phere was introduced, 900 mg. (2.75 mmoles) of 1-azulylmethyltrimethylammonium iodide[4b] was added, and the solution was heated at 100–110° for 3.5 hr. The solvent was removed under reduced pressure and the residue was chromatographed on an alumina column. The blue fraction eluted by 3:1 dichloromethane–petroleum ether gave 836 mg. of a blue oil presumed to be ethyl α-acetamido-α-cyano-β-(1-azulyl)propionate.

A solution of 340 mg. (1:1 mmoles) of the blue oil in 20 ml. of a 10% solution of potassium hydroxide in 50% ethanol was heated under reflux for 2 hr. Water (50 ml.) was added and the whole was extracted with 100 ml. of ether. The separated aqueous layer was acidified with 6 *N* hydrochloric acid and then extracted with ether. The residue from the dried (sodium sulfate) ethereal solution was chromatographed on a column of silica gel. Removal of the solvent from the blue fraction eluted by ether and recrystallization of the blue solid from water gave 171 mg. (64%) of α-acetamido-β-(1-azulyl)propionic acid as blue crystals, m.p. 126–128°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 69.99; H, 5.85; N, 5.44. Found: C, 69.66; H, 6.12; N, 5.20.

Proton Nuclear Magnetic Resonance Spectra of 1-Acyl Pyrazoles

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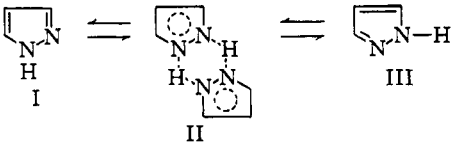
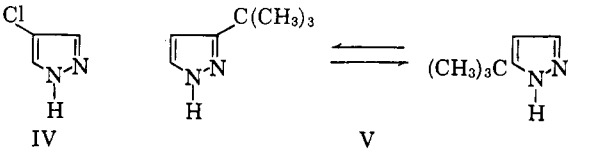
The n.m.r. spectra of the annular protons of 1-acyl pyrazoles are useful in determining the structures of isomers formed by acylation of unsymmetrically substituted pyrazoles. The spin–spin coupling constants of the annular protons fall into narrow ranges that are characteristic of the position of the protons on the pyrazole ring. The relative chemical shifts of these protons are also dependent upon their location on the ring. A 1-acyl pyrazole with an unambiguous structure has been prepared to aid in these correlations.

When the 1-position of a pyrazole is unsubstituted, the 3- and 5-positions are equivalent in the sense that tautomers of unsymmetrically substituted pyrazoles cannot be separated. It has been suggested that pyrazoles exist in solution largely as hydrogen-bonded dimers[1,2] (II), and that the equivalency of the 3- and 5-positions results from delocalization of electrons in the dimer.[3] No available evidence precludes the existence of monomeric species (I and III) in dilute solution, but in any event, if present, they would be in rapid equilibrium with each other *via* the dimeric, hydrogen-bonded species.



I II III

Evidence for the equivalency of the 3- and 5-positions of pyrazoles unsubstituted in the 1-position can be found by examining their proton n.m.r. spectra.[4] For 4-chloropyrazole (IV) only two resonances in the ratio of 1:2 are observed: a single low-field resonance at τ −3.27 corresponding to the N–H, and a single unsplit resonance at τ 2.32 corresponding to the protons on the 3- and 5-positions. If unassociated forms such as I and III were present, they would not be detectable by n.m.r. if the frequency at which they are interconverted, *via* II, is higher than that used in making the observation.[5] Because of the equivalency of the 3- and 5-protons, no spin–spin splitting is observed. Similarly, for 3(5)-*t*-butylpyrazole (V), a single, sharp resonance is observed for the protons of the *t*-butyl group at τ 8.63, and a single resonance at τ −2.96 for



IV V

the N–H. The two annular protons split each other into doublets appearing at τ 2.49 and 3.91 with a coupling constant, *J*, of 2.0 c.p.s. This coupling constant must be an average of the coupling constants J_{34} and J_{45} weighted by the population of each tautomer in the equilibrium mixture. Comparison of the spectrum of IV with that of V suggests that the higher field doublet at τ 3.91 is the 4-proton, since it is missing in the spectrum of IV.

The most complicated spectrum is produced by pyrazole itself. The N–H appears as a single resonance at τ −3.60. The 4-proton appears as a triplet at τ 3.60, split by the equivalent 3- and 5-protons, while the 3- and 5-protons appear as a single doublet at τ 2.26. The coupling constant for this A_2B system is 2.1 c.p.s.

When pyrazole is acetylated on the 1-nitrogen the 3- and 5-positions become nonequivalent. As a result the three annular protons of 1-acetylpyrazole (VI) appear as three separate quadruplets at τ 1.78, 2.36, and 3.60. Analysis of the splitting in these quadruplets shows that all three protons are coupled to each other and that the coupling constants have values of 0.6, 1.5, and 2.9 c.p.s. Examination of the spectrum of 1-acetyl-4-chloropyrazole (VII) reveals that the 3- and 5-protons are split by 0.7 c.p.s. into doublets that appear at τ 1.81 and 2.44. Clearly the coupling constant across the ring between the 3- and 5-protons (J_{35}) must be 0.6–0.7 c.p.s. The remaining two coupling constants of 1.5 and 2.9 c.p.s. observed in the spectrum of VI must be J_{34} and J_{45}. The problem remains of deciding which corresponds to J_{34} and which to J_{45}.

When the unsymmetrically substituted *t*-butylpyrazole (V) is acetylated, two isomeric 1-acetyl compounds, VIII and IX, could be formed. Actually, acetylation of V leads to a single product having a pair of doublets in its spectrum at τ 1.88 and 3.71 with a coupling con-

(1) W. Huckel, J. Datow, and E. Simersbach, *Z. physik. Chem.* (Leipzig), **186A**, 129 (1940).

(2) H. Hayes and L. Hunter, *J. Chem. Soc.*, 1 (1941).

(3) L. Hunter, *ibid.*, 806 (1945).

(4) All spectra were measured with a Varian A60 n.m.r. spectrometer at room temperature on 0.5 *M* solutions in carbon tetrachloride containing 0.05 *M* tetramethylsilane as an internal standard.

(5) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959.

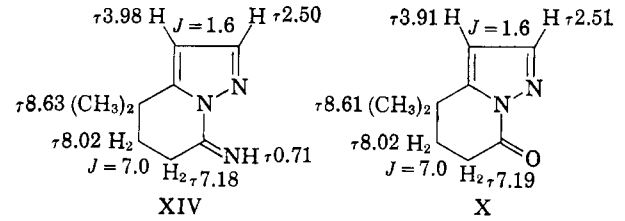
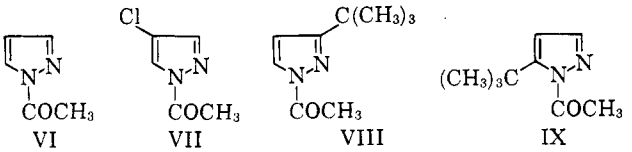
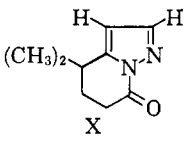


Fig. 1.—Spin–spin coupling constants (J, c.p.s.) are indicated between atoms, and chemical shifts[4] in τ (p.p.m.) are indicated adjacent to the corresponding protons.

stant of 2.9 c.p.s. On steric grounds, one would guess that the entering acetyl group would prefer the nitrogen furthest from the *t*-butyl group and that the product would be the 3-*t*-butyl isomer, VIII. On this basis J_{45} would be 2.9 c.p.s. To confirm this conclusion a 1-acyl pyrazole with an unambiguous structure (X) was prepared.



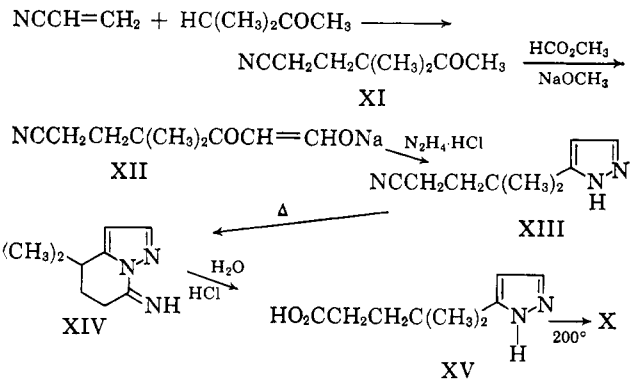
Because of its lactam ring, the identity of the protons on the pyrazole ring of 4,4-dimethyl-4,5,6,7-tetrahydro-7-ketopyrazole[2,3-*a*]pyridine (X) are fixed on the 3- and 4-positions. Consequently, the coupling constant between them must represent J_{34}. The spectrum of X showed a pair of doublets at τ 2.51 and 3.91 cor-



responding to the 3- and 4-protons with a coupling constant, J_{34}, of 1.6 c.p.s. Thus, the conclusions based on VIII are confirmed, and the coupling constants for the 1-acyl pyrazole system are J_{35} = 0.6–0.7 c.p.s., J_{34} = 1.6 c.p.s., and J_{45} = 2.9 c.p.s. In addition, the relative shifts for these protons place the 5-proton at lowest field, the 3-proton at higher field, and the 4-proton at highest field. That the resonance for the 4-proton is at highest field is consistent with the fact that the 4-position has the highest electron density and is the point at which electrophilic substitution takes place.[6]

The synthesis of X began with the known[7] cyanoethylation product of methyl isopropyl ketone, 3,3-dimethyl-5-cyano-2-pentanone (XI). This ketone was formylated, and the sodium salt of the formyl compound (XII) was converted without isolation to the pyrazole derivative (XIII) by reaction with hydrazine hydrochloride. Upon distillation, XIII partly cyclized to the imino compound XIV. Hydrolysis of XIV gave the acid (XV) which cyclized smoothly to X when it was heated.

As a result of the monumental work of Auwers,[8] much is known of the products obtained by acylating unsymmetrically substituted pyrazoles. Nevertheless, the use of n.m.r. offers a rapid, unambigous method for



determining the structures of such acylation products. The utility of the data and generalizations discussed in this paper will be illustrated in a forthcoming publication describing the acylation of a number of unsymmetrically substituted pyrazoles and the identification of the isomer mixtures obtained.

Experimental

1-Acetylpyrazole (VI),[9] 4-chloropyrazole (IV),[10] 1-acetyl-4-chloropyrazole (VII),[10] and 3(5)-*t*-butylpyrazole (V)[11] were prepared by methods described in the literature.

1-Acetyl-3-*t*-butylpyrazole (VIII).—To a mixture of 37.2 g. of 3(5)-*t*-butylpyrazole,[11] 27.0 g. of pyridine, and 500 ml. of ether was added a mixture of 27 g. of acetyl chloride and 50 ml. of ether. The addition required 10 min., and after it was complete the mixture was stirred for 2 hr. Water (100 ml.) was added, and stirring was continued for 1 hr. The ether layer was separated, washed with two 250-ml. portions of water and then with 250 ml. of saturated sodium chloride solution, and dried over magnesium sulfate. Distillation gave 39.0 g. (79%) of 1-acetyl-3-*t*-butylpyrazole, b.p. 87–88° (16 mm.), n^{25}D 1.4756. The infrared spectrum showed λ_{max}^{liq} 2.87, 313, 317, and 5.73 μ. The n.m.r. of the pure liquid showed no detectable amount of the 5-*t*-butyl isomer. The sensitivity of the n.m.r. analysis would probably have allowed detection of 5% of the 5-isomer in the 3-isomer.

Anal. Calcd. for $C_9H_{14}N_2O$: C, 65.1; H, 8.49; N, 16.9. Found: C, 64.9; H, 8.50; N, 17.1.

3,3-Dimethyl-5-cyano-2-pentanone (XI).—This material was prepared in 45% yield by the method described in the literature.[7] The infrared spectrum showed λ_{max}^{liq} 4.44 and 5.83 μ. The n.m.r. spectrum[4] showed an A_2B_2 pattern centered at τ 7.92, a single CH_3 at τ 7.88, and another resonance for six protons ($2CH_3$) at τ 8.82.

4-Methyl-4-(5-pyrazolyl)pentanenitrile (XIII) and 4,4-Dimethyl-4,5,6,7-tetrahydro-7-iminopyrazolo[2,3-*a*]pyridine (XIV).—To a slurry of 84 g. of sodium methoxide in 640 ml. of ether was added a mixture of 208 g. of 3,3-dimethyl-5-cyano-2-pentanone and 108 g. of methyl formate over 20 min. The reaction mixture boiled spontaneously after one-third of the ketone ester mixture had been added. After the addition was complete, the reaction flask was cooled in ice and an additional 30 g. of methyl formate was added. The mixture was stirred at room temperature for 16 hr., reduced in volume by 200 ml. by distillation, and then cooled in ice. A solution of 77.5 g. of hydrazine hydrate and 130 ml. of concentrated hydrochloric acid in 500 ml. of water was added. A mildly exothermic reaction took place. The mixture was stirred at room temperature for 3 hr. The ether layer was separated, washed with two 150-ml. portions of saturated sodium chloride solution, and dried over magnesium sulfate. The ether was removed on a steam bath to leave a pale amber oil. The infrared spectrum of this crude product had λ_{max}^{liq} 4.45 μ (–CN) and a weak band at 5.83 μ (C=O of XI), but no band at 6.01 μ. Distillation of this oil gave 196 g. (81%) of a mixture of 4-methyl-4-(5-pyrazolyl)pentanenitrile (XIII) and 4,4-dimethyl-

(6) E. Buchner and M. Fritsch, *Ann.*, **273**, 265 (1893).
(7) A. Campbell, C. Carter, and S. Slater, *J. Chem. Soc.*, 174 (1948).
(8) See for example, K. V. Auwers and E. Cauer, *J. prakt. Chem.*, [2]**126**, 177 (1930).
(9) L. Knorr, *Ber.*, **28**, 716 (1895).
(10) R. Huttel, O. Schafer, and G. Welzel, *Ann.*, **598**, 186 (1956).
(11) P. Dayton, *Compt. rend.*, **236**, 2515 (1953).

4,5,6,7-tetrahydro-7-iminopyrazolo[2,3-*a*]pyridine (XIV), b.p. 123–126° (0.06 mm.). When the viscous distillate was allowed to stand at room temperature, massive crystals of XIV separated.

A sample of this solid was pressed on a clay plate to free it from oil and was crystallized twice from petroleum ether (b.p. 30–60°) and once from hexane to give 4,4-dimethyl-4,5,6,7-tetrahydro-7-iminopyrazolo[2,3-*a*]pyridine (XIV), m.p. 69–71°. The infrared spectrum showed λ_{max}^{KBr} 3.08, 3.22, 3.40, 6.01, and 6.45 μ, but no bands at 4.45 or 5.83 μ.

The n.m.r. spectrum of XIV is summarized in Fig. 1.

Anal. Calcd. for $C_9H_{13}N_3$: C, 66.3; H, 8.04; N, 25.8. Found: C, 66.7; H, 8.10; N, 25.7.

4-[3(5)-Pyrazolyl]-4-methylpentanoic Acid (XV).—A mixture of 169.5 g. of the crude distillate containing XIII and XIV, 92 ml. of concentrated hydrochloric acid, and 250 ml. of water was heated at 90–95° with stirring for 3 hr. The mixture was cooled with stirring, and the solid that crystallized was collected and washed with cold water to give 122.6 g. (62%) of 4-[3(5)-pyrazolyl]-4-methylpentanoic acid (XV), m.p. 157.7–159.0°. The infrared spectrum had λ_{max}^{KBr} 2.98, 3.17, 5.92, 7.18, and 7.30 μ. In another experiment, a sample that had been recrystallized from water had m.p. 155–157° and was analyzed.

Anal. Calcd. for $C_9H_{14}N_2O_2$: C, 59.3; H, 7.75; N, 15.4. Found: C, 59.6; H, 6.00; N, 15.1.

4,4-Dimethyl-4,5,6,7-tetrahydro-7-ketopyrazolo[2,3-*a*]pyridine (X).—An erlenmeyer flask containing 1.0 g. of XV was heated in an oil bath maintained at 200° for 0.25 hr. During the heating period the solid melted, and water distilled out of the melt. The solid obtained when the contents of the flask had cooled was crystallized from hexane to give 0.7 g. (80%) of 4,4-dimethyl-4,5,6,7-tetrahydro-7-ketopyrazolo[2,3-*a*]pyridine (X), m.p. 196.5–198.0°. A sample with the same melting point obtained by recrystallization from heptane was analyzed. The infrared spectrum had λ_{max}^{KBr} 5.72, 6.39, 7.20, and 7.33 μ.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.9; H, 7.38; N, 17.1. Found: C, 66.0; H, 7.33; N, 16.8.

A Synthesis of Cyclopropyl Acetates[1,2]

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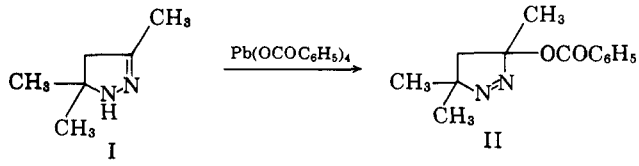
Received July 15, 1963

A variety of cyclopropyl acetates may be prepared by pyrolysis of 3-acetoxy-1-pyrazolines which are obtained by the action of lead tetraacetate on 2-pyrazolines. The scope and limitations of the method and the use of n.m.r. spectra for assignment of stereochemistry is discussed.

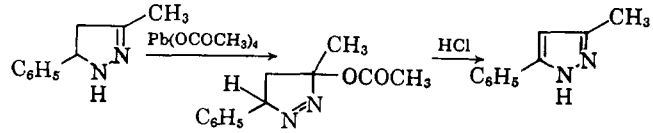
Recent interest in small ring chemistry and in particular that expressed in cyclopropanols[3] prompted an examination of the synthesis and decomposition of 3-acetoxy-1-pyrazolines. The cyclopropyl acetates expected from this decomposition can be cleaved to the desired alcohols.[3] It had been observed in connection with another investigation that 3,5,5-trimethyl-2-pyrazoline (I) could be converted to 3-benzoyloxy-3,5,5-trimethyl-1-pyrazoline (II) by the action of lead



I II

tetrabenzoate.[4] This reaction was an extension of Iffland's hydrazone oxidation reaction[5] to the pyrazoline series.

1-Pyrazolines.—This reaction, now employing lead tetraacetate, is a general one for pyrazolines even for those bearing a hydrogen atom at position 5. It might have been expected that these compounds would be oxidized to pyrazoles based upon the report that 5-ethylpyrazoline is converted to 5-ethylpyrazole by this reagent.[6] Under the mild conditions employed in the present work the pyrazolines were not aromatized nor were the 1-pyrazolines isomerized to 2-pyrazolines during the lead tetraacetate reaction. However, it was possible to isomerize and aromatize 3-acetoxy-3-methyl-5-phenyl-1-pyrazoline (III) to 3-methyl-5-phenylpyrazole by heating it in dilute ethanolic hydrochloric acid. This isomerization also occurred upon standing or upon warming below the decomposition

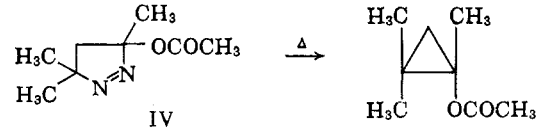


III

point. For best results, the thermal decomposition of the crude pyrazolines was conducted immediately after their preparation.

In some cases the intermediate 1-pyrazolines were isolated and characterized. However, those bearing α-phenyl substituents appeared to be particularly prone to decomposition and little effort was made to purify them. The 1-pyrazolines were characterized by a band at 1565 cm.$^{-1}$ in their infrared spectra which may be attributed to the *cis*-azo function and by low intensity absorption at 330 mμ in the ultraviolet. Other 1-pyrazolines are characterized by similar spectral properties.[7]

Cyclopropyl Acetates.—Preliminary efforts to decompose pyrazoline IV with ultraviolet light[7] indicated that this method was effective but slow. However, by simply heating the compound under reflux, nitrogen



IV

(1) This research was carried out under Army Ordnance Contract DA-01-021 ORD-11878.

(2) A preliminary report of this work has been published: J. P. Freeman, *J. Org. Chem.*, **28**, 885 (1963).

(3) C. H. DePuy, L. R. Mahoney, and K. L. Eilers, *ibid.*, **26**, 3616 (1961); C. H. DePuy, R. A. Klein, and G. M. Dappen, *ibid.*, **27**, 3742 (1962).

(4) J. P. Freeman, *Tetrahedron Letters*, **No. 21**, 749 (1961).

(5) D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Am. Chem. Soc.*, **83**, 747 (1961).

(6) R. Kuhn and K. Henkel, *Ann.*, **549**, 279 (1941). An azoacetate may have been involved in this aromatization, since an intermediate impure product was further treated with acid dichromate to obtain the pyrazole.

(7) K. L. Rinehart, Jr., and T. V. Van Auken, *J. Am. Chem. Soc.*, **84**, 3736 (1962).