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REACTIONS OF 3-METHYL-8*H*-CYCLOHEPT[*d*]ISOXAZOL-8-ONE WITH 1,2-ALKANEDIAMINES

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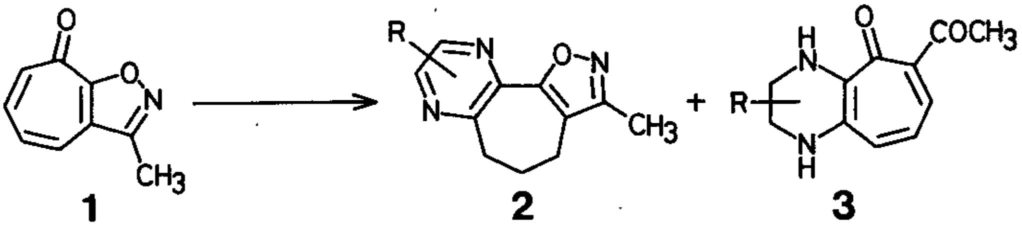
Abstract — 3-Methyl-8*H*-cyclohept[*d*]isoxazol-8-one (**1**) reacted with 1,2-ethanediamine to afford 3-methyl-5,6-dihydroisoxazolo-[4,5-*a*]pyrazino[2,3-*c*]cycloheptene (**2a**) and 6-acetyl-1,2,3,4-tetrahydro-5*H*-cyclohepta[*b*]pyrazin-5-one (**3a**). The reaction with 1,2-propanediamine also gave two mixtures of methyl-substituted compounds [(**2b** and **2c**) and (**3b** and **3c**)]. The mixture of **3b** and **3c** was dehydrogenated to afford a mixture of 6-acetyl-2-methyl- and 6-acetyl-3-methyl-5*H*-cyclohepta[*b*]pyrazin-5-one (**4b** and **4c**).

On the extension of 3-acetyltropolone chemistry, we reported that 3-methyl-1,8-dihydrocyclohepta[*c*]pyrazol-8-one hydrazone reacted with acyl halides or orthoesters and with aliphatic aldehydes or ketones to give 2,2a,4,5-tetraazabenz[*cd*]azulene derivatives[1] and their 3,4-dihydro compounds,[2] respectively. On the other hand, Chisaka *et al*. found that 2-methyl-8*H*-cyclohepta[*b*]furan-8-one reacted with 1,2-ethanediamine to afford 2-methyl-3,4-dihydro-2a,5-diazabenz[*cd*]azulene,[3] which had a ring system similar to that of the above tricyclic compounds. Then, we carried out the reactions of 3-methyl-8*H*-cyclohept[*d*]isoxazol-8-one[4] with 1,2-ethanediamine and 1,2-propanediamine. However, the expected compounds were not isolated and new types of compounds were obtained.

When a mixture of 3-methyl-8*H*-cyclohept[*d*]isoxazol-8-one (**1**) and 1,2-ethanediamine in ethanol was refluxed for 6.5 h, the starting material (**1**) was recovered in 96% yield. Reactions in water gave similar results [recoveries of **1**: 68% (3 h) and 61% (24 h)]. From the reactions of **1** with 1,2-propanediamine in the same conditions, **1** was recovered [recoveries: 95% (10 h) in ethanol, 86% (6 h) and 67% (24 h) in water].

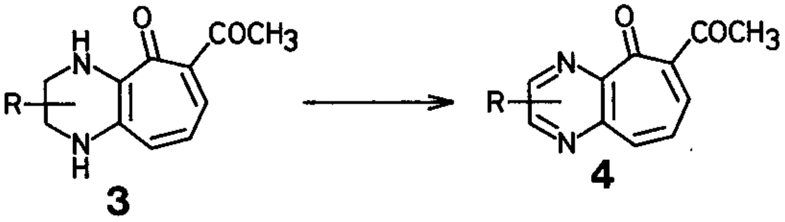
The reactions were carried out without solvent. A mixture of **1** and 1,2-ethanediamine (15 molar equivalents) was refluxed for 30 min to afford 3-methyl-5,6-dihydroisoxazolo[4,5-a]pyrazino[2,3-c]cycloheptene (2a) and 6-acetyl-1,2,3,4-tetrahydro-5H-



1 2 3

a R = H
b R = 8-CH$_3$
c R = 9-CH$_3$

a R = H
b R = 2-CH$_3$
c R = 3-CH$_3$



3 4

b R = 2-CH$_3$
c R = 3-CH$_3$

b R = 2-CH$_3$
c R = 3-CH$_3$

cyclohepta[b]pyrazin-5-one (3a) in 2.4 and 2.3% yields, respectively. The structures were determined by their elemental analysis and spectral data.

In the structure of 2a, the double bonds in the seven-membered ring migrated into the heterocyclic ring to form the pyrazine. This assignment was based on the nmr spectrum, which showed signals for the methyl group at δ 2.31 (s, 3H), the three methylene groups at δ 1.9-2.4 (m, 2H, 5-CH$_2$), 2.6-3.0 (m, 2H, 4-CH$_2$), and 3.1-3.4 (m, 2H, 6-CH$_2$), and two protons in the pyrazine ring as two AB doublets at δ 8.44 (d, 1H, J = 8 Hz, 8-H) and 8.58 (d, 1H, J = 8 Hz, 9-H). Such migration of hydrogen atoms has been observed in the reaction product of 4,5-benzotropolone with 1,2-ethanediamine.

The ir spectrum of the compound (3a) showed absorptions at 3420 and 3300 cm^{-1} for the NH groups and at 1700 and 1600 cm^{-1} for the acetyl and tropone carbonyl groups, respectively. The nmr spectrum showed signals for the acetyl group at δ 2.55 (s, 3H), the two methylene groups at δ 3.2-3.8 (m, 4H), the aromatic protons at δ 6.3-7.1 (m, 3H), and the two broad NH protons at δ 4.5-6.0 (1H, 1-NH) and 7.5 (1H, 4-NH). These peaks for the NH protons were disappeared by D$_2$O addition.

The reaction of 1 with 1,2-propanediamine also gave two mixtures of 3,8-dimethyl-

Table 1. Spectral Data

Compd	Ir($CHCl_3$) [cm^{-1}]	Uv(CH_3OH) [nm(log ε)]	Nmr($CDCl_3$) [δ]	Analysis [%] Found (Calcd)
2a		241sh(3.67) 260 (3.71) 302 (4.03)	1.9-2.4(m,2H,5-CH_2) 2.31(s,3H,CH_3) 2.6-3.0(m,2H,4-CH_2) 3.1-3.4(m,2H,6-CH_2) 8.50(d,1H,J=8Hz,9-H) 8.52(d,1H,J=8Hz,8-H)	m/e M^+ for $C_{11}H_{11}N_3O$ 201.1032(201.0902)
3a	3420 3300 1700 1600	246 (4.22) 282 (4.17) 308 (4.17) 378 (3.97) 468 (3.86)	2.55(s,3H,CH_3) 3.2-3.8(m,4H,CH_2x2) 4.5-6.0(br,1H,1-NH) 6.3-7.1(m,3H,7,8,9-H) 7.5(br,1H,4-NH)	Anal. for picrate $C_{17}H_{15}N_5O_9$ C 47.05 (47.13) H 3.46 (3.49) N 15.84 (16.16)
2b,c		245sh(3.55) 260 (3.61) 307 (3.91)	1.8-2.4(m,2H,5-CH_2) 2.29(s,3H,3-CH_3) 2.4-2.8(m,2H,4-CH_2) 2.56(s,minor,9-CH_3 of 2c) 2.62(s,major,8-CH_3 of 2b) 3.0-3.3(m,2H,6-CH_2) 8.21(s,major,9-H of 2b) 8.35(s,minor,8-H of 2c)	m/e M^+ for $C_{12}H_{13}N_3O$ 215.1101(215.1059)
3b,c	3410 3300 1700 1600	247 (4.29) 281 (4.25) 307 (4.24) 378 (4.04) 468 (3.86)	1.22(d,J=7Hz,minor,2-CH_3 of 3b) 1.26(d,J=7Hz,major,3-CH_3 of 3c) 2.2-3.9(m,3H,CH_2+CH) 2.54(s,3H,$COCH_3$) 5.05(br,minor,1-NH of 3b) 5.34(br,major,1-NH of 3c) 6.3-7.1(m,3H,7,8,9-H) 7.22(br,major,4-NH of 3c) 7.38(br,minor,4-NH of 3b)	Anal. for picrate $C_{18}H_{17}N_5O_9$ C 48.15 (48.32) H 3.84 (3.83) N 15.50 (15.66)
4b,c	1710 1655	238 (4.16) 260sh(3.94) 348 (3.75)	2.50(s,3H,$COCH_3$) 2.73(s,minor,2-CH_3 of 4b) 2.77(s,major,3-CH_3 of 4c) 6.84-7.24(m,1H,8-H) 7.45-7.89(m,2H,7,9-H) 8.75(s,minor,3-H of 4b) 8.78(m,major,2-H, of 4c)	m/e M^+ for $C_{12}H_{10}N_2O_2$ 214.0794(214.0742)

and 3,9-dimethyl-5,6-dihydroisoxazolo[4,5-*a*]pyrazino[2,3-*c*]cycloheptenes (2b and 2c) and 6-acetyl-2-methyl- and 6-acetyl-3-methyl-1,2,3,4-tetrahydro-5*H*-cyclohepta[*b*]-pyrazin-5-ones (3b and 3c) in 1.9 and 13.7% yields, respectively. Both the mixtures could not be separated to each single compound because of their very low yields. The structures were also determined by their spectral data.

The nmr spectrum of the mixture of 2b and 2c showed two singlet peaks at δ 8.21 and 8.35 for the protons in the pyrazine ring. When a shift reagent [Eu(fod)$_3$] was added to the solution, the peak at δ 8.21 shifted towards lower magnetic field (see: Fig. 1) by chelation of the reagent to the oxygen and nitrogen atoms at the 1- and 10-positions, respectively. Thus, the peak at δ 8.21 was assigned to the 9-H proton of 2b and the peak at δ 8.35 to the 8-H proton of 2c. The ratio of the intensities of the former to the latter was *ca*. 2 : 1. The methyl protons for 2b and 2c were appeared at δ 2.62 and 2.56 in the ratio of *ca*. 2 : 1.

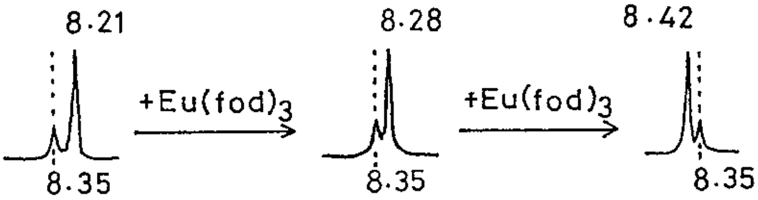


Fig. 1. ^{1}H Nmr study of the compounds (2b and 2c) by using Eu(fod)$_3$

The ir spectrum of 3b and 3c showed two NH absorptions at 3410 and 3300 cm^{-1} and two carbonyl absorptions at 1700 (acetyl C=O) and 1600 cm^{-1} (tropone C=O). Differences between the compounds (3b and 3c) were found in the nmr spectrum of the mixture as described as follow. The compound (3c) was a major product. The two methyl protons were observed at δ 1.26 (d, J = 7 Hz, major) for 3-CH$_3$ of 3c and 1.22 (d, J = 7 Hz, minor) for 2-CH$_3$ of 3b. Both the protons for the 1-NH and 4-NH were also observed as two major and minor broad peaks, respectively. These assignments were based on the anisotropic effects of the tropone carbonyl group and the C-C bond between the methyl group and the piperazine ring.

The mixture of the compound (3b and 3c) was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone to afford a mixture of 6-acetyl-2-methyl- and 6-acetyl-3-methyl-5*H*-cyclohepta[*b*]pyrazin-5-ones (4b and 4c). The structures were also determined by their spectral data. In the ir spectrum, the NH absorption bands observed in

the spectrum of the mixture of **3b** and **3c** were disappeared and the tropone carbonyl absorption shifted to 1655 cm^{-1} by loss of hydrogen bond with the NH proton. The nmr spectrum showed two singlet peaks at δ 2.73 for 2-CH_3 of **4b** and 2.77 for 3-CH_3 of **4c** in the ratio of *ca*. 1 : 2. The assignment was based on the anisotropic effect of the tropone carbonyl group on the 3-CH_3 protons of **4c**.
In addition, tropones condensed with six-membered heteroaroamtic ring containing two nitrogen atoms, such as pyridazine,[6] pyrimidine,[7,8] and pyrazine[9] have been reported.

EXPERIMENTAL

The ir spectra were taken on a JASCO IRA-1 spectrophotometer, and the uv spectra on a Hitachi EPS-3T spectrophotometer. The nmr spectra were recorded with a Hitachi-Perkin-Elmer R-24 spectrometer (60 MHz). The high-resolution mass spectra were obtained with a JEOL JMS-DX-300 mass spectrometer.

Reaction of 3-Methyl-8H-cyclohept[d]isoxazol-8-one (1) with 1,2-Ethanediamine.
A mixture of **1** (161 mg, 1.0 mmol) and 1,2-ethanediamine (1.0 ml, *ca*. 15 mmol) was refluxed for 30 min. The reaction mixture was diluted with small amount of chloroform and twice chromatographed on two Wakogel B-10 plates (30 x 30 cm^2) with ethyl acetate to give 3-methyl-5,6-dihydroisoxazolo[4,5-*a*]pyrazino[2,3-*c*]cycloheptene (**2a**) as colorless needles [yield, 4.8 mg (2.4%); mp 146-148°C] and 6-acetyl-1,2,3,4-tetrahydro-5*H*-cyclohepta[*b*]pyrazin-5-one (**3a**) as a red oil [yield, 4.8 mg (2.3%). Picrate: mp 183°C].

Reaction of 3-Methyl-8H-cyclohept[d]isoxazol-8-one (1) with 1,2-Propanediamine.
A mixture of **1** (160 mg, 1.0 mmol) and 1,2-propanediamine (1.0 ml, *ca*. 12 mmol) was refluxed for 90 min and worked up, as mentioned above, to give a mixture of 3,8-dimethyl- and 3,9-dimethyl-5,6-dihydroisoxazolo[4,5-*a*]pyrazino[2,3-*c*]cycloheptene (**2b** and **2c**) as colorless needles [yield, 4.0 mg (1.9%); mp 159-160°C] and a mixture of 6-acetyl-2-methyl- and 6-acetyl-3-methyl-1,2,3,4-tetrahydro-5*H*-cyclohepta[*b*]pyrazin-5-ones (**3b** and **3c**) as a red oil [yield, 30.0 mg (13.7%). Picrate: mp 151°C].

Dehydrogenation of a Mixture of the Compounds (3b and 3c). A mixture (103 mg, 0.5 mmol) of the compounds (**3b** and **3c**) and 2,3-dichloro-5,6-dicyanobenzoquinone (229 mg, 1.0 mmol) in dry benzene (10 ml) was refluxed for 2 h. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm^2) with ethyl acetate to give a mixture of 6-acetyl-2-methyl- and 6-acetyl-3-methyl-5*H*-cyclohepta[*b*]pyrazin-5-ones (**4**b and **4**c) as colorless crystals [yield, 29.6 mg (29.3%); mp 135°C].

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