**Zinc–Acetic Acid Reduction of 32a.**—Activated zinc dust[39] (5.0 g, 77 mg-atoms) was added in portions to a solution of 913 mg (2.9 mmol) of **32a** in 30 ml of 50% aqueous acetic acid. The resulting mixture was then heated at 100° with vigorous stirring for 50 hr. At the end of this time, the residual zinc dust was filtered and washed with water. The filtrate was acidified with 3 ml of concentrated hydrochloric acid and was evaporated *in vacuo*. Upon treatment of the residue with excess 25% aqueous sodium hydroxide, an amine mixture was liberated. This was extracted into ether and the combined extracts were dried over anhydrous potassium carbonate. The ether was then removed by slow distillation through a 6-in. Vigreux column. Glpc analysis (80–200°) of the residual liquid demonstrated the presence of two major components, the retention times of which were found to be identical with those of authentic **2,2,3-trimethylpyrrolidine** (**33**) and **4-(N-benzyl-N-methylamino)-2-methyl-2-butanol** (**34**). Integration of the glpc trace indicated that the yields of the trimethylpyrrolidine and the amino alcohol were 94% and quantitative, respectively.[40] Small samples of both components were collected (70–200°). The infrared and nmr spectra of these compounds proved to be identical in all respects with those of authentic **33** and **34**.

**2,2,3-Trimethylpyrrolidine** (**33**) was prepared as described previously[1] by deoxygenation of nitrone **30a** with triphenylphosphine followed by lithium aluminum hydride reduction of the intermediate 4,5,5-trimethyl-$\Delta^1$-pyrroline.

**Methyl 3-(N-Benzyl-N-methylamino)propionate** (**35**).—A solution of 34.4 g (0.40 mol) of methyl acrylate and 52.0 g (0.43 mol) of benzylmethylamine in 150 ml of methanol was allowed to stand at room temperature for 9 days. The methanol was then removed *in vacuo* and the residue was distilled to yield 77.2 g (93%) of the amino ester as a clear colorless liquid: bp 73–75° (0.001 mm); $\nu_{max}^{film}$ 1745 cm$^{-1}$ (C=O); nmr (in $CDCl_3$), at $\tau$ 2.75 (s, $C_6H_5$), 6.40 (s, $CH_3$–O), 6.54 (s, $ArCH_2$–N), 7.41 ($A_2B_2$ system, C–$CH_2CH_2$–N), 7.85 (s, $CH_3$–N).

*Anal.* Calcd for $C_{12}N_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.57; H, 8.35; N, 6.90.

**4-(N-Benzyl-N-methylamino)-2-methyl-2-butanol** (**34**).—To 7.3 g (0.30 g-atom) of magnesium turnings under nitrogen was added a small portion of a solution of 45.5 g (0.32 mol) of methyl iodide in 150 ml of ether. As soon as a turbidity began to develop, stirring was started, and the initial vigorous reaction was moderated by cooling in an ice bath. The remainder of the methyl iodide solution was then added dropwise at a rate such that gentle reflux was maintained. The resulting solution was treated with an additional 50 ml of ether and was stirred for 1 hr at room temperature. A solution of 10.4 g (0.05 mol) of methyl 3-(N-benzyl-N-methylamino)propionate (**35**) in 100 ml of ether was then added dropwise with stirring. Following this addition, the mixture was heated under reflux for 5 hr. Work-up was effected by cooling the mixture in an ice bath and adding saturated aqueous ammonium chloride dropwise with stirring until the precipitate of magnesium salts became granular. The precipitate was filtered and washed thoroughly with ether. The filtrate was then dried over anhydrous potassium carbonate and evaporated *in vacuo*. Distillation of the residue through a 12-in. spinning-band column afforded 2.36 g (23%) of the amino alcohol as a clear colorless oil: bp 66–67° (0.025 mm); $\nu_{max}^{film}$ 3350 (broad, O–H), 1167 cm$^{-1}$ (C–O); nmr (in $CDCl_3$), at $\tau$ 2.72 (s, $C_6H_5$), 4.12 (s, OH), 6.50 (s, $ACH_2$–N), 7.32 and 8.38 ($A_2X_2$ system, C–$CH_2CH_2$–N), 7.79 (s, $CH_3$–N), 8.86 (s, $(CH_3)_2$C–O).

*Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.20; H, 10.22; N, 6.96.

(39) Fischer reagent grade zinc dust was treated successively with 2% aqueous hydrochloric acid, water, 95% ethanol, and ether. The metal thus activated was dried and stored in a vacuum desiccator.

(40) An integrated glpc trace was also obtained for a known mixture of authentic **33** and **34** so as to correct for the difference in detector response toward the two components.

# Some Reactions of Methylpyrazines with Organolithium Reagents

GEORGE P. RIZZI

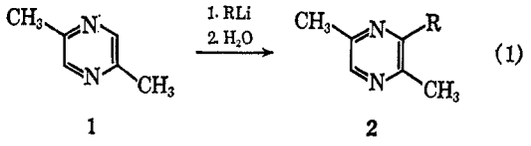
*The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239*

*Received September 25, 1967*

Reactions of isomeric dimethylpyrazines and trimethylpyrazine with methyllithium were studied in some detail. Evidence was found for hydropyrazine intermediates in the ring methylation of 2,5-dimethylpyrazine (**1**). Metalation of the side chain of **1** was observed, as well as ring methylation. In ether solvent vicinally dimethylated pyrazines gave products resulting exclusively from side-chain metalation. Subsequent alkylation and carbethoxylation of these metalated species gave low to moderate yields of side-chain-extended products. In hexane and benzene solvents 2,3-dimethylpyrazine underwent partial ring alkylation with ethyllithium and *n*-butyllithium to form trialkylpyrazines.

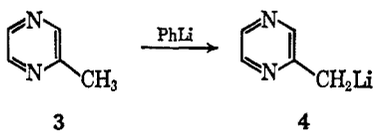
Methyl-substituted pyrazines react with organolithium reagents to form products resulting from ring alkylation (or arylation) and side-chain metalation.

Examples of ring alkylation were first reported by Spoerri[1,2] who found that 2,5-dimethylpyrazine (**1**) reacted to form 3-alkyl-2,5-dimethylpyrazines (**2**) (eq 1).




1 2 (1)

In the metalation reaction organolithium reagents attack the side chain of a methylpyrazine to form the corresponding pyrazylmethyllithium. Thus Levine[3] found that methylpyrazine (**3**) reacted with phenyllithium to produce pyrazylmethyllithium (**4**) (eq 2),




3 4 (2)

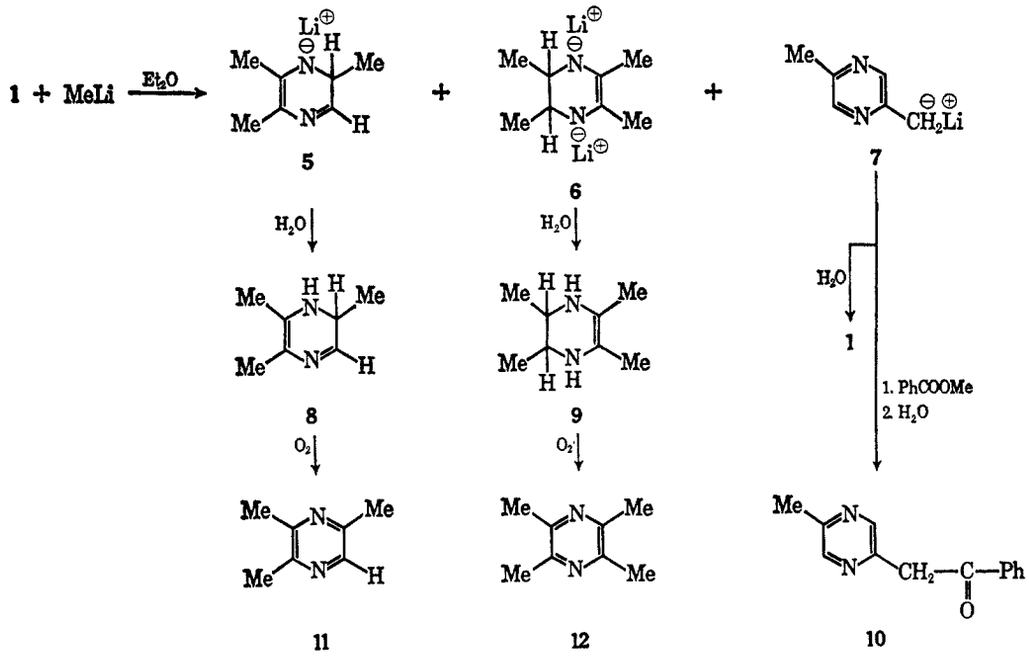
instead of products resulting from ring phenylation.

In contrast to the result obtained with **3**, no successful attempt to metalate the side chain of a dimethylpyrazine or trimethylpyrazine with an organolithium reagent has been reported. In fact it was only very recently that a monolithio derivative of tetramethylpyrazine was prepared.[4]

In the present study we investigated some reactions of dimethylpyrazines and trimethylpyrazine with organolithium reagents in order to learn more about the mechanism of ring alkylation, and also to gain further insight into factors involved in the competition between ring alkylation and side-chain metalation reactions.

(1) B. Klein and P. E. Spoerri, *J. Amer. Chem. Soc.*, **72**, 1844 (1950).
(2) B. Klein and P. E. Spoerri, *ibid.*, **73**, 2949 (1951).
(3) J. D. Behun and R. Levine, *ibid.*, **81**, 5157 (1959).
(4) S. K. Chakrabartty and R. Levine, *J. Heterocycl. Chem.*, **1**, 196 (1964).

SCHEME I



## Results

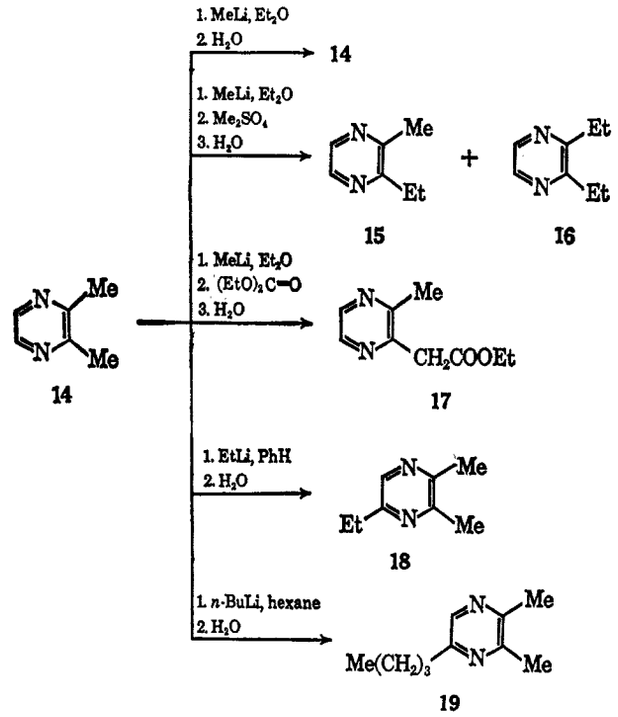
**Evidence for Hydropyrazine Intermediates in the Ring Alkylation of Methylpyrazines.**—The methylation of 2,5-dimethylpyrazine (1) with methyllithium was reinvestigated and the reactions involved are shown in Scheme I. Addition of 1 molar equiv of 1 to ethereal methyllithium at 0° yielded a solid red adduct which was hydrolyzed with water to form trimethylpyrazine (11) in 31% yield together with 4.5% of a previously undetected reaction product, tetramethylpyrazine (12). A quantity (18%) of 1 was recovered unchanged. In a separate experiment it was shown that 1, 11, and 12 were indeed products resulting from hydrolysis of the solid adduct since only traces of pyrazines could be detected when the solid was removed by filtration prior to the water addition step. Also, a low yield of gaseous products was observed during hydrolysis (*ca.* 0.05 mol of gas/mol of methyllithium used), which precluded the presence of any significant amount of free or complexed lithium hydride. These observations did not agree with previously postulated hydride elimination mechanisms,[1,5] but instead they suggested that the initially formed red precipitate was probably a mixture of the adducts 5 and 6 and possibly a methyl-metalated species 7. Hydrolysis of 5 and 6 should have yielded the 1,2-dihydropyrazine (8) and the 1,2,3,4-tetrahydropyrazine (9). Indeed, infrared analysis of a crude, hydrolyzed reaction mixture known to contain 1, 11, and 12 showed absorptions in regions not attributable to fully aromatic pyrazine species [5.98 and 6.07 (C=N) and 2.88 $\mu$ (broad NH)]. Similar absorption maxima were observed by Cornforth[6] who interpreted them as being characteristic of 1,2-dihydropyrazines. We concluded that dihydropyrazines and tetrahydropyrazines were probably formed as transient intermediates during the alkylation of methylpyrazines and that subsequent oxidation of these labile species[7] with atmospheric oxygen during work-up yielded the isolable alkylmethylpyrazines. Additions of organolithium compounds to pyridine[8] and phthalazines[9] have been shown to proceed *via* similar hydroaromatic intermediates, and the instability of these partially reduced aromatic systems toward oxidation is well known. Several attempts to trap the fugitive intermediates 8 and 9 by treating initial methyllithium reaction products with dimethyl sulfate and methyl benzoate were not successful. The result obtained with dimethyl sulfate was understandable since an N-methylated homolog of 8 which was prepared earlier by Karrer[10] was shown to be rather sensitive to chemical manipulation.

The tetramethylpyrazine (12) observed in the reaction of 1 and methyllithium was probably formed *via* the bis adduct 6, (presumably formed by further attack of methyllithium on 5) since it was found that 11 could not be converted into 12 with methyllithium under similar reaction conditions. In fact, addition of pure 11 to an ethereal solution of methyllithium led only to side-chain metalation (see below) with complete recovery of starting material after hydrolysis. The proposed intermediate tetrahydropyrazine 9 would readily yield 12 during work-up by air oxidation.[11]

The reaction of 2,6-dimethylpyrazine (13) with methyllithium appeared to take a similar course to that observed for the 2,5 isomer 1.[12] In this case addition of 1 molar equiv of 13 to ethereal methyllithium gave, after hydrolysis, a 7% yield of 11 plus 51% recovered 13. In the case of 13, no 12 could be detected in the crude reaction product.

(5) M. E. Strem, *Dissertation Abstr.*, **26**, 1355 (1965).
(6) J. W. Cornforth, *J. Chem. Soc.*, 1174 (1958).
(7) The great facility of dihydropyrazines to undergo oxidation with atmospheric $O_2$ to form pyrazines is well known; *cf.* Y. T. Pratt in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 408.
(8) K. Ziegler and H. Zeiser, *Chem. Ber.*, **63**, 1847 (1930).
(9) A. Hirsch and D. G. Orphanos, *J. Heterocycl. Chem.*, **3**, 38 (1966).
(10) P. Karrer, T. Isii, F. W. Kahnt, and J. van Bergen, *Helv. Chim. Acta*, **21**, 1174 (1938).
(11) H. I. X. Mager and W. Berends, *Rec. Trav. Chim.*, **84**, 314 (1965).
(12) Compound **13** has been successfully metalated with sodium amide in liquid $NH_3$; *cf.* R. Levine and coworkers, *J. Org. Chem.*, **29**, 191 (1964), and earlier papers.

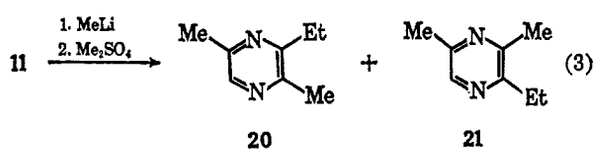
SCHEME II




**Metalation of 2,5-Dimethylpyrazine with Methyllithium.**—The presence of a methyl metalated species **7** in the initial reaction mixture of 2,5-dimethylpyrazine (**1**) and methyllithium was established by trapping it with methyl benzoate. The initial red adduct of **1** and methyllithium was treated with methyl benzoate *in situ* at 0°. In this way there was obtained a 14% yield of 2-methyl-5-phenacylpyrazine (**10**) which was identical with the authentic ketone prepared by the method of Strem.[5] Since it is known that pyrazylmethyllithium reagents are benzoylated with methyl benzoate,[4] it was concluded that methyl metalation had taken place during the reaction of **1** with methyllithium, and that the extent of metalation was probably in the order of 20%.

**Reactions of 2,3-Dimethylpyrazine (14) and Trimethylpyrazine (11) with Organolithium Reagents.**—Reactions involving **14** are shown in Scheme II. The addition of **14** to ethereal methyllithium at 0° afforded an insoluble red precipitate, apparently similar to those formed from **1** and **13**, but its formation was accompanied by an evolution of a gas (71% yield, presumed to be methane). Subsequent hydrolysis led only to the recovery of **14**; no trace of **11** could be detected. These results suggested that metalation of **14** had occurred to the complete exclusion of azomethine addition. Attempts to alkylate the ring with methyllithium and ethyllithium in ether under more forcing conditions (*i.e.*, excess reagent at *ca.* 25°) still did not yield trialkylpyrazines, but rather resulted in decomposition of starting materials to unidentified tarry products. The presence of methyl-metalated species in the original reaction mixture was confirmed by treating the red precipitate with dimethyl sulfate. As a result side-chain alkylation took place to form 2-ethyl-3-methylpyrazine (**15**) and 2,3-diethylpyrazine (**16**) in 39 and 10% yields, respectively. Similar reaction of the red precipitate with diethyl carbonate produced 2-carbethoxymethyl-3-methylpyrazine (**17**) in 17% yield. When the metalation reactions were attempted in benzene or hexane solvent some ring alkylation did occur. Thus reactions of **14** with ethyllithium and *n*-butyllithium, respectively, produced 2,3-dimethyl-5-ethylpyrazine (**18**) and 2-*n*-butyl-5,6-dimethylpyrazine (**19**) in 6 and 8% yields.

As mentioned previously trimethylpyrazine (**11**) and methyllithium did not react to yield tetramethylpyrazine (**12**) but instead methyl metalation was the only reaction observed. In this case treatment of the initially formed lithium derivatives with dimethyl sulfate produced 2,5-dimethyl-3-ethylpyrazine (**20**) and 2,6-dimethyl-3-ethylpyrazine (**21**) each in 4% yield together with 27% recovered **11** (eq 3). No trace




(3)

of **18** was observed in the crude reaction product. The reason for the observed solvent effect in reactions of **14** with ethyllithium is still not clear. It is possible that the smaller steric requirement of a presumably monomeric, unsolvated lithium reagent compared with the same reagent in ether, would favor its adding across the pyrazine–azomethine linkage.

## Experimental Section

Reactions involving organometallic compounds were carried out in an atmosphere of predried nitrogen. Gas chromatographic analyses and preparative separations of alkylpyrazines were accomplished using a 20 ft × 0.25 in. stainless steel column packed with 18% DEGS on 60–80 mesh, silanized, acid-washed Chromosorb W, and a 10 ft × 0.25 in. stainless steel column packed with 15% SF-96 on a similar support. Nominal column temperatures ranged from 100–150° and the flow rate of carrier gas (He) was 50 ml/min. The first-mentioned column was more effective for resolving isomeric alkylpyrazines. Infrared spectra were obtained on $CS_2$ solutions unless otherwise specified using

a Perkin-Elmer Model 137 "Infracord" spectrophotometer. Nmr spectra were determined with a Varian HA-100 instrument. Samples were run as 5–10% solutions in $CCl_4$ and chemical shifts observed at 100 MHz are expressed in $\tau$ units relative to tetramethylsilane (internal standard). Multiplicity is indicated by letters in parentheses where s = singlet, d = doublet, t = triplet, q = quartet, and m = complex, unresolved multiplet. Melting points were observed in open capillaries and are uncorrected. Microanalyses were performed by Mr. T. Atanovich and associates of these laboratories and by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Samples of methylpyrazine, 2,5-dimethylpyrazine, 2,6-dimethylpyrazine, and tetramethylpyrazine were obtained commercially and the first three named were distilled from $CaH_2$ prior to use.

**Reactions of 2,5-Dimethylpyrazine (1) with Methyllithium (MeLi). A. Ring Methylation.**—The procedure of Spoerri[1] was repeated with slight modification. A stirred, ice-cold solution of MeLi in ether (125 ml of 1.62 *M* MeLi reagent, Alpha Inorganics, Inc.) was treated dropwise with a solution of 2,5-dimethylpyrazine (**1**) (21.6 g, 0.20 mol) in 25 ml of ether. The dark red solid which formed was stirred vigorously for 10 min at 0° and for 30 min at 25° and finally was cooled again to 0°. Water was added to decompose the red precipitate, and organic products were isolated by continuous ether extraction (16 hr). Distillation of the crude product afforded 13.76 g of a pale orange oil, bp 35–83° (35 mm), which was shown by glpc and infrared analysis to consist of **1** (18% recovery), trimethylpyrazine (**11**) (31% yield), and tetramethylpyrazine (**12**) (4.5% yield). In a similar experiment (run on 0.02-mol scale) the initially formed red solid was removed from the reaction mixture by filtration prior to aqueous hydrolysis. The resulting clear filtrate was washed with saturated brine and dried over $MgSO_4$. Evaporation of the filtered ether solution afforded 0.074 g of **11** (0.03% yield). In another experiment (run on 0.00167-mol scale) an attempt was made to measure gas evolution during hydrolysis of the MeLi adduct at 0°. Thus, addition of 1 ml of water led to the evolution of 3.4 ml of gas (collected over water at 26.5° and 745 mm). Under these conditions 0.00167 mol of $H_2$ would have occupied 44.8 ml.[13]

**B. Side-Chain Metalation.**—A stirred, ice-cold solution of **1** (8.64 g, 0.080 mol) in 80 ml of ether was treated dropwise with 50.0 ml of 1.62 *M* ethereal MeLi (0.081 mol) over *ca.* 10 min. Then, at 0°, a solution containing 10.87 g (0.080 mol) of freshly distilled methyl benzoate in 40 ml of ether was added and stirring was continued for 1 hr. After standing 2 hr at 25° the reaction mixture was worked up with water and ether as described in part A (above) to yield 17.9 g of a dark, viscous oil. The crude product was chromatographed over silica (60–90 mesh Florex) using benzene and increasing amounts of ether in benzene as eluting solvents. Elution with 2–10% ether afforded 14% of **10** which, after two recrystallizations from 95:5 ethanol–methanol, had mp 104.5–106.5°.

*Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.3; H, 5.3; N, 13.2.

The **2,4-dinitrophenylhydrazone** was obtained in the form of yellow-orange needles from methanol, mp 215–218.5°.

*Anal.* Calcd for $C_{19}H_{16}N_6O_4$: C, 58.16; H, 4.11; N, 21.42. Found: C, 58.3; H, 4.3; N, 21.4.

The infrared ($CH_2Cl_2$ and $CS_2$ solution) and nmr spectra of **10** were identical with those of the authentic ketone,[5] and a mixture melting point of the two substances was not depressed.

**Reaction of 2,6-Dimethylpyrazine (13) with MeLi.**—Addition of 2.16 g (0.020 mol) of **13** to 1 molar equiv of ethereal MeLi in the manner described for **1** (above) yielded, after work-up and distillation, 1.29 g of volatile products, bp 52–80° (10 mm). Glpc analysis indicated a 7% yield of **11** plus 51% recovered **13**.

**Reactions of 2,3-Dimethylpyrazine (14) with MeLi. A. Ring Methylation Attempts.**—An ether solution containing 3.51 g (0.0325 mol) of **14** was added to an equivalent amount of ethereal MeLi in the manner described for **1** (above). Decomposition of the initially formed red solid with water followed by ether extraction yielded 3.28 g (94%) of crude **14**. Short-path distillation of this material afforded 2.85 g (81%) of glpc pure **14**, bp 52–60° (12 mm).

Glpc analysis of the crude product showed only a trace of **11**. Similar experiments carried out with a large (~tenfold) molar excess of MeLi or EtLi at 25° also led only to **14**.

(13) Corrected for the solubility of $H_2$ in ether at 0°.

**B. Side-Chain Metalation.**—A flask arranged for collection of evolved gases was charged with 10.0 ml of 1.62 *M* ethereal MeLi and stirred at 0°. Dropwise addition of 1.71 ml (0.0162 mol) of anhydrous **14** to the MeLi solution led to immediate gas evolution (0.0112 mol) and concomitant precipitation of a deep red solid. The red precipitate was treated dropwise with a solution of freshly distilled dimethyl sulfate (1.51 ml, 0.0162 mol) in 5 ml of ether. After 30 min at 0° and 2 hr at 25° water was added; the mixture was worked up as described in A to give 1.64 g of yellow oil. Distillation gave 1.27 g of distillate, bp 63–88° (16 mm). Glpc analysis indicated three compounds which were isolated (preparative glpc) and identified as **14**, 2-ethyl-3-methylpyrazine (**15**), and 2,3-diethylpyrazine (**16**) by their nmr and infrared spectra. The glpc yields of **15** and **16** were 39 and 10%, respectively. Recovery of **14** was 15%.

**C. Carbethoxylation of Metalated 14 with Diethyl Carbonate.**—The metalation reaction described in part B was repeated on a 0.02-mol scale. The red suspension was stirred at 0° while a solution of diethyl carbonate (1.21 ml, 0.010 mol) in 5 ml of ether was added dropwise over 5 min. After stirring 30 min at 0° and 2 hr at 25°, the mixture was decomposed with water and extracted with ether. Distillation of the crude product obtained after concentration of the dried ($MgSO_4$) ether solution yielded 1.58 g of an oil, bp 64–157° (27 mm), which was shown by glpc analysis to contain **14** (32% recovery) and 2-carbethoxymethyl-3-methylpyrazine (**17**) (17% yield). Compound **17** was isolated by preparative glpc as a clear, pale yellow oil.

*Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.9; H, 6.8; N, 15.6.

The infrared spectrum showed characteristic ester absorption at 5.75 $\mu$. Nmr analysis showed peaks at $\tau$ 1.78 (m, ring protons, 2 H), 5.90 (q, $CH_2C\leqslant$, 2 H), 6.27 (s, $-CH_2-$, 2 H), 7.51 (s, ring methyl, 3 H), 8.74 (t, $CH_3C<$, 3 H).

**Reactions of Trimethylpyrazine (11) with MeLi.**—To a stirred, ice-cold mixture of 3.0 ml of 1.62 *M* ethereal MeLi and 3.0 ml of ether was added a solution containing 0.237 g (0.00194 mol) of glpc pure **11** in 2 ml of ether. After 2 hr at 0°, water (2 ml) was added, and the mixture was extracted with ether. Concentration of the dried ($MgSO_4$) ether solution afforded 100% recovery of **11**. No **12** could be detected in the crude product by glpc. A similar reaction mixture prepared from 0.253 g (0.0021 mol) of **11** and an equivalent amount of MeLi was treated dropwise with 0.20 ml (0.0021 mol) of dimethyl sulfate in a few milliliters of ether. Addition of water followed by ether work-up yielded 0.235 g of crude product. Evaporative distillation at 80–160° (15 mm) afforded 0.117 g of a yellow oil which was resolved into three components by preparative glpc. The compounds identified (infrared spectra and glpc retention times) were **11**, 2,5-dimethyl-3-ethylpyrazine[2,14] (**20**), and 2,6-dimethyl-3-ethylpyrazine[14] (**21**). Materials **20** and **21** were obtained in 4 and 6% yields, respectively, together with 27% of recovered **11**.

**2,3-Dimethylpyrazine (14).**—To 64.0 g (0.582 mol) of 2,3-dimethyl-5,6-dihydropyrazine[15] contained in a 3-l., round-bottomed flask were added 1200 ml of 33% aqueous KOH solution and 320 g of reagent-grade $HgCl_2$. After heating and stirring 2.5 hr on a steam bath, the flask was arranged for steam distillation, and 1 l. of aqueous distillate was collected. Continuous ether extraction (16 hr) followed by distillation afforded 17.6 g (28%) of **14**, bp 156–158°, picrate derivative, mp 151–153° (lit.[16] bp 156°, picrate mp 150°).

**2-Ethyl-3-methylpyrazine (15).**—Compound **15** was prepared in a manner similar to **14**. Thus 59.0 g (0.476 mol) of 2-ethyl-3-methyl-5,6-dihydropyrazine (prepared from 2,3-pentanedione and ethylenediamine by the method reported for the synthesis of the 2,3-dimethyl homolog)[15] was oxidized with $HgCl_2$ to yield, after distillation, 9.8 g (17%) of **15**: bp 69–70° (16 mm); nmr, $\tau$ 1.88 (m, ring protons, 2 H), 7.57 (s, ring $CH_3$, 3 H), 7.28 (q, $CH_2$, 2 H), 8.77 (t, chain $CH_3$, 3 H).

*Anal.* Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.9; H, 8.5; N, 22.5.

**2,3-Diethylpyrazine (16).**—The pyrazine **16** was prepared by the method outlined for **14** and **15** starting with 3,4-hexanedione[17] and ethylenediamine. The over-all yield of steam distilled, glpc pure **16** was 15%. A sample of the oily product was purified for

(14) G. P. Rizzi, *J. Agr. Food Chem.*, **15**, 549 (1967).

(15) T. Ishiguro and M. Matsumura, *Yakugaku Zasshi*, **78**, 229 (1958); *Chem. Abstr.*, **52**, 11862 (1958).

(16) Beilstein, "Handbook of Organic Chemistry," Vol. 23, Springer-Verlag, Berlin, 1936, p 95.

(17) W. Rigby, *J. Chem. Soc.*, 793 (1951).

analysis by preparative glpc. Nmr analysis gave peaks at $\tau$ 1.84 (s, ring protons, 2 H), 7.24 (q, $CH_2$, 4 H), 8.75 (t, chain $CH_3$, 6 H).

*Anal.* Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.7; H, 8.9; N, 20.7.

**2,3-Dimethyl-5-ethylpyrazine (18).**—A 50-ml portion of 2.22 *M* ethyllithium in benzene (0.111 mol, Alpha Inorganics, Inc.) was stirred and cooled to 10° while a solution of **14** (2.17 g, 0.020 mol) in benzene (10 ml) was added dropwise. The dark red slurry which formed was stirred 0.5 hr at 0° and 21.5 hr at 25°. After recooling to 0°, water was admitted and organic products were extracted with ether. Short-path distillation yielded 0.548 g of pale yellow oil, bp 60–102° (15 mm). Analysis of this oil by glpc indicated two major products, recovered **14** and 2,3-dimethyl-5-ethylpyrazine. The glpc yields of **14** and **18** were 18 and 6%, respectively. An analytical specimen of **18** was isolated by preparative glpc and further purified by evaporative distillation. Nmr analysis gave peaks at $\tau$ 2.03 (s, ring proton, 1 H), 7.61 (s, ring methyls, 6 H), 7.36 (q, $CH_2$, 2 H), 8.76 (t, ethyl $CH_3$, 3 H).

*Anal.* Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.6; H, 8.9; N, 20.6.

**2-*n*-Butyl-5,6-dimethylpyrazine (19).**—A mixture containing 10 ml of dry hexane and 20.0 ml (0.032 mol) of 1.6 *M* *n*-butyllithium in hexane (Foote Mineral Co.) was stirred at 0° and treated dropwise (over 10 min) with a solution of **14** (1.74 g, 0.016 mol) in 5 ml of hexane. After stirring 1 hr at 0° and 1 hr at 25°, the reaction mixture was cooled and decomposed with water (10 ml). Ether extraction afforded 1.8 g of crude product which, after short-path distillation, yielded 1.01 g of a yellow oil, bp 59–114° (16 mm). Glpc analysis indicated two oily components which were trapped and identified as **14** and 2-*n*-butyl-5,6-dimethylpyrazine (**19**). Glpc yields of **14** and **19** were 42 and 8%, respectively. A sample of **19** was evaporatively distilled prior to analysis. Nmr analysis gave peaks at $\tau$ 2.07 (s, ring proton, 1 H), 7.64 (s, ring methyl, 6 H), 7.42 (t, ring $CH_2$, 2 H), 9.11 (t, *n*-butyl $CH_3$, 3 H).

*Anal.* Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 72.9; H, 9.8; N, 17.2.

**Registry No.**—**1,** 123-32-0; **10,** 15707-19-4; **10** 2,4-dinitrophenylhydrazone, 15707-20-7; **11,** 14667-55-1; **13,** 108-50-9; **14,** 5910-89-4; **15,** 15707-23-0; **16,** 15707-24-1; **17,** 15707-25-2; **18,** 15707-34-3; **19,** 15834-78-3.

**Acknowledgment.**—The author gratefully acknowledges helpful suggestions provided by Drs. N. R. Artman, W. F. Erman, and C. D. Broaddus. Credit is also due Mr. Norvin Gullion, who performed some of the experimental work described.

# Synthesis of a Pyridoxal Analog, 4,5-Diformyl-3-hydroxy-2-methylpyridine[1a]

P. D. SATTSANGI AND C. J. ARGOUDELIS[1b]

*Department of Food Science, The Burnsides Research Laboratory, University of Illinois, Urbana, Illinois 61801*

*Received October 24, 1967*

A route for the synthesis of the compound 4,5-diformyl-3-hydroxy-2-methylpyridine (X) (an analog of pyridoxal) is described. The key intermediate in this synthesis was the previously undescribed dimethyl acetal of isopyridoxal (VI) which was synthesized from the corresponding acetylated diethyl mercaptal (V) by demercaptalation in methanol using mercuric chloride and mercuric oxide. For the removal of the mercuric chloride, ammonium hydroxide has been found to be the most suitable reagent. Oxidation of the 4-hydroxymethyl group of this intermediate (VI) with manganese dioxide "B" and acid hydrolysis of the product of oxidation gave the desired dialdehyde X which has been shown to exist in a hydrated form as a dihemiacetal. Derivatives like the bismethoxyoxime (XI) and bisthiosemicarbazone (XII) were prepared. Reduction of the *o*-dialdehyde X with sodium borohydride gave pyridoxol.

In the course of investigations concerning the biosynthetic pathway of vitamin $B_6$ in yeast[2] and its catabolism in rats,[3,4] we have isolated compounds, related to this vitamin, that showed growth-promoting activity for *Lactobacillus casei* and/or *Saccharomyces carlsbergensis*. Pyridoxal and isopyridoxal,[5] which have a formyl group in place of the hydroxymethyl group at the 4 or 5 position of the pyridoxol molecule, respectively, are both growth-promoting factors for *Saccharomyces carlsbergensis*.[6,7] Therefore, the compound 4,5-diformyl-3-hydroxy-2-methylpyridine (*o*-pyridoxidial[8]) (X, Scheme I), which has both the 4- and 5-hydroxymethyl groups of the pyridoxol molecule replaced by formyl groups, was needed to be tested as a possible precursor or catabolite of the vitamin. A synthesis of this pyridoxal analog is herein described; its biological properties are under investigation.

Gardner, *et al.*,[9] have described a synthesis of the bisthiosemicarbazone derivative of compound X using a double Sommelet reaction; however, the identity of this product was not conclusively established.[10] A detailed study[10–15] of the Sommelet reaction seems to show no promise for the synthesis of *o*-dialdehydes through a double Sommelet reaction. Ried and Bodem[16] have made many aromatic and heteroaromatic *o*-dialdehydes using vicinal dibromides and N-bromosuccinimide in the presence of peroxides, but this method did not seem to be applicable in the

(1) (a) This investigation was supported by a U. S. Public Health Service Research Grant (AM 00257). (b) To whom inquiries should be addressed.

(2) R. S. Pardini and C. J. Argoudelis, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p C309.

(3) C. J. Argoudelis and F. A. Kummerow, *Biochemistry*, **5**, 1 (1966).

(4) C. J. Argoudelis, unpublished data.

(5) The growth-promoting activity of isopyridoxal is, unquestionably, a result of its conversion into pyridoxol and thence to pyridoxal phosphate: E. E. Snell, *Vitamins Hormones*, **16**, 77 (1958)).

(6) E. E. Snell, *J. Biol. Chem.*, **154**, 313 (1944).

(7) E. E. Snell and A. N. Rannefeld, *ibid.*, **157**, 475 (1945).

(8) Three new pyridine dialdehydes related to vitamin $B_6$ have been named trivially as *o*-, *m*-, and *p*-pyridoxidial. These dialdehydes have the two formyl groups in the *ortho* (4,5), *meta* (2,4), and *para* (2,5) positions of the pyridoxol molecule, respectively. Syntheses of the *m*- and *p*-pyridoxidials are in progess.

(9) T. S. Gardner, F. A. Smith, E. Wenis, and J. Lee, *J. Org. Chem.*, **16**, 1121 (1951).

(10) S. J. Angyal, *Org. Reactions*, **8**, 197 (1954).

(11) S. A. Harris, D. Heyl, and K. Folkers, *J. Amer. Chem. Soc.*, **66**, 2088 (1944).

(12) S. J. Angyal, P. J. Morris, R. C. Rassac, and J. A. Waterer, *J. Chem. Soc.*, 2704 (1949).

(13) R. C. Fuson and J. J. Denton, *J. Amer. Chem. Soc.*, **63**, 654 (1941).

(14) S. J. Angyal, G. B. Barlin, and P. C. Wailes, *J. Chem. Soc.*, 1740 (1953).

(15) J. H. Wood, C. C. Tung, M. A. Perry, and R. E. Gibson, *J. Amer. Chem. Soc.*, **72**, 2992 (1950).

(16) W. Ried and H. Bodem, *Chem. Ber.*, **89**, 708 (1956); **89**, 2328 (1956).