Studies of Heterocyclic Compouds. XII.[1] Structures of Acetylated Products of 5-Hydroxy-4-(2-hydroxyethyl)-3-methylpyrazole

Hisao Ochi, Tadashi Miyasaka, and Kiichi Arakawa

School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo 142

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Acetylation of 5-hydroxy-4-(2-hydroxyethyl)-3-methylpyrazole (**1**) produced five acetyl derivatives: 4-(2-acetoxyethyl)-5-hydroxy-3-methylpyrazole (**2**), 4-(2-acetoxyethyl)-2-acetyl-5-hydroxy-3-methylpyrazole (**3**), 4-(2-acetoxyethyl)-1-acetyl-5-hydroxy-3-methylpyrazole (**4**), 5-acetoxy-4-(2-acetoxyethyl)-2-acetyl-3-methylpyrazole (**5**), and 1-acetyl-5-hydroxy-4-(2-hydroxyethyl)-3-methylpyrazole (**6**). The partial hydrolysis of **3** and **5** in aq acetic acid gave the monoacetate (**2**). The triacetate (**5**) afforded **3** by heating in a mixture of pyridine and methanol. Migration of the acetyl group from the N_1-position to the C_5-O- and to the side chain-O-position is suggested. It is also suggested that the triacetate (**5**) may be effective for acetylation of amines.

In previous papers we have shown that five mono- and diacetyl derivatives could be prepared from 5-hydroxy-3-methylpyrazole by acetylation with acetic anhydride.[2,3] We have also shown that the acetyl derivatives were useful as mild acetylating reagents.[3]

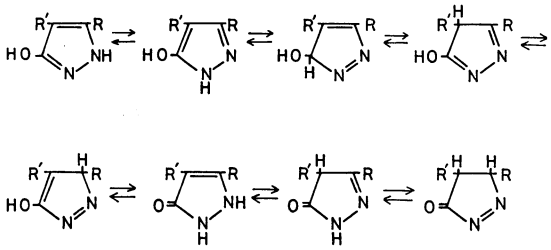
In order to improve the usefulness of this type of acetylating reagent we have prepared vinylpyrazole derivatives as a monomeric source of acetyl group-exchange resins.

In this paper we deal with the acetylation of 5-hydroxy-4-(2-hydroxyethyl)-3-methylpyrazole (**1**),[4] which is readily prepared from α-acetyl-γ-butyrolactone.[5]

The pyrazole (**1**) can be expected to give a very complicated mixture of mono-, di- and triacetyl derivatives, because, as Katritzky and Lagowski have predicted, **1** has eight possible tautomers[6] (Scheme 1), and the first attack of the acetylating reagent may occur either at N_1-, N_2-, C_5-O-, or the side chain-O-position. The structures of the reaction products were determined based on the IR, the NMR, and the UV spectra and the ferric chloride coloration test.[7]

By heating in refluxing acetic acid, **1** gave a monoacetate (**2**), whose UV spectrum was almost superimposable with that of the starting material. The IR spectrum (1750 cm^{-1}) and the NMR spectrum (1.98, 2.08 ppm) indicated that the acetyl group bonded to the oxygen atom on the side chain to furnish 4-(2-acetoxyethyl)-5-hydroxy-3-methylpyrazole.

When **1** was heated with two molar equivalents of acetic anhydride in pyridine under reflux, diacetate (**3**) was formed in good yield; this was identical in every respect with the specimen prepared by acetylation of **2** with an equimolar amount of acetic anhydride in pyridine. Hydrolysis of **3** in aq acetic acid afforded **2**. The diacetate (**3**) gave a reddish brown coloration with methanolic ferric chloride; there was one absorption maximum (257.5 nm) in the UV spectrum and a chemical shift of C_3–CH_3 at 2.50 (or 2.52) ppm.



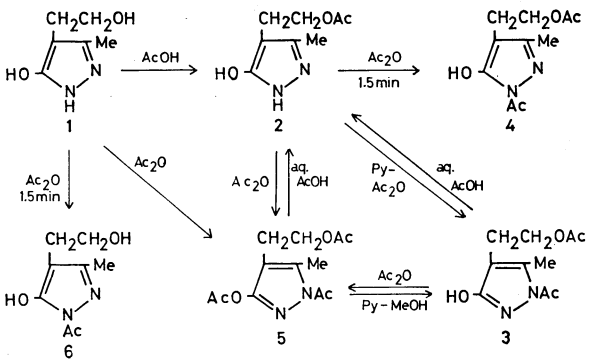
Scheme 1.

By heating **2** in acetic anhydride at 110 °C for 1.5 min the diacetate (**4**) separated; its UV spectrum displayed two absorption maxima (224 and 295.5 nm) and the NMR spectrum displayed the C_3–CH_3 peak at 2.21 ppm. According to the empirical rule that N_2-acetyl groups bring about low field shifts of a C_3–CH_3 signal,[2] the diacetate (**3**) which showed a C_3–CH_3 signal at the lower field of 2.50 (or 2.52) ppm has the N_2-acetyl group, which is 4-(2-acetoxyethyl)-2-acetyl-5-hydroxy-3-methylpyrazole, while the diacetate (**4**) is 4-(2-acetoxyethyl)-1-acetyl-5-hydroxy-3-methylpyrazole.

Heating a suspension of **1** in acetic anhydride under reflux for 4 h afforded triacetate (**5**), which did not show any coloration with ferric chloride. The IR spectrum showed a phenol ester band at 1785 cm^{-1}, and the NMR spectrum displayed a C_3–CH_3 signal at 2.53 ppm. Since the C_3–CH_3 signal shifted to the lower field of 2.53 ppm compared with that of the parent compound (**1**), the structure of **5** corresponds to 5-acetoxy-4-(2-acetoxyethyl)-2-acetyl-3-methylpyrazole.

Further acetylation of the diacetate (**3**) and monoacetate (**2**) with acetic anhydride produced the triacetate (**5**). The partial hydrolysis of **5** in aq acetic acid afforded the monoacetate (**2**) and milder hydrolysis of **5** in a mixture of methanol and pyridine afforded the diacetate (**3**). These results further supported the similarity of the structures of the triacetate (**5**), the diacetate (**3**), and the monoacetate (**2**).

Heating of **1** in acetic anhydride at 110 °C for 1.5 min gave monoacetate (**6**). In contrast to the other



Scheme 2.

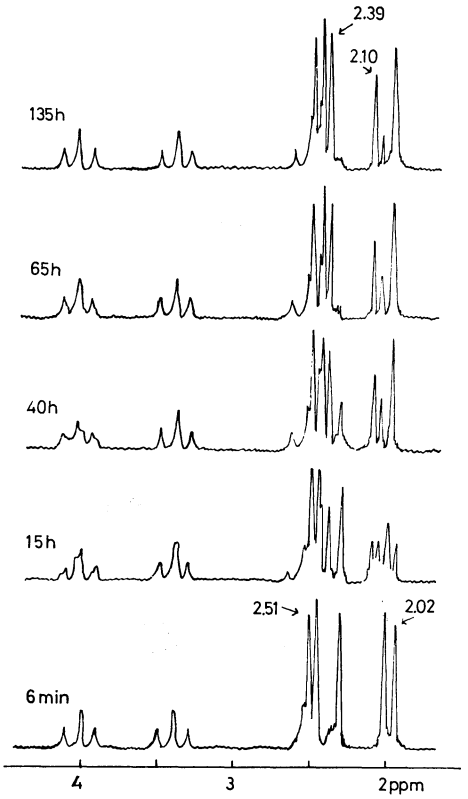


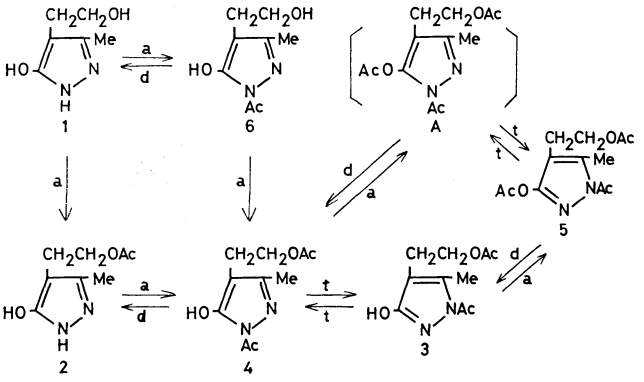
Fig. 1. NMR spectra of the time-course of the conversion of a mixture of **1** and **5** at 35 °C in DMSO-d_6 into a mixture of **3** and **6**.

monoacetate (**2**), **6** gave bluish green coloration with ferric chloride and had two distinct absorption maxima (225.5, 296.5 nm) in the UV spectrum. The methyl signal of C_3-position (2.10 ppm) is not so much lowered in contrast to the parent compound (**1**) which has its methyl signal at 2.02 ppm; the carbonyl band shifted to the lower wave number of 1715 cm^{-1} as a result of hydrogen bonding with C_5–OH. So **6** has the N_1-acetyl group and its structure corresponds to 1-acetyl-5-hydroxy-4-(2-hydroxyethyl)-3-methylpyrazole.

Next we examined the mode of acetyl-transfer reaction during the formation of the acetyl derivatives.

Heating a solution of **5** and an equimolar amount of **1** in benzene under reflux for 28 h afforded a mixture of **1**, **2**, **3**, **5**, and **6**. Fig. 1 shows the time dependence of the NMR signals of the reaction mixture in DMSO-d_6. The chemical shifts of the methyl proton and ethylene proton signals of a mixture of **1** and **5** in DMSO-d_6 were changed at 35 °C and finally the NMR spectrum turned into that of a mixture of diacetate (**3**) and monoacetate (**6**) after 135 h. These results suggest that the acetyl group at the C_5-O-position of **5** migrates to the N_1- or N_2-position of the other pyrazole molecule.

A solution of monoacetate (**6**) in chlorobenzene was heated at 130 °C for 1 h; colorless crystals separated after cooling, and their IR and NMR spectra indicated that the product was monoacetate (**2**). On the other hand 5-hydroxy-4-(2-hydroxyethyl)-1,3-dimethylpyrazole (**7**) was heated with acetic acid under reflux to afford 4-(2-acetoxyethyl)-5-hydroxy-1,3-dimethylpyrazole (**8**). A mixture of an equivalent amount of **5** and **7** was converted by heating under reflux in benzene into four components; **2**, **3**, **4**, and **8**. This result suggests that the acetyl group at the C_5-O-position of the triacetate (**5**) was transferred to the alcoholic group at the side chain of **7** to form **3** and **8**. The fact that the two isomeric diacetates **3** and **4** were isolated from the reaction mixture suggests the existence of an equilibrium between **3** and **4**. Indeed, heating of **4** in chlorobenzene under reflux for 8 h afforded a mixture of **3** (53%) and **4** (47%). A mixture of **3** and **4** in almost the same ratio was also formed from **3**.



Scheme 3. a: acetylation t: acetyl transfer d: deacetylation

The reaction path of these conversions can be formulated as shown in Scheme 3. In the acetylation of **1**, the kinetically controlled product (**6**) was formed at the first stage. The acetyl group of 1-acetyl-5-hydroxypyrazole was formed, which easily migrates to a position like N_2- or C_5-O-.[3] By heating **6**, therefore, acetyl group at N_1-position migrated either intermolecularly or intramolecularly to the side chain-oxygen to form **2**. The formation of **2** was promptly followed by acetylation at N_1-position to give diacetate (**4**), which was rearranged by heating into the thermally more stable isomer (**3**), and the hydroxyl group at C_5-position of **3** was finally acetylated to form the stable triacetate (**5**). At this stage acetylation of **4** may promptly rearrange into **5** under the present reaction conditions.

The acetoxyl group of the compound **5** was considered to be effective as an acetylating reagent of amines, as shown in the case of 5-acetoxy-2-acetyl-3-methylpyrazole.[3,8] When **5** was treated with an equimolar amounr of aniline, acetanilide was separated in quantitative yield. Further investigation concerning the application of this reagent to other materials is proceeding in this laboratory and will be reported elswhere.

Experimental

All the melting points were measured in capillary tubes and were uncorrected. NMR spectra were measured on Hitachi R-20 60 MHz and Hitachi R-22 90 MHz spectrophotometers, using tetramethylsilane as an internal reference. IR and UV spectra were measured on a JASCO IRA-1 spectrophotometer and a Hitachi EPS-3 spectrophotometer, respectively. Column chromatography was carried out through silica gel (Merck, art. 7734, 70—230 mesh) using chloroform containing 5% methanol as the eluting solvent.

*4-(2-Acetoxyethyl)-5-hydroxy-3-methylpyrazole (**2**).* After 4-(2-hydroxyethyl)-5-hydroxy-3-methylpyrazole (**1**) (1.00 g) was heated in acetic acid (10 ml) under reflux for 1 h, the reaction mixture was evaporated to dryness *in vacuo*. The residual mass was recrystallized from methanol to give colorless plates (995 mg, 76.9% yield), mp 186—188 °C, which gave reddish brown coloration with methanolic ferric chloride. Found: C, 52.11; H, 6.38; N, 15.38%. Calcd for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21%. IR (KBr): 1750 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 227 (3.72), 239 (3.77). NMR δ ppm (DMSO-d_6): 1.98 (3H), 2.08 (3H), 3.99 (t, 2H, J= 7.5 Hz), 4.29 (t, 2H, J=7.5 Hz).

*4-(2-Acetoxyethyl)-2-acetyl-5-hydroxy-3-methylpyrazole (**3**).* A solution of **1** (284 mg) and acetic anhydride (420 mg) in pyridine (3 ml) was heated under reflux for 3 h. After pyridine was evaporated *in vacuo*, the residue was added onto ice-water. The colorless powder was collected by filtration, and recrystallized from ethyl acetate to give colorless needdles (396 mg, 88.6%), mp 113—114 °C. The material showed reddish brown coloration with methanolic ferric chloride. Found: C, 53.10; H, 6.30; N, 12.11%. Calcd for $C_{10}H_{14}O_4N_2$: C, 53.09: H, 6.24; N, 12.38%. IR (KBr): 1740, 1720, 1640 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 257.5 (4.28). NMR δ ppm ($CDCl_3$): 2.02 (3H), 2.50 (3H), 2.52 (3H), 2.68 (t, 2H, J=7 Hz), 4.19 (t, 2H, J=7 Hz).

*4-(2-Acetoxyethyl)-1-acetyl-5-hydroxy-3-methylpyrazole (**4**).* A suspension of **2** (300 mg) in acetic anhydride (3 ml) was heated at 110 °C for 1.5 min with vigorous agitation. After cooling in an ice-salt bath crystals separated; these were collected by filtration and washed with cold ether to give a colorless powder (192 mg, 52%), mp 115—117 °C. The compound was too unstable to be purified by recrystallization from an ordinary organic solvent. The material showed bluish green coloration wtih methanolic ferric chloride. IR (KBr): 1740, 1720, 1650 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 224 (4.00), 295.5 (3.75). NMR δ ppm ($CDCl_3$) 2.03 (3H), 2.21 (3H), 2.60 (t, 2H, J=7 Hz), 2.62 (3H), 4.18 (t, 2H, J=7 Hz).

*5-Acetoxy-4-(2-acetoxyethyl)-2-acetyl-3-methylpyrazole (**5**).* After **1** (1.00 g) was heated in acetic anhydride (20 ml) under reflux for 4 h, the acetic anhydride was evaporated *in vacuo*. The residual oil was distilled under reduced pressure to give a colorless oil (1.55 g, 81.6%), bp 178 °C (6 mmHg). The material did not show any coloration with ferric chloride. Found: C, 53.62; H, 6.04; N, 10.35%. Calcd for $C_{12}H_{16}O_5N_2$: C, 53.72; H, 6.01; N, 10.44%. IR ($CHCl_3$): 1785, 1750, 1730 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 247 (4.06). NMR δ ppm ($CDCl_3$): 2.02 (3H), 2.33 (3H), 2.53 (3H), 2.59 (m, 5H), 4.09 (t, 2H, J=7.5 Hz).

*1-Acetyl-5-hydroxy-4-(2-hydroxyethyl)-3-methylpyrazole (**6**).* A mixture of **1** (300 mg) and acetic anhydride (3 ml) was heated at 110 °C for 1.5 min with vigorous agitation. After cooling in an ice-salt bath crystals separated; these were collected by filtration and washed with cold ether to give a colorless powder (132 mg, 33.8%), mp 115—118 °C. The compound was too unstable to be purified by recrystallization from an ordinary organic solvent. The material showed bluish green coloration with methanolic ferric chloride. IR (KBr): 1715, 1675 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 225.5 (4.31), 296.5 (3.76). NMR δ ppm (DMSO-d_6): 2.10 (3H), 2.28 (t, 2H, J=7 Hz), 2.50 (3H), 3.43 (t, 2H, J=7 Hz).

*4-(2-Acetoxyethyl)-5-hydroxy-1,3-dimethylpyrazole (**8**).* 5-Hydroxy-4-(2-hydroxyethyl)-1,3-dimethylpyrazole (**7**) (1.00 g) was heated in acetic acid (30 ml) under reflex for 5 h. After the acetic acid was evaporated, the residue was separated by column chromatography to give colorless crystals (1.71 g) and the starting material (**7**) (78 mg). The former was recrystallized from benzene to give colorless needles (900 mg, 72%), mp 64—65 °C. Found: C, 54.43; H, 7.22; N, 14.32%. Calcd for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.13%. IR (KBr): 1755, 1750 cm^{-1}. UV λ_{max}^{MeOH} nm (log ε): 221 (3.72). NMR δ ppm ($CDCl_3$): 2.00 (3H), 2.12 (3H), 2.58 (t, 2H, J=7.5 Hz) 3.39 (3H), 4.10 (t, 2H, J=7.5 Hz).

*Partial Hydrolysis of the Triacetate (**5**) in 60% Aq Acetic Acid.* After **5** (500 mg) was heated in 60% aq acetic acid (10 ml) under reflux for 3 h, the solvent was evaporated under reduced pressure to give a colorless powder (270 mg, 78.7%), mp 186—188 °C. The mixed melting point and the IR spectrum showed that the material was identical with the monoacetate (**2**).

*Partial Hydrolysis of the Diacetate (**3**) in 60% Aq Acetic Acid.* The diacetate (**3**) (100 mg) was treated as described above to give colorless powder (79 mg, 96%). The IR and the NMR spectra were completely identical with those of the monoacetate (**2**).

*Partial Deacetylation of the Triacetate (**5**) with Methanolic Pyridine.* A solution of **5** (200 mg) and pyridine (0.3 ml) in methanol (3 ml) was heated under reflux for 1 h. After evaporation of the solvent *in vacuo* the residue was washed with cold ether to afford colorless crystals (155 mg, 92%), mp 112—114 °C. The IR and the NMR spectra were completely identical with those of the diacetate (**3**).

*Treatment of the Monoacetate (**2**) with an Equimolar Amount of Acetic Anhydride in Pyridine.* A mixture of **2** (368 mg), pyridine (3 ml), and acetic anhydride (210 mg) was heated at 100 °C for 1.5 h. After the pyridine was evaporated *in vacuo*, the reaction mixture was poured onto ice-water. The separated crystals (298 mg, 65.8%) were collected by filtration. The filtrate was extracted with chloroform. The organic layer was dried over magnesium sulfate and the solvent was removed to give colorless crystals (130 mg, 28.7%). The IR and the NMR spectra of each sample indicated that both of them were identical with the authentic specimen of the diacetate (**3**).

*Treatment of the Monoacetate (**2**) with Excess Acetic Anhydride.* After **2** (300 mg) was heated in acetic anhydride (6 ml) under reflux for 2 h, the acetic anhydride was evaporated *in vacuo*. The residual oil was distilled *in vacuo* to give a colorless oil (353 mg), 84.8%), bp 176—178 °C (6 mmHg). The IR and the NMR spectra were completely identical with those of the triacetate (**5**).

*Treatment of the Diacetate (**3**) with Excess Acetic Anhydride.* Diacetate (**3**) (300 mg) was treated as described above to give the triacetate (**5**) (293 mg, 82.4%), bp 176—178 °C (6 mmHg), after distillation.

*Treatment of the Pyrazole (**1**) with the Triacetate (**5**) at 80 °C in Benzene.* Into a solution of **5** (140 mg) in benzene (20 ml) was added finely powdered **1** (70 mg), after being heated under reflux for 28 h, the benzene was evaporated *in vacuo*. The residue was separated by column chromatography to give **5** (32 mg), **3** (90 mg), **6** (5 mg) **2** (958 mg), and **1** (16 mg). These materials were identical with the authentic samples by comparing the IR spectra.

*Treatment of the Pyrazole (**1**) with the Triacetate (**5**) at 35 °C in DMSO-*d_6. A sample tube for the NMR measurement which contained **5** (27 mg), **1** (14 mg), and DMSO-d_6 (0.3 ml) was sealed under a nitrogen stream. The sample tube was warmed to 35 °C and the NMR spectra were measured (TMS as an internal reference). The results are shown in Fig. 1.

*Thermal Treatment of the Monoacetate (**6**) in Chlorobenzene.* After a solution of **6** (100 mg) in chlorobenzene (8 ml) was heated under reflux for 4 h, it was cooled in an ice-salt bath.

The separated crystals were collected by filtration to give colorless leaflets (85 mg, 85%), mp 185—188 °C. The IR spectrum showed that it was identical with the monoacetate (**2**).

*Treatment of the Pyrazole (**7**) with the Triacetate (**5**) at 80 °C in Benzene.* A mixture of **7** (156 mg) and **5** (270 mg) in bezene (5 ml) was heated under reflux for 5 h. After the benzene was evaporated *in vacuo*, the residual solid was separated by column chromatography to give **4** (23 mg), **3** (157 mg), **8** (190 mg), and **2** (30 mg). These materials were found to be identical with the authentic samples by comparing the IR and the NMR spectra.

*Thermal Treatment of the Diacetate (**4**) in Chlorobenzene.* After **4** (100 mg) was heated in chlorobenzene (5 ml) under reflux for 8 h, the solvent was evaporated *in vacuo* to give a colorless powder (98 mg, 98%). The NMR spectrum indicated that the substance was a mixture of **3** and **4** (17 : 15).

*Thermal Treatment of the Diacetate (**3**) in Chlorobenzene.* The diacetate (**3**) (100 mg) was treated in the same manner as described in the case of the diacetate (**4**). After 8 hours' heating the NMR spectrum became identical with that of the compound **4**.

*Acetylation of Aniline with the Triacetate (**5**).* The triacetate (**5**) (270 mg) was added into a solution of aniline (93 mg) in benzene (7 ml) and the mixture was heated under reflux for 2 h. After the solvent was evaporated, the residue was separated by column chromatography to give diacetate (**3**) (215 mg) and acetanilide (131 mg, 97%), which was recrystallized from water to give colorless plates, mp 112—114 °C. The material was proved to be identical with the authentic sample of acetanilide by comparing the IR spectra.

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References

1) Part XI: K. Satoh, T. Miyasaka, and K. Arakawa, *Yakugaku Zasshi*, **97**, 422 (1977)

2) K. Arakawa, T. Miyasaka, and H. Ochi, *Chem. Pharm. Bull.*, **22**, 207 (1974)

3) K. Arakawa, T. Miyasaka, and H. Ochi, *Chem. Pharm. Bull.*, **22**, 214 (1974)

4) The nomenclature and structure form of this compound series are represented by enol form, which have some possible tautomers as shown in Scheme 1.

5) a) G. B. Bachman and L. V. Heisey, *J. Am. Chem. Soc.*, **71**, 1985 (1949)
b) H. Wamhoff and E. Korte, *Chem. Ber.*, **99**, 2962 (1966)
c) E. Magien and W. Tom, *J. Org. Chem.*, **1967**, 1229

6) A. R. Katritzky and J. M. Lagowski, "Advances in Heterocyclic Compounds," Vol. 2, Academic Press, New York and London (1963), p. 44.

7) The chemical shift of C_3–CH_3 is lowered in the case that it is adjacent to the *N*-acetyl group. 1-Acetyl-3-methyl-5-hydroxypyrazole showed two absorption maxima at 227 and 289 nm in the UV spectrum and deep purple coloration with methanolic ferric chloride. 2-Acetyl-3-methyl-5-hydroxypyrazole showed one absorption maximum at 253 nm in the UV spectrum and reddish brown coloration with ferric chloride.[2]

8) M. Irie, T. Miyasaka, and K. Arakawa, *J. Biochem.*, **72**, 65 (1972)