

Alkylidenebis-1-methyl-2-alkylidenehydrazines as
Intermediates in the Reaction of Methylhydrazine with Aliphatic Aldehydes (1)

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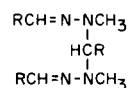
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It has been shown that heptylidenebis-1-methyl-2-heptylidenehydrazine (Va) is an intermediate in the reaction of methylhydrazine with heptanal. The bis-compound (Va) reacts with methylhydrazine to give heptanal methylhydrazone (IIa), or with heptanal, in the presence of acid, to afford 5-hexyl-1-methyl-4-pentyl-2-pyrazoline (Ia). The latter also results from the treatment of IIa with acid.

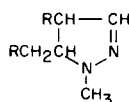
A previous investigation (3) reported a convenient synthesis of 1,4,5-trialkyl-2-pyrazolines (I) from equal amounts of an aldehyde and a methylhydrazone (II), or from two moles of an aldehyde and one mole of methylhydrazine. It was proposed that structures such as III might be intermediates in the formation of the pyrazolines (I). Carbinolamines are believed to be involved in reactions which lead to oximes, semicarbazones and Schiff's bases (4), and similar molecules should be expected from aldehydes and methylhydrazine.

Since an excess of an aldehyde was present in the condensation with methylhydrazine to obtain II according to the method of Wiley and Irick (5), and a comparable situation existed in the procedure used for synthesizing the pyrazolines (I) (3), it seemed likely that III or IV might be common intermediates in hydrazone and pyrazoline formation, and that experimental conditions could determine which type of product would result.

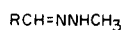
An nmr spectrum of a reaction mixture obtained by adding methylhydrazine to a cold, well-stirred solution of heptanal (5) showed the presence of IIa and an unknown component. The latter was identified as heptylidenebis-1-methyl-2-heptylidenehydrazine (Va) by comparing the $\text{CH}_3\text{-N}$ (δ 2.60, s, 6), CH=N (δ 6.25, t, 2, J = 5 Hz) and N-CH-N (δ 4.53, t, 1, J = 7 Hz) absorptions with those of authentic Va. Alkylidenebis-1-methyl-2-alkylidenehydrazines (V) have been found (3,6) to be involved in the thermal decomposition of II which led to nitriles and methylamine.



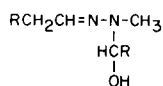
Va, R = C₆H₁₃
b, R = iso-C₃H₇



Ia, R = C₅H₁₁



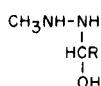
IIa, R = C₆H₁₃
b, R = iso-C₃H₇



III



or



IV

Similarly, nmr spectra of reaction mixtures prepared by adding IIa to heptanal, or the inverse, indicated that Va and an approximately equal amount of heptanal were present rather than Ia. Qualitative studies then were undertaken to determine the effects of experimental variables on the formation of IIa (from 1 mole of aldehyde and 1 mole of methylhydrazine). The results, obtained by nmr, are given in Table I and in the Experimental.

It is evident from these data that Va is an intermediate in the formation of both Ia and IIa, and that its extent is related to a number of variables. The relatively good yields of Ia and IIa reported in the literature (3,5) were

TABLE I

Reaction of Heptanal and Isobutyraldehyde with Methylhydrazine (a)

Aldehyde	Temp. °C	Time, Hours	Solvent	Addition Technique (b)	Alkylidene Ratio (c)
C ₆ H ₁₃ CHO	0	3	C ₆ H ₆	N	1.6
C ₆ H ₁₃ CHO	10	3	C ₆ H ₆	N	1.5
C ₆ H ₁₃ CHO	20	3	C ₆ H ₆	N	1.8
C ₆ H ₁₃ CHO	30	3	C ₆ H ₆	N	1.6
C ₆ H ₁₃ CHO	50	3	C ₆ H ₆	N	1.6
C ₆ H ₁₃ CHO	50	3	C ₆ H ₆	I	0 (d)
C ₆ H ₁₃ CHO	0	3	C ₂ H ₅ OH	N	0.04 (e)
C ₆ H ₁₃ CHO	20	3	C ₂ H ₅ OH	N	0.07
C ₆ H ₁₃ CHO	50	3	C ₂ H ₅ OH	N	0.2
C ₆ H ₁₃ CHO (f)	50	3	C ₂ H ₅ OH	N	0.3
C ₆ H ₁₃ CHO	0	3	H ₂ O	N	2.2
C ₆ H ₁₃ CHO	20	3	H ₂ O	N	1.5
C ₆ H ₁₃ CHO	50	3	H ₂ O	N	3.0
C ₆ H ₁₃ CHO	50	3	C ₂ H ₅ OH-H ₂ O 50:50	N	0.3
iso-C ₃ H ₇ CHO	10	3,6	H ₂ O	N	1.3, 0.9
iso-C ₃ H ₇ CHO	30	3,6	H ₂ O	N	4.0, 2.7
iso-C ₃ H ₇ CHO	50	3,6	H ₂ O	N	8.0, 5.3
iso-C ₃ H ₇ CHO	50	3	C ₂ H ₅ OH	N	0 (d)

(a) The molar ratio of aldehyde to methylhydrazine was 1:1 in all cases. (b) N, hydrazine added to aldehyde; I, inverse order. (c) Alkylidene ratios were calculated from nmr spectra and are the ratio of alkylidene groups present as Va to IIa or Vb to IIb. (d) NMR indicated that only hydrazone was present; (e) the alkylidene ratios are based on the assumption

that the area measured is due to Va. The proximity of the CH_3NHNH_2 and $\text{CH}_3\text{N} \begin{array}{l} \nearrow \text{N=} \\ \searrow \text{CH-N} \end{array}$ absorptions would make it

difficult to distinguish between the species if any of the former were present due to its solubility in ethanol; however, the trend indicated appears to be qualitatively correct; (f) the molar ratio of aldehyde to solvent was 1:10 except in this case where it was 1:5.

due to fortuitous isolation procedures since Va and heptanal and IIa and Va apparently were the principal initial products of the respective condensation reactions. Unreacted methylhydrazine would be present also in such mixtures, and equilibration of it with V, similar to that described for imine formation (7), could lead to II.

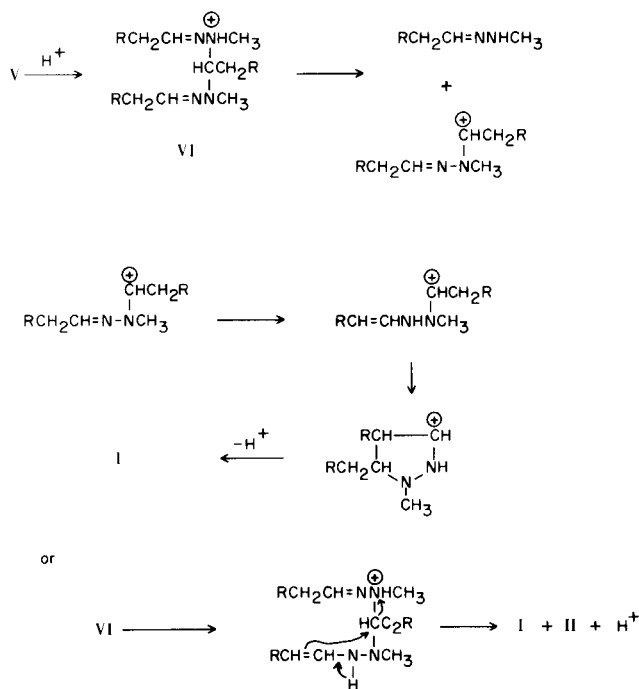
This was substantiated by reacting methylhydrazine with Va giving a nearly quantitative yield of IIa. The small amounts of pyrazolines (I) which are sometimes observed during the preparation of methylhydrazones may be rationalized by the fact that compounds V are known to decompose at 110-130° to give I and II (6).

The reaction of 2 moles of an aldehyde and 1 mole of

methylhydrazine which had been used to obtain I (3), seemingly led initially to a mixture of V and unchanged aldehyde. It also was found that, although in most cases some pyrazoline (I) is obtained after refluxing the reaction mixtures for 1.5 hours, complete formation of I resulted from the acid wash that was employed supposedly to remove any unreacted II. Only trace amounts of an aqueous acid were needed to convert the mixture of Va and heptanal to Ia. If a large excess of acid was used, a 3-phase system resulted in which the relative sizes of the two organic layers depended upon the amount of acid present. The system is believed to consist of Ia, hydrated Ia hydrochloride, and aqueous acid phases since the

addition of more water, or neutralization, led to free Ia.

When Va alone was allowed to react with 0.5 mole of 10% hydrochloric acid, Ia resulted immediately. The use of more than 0.5 mole equivalent of dilute acid gave the 3-phase system described above. The acid-catalyzed formation of I from V conceivably is represented by the following equations.



It was surmised from the stoichiometry of the above reaction that the pyrazolines (I) should be obtained when the methylhydrazones (II) are treated with aqueous acid. This was found to occur, for IIa afforded an 82% yield of Ia when it was reacted with 0.5 mole equivalent of 10% hydrochloric acid. A similar reaction has been reported by Kost and Sagitullin (8); however, they used anhydrous reagents and obtained quite low yields of pyrazolines.

The results of Run 6, Table I, are interesting in that they suggest that methylhydrazones should be prepared by adding an aldehyde to methylhydrazine. This procedure has afforded consistently high yields (85%) of methylhydrazones.

Although no evidence was obtained from the nmr data for carbinolamine intermediates such as III and IV, it seems reasonable that they are involved in the formation of V. Apparently they are too unstable to have been detected by nmr under the conditions employed in the present study.

EXPERIMENTAL

Boiling points are uncorrected; the microanalyses were

performed by Drs. Weiler and Strauss, Oxford, England. Infrared spectra were recorded on a Perkin-Elmer 237-B spectrophotometer, and the nmr spectra were determined at 60 MHz on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Gas chromatography was performed at various temperatures with a helium flow of 50 ml./min. on an Aerograph A90-P3 chromatograph.

Materials.

The methylhydrazine, heptanal and isobutyraldehyde were purchased from the Aldrich Chemical Co. The heptanal and isobutyraldehyde were distilled prior to use: b.p. 146-147°/746 mm., n_D^{25} 1.4110 (lit. (9a) b.p. 152.8°/760 mm., n_D^{20} 1.4257); b.p. 62-63°/746 mm.; n_D^{25} 1.3710 (lit. (9b) b.p. 63-64°/757 mm., n_D^{20} 1.3730).

Reaction of Methylhydrazine With Two Moles of Heptanal.

The general procedure described by Rabjohn, Havens and Rutter (3) was followed. A solution of 2.3 g. (0.05 mole) of methylhydrazine in 13 ml. of chloroform was added slowly to 11.4 g. (0.1 mole) of heptanal in 25 ml. of chloroform at such a rate as to keep the temperature at 50°. After the addition was completed, the reaction mixture was allowed to cool to room temperature at which time nmr analysis showed that only bis-compound (Va) and heptanal were present. The mixture was separated into two portions of about 25 ml. each. One portion was heated at reflux (80°) for 1.5 hours, cooled, and analyzed by nmr. Only incomplete pyrazoline (Ia) formation was detected, and an alkylidene ratio of 1.1 was recorded. Treatment of the other portion with 10 ml. of 10% hydrochloric acid, followed by 12 ml. of 10% sodium hydroxide resulted in complete decomposition of Va. Only Ia could be detected by nmr.

Reaction of Methylhydrazine with Two moles of Isobutyraldehyde.

A solution of 2.2 g. (0.048 mole) of methylhydrazine in 13 ml. of chloroform was added to 6.8 g. (0.095 mole) of isobutyraldehyde dissolved in 23 ml. of chloroform in the manner described in the previous experiment. After the reaction mixture had cooled to room temperature, only Vb and isobutyraldehyde could be detected by nmr. It was refluxed (80°) for 1.5 hours, but no change in its composition could be observed. The mixture then was treated with 20 ml. of 10% hydrochloric acid and neutralized. Although some decomposition of Vb was apparent, no pyrazoline was observed by nmr.

Addition of Methylhydrazine to Heptanal.

The procedure reported by Wiley and Irick (5) for synthesizing methylhydrazones was followed. Methylhydrazine (4.6 g., 0.1 mole) was added dropwise to 11.4 g. (0.1 mole) of heptanal, cooled to about -46° by a dry ice-acetone bath. The reaction mixture was allowed to warm to room temperature and nmr analysis showed an alkylidene ratio of 3. The mixture was heated to 120° for 0.5 hour, cooled and analyzed by nmr. An alkylidene ratio of 0.3 was observed. Water (15 ml.) and ether (50 ml.) were added, the layers were separated and the organic phase was dried over magnesium sulfate. The solvent was removed and the residue was distilled to give 6 g. (42%) of hydrazone, b.p. 60-61°/1.5 mm., n_D^{25} 1.4548 (lit. (5) b.p. 62°/0.2 mm., n_D^{26} 1.4555).

Preparation of Heptanal Methylhydrazone (IIa).

To a stirred solution of 92 g. (2 moles) of methylhydrazine in

100 ml. of benzene was added slowly 225 g. (1.97 moles) of heptanal. The mixture was refluxed under a Dean-Stark trap to remove the water. The residue was concentrated and distilled to give 241 g. (86%) of IIa, b.p. 75-76°/8 mm., n_D^{25} 1.4552.

This method appears to be general, and its success is based upon the inverse addition of the aldehyde to the methylhydrazine.

Preparation of Alkylidenebis-1-methyl-2-alkylidenehydrazines (V).

The general procedure followed for preparing V was to add 0.1 mole of an aldehyde to a solution of 0.2 mole of an *N*-methylhydrazone in 30 ml. of chloroform. The reactions were quite exothermic, and after allowing them to stir at room temperature for 6 hours, the water layers were separated, the chloroform solutions dried over anhydrous magnesium sulfate and the solvent evaporated. The residues were too sensitive to heat to permit distillation; however, they gave satisfactory analytical data without further purification.

In this way Va and Vb were obtained in 83% and 60% yields, respectively. Va, n_D^{25} 1.4692; nmr (carbon tetrachloride) δ 2.60 (s, 6, NCH₃), δ 4.53 (t, 1, *J* = 7 Hz, N-CH-N), δ 6.25 (t, 2, *J* = 5 Hz, CH=N) and δ 2.15 (m, 4, CH₂CH=N).

Anal. Calcd. for C₂₃H₄₈N₄: C, 72.57; H, 12.71; N, 14.72. Found: C, 72.79; H, 12.80; N, 14.45.

For compound Vb, n_D^{25} 1.4680, nmr (carbon tetrachloride) δ 2.60 (s, 6, NCH₃), δ 4.08 (d, 1, *J* = 10 Hz, N-CH-N) and δ 6.27 (d, 2, *J* = 4 Hz, CH=N).

Anal. Calcd. for C₁₄H₃₀N₄: C, 66.09; H, 11.89; N, 22.02. Found: C, 66.25; H, 12.07; N, 21.80.

Reaction of Methylhydrazine with Va.

A solution of 18 g. (0.127 mole) of IIa in 20 ml. of chloroform was treated with 7.2 g. (0.063 mole) of heptanal, the mixture was stirred for 30 minutes, and the water layer was separated. The solution was dried over anhydrous magnesium sulfate, and the chloroform was removed by distillation. To the residue (25 g.) was added 3.6 g. (0.079 mole) of methylhydrazine and the mixture was heated at 60° for 12 hours. At this time an nmr spectrum showed only absorptions due to methylhydrazine and IIa. A similar reaction mixture was held at room temperature for 12 hours, and an nmr spectrum indicated that only Va was present.

Effect of Acid on a Mixture of Heptanal and Va.

A solution of 9 g. (0.08 mole) of heptanal in 20 ml. of benzene was stirred in an ice bath while 11.2 g. (0.08 mole) of IIa was added dropwise in 15 minutes. The mixture was stirred for 1 hour, the water was separated, and the benzene was removed. An nmr spectrum indicated that equal amounts of heptanal and Va were present. The same results were obtained when heptanal was added to a benzene solution of IIa.

The reaction mixture was treated with 20 ml. of 10% hydrochloric acid and a 3-phase system developed. The upper layer was a colorless liquid whose nmr spectrum indicated that it was Ia contaminated with only small amounts of benzene and heptanal. The lower layer consisted of dilute acid and some methylhydrazine. The middle layer was dark yellow, insoluble in carbon tetrachloride, and had an nmr spectrum similar to Ia except the absorptions were shifted downfield; nmr (neat) δ 3.01 (d, 3, NCH₃), δ 7.58 (d, 1, CH=N), δ 3.31 (m, 1, CH ring) and δ 5.08 (s, 18, H₂O). The ratio of water to pyrazoline precursor was 9:1. Since this ratio remained fairly constant for a series of reactions and the nmr spectra of the products resembled I, it seems that the materials are hydrates of hydrochloride of Ia. Treatment of the entire reaction mixture with 20 ml. of 10% sodium hydroxide gave an 87% yield of Ia by glc. A similar reaction mixture was diluted with a large

excess of water, without neutralization, and Ia resulted in 88% yield by glc.

Effect of Acid on Va.

Twenty-two grams (0.058 mole) of Va was stirred while 20 ml. of 10% hydrochloric acid (0.058 mole) was added. The reaction mixture became quite warm and separated into 3 phases. The top layer weighed 11.5 g. and consisted of Ia as shown by an nmr spectrum. The center layer which weighed 13 g. was considered to be hydrated Ia hydrochloride. The three layers were recombined, allowed to stand overnight, and diluted with 50 ml. of water. A single organic phase resulted which weighed 18.5 g. (88%). An nmr spectrum indicated that it was Ia.

When a similar reaction was carried out, except that 0.25 equivalent of 10% hydrochloric acid was used, the yield of Ia was only 60%.

Reaction of Acid with IIa.

Heptanal (27.4 g., 0.23 mole) was added slowly to a solution of 10.5 g. (0.23 mole) of methylhydrazine in 20 ml. of ether without cooling. The addition was completed in 1 hour, and after an additional hour of stirring 10 ml. (0.12 mole) of concentrated hydrochloric acid was added to the mixture. It was stirred for 6 hours, neutralized, and the organic layer was separated. The ether was removed by distillation and the residue was distilled to give 22.5 g. (82%) of Ia, b.p. 122-125°/1 mm., n_D^{25} 1.4580 (lit. (3), b.p. 118-120°/0.3 mm., n_D^{25} 1.4603).

Effect of Temperature, Time and Mode of Addition of Reactants on Formation of II.

Table I contains the data obtained on the indicated variables. Each reaction was carried out on a 0.1 mole scale, and the mole ratio of aldehyde to solvent was held constant to lessen concentration effects. The results of Runs No. 9 and 10 suggest that the latter are possible. The alkylidene ratios were obtained from calculations using CH=N and N-CH₃ nmr absorptions. The reaction temperatures were maintained by a cooling bath until the additions were completed. The reaction mixtures were then allowed to come to room temperature after which they were analyzed by nmr.

REFERENCES

- (1) Presented in part at the 1968 Midwest Regional Meeting of the American Chemical Society, Manhattan, Kansas, October 31-November 1, 1968.
- (2) NDEA Fellow in Chemistry, 1966-1968; Shell Oil Fellow, 1968-1969.
- (3) Norman Rabjohn, H. R. Havens, and J. L. Rutter, *J. Heterocyclic Chem.*, **3**, 413 (1966).
- (4) W. P. Jencks and E. H. Cordes, *J. Am. Chem. Soc.*, **84**, 832 (1962).
- (5) R. H. Wiley and G. Irick, *J. Org. Chem.*, **24**, 1925 (1959).
- (6) Norman Rabjohn, K. B. Sloan and W. Vanderlinde, unpublished results.
- (7) T. I. Crowell and R. K. McLeod, *J. Org. Chem.*, **32**, 4030 (1967).
- (8) A. W. Kost and R. S. Sagitullin, *Zh. Obshch. Khim.*, **33**, 237 (1963); *Chem. Abstr.*, **58**, 13933 (1963).
- (9a) I. Heilbron, "Dictionary of Organic Compounds," 4th ed., Vol. 3, Oxford University Press, New York, N. Y., 1965, p. 1573; (b) p. 1896.

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