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The Chemistry of Pyrazine and its Derivatives. II. The Acylation of Methylpyrazine[1]

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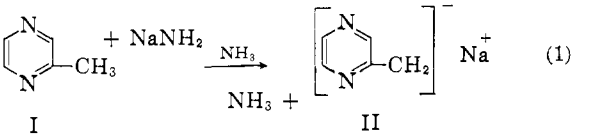
The reactions of pyrazylmethylsodium, prepared from methylpyrazine and sodium amide in liquid ammonia, with a series of aliphatic, aromatic and heterocyclic esters are described. While in most cases pyrazyl methyl ketones were the only products and were obtained in high yields, the acylation of pyrazylmethylsodium with methyl picolinate gave a mixture of 2-pyridyl pyrazylmethyl ketone (42.6%) and 2-pyridyl-bis-(pyrazylmethyl)-carbinol (22.8%) and its acylation with ethyl formate gave only bis-(pyrazylmethyl)-carbinol (48.7%).

As part of an extensive study of the chemistry of pyrazine and its derivatives, we have prepared a series of ketones containing the pyrazylmethyl group. Since the methyl group of methylpyrazine is bonded to a carbon atom which is *ortho* to one of its nitrogen atoms and *meta* to the other, it appeared that the methyl group might have properties similar to those which are exhibited by 2- and/or 3-picoline.

In previous papers from these and other laboratories, it was reported that the side chain of 2-picoline can be metalated by reaction with phenyllithium[3,4] and sodium amide.[5] Furthermore, although the lateral metalation of 3-picoline can be effected by potassium amide[6] it fails with phenyllithium.[6] The metallic derivatives thus obtained may be acylated with esters to give the corresponding 2- and 3-picolyl ketones.

In the present study it was found that the side chain of methylpyrazine is not appreciably metalated by phenyllithium since the interaction of methylpyrazine with an ethereal solution of phenyllithium followed by the addition of methyl benzoate gave a mixture of a very low yield (4%) of phenacylpyrazine, triphenylcarbinol (9%) and a large amount of an intractable tar. In this connection, it is of interest to note that Klein and Spoerri[7] treated 2,5-dimethylpyrazine with methyllithium with subsequent addition of propionaldehyde and obtained a 44.4% yield of the azomethine addition product, 2,3,5-trimethylpyrazine, and none of the carbinol, 1-(2-methyl-5-pyrazyl)-butanol-2, which would have been formed if the 2,5-dimethylpyrazine had undergone lateral metalation when treated with methyllithium.

Next, methylpyrazine (two equivalents) was treated with lithium amide, sodium amide and potassium amide (two equivalents) in liquid ammonia followed by the addition of methyl benzoate (one equivalent). From these reactions, 95.5, 94.6 and 92.2% yields, respectively, of phenacylpyrazine were obtained.[8] However, when a 1:1:1 molar ratio of methylpyrazine:sodium amide:ester was used, the yield of phenacylpyrazine dropped to 48.4% based on the ester. These results suggest that the course of the reaction may be represented by the scheme shown, which is analogous to that which was suggested by Goldberg and Levine[4,9] for the acylation of tar bases. This scheme rationalizes the fact that a 2:2:1 molar ratio of methylpyrazine:sodium amide:ester is required to give a maximum yield of product.



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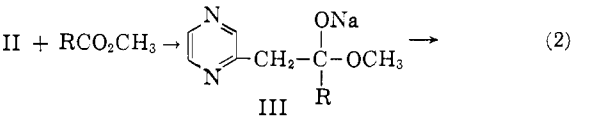

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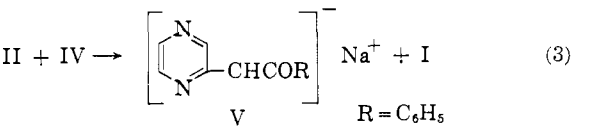

V $R = C_6H_5$ (3)

It is of interest to note that previously[6] only a 38.2% yield of 3-phenacylpyridine was isolated from the interaction of a 2:2:1 molar ratio of 3-picoline:potassium amide:methyl benzoate. Thus, it can be seen that although similar conditions are needed to effect the lateral metalation of 3-picoline and methylpyrazine, metalation of the latter compound proceeds more readily. These results support the conclusion that the activation of the methyl group of 3-picoline can occur only by an inductive effect[10] whereas the methyl group of methylpyrazine can be activated inductively by the *meta* nitrogen atom and by resonance with the adjacent azomethine linkage. Therefore, methylpyrazine appears to have some of the characteristics of 3-picoline since it is metalated extensively only by specific reagents, and some of the characteristics of 2-picoline since its metallic derivatives may be acylated in high yields.[3]

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

(3) N. N. Goldberg, L. B. Barkley and R. Levine, THIS JOURNAL, **73**, 430 (1951).

(4) N. N. Goldberg and R. Levine, *ibid.*, **74**, 5217 (1952)

(5) M. J. Weiss and C. R. Hauser, *ibid.*, **71**, 2033 (1949).

(6) A. D. Miller, C. Osuch, N. N. Goldberg and R. Levine, *ibid.*, **78**, 674 (1956).

(7) B. Klein and P. E. Spoerri, *ibid.*, **72**, 1844 (1950).

(8) It was not possible to prepare phenacylpyrazine when methylpyrazine (two equivalents) was added to lithium amide or sodium amide (two equivalents) suspended in ether followed by the addition of methyl benzoate (one equivalent).

(9) N. N. Goldberg and R. Levine, THIS JOURNAL, **77**, 4926 (1955).

(10) H. C. Brown and W. A. Murphey, *ibid.*, **73**, 3308 (1951).

TABLE I

PYRAZYLMETHYL KETONES, $C_4H_3N_2CH_2COR$, BY ACYLATING METHYLPYRAZINE WITH ESTERS[a] IN THE PRESENCE OF SODIUM AMIDE

R	Yield, %	M.p. or b.p. °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_6H_5[b]	94.6	82.0–83.0[k]		$C_{12}H_{10}N_2O$	72.71	72.22	5.09	4.83
p-$CH_3OC_6H_4$	98.5	78.6–79.5[l]		$C_{13}H_{12}N_2O_2$	68.41	68.48	5.30	5.27
p-ClC_6H_4	90.7	91.0–92.0[l]		$C_{12}H_9N_2OCl$	61.95	61.55	3.90	3.68
2-C_5H_4N[b,c]	42.6[f]	87.0–87.6[m]		$C_{11}H_9N_3O$	66.31	66.35	4.55	4.38
3-C_5H_4N[c]	70.3	129.2–130.0[l]				66.20		4.13
4-C_5H_4N[c]	80.5	142.2–142.8[n]				66.14		4.42
2-C_4H_3O[b,d]	63.7	65.5–66.4[l]		$C_{10}H_8N_2O_2$	63.81	64.13	4.29	4.00
2-C_4H_3S[b,e]	76.5	56.0–56.8[l]		$C_{10}H_8N_2OS$	58.80	58.94	3.95	3.59
CH_3[b]	36.3[g]	113.0–114.0	9	$C_7H_8N_2O$	61.74	61.31	5.92	6.21
C_2H_5	58.5	111.0–112.0	6	$C_8H_{10}N_2O$	63.97	64.35	6.71	7.05
n-C_3H_7	61.0[h]	121.5–122.0	6	$C_9H_{12}N_2O$	65.83	65.62	7.37	7.26
i-C_3H_7[b]	71.0[i]	115.0–116.0	6			65.79		7.35
n-C_4H_9	63.5[j]	130.0–130.5	6	$C_{10}H_{14}N_2O$	67.39	66.86	7.94	8.40
t-C_4H_9[b]	78.0	114.0–114.5	5			67.05		7.52
			Derivatives					
2,4-D[o,p]		180.5–182.0		$C_{18}H_{14}N_6O_4$	57.26	56.91	3.73	3.58
Semicarbazone[p]		175.2–175.8		$C_{13}H_{13}N_5O$	61.45	61.38	5.13	5.16
Oxime[p]		133.6–134.2		$C_{12}H_{11}N_3O$	67.44	67.81	5.20	5.14
2,4-D[o]		187.0–187.5		$C_{19}H_{16}N_6O_5$	55.87	56.20	3.95	4.03
2,4-D[o]		215.0–216.0		$C_{18}H_{13}N_6O_4Cl$	52.37	52.34	3.17	3.06
Picrate		166.0–167.0		$C_{17}H_{12}N_6O_8$	47.67	47.20	2.83	2.70
Picrate		209.0–210.0				47.20		2.65
Picrate		228.0–229.0				47.91		3.13
2,4-D[o]		205.0–206.0		$C_{16}H_{12}N_6O_5$	52.18	52.49	3.28	3.23
2,4-D[o]		213.0–214.0		$C_{16}H_{12}N_6O_4S$	49.99	50.00	3.14	2.91
2,4-D[o]		132.2–133.0		$C_{13}H_{12}N_6O_4$	49.37	49.21	3.83	3.68
2,4-D[o]		136.2–136.6		$C_{14}H_{14}N_6O_4$	50.91	51.15	4.27	4.32
Copper chelate		212.0–213.0		$C_{18}H_{22}N_4O_2Cu$[q]	55.44	54.81	5.69	5.25
2,4-D[o]		171.0–171.5		$C_{15}H_{16}N_6O_4$	52.31	52.16	4.68	4.33
Copper chelate		186.0–187.0		$C_{20}H_{26}N_4O_2Cu$	57.46	57.30	6.27	5.80
2,4-D[o]		166.0–166.6		$C_{16}H_{18}N_6O_4$	53.62	54.07	5.06	4.62

[a] The aromatic and heterocyclic esters are methyl esters and the aliphatic are ethyl esters. [b] Time for forming methylpyrazine anion is 30 minutes; in reactions not so marked, the anion time is two hours. [c] 2-, 3- and 4-C_5H_4N represent the 2-, 3- and 4-pyridyl radicals. [d] 2-C_4H_3O = 2-furyl radical. [e] 2-C_4H_3S = 2-thienyl radical. [f] In addition, 22.8% of 2-pyridyl-bis-(pyrazylmethyl)-carbinol was obtained. [g] Ethyl acetoacetate (11%) also was obtained. [h] n-Butyramide (2.3%, m.p. 115.0–116.0° alone and when mixed with an authentic sample) also was obtained. [i] Isobutyramide (12.2%, m.p. 126.5–127.0° alone and when mixed with an authentic sample) also was obtained. [j] A trace of n-valeramide, m.p. 103.0–105.0°, also was obtained. [k] This melting point was obtained by dissolving the material in 20% aqueous sodium hydroxide and reprecipitating it with dilute hydrochloric acid at a pH of 7. [l] Recrystallized from an ethanol–water mixture. [m] Recrystallized from an ether–petroleum ether (60–70°) mixture. [n] Recrystallized from a benzene–petroleum ether (60–70°) mixture. [o] 2,4-D = 2,4-dinitrophenylhydrazone. [p] These three derivatives were prepared from the ketone where R = C_6H_5. [q] Calcd.: Cu, 16.30. Found: Cu, 16.25.

The results of the acylation of methylpyrazine with a series of aromatic and heterocyclic esters are found in Table I. It can be seen that in all of these acylations, high yields of only pyrazyl methyl ketones, $PzCH_2COR$ (Pz = pyrazyl radical), were obtained except in the acylation with methyl picolinate. In this case, a mixture of 2-pyridyl pyrazylmethyl ketone (42.6%) and 2-pyridyl-bis-(pyrazylmethyl)-carbinol (22.8%) was obtained. At the present time, it is not clear why carbinol formation should occur only when the acylating ester is methyl picolinate. All that can be said with certainty is that the carbinol does not arise from the nucleophilic attack of II on the free ketone (equation 2, structure IV where R = the 2-pyridyl radical) but probably *via* a displacement reaction between II and III (R = the 2-pyridyl radical). In support of this argument it was found that the reaction of pyrazylmethyl 2-pyridyl ketone with the sodium derivative of methylpyrazine, II, resulted in the recovery of the ketone and none of the carbinol was obtained.

The acylation of pyrazylmethylsodium with a series of aliphatic esters was studied next. These results also appear in Table I. It can be seen that in most of these cases only ketones were isolated and that the yield of ketone *increases* rather than *decreases* with increasing size and complexity of the ester.

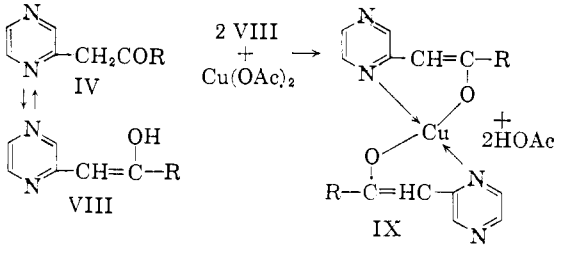
However, the observed results can be rationalized in the following manner. When ethyl n-butyrate, ethyl isobutyrate and ethyl n-valerate were used as acylating esters, small amounts of the corresponding amides were isolated. Also, when ethyl acetate was used as the acylating ester, some acetoacetic ester was obtained. The extent to which the side reactions of amide and β-ketoester formation occur should be reflected on the yield of the desired pyrazylmethyl ketones, *i.e.*, the greater the extent to which these side reactions occur, the less ester

will be available for acylating the pyrazylmethyl sodium and the lower will be the yield of the pyrazylmethyl ketone. It is apparent that these side reactions should be less important as the complexity of the acid portion of the ester is increased and hence it is not too surprising that the yield of the ketone is thereby increased.

That the size of the alkyl group in the alkoxy portion of the acylating ester also has a marked effect on the yield of the ketone was shown by the facts that while the acylation of pyrazylmethylsodium with ethyl propionate gave a 58.6% yield of ethyl pyrazylmethyl ketone, the use of *t*-butyl propionate as the acylating ester gave only a 39.0% yield of ketone. Thus, the bulky *t*-butyl group apparently hinders the attack of the methylpyrazine anion on the carbonyl carbon atom of the ester.

In agreement with the results which were obtained in the acylation of pyrazylmethylsodium with methyl benzoate, the 61.0% yield of *n*-propyl pyrazylmethyl ketone, which was obtained with a 2:2:1 molar ratio of methylpyrazine:sodium amide:ethyl *n*-butyrate, dropped to 30.2% when a 1:1:1 molar ratio of reactants was used.

It was also found that the reaction of pyrazylmethylsodium with ethyl formate gave none of the expected pyrazylacetaldehyde. Instead, bis-(pyrazylmethyl)-carbinol was obtained in 48.7% yield. Apparently the initially-formed adduct VI between pyrazylmethylsodium (II) and ethyl formate reacts, as rapidly as it is formed, with more pyrazylmethylsodium to give the sodium derivative of the carbinol, VII. In this connection it is of interest to recall that an earlier attempt[11] to obtain pyrazylacetic acid by subjecting acetonylpyrazine to the haloform reaction gave none of the desired acid. Instead, a 35.8% yield of dichloromethylpyrazine was obtained.



Finally, it is of interest to note that the pyrazyl methyl ketones may be regarded as being structurally analogous to 1,3-diketones in which one of the carbonyl groups has been replaced by an azomethine linkage of the pyrazine ring. Hence, as shown below, it is not surprising that these ketones give an enol test (green color) when treated with alcoholic iron(III) chloride solution and react with copper(II) acetate to give copper chelates, IX. The analogous 2-picolyl ketones have been shown[3] to behave similarly.

(11) J. D. Behun and R. Levine, *J. Org. Chem.*, **23**, 406 (1958).

Experimental[12]

In this section four typical experiments are described.

Reaction of Methylpyrazine with Methyl Benzoate.—A typical procedure for the acylation of methylpyrazine with aromatic and heterocyclic esters (other than esters of the isomeric pyridine carboxylic acids) is given.

Methylpyrazine (0.4 mole, 37.6 g.) was added over a 20-minute period to a suspension of sodium amide in liquid ammonia, which was prepared from sodium (0.4 mole, 9.2 g.) and 350–400 ml. of anhydrous liquid ammonia. The resulting blood-red mixture was stirred for 30 minutes and then methyl benzoate (0.2 mole, 27.2 g.), diluted with an equal volume of anhydrous ether, was added over a 20-minute period. The mixture was stirred for one additional hour and then the reaction was quenched by the addition of solid ammonium chloride (25.0 g.). The ammonia was replaced with 200 ml. of ether by warming the reactor on a steam-bath. When the liquid ammonia was completely displaced, as was indicated by the refluxing of the ether, the reaction mixture was poured onto ice and was made strongly acidic with concentrated hydrochloric acid. Filtering the solid which was present at this point gave 37.5 g. (94.6%) of crude phenacylpyrazine. A sharp melting product, m.p. 82.0–83.0°, was obtained quantitatively by dissolving the material in 20% aqueous sodium hydroxide solution and reprecipitating it with dilute hydrochloric acid at a *p*H of 7.

Reaction of Methylpyrazine with Methyl Picolinate.—Sodium amide (0.4 mole), prepared as described above, was allowed to react with methylpyrazine (0.4 mole, 37.6 g.) and methyl picolinate (0.2 mole, 27.4 g.). The reaction was processed as described in the last experiment through the addition of the ammonium chloride and pouring the mixture onto ice. The solid which was present was filtered to give 17.0 g. (42.6%) of 2-pyridyl pyrazylmethyl ketone, m.p. 87.0–87.6° [from ether–petroleum ether (60–70°)]. The filtrate was made basic with solid sodium carbonate, was extracted with several portions of chloroform and the combined chloroform extracts were distilled to remove the unreacted methylpyrazine. The semi-solid residue was extracted with an ether–petroleum ether (60–70°) mixture to give 13.4 g. (22.8%) of 2-pyridyl-bis-(pyrazylmethyl)-carbinol, m.p. 110.8–111.2° (from 60–70° petroleum ether).

Anal. Calcd. for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.14. Found: C, 65.40; H, 5.06.

This compound gave a picrate, m.p. 166.0–166.2° (from ether). *Anal.* Calcd. for $C_{22}H_{18}N_8O_8$: C, 50.58; H, 3.47. Found: C, 50.70; H, 3.61.

Reaction of Methylpyrazine with Ethyl Acetate.—A typical procedure for the acylation of methylpyrazine with an aliphatic ester is given.

To 0.8 mole of pyrazylmethylsodium, prepared as described above, ethyl acetate (0.4 mole, 35.2 g.), diluted with an equal volume of ether, was added. After the reaction was quenched by the addition of ammonium chloride and the liquid ammonia had been replaced by ether, the mixture was poured onto a slurry of ice and 50 ml. of concentrated hydrochloric acid and was extracted with several portions of ether. Distillation of the dried ether extracts gave 2.9 g. (11.1%) of ethyl acetoacetate, b.p. 92–109° at 77 mm. This material gave a copper chelate, m.p. 192–193° alone and when mixed with an authentic sample. The remaining aqueous solution was made basic with solid sodium carbonate, was salted out with sodium chloride and was extracted with several portions of chloroform. The combined extracts were distilled to give 19.7 g. (36.3%) of pyrazylacetone, b.p. 113–114° at 9 mm.

Reaction of Methylpyrazine with Ethyl Formate.—Sodium amide (0.3 mole) was allowed to react with methylpyrazine (0.3 mole, 28.2 g.) and ethyl formate (0.15 mole, 11.1 g.) and the mixture was processed as described in the last experiment to give 14.7 g. (48.7%) of bis-(pyrazylmethyl)-carbinol, m.p. 102.4–103.2° [from a benzene–petroleum ether (60–70°) mixture]. *Anal.* Calcd. for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.60. Found: C, 60.82; H, 5.34.

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(12) The methylpyrazine for this study was generously supplied by Wyandotte Chemicals Corp.