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Studies of Heterocyclic Compounds. II.[1] Acetyl Transfer Reactions of 3-Acetoxy-1-acetyl-5-methylpyrazole and the Related Compounds

Kiichi Arakawa, Tadashi Miyasaka, and Hisao Ochi

School of Pharmaceutical Sciences, Showa University[2]

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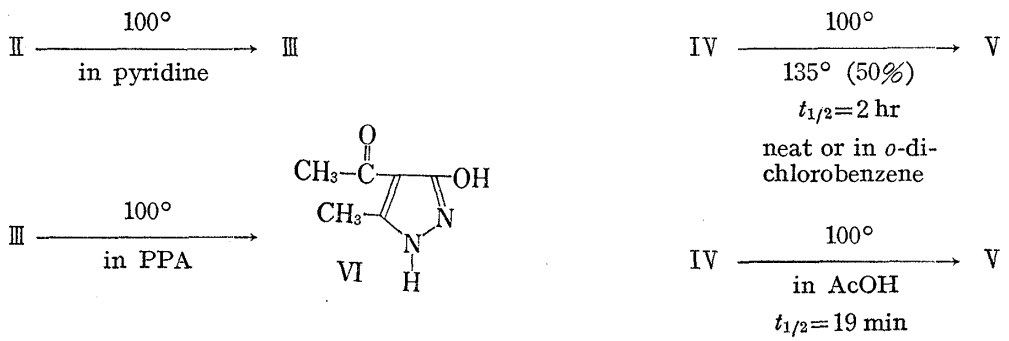
The individual reactions of acetyl group rearrangement are examined to elucidate the complicated formation of five acetylated products of 3-methylpyrazol-5-one (I). In heated acetic acid–anhydride mixture the initially formed 2-acetyl-3-hydroxy-5-methylpyrazole (II) reacts further to produce 1-acetyl-3-hydroxy-5-methylpyrazole (III), 3-acetoxy-2-acetyl-5-methylpyrazole (IV) and finally 3-acetoxy-1-acetyl-5-methylpyrazole (V), while inter- as well as intra-molecular acetyl transfer reaction takes place. The diacetate (V) is a sort of activated ester and is proved to be effective as a mild acetylating reagent of primary and secondary amines.

In the preceding paper, we have shown that five mono- and di-acetyl derivatives can be prepared from 3-methylpyrazol-5-one (I) by acetylation with acetic anhydride.[1] The relationships among the starting material and the products, as revealed by inspection of the sequential formation of the acetyl derivatives, would seemingly require that in the course of the reaction, intramolecular rearrangement of acetyl group must have taken place. Facile intermolecular displacement of acetyl group has now been observed and the acetylated derivatives have been shown to be useful as an activated ester for acetylation of primary and secondary amines.

Treatment of 2-acetyl-3-hydroxy-5-methylpyrazole (II)[1] with pyridine under heating gave 1-acetyl-3-hydroxy-5-methylpyrazole (III).[1] 3-Acetoxy-2-acetyl-5-methylpyrazole (IV)[1] was heated in a sealed tube at 100° for 24 hours only to recover the starting material. Two hours' heating at 100° was sufficient to convert half amount of it into the stable 3-acetoxy-1-acetyl-5-methylpyrazole (V).[1] When *o*-dichlorobenzene was employed as solvent, the reaction proceeded similarly at 140° and the conversion was completed in 10 hours to produce V in 85% yield. Monoacetate (III) afforded 4-acetyl-3-hydroxy-5-methylpyrazole (VI)[1] in 30% yield by heating at 100° in polyphosphoric acid (PPA).



A solution of II in acetic acid was heated at 100° for half an hour and there was obtained a syrupy mixture, which was separated into five components, (I, II, III, IV and V) (8, 17, 22, 4, and 6% yield, each), by means of vacuum distillation, sublimation, column chromatography

1) Part I: K. Arakawa, T. Miyasaka, and H. Ochi, *Chem. Pharm. Bull.* (Tokyo), **21**, 207 (1974). The preceding paper.

2) Location: *1-5-8, Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*

and fractional crystallization. The five components were also isolated in almost the same ratio when the procedure was applied to the monoacetate (III). A similar result was obtained on heating of I in acetic acid in the presence of an equimolar amount of acetic anhydride.

The time-course of the rearrangement was followed spectrophotometrically in the sample tube for nuclear magnetic resonance (NMR) measurement. The chemical shifts of C_4-protons of all the concerning compounds separated one another distinctly enough to allow to estimate their area-intensities. The peaks assigned to the C_4-proton of II, I, III, IV and V appeared respectively at 5.23, 5.40, 5.68, 5.87 and 6.10 ppm from tetramethylsilane as the internal reference in acetic acid or in acetic anhydride.

$$\text{II} \xrightarrow[\text{in AcOH}]{100^\circ} \underset{(16:30:38:8:8)}{\text{I}+\text{II}+\text{III}+\text{IV}+\text{V}}$$

(40 min)

$$\text{III} \xrightarrow[\text{in AcOH}]{100^\circ} \underset{(16:30:38:8:8)}{\text{I}+\text{II}+\text{III}+\text{IV}+\text{V}}$$

(40 min)

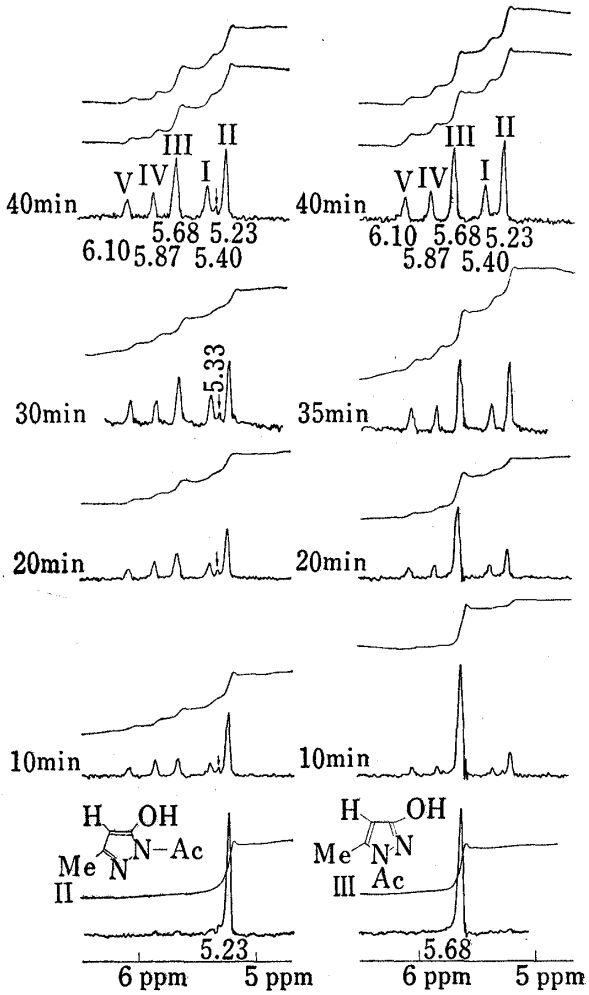


Fig. 1. NMR Spectra of C_4-Proton during the Time-Course of the Thermal Conversion of II and III at 100° in Acetic Acid into an Equililbrated Mixture of the Five Components, (I II, III, IV and V)

During the course of the thermal conversion of IV into V in acetic acid the peak at 5.87 ppm gradually decreased its intensity, a new one appearing at 6.10 ppm and finally the latter took the part of the former with the half-life period of about 19 minutes at 100°. When acetic anhydride was added into a solution of I in acetic acid, the peak at 5.40 ppm spontaneously shifted to 5.23 ppm. By warming, the peak at 5.23 ppm collapsed gradually into all the five peaks mentioned above and finally it combined together to form one peak at 6.10 ppm after 40 minutes' heating at 100°. When II was heated at 100° in acetic acid, the peak at 5.23 ppm also collapsed into the five peaks and after 40 minutes, the intensity-ratio of the C_4-proton resonance peaks of II, I, III, IV and V approached to 30: 16: 38: 8: 8. Starting from III the peak at 5.68 ppm collapsed in the same manner and exactly the same intensity-ratio was attained after 40 minutes' heating at 100° (Fig. 1).[3]

The fact that both of the monoacetates, II and III, yielded the same equilibrated mixture of all the five components strongly suggested that the rearrangements observed here proceeded intermolecularly at least in acetic acid solution. The formation of the more stable diacetate (V) from I, II, III and IV is diagramed in Chart 1, which also shows the relationships between kinetically controlled products, II and IV, and thermodynamically stable products, III and

3) A minor peak which consistently appears at 5.33 ppm in the C_4-proton magnetic resonance region of the spectra of the heated mixture of II in acetic acid indicates some degree of participation of another kind of isomer for the equilibration. Preparative scale experiments did not offer successful separation of any species responsible for this resonance peak.

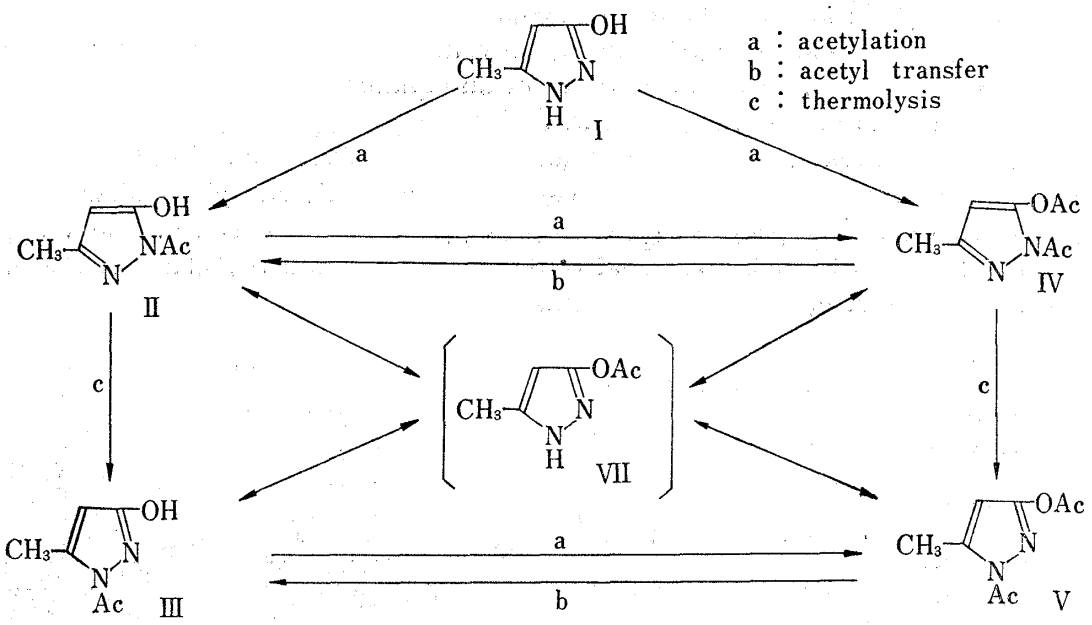


Chart 1

V. In the case of 3-phenylpyrazole derivatives, the isolation of 3-acetoxy-5-phenylpyrazole was reported by Weissberger and Porter,[4] which persuaded us to postulate the intervention of 3-acetoxy-5-methylpyrazole (VII) that could be such a transient intermediate as to discharge its acetyl group promptly to the other ring position and as to accept an acetyl group onto its N_1- or N_2-position from the other acetylated molecules. Also the intervention of very unstable diacetylated isomer, 1,2-diacetyl-5-methyl-4-pyrazolin-3-one (VIII) could tentatively be postulated, which might either discharge one acetyl group intermolecularly to the other species or shift its N_2-acetyl group to C_3-oxygen through 1,3-acetyl transfer mechanism.

Recent publications concerning 1,3-acyl migrations have revealed that rearrangement proceeded intramolecularly in tautomerization between straight-chained isoimide and diacylimide.[5] Korte and co-workers proved 4-acetoxycoumarin underwent Fries type rearrangement of acetyl group intramolecularly from oxygen to carbon through four-membered intermediate.[6] Intermolecular acyl migrations were observed in five- and six-membered nitrogen-heteroaromatics, acyl transfer reaction taking place from nitrogen either to oxygen or to nitrogen or *vice versa*.[7] Lack of reference on acyl or alkyl migration from nitrogen to carbon on pyrazole-rings was pointed out by Albert.[8]

We observed that polyphosphoric acid effected migration of acetyl group from N_1 to C_4 and pyridine effected migration from N_2 to N_1.[9] Taking account of the property of acetylated pyrazolone as acetyl donor, monoacetate (III) might have performed intermolecular electrophilic displacement of acetyl group at C_4 position with the aid of strong acid. Likewise, in the presence of pyridine monoacetate II, which seems to be the first species to be formed in acetic anhydride, might have discharged acetyl group to pyridine to produce unstable

4) A. Weissberger and H.D. Porter, *J. Am. Chem. Soc.*, **64**, 1495 (1943).
5) D.Y. Curtin and L.L. Miller, *J. Am. Chem. Soc.*, **89**, 637 (1967).
6) N. Matzart, H. Wamhof, and F. Korte, *Chem. Ber.*, **102**, 3122 (1969).
7) *a*) J.D. Druliner, *J. Am. Chem. Soc.*, **90**, 6879 (1968); *b*) Y. Ueno, T. Tanaka, and E. Imoto, *Bull. Chem. Soc. Japan*, **37**, 864 (1964); *c*) A. McKillop, M.J. Zelesko, and E.C. Taylor, *Tetrahedron Letters*, **1968**, 4945; *d*) D.Y. Curtin and J.H. Engelmann, *ibid.*, **1968**, 3911.
8) A. Albert, "Heterocyclic Chemistry, An Introduction," 2 nd ed., Athlone Press, University of London, 1968. p. 219.
9) A possible mode of intramolecular migration of acetyl group either from N_1 to C_4, or stepwisely from N_2 to oxygen and then from oxygen to C_4 would be depicted as shown in Chart 2.[5,6]

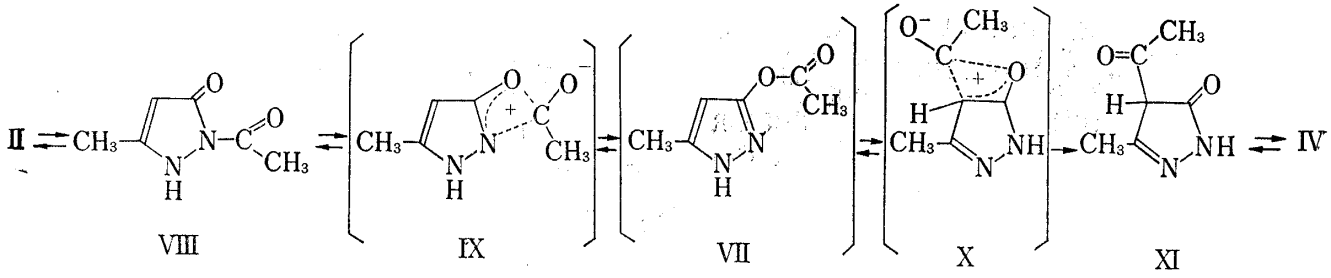
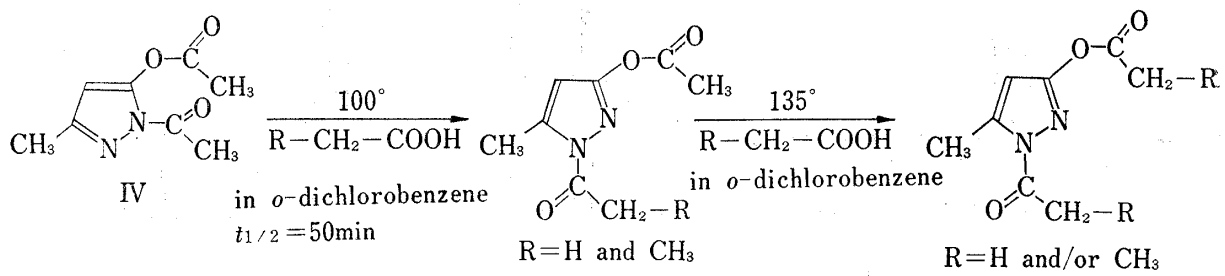


Chart 2

acetyl-pyridinium complex, which acetylates at less weakly basic N_1 position to form thermodynamically more stable monoacetate III.



Very sluggish rearrangement of the neat 3-acetoxy-2-acetyl-5-methylpyrazole (IV), as well as in the solution in *o*-dichlorobenzene, into 3-acetoxy-1-acetyl-5-methylpyrazole (V) seems to be a result of slow intramolecular 1,2- or 1,5-migration of acetyl group from N_2 to N_1. Enhancement of the reaction by the addition of small amount of acetic acid was examined by NMR spectroscopy. The half-life time of the conversion was greatly shortened (see the Experimental part). The acceleration of the conversion by acetic acid seems likely

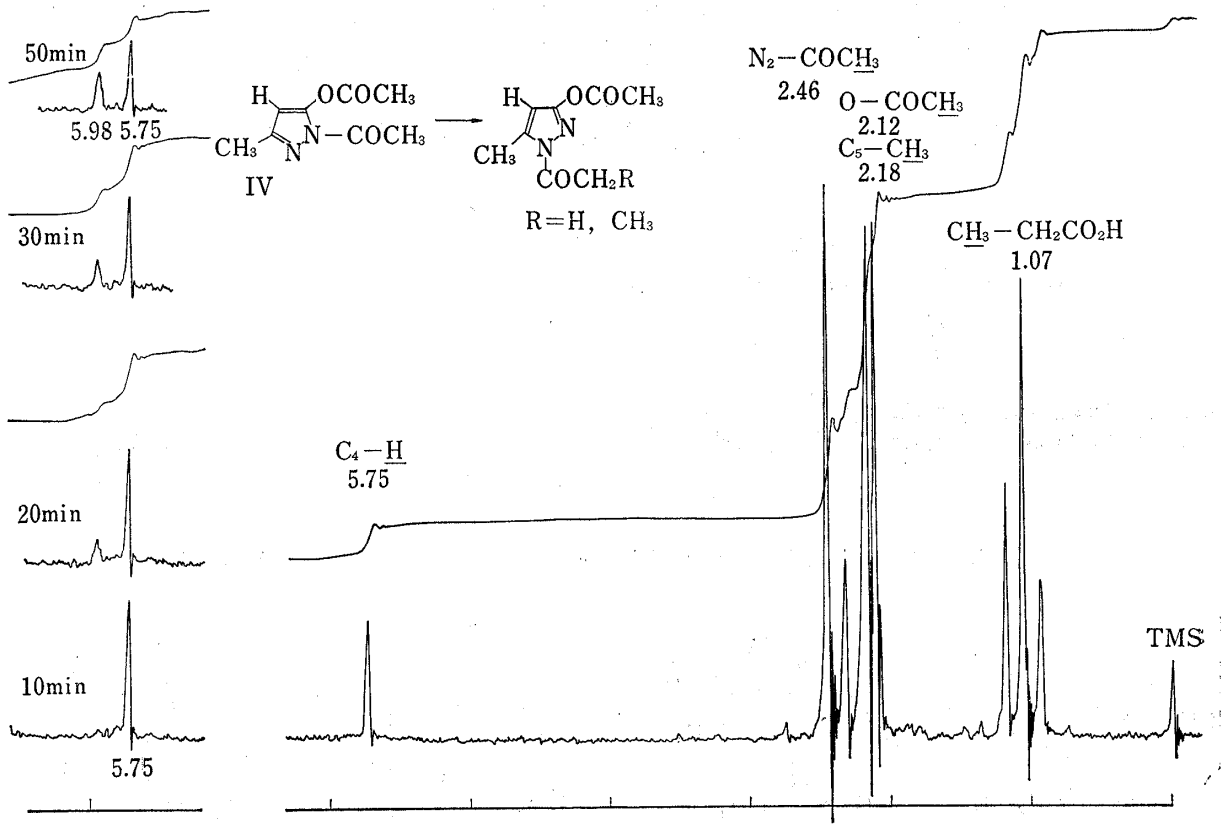


Fig. 2. NMR Spectra of IV and of C_4-Proton during the Course of the Acyl-Group Migration from N_2 to N_1 at 100° in *o*-Dichlorobenzene in the Presence of Propionic Acid

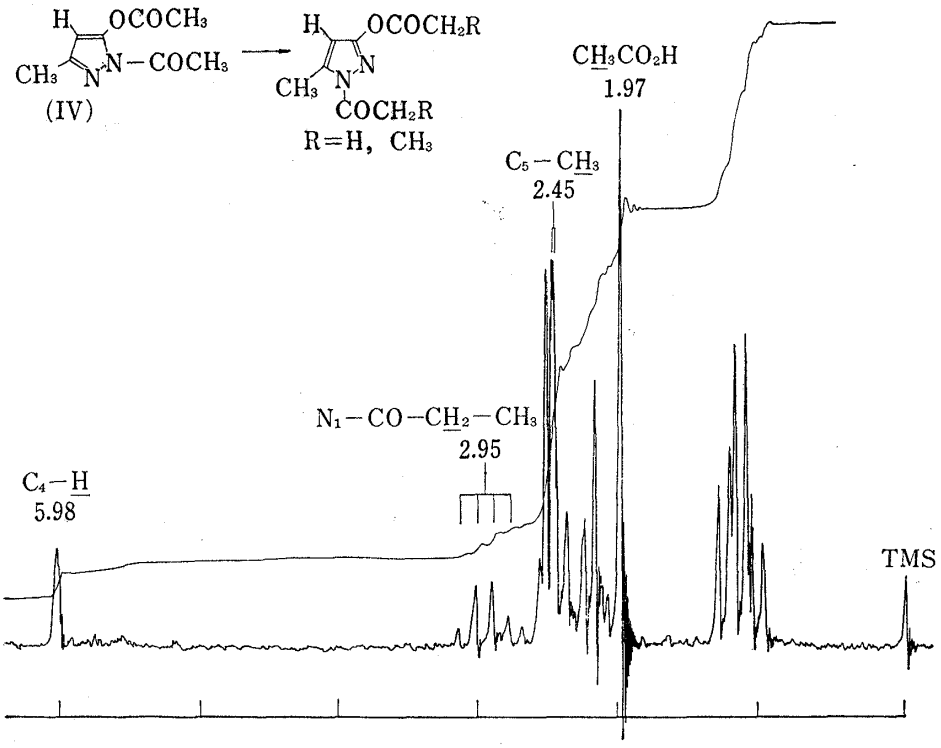


Fig. 3. NMR Spectrum of IV after the Thermal Treatment at 135° for 12 Hours in *o*-Dichlorobenzene in the Presence of Propionic Acid

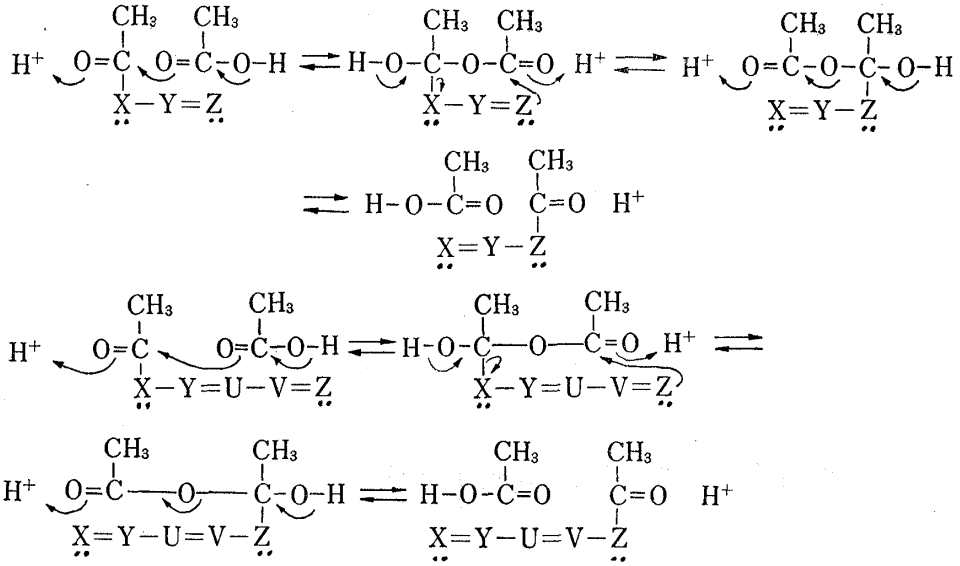


Chart 3. 1, 3- and 1, 5-Transfer of Acetyl Group in the Presence of Acetic Acid

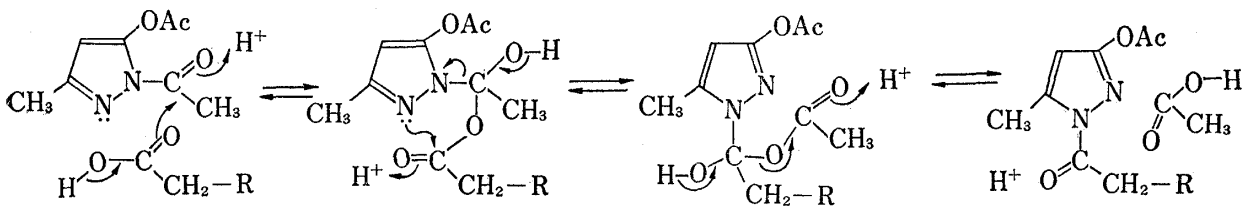


Chart 4. Acyl Transfer Mechanism of the Diacetates (IV and V) in the Presence of Carboxylic Acid

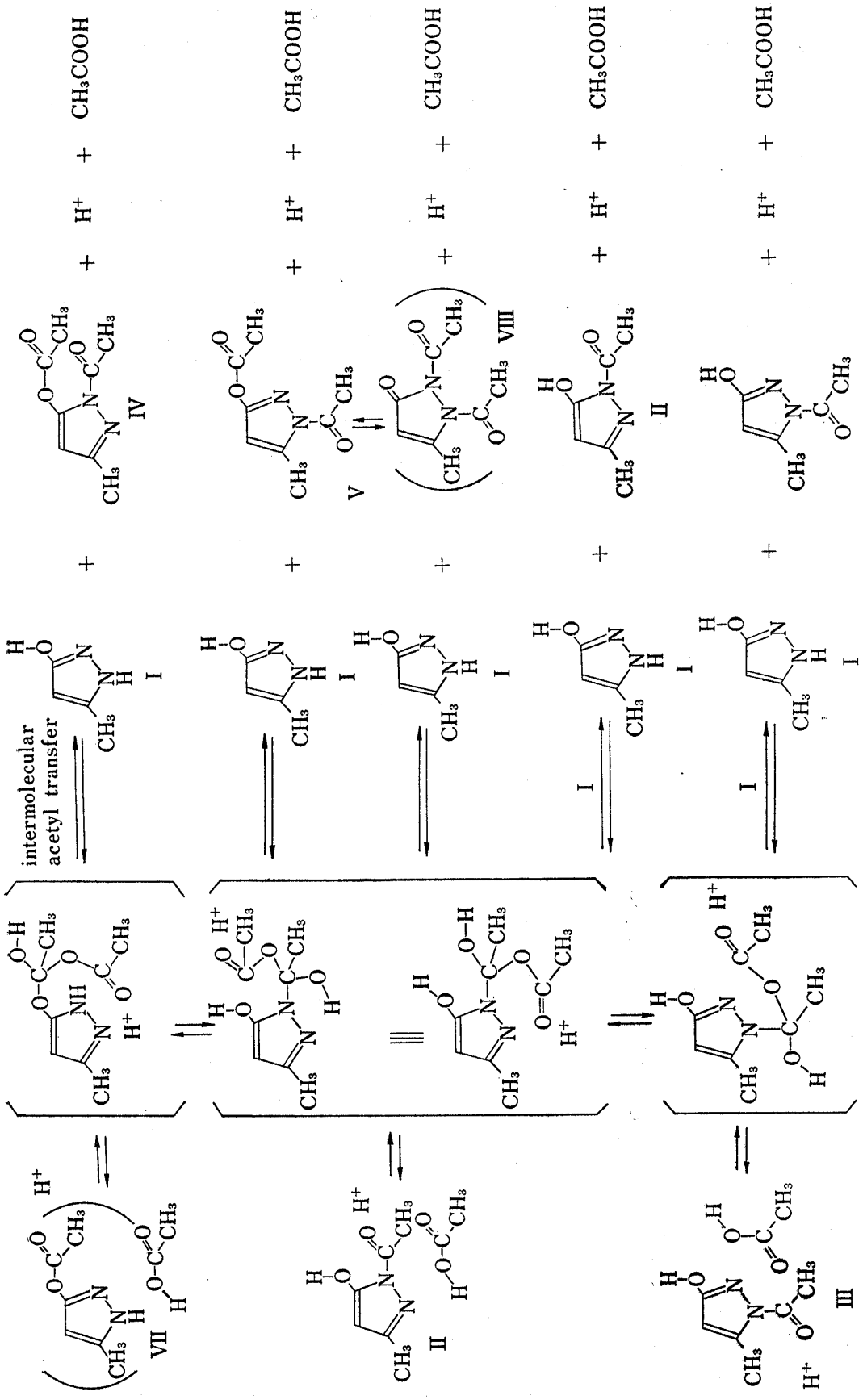


Chart 5. Acetyl Transfer Mechanism of Acetylated Pyrazole Derivatives in the Presence of Acetic Acid

to be a result of protonation and solvolytic addition of acetic acid. Participation of extra molecule of acetic acid was ascertained by performing the reaction in the presence of propionic acid. A solution of 3-acetoxy-2-acetyl-5-methylpyrazole (IV) in *o*-dichlorobenzene was heated at 100° in the presence of propionic acid (slightly exess molar amount). The half-life time of the conversion into V was approximately 50 minutes and incorporation of propionyl function at N_1-position was observed through the quartet pattern at 2.95 ppm in the NMR spectra (Fig. 2, 3). After further 12 hours' heating incorporation of propionyl group at N_1 and C_3-O was estimated approximately 65% and 57% each. Acyl A possible transfer mechanism from IV into V in the presence of carboxylic acid is shown in Chart 4.[10] path way of the formation of five kinds of pyrazolone derivatives from II or III in Acetic acid is summarized in Chart 5.[10]

The diacetate (IV and V) were proved to be susceptible to mild basic hydrolysis to form II and III respectively.[1] When the diacetate (V) was treated with equimolar amount of aniline in dichloromethane at room temperature, exothermic reaction took place and acetanilide and the monoacetate (III) separated in good yield. The applicability of 3-acetoxy-1-acetyl-5-methylpyrazole (V) was also examined in acetylation of 3,5-dimethylpyrazole and piperidine. The reagent was proved in both cases to be useful as a mild acetylating reagent. Special features of the new acetylating reagent are (i) sufficient stability in the variety of solvent including water, (ii) fairly good selectivity for the acetylation of amines, and (iii) ease of the separation of the rest of the reagent from the reaction mixture after the reaction.

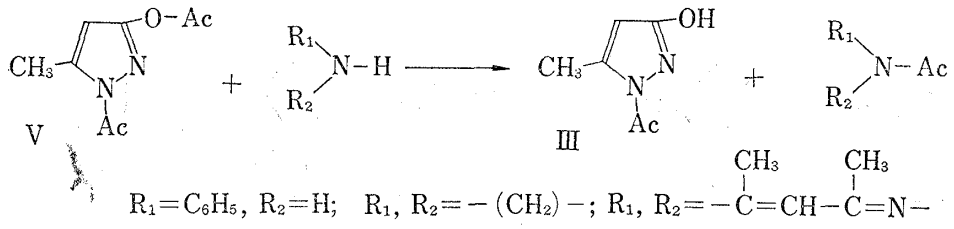


Chart 6

Quantitative comparison of this reagent with the other reagents[11] for chemical modification of proteins[12] and other high-molecular bioorganic materials and for peptide synthesis as an activated ester will be discussed elsewhere.[13]

Experimental[14]

Treatment of 2-Acetyl-3-hydroxy-5-methylpyrazole (II) with Pyridine——A solution of 2-acetyl-3-hydroxy-5-methylpyrazole (II) (400 mg) in dry pyridine (2 ml) was heated on a water-bath (90—95°) for 30 minutes. The mixture was cooled and poured onto ice-water (4 ml) and extracted with ether. The ether extracts were washed with 10% HCl, dried over Na_2SO_4, filtered and evaporated to give colorless powder (124 mg, 31%). Recrystallization of this material from benzene afforded colorless needles, mp 152—153° (70 mg). The mixed melting point and the infrared (IR) spectrum were identical with the authentic sample of 1-acetyl-3-hydroxy-5-methylpyrazole (III).[1]

10) Concerning the significance of general acid-catalysis and sigma-bonded intermediates in the hydrolysis of ester and amide, see T.C. Bruice and S.J. Benkovic, "Bioorganic Mechanisms," Vol. I, W.A. Benjamin, Inc., New York, 1966, p. 1.
11) Concerning acetylimidazole as acetylating reagent for proteins, see J.F. Riordan, W.E.C. Wacker, and B.L. Vallee, *Biochemistry*, 4, 1758 (1965).
12) M. Irie, T. Miyasaka, and K. Arakawa, *J. Biochem.*, 72, 65 (1972).
13) *cf.* K. Arakawa, T. Miyasaka, K. Morita, and M. Okada, Summary of the Lectures of the 23rd Annual Meeting of the Chemical Society of Japan, April, 1970, Tokyo, p. 18412.
14) All melting points were uncorrected. NMR spectra were measured by a HITACHI R-20 60 MC spectrophotometer, using tetramethylsilane as the internal reference. IR spectra were measured on a JASCO IRS spectrophotometer.

Thermal Treatment of 3-Acetoxy-2-acetyl-5-methylpyrazole (IV) (neat) at 100°——3-Acetoxy-2-acetyl-5-methylpyrazole (IV) (50 mg) was sealed under nitrogen-stream in a Pyrex glass tube. The sealed tube was heatedin an oil-bath for 24 hr. After the treatment IR and NMR spectra and thin-layer chromatogram (TLC) of the material were completely identical with the starting diacetate (IV).

Thermal Treatment of 3-Acetoxy-2-acetyl-5-methylpyrazole (IV) (neat) at 140°——The diacetate (IV) (50 mg) was sealed under dry nitrogen-stream in a Pyrex tube. The sealed tube was heated at 140° in an oil-bath for 2 hr. After the treatment the TLC showed two spots at $Rf=0.48$ and 0.45 (CH_2Cl_2, on the plate of Kieselgel GF_{254} nach Stahl (Typ 60) "Merck"). The NMR spectrum [δ ppm (in $CDCl_3$): 2.24 (3H, s), 2.30 (6H, s), 2.57 (3H, s), 2.60 (3H, s), 5.87 (1H, s), 6.10 (1H, s)] indicated approximately 1: 1 mixture of the starting diacetate (IV) and 3-acetoxy-1-acetyl-5-methylpyrazole (V).

Thermal Conversion of 3-Acetoxy-2-acetyl-5-methylpyrazole (IV) into 3-Acetoxy-1-acetyl-5-methylpyrazole (V) in *o*-Dichlorobenzene——3-Acetoxy-2-acetyl-5-methylpyrazole (IV) (200 mg) and *o*-dichlorobenzene (1.0 ml) were sealed under dry nitrogen-stream in a Pyrex glass tube. The sealed tube was heated at 140° in an oil-bath for 10 hr. After cooling the solvent was evaporated under evacuated pressure and the crystalline residue was recrystallized from benzene–petroleum ether to give prisms (mp 48—49°, 170 mg (85%)). The mixed melting point and IR and NMR spectra were identical with the authentic sample of 3-acetoxy-1-acetyl-5-methylpyrazole (V).

Thermal Treatment of 1-Acetyl-3-hydroxy-5-methylpyrazole (III) in the Presence of Polyphosphoric Acid——1-Acetyl-3-hydroxy-5-methylpyrazole (III) (400 mg) was added into PPA (8.5 g) and the mixture was heated on a boiling water-bath for 1.5 hr. After cooling the mixture was poured onto ice-water (20 g) and the pH value was adjusted to 4. The precipitate was filtered and dried to give pale yellow powder (120 mg, 30%). Recrystallization from water afforded powderous crystals, mp 266° (decomp.) (50 mg), which showed identical melting point and IR spectrum with the authentic sample of 4-acetyl-3-hydroxy-5-methylpyrazole (VI).[1)]

Thermal Treatment of 2-Acetyl-3-hydroxy-5-methylpyrazole (II) in Acetic Acid at 100°——A solution of 2-acetyl-3-hydroxy-5-methylpyrazole (II) (7.00 g) in acetic acid (70 ml) was heated at 100° on an oil-bath for 30 minutes. After cooling, the solution was evaporated under evacuated pressure to one-fourth of the volume and the separated crystals were collected by filtration. They were recrystallized from benzene and then from methanol to give colorless prisms, the starting monoacetate (II), mp 147—148.5° (1.19 g, 17%), which showed identical mixed melting point and IR spectrum with the authentic sample. The mother liquor was combined and evaporated to dryness under reduced pressure to give crystalline residue, which was sublimed at 0.6 mmHg at 70—80° (bath temp.). The sublimed crystals, thus obtained, melted at 242° (0.392 g, 8%) and showed identical IR spectrum with the authentic sample of 3-methylpyrazol-5-one (I).

The filtrate (acetic acid solution) was evaporated *in vacuo* and benzene was added to the residual syrup. Cooling and trituration with a glass rod caused crystallization. Filtration and recrystallization from benzene afforded colorless needles, mp 153—154° (1.504 g, 22%), which showed identical IR spectrum with the authentic sample of 1-acetyl-3-hydroxy-5-methylpyrazole (III). The mother liquor was evaporated to dryness to give a residue which was chromatographed on silica gel (20 g) in $CHCl_3$ (50 ml). The eluate was evaporated to give colorless syrup. Benzene and petroleum ether were added to the syrup and the solution was left stand in a refrigerator. Precipitated crystals were collected by filtration and recrystallized from benzene–petroleum ether to give colorless plates, mp 48—49° (0.546 g, 6%), which showed identical IR spectrum with the authentic 3-acetoxy-1-acetyl-5-methylpyrazole (V).

The filtrate (benzene solution) was passed through a short column of silica gel (20 g). The filtrate was evaporated and the residual syrup was distilled under reduced pressure. The oily distillate ($bp_{0.6}$ 70—75°), (0.365 g, 4%), showed one spot ($Rf=0.45$) on the TLC plate and nearly identical IR spectrum with the authentic sample of 3-acetoxy-2-acetyl-5-methylpyrazole (IV). The NMR spectrum was superimposible to that of the diacetate (IV) except approximately 5% comtamination of the other diacetate (V).

Thermal Treatment of 1-Acetyl-3-hydroxy-5-methylpyrazole (III) in Acetic Acid at 100°——After a solution of 1-acetyl-3-hydroxy-5-methylpyrazole (III) (7.00 g) in acetic acid (70 ml) was heated at 100° on an oil-bath for 30 minutes, the reaction mixture was treated in the same manner as the case of the monoacetate (II) to give 2-acetyl-3-hydroxy-5-methylpyrazole (II) (1.15 g, 16.5%), 3-methylpyrazol-5-one (I) (0.38 g, 7.8%), 1-acetyl-3-hydroxy-5-methylpyrazole (III) (1.59 g, 22.7%), 3-acetoxy-1-acetyl-5-methylpyrazole (V) (0.55 g, 6%), and 3-acetoxy-2-acetyl-5-methylpyrazole (IV) (0.35 g, 3.9%).

Treatment of 3-Methylpyrazol-5-one (I) in Acetic Acid in the Presence of an Equimolar Amount of Acetic Anhydride at 100°——Acetic anhydride (5.88 g) was added to a solution of 3-methylpyrazol-5-one (I) (4.90 g) in acetic acid (66 ml). After the solution was heated at 100° on an oil-bath for 30 minutes, the reaction mixture was treated in the same manner as that of the monoacetate (II) to give 2-acetyl-3-hydroxy-5-methylpyrazole (II) (1.23 g, 17.6%), 3-methylpyrazol-5-one (I) (0.40 g, 8.2%), 1-acetyl-3-hydroxy-5-methylpyrazole (III) (1.50 g, 21.4%), 3-acetoxy-1-acetyl-5-methylpyrazole (V) (0.52 g, 5.7%), and 3-acetoxy-2-acetyl-5-methylpyrazole (IV) (0.36 g, 4.0%).

Time-course Detection of the Thermal Rearrangement of 2-Acetyl-3-hydroxy-5-methylpyrazole (IV) and 1-Acetyl-3-hydroxy-5-methylpyrazole (V) in Acetic Acid at 100°——Five sample tubes for the NMR measurement which contained each of the pyrazole derivatives, (I, II, III, IV, and V) (50 mg, 70 mg, 70 mg,

90 mg, and 90 mg each in 0.5 ml acetic acid and TMS as the internal reference) were sealed under dry nitrogen-stream. The sample tubes were heated at 100° on an oil-bath and the NMR spectra were measured after every 10 minutes' interval.

(i) The NMR spectrum of 3-methylpyrazol-5-one (I) did not change after over-all 2 hours' heating.

(ii) The NMR spectrum of 2-acetyl-3-hydroxy-5-methylpyrazole (II) changed by heating and it showed, after 40 minutes' heating, an equilibrated mixture of II, I, III, IV, and V (30: 16: 38: 8: 8) (Fig. 1).

(iii) The NMR spectrum of 1-acetyl-3-hydroxy-5-methylpyrazole (III) changed by heating and it showed, after 40 minutes' heating, an equilibrated mixture of II, I, III, IV, and V (30: 16: 38: 8: 8) (Fig. 1).

(iv) The NMR spectrum of 3-acetoxy-2-acetyl-5-methylpyrazole (IV) was measured every other minute during heating at 100°. It gradually changed and after 40 minutes' heating the spectrum was identical with that of 3-acetoxy-1-acetyl-5-methylpyrazole (V). The half-lifetime of the transformation was approximately 19 minutes.

(v) The NMR spectrum of 3-acetoxy-1-acetyl-5-methylpyrazole (V) did not change after over-all 2 hours' heating.

Time-Course Detection of the Thermal Rearrangement of 3-Hydroxy-5-methylpyrazole (I) in Acetic Acid in the Presence of an Equimolar Amount of Acetic Anhydride——The NMR spectrum of 3-methylpyrazol-5-one (I) (50 mg) in acetic acid was examined promptly after adding acetic anhydride (11 mg) into the solution. The C_4-proton resonance peak of I at 5.40 ppm in acetic acid itself had completely shifted at 4.23 ppm. The solution was then heated at 100° and the NMR spectrum was measured after 10 minutes' interval. After 40 minutes' heating an analogous equilibrated mixture as mentioned above (*cf.* (ii)) was obtained. At this period further 100 mg of acetic anhydride was added into the mixture and the spectrum was measured again after every 10 minutes' heating at 100°. After 40 minutes' heating the spectrum became identical with that of 3-acetoxy-1-acetyl-5-methylpyrazole (V) showing C_4-proton resonance peak at 6.10 ppm.

Time-Course Detection of the Rearrangement of 3-Acetoxy-2-acetyl-3-methylpyrazole (IV) in *o*-Dichlorobenzene——The NMR spectra of the following compounds were measured: *o*-Dichlorobenzene [δ ppm (neat): 6.80—7.35 (m)], acetic acid [δ ppm (*o*-dichlorobenzene): 1.97 (3H, s), 11.80 (1H, br)], acetic anhydride [δ ppm (*o*-dichlorobenzene): 2.08 (s)], propionic acid [δ ppm (*o*-dichlorobenzene): 1.05 (3H, t, J=7.2 Hz), 2.25 (2H, q, J=7.2 Hz) 11.84 (1H, br)], 3-acetoxy-2-acetyl-5-methylpyrazole (IV) [δ ppm (*o*-dichlorobenzene): 2.10 (3H, s), 2.17 (3H, s), 2.44 (3H, s), 5.74 (1H, s)] and 3-acetoxy-1-acetyl-5-methylpyrazole (V) [δ ppm (*o*-dichlorobenzene): 2.16 (3H, s), 2.46 (sH, d, J=1.2 Hz), 2.49 (3H, s), 5.99 (1H, q, J=1.2 Hz)].

(i) A solution of 3-acetoxy-2-acetyl-5-methylpyrazole (IV) (45 mg), and small amount of TMS in *o*-dichlorobenzene (4 ml) was sealed under dry nitrogen-stream in a sample tube for NMR measurement. The spectrum was measured after every 10 minutes' heating at 100°. The spectrum pattern did not change after over-all 2 hours' heating.

(ii) A solution of 3-acetoxy-2-acetyl-5-methylpyrazole (IV), acetic acid (30 mg) and small amount of TMS in *o*-dichlorobenzene (0.4 ml) was sealed under nitrogen-stream in a sample tube for NMR measurement. The spectrum was measured after every 10 minutes' heating at 100°. The C_4-proton resonance peak at 5.74 ppm gradually decreased its intensity and after over-all 2 hours' heating the spectrum completely changed to that of 3-acetoxy-1-acetyl-5-methylpyrazole (V). The half-lifetime of the conversion was approximately 40 minutes.

(iii) A solution of 3-acetoxy-2-acetyl-5-methylpyrazole (IV), propionic acid (35 mg) and small amount of TMS in *o*-dichlorobenzene (0.4 ml) was sealed under dry nitrogen-stream in a sample tube for NMR measurement. The spectrum was measured after every 10 minutes' heating at 100°. The C_4-proton resonance peak at 5.74 ppm gradually decreased its intensity and after over-all 3 hours' heating the peak at 5.98 ppm completely took the part of it. The half-lifetime of the conversion was approximately 50 minutes (Fig. 2).

(iv) The NMR spectrum of 3-acetoxy-2-acetyl-5-methylpyrazole (IV) in the presence of propionic acid was measured after heating at 135° for 12 hours, which revealed that there appeared new peaks at 2.95 ppm (1.3 H, q, J=7.5 Hz) and 1.97 ppm (2.35 H, s) comparing to the peak at 5.98 ppm (1H, broad singlet), indicating incorporation of propionyl group at N_1 (*ca.* 65%) and at C_3-O (*ca.* 57%) by releasing corresponding amount of acetic acid into the solution (*cf.* Fig. 3).

(v) The NMR spectrum of 3-acetoxy-1-acetyl-5-methylpyrazole (V) in the presence of propionic acid changed by heating at 135° and after 12 hours' heating nearly the same pattern as stated in (iv) was obtained.

Intermolecular Acetyl Group Migration Experiments of 3-Acetoxy-1-acetyl-5-methylpyrazole (V)——(i) 1-Acetyl-3,5-dimethylpyrazole from 3,5-Dimethylpyrazole: 3-Acetoxy-1-acetyl-5-methylpyrazole (V) (400 mg) was added into a solution of 3,5-dimethylpyrazole (200 mg) in dry benzene (3 ml) and the mixture was heated for 30 minutes under reflux. After cooling the precipitated crystals were filtered and recrystallized from benzene afforded colorless needles mp 147—148° (110 mg), which were identified with the authentic sample of 1-acetyl-3-hydroxy-5-methylpyrazole (III) by comparing the mixed melting point and the IR spectra. The filtrate was evaporated to dryness and distilled under reduced pressure to give colorless oil (bp_5 80°) (125 mg). The material showed identical IR spectrum with the sample of 1-acetyl-3,5-dimethylpyrazole prepared from 3,5-dimethylpyrazole and acetic anhydride.

(ii) N-Acetylpiperidine from Piperidine: A solution of piperidine (200 mg), diacetate (III) (370 mg) in dry benzene (5 ml) was heated under reflux for an hour. The precipitated crystals of monoacetiate (III) were filtered off and the filtrate was evaporated and the residue was distilled under reduced pressure. The oily distillate (116 mg) (bp_5 80°) showed identical IR spectrum with the authentic N-acetylpiperidine.

(iii) Acetanilide from Aniline: The diacetate (V) was added into a solution of aniline (200 mg) in THF (5 ml). Slightly exothermic reaction occurred and after the mixture was left at room temperature for 30 minutes the separated crystals of the monoacetate (III) were filtered off. The filtrate was evaporated to give colorless crystals. Recrystallization from water afforded colorless plates mp 112—114° (240 mg) which were identical with the authentic sample of acetanilide.