

The Synthesis of Alkyl Substituted 2-Pyrazolines by the Reaction of Acids with Hydrazine Derivatives.

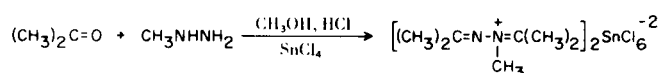
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A convenient synthesis of alkyl substituted 2-pyrazolines (III) has been developed from the reaction of acids with hydrazones (I) and azines (IV). An alkylidenebis-1-methyl-2-alkylidenehydrazine (V) was isolated as an intermediate in the preparation of 5-isopropyl-1,4,4-trimethyl-2-pyrazoline (III_d), and protonated vinylhydrazones (II) are proposed as common intermediates in the formation of III, IV and V. The 4,5-dialkyl-2-pyrazolines (III_{k-m}) that were prepared were shown to be free of isomers by nmr. The thermal isomerization of III_{k-m} to 3,4-dialkyl-2-pyrazolines (III_{n-o}) was found to be incomplete at the temperatures studied. The reaction of III_{n-o} with acetone afforded 3,4-dialkyl-1-[2-(2-methyl-4-oxopentyl)]-2-pyrazolines (III_{p-q}). The nmr and mass spectral data of III are discussed.

The well-known aryl hydrazones are prepared from the corresponding hydrazines and aldehydes or ketones, usually in the presence of acid catalysts (2). Cyclization of aryl hydrazones often takes place under more vigorous acidic conditions to afford indoles (3) or other heterocyclic compounds (4), and has been the subject of extensive investigations. In contrast, relatively little study has been given to the reactions of alkyl and *N*-unsubstituted hydrazones in the presence of acids.

Lamchen and Stephen (5) noted that the condensation of acetone with methylhydrazine in an acidic methanol solution containing stannic chloride gave acetone-methylazinium chlorostannate. Aromatic aldehydes underwent



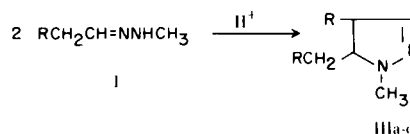
a similar reaction, but it could not be extended to aliphatic aldehydes. Acetone and hydrazine, under the same conditions, produced bis-3,5,5-trimethyl-2-pyrazoline chlorostannate (6).

Kost and coworkers (7) isolated a variety of products, including 2-pyrazolines, from the high-temperature reaction of ketone alkylhydrazones with hydrogen chloride and zinc chloride; however, the yields of the pyrazolines were low, perhaps due to decomposition under the somewhat extreme conditions. The reaction of hydrazine with carbonyl compounds, depending upon the structure of the latter, leads to azines or hydrazones, which can be transformed to azines by treatment with acid under mild conditions (8). Further reaction of acids with aldazines (9) and ketazines (10) has been reported to lead to 2-pyrazolines.

As early as 1899, Franke (11) demonstrated that 4,4-dimethyl-5-isopropyl-2-pyrazoline can be prepared from isobutyraldehyde azine and an equivalent of cold, concentrated hydrochloric acid. 1-Formyl-4,5-dialkyl-2-pyrazolines have been obtained by treating aldehyde azines with formic acid (12), but efforts to hydrolyze them to the 4,5-dialkyl-2-pyrazolines apparently led to mixtures of 3,4- and 4,5-dialkyl-2-pyrazolines (13).

Recently the reaction of heptanal methylhydrazone with acid was observed to give 5-hexyl-1-methyl-4-pentyl-2-pyrazoline (III_e) in good yield (14). We now wish to describe the satisfactory syntheses of a number of other 2-pyrazolines by similar treatment of aldehyde methylhydrazones, ketone methylhydrazones, ketazines and aldazines.

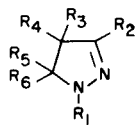
4,5-Dialkyl-1-methyl-2-pyrazolines (III_{a-c}) were prepared merely by adding acid to an ether solution of the aldehyde methylhydrazone (I), neutralizing the resulting mixture and distilling the ether layer. No hydrolysis products, such as aldehydes, were observed although some



nitrile was obtained as a by-product (15) in one instance. Methyl iodide, boron trifluoride etherate, ethyl iodide and *p*-toluenesulfonic acid also were employed and gave comparable results by glc analysis; however, the best yields of isolated products were obtained when hydrochloric acid was used (Table I-IV).

TABLE I

Physical Properties of 2-Pyrazolines and Derivatives



| Compound | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | R ₆ | B.p. ° (mm.) | n _D ²⁵ |
|----------|--|--------------------------------|-----------------|--------------------------------|-----------------------------------|-----------------|--------------|------------------------------|
| IIIa | CH ₃ | H | H | CH ₃ | C ₂ H ₅ | H | 58 (30) | 1.4515 |
| b | CH ₃ | H | H | C ₂ H ₅ | C ₃ H ₇ | H | 90 (22) | 1.4548 |
| c | CH ₃ | H | H | C ₅ H ₁₁ | C ₆ H ₁₃ | H | 125 (1) | 1.4580 |
| d | CH ₃ | H | CH ₃ | CH ₃ | CH(CH ₃) ₂ | H | 65 (35) | 1.4552 |
| e | CH ₃ | CH ₃ | H | H | CH ₃ | CH ₃ | 146 (150) | 1.4500 |
| f | CH ₃ | C ₂ H ₅ | H | H | C ₂ H ₅ | CH ₃ | 110 (67) | 1.4574 |
| g | CH ₃ | C ₅ H ₁₁ | H | H | C ₅ H ₁₁ | CH ₃ | 116 (0.5) | 1.4605 |
| h | H | CH ₃ | H | H | CH ₃ | CH ₃ | 48 (9) | 1.4575 |
| i | H | C ₂ H ₅ | H | H | C ₂ H ₅ | CH ₃ | 65 (2.5) | 1.4602 |
| j | H | C ₅ H ₁₁ | H | H | C ₅ H ₁₁ | CH ₃ | 116 (0.5) | 1.4615 |
| k | H | H | H | CH ₃ | C ₂ H ₅ | H | 56 (3) | 1.4619 |
| l | H | H | H | C ₂ H ₅ | C ₃ H ₇ | H | 76 (3) | 1.4621 |
| m | H | H | H | C ₅ H ₁₁ | C ₆ H ₁₃ | H | 126 (0.5) | 1.4650 |
| n | H | C ₃ H ₇ | H | C ₂ H ₅ | H | H | 95 (15) | 1.4668 |
| o | H | C ₆ H ₁₃ | H | C ₅ H ₁₁ | H | H | 120 (0.5) | 1.4665 |
| p | (CH ₃) ₂ CCH ₂ COCH ₃ | C ₃ H ₇ | H | C ₂ H ₅ | H | H | (a) | 1.4682 |
| q | (CH ₃) ₂ CCH ₂ COCH ₃ | C ₆ H ₁₃ | H | C ₅ H ₁₁ | H | H | (a) | 1.4697 |

(a) Unstable to heat and were not distilled.

Isobutyronitrile and isobutyraldehyde methylimine resulted, instead of 5-isopropyl-1,4,4-trimethyl-2-pyrazoline (III_d), when isobutyraldehyde methylhydrazone was allowed to react with 0.5 mole equivalent of concentrated hydrochloric acid under the same conditions that the unbranched aldehyde methylhydrazones afforded III_{a-c}. When the addition of the acid was conducted at ice bath temperatures, the product was found to be isobutylidene-

bis-1-methyl-2-isobutylidenehydrazine (V, where R'CH₂C=

$$\begin{array}{c} \text{R} \\ | \\ \text{H} \end{array}$$

is (CH₃)₂CHC=, and R'' is CH₃) in 96% yield, and none of the desired III_d was observed. Further treatment of the bis-compound with 1.5 moles equivalent of concentrated hydrochloric acid gave a mixture which contained 57% (by nmr) of III_d. The mixture was heated at 140° for 12 hours to decompose the remaining bis-compound (16), and distilled to give 49% of the 2-pyrazoline (III_d), based upon isobutyraldehyde. This pyrazoline also could not be prepared by the previously described procedure (15) from the reaction of the aldehyde with the aldehyde methylhydrazone. On the basis of refractive indexes (17), the

compound reported earlier as III_d appears to have been impure.

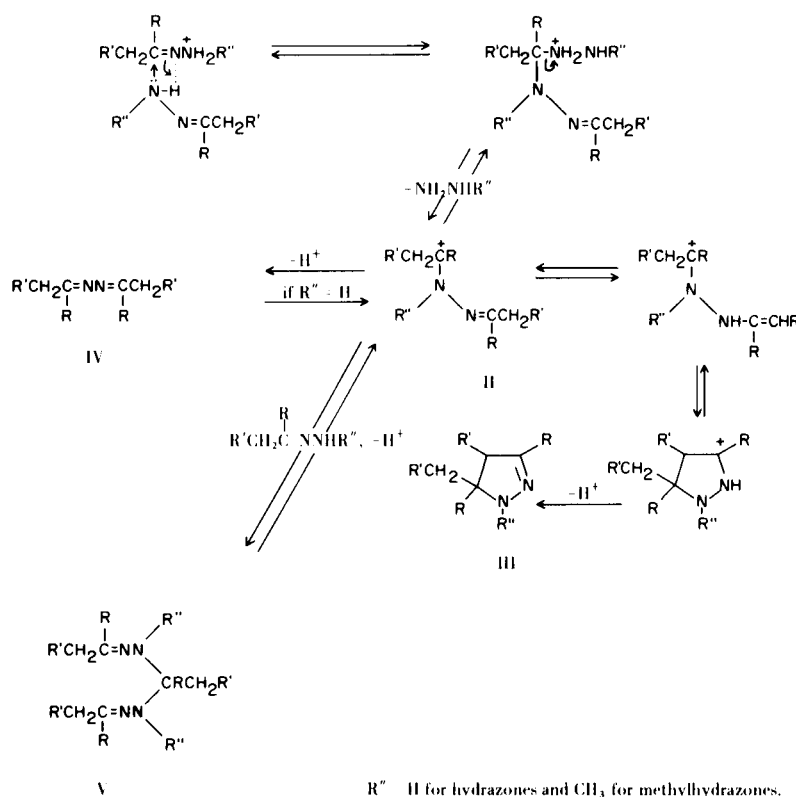
The formation of III from I on treatment with acid might be rationalized on the basis of the following series of reactions, which is similar to that proposed for the formation of azines from the reaction of acid with *N*-unsubstituted hydrazones (8b). The isolation of a bis-compound, V, from the reaction of isobutyraldehyde methylhydrazone with acid, and the previously mentioned formation of acetone-methylazinium chlorostannate (5), lend support to this speculation.

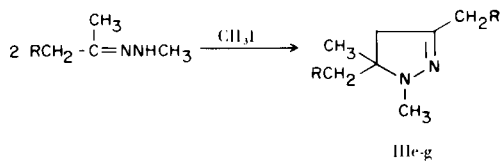
Methyl ketone methyl hydrazones did not give the corresponding 3,5-dialkyl-1,5-dimethyl-2-pyrazolines (III_{e-g}) when treated with concentrated hydrochloric acid, or heated at reflux with an equivalent of the same ketone (18). In the former instance, hydrolysis became a competing reaction; however, when methyl ketone methylhydrazones were caused to react with 0.5 mole equivalent of methyl iodide and the heterogeneous mixtures were heated at 160° for 28 hours, 40-60% yields of 2-pyrazolines (III_{e-g}) resulted after distillation (Table I-IV). The use of only 0.5 equivalent of acid and the relatively low temperature employed probably account for the good yields of

TABLE II
Analytical Data of 2-Pyrazolines and Derivatives

| Compound | Formula | Yield, % | Elemental Analysis | | | | | |
|----------|--------------------|----------------|--------------------|-------|-------|-------|-------|-------|
| | | | C | H | N | C | H | N |
| IIIa | $C_7H_{14}N_2$ | 61 | (d) | | | | | |
| b | $C_9H_{18}N_2$ | 63 | (d) | | | | | |
| c | $C_{15}H_{30}N_2$ | 82 | (d) | | | | | |
| d | $C_9H_{18}N_2$ | 49 | 70.07 | 11.76 | 18.16 | 69.98 | 11.57 | 18.30 |
| e | $C_7H_{14}N_2$ | 40 | 66.62 | 11.18 | 22.20 | 66.46 | 11.08 | 21.94 |
| f | $C_9H_{18}N_2$ | 61 | 70.07 | 11.76 | 18.16 | 69.84 | 12.00 | 18.30 |
| g | $C_{15}H_{30}N_2$ | 55 | 75.56 | 12.68 | 11.75 | 75.33 | 12.50 | 11.79 |
| h | $C_6H_{12}N_2$ | 64.5 | (e) | | | | | |
| i | $C_8H_{16}N_2$ | 78.5 | 68.52 | 11.50 | 19.98 | 68.57 | 11.35 | 19.69 |
| j | $C_{14}H_{28}N_2$ | 77.5 | 74.94 | 12.58 | 12.49 | 75.26 | 12.44 | 12.25 |
| k | $C_6H_{12}N_2$ | 49, (54) (b) | 64.24 | 10.78 | 24.98 | 63.89 | 10.59 | 24.75 |
| l | $C_8H_{16}N_2$ | 51, (61.5) (b) | 68.52 | 11.50 | 19.98 | 68.76 | 11.68 | 19.91 |
| m | $C_{14}H_{28}N_2$ | 53 | 74.94 | 12.58 | 12.49 | 75.21 | 12.29 | 12.70 |
| n | $C_8H_{16}N_2$ | 59 | 68.52 | 11.50 | 19.98 | 68.29 | 11.41 | 19.76 |
| o | $C_{14}H_{28}N_2$ | 83.5 (c) | 74.94 | 12.58 | 12.49 | 75.13 | 12.50 | 12.35 |
| p | $C_{14}H_{26}N_2O$ | 56 | 70.54 | 10.98 | 11.75 | 70.40 | 11.00 | 11.51 |
| q | $C_{20}H_{38}N_2O$ | 68 | 74.48 | 11.88 | 8.69 | 74.56 | 11.73 | 8.85 |

(b) Yield when a trace of acid was used. (c) Yield from III_n. (d) Ref. 15. (e) Ref. 10a.

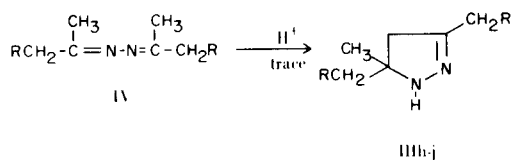




III-g compared to those reported previously (7).

Methyl ketone *N*-unsubstituted hydrazones gave the corresponding azines (IV) when they were caused to react with 0.5 mole equivalent of either methyl iodide or concentrated hydrochloric acid. However, such mixtures could be made to undergo further reaction, for a 55% yield of IIIj resulted on refluxing a mixture of 2-heptanone hydrazone and methyl iodide. The 1-methyl derivative was not observed even though the conditions were comparable to those employed to prepare 1-alkyl-2-pyrazolines from the corresponding *N*-unsubstituted 2-pyrazolines (10a).

Since the synthesis of ketone hydrazones is time-consuming (19), it was more convenient to prepare IIIh-j directly from the corresponding azines. As stated previously, the formation of 2-pyrazolines from equivalent amounts of ketazines and acids is well-known (10); however, the conditions under which IIIj was obtained suggested that only a limited amount of acid should be needed to effect the cyclization. This was found to be true for when azines of methyl ketones were heated with trace amounts of concentrated hydrochloric acid at 140° for 100 hours, 65-78% yields of 3,5-dialkyl-5-methyl-2-pyrazolines (IIIh-j) were realized.



As mentioned earlier, Franke (11) has prepared 4,5-dialkyl-2-pyrazolines by treating aldazines with acids. These reagents are more satisfactory precursors of pyrazolines than aldehyde hydrazones not only from a synthesis point of view, but also because aldehyde hydrazone dimers (20) are practically impossible to separate by distillation from the desired 4,5-dialkyl-2-pyrazolines without causing some rearrangement of the latter to 3,4-dialkyl-2-pyrazolines. When equivalent amounts of concentrated hydrochloric acid were allowed to react with aldazines, a low yield (17%) of pure IIIk was obtained from propanal azine, in one instance, while in other reactions good yields of mixtures of the isomeric 3,4- and 4,5-dialkyl-2-pyrazolines resulted. In contrast, the reaction of aldazines with catalytic amounts of concentrated hydrochloric acid

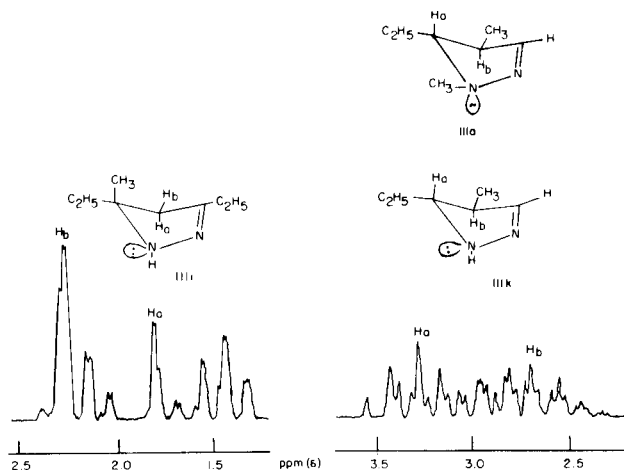
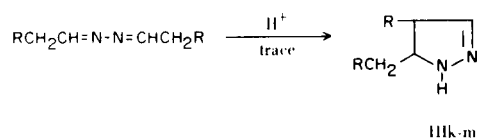


FIGURE 1

at 125° for 24 hours consistently afforded 55-60% yields of 4,5-dialkyl-2-pyrazolines (IIIk-m) which were shown to be isomerically pure by nmr analysis (21). This appears to be the method of choice for preparing IIIk-l, although



treatment of aldazines with 0.13 mole equivalent of concentrated hydrochloric acid at 85° for 3 hours also produced them, but in lower yields (50%). Attempts to vary the equivalents of acid and the temperature employed led to poorer results in terms of yield and isomeric purity.

Care was taken to exclude oxygen during the preparation of 3,5-dialkyl-5-methyl- and 4,5-dialkyl-2-pyrazolines since *N*-unsubstituted 2-pyrazolines are easily oxidized and in some cases ignite spontaneously (22). The preparations of these 2-pyrazolines were therefore carried out under nitrogen, and their handling was performed with a minimum of contact with air.

The distillation residues from the preparation of IIIk-m were considerable, using either method of preparation. They appeared to be polymeric substances with continuous boiling point ranges, and together with the pyrazolines obtained, accounted for satisfactory material balances (85%). The residues did not seem to come from the reaction of hydrochloric acid with the 4,5- or 3,4-dialkyl-2-pyrazolines since both were recovered unchanged after being treated with molar equivalents of concentrated hydrochloric acid at ice bath temperatures, followed by neutralization of the acid solutions with aqueous base. The formation of such polymers is therefore envisaged as an intermolecular condensation of the azines.

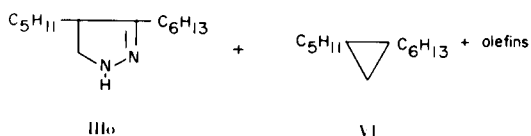
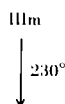
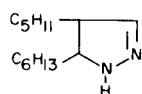
TABLE III

UV and IR Data of 2-Pyrazolines and Derivatives

| Compound | UV λ max, $m\mu$ (log ϵ) | | IR, cm^{-1} | |
|----------|--|-------------|----------------|------|
| | 95% Ethanol | Cyclohexane | C=N | N-R |
| IIIa | 243 (3.52) (d) | | 1580 | 2775 |
| b | 243 (3.54) (d) | | 1580 | 2780 |
| c | 245 (3.56) (d) | | 1590 | 2815 |
| d | 242 (3.46) | 246 (3.61) | 1585, 1600 | 2800 |
| e | 247 (3.60) | | 1615 | 2800 |
| f | 247 (3.58) | | 1615 | 2800 |
| g | 247 (3.59) | 251 (3.67) | 1615 | 2800 |
| h | 227 (3.53) | 231 (3.53) | 1600, 1700 | 3275 |
| i | 226 (3.58) | 231 (3.57) | 1600, 1700 | 3300 |
| j | 226 (3.59) | 232 (3.56) | 1625 | 3300 |
| k | 231 (3.54) | 234 (3.58) | 1585 | 3300 |
| l | 231 (3.49) | 235 (3.50) | 1585 | 3315 |
| m | 230 (3.50) | 235 (3.51) | 1585 | 3300 |
| n | 226 (3.57) | 219 (3.09) | 1610, 1700 | 3300 |
| o | 225 (3.50) | 219 (3.16) | 1610, 1700 | 3300 |
| p | 245 (3.80) | | 1600, 1700 (f) | |
| q | 244 (3.71) | | 1610, 1700 (f) | |

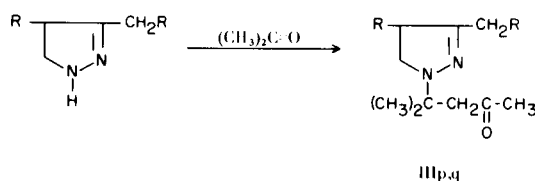
(f) C=O.

During the course of preparing IIIk-m, it was noted that if the contents of the distillation flask were heated above 180° , or if the distillations were not carried out rapidly, considerable amounts of 3,4-dialkyl-2-pyrazolines (III n-o) resulted. The thermal decomposition of III m at 230° for 48 hours gave 33% of III o, and 21% of a complex mixture of 1-hexyl-2-pentylcyclopropane (VI) and olefins as shown by nmr; at 200° an 80% yield of III o (98% pure by nmr analysis) was obtained. However, this method of preparing 3,4-dialkyl-2-pyrazolines from the corresponding 4,5-isomers (I3a) was unsuccessful when applied to III k and III l. Mixtures of isomers resulted which could not be



separated by distillation. Attempts to remove the residual III k (ca. 15%) from a reaction mixture containing 3-ethyl-4-methyl-2-pyrazoline by preferential decomposition of III k at 250° for 93 hours caused a slight decrease in this isomer, but no olefin or cyclopropane formation was observed. 4-Ethyl-3-propyl-2-pyrazoline (III n) was obtained (59%, 98% pure by nmr) by distillation, prior to neutralization, of the crude product from the reaction of concentrated hydrochloric acid with butanal azine.

3,4-Dialkyl-2-pyrazolines apparently are more basic than either 4,5-dialkyl- or 3,5-dialkyl-5-methyl-2-pyrazolines and were observed to condense with acetone to form 3,4-dialkyl-1[2-(2-methyl-4-oxopentyl)]-2-pyrazolines (III p,q) in yields of 56-68%. They have ultraviolet spectra that are similar to those of other *N*-alkyl-2-pyrazolines,



and have well-defined C=N and C=O absorptions in the infrared. Their nmr spectra also are consistent with the structural assignment (Table IV).

TABLE IV

NMR Data of 2-Pyrazolines and Derivatives

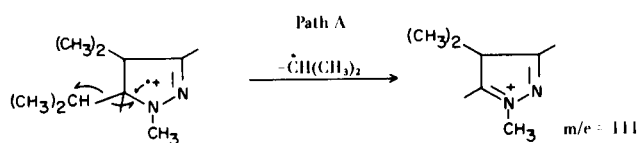
| Compound | R ₂ -C=N | NMR, δ R ₁ -N-N= | Miscellaneous |
|----------|--|---------------------------------------|--|
| IIIa | 6.60 (m, 0.8, CH=N) 6.35 (m, 0.2, CH=N) | 2.64 (m, 3, CH ₃ -N) | 2.50 (m, 2, ring protons) |
| b | 6.65 (m, 0.8, CH=N) 6.35 (m, 0.2, CH=N) | 2.62 (m, 3, CH ₃ -N) | 2.50 (m, 2, ring protons) |
| c | 6.63 (m, 0.8, CH=N) 6.35 (m, 0.2, CH=N) | 2.62 (m, 3, CH ₃ -N) | 2.50 (m, 2, ring protons) |
| d | 6.22 (s, 1, CH=N) | 2.68 (s, 3, CH ₃ -N) | 2.10 (m, 1, ring protons) |
| e | 1.83 (m, 3, CH ₃ C=N) | 2.57 (s, 3, CH ₃ -N) | 2.33 (m, 2, ring protons) |
| f | | 2.60 (s, 3, CH ₃ -N) | 0.97 (s, 3, CH ₃ -C-R ₅) |
| g | | 2.60 (s, 3, CH ₃ -N) | 0.97 (s, 3, CH ₃ -C-R ₅) |
| h | 1.87 (m, 3, CH ₃ C=N) | 5.10 (m, 1, N-H) | 2.31 (m, 2, ring protons) |
| i | | 4.90 (m, 1, N-H) | 1.11 (s, 3, CH ₃ -C-R ₅) |
| j | | 5.05 (m, 1, N-H) | 1.12 (s, 3, CH ₃ -C-R ₅) |
| k | 6.58 (m, 0.7, CH=N) 6.47 (m, 0.3, CH=N) | 5.55 (m, 1, N-H) | 3.28 (m, 1, ring protons) 2.58 (m, 1, ring protons) |
| l | 6.58 (m, 0.6, CH=N) 6.46 (m, 0.4, CH=N) | 5.60 (m, 1, N-H) | 3.40 (m, 1, ring protons) 2.63 (m, 1, ring protons) |
| m | 6.60 (m, 0.6, CH=N) 6.46 (m, 0.4, CH=N) | 5.65 (m, 1, N-H) | 3.40 (m, 1, ring protons) 2.62 (m, 1, ring protons) |
| n | | 5.40 (m, 1, N-H) | |
| o | | 5.50 (m, 1, N-H) | |
| p (g) | | | 2.12 (s, 3, CH ₃ -C=O) |
| q (g) | | | 2.12 (s, 3, CH ₃ -C=O) |

(g) IIIp,q also have a characteristic absorption centered at δ 0.93 (m, 6, (CH₃)₂C-N).

Nmr data for the 2-pyrazolines synthesized in the present study are given in Table IV, and a few appear to be of interest. A portion of the spectrum of 3,5-diethyl-5-methyl-2-pyrazoline (IIIi) is shown in Figure 1, and the assignments of Ha (δ 1.81) and Hb (δ 2.27) are made on the basis of analogy to a nucleus being shielded in the conical regions above and below the plane of a carbonyl group while one in the plane is deshielded (23). No difference is observed in the chemical shifts of Ha and Hb in IIIh since the 5-substituents are identical. However, there is a significant difference in the chemical shifts for Ha and Hb of IIIk-m (Table IV and Figure 1) which is not observed for the 1-methyl isomers (IIIa-c). In the latter, the protons attached to the 4- and 5- positions absorb at approximately δ 2.5, while in IIIk-m the difference in chemical shifts is almost 50 Hz. It seems likely that the upfield shift of the proton on C-5 of IIIa-c, relative to IIIk-m, is due to the shielding effect of the axial, anti-coplanar, lone pair of electrons on nitrogen in IIIa-c (24),

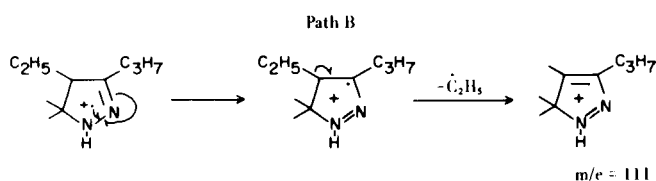
while in IIIk-m the lone pair assumes a pseudo equatorial position (Figure 1).

Mass spectra were recorded for a representative number of the 2-pyrazolines described. The principle fragmentation in all five samples that were run was the loss of an alkyl radical from the molecular ion. The decomposition was rationalized in two different ways depending on the position of substituents on the pyrazoline ring. Path A (α -cleavage) dominates the spectra of 5-alkylsubstituted 2-pyrazolines and is illustrated below for 5-isopropyl-1,4,4-trimethyl-2-pyrazoline (IIIId) where the ion at $m/e = 111$ accounts for 43% of the ion current from the sample.



In 3,5-diethyl-5-methyl-2-pyrazoline (IIIi) α -cleavage can result in the loss of either a methyl or an ethyl radical. As expected, the propensity to lose an ethyl radical was about ten times greater than that for a methyl radical. The spectrum of 3,5-diethyl-1,5-dimethyl-2-pyrazoline (IIIf) was essentially identical to that of IIIi so that the addition of an *N*-methyl group does not appear to change the decomposition pattern of the molecular ion.

3,4-Dialkyl-2-pyrazolines which do not contain a 5-substituent appear to lose an alkyl radical in the following manner (Path B) as illustrated for 4-ethyl-3-propyl-2-pyrazoline (IIIh). Competition between Path A and Path B



was observed in the mass spectra of several of the 2-pyrazolines; notably 4-ethyl-5-propyl-2-pyrazoline (IIIj) where α -cleavage was favored by a factor of 4.7.

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 ultraviolet spectra were determined with a Beckmann DB-2 instrument. 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. The mass spectra were obtained with a Hitachi-Perkin-Elmer model RMU-6D low resolution mass spectrometer. The samples were introduced through the heated, all glass inlet system which was maintained at 185°.

All aldehydes and ketones were redistilled, and the 95% hydrazine, 100% hydrazine hydrate, and methylhydrazine were used as received.

Preparation of 4,5-Dialkyl-1-methyl-2-pyrazolines (IIIa-c).

The aldehyde methylhydrazones were prepared by adding aldehydes slowly to well-stirred ether solutions which contained equal molar amounts of methylhydrazine (14). The reaction mixtures were allowed to cool to room temperature, the water that had formed was separated and 0.5 mole equivalent of concentrated hydrochloric acid was added slowly. The reaction mixtures were stirred at room temperature for 1 hour and then neutralized with 10% aqueous sodium hydroxide. The organic layers were separated, dried over magnesium sulfate, concentrated and distilled to give the 2-pyrazolines, IIIa-c, from propanal, butanal and heptanal methylhydrazones, respectively (Table I-IV).

Glc analyses of the reaction mixtures from methyl iodide, ethyl iodide, boron trifluoride etherate and *p*-toluenesulfonic acid with heptanal methylhydrazone showed the presence of 80-87% of IIIc. Distillation of the methyl iodide-heptanal methylhydrazone reaction product afforded a 50% yield of pure IIIc (by glc).

Preparation of 5-Isopropyl-1,4,4-trimethyl-2-pyrazoline (IIId).

Isobutyraldehyde methylhydrazone (52.0 g., 0.52 mole), prepared in the usual manner (14), was cooled and stirred while 22 ml. (0.26 mole) of concentrated hydrochloric acid was added slowly. After neutralization, the organic layer (41.5 g.) was identified as isobutyraldehydebis-1-methyl-2-isobutyraldehydehydrazine by nmr; nmr (carbon tetrachloride) δ 2.6 (s, 6, N-CH₃), δ 4.08 (d, 1, J = 10 Hz, N-CH-N) and δ 6.27 (d, 2, J = 4 Hz, CH=N). If the methylhydrazine was not kept cool during the addition of the acid, isobutyronitrile and isobutyraldehyde methylimine were the only products which could be identified by nmr and glc analyses.

The bis-compound was cooled in an ice bath and 30 ml. (0.36 mole) of concentrated hydrochloric acid was added. The mixture was allowed to stand at room temperature for 12 hours, neutralized and the organic layer separated. Nmr analysis indicated that only the 2-pyrazoline, IIId, and bis-compound were present. When the mixture was injected on a glc column (15% SE-30) at 130°, IIId, isobutyraldehyde methylhydrazone, and an unknown component with a peak at about one-half the retention time of IIId were present; however, when the column temperature was increased to 180°, there were observed IIId, isobutyraldehyde methylhydrazone, isobutyraldehyde methylimine and isobutyronitrile. Slow distillation of a mixture of IIId and the bis-compound afforded a mixture of IIId and an unknown material which appeared to correspond to the unknown peak present in the glc determination which was run at 130°.

Further addition of concentrated hydrochloric acid to the mixture of IIId and the bis-compound followed by neutralization, did not cause any changes which could be detected by glc analysis. It then was heated at 140° for 16 hours and nmr showed that only IIId, isobutyraldehyde methylimine and isobutyronitrile remained. Distillation afforded 19.5 g. (49%) of IIId (Table I-IV).

Preparation of 3,5-Dialkyl-1,5-dimethyl-2-pyrazolines (IIIe-g).

The appropriate methyl ketones were added to benzene solutions of equal molar amount of methylhydrazine and the mixtures were heated at reflux under a Dean and Stark trap to remove water. The solutions were cooled, 0.5 mole equivalent of methyl iodide was added and the resulting heterogeneous mixtures were heated with vigorous stirring for 24 hours at an oil bath temperature of 165°. The mixtures were cooled, filtered to remove precipitated solids, and the filtrates were distilled to give IIIe-g from acetone, 2-butanone and 2-heptanone, respectively (Table I-IV).

When concentrated hydrochloric acid was used in place of methyl iodide, either in trace or 0.5 mole equivalent amounts, little or no formation of IIIe-g was observed even after the reaction mixtures had been heated at 170° for 72 hours.

Attempted Reaction of 2-Butanone with 2-Butanone Methylhydrazone.

A solution of 5.0 g. (0.05 mole) of 2-butanone methylhydrazone in 3.6 g. (0.05 mole) of 2-butanone was heated under reflux for 12 hours at an oil bath temperature of 115°. Glc analysis suggested the presence of a small amount of IIIf so heating was continued for an additional 12 hours. The glc peak attributed to IIIf did not increase and corresponded to a yield of approximately 2-5% by comparison of peak areas.

Preparation of 3,5-Dialkyl-5-methyl-2-pyrazolines (IIIh-j).

Methyl ketazines were synthesized by adding the appropriate methyl ketones to a 0.5 mole equivalent of 100% hydrazine hydrate in benzene and heating the mixtures under a Dean and

Stark trap until water no longer separated. The reaction mixtures then were treated with 0.02-0.03 mole equivalent of concentrated hydrochloric acid and heated under nitrogen at an oil bath temperature of 140° for 100 hours. The progress of a reaction was assumed to be complete upon disappearance of the $CH_3C=N$ absorption at δ 1.67. The reaction mixtures were neutralized with aqueous base, separated and distilled to give IIIh-j from acetone, 2-butanone and 2-heptanone azines, respectively (Table I-IV).

Preparation of 3,5-Dipentyl-5-methyl-2-pyrazoline (IIIj).

A solution of 21.5 g. (0.14 mole) of 2-heptanone dimethylhydrazone [nmr (carbon tetrachloride) δ 1.93 (s, 3, $CH_3C=N$) and δ 2.40 (s, 6, $N-CH_3$), 13.5 g. (0.42 mole) of 95% hydrazine and 30 ml. of absolute ethanol was refluxed for 16 hours according to the method of Newkome and Fishel (19). The solvent and excess hydrazines were removed by warming under reduced pressure for 7 hours. The residue weighed 13 g. (0.099 mole, 70%) and was identified as 2-heptanone hydrazone by its characteristic nmr absorption at δ 1.73 ($CH_3C=N$) (20c). Methyl iodide (7.0 g., 0.049 mole) was added to the hydrazone and the mixture was heated at reflux for 16 hours. It was distilled to afford 6.1 g. (55%) of IIIj (Table I-IV).

Preparation of 4,5-Dialkyl-2-pyrazolines (IIIk-m).

The desired aldazines were prepared by adding a 0.5 mole equivalent of 100% hydrazine hydrate to the proper aldehyde and removing the water formed in a separatory funnel after 1 hour. The aldazines then were treated with 0.13 mole of concentrated hydrochloric acid and heated under nitrogen at 80° for 3 hours. The reaction mixtures were neutralized with dilute base and distilled to give IIIk-m from propanal, butanal and heptanal azines, respectively (Table I-IV). The synthetic method of choice however, was to heat the crude aldazines with 0.002 mole equivalent of concentrated hydrochloric acid at an oil bath temperature of 125° for 24 hours under nitrogen, neutralize and distill the residues. In this way, IIIk-m were obtained in 53-61% yield.

The compositions of the high-boiling residues from the preparation of IIIk-m were not determined. However, the higher-boiling residue from the preparation of IIIl gave a fraction, b.p. 155-157°/1 mm., n_D^{25} 1.4845, ir (neat) 3300 cm^{-1} (N-H) and 1650 and 1635 cm^{-1} (C=N). Analytical data suggested that the compound contained oxygen, besides carbon, hydrogen and nitrogen.

Preparation of 5-Ethyl-4-methyl-2-pyrazoline (IIIk).

Hydrazine hydrate (41.5 g., 0.83 mole) was added to a solution of 95.5 g. (1.65 moles) of propanal in 40 ml. of benzene and the mixture was heated at reflux under a Dean and Stark trap until water was no longer collected. It was cooled, 65 ml. (0.78 mole) of concentrated hydrochloric acid was added slowly and the mixture was stirred overnight under a nitrogen atmosphere. After neutralization with dilute base, the organic layer was distilled to give 15.8 g. (17%) of IIIk (Table I-IV).

Attempted Preparation of 5-Hexyl-4-pentyl-2-pyrazoline (IIIm).

A modification of the method of Franke (11) was used. A mixture of 27.5 g. (0.24 mole) of heptanal, 6.0 g. (0.12 mole) of 100% hydrazine hydrate and 40 ml. of benzene was refluxed under a Dean and Stark trap until water was no longer collected. The resulting benzene solution was cooled and 13 ml. of concentrated hydrochloric acid was added. The mixture turned dark-orange, and after 1 hour it was neutralized with dilute base. The organic layer was distilled to give 13.5 g. of material which boiled at 122-127°/0.1 mm., n_D^{25} 1.4639 and 3.2 g., b.p. 122-132°/0.1 mm.,

n_D^{25} 1.4658; total yield 62%. Nmr analysis showed that IIIo and IIIm were present in both fractions.

Pyrolysis of 5-Hexyl-4-pentyl-2-pyrazoline (IIIm).

(a) A mixture (20.2 g.) of IIIm and 3-hexyl-4-pentyl-2-pyrazoline (IIIo) containing 46% of the former, according to nmr, was heated under nitrogen at 220° for 48 hours. Distillation of the resulting material gave 5.8 g. of a low-boiling component, b.p. 72-73°/0.8 mm., n_D^{25} 1.4337. A sample of the latter decolorized a carbon tetrachloride solution of bromine, and infrared absorptions at 1650 and 850 cm^{-1} indicated the presence of terminal olefins. The integration of the nmr absorptions at δ 5.0 and in the region of δ 5.3-5.6 suggested that the mixture contained about 43% of olefins. The remainder of the material appeared to be 1-hexyl-2-pentylcyclopropane (VI), based upon nmr absorption in the region of δ 0.0-0.70 and an ir absorption at 1040 cm^{-1} .

Anal. Calcd. for $C_{14}H_{28}$: C, 85.63; H, 14.37. Found: C, 85.69; H, 14.33.

The distillation residue was shown to be IIIo by nmr and glc analyses.

(b) The 2-pyrazoline (IIIm, 25 g.) was heated under nitrogen at 230° for 48 hours and then distilled. There was obtained a mixture of cyclopropane (VI) and olefins (4.6 g., 21%), b.p. 88-90°/1 mm., nmr identical to that of the mixture obtained in (a); IIIo (8.3 g., 33%) b.p. 135-142°/1 mm., n_D^{25} 1.4663, and an unknown compound (2.8 g.), b.p. 160-165°/0.5 mm., n_D^{25} 1.4670; ir (neat) 3200 cm^{-1} (N-H) and 1700, 1650, 1625, 1600 and 1550 cm^{-1} (C=N and C=C); uv (95% ethanol) λ max 226 μ , log ϵ 3.75; nmr (carbon tetrachloride) δ 2.43 (m, 6, $CH_2-C=$), δ 3.93 (t, 1, $J = 6$ Hz) and δ 7.17 (m, 1), one component by tlc. No structural assignment was made. Similar materials have been observed in the pyrolysates of aliphatic aldazines (25).

Anal. Calcd. for $C_{21}H_{40}N_2$: C, 78.68; H, 12.58; N, 8.74. Found: C, 78.81; H, 12.27; N, 9.00.

Thermal Rearrangement of 4,5-Dialkyl-2-pyrazolines to 3,4-Dialkyl-2-pyrazolines.

The 4,5-dialkyl-2-pyrazolines (IIIk-m) were heated under nitrogen at 175-200°. After 36 hours, IIIm had rearranged to IIIo, and the latter resulted in 83% yield on distillation. Similar treatment of IIIk and IIIl afforded mixtures of IIIk and 3-ethyl-4-methyl-2-pyrazoline (13:87), and IIIl and IIIn (7:93). The mixture of IIIk and its 3,4-isomer was heated at 250° under nitrogen for 93 hours; however, the ratio of isomers was changed only to 15:85.

Preparation of 4-Ethyl-3-propyl-2-pyrazoline (IIIn).

Butanal (99.0 g., 1.38 moles) was added to a stirred mixture of 76.0 g. (1.52 moles) of 100% hydrazine hydrate and 100 ml. of ether. The resulting reaction mixture was treated with 64 ml. (0.79 mole) of concentrated hydrochloric acid and considerable heat was evolved; nmr analysis indicated that only the azine was present. An additional 15 ml. (0.18 mole) of concentrated hydrochloric acid was added over 3 days at which time the nmr absorption ($CH=N$) of the azine had disappeared. The reaction mixture was separated and distilled, without neutralization, to give 57 g. of material which contained two compounds as shown by glc. Further distillation was not successful in separating the components so the mixture was heated at 185° under nitrogen for 17 hours. Analysis by glc of the resulting residue showed that only one component was present, and distillation afforded 49.6 g. (59%) of IIIn (Table I-IV).

Reaction of Acetone with 3,4-Dialkyl-2-pyrazolines (III_n-o).

Solutions of III_n and III_o in acetone (3-4 mole excess) were allowed to stand for several hours, dried over magnesium sulfate and concentrated on a rotary evaporator. The substituted 2-pyrazolines which resulted, III_p-q, could not be purified by distillation due to thermal instability. After the excess acetone had been removed at reduced pressure the residues gave satisfactory analytical data (Table II).

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