(0.10 mole) of potassium thiocyanate in 260 ml. of ethanol maintained at 65°. The mixture was heated to a boil for a brief time, and then cooled to 50°, filtered, and the filtrate concentrated to 100 ml. After charcoal treatment and cooling, the product along with some potassium bromide separated. The solid was collected by filtration and washed with water. The residual material was then recrystallized from ethanol to give 1.1 g. (47%) of product melting at 81–83°.

*Anal.* Calcd. for $C_7H_4N_2O_4S$: C, 39.63; H, 1.90; N, 13.21. Found: C, 39.75; H, 2.14; N, 13.44.

*4-(5-Nitro-2-furyl)thiazol-2-one* (XI). A solution of 11 g. (0.052 mole) of thiocyanomethyl 5-nitro-2-furyl ketone and 50 ml. of concentrated sulfuric acid was prepared at −10° and allowed to stand at 0° for 2 days. At the end of this time the solution was poured into ice water and the precipitated product collected by filtration. When dry, this material melted with decomposition at 223–226° and weighed 10.5 g. (95%). Crystallization from ethanol gave bright yellow-orange crystals, m.p. 225–227° with decomposition, with a 40% recovery.

*Anal.* Calcd. for $C_7H_4N_2O_4S$: C, 39.63; H, 1.90; N, 13.21. Found: C, 39.71; H, 2.02; N, 13.05.

*2-Chloro-4-(5-nitro-2-furyl)thiazole* (XII). A solution of 0.25 g. (0.0012 mole) of thiocyanomethyl 5-nitro-2-furyl ketone in 70 ml. of diethyl ether was cooled to 5° and hydrogen chloride bubbled through in a slow stream. After 30 min. the solution was concentrated to 15 ml. and cooled. The product which separated was collected by filtration. Recrystallization from ether gave 0.10 g. (36%) of yellow powder, m.p. 164–166°. Recrystallization from ethanol did not raise the melting point.

*Anal.* Calcd. for $C_7H_3ClN_2O_3S$: C, 36.45; H, 1.31; Cl, 15.38; N, 12.15. Found: C, 36.46; H, 1.56; Cl, 15.24; N, 12.07.

(12) Supplied by the Mallinckrodt Chemical Works, St. Louis, Mo.

[CONTRIBUTION NO. 1113 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

# Chemistry of Pyrazine and Its Derivatives. V. Acylation and Alkylation of 2,6-Dimethylpyrazine and Certain Other Pyrazine Derivatives[1]

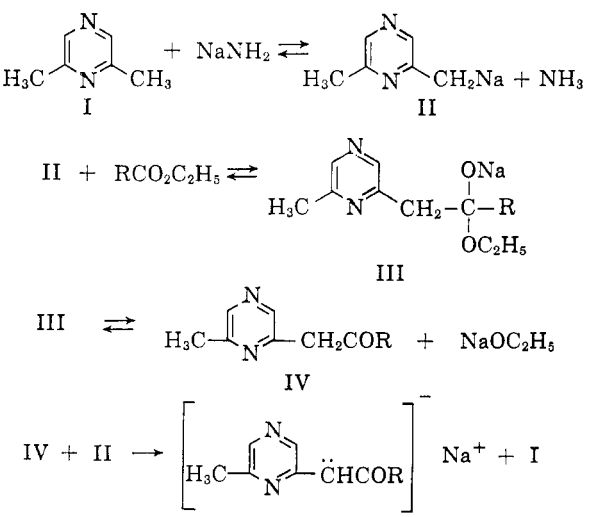
MARWAN R. KAMAL[2] AND ROBERT LEVINE

*Received September 29, 1961*

Sodium amide in liquid ammonia was used to effect the metalation of the side chains of 2,6-dimethylpyrazine and 1-pyrazyl-3-dimethylaminopropane. The metallated intermediates were condensed with aliphatic, aromatic, and heterocyclic esters to yield the corresponding ketones. In addition, several alkyl halides and benzyl chloride were condensed with 2-methyl-6-pyrazylmethylsodium leading to the corresponding 2-methyl-6-alkylpyrazines and 2-methyl-6-phenylethylpyrazine, respectively, in good yields. Phenacylpyrazine was also alkylated with β-dimethylaminoethyl chloride to give only the *O*-alkylated product, the enol ether [(1-phenyl-2-pyrazyl)-1-ethenyl]2-dimethylaminoethyl ether.

It has been previously established in these and other laboratories, that the side chains of methylpyrazine and 2,5-dimethylpyrazine are active centers in acid and base effected reactions. Thus Franke[3] has shown that the methyl groups of 2,5-dimethylpyrazine react with aromatic aldehydes using zinc chloride as a catalyst. In the previous papers of this series it was reported that methylpyrazine can be acylated by the reaction[4] of its sodio derivative with esters to give the corresponding pyrazylmethyl ketones, $PzCH_2COR$. Sodium amide in liquid ammonia was shown to be an effective condensing agent for such acylations while phenyllithium did not lead to any appreciable metalation of the side chain, in spite of its usefulness in the metalation of the side chain of 2-picoline.[5,6]

In the present study we have found that the side chain of 2,6-dimethylpyrazine can be effectively metalated by using the sodium amide–liquid ammonia method to yield 2-methyl-6-pyrazyl methyl ketones. The molar ratio of the reactants used was 2:2:1, *i.e.*, two equivalents of 2,6-dimethylpyrazine: two equivalents of sodium amide: one equivalent of ester. This condensation can be pictured by the following sequence of reactions.



(1) This work was supported by a grant from Wyandotte Chemicals Corp.

(2) This paper is based on part of a thesis presented by M. R. Kamal to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

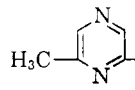
(3) R. Franke, *Ber.*, **38**, 3724 (1905).

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

(5) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 430 (1951).

(6) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

TABLE I

2-METHYL-6-PYRAZYLMETHYL KETONES,  , BY ACYLATING 2,6-DIMETHYLPYRAZINE WITH ESTERS[a] IN THE PRESENCE OF SODIUM AMIDE

| R | Yield, % | M.P. or B.P. | Mm. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| $C_6H_5$[b] | 53.5 | 50–52 | | $C_{13}H_{12}N_2O$ | 73.56 | 73.29 | 5.70 | 5.98 |
| $p$-$CH_3OC_6H_4$[c] | 83.6 | 72–73 | | $C_{14}H_{14}N_2O_2$ | 69.40 | 69.88 | 5.82 | 5.90 |
| $o$-$ClC_6H_4$[c] | 70.0 | 78–79 | | $C_{13}H_{11}N_2OCl$ | 63.29 | 63.27 | 4.49 | 4.53 |
| 4-$C_5H_4N$[d,e] | 72.7 | 133.6–134.6 | | $C_{12}H_{11}N_3O$ | 67.59 | 67.70 | 5.21 | 5.63 |
| 2-$C_4H_3O$[c,f] | 71.5 | 75–76 | | $C_{11}H_{10}N_2O_2$ | 65.33 | 65.40 | 4.98 | 5.15 |
| 2-$C_4H_3S$[g,h] | 62.0 | 80–81 | | $C_{11}H_{10}N_2OS$ | 60.53 | 60.37 | 4.62 | 4.53 |
| $CH_3$ | 17.4[i] | 50–52 | 4.5 | $C_8H_{10}N_2O$ | 63.98 | 64.01 | 6.75 | 6.83 |
| $C_2H_5$ | 58.5 | 106–108 | 4 | $C_9H_{12}N_2O$ | 65.82 | 65.58 | 7.37 | 7.48 |
| $n$-$C_3H_7$ | 65.6 | 115–116 | 5 | $C_{10}H_{14}N_2O$ | 67.38 | 67.11 | 7.92 | 8.17 |
| $i$-$C_3H_7$ | 82.5 | 109–109.5 | 4 | $C_{10}H_{14}N_2O$ | 67.38 | 67.19 | 7.92 | 8.08 |
| $t$-$C_4H_9$ | 80.5 | 114–115 | 4 | $C_{11}H_{16}N_2O$ | 68.72 | 69.25 | 8.39 | 8.53 |
| | | | | Derivatives | | | | |
| Oxime[j] | | 160–161 | | $C_{13}H_{13}N_3O$ | 68.70 | 68.92 | 5.77 | 5.95 |
| Oxime[j] | | 128–129 | | $C_{14}H_{15}N_3O_2$ | 65.35 | 65.80 | 5.88 | 6.09 |
| 2,4-D[h,k] | | 159–160 | | $C_{19}H_{15}N_6O_4Cl$ | 53.70 | 53.94 | 3.54 | 3.71 |
| Oxime[c] | | 144–145 | | $C_{12}H_{12}N_4O$ | 63.14 | 63.40 | 5.31 | 5.31 |
| Oxime[c] | | 153–154 | | $C_{11}H_{11}N_3O_2$ | 60.82 | 60.31 | 5.11 | 5.22 |
| 2,4-D[h,k] | | 220–221 | | $C_{17}H_{14}N_6O_4S$ | 51.23 | 51.35 | 3.54 | 3.83 |
| 2,4-D[c,k] | | 144–145 | | $C_{14}H_{14}N_6O_4$ | 50.90 | 51.10 | 4.27 | 4.60 |
| 2,4-D[c,k] | | 104–105 | | $C_{15}H_{16}N_6O_4$ | 52.32 | 52.41 | 4.68 | 4.67 |
| Oxime[c] | | 117–118 | | $C_{10}H_{15}N_3O$ | 62.10 | 61.89 | 7.82 | 7.71 |
| 2,4-D[c,k] | | 105–106 | | $C_{16}H_{18}N_6O_4$ | 53.60 | 53.86 | 4.75 | 4.89 |
| Oxime[c] | | 93.2–94 | | $C_{11}H_{17}N_3O$ | 63.74 | 64.01 | 8.27 | 8.39 |

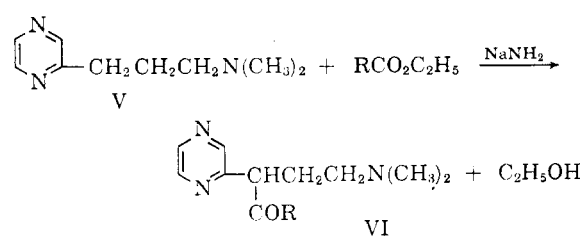
[a] All esters were ethyl esters except methyl isonicotinate and methyl propionate. [b] Recrystallized from an ether-pentane mixture. [c] Recrystallized from ethanol-water mixture. [d] 4-$C_4H_4N$ = 4-pyridyl radical. [e] Recrystallized from a benzene–petroleum ether (b.p. 60–70°) mixture. [f] 2-$C_4H_3O$ = 2-furyl radical. [g] 2-$C_4H_3S$ = 2-thienyl radical. [h] Recrystallized from 95% ethanol. [i] Ethylacetoacetate (5.5%) was also isolated, b.p. 50–52° at 4.5 mm. and forms a copper chelate, m.p. 192–193° alone and when mixed with an authentic sample. [j] Recrystallized from methanol. [k] 2,4-D = 2,4-dinitrophenylhydrazone.

It can be seen from the above scheme why a molar ratio of 2:2:1 of the reactants is required to obtain high yields of ketones. Actually it was demonstrated previously in these laboratories[4] that when methylpyrazine, sodium amide, and methyl benzoate were allowed to react in equivalent quantities, a 48.4% yield of the ketone was obtained. However, when these reagents were allowed to react in the molar ratio of 2:2:1, the yield of the ketone was almost doubled to 94.6%. This is also consistent with the results in the acylation of tar bases.[7]

The results of the acylation of 2,6-dimethylpyrazine with aromatic, heterocyclic and aliphatic esters are summarized in Table I. With the exception of the condensation of 2,6-dimethylpyrazine with ethyl acetate to yield the 2-methyl-6-acetonylpyrazine (17.4%), the yields appear to be good. The self-condensation of ethyl acetate to form ethyl acetoacetate and also the possibility of acetamide formation may well be the reasons for the low yield of the ketone obtained. Such side reactions as the self-condensation of the ester and the formation of an amide from the acylation of ketones with esters when sodium amide is used as the condensing agent have been observed earlier.[8,9]

Carbinol formation was observed as a side reaction when 2,6-lutidine was acylated with aliphatic esters using phenyllithium as the condensing agent. In the present investigation in which 2,6-dimethylpyrazine was condensed with aliphatic esters using sodium amide in liquid ammonia as the condensing agent, no carbinols were isolated.

The acylation of 1-pyrazyl-3-dimethylaminopropane, V, was also effected with four representative esters to give ketones of the type VI, by using



V VI

(7) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **77**, 4926 (1955).

(8) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **VIII**, 62 (1954).

(9) C. R. Hauser, R. Levine, and R. J. Kibler, *J. Am. Chem. Soc.*, **68**, 26 (1946).

TABLE II

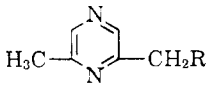
ACYLATION OF $C_4H_3N_2(CH_2)_3N(CH_3)_2$[a] (V) TO GIVE KETONES $C_4H_3N_2CH(COR)(CH_2)_2N(CH_3)_2$ (VI)

| R | Yield, % | M.P. or B.P. °C | Mm. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| $C_6H_5$[b,c,d] | 99.5 | 51.4–52 | | $C_{16}H_{19}N_3O$ | 71.35 | 71.28 | 7.11 | 7.30 |
| 4-$C_5H_4N$[b,c,e] | 89.5 | 60–61 | | $C_{15}H_{18}N_4O$ | 66.64 | 66.41 | 6.71 | 6.89 |
| $CH_3$[f] | 16.4 | 103–106 | 0.6 | $C_{11}H_{17}N_3O$ | 63.74 | 63.31 | 8.27 | 8.33 |
| $i$-$C_3H_7$[f] | 81.5 | 123–124 | 2.0 | $C_{13}H_{21}N_3O$ | 66.35 | 65.82 | 9.00 | 9.38 |

[a] Prepared by the alkylation of methylpyrazine with β-dimethylaminoethyl chloride using sodium amide as condensing agent. (J. D. Behun and R. Levine, *J. Org. Chem.*, **26**, 3379 (1961). [b] The methyl esters were used. [c] Recrystallized from pentane. [d] Formed picrate, m.p. 143.8–144.6° (from methanol). *Anal.* Calcd. for $C_{22}H_{22}N_6O_8$: C, 53.01; H, 4.45. Found: C, 53.04; H, 5.00. [e] 4-$C_5H_4N$ = 4-pyridyl radical. [f] Ethyl esters were used.

TABLE III

ALKYLATION OF 2,6-DIMETHYLPYRAZINE WITH ALKYL HALIDES RX TO GIVE 2-METHYL-6-ALKYLPYRAZINES



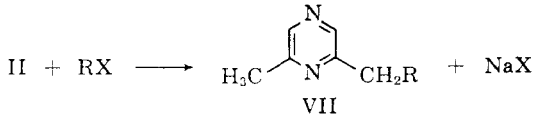
| Compound | R | Yield, % | B.P. or M.P., °C. | Mm. | $n^{25}D$ | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | $C_2H_5$ | 54.9 | 186–187 | 739 | 1.4898 | $C_8H_{12}N_2$ | 70.54 | 70.39 | 8.88 | 9.21 |
| 2. | $n$-$C_3H_7$ | 68.4 | 105–108 | 22 | 1.4888 | $C_9H_{14}N_2$ | 71.95 | 72.05 | 9.39 | 9.58 |
| 3. | $i$-$C_3H_7$ | 69.3 | 57–58 | 2.3 | 1.4853 | $C_9H_{14}N_2$ | 71.95 | 71.83 | 9.39 | 9.37 |
| 4. | $n$-$C_4H_9$ | 81.5 | 82–84 | 4 | 1.4865 | $C_{10}H_{16}N_2$ | 73.12 | 73.18 | 9.82 | 9.87 |
| 5. | $i$-$C_4H_9$ | 98.5 | 98–100 | 12 | 1.4855 | $C_{10}H_{16}N_2$ | 73.12 | 73.62 | 9.82 | 10.11 |
| 6. | $n$-$C_5H_{11}$ | 85.3 | 88–89 | 2.3 | 1.4840 | $C_{11}H_{18}N_2$ | 73.94 | 74.11 | 10.13 | 10.17 |
| 7. | $CH_2C_6H_5$[a] | 72.6 | 118–121 | 1.5 | 1.5622 | $C_{13}H_{14}N_2$ | 78.75 | 78.44 | 7.12 | 7.15 |
| 8. | $CH_2CH_2N(CH_3)_2$[a,b] | 77.5 | 90–91 | 2.3 | 1.4968 | $C_{10}H_{17}N_3$ | 67.00 | 66.72 | 9.56 | 9.71 |
| 9. | $C_3H_3$[c] | 45.0 | 103–104 | 12 | 1.5205 | $C_9H_{10}N_2$ | 73.94 | 73.82 | 6.84 | 7.14 |
| | | | Picrates | | | | | | | |
| 1a. | | | 94.0–94.6[d] | | | $C_{14}H_{15}N_5O_7$ | | | | |
| 2a. | | | 97.4–97.8[d] | | | $C_{15}H_{17}N_5O_7$ | 47.49 | 47.71 | 4.52 | 4.63 |
| 3a. | | | 88.8–89.6[d] | | | $C_{15}H_{17}N_5O_7$ | 47.49 | 47.33 | 4.52 | 4.72 |
| 4a. | | | 92.4–93.2[e] | | | $C_{16}H_{19}N_5O_7$ | 48.85 | 48.94 | 4.87 | 5.03 |
| 5a. | | | 117.5–118.5[d] | | | $C_{16}H_{19}N_5O_7$ | 48.85 | 49.03 | 4.87 | 4.94 |
| 6a. | | | 90.8–91.6[d] | | | $C_{17}H_{21}N_5O_7$ | 50.12 | 50.36 | 5.12 | 5.48 |
| 7a. | | | 126.8–128[e] | | | $C_{19}H_{17}N_5O_7$ | 53.41 | 53.93 | 4.01 | 4.01 |
| 8a. | | | 142.6–143.4[e,f] | | | $C_{22}H_{23}N_9O_{14}$ | 41.67 | 41.45 | 3.81 | 3.64 |
| 9a. | | | 89.8–91.8[d] | | | $C_{15}H_{13}N_5O_7$ | 48.00 | 48.28 | 3.49 | 3.46 |

[a] Alkyl halide was the chloride; in all other cases bromides were used. [b] $CH_2CH_2N(CH_3)_2$ = β-dimethylaminoethyl radical. [c] $C_3H_3$ = propargyl radical. [d] Recrystallized from methanol. Picrate 1a, *Anal.* Calcd. for $C_{14}H_{15}N_5O_7$: N, 19.17. Found: N, 19.09. [e] Recrystallized from ethanol. [f] Dipicrate; all others are monopicrates.

the same procedure as for the condensation of 2,6-dimethylpyrazine.

As can be seen from Table II, the yields of the ketones are good with the exception of the case where ethyl acetate was the condensing ester, which is consistent with the above results for the acylation of 2,6-dimethylpyrazine. The molar ratio of the reactants employed was again 2:2:1, *i.e.*, two equivalents of the alkylpyrazine, two equivalents of sodium amide and one equivalent of ester. Compounds of the type VI have been previously reported in the pyridine series. Sperber[10] condensed 2-phenacylpyridine with β-dimethylaminoethyl chloride to obtain the ketone, 2-$C_5H_4NCH(COC_6H_5)(CH_2)_2N(CH_3)_2$ in a 19% yield. More recently[11] the acylation of 1-(2-pyridyl)-3-dimethylaminopropane with several esters to give corresponding ketones was effected in high yields using phenylsodium in benzene and/or phenyllithium in ether as the condensing agents.

We next studied the alkylation of 2-methylpyrazylmethylsodium, II, as a route to the synthesis of 2-methyl-6-alkylpyrazines, VII. These results are summarized in Table III.

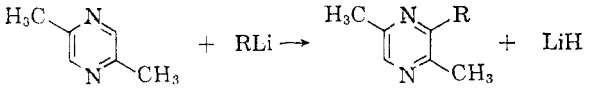


VII

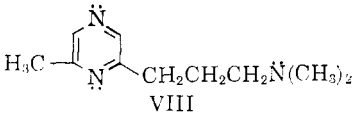
(10) N. Sperber, R. Fricano, and D. Papa, *J. Am. Chem. Soc.*, **72**, 3069 (1950).

(11) S. Raynolds and R. Levine, *J. Am. Chem. Soc.*, **82**, 1152 (1960).

While sodium amide in liquid ammonia appears to be an effective metalating agent for the side chain of methylpyrazine[12] and 2,6-dimethylpyrazine, alkyl- and aryllithium compounds do not lead to metallation of the side chains of these compounds. Thus, Klein and Spoerri[13,14] reported that when 2,5-dimethylpyrazine was treated with alkyl- or phenyllithium, ring substitution rather than side chain metalation was effected.



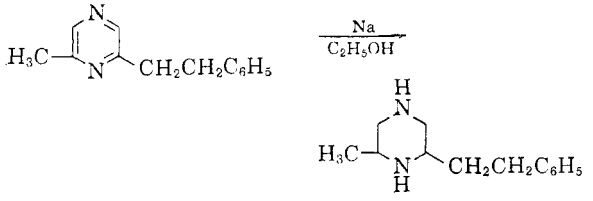
Although the 2-alkylpyrazines which were synthesized from methylpyrazine[12] did not form the customary tar base derivatives, *i.e.* picrates, cresolates, and styphnates, we have been able to prepare monopicrates from the 2-methyl-6-alkylpyrazines. These picrates were generally low melting compounds. The compound 2-methyl-6-(3-dimethylamino-1-propyl)pyrazine, VIII, formed a



VIII

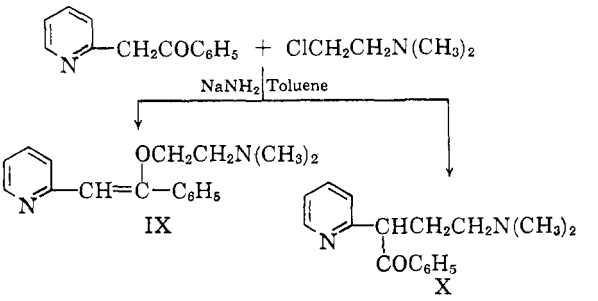
high melting dipicrate unlike the others which formed monopicrates. This is due presumably to the presence of the highly basic nitrogen atom of the dimethylamino group.

The compound 2-methyl-6-(2-phenylethyl)pyrazine was easily reduced to the corresponding piperazine in 41.3% yield using sodium and alcohol as the reducing system.



The piperazine formed a high melting dipicrate (m.p. 248–249°).

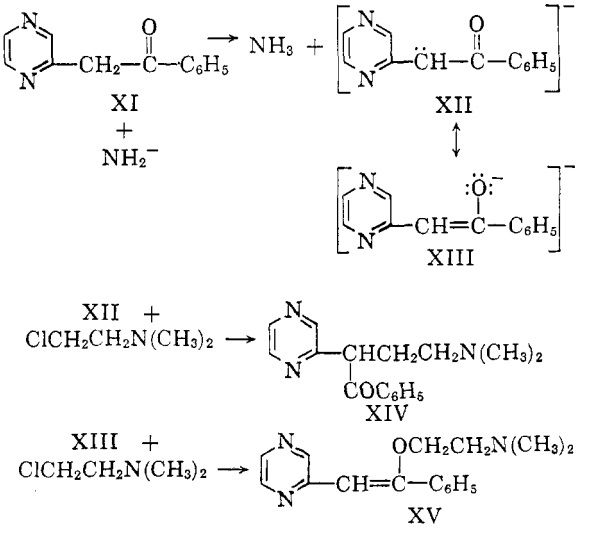
Although the alkylation of 2-phenacylpyridine with β-dimethylaminoethyl chloride has been reported previously, there has been some question concerning the nature of product(s). Sperber, Fricano, and Papa[10] claim that a mixture of two products was obtained from the sodium amide-effected alkylation of phenacylpyridine with β-dimethylaminoethyl chloride. The major product was the *O*-alkylated product, IX, (65.0%) and the minor product was the C-alkylated compound X (19%).



Beckett and Kerridge[15] claimed that using the above conditions, only the *O*-alkylated product IX was obtained.

We have attempted the alkylation of phenacylpyrazine XI, with β-dimethylaminoethyl chloride under a variety of conditions. In each case the anion of phenacylpyrazine was formed first by the reaction of one equivalent of phenacylpyrazine with one equivalent of sodium amide in liquid ammonia. Then, in the runs where solvents other than ammonia were used, the ammonia was replaced before the addition of one equivalent of β-dimethylaminoethyl chloride. When the condensation was attempted using liquid ammonia as the solvent no reaction occurred even after allowing twelve hours for the condensation. Benzene was also tried as a solvent, but again the phenacylpyrazine was recovered. Using toluene as a solvent and refluxing the reaction mixture for 33 hours, a 40% yield of alkylated product was obtained.

A possible scheme for this alkylation follows.



Earlier in this paper we discussed the synthesis of XIV and related compounds by the condensation of 1-pyrazyl-3-dimethylaminopropane with esters. The product obtained from alkylation of phenacylpyrazine did not seem to contain any of the ketone, XIV. When the alkylation product was hydrolyzed with concentrated sulfuric acid, phen-

(12) J. D. Behun, *J. Org. Chem.*, **26**, 3379 (1961).

(13) B. Klein and P. E. Spoerri, *J. Am. Chem. Soc.*, **72**, 1844 (1950).

(14) B. Klein and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 2949 (1959).

(15) A. H. Beckett and K. A. Kerridge, *J. Chem. Soc.*, 2948–51 (1954).

acylpyrazine was obtained. Only the enol ether XV would be expected to undergo cleavage under these conditions to yield phenacylpyrazine.

$$\text{XV} \xrightarrow{\text{concd. } H_2SO_4} \underset{73.2\%}{\text{XI}} + HO(CH_2)_2N(CH_3)_2$$

Thus, it appears that only the enol ether XV was produced. The formation of only XV may indicate the operation of a steric factor, since the existence of β-dimethylaminoethyl chloride in the bulky cationic form, XVI, is known.[16]

$$ClCH_2CH_2N(CH_3)_2 \rightleftharpoons \left[\begin{array}{c} H_3C \quad CH_3 \\ \diagdown \; \diagup \\ N \\ \diagup \; \diagdown \\ CH_2{-}CH_2 \end{array}\right]^+ Cl^-$$

XVI

## EXPERIMENTAL[17]

*1. Synthesis of 2-methyl-6-phenylethylpyrazine as an example of the procedure used in the acylation and alkylation of 2,6-dimethylpyrazine.* The alkylation was performed in a 1-l., three-neck, round-bottom flask which was equipped with a slip-sealed stirrer, a Dry Ice condenser and a dropping funnel. To sodium amide[18] (0.5 mole) in 500 ml. of commercial anhydrous liquid ammonia was added 0.5 mole (54.0 g.) of 2,6-dimethylpyrazine dissolved in 50 ml. of anhydrous ether over a 15-min. period and then the reaction mixture was stirred for another 0.5 hr. Benzyl chloride (0.25 mole, 31.7 g.), mixed with an equal volume of dry ether, was added to the deep red-colored reaction mixture over a 20-min. period. The reaction mixture was then stirred for an additional hour, after which it was quenched by the slow addition of 30 g. of ammonium chloride. After replacing the ammonia with ether, the reaction mixture was poured onto ice, acidified with concentrated hydrochloric acid, and then extracted with several portions of ether. The aqueous phase was made basic with dilute sodium hydroxide and was extracted with several portions of chloroform.

From the distillation of the ether and chloroform extracts, there was obtained 38.5 g. (72.6%) of 2-methyl-6-(2-phenylethyl)pyrazine, b.p. 118–121° at 1.5 mm.

*2. Reduction of 2-methyl-6-(2-phenylethyl)pyrazine.* To 7.5 g. (0.038 mole) of 2-methyl-6-(2-phenylethyl)pyrazine dissolved in 100 ml. of absolute ethanol was added 8.0 g. (0.348 mole) of sodium over a period of 5 hr. The reaction mixture was poured onto ice after cooling it to room temperature. Then, it was made basic with dilute sodium hydroxide, and extracted with chloroform. From the chloroform extracts there was obtained 3.2 g. (41.3%) of 2-methyl-6-(2-phenylethyl)piperazine, m.p. 84.8–85.4° after recrystallization from petroleum ether (b.p. 60–70°).

*Anal.* Calcd. for $C_{22}H_{23}N_9O_{14}$: C, 41.67; H, 3.81. Found: C, 41.45; H, 3.64.

*3. Alkylation of phenacylpyrazine with β-dimethylaminoethyl chloride.* To sodium amide[18] (0.075 mole) in 100 ml. of anhydrous liquid ammonia was added 14.9 g. (0.075 mole) of phenacylpyrazine (prepared from the sodium amide-effected acylation of methylpyrazine with ethyl benzoate.)[19] The deep red-colored reaction mixture was stirred for 0.5 hr. The liquid ammonia was replaced by 100 ml. of anhydrous toluene. After all the ammonia was replaced, a yellow solid separated. A toluene solution of β-dimethylaminoethyl chloride (0.075 mole), prepared from β-dimethylaminoethyl chloride hydrochloride (0.075 mole, 10.8 g.) was added to the reaction mixture. The reaction mixture was refluxed for 33 hr., after which most of the yellow solid appeared to have gone into solution. The reaction mixture was cooled to room temperature and several milliliters of absolute ethanol were added. Then the reaction mixture was poured over ice and processed in the regular manner. There was obtained 8.1 g. (40%) of the enol ether, [(1-phenyl-2-pyrazyl)-1-ethenyl]-2-dimethylaminoethyl ether, b.p. 161–165° at 0.6 mm.

*Anal.* Calcd. for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11. Found: C, 70.86; H, 7.17.

*4. Acid cleavage of [(1-phenyl-2-pyrazyl)-1-ethenyl]-2-dimethylaminoethyl ether.* The enol ether (0.018 mole, 5.0 g.) was heated with 25 ml. of concentrated sulfuric acid for 1 hr. on a steam bath. The mixture was cooled to room temperature and was then poured onto ice. A solid separated which weighed 2.6 g. (73.2%) m.p. 80–82° alone and when mixed with an authentic sample of phenacylpyrazine.

PITTSBURGH 13, PA.

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(17) The methylpyrazine and 2,6-dimethylpyrazine used in this study was supplied through the courtesy of Wyandotte Chemicals Corp.

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