RING TRANSFORMATIONS OF 6H-CYCLOPROPA[5a,6a]PYRAZOLO[1,5-a]PYRIMIDINE

Takushi Kurihara*, Tsutomu Tani, and Keiko Nasu
Osaka College of Pharmacy, 2-10-65, Kawai, Matsubara, Osaka 580, Japan

Abstract --- The ring transformations of 5a-acetyl-6a-carbethoxy-5a,6a-dihydro-6H-cyclopropa[5a,6a]pyrazolo[1,5-a]pyrimidine-3-carbonitrile (2) and the corresponding 5-methyl derivative (3) into pyrazolylpyrroles (7 and 8), pyrazolopyrimidine (10), and pyrazolylpyridone (12) under the basic, acidic, and neutral condition are described.

Recently, we reported[1] that the hydrogenation or nucleophilic addition of 6-acetyl-7-carbethoxypyrazolo[1,5-a]pyrimidine-3-carbonitrile (1), prepared readily by condensation of ethyl 3-ethoxymethylene-2,4-dioxovalerate with 3-aminopyrazole-4-carbonitrile, and its analogs occurred on the pyrimidine ring in a 1,4-fashion. It was also reported[1] that compound 1 afforded 5a-acetyl-6a-carbethoxy-5a,6a-dihydro-6H-cyclopropa[5a,6a]pyrazolo[1,5-a]pyrimidine-3-carbonitrile (2) and the corresponding 5-methyl derivative (3) by the reaction with diazomethane in ether under ice cooling or at room temperature in good yields, respectively. Ring enlargement and rearrangement of condensed cyclopropanes have been the object of extensive investigation[2]. The present paper deals with the interesting ring transformations of compounds 2 and 3 into pyrazolylpyrrole, pyrazolylpyridone, and pyrazolopyrimidine derivatives.

Treatment of 2 with an equivalent amount of potassium hydroxide in ethanol resulted in a carboxylic acid (6) (mp 115-117°) in 80.6% yield, whose nuclear magnetic resonance (nmr) spectrum[3] [δ 0.90 (3H, t, J=6 Hz, OCH_2CH_3), 2.27 (3H, s, $COCH_3$), 2.76 and 3.45 (each 1H, each d, J=16 Hz, CH_2), 3.15 and 3.70 (each 1H, each m, OCH_2CH_3), 7.35 (1H, d, J=6 Hz, C_5-H), 7.90 (1H, s, C_2-H), and 10.60 (1H, d, J=6 Hz, exchanged with D_2O, NH)] showed the presence of ethoxy group and the lack of cyclopropane ring. The ultraviolet spectrum of 6 is similar to that of the 4,7-dihydro derivative of 1[1]. Thus, the structure of 6 was assigned as 6-acetyl-3-cyano-7,8-dihydro-8-ethoxy-4H-pyrazolo[1,5-a][1,3]diazepine-8-carboxylic acid.

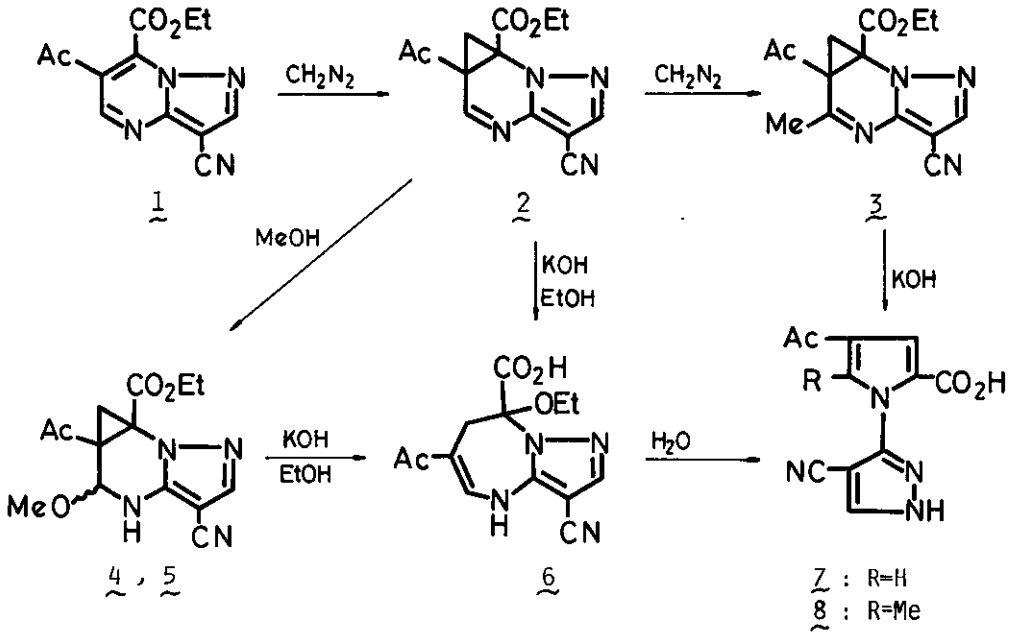
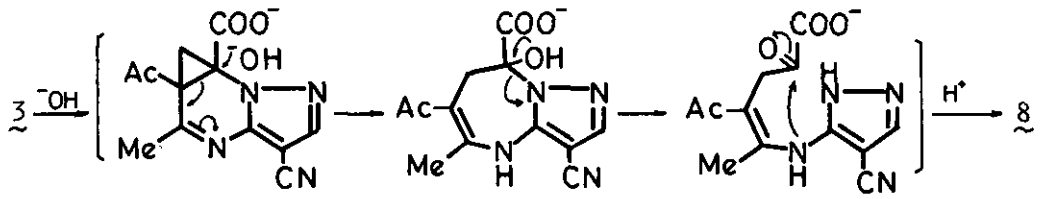


Chart 1

Product 6 was also obtained in the following manner. Compound 2 was allowed to stand in methanol to give a mixture of cis and trans isomeric mixture of methanol adducts (4 and 5)[4], whose nmr data indicated the presence of cyclopropane ring ; namely signals due to cyclopropane ring protons appeared at 1.70 and 2.53 in 4, and 1.65 and 2.10 in 5 as doublet (J=6 Hz), respectively. The mixture was then treated with an equivalent amount of potassium hydroxide in ethanol to yield 6 in good yield. On the other hand, when 3[5] was treated with potassium hydroxide under the same condition, a carboxylic acid (8)[6] (mp 297-280°) was obtained in 69.5% yield. The nmr spectrum exhibited the two singlet signals due to the C_3 and C_5, protons at 7.39 and 8.63. This structure was confirmed by X-ray structure analysis to be 4-acetyl-1-(4-cyanopyrazol-3-yl)-5-methylpyrrole-2-caboxylic acid[7]. Interestingly, refluxing of 6 in water gave 4-acetyl-1-(4-cyanopyrazol-3-yl)-pyrrole-2-carboxylic acid (7)[8] (mp 275-277°), the structure of which was easily confirmed on the basis of its spectral data, comparing with those of 8.
The mechanism of the ring transformation of 3 to 8 is proposed as follows.



Heating of 2 in glacial acetic acid yielded ethyl 6-acetyl-3-cyano-7,8-dihydro-8-acetoxy-4H-pyrazolo[1,5-a][1,3]diazepine-8-carboxylate (9)[9] in 62.8% yield. The structure of the product was established on the basis of its elemental analysis and spectral data, comparing with those of 6. Furthermore, refluxing of 2 in 80% aqueous dioxane for 10 hr gave ethyl 3-cyano-7-methyl-6-pyrazolo[1,5-a] pyrimidinepyruvate (10) in 74% yield, which was also obtained by prolonged heating of 9 in aqueous acetic acid. The compound gave a positive ferric chloride test (dark green) and , on treatment with acetic anhydride, gave the acetate (11).

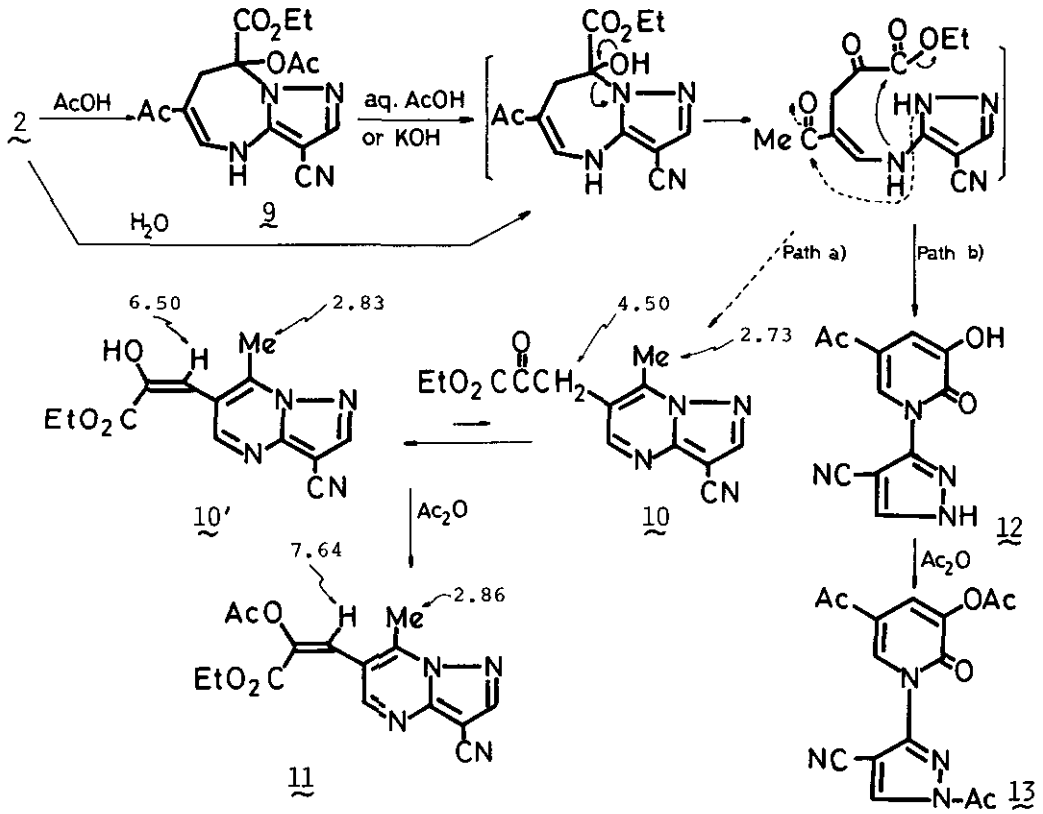


Chart 2

The nmr spectrum of 10 indicated the presence of 31.5 : 68.5 mixture of a keto (10) and an enol (10') tautomers. The chemical shifts representing the above tautomerism are recorded in Chart 2.

Finally, treatment of the acetate (9) with an equivalent amount of potassium hydroxide in ethanol at room temperature gave a 93% yield of 5-acetyl-3-hydroxy-1-(4-cyanopyrazol-3-yl)-2-pyridone (12) (mp >300°) [ir ν (KBr) : 3300, 2240, 1660, 1630, nmr δ : 2.41 (3H, s, $COCH_3$), 7.18 (1H, d, J=2 Hz, C_4-H), 8.13 (1H, d, J= 2 Hz, C_6-H), 8.75 (1H, s, C_5,-H), 10.25 and 14.35 (each 1H, each bs, NH and/or OH)], which has a positive ferric chloride test (dark green) and afforded the diacetate (13) upon treatment with acetic anhydride.

On the bases of these results, the mechanism of the ring transformations of 2 into 10 and 12 is considered as follows. The first step is the attack of oxygen functions on the 6a position of 2 with the ring enlargement, followed by prototropy, resulting in the formation of α-keto ester. Then, while in the acidic or neutral media (path a) the ring nitrogen atom attacks on the acetyl carbonyl carbon atom to give 10, the attack of the 3-amino nitrogen atom on the ester carbonyl carbon atom occurrs in the basic media (path b) resulting in 12 as shown in chart 2.

REFERENCES

1 T. Kurihara, K. Nasu, F. Ishimori, and T. Tani, J. Heterocyclic Chem., submitted.

2 E. Wenkert, B.L. Buckwalter, and S.S. Sathe, Synthetic Commun., 1973, 3, 216; J.D. White and L.G. Wade, Jr, J. Org. Chem., 1975, 40, 118; U.K. Pandi and S.A.G. Degraaf, Chem. Comm., 1972, 659; L. Garanti and G. Zecchi, J. Heterocyclic Chem., 1978, 15, 509.

3 All of the nmr spectra were recorded on a Hitachi R-24A in DMSO-d_6 using TMS as the internal standard and the chemical shifts are expressed as δ ppm.

4 The mixture was separated by fractional recrystallization from MeOH (4, mp 148-150° and 5, mp 150-152°), but their stereochemistry is remained unsolved.

5 This compound did not give the methanol adduct even in refluxing methanol.

6 ir ν (KBr) : 3300, 2240, 1720, 1660 cm^{-1}, nmr δ : 2.23 (3H, s, CH_3), 2.42

(3H, s, CH_3), 2.42 (3H, s, $COCH_3$), 7.39 (1H, s, C_3-H), 8.63 (1H, s, $C_{5'}$-H), 12.50 and 13.78 (each 1H, each bs, NH and/or OH).

7 The X-ray structure analysis was carried out by Dr. T. Ishida of Osaka College of Pharmacy. The crystal data are as follows : a=7.688(2)Å, b=9.124(2)Å, c=17.357(5)Å, β=93.36(1)°, space group P2/c.

8 ir ν (KBr) : 3150, 2240, 1720, 1660 cm^{-1}, nmr δ 2.42 (3H, s, $COCH_3$), 7.18 (1H, d, J=2 Hz, C_3-H), 7.98 (1H, d, J=2 Hz, C_5-H), 8.65 (1H, s, $C_{5'}$-H), 13.93 (1H, bs, NH).

9 ir δ (KBr) : 3000-3200, 2240, 1760, 1600 cm^{-1}, nmr δ : 1.13 (3H, t, J=6 Hz, CH_2CH_3), 2.08 (3H, s, $OCOCH_3$), 2.23 (3H, s, $COCH_3$), 3.45 (2H, q, J=15 Hz, CH_2), 4.15 (2H, q, J=6 Hz, CH_2CH_3), 7.37 (1H, s, C_5-H), 7.93 (1H, s, C_2-H), 10.85 (1H, bs, NH).

Received, 4th July, 1980