Some Aspects of the Selective Acetylation of Methylhydrazine. 1-Acetyl-1-methyl- and 1-Acetyl-2-methylhydrazine

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The selective acetylation of methylhydrazine—with acetic anhydride to give chiefly 1-acetyl-1-methylhydrazine (1) and with ethyl acetate to give chiefly 1-acetyl-2-methylhydrazine (2)—was studied, with nmr spectroscopy as the method of analysis. The ratio, 1/2, was found to be ~0.30 with ethyl acetate as acetylating agent, ~38 with acetic anhydride in pyridine or triethylamine as solvent, and >100 with acetic anhydride in acetic acid. The ratios result from kinetic control. The equilibrium ratio, 1/2, was found to be 0.39 at 27° and 0.49 at 87°, from which $\Delta H^0 = 785 \pm 40$ cal/mol and $\Delta S^0 = 0.75 \pm 0.6$ cal/deg mol for the process 2 → 1. The isomerization is ~1/6 as fast as the acetylation of methylhydrazine with ethyl acetate at 80–90°. Isomer 2 is ~1.5 times as rapidly acetylated as 1 with acetic anhydride to give 1,2-diacetyl-1-methylhydrazine, and, judging from the compositions of reaction mixtures, 1 and 2 appeared to be <1/50 as reactive as methylhydrazine toward ethyl acetate and ~1/5 as reactive toward acetic anhydride. The acetylation of methylhydrazine with ethyl acetate is acid catalyzed, with ethanol, water, and acetic acid being increasingly effective in that order. The results are rationalized in terms of a difference in mechanisms, with the anhydride reacting by nucleophilic displacement of the BAc2 type and the ester by an addition–elimination mechanism. The isomers 1 (mp 16°) and 2 (mp 42°) were isolated and characterized.

Hinman and Fulton[1a] have shown and Theuer and Moore confirmed[1b] that the acylation of methylhydrazine with acid anhydrides produces chiefly 1-acyl-1-methylhydrazines, while acylation with esters gives chiefly 1-acyl-2-methylhydrazines. The phenomenon cannot be reconciled with the reactivity–selectivity principle—the less reactive a reagent, the more selective it is between a pair of substrates or sites within a given substrate.[2] Given that an anhydride shows preference for the methylated nitrogen of methylhydrazine, the principle would lead one to expect an even greater preference for that same nitrogen to be shown by the less active esters, or, given that an ester shows preference for the nonmethylated nitrogen, one would expect the anhydrides to show a lesser preference for that nitrogen or, at most, no selectivity at all between the two nitrogens. The complementary specificities exhibited by the two classes of reagents toward methylhydrazine is uncommon in its clarity and in the simplicity of the substances involved and resembles that found in biological systems.

In this paper are presented some results of further study of the selective acylation of methylhydrazine in which ethyl acetate and acetic anhydride were the acylating agents and nmr spectroscopy was used extensively in examination and analysis of reaction mixtures. This work had two objectives: (i) to acquire some understanding of the phenomenon of selective acylation; and (ii) to use the selective acylation as a means of preparing the two isomers, 1-acetyl-1-methylhydrazine (1) and 1-acetyl-2-methylhydrazine (2) in a high enough state of purity for use as intermediates in syntheses of 1-ethyl-2-methylhydrazine as shown in eq 1 and 2. These isomers had not yet been isolated and characterized.[3]

Isomer 1 was isolated in high yield and purity and was then shown to be a useful intermediate for synthesis of not only 1-ethyl-2-methylhydrazine but also many other 1-alkyl-2-methylhydrazines as shown in eq 3. Isomer 2 was also isolated and characterized, but it was almost wholly converted to methylhydrazine by reaction with lithium aluminum hydride, ~10% being reduced in accordance with eq 2. That work is described in another paper, this one being limited to the acetylation reaction, the first step in eq 1 and 2.

$$\mathrm{MeNHNH_2} \xrightarrow{\mathrm{Ac_2O}} \underset{1}{\mathrm{MeNAcNH_2}} \xrightarrow{\mathrm{CH_3CHO}} \mathrm{MeNAcN{=}CHCH_3} \xrightarrow{\mathrm{NaBH_4}} \mathrm{MeNAcNHCH_2CH_3} \xrightarrow{\mathrm{H_2O,\ HCl}} \mathrm{MeNHNHEt\cdot 2HCl} \quad (1)$$

$$\mathrm{MeNHNH_2} \xrightarrow{\mathrm{EtOAc}} \underset{2}{\mathrm{MeNHNHAc}} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{MeNHNHEt} \quad (2)$$

$$\mathbf{1} \xrightarrow{\mathrm{R_1R_2CO}} \mathrm{MeNAcN{=}CR_1R_2} \xrightarrow{\mathrm{NaBH_4}} \mathrm{MeNAcNHCHR_1R_2} \xrightarrow{\mathrm{H_2O,\ etc.}} \mathrm{MeNHNHCHR_1R_2} \quad (3)$$

Results

Acetylation of Methylhydrazine.—In Table I are presented results of acetylation of methylhydrazine with ethyl acetate and with acetic anhydride under various conditions. Product compositions are based on analysis of fractions from distillation, by means of nmr spectroscopy. The isomers, 1 and 2, were easily distinguished by means of their *N*-methyl peaks, which came at ~3.2 ppm downfield for 1 and at 2.56 ppm for 2. A diacetylmethylhydrazine, presumably 1,2-diacetyl-1-methylhydrazine,[4] which was not reported by Hinman and Fulton,[1a] was always found as a residue from distillation of the acetylation products under reduced pressure. Its boiling point was so much higher than those of the monoacetyl derivatives that a fairly sharp separation was possible by distillation. Small amounts of it were detectable by nmr in the last volatile fraction and could be accounted for by use of its singlets at 2.01, 2.04, and 3.07 ppm.

Table I is concerned with the influences of choice of acetylating agent (ethyl acetate or acetic anhydride) and, in the case of acetic anhydride, of solvent and method of work-up on two observables: the selectivity

(1) (a) R. L. Hinman and D. Fulton, *J. Amer. Chem. Soc.*, **80**, 1895 (1958); (b) W. J. Theuer and J. A. Moore, *J. Org. Chem.*, **29**, 3734 (1964).

(2) (a) L. M. Stock and H. C. Brown, *J. Amer. Chem. Soc.*, **81**, 3323 (1959), and references cited therein; (b) F. E. Condon and H. Meislich, "Introduction to Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, N. Y., 1960, pp 51–52.

(3) *Chemical Abstracts* through 1970 was searched under the heading, "Hydrazine, acetyl-methyl."

(4) A. Michaelis and E. Hadanck, *Ber.*, **41**, 3285 (1908).

TABLE I

INFLUENCES OF SOLVENT AND ACETYLATING AGENT ON RESULTS OF ACETYLATION OF METHYLHYDRAZINE

Run no.	1	2	3	4	5	6	7	8	9	10
Scale, mol of $MeNHNH_2$	1.025	1.11	0.99	0.49	1.00	0.695	1.00	4.00	2.42	1.00
Solvent	EtOAc[a]–H_2O				HOAc	Pyridine				Et_3N[b]
Solvent, mol[c]	1.19/0.1	1.35/0.06	1.26/0.05	1.27/0.06	1.01	1.23	1.33	1.20	1.20	1.20
Ac_2O, mol[c]					1.00	1.00	1.00	1.00	1.00	1.00
Temperature, °C	80–90[d]	78–87[e]	80–90[f]	80–90[f]	10–15	10–20	30–40	10–15	15–20	15–20
Extractive[g,h]					py	Ether	Ether	py	py	ch
Product, mol[c,i]										
$MeNHNH_2$	0.115	0.020	0.180	0.163	0.109	0.104	0.070	0.0650	0.014	0.013
$MeNAcNH_2$, 1	0.176	0.213	0.170	0.517[j]	0.529	0.430	0.255	0.6550	0.814	0.677
MeNHNHAc, 2	0.620	0.656	0.592	0.736	0.005	0.011	0.0055	0.0156	0.027	0.020
MeNAcNHAc	0.023	0.042	0.018	0.020	0.164	0.115	0.066	0.065[k]	0.049	0.022
Loss	0.066	0.069	0.040	0.074	0.193	0.340	0.6035	0.1994	0.096	0.268
$MeNAcNH_2$/MeNHNHAc	0.28	0.32[l]	0.29		~100	39	46	42	30	34
k/k'[m]	51	62	46		4.9	5.1	4.8	(18.5)[n]	(58)[n]	~100

[a] Solvent and acetylating agent. [b] Heterogeneous reaction mixture. [c] Basis: 1 mol of methylhydrazine. [d] 50 hr of refluxing. [e] 141 hr of refluxing, followed by 6 months at room temperature. [f] 68 hr of refluxing. [g] For the solid $NaOAc \cdot 3H_2O$ produced by neutralization of by-product HOAc with 50% NaOH. [h] py, pyridine; ch, chloroform. [i] Based on nmr analysis of fractions from distillation. [j] In this run, 0.51 mol of $MeNAcNH_2$ (per mole of $MeNHNH_2$) was introduced at the start to determine the extent of its isomerization under acetylating conditions. [k] Approximate value equated to recovered $MeNHNH_2$. [l] There may have been some rearrangement of MeNHNHAc to $MeNAcNH_2$ as the reaction mixture stood for 6 months at room temperature before work-up. [m] Indicated ratio of specific rates of acetylation of methylhydrazine and acetylmethylhydrazine. [n] Unreliable because of loss of methylhydrazine during work-up.

between the two positions in methylhydrazine, as measured by the isomer ratio, $MeNAcNH_2$/MeNHNHAc, and the selectivity between methylhydrazine and acetylmethylhydrazine, as measured by the ratio of specific rate constants, k/k', presented in the last row of the table. For the latter, the system is regarded as an instance of competing consecutive second-order reactions, as in eq 4, where AcX stands for the acetylating

$$\underset{A}{MeNHNH_2} \xrightarrow[k]{AcX} \left[\begin{matrix} MeNAcNH_2 \\ MeNHNHAc \end{matrix}\right]_B \xrightarrow[k']{AcX} \underset{C}{MeNAcNHAc} \quad (4)$$

agent and k and k' are second-order rate constants. The ratio, k/k', was computed from the data by use of eq 5,[5] in which A and B stand for the mole fractions of

$$\frac{k'}{k} \log A = \log \left(A + B - \frac{k'}{k} B\right) \quad (5)$$

methylhydrazine and acetylmethylhydrazine, respectively, in a particular product.[6]

In runs 1–3, with ethyl acetate as acetylating agent, fairly consistent values for the two aforementioned ratios were obtained. The isomer ratio, **1**/**2**, averaged 0.30 ± 0.02 in the three runs, and this result is similar to the findings of Hinman and Fulton with *methyl* acetate.[1a] An average of 53 ± 6 was obtained for the ratio of k/k'.

In runs with acetic anhydride as acylating agent, it was found that the products underwent marked changes in composition if left overnight at room temperature or if distilled without prior removal of the acetic acid by-product, apparently as a result of catalysis by the acid. In runs 6–10, in which pyridine or triethylamine was used as a solvent, the acetic acid was neutralized with concentrated sodium hydroxide, and ether, pyridine, or chloroform was used as an extractive for the solid sodium acetate trihydrate produced. Fairly consistent values for the isomer ratio, **1**/**2**, in the range of 30–46, were obtained. In run 5, in which acetylation was carried out in acetic acid as solvent, the acetic acid was neutralized with sodium hydroxide and the extractive was pyridine, an isomer ratio of >100 was obtained. In other runs not shown, in which reaction mixtures were distilled without treatment with sodium hydroxide, or in which neutralization of the acetic acid was incomplete, much lower values of the isomer ratio were obtained as a result of isomerization of **1** to **2** during work-up. Such results could not be used, of course, as a measure of the selectivity of acetic anhydride toward the two nitrogens of methylhydrazine. From the data shown the selectivity appears to be 38 ± 5 in favor of the methylated nitrogen in the presence of pyridine or triethylamine and >100 when the acetylation is done in excess acetic acid.

For the selectivity of acetic anhydride for methylhydrazine over acetylmethylhydrazine, k/k', the most reliable value seems to be 5.0 ± 0.2, regardless of whether the acetylation is carried out in pyridine or acetic acid (runs 5–7). In triethylamine, however, the selectivity was much higher, approaching 100. Here the reaction mixture consisted of two phases, and there may have been a favorable partitioning of the components between the two phases.

Further theoretical discussion of the anomalous results with acetic acid and triethylamine seems premature at this time. The data are sparse and in need of verification and amplification.

From a practical point of view, however, acetylation of methylhydrazine with acetic anhydride provided isomer **1** of 99% purity in 46% yield (acetylation in acetic acid, run 5) or of 96% purity in 76% yield (ace-

(5) F. E. Condon, *J. Amer. Chem. Soc.*, **70**, 2053 (1948).

(6) (a) Although the amount of methylhydrazine used in the several runs varied from 0.49 mol (run 4) to 4 mol (run 8), product compositions have been reduced to a common charge of 1.00 mol for presentation in Table I, to facilitate comparison of the several results. (b) For the purpose of eq 5, each product composition was necessarily converted to a "no-loss" basis by dividing the number of moles of each component by the total number of moles of methylhydrazine and its derivatives found in that product.

TABLE II

COMPETITIVE ACETYLATION OF 1-ACETYL-1-METHYLHYDRAZINE AND 1-ACETYL-2-METHYLHYDRAZINE

Ac_2O, portions added	0	1	2	3	4	5	6
Nmr peak areas[a]							
$MeNAcNH_2$ + MeNAcNHAc	57.0 (n_1^0)	60.0	63.5	69.2	76.6	78.0	80.8
MeNHNHAc, n_2	43.0 (n_2^0)	40.0	36.5	30.8	23.4	22.0	19.2
MeNHNHAc, decrease		3.0	6.5	12.2	19.6	21.0	23.8
Total $-COCH_3$	106.0	117.5	132.2	156.5	184.0	188.4	196.0
Total $-COCH_3$, increase		11.5	26.2	50.5	78.0	82.4	90.0
$-COCH_3$ increase, less HOAc		5.7	13.1	25.2	39.0	41.2	45.0
$-COCH_3$ above, less decrease in MeNHNHAc		2.7	6.6	13.0	19.4	20.2	21.2
Net $MeNAcNH_2$, n_1	57.0 (n_1^0)	54.3	50.4	44.0	37.6	36.8	35.8
n_2/n_2^0		0.930	0.848	0.716	0.544	0.511	0.446
n_1/n_1^0		0.953	0.884	0.772	0.660	0.645	0.628
$-\text{Log } n_2/n_2^0$ ($\log_2$)		0.0315	0.0715	0.145	0.265	0.292	0.351
$-\text{Log } n_1/n_1^0$ ($\log_1$)		0.0210	0.0535	0.112	0.181	0.190	0.202
k_2/k_1 ($\log_2/\log_1$)		1.50	1.34	1.30	1.46	1.54	1.74
				Average 1.48 ± 0.11			

[a] Basis: $MeNAcNH_2$ + MeNAcNHAc + MeNHNHAc = 100.

tylation in pyridine, run 9).[7] Furthermore, it seems likely the yields could be improved by a more thorough extraction of the solid sodium acetate trihydrate than was achieved in the runs described in the table.

Isomer **2** of 96% purity was obtained in 28% yield by crystallization from the product of acetylation with ethyl acetate. The melting points of **1** and **2** were 16° and 42°, respectively, which are in accord with a generalization made by Hinman and Fulton.[1a]

Competitive Acetylation of 1 and 2.—It was of interest to determine the relative reactivities of **1** and **2** toward acetic anhydride, as it was possible that the high isomer ratio, 1/2, obtained with this reagent was a consequence of strongly selective further acetylation of **2** to 1,2-diacetyl-1-methylhydrazine. A mixture of the two isomers was therefore treated in an nmr sample tube with successive small portions of acetic anhydride, and changes in the composition of the mixture were determined by means of nmr. Data and results are presented in Table II, and further procedural details are given in the Experimental Section.

The ratio of reactivities, k_2/k_1, was calculated as a ratio of logarithms as shown in Table II, in accordance with the theory for competing reactions, first order in acetylating agent and first order in acetylmethylhydrazine.[5] The nearly constant value for the ratio throughout the course of the experiment indicates that **2** is only ~1.5 times as rapidly acetylated as **1**, and this cannot be an important cause of the high ratio of 1/2 in the products of acetylation with acetic anhydride. It is noteworthy, however, that in its reaction with the mixture of acetylmethylhydrazines, as in its reaction with methylhydrazine, acetic anhydride prefers the methylated (more nucleophilic) nitrogen.

Acid Catalysis.—In monitoring by nmr the reaction between methylhydrazine and ethyl acetate, an initial slow period was observed, which was suggestive of acid catalysis by the ethanol produced as a by-product. The acid catalysis was confirmed strikingly in parallel runs made in nmr sample tubes heated in an oil bath, in which the rates with added ethanol, with water, and with acetic acid were compared with the rate with no additive. The results are presented in Figure 1. Ethanol, water, and acetic acid were increasingly effective in that order, which is the order of increasing acidity.

Tests for Thermodynamic Control.—The possibility was considered that the difference in the results with anhydrides and esters is a consequence of kinetic vis-à-vis thermodynamic control. The reaction with an anhydride is very fast at ambient temperatures and gives a ratio, 1/2, that is much different from the isomerization equilibrium ratio (see below). The result is very likely one of kinetic control. The reaction with an ester, however, requires prolonged heating at the boiling point of the mixture, and it seemed possible that under these conditions a first-formed 1-acyl-1-methylhydrazine might undergo rearrangement to a more stable 1-acyl-2-methylhydrazine to give a result thermodynamically controlled.

To test for thermodynamic control, the stability of **1** under acetylating conditions leading mainly to **2** (boiling ethanol–ethyl acetate, 87°) was determined. No rearrangement of **1** to **2** was observed after 71 hr of heating with ethyl acetate. Upon addition of ethanol, then water, and then acetic acid to the same mixture, each addition being followed by periods of heating and examination by nmr spectroscopy, a very slow acid-catalyzed rearrangement, accompanied by a similar amount of acetylation (by acetic acid) to 1,2-diacetyl-1-methylhydrazine, was observed. The data are not presented in detail because of a more cogent experiment, presented as run 4 in Table I.

In run 4, Table I, methylhydrazine was acetylated with ethyl acetate in the presence of much added **1**. The results should be compared with those of run 3, made under essentially the same conditions, but without added **1**. In both runs, ~80% (0.8 mol) of the methylhydrazine was acetylated. In run 4, however, there was almost no *net* production of **1**, whereas comparison with run 3 indicates ~0.2 mol must have been produced. About 0.2 mol of **1**, 40% of that originally present, must have isomerized to **2**.

The reactions may be treated as first order, since the ethyl acetate was present in excess. Applying the first-order rate law to the data in the preceding paragraph leads to the conclusion that the specific rate of

(7) These practical yields are a little lower than what is indicated by the data in Table I because the data in the table include the **1** and **2** contained in other fractions from the distillation.

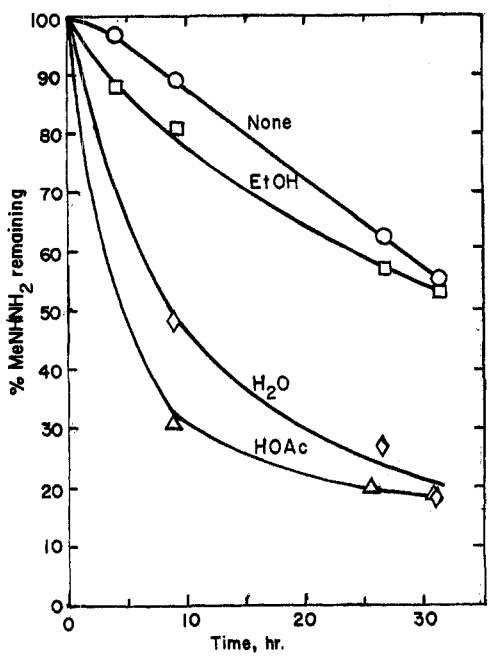


Figure 1.—Brønsted acid catalysis of the acetylation of methylhydrazine with ethyl acetate at 82°.

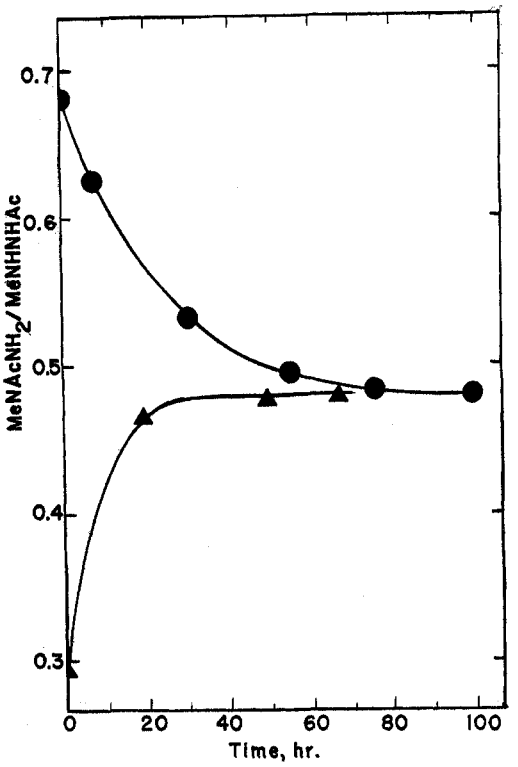


Figure 2.—Equilibration of 1-acetyl-1- and 1-acetyl-2-methylhydrazine with acetic acid in ethanol at 87°.

isomerization of **1** to **2** is about $^1/_3$ the specific rate of acetylation of methylhydrazine with ethyl acetate. Below it is shown that the equilibrium ratio, **1**/**2**, at 87° is 0.49, which is larger than the ratio, 0.30, obtained from the reaction with ethyl acetate, If anything, therefore, the acetylation with ethyl acetate must be accompanied by isomerization of **2** to **1**, rather than the reverse. From the equilibrium ratio it is clear that the rate of isomerization of **2** to **1** is $\sim^1/_2$ the rate of isomerization of **1** to **2**, or $\sim^1/_6$ the rate of acetylation of methylhydrazine with ethyl acetate. The latter reaction is therefore predominantly a kinetically controlled process.[8]

Equilibrium between 1 and 2.—For the analysis in the foregoing section, it was necessary to know the equilibrium ratio, **1**/**2**. This was determined at two temperatures, 27 and 87°, to permit calculation of the thermodynamic functions, ΔH^0 and ΔS^0. Mixtures of the two isomers with 10–20 mol % of acetic acid in nmr sample tubes were kept at the appropriate temperature and examined by nmr from time to time, until the ratio of **1**/**2**, became constant. The isomerization was accompanied by a relatively rapid disproportionation of 10–20% of the material to methylhydrazine (present in part as the acetate) and 1,2-diacetyl-1-methylhydrazine, and by some further acetylation to 1,2-diacetyl-1-methylhydrazine. Typical data are presented in Figure 2, and the results in Table III.

TABLE III

THE EQUILIBRIUM, MeNHNHAc (**2**) ⇌ $MeNAcNH_2$ (**1**)

Temp, °C	27	87
K, **1**/**2**	0.39 ± 0.02	0.49 ± 0.01
ΔG^0, cal/mol (liquid)	560 ± 30	512 ± 15
ΔH^0, cal/mol	785 ± 40	
ΔS^0, cal/deg mol	0.75 ± 0.6	

Discussion

The failure of esters and anhydrides to obey the reactivity–selectivity principle in their reactions with methylhydrazine may be a consequence of a difference in mechanism. A nucleophilic displacement of the BAC2 type would be expected to occur with anhydrides,[9] while an addition–elimination mechanism, like that proposed for ester and amide hydrolyses,[10] would be expected with esters. Application of these ideas to be present study may be made clear by reference to eq 6 and 7 and Figures 3 and 4.

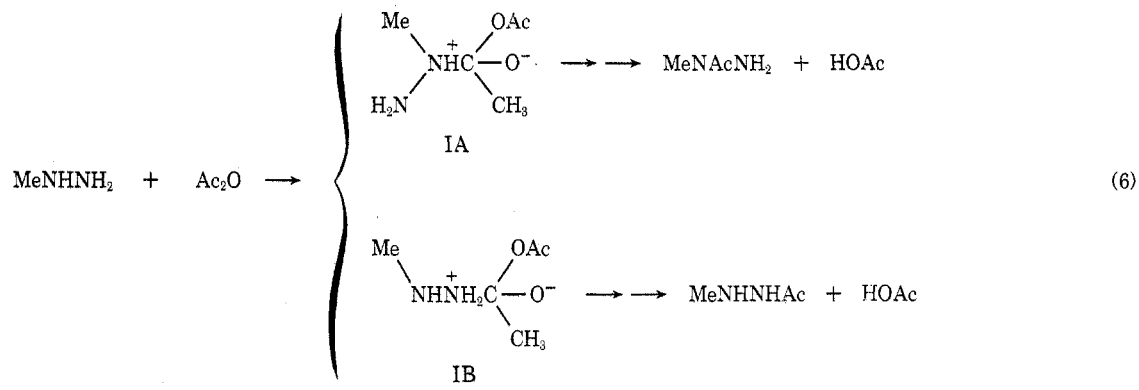
Both reactions may be initiated by nucleophilic attack by either nitrogen on the carbon of the carbonyl group to give the dipolar ions IA and IB (from acetic anhydride) or IIA-1 and IIB-1 (from ethyl acetate). The reaction with acetic anhydride is very fast, even at subambient temperatures, and is also sensibly exergonic, as cooling with ice is necessary to control the temperature. A reasonable estimate for its activation free energy, ΔG^*, would be not much more than 15 kcal/mol, and a reasonable estimate for ΔH and ΔG would be −15 kcal/mol. From the product ratio, **1**/**2**, of 38, a difference in activation free energies, $\Delta\Delta G^*$, of 2.2 kcal at 27° can be calculated ($2.303RT$ log 38). The dipolar ions IA and IB shed an acetate ion readily and go on by way of proton transfers to form products having a free-energy difference of 560 cal at 27°. These energy relationships are depicted in Figure 3.

The fact that the less stable product is formed the

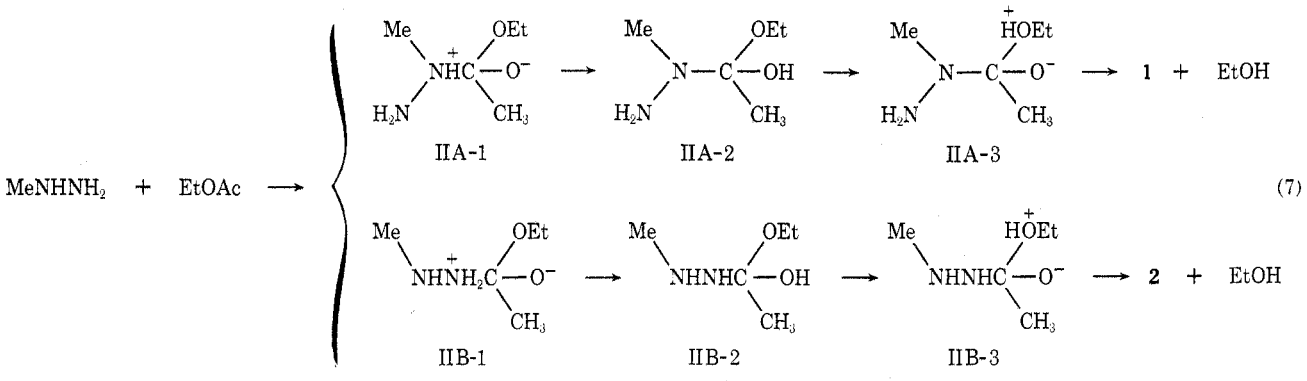
(8) Further evidence is available from monitoring the reaction by nmr. The ratio, **1**/**2**, is seen to be ~0.3 right from the start. Both **1** and **2** are primary products, therefore.

(9) (a) V. Gold, *Trans. Faraday Soc.*, **44**, 506 (1948); (b) E. Berliner and L. H. Altschul, *J. Amer. Chem. Soc.*, **74**, 4110 (1952); (c) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 754.

(10) (a) M. L. Bender, *J. Amer. Chem. Soc.*, **73**, 1626 (1950); (b) M. L. Bender and R. D. Ginger, *ibid.*, **77**, 348 (1955).



(6)



(7)

most rapidly is a consequence of the greater nucleophilicity of the methylated nitrogen, which is observed also in the reactions of alkylhydrazines with alkyl halides.[11] The dipolar ions IA and IB differ essentially only in having a methyl replacing hydrogen on a positively charged nitrogen. From earlier work,[12] the inductive effect of a methyl replacing hydrogen in stabilizing an ammonium ion can be calculated. It is a factor of 46, or 2.3 kcal at 27°, *almost precisely the same as is indicated by the results here with acetic anhydride!*

The reaction with ethyl acetate, by comparison, is slow, even at elevated temperatures (87°) and is not sensibly exergonic. In no case was the reaction observed to go to completion, even in a reaction mixture that stood at room temperature for 6 months (run 2). A nearly isergonic reaction is indicated, and a reasonable estimate for the activation free energy would be not much less than 25 kcal/mol.

The activation energy barriers leading to IIA-1 and IIB-1 may not be much different from those leading to IA and IB. In both cases, A and B differ essentially in having a methyl replacing hydrogen on a positively charged nitrogen, and the same stabilizing inductive effect would be expected. The dipolar ions, IIA-1 and IIB-1, do not readily shed an ethoxide ion, however, but find it easier to revert to starting materials by shedding the weaker base, methylhydrazine. They may, however, be converted by tautomerization into the addition products, IIA-2 and IIB-2, and thence into the new dipolar ions, IIA-3 and IIB-3, which can readily shed an alcohol molecule to give the final products.

The dipolar ions, IIA-3 and IIB-3, with protonated ether-type oxygen, must certainly be higher in energy than the dipolar ions, IIA-1 and IIB-1, with protonated amine-type nitrogen. An energy difference of 13 kcal/mol, which corresponds to a ΔpK of ~8 at 87°, is not unreasonable. The nonpolar intermediates, IIA-2 and IIB-2, must be lower in energy than either of the dipolar forms but, to remain undetected, must be much richer in energy (10 kcal?) than the starting materials. These energy relationships are depicted in Figure 4.

The ester reaction, then, involves a relatively rapid establishment of equilibrium between the starting materials and the intermediate addition products, IIA-2 and IIB-2, followed by slow conversion of these to the products at equal rates. The product ratio is determined by the relative stabilities of the intermediates, which are similar to, but not identical with, the products. The product ratio, 0.3, ignoring possible isomerization of **2** to **1** during acetylation, corresponds to an energy difference of 860 cal at 87°. It is probable that steric factors determine the relative stabilities, for **1** and IIA-2, with two bulky substituents on the same nitrogen, are more crowded molecules than **2** and IIB-2.

The acid catalysis observed with the ester reaction is presumably a consequence of an acid's aiding in protonation to form the intermediates, IIA-3 and IIB-3. It should be obvious, furthermore, that the reaction could be discussed in terms of intermediates differing by a proton from those used here. They would simply have to be drawn on another energy profile, similar to the one used here.

An intermediate like IIA-3 and IIB-3 has been implicated in the aminolysis of esters in aqueous solution,[13] and seems particularly likely in the case of methyl formate at low pH.[14] These and other extensive studies of the kinetics of aminolysis in aqueous solution[15] are

(11) (a) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 4400 (1967); (b) R. A. Hasty and S. L. Sutter, *J. Phys. Chem.*, **73**, 3154 (1969); (c) H. H. Sisler, G. M. Omietamski, and B. Rudner, *Chem. Rev.*, **57**, 1021 (1957), and references therein.

(12) F. E. Condon, *J. Amer. Chem. Soc.*, **87**, 4485 (1965). In the absence of hydration, $\Delta pK_2 = 3.38\Delta\sigma^*$ for ammonium ions, and $\Delta\sigma^* = 0.49$ for methyl and hydrogen.

(13) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

(14) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).

(15) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967), and references therein.

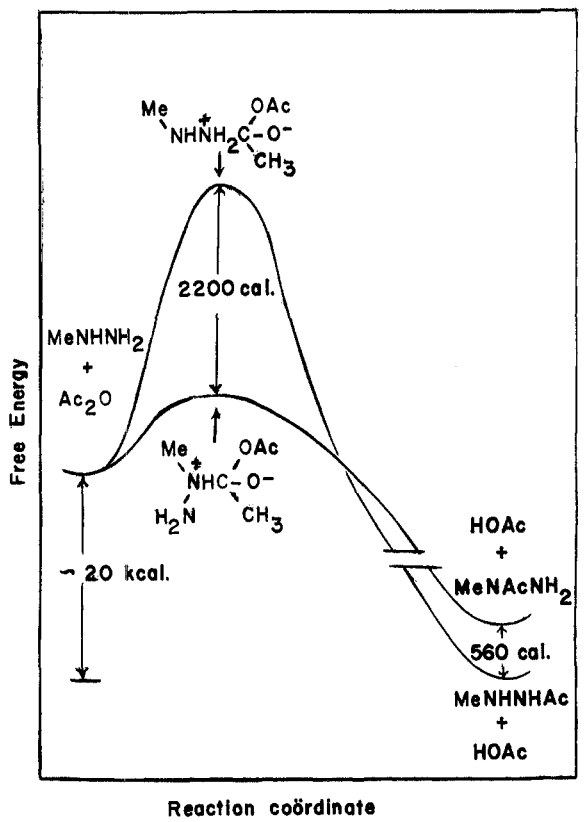


Figure 3.—Potential energy profile for acetylation of methylhydrazine with acetic anhydride at 27°.

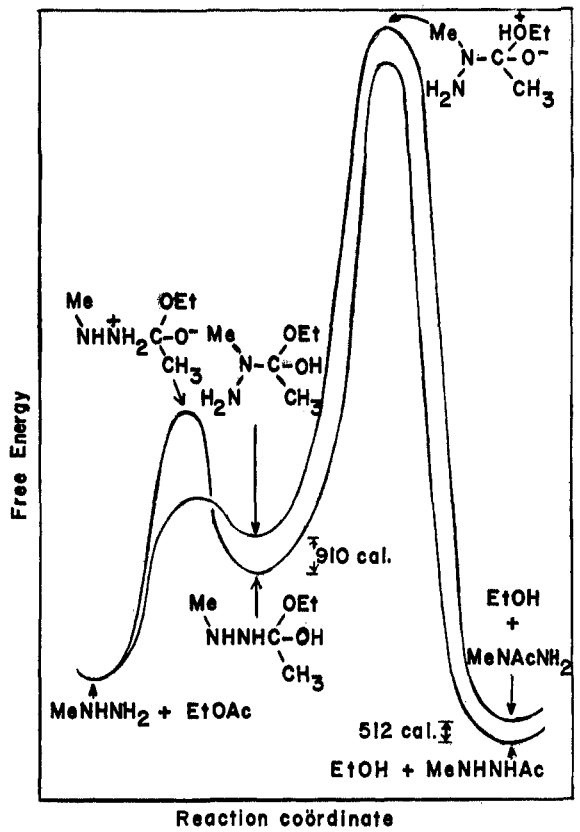


Figure 4.—Potential energy profile for acetylation of methylhydrazine with ethyl acetate at 87°.

not of much help, however, in understanding the phenomena described here. The failure to detect acid catalysis of the hydrazinolysis of phenyl acetate in aqueous solution,[15] for example, may be due to overriding catalysis by the water present. The conditions used here resemble more those of ammonolysis of esters in liquid ammonia, where acid catalysis by ammonium salts has been observed,[16] and in butylamine, where catalysis by water has been demonstrated.[17]

If the mechanisms with the two types of acetylating agents are different, their failure to conform to the reactivity–selectivity principle is not surprising, since this principle should be applied only to reagents that react by essentially the same mechanism.[2] The result with anhydrides, then, is a consequence of the greater nucleophilicity of the methylated nitrogen, while an explanation of the results with esters must be sought in the reasons, possibly steric,[1a] for differences in the stabilities of two alternative metastable intermediate addition products.

Experimental Section

Materials and Instruments. **Methylhydrazine** was obtained from Matheson Coleman and Bell, Inc., E. Rutherford, N. J. With 0.1 *N* HCl it gave a titer indicating 100% purity. It was used without prior treatment.

Nmr spectra were obtained on a Varian A-60 instrument. Melting points were taken with a Hoover-Thomas capillary melting point apparatus and are uncorrected.

Acetylation of Methylhydrazine with Ethyl Acetate.—Run 1, Table I, is described in detail. A mixture of 47.2 g (1.025 mol) of methylhydrazine, 107.4 g (1.22 mol) ethyl acetate, and 1.9 g (0.1 mol) water as catalyst was heated under reflux with protection from atmospheric moisture for a total of 50 hr in the course of 11 days. Heating periods alternated with periods during which the reaction mixture stood at room temperature, and the mixture was sampled almost daily by nmr spectroscopy. Near the end of the heating period, the temperature of the boiling mixture was 89°, and the nmr spectrum indicated that ~80% of the methylhydrazine had reacted.

The reaction mixture, now 147 g because of a 9.5-g loss due to evaporation, sampling for nmr analysis, and handling, was distilled under reduced pressure[18] and yielded fraction 1, boiling to 83° (60 Torr), 69.0 g; fraction 2, boiling to 140° (12 Torr), 71.5 g; residue, 3.0 g; loss on distillation, 3.5 g. Analysis by nmr spectroscopy showed that fraction 1 consisted of ethyl acetate (24.1 g), ethanol (37.6 g), methylhydrazine (5.4 g), and water (1.9 g). fraction 2 consisted of 1-acetyl-1-methylhydrazine (15.8 g) and 1-acetyl-2-methylhydrazine (55.7 g). The residue was 1,2-diacetylmethylhydrazine. The nmr spectrum ($CHCl_3$ with internal TMS) showed singlets at 2.01, 2.04, and 3.07 ppm ($CHCl_3$, 60% by wt, singlet at 463.4. Hz).

Run 2, Table I, was done similarly except that the heating period was uninterrupted, and the reaction mixture stood for 6 months at room temperature before being distilled.

Isolation of 1-Acetyl-2-methylhydrazine.—Fraction 2, above, was cooled in an ice bath, and the crystalline product so formed was collected by filtration with suction: yield 25 g; white needles; mp 38–42°; bp (observed during distillation above) ~110–111° (12 Torr). The nmr spectrum, in CCl_4 with TMS, consisted of two somewhat broadened singlets at δ 1.93 and 2.56 ppm. The nmr spectrum indicated 4% isomer 1.

Anal.[19] Calcd for $C_3H_8N_2O$: C, 40.90; H, 9.15. Found: C, 40.90; H, 9.07.

A second crop of less pure material was obtained by rechilling the filtrate in ice and refiltering, and a third crop of 3 g was obtained by cooling the filtrate from the second crop in a freezer at

(16) L. F. Audrieth and J. Kleinberg, *J. Org. Chem.*, **3**, 312 (1938).

(17) P. K. Glasoe, L. D. Scott, and L. F. Audrieth, *J. Amer. Chem. Soc.*, **63**, 2965 (1941).

(18) To minimize losses, a simple Claisen flask was used, with a receiver consisting of a simple distilling flask attached to the side arm by means of a rubber stopper, and an extremely fine capillary bleed was used as an aid to smooth ebullition. *Cf.* R. Adams and J. R. Johnson, "Laboratory Experiments in Organic Chemistry," Macmillan, New York, N. Y., 1949, p 365.

(19) All analyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

−10°. Total yield of solid product was 36 g (40%). The compound yellowed on standing, as was observed by Hinman and Fulton with other 1-acyl-2-methylhydrazines.[1,20]

Acetylations with Acetic Anhydride.—The most consistent results were obtained by use of mechanical stirring and the procedure now to be described, which was used in runs 5, 8, 9, and 10. A 1-l. or (in run 8) 2-l. three-necked flask was fitted with a sealed motor-driven stirrer, a thermometer, and, in the other side neck, a 125- or (in run 8) 250-ml pressure-equilizing dropping funnel. The stem of the dropping funnel was extended into the liquid (later charged to the flask) by attachment (by means of a short length of Tygon tubing) of a glass tube constricted at the lower end to ~1 mm (Pasteur pipet).

The solvent and then the methylhydrazine were placed in the flask. When acetic acid was the solvent, the methylhydrazine was introduced with cooling beneath the surface of the acid by means of the modified dropping funnel already described. The contents of the flask were cooled to 10°, and the acetic anhydride was introduced in a thin stream beneath the surface of the liquid with stirring and cooling at such a rate as to maintain the temperature within desired limits (1–9 hr).[22] In runs with acetic acid as solvent, pyridine (1.2 mol/mol of $MeNHNH_2$) was introduced at this point in the same manner as the acetic anhydride.

The glass tubing extension to the dropping funnel was removed, and 50% sodium hydroxide (1.05 mol/mol of HOAc)[23] was added in the course of ~1 hr with stirring and cooling so as to maintain the temperature below 25°. The mixture was then stored at least overnite in a freezer at −10° to complete crystallization of the sodium acetate trihydrate.

The solid was filtered with suction. A Dry Ice cooled trap was interposed between the aspirator and filter flask to prevent loss.[24] The solid was transferred to a beaker and mixed throughly with solvent for extraction (ether, pyridine, or chloroform, 50 ml/mol of $MeNHNH_2$ charged; see Table I). The mixture was filtered with suction into a clean, dry flask. The extraction was repeated twice. The combined extracts, kept separate from the primary filtrate, were distilled at 30–40°, ether being distilled at atmospheric pressure, chloroform at 140 Torr, and pyridine at 20–30 Torr. A Dry Ice trap was used to prevent loss.[18]

The primary filtrate was added to the residue from distillation of the extracts, and distillation was continued under reduced pressure. After removal of pyridine (in run 10, triethylamine and chloroform), some water, and unchanged methylhydrazine, a small intermediate fraction was collected, boiling to ~100° (25 Torr). At this point, the residue in the flask usually became thick with solid (sodium acetate?), which interfered with further distillation. It was cooled, therefore, mixed with a little ether or, better, chloroform, and filtered with suction through a small fritted-glass funnel. Distillation was then continued with an oil pump at 1–2 Torr. A fraction consisting almost wholly of **1** and **2**, with ~2% 1,2-diacetylmethylhydrazine, was collected in the range of 80–130° (2 Torr). The residue was weighed and then dissolved in chloroform or water for analysis by nmr spectroscopy. All the fractions, including those collected in the Dry Ice trap, were weighed and analyzed by means of nmr spectroscopy.

In early modifications of the above-described procedure, used in the other runs in Table I, the acetylation was carried out in an erlenmeyer flask open to the atmosphere; the acetic anhydride was introduced by hand by means of a Pasteur pipet; and mixing was by hand swirling of the flask.

Isolation of 1-Acetyl-1-methylhydrazine.—The acetylmethylhydrazine fraction from run 6, amounting to 24.5 g, was found by nmr spectroscopy to be ~96% **1** and ~2% each of **2** and diacetylmethylhydrazine. Redistillation under reduced pressure gave 23 g (0.26 mol, 39%) of 98% pure **1**, bp 103° (8 Torr), mp 16°. The nmr spectrum, in CCl_4 with internal TMS, consisted of two sets of singlets, indicative of the syn–anti isomerism characteristic of amides. An inner set, with δ 2.16 and 3.15 ppm, was ~2.5–3.0 times as intense as the outer set, with δ 2.06 and 3.23 ppm, D^{25} 1.0678 g/cm³.

Anal. Calcd for $C_3H_8N_2O$: C, 40.90; H, 9.15. Found: C, 40.72; H, 8.88.

Work-Up of Synthetic Mixtures.—The method of work-up and analysis of the products of acetylation with acetic anhydride entailed extensive handling and was accompanied by some loss, apparently because of retention of material by the sodium acetate trihydrate. Two synthetic mixtures of known composition were worked up and analyzed by the same method, therefore, to determine whether the loss was strongly selective of any of the components. Results are presented in Table IV. In addition to the components listed there, mixture 1 contained at the start acetic acid and pyridine in proportions similar to those present at the conclusion of the acetylation runs, 6–9, Table I. Mixture 2 was made to contain acetic acid and triethylamine, as in run 10. Each mixture was treated with 50% sodium hydroxide sufficient to neutralize the acetic acid and was then worked up and analyzed as described above.

TABLE IV
RESULTS OF WORK-UP OF SYNTHETIC MIXTURES

Mixture	1	2
Extractive	Pyridine	Chloroform
Component, mol charged (found)		
$MeNHNH_2$	0.236 (0.182)	0.137 (0.111)
$MeNAcNH_2$	0.203 (0.210)	0.166 (0.133)
MeNHNHAc	0.268 (0.250)	0.207 (0.145)
MeNAcNHAc	0.210 (0.122)	0.182 (0.126)
Loss, mol	(0.153)	(0.177)

On the whole, the results in Table IV show that the losses were not strongly selective of any one component, the relatively low recoveries of methylhydrazine and diacetylmethylhydrazine from mixture 1 being regarded as artifacts of that experiment. They provide an indication of the limits of uncertainty of the results in Table I, but to use them as the basis of an "adjustment" of the earlier data does not seem justified.

Competitive Acetylation of 1 and 2.—A nearly equimolar mixture of the isomers was prepared in an nmr sample tube and the nmr spectrum and integrator curves were run. A small amount of acetic anhydride was introduced beneath the surface of the mixture by means of an elongated Pasteur pipet, care being taken to distribute the anhydride throughout the mixture during its addition, so as to avoid an effect of localized depletion of one of the isomers through reaction with the anhydride. The nmr spectrum and integrator curves were run again. Additions of acetic anhydride and spectral determinations were continued until a total of six portions of the anhydride had been added and almost half of the acetylmethylhydrazines had been consumed.

Data and results are presented in Table II. The $MeNAcNH_2$ and MeNAcNHAc were measured together by means of their N-CH_3 signals in the region of δ 3.0–3.3 ppm from TMS. The MeNHNHAc, n_2, was measured by its isolated N-CH_3 signal at 2.56 ppm. In addition, the total of the acetyl group signals (including that due to acetic acid) was measured in the region of 1.8–2.2 ppm. The integrator data were reduced to a common basis of 100 for the total of the N-CH_3 signals. The decrease in the relative number of moles of MeNHNHAc was then clearly apparent. The increase in the total acetyl was divided by two to correct for the acetic acid contribution. From this quotient was subtracted a contribution due to MeNAcNHAc produced from MeNHNHAc, equal to the decrease in MeNHNHAc. The remainder was regarded as a contribution due to MeNAcNHAc produced from $MeNAcNH_2$ and provided the means of calculating the remaining $MeNAcNH_2$, n_1.

Acid Catalysis.—Four identical nmr sample tubes were charged as follows: (1) EtOAc + $MeNHNH_2$, (2) EtOAc + EtOH + $MeNHNH_2$, (3) EtOAc + H_2O + $MeNHNH_2$, and (4) EtOAc + HOAc + $MeNHNH_2$. The nmr spectra and integrator curves were obtained before and after addition of the $MeNHNH_2$, and again after about 4, 9, 26, and 31 hr of heating in an oil bath at

(20) The yellowing was thought to be due to air oxidation to acetylazomethane, $CH_3CON{=}NCH_3$, but an attempted oxidation of **2** with mercuric oxide according to published procedures[21] was accompanied by gas (N_2?) evolution and failed to give any acetylazomethane.

(21) R. Renaud and L. C. Leitch, *Can. J. Chem.*, **32**, 545 (1954).

(22) In runs with pyridine as solvent, the nmr spectrum of the mixture at this stage shows that **1** and **2** are present in a ratio of 40:1. If the mixture is allowed to stand overnight at room temperature, however, the ratio decreases to ~10:1. Similarly, if the reaction mixture is distilled under reduced pressure (~25 Torr) at this stage, the ratio of **1**/**2** in the distillate is generally found to be somewhat less than 10, apparently because of acetic acid catalyzed rearrangement of **1** to **2**.

(23) A slight excess of sodium hydroxide is used to ensure complete neutralization of the acetic acid, but a large excess is avoided, as it causes saponification later during distillation of the product.

(24) If the objective were simply the preparation and isolation of **1**, the trap could be omitted.

82°. The following signals were variously used for analysis of the mixtures (δ, parts per million, from TMS external standard): CH_2CH_3 triplets, 1.0–1.5; $MeNHNHCOCH_3$, 1.93; $EtOCOCH_3$, 2.00; total $COCH_3$, 1.8–2.3; $CH_3NHNHAc$, 2.56; CH_3NHNH_2, 2.56 in neutral medium, 2.59 with water present, and 2.83 with HOAc present; $CH_3NAcNHAc + CH_3NAcNH_2$, 3.0–3.3; CH_3CH_2OH quartet, 3.4–3.9; CH_3CH_2OAc quartet, 3.9–4.4; and NH and OH, further downfield. The initial compositions (molar ratios, averages based on nmr analyses) were as follows: (1) $MeNHNH_2$/EtOAc, 1.0/1.3; (2) $MeNHNH_2$/EtOAc/EtOH, 1.0/1.3/0.5; (3) $MeNHNH_2$/EtOAc/H_2O, 1.0/1.4/0.7; and (4) $MeNHNH_2$/EtOAc/HOAc, 1.0/0.85/0.6. The percentages of methylhydrazine reacted at various times are shown in Figure 1.

Equilibrations of 1 and 2.—About 0.4-ml samples of mixtures of the two isomers were placed in nmr sample tubes and a few drops of glacial acetic acid were added. In some runs at 87°, ethanol was added to approximate the conditions of acetylation of methylhydrazine with ethyl acetate. The air was displaced by nitrogen, the tubes were tightly capped, and the contents were mixed by thorough shaking. The tubes were either kept at room temperature (27°) or in a constant-temperature bath at 87°, comprised of ~400 ml of water contained in a 500-ml erlenmeyer flask resting on a thermostated hot plate and loosely stoppered to retard evaporation of the water.

They were examined from time to time by nmr. The amounts of acetic acid and alcohol were estimated from the nmr spectra. The acetic acid was 10–20 mol % and the alcohol 80 mol % of the total hydrazine content. In one sample at room temperature, the ratio, **1**/**2**, changed from 16 to 0.37 in the course of 154 days, while in another the ratio went from 0.32 to 0.41 in the same period, to give an average equilibrium ratio of 0.39 ± 0.02. Runs at 87° required ~100 hr for equilibration and gave an average equilibrium ratio of 0.49 ± 0.01, with or without alcohol. (See Figure 2.)

Registry No.—**1**, 3530-13-0; **2**, 29817-35-4; methylhydrazine, 60-34-4; acetic anhydride, 108-24-7; ethyl acetate, 141-78-6.

Synthesis of 1-Alkyl-2-methylhydrazines by Way of Hydrazones of 1-Acetyl-1-methylhydrazine

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1-Acetyl-1-methylhydrazine was converted to acetylmethylhydrazones by reaction with the aldehydes and ketones: formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, benzaldehyde, acetone, and 2-butanone. Boiling points, densities, and nmr spectra of these hydrazones are reported. By reduction with sodium borohydride in ethanol, followed by hydrolysis with dilute hydrochloric acid, each hydrazone, except benzaldehyde acetylmethylhydrazone, was converted to the corresponding 1-alkyl-2-methylhydrazine. Boiling points and nmr spectra of the following are reported: 1-ethyl-2-methyl-, 1-methyl-2-propyl-, 1-isopropyl-2-methyl-, 1-butyl-2-methyl-, 1-isobutyl-2-methyl-, and 1-*sec*-butyl-2-methylhydrazine and 1-acetyl-1-methyl-2-ethylhydrazine.

It has been shown that the acetylation of methylhydrazine with acetic anhydride can be controlled so as to give chiefly 1-acetyl-1-methylhydrazine (**1**), accompanied by small amounts of its isomer, 1-acetyl-2-methylhydrazine (**2**), and 1,2-diacetyl-1-methylhydrazine; and **1** of 96% purity was obtained in 76% yield.[1] In this paper is described the use of **1** for the synthesis of some 1-alkyl-2-methylhydrazines as shown in eq 1.

$$\underset{\mathbf{1}}{MeNAcNH_2} + R_1R_2C{=}O \longrightarrow MeNAcN{=}CR_1R_2 \xrightarrow{NaBH_4} MeNAcNHCHR_1R_2 \xrightarrow[2.\ NaOH]{1.\ H_2O,\ HCl} MeNHNHCHR_1R_2 \quad (1)$$

The hydrazines obtained in good yield were 1,2-dimethyl-,[2] 1-ethyl-2-methyl-,[3] 1-isopropyl-2-methyl-,[3,4] 1-methyl-2-propyl-,[4b] 1-butyl-2-methyl-,[5] 1-isobutyl-2-methyl-, and 1-*sec*-butyl-2-methylhydrazine. The method failed in the case of 1-benzyl-2-methylhydrazine.[5a,6] Those for which references are given had been synthesized before by one method or another. The route from **1**, eq 1, provides an alternative method which seems preferable in many cases.

Each of the 1-alkyl-2-methylhydrazines made here might have been made by lithium aluminum hydride reduction of an appropriate formylhydrazone, $HCONHN{=}CR_1R_2$, for example.[4b] Lithium aluminum hydride reduction of hydrazides, however, is frequently accompanied by cleavage at the acyl–nitrogen bond.[7] In the present case, this would have led to 1-alkyl-2-methylhydrazine accompanied by a monoalkylhydrazine having nearly the same boiling point. This possibility may account for the failure of the earlier workers to obtain good analytical results for dialkylhydrazines made that way and for the low yields of azoalkanes obtained from them by mercuric oxide oxidation. The new route described here is free of this complication and gave dialkylhydrazines for which acceptable analyses were obtained.

Experimental Section

Materials and Instruments.—These were as described in previous publications from this laboratory.[1,8] Liquid densities were obtained with a U-shaped pyknometer having a volume of ~3.3 cm^3.

Preparation of Acetylmethylhydrazones. A. From Aldehydes.—Forty-six grams (0.50 mol) of 96% 1-acetyl-1-methylhydrazine[1] (containing 2% each of **2** and 1,2-diacetyl-1-methylhydrazine) was placed in a 250-ml erlenmeyer flask cooled in an ice bath, and 0.55 mol of freshly distilled aldehyde was introduced beneath the surface by means of a Pasteur pipet with swirling and cooling so as to maintain the temperature below 25°. Formaldehyde was used as a 37% aqueous solution, and acetaldehyde as a 58% aqueous solution. In these two cases, 15 g of sodium

(1) F. E. Condon, *J. Org. Chem.*, **37**, 3608 (1972).

(2) 1,2-Dimethylhydrazine dihydrochloride is available commercially from Aldrich Chemical Co., Milwaukee, Wis.

(3) N. V. Khromov-Borisov and T. N. Kononova, *Probl. Poluch. Poluprod. Prom. Org. Sin., Akad. Nauk SSSR, Otd. Obshch. Tekh. Khim.*, 10 (1967); *Chem. Abstr.*, **68**, 4721 (1968).

(4) (a) H. C. Ramsperger, *J. Amer. Chem. Soc.*, **51**, 918 (1929); (b) L. Spialter, D. H. O'Brien, G. L. Untereiner, and W. A. Rush, *J. Org. Chem.*, **30**, 3278 (1965).

(5) (a) G. H. Coleman, H. Gilman, C. E. Adams, and P. E. Pratt, *ibid.*, **3**, 99 (1938); (b) E. Schmitz, *Angew. Chem.*, **73**, 23 (1961).

(6) J. Thiele, *Ann.*, **376**, 239 (1910).

(7) R. L. Hinman, *J. Amer. Chem. Soc.*, **78**, 1645 (1956).

(8) F. E. Condon and D. Fărcasiu, *ibid.*, **92**, 6625 (1970).