone this phosphorochloridothioate reacted preferentially and violently with the solvents. It is possible that higher homologs also reacted with the solvents to some extent, and this competing reaction may account in part for the low yields obtained in many of the preparations.[4]

(1) Registered Trademark of J. R. Geigy A.-G.

(1)(a) H. Gysin and A. Margot, U. S. Patent **2,754,243**, July 10, 1956 (to J. R. Geigy A.-G.).

(2) H. Gysin and A. Margot, U. S. Patent **2,754,244**, July 10, 1956 (to J. R. Geigy A.-G.).

(3) A. Albert and J. N. Philips, *J. Chem. Soc.*, 1294 (1956).