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The Chemistry of Pyrazine and its Derivatives. XI. The Participation of Tetramethylpyrazine in Alkylation and Aldol-type Reactions

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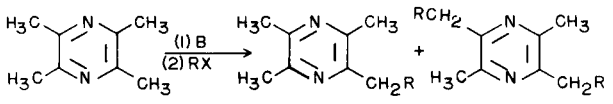
Using sodium amide and phenyllithium as the condensing agents, tetramethylpyrazine has been alkylated with several alkyl halides to give mixtures of alkyltrimethylpyrazines and what are believed to be 2,5-dialkyl-3,6-dimethylpyrazines. Evidence in support of the structures of the dialkylated compounds is presented for the case where the alkylating agent is *n*-butyl bromide. A number of carbinols have been prepared by the reaction of tetramethylpyrazine with aldehydes and ketones using phenyllithium as the condensing agent. One of these, 1-(trimethylpyrazyl)-2,4-dimethyl-2-pentanol has been dehydrated to 1-(trimethylpyrazyl)-2,4-dimethyl-1-pentene.

Earlier (2) it had been shown that one of the methyl groups of tetramethylpyrazine can be metalated by reaction with sodium amide in liquid ammonia or phenyllithium in ether and that the resulting alkali metal derivatives can be acylated with esters to give acylmethyltrimethylpyrazines.

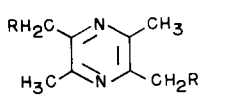
In the present paper we report the participation of tetramethylpyrazine in alkylation and aldol-type reactions. The results of the alkylations, which in all except one case were effected using a 1:1:1 molar ratio of tetramethylpyrazine to sodium amide or phenyllithium to alkyl halide, appear in Table I. Using this molar ratio mixtures of mono- and dialkylated products were isolated. However, when a 2:2:1 molar ratio of the pyrazine derivative to phenyllithium to *n*-butyl bromide was employed a high yield (82%) of only the monoalkylated product, *n*-amyltrimethylpyrazine was obtained.

While there is no doubt about the structures of the monoalkylated derivatives (I) the dialkylated compounds could have four isomeric structures. It will be shown later that the dialkylated products are probably 2,5-dialkyl-3,6-dimethylpyrazines (II). The overall reactions appear in the following equation.

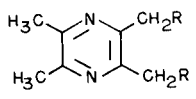


I II

B = $NaNH_2$ and C_6H_5Li

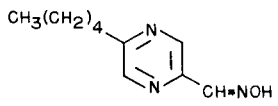


II

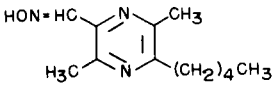


III

R = n-C_4H_9



IV

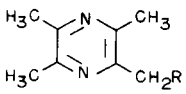
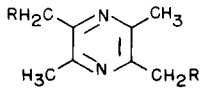


V

It was found that the dialkylated product (9.0%) which was obtained from a 1:1:1 molar ratio of tetramethylpyrazine to phenyllithium to *n*-butyl bromide is identical in its properties with the material (15%) obtained using sodium amide as the condensing agent and the product obtained in 44.4% yield from the alkylation of *n*-amyltrimethylpyrazine with *n*-butyl bromide. The absence of a methinyl hydrogen atom peak in the n.m.r. spectra of these three samples definitely indicates that dialkylation did not occur on the same carbon atom. Thus, the structure of the product may be described reasonably as a di-*n*-amyldimethylpyrazine.

This dialkylated product was shown to be a single compound since only one mono-*N*-oxide was obtained by treating it with an equimolar quantity of 30% hydrogen peroxide in glacial acetic acid (3). The n.m.r. spectrum of the *N*-oxide shows two different ring-methyl hydrogen singlet peaks (τ = 7.53 and 7.58 p.p.m.) with a ratio of integrated peak areas

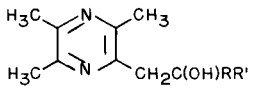
TABLE I

Alkyltrimethylpyrazines,  , and 2,5-Dialkyl-3,6-dimethylpyrazines, 

Compound	R	Yield % NaNH$_2$ I	Yield % NaNH$_2$ II	Yield % C_6H_5Li I	Yield % C_6H_5Li II	B.p. (mm.) or M.p. °C	n_D^{25}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	n-C_3H_7	47.5		45.0		65-66 (0.3)	1.4932	$C_{11}H_{18}N_2$	74.10	73.76	10.18	10.05
2		12.0		10.9		82-83 (0.3)	1.4880	$C_{14}H_{24}N_2$	76.30	76.51	10.98	11.03
3	i-C_3H_7	40.0		(a)		55-56 (0.7)	1.4934			73.81		10.08
4		19.0		(a)		74-75 (0.5)	1.4820			76.75		10.79
5	n-C_4H_9	45.6		52.0 (82.0) (b)		73-74 (0.6)	1.4926	$C_{12}H_{20}N_2$	74.95	74.76	10.48	10.15
6		15.0		9.0 (0) (b)		108-109 (0.6)	1.4875	$C_{16}H_{28}N_2$	77.36	77.60	11.36	11.11
7	i-C_4H_9	60.0		38.4		65-67 (0.4)	1.4902			75.00		10.50
8		10.8		12.5		96-98 (0.45)	1.4850			77.39		11.28
9	n-C_5H_{11}	13.1		60.0		92-94 (0.8)	1.4939	$C_{13}H_{22}N_2$	75.67	75.54	10.74	10.78
10		9.0		14.2		113-114 (0.3)	1.4863	$C_{18}H_{32}N_2$	78.20	78.42	11.67	11.65
11	$C_6H_5CH_2$ (e)	33.0		53.5		113 (0.45)	(c)	$C_{15}H_{18}N_2$	79.61	79.88	8.02	8.33
12		25.2		38.0		102-104 (d)		$C_{22}H_{24}N_2$	83.49	83.09	7.64	7.59
						Monopicrolonates (f)						
1a						122-123		$C_{21}H_{26}O_5N_6$	57.00	56.94	5.92	5.82
2a						120.5-121		$C_{24}H_{32}O_5N_6$	59.49	59.20	6.68	6.82
3a						114.8-115.2				57.13		5.62
4a						113-115				59.08		6.38
5a						132-133		$C_{22}H_{28}O_5N_6$	57.88	58.15	6.18	6.19
6a						120-122		$C_{26}H_{36}O_5N_6$	60.92	60.54	7.07	7.17
7a						119.5-120				57.74		6.27
8a						116-117				60.86		7.04
9a						144-144.5		$C_{23}H_{30}O_5N_6$	58.71	58.51	6.43	6.49
10a						110-111		$C_{28}H_{40}O_5N_6$	62.20	62.34	7.46	7.38
11a						133-135		$C_{25}H_{26}O_5N_6$	61.21	61.25	5.34	5.44
12a						145-145.5		$C_{32}H_{32}O_5N_6$	66.18	66.31	5.55	5.58

(a) This reaction was not performed with phenyllithium. (b) In this reaction a 2:2:1 molar ratio of tetramethylpyrazine to condensing agent to alkyl halide was used. In all other reactions a 1:1:1 molar ratio of reactants was employed. (c) Solidified when spread in a thin film. (d) Recrystallized from 60-70° petroleum ether. (e) This halide was the chloride, all the others were bromides. (f) Recrystallized from absolute ethanol.

TABLE II

Carbinols of the Type 

R	R'	Yield, %	B.p. (mm.) or M.p., °C	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	i-C_3H_7	33.6	96-97 (1.0)	$C_{12}H_{20}N_2O$	69.19	69.49	9.67	9.68
H	C_6H_5	50.8	126-127 (a)	$C_{15}H_{18}N_2O$ (b)	74.35	74.74	7.49	7.68
CH_3	CH_3	36.0	89-90 (1.0)	$C_{11}H_{18}N_2O$	68.01	68.17	9.34	9.60
CH_3	i-C_4H_9	58.0	109 (0.6)	$C_{14}H_{24}N_2O$	71.14	71.39	10.23	10.51
CH_3	C_6H_5	54.6	136-137 (0.7)	$C_{16}H_{20}N_2O$	74.96	74.66	7.86	7.57
n-C_3H_7	C_6H_5	57.8	158-160 (1.2)	$C_{18}H_{24}N_2O$	76.02	75.80	8.51	8.33
cyclohexanone		44.6	106-107 (0.6)	$C_{14}H_{22}N_2O$	71.75	71.68	9.47	9.25

(a) Recrystallized from ethyl ether. (b) This compound gave a urethane, m.p. 110-113°; *Anal.* Calcd. for $C_{22}H_{23}N_3O_2$: C, 73.10; H, 6.72. Found: C, 73.24; H, 6.93. None of the other compounds in this table could be converted to a urethane, a picrolonate or a picrate.

of the ring-methyl and ring-methylene hydrogen atoms to the other methyl and methylene hydrogen atoms of 10 to 18.6. This spectral evidence also indicates that in the formation of the di-*n*-amyldimethylpyrazine from the initially produced *n*-amyltrimethylpyrazine, the second *n*-butyl group is introduced neither onto the carbon atom carrying the first *n*-butyl group nor onto the carbon atom of the methyl group at the 6-position of the ring. Thus, the di-*n*-amyldimethylpyrazine appears to be either II or III.

Since in the formation of the di-*n*-amyldimethylpyrazine from the *n*-amyltrimethylpyrazine, the latter compound must be converted to its anion at one of the remaining three methyl groups and then this anion is alkylated, it was of importance to determine whether another reaction involving anion formation could be used to help in establishing the structure of the di-*n*-amyldimethylpyrazine.

Therefore, the oximation of *n*-amyltrimethylpyrazine was studied. The oximation of alkylated, heterocyclic nitrogen compounds has been investigated by several workers (4-7) by treating the anion of the heterocyclic compound with an alkyl nitrite. The results of Strem and Levine (7) are of particular interest in connection with the present study. They alkylated 2,5-dimethylpyrazine with a number of alkyl halides using sodium amide as the condensing agent to give 5-alkyl-2-methylpyrazines, which were converted to their anions with sodium amide and oximated with *n*-butyl nitrite to give, *e.g.*, 5-*n*-amyl-2-pyrazinecarboxaldehyde oxime (IV) as shown by n.m.r. spectral evidence. Thus, oximation occurred at the ring methyl group rather than at the ring methylene group of 5-*n*-amyl-2-methylpyrazine.

In the present study, the anion of *n*-amyltrimethylpyrazine was oximated with *n*-butyl nitrite to give a dimethyl-*n*-amylpyrazinecarboxaldehyde oxime. The n.m.r. spectrum did not establish the structure of the oxime since based on (1) the ratio of the integrated peak areas of the methyl and methylene hydrogen atoms (*alpha* to the ring) to those of the other methyl and methylene hydrogen atoms and (2) the presence of an aldoxime hydrogen atom peak, three isomeric structures are possible.

However, for the following reasons it appears that the oxime is 2-*n*-amyl-3,6-dimethyl-5-pyrazinecarboxaldehyde oxime (V). A comparison of the ultraviolet spectrum of V with that of IV indicates that oximation probably occurred at position five rather than on one of the methyl groups at positions three or six of I (R = *n*-C_4H_9). Oxime V showed maximum absorption at λ = 298 mμ and minimum absorption at λ = 268 mμ whereas oxime IV has maximum absorption at λ = 288 mμ and minimum absorption at λ = 268 mμ. Although it appears quite reasonable to assign V to the structure of the oxime of *n*-amyltrimethylpyrazine, it should be noted that this assignment is by no means completely rigorous since it is difficult to evaluate the relative steric and inductive effects of an adjacent alkyl group on the oximino pyrazine chromophore.

Since the methyl group at position five of an alkyltrimethylpyrazine appears to have greater prototropic activity than a methyl group at position three and six, it is not unreasonable to conclude that the di-*n*-amyldimethylpyrazine has structure II, *i.e.*, it is 2,5-di-*n*-amyl-3,6-dimethylpyrazine. By analogy, all the other dialkylated compounds which appear in Table I have been assumed to have structures similar to II.

In earlier reports from this laboratory, methylpyrazine (8) and 2,6-dimethylpyrazine (9) were shown to participate in aldol-type reactions with aldehydes and ketones to give carbinols using sodium amide in liquid ammonia as the condensing agent. This reaction has now been extended to the synthesis of a series of carbinols (Table II) by the reaction of tetramethylpyrazine with a series of aldehydes and ketones using phenyllithium as the condensing agent. One of these carbinols, 1-(trimethylpyrazyl)-2,4-dimethyl-2-pentanol was dehydrated to the substituted vinylpyrazine, 1-(trimethylpyrazyl)-2,4-dimethyl-1-pentene (81%) using iodine in refluxing toluene as the dehydrating agent. This method has been used earlier (10) for dehydrating other carbinols containing the pyrazine ring.

EXPERIMENTAL

Alkylation of Tetramethylpyrazine with *n*-Butyl Bromide. (a) Using Sodium Amide in Liquid Ammonia as the Condensing Agent.

To a freshly prepared suspension of sodium amide (from 2.3 g., 0.1 g. atom of sodium in 200 ml. of liquid ammonia), tetramethylpyrazine (13.6 g., 0.1 mole in an equal volume of anhydrous ether) was added and the mixture was stirred for 3 hours. Then, *n*-butyl bromide (13.7 g., 0.1 mole in an equal volume of dry ether) was added and the mixture was stirred for one hour. Ammonium chloride (5.5 g.) was added and the reaction mixture was processed as described earlier (2) for the acylation of tetramethylpyrazine to give recovered tetramethylpyrazine (4.1 g., 30.0%), *n*-amyltrimethylpyrazine (8.76 g., 45.6%, b.p. 73-74° at 0.6 mm.) and 2,5-di-*n*-amyl-3,6-dimethylpyrazine (3.7 g., 15%, b.p. 108-109° at 0.6 mm.). Although the structure of the dialkylated product is assumed at this point, it will be elucidated in the experiments which follow.

(b) Using Phenyllithium as the Condensing Agent.

To a cooled solution (ice bath) of phenyllithium (0.1 mole in 200 ml. of anhydrous ether, prepared from lithium ribbon (1.4 g., 0.2 g. atom) and bromobenzene (15.7 g., 0.1 mole), tetramethylpyrazine (13.6 g., 0.1 mole in an equal volume of anhydrous ether) was added and the solution was refluxed for three hours. Then, *n*-butyl bromide (13.7 g., 0.1 mole in an equal volume of ether) was added and the mixture was refluxed for one hour. Processing the reaction as described earlier (2) for the acylation of tetramethylpyrazine gave recovered tetramethylpyrazine (3.0 g., 22%), *n*-amyltrimethylpyrazine (10.2 g., 52%, b.p. 73-74° at 0.6 mm.) and 2,5-di-*n*-amyl-3,6-dimethylpyrazine (2.2 g., 9.0%, b.p. 108-109° at 0.6 mm.). When this reaction was repeated except that phenyllithium (0.2 mole), tetramethylpyrazine (0.2 mole) and *n*-butyl bromide (0.1 mole) were employed, there was obtained recovered tetramethylpyrazine (7.4 g., 54%) and *n*-amyltrimethylpyrazine (8.1 g., 82%, b.p. 88-89° at 1.0 mm. and 73-74° at 0.6 mm.).

Alkylation of *n*-Amyltrimethylpyrazine with *n*-Butyl Bromide.

A mixture of phenyllithium (0.05 mole) and *n*-amyltrimethylpyrazine (9.7 g., 0.05 mole) in 200 ml. of anhydrous ether was refluxed for 4 hours. Then, *n*-butyl bromide (6.9 g., 0.05 mole) in an equal volume of anhydrous ether was added, the mixture was refluxed for an additional hour and then processed in the regular manner to give

recovered *n*-amyltrimethylpyrazine (3.2 g., 33.0%, b.p. 90-95° at 1.3 mm.) and 2,5-di-*n*-amyl-3,6-dimethylpyrazine (5.5 g., 44.4%, b.p. 122-127° at 1.0 mm. and 108-109° at 0.6 mm.). The n.m.r. spectrum of the dialkylated material obtained in this and the first two experiments was determined in deuteriochloroform using tetramethylsilane as the internal standard. While these results do not

Group	τ p.p.m.	Integrated Peak Area
α-CH_2	7.36	4.0
α-CH_3	7.58	5.8
other-CH_2	8.58	12.08
terminal-CH_3	9.10	6.2

definitely establish the structure of the dialkylated product, they do show that the two *n*-butyl groups are not on the same carbon atom.

Preparation of 2,5-Di-*n*-amyl-3,6-dimethylpyrazine-mono-*N*-oxide.

The procedure used was modelled after that used by Klein and Berkowitz (3) for preparing other pyrazine-mono-*N*-oxides. A mixture of 2,5-di-*n*-amyl-3,6-dimethylpyrazine (1.22 g., 0.005 mole), 30% hydrogen peroxide (0.5 g., 0.0045 mole) and 30 ml. of glacial acetic acid was stirred and heated at 40-50° for 18 hours. About 75 ml. of water was added, the mixture was made basic with 20% sodium hydroxide and was extracted with several portions of chloroform. The solvent was removed at atmospheric pressure and the residue was distilled in vacuum to give recovered 2,5-di-*n*-amyl-3,6-dimethylpyrazine (300 mg., 24.6%, b.p. 108-111° at 0.5 mm.) and 2,5-di-*n*-amyl-3,6-dimethylpyrazine-mono-*N*-oxide (340 mg., 26%, b.p. 138-140° at 0.6 mm.).

Anal. Calcd. for $C_{16}H_{28}N_2O$: C, 72.68; H, 10.67. Found: C, 72.71; H, 10.60.

The infrared spectrum (liquid film without solvent) showed a band with strong intensity at 1330 cm^{-1} which is characteristic of the N⟶O stretching frequency in pyrazine-*N*-oxides (3). The ultraviolet spectrum taken in 95% ethanol shows three peaks at (1) 300 mμ (broad shoulder), (2) 277 mμ (broad band, medium absorption) and (3) 266 mμ (strong, maximum absorption). The n.m.r. spectrum of this *N*-oxide was taken in carbon tetrachloride using tetramethylsilane as the internal standard. These n.m.r. data show (1) that the two *n*-butyl

Group	p.p.m.	Integrated Peak Area
α-CH_2	7.25	10.0
α-CH_3	7.53 and 7.58	
other-CH_2	8.56	18.6
terminal-CH_3	9.10	

groups in the dialkylated *N*-oxide are not on the same carbon atom and (2) that the second *n*-butyl group is not located on the carbon atom of the methyl group which is bonded to the 6-position of the pyrazine ring.

Oximation of *n*-Amyltrimethylpyrazine.

n-Amyltrimethylpyrazine (10.0 g., 0.05 mole) was allowed to react with *n*-butyl nitrite (5.7 ml., 0.05 mole) in the presence of sodium amide (0.1 mole) in liquid ammonia using the procedure of Strem and Levine (7), which will be described in a future publication, to give recovered *n*-amyltrimethylpyrazine (3.8 g., 38%, b.p. 85-87° at 0.9 mm.) and 2-*n*-amyl-3,6-dimethyl-5-pyrazinecarboxaldehyde oxime, 2.2 g., 20.0%, m.p. 127-128.2° from 60-70° petroleum ether.

Anal. Calcd. for $C_{12}H_{19}N_3O$: C, 65.12; H, 8.65. Found: C, 64.81; H, 8.48.

The ultraviolet spectrum of this oxime taken in 95% ethanol showed two peaks at (1) 298 mμ (broad band, medium absorption) and 268 mμ. It is of importance to note that the ultraviolet spectrum of an authentic sample of 5-*n*-amyl-2-pyrazinecarboxaldehyde oxime in 95% ethanol showed peaks at 288 mμ (broad band, medium absorption) and at 268 mμ. Based on the data given in this and the two preceding experiments there is not much doubt that the structure of the di-*n*-butylated derivative of tetramethylpyrazine is 2,5-di-*n*-amyl-3,6-dimethylpyrazine.

Synthesis of 1-(Trimethylpyrazyl)-2,4-dimethyl-2-pentanol.

Phenyllithium (0.1 mole), tetramethylpyrazine (13.6 g., 0.1 mole) and methyl isobutyl ketone (10.0 g., 0.1 mole) were allowed to react as described above for the acylation of tetramethylpyrazine to give recovered tetramethylpyrazine (3.5 g., 25.8%) and 1-(trimethylpyrazyl)-2,4-dimethyl-2-pentanol, b.p. 109° at 0.6 mm., n_D^{25} 1.4963.

Dehydration of 1-(Trimethylpyrazyl)-2,4-dimethyl-2-pentanol.

A mixture of the carbinol (2.4 g., 0.01 mole), 50 ml. of toluene and iodine (0.3 g.) was refluxed for 16 hours and was then processed using the procedure employed (10) for similar dehydrations to give 1-(trimethylpyrazyl)-2,4-dimethyl-1-pentene, b.p. 115-119° at 2 mm.

Anal. Calcd. for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16. Found: C, 76.78; H, 9.82.

REFERENCES

(1) This paper is based on part of the thesis submitted by S.K.C. to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree. Part of this work was done under Contract AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(2) S. K. Chakrabartty and R. Levine, *J. Heterocyclic Chem.*, 1, 196 (1964).

(3) B. Klein and J. Berkowitz, *J. Am. Chem. Soc.*, 81, 5160 (1959).

(4) T. Kato and Y. Goto, *Chem. Pharm. Bull. (Japan)*, 11, 461 (1963).

(5) S. E. Forman, *J. Org. Chem.*, 29, 3323 (1964).

(6) C. Grundmann and V. Mini, *ibid.*, 29, 678 (1964).

(7) M. E. Strem and R. Levine, unpublished observations.

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

(9) M. R. Kamal and R. Levine, *J. Org. Chem.*, 27, 1360 (1962).

(10) M. R. Kamal, M. Neubert and R. Levine, *ibid.*, 27, 1363 (1962).

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