1*H*-PYRAZOLO[1,5-*a*]INDOLES: ISOELECTRONIC ANALOGUES OF AZULENE (PSEUDOAZULENE)

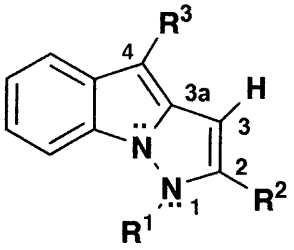
Jing-Kang SHEN and Hajime KATAYAMA*
Niigata College of Pharmacy, 5-13-2 Kamishin'ei-cho, Niigata, 950-21, Japan

1*H*-Pyrazolo[1,5-*a*]indole derivatives were prepared for the first time and found to have the chemical behaviors as the isoelectronic analogues of azulene.

KEYWORDS 1-methyl-1*H*-pyrazolo[1,5-*a*]indole; pseudoazulene; 1-methyl-2-phenyl-1*H*-pyrazolo[1,5-*a*]indole; azulene isoelectronic

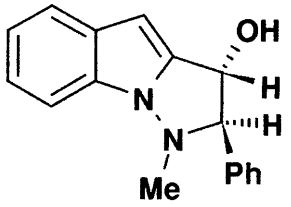
Among the three isomers of 1*H*-, 3*H*- and 4*H*-pyrazolo[1,5-*a*]indoles, no chemistry has been reported for 1*H*-isomer (**1a**, RN=42318-55-8). 1*H*-Isomer is an interesting compound since it has a condensed indole nucleus and constitutes an 3-aza analogue of the mitomycin's skeletal compound. In this paper we report the first synthesis of 1*H*-pyrazolo[1,5-*a*]indole derivatives and their chemical behaviors as the novel isoelectronic analogues of azulene (pseudoazulene).[1)]

Initially we planned to prepare 1-methyl-2-phenyl-1*H*-pyrazolo[1,5-*a*]indole (**1c**) by the elimination reaction of (**2**).[2)] When (**2**) was reacted with methanesulfonyl(mesyl) chloride in the presence of triethylamine, the sole product was (**1e**), mp 220-221°C (69% yield by excess reagent) which has one vinylic proton (δ 6.74, s) but also retains mesyl group (δ 3.15, s) according to ^{1}H-NMR analysis. The formation of (**1e**), instead of (**1c**), suggested the high reactivity of 1*H*-isomer (**1c**) against electrophilic reagent. In fact, when 1*H*-isomer (**1c**), *vide infra*, was reacted with mesyl chloride independently, C-mesylated product (**1e**) was formed in 89% yield. The position of the mesyl group was assigned when (**1d**), *vide infra*, was obtained by the same reaction and its adjacent vinylic proton signals appeared at δ 6.43 and 7.27 (each d, J=3.4Hz). The high nucleophilicity of 4-C of 1*H*-isomer was also demonstrated when 4*H*-Isomer (**3b**)[3)] was treated with butyl lithium and the lithiated product was trapped with acetyl chloride. The product was the diacetylated product (**1f**), mp 158-159°C (40% yield). Then we turned our attention to the other approach. 4*H*-Isomer (**3b**) was methylated with methyl trifluoromethanesulfonate to give the quaternary salt (**4b**), mp 144-145°C in quantitative yield. The N-methyl group of (**4b**) appears at δ 4.45 as a singlet. When (**4b**) was treated with lithium diisopropyl amide, 4-H was removed and the basic product (**1c**), mp 80-81°C was obtained. This reaction was better effected with sodium hydroxide in ethanol (87% yield). The product (**1c**) has two vinylic protons at δ 6.15 and 6.44, both as singlets. It has a characteristic UV absorption spectrum at λmax (MeCN) nm (log ε): 268 (4.44), 321(3.97), 383(4.02). Similarly (**1b**), mp 103-104°C was obtained from (**4a**), mp 181-182°C in 61% yield. This product has three vinylic proton signals at δ 6.09 (s), 6.21(d, J=3.7Hz) and 6.99 (d, J=3.7Hz). The

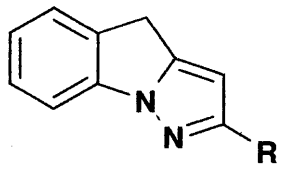


(1)

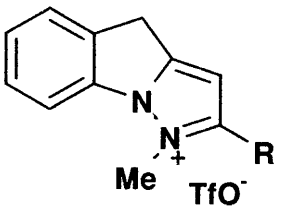
a: $R^1=R^2=R^3=H$
b: $R^1=Me$, $R^2=R^3=H$
c: $R^1=Me$, $R^2=Ph$, $R^3=H$
d: $R^1=Me$, $R^2=H$, $R^3=Ms$
e: $R^1=Me$, $R^2=Ph$, $R^3=Ms$
f: $R^1=R^3=Ac$, $R^2=Ph$
g: $R^1=Me$, $R^2=Ph$, $R^3=CHO$



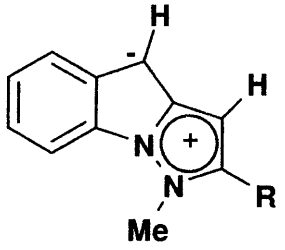
(2)



(3) a:R=H; b:R=Ph



(4) a:R=H; b:R=Ph



(5) a:R=H; b:R=Ph

1*H*-isomer (**1c**) was not stable, so that it was transferred into picrate. The ^{1}H-NMR spectrum of the picrate showed that the protonation took place at 4-C but not at the nitrogen atom. The treatment of (**1c**) with trifluoromethanesulfonic acid afforded the quaternary salt (**4b**) in quantitative yield. These transformations mean that the salts (**4a**) and (**4b**) are the conjugate acids of the bases (**1b**) and (**1c**). When (**4b**) was reacted with lithium aluminum hydride in ether, (**4b**) worked as a conjugate acid and (**1c**)was formed as a sole product. These chemical behaviors of 1*H*-isomer are typical of the isoelectronic analogues of azulene, and the meso-ionic form (**5**) represents their characters.[4] The participation of the meso-ionic form is also supported by the ^{1}H-NMR spectra of 1*H*-isomer (**1c**) in different solvents (Table I). The increase of the solvent polarity from C_6D_6 to CD_3CN shifted the signals for N-methyl and 3-H to the lower magnetic field. In contrasts, 4-H signal moved to the higher magnetic field. However, no remarkable change of UV absorption pattern was observed in these solvents. A similar solvent effect has been reported for 2-ethyl-3-methyl-1-phenyl-1,2-dihydroindeno[2,1-*c*]pyrazole.[1e] 1*H*-isomer (**1b**) and (**1c**) have similar chemical behaviors to 1,2-dihydroindeno[2,1-*c*]pyrazoles.[1d,1e] When (**1c**) was subjected to the Vilsmeyer-Haack reaction, the formyl group (δ 9.93, s) was introduced at 4-C to give (**1g**). The ^{1}H-NMR spectra of 1*H*-isomer with the electron-attracting groups at 4-C show the shifts of N-methyl and 3-H signals to the lower magnetic field, as shown in Table II. In 1*H*-isomer (**1e**) and (**1g**), the contribution of the meso-ionic forms such as (**5**) became more important. When deuterium oxide was added to the solution of 1*H*-isomer (**1c**) in $CDCl_3$, the 4-H signal disappeared from the ^{1}H-NMR spectrum. No 4-H signal was detected in CD_3OD either. These ready exchanges of 4-H in neutral protic solvent suggest the strong basicity of the 1*H*-isomer (**1b**), as reported for 1,2,3-trimethyl-1,2-dihydroindeno[2,1-*c*]pyrazole.[1e]

Table I. The Solvent Effects of ^{1}H-NMR Spectra of **1c** (δ)

Solvent	ε*	N-Me	3-H	4-H
C_6D_6	2.2	2.87	6.11	6.34
$CDCl_3$	4.8	3.50	6.44	6.15
CD_3OD	32.6	3.47	6.52	-
CD_3CN	37.5	3.51	6.54	6.10

* Dielectric constant of proton solvent.

Table II. ^{1}H-NMR Spectra for **1c,e,g** in $CDCl_3$(δ)

Compds	N-Me	3-H
1c	3.50	6.44
1e	3.83	6.74
1g	4.05	6.95

In summary, we were the first to prepare 1*H*-pyrazolo[1,5-*a*]indole derivatives and have demonstrated their peculiar behaviors as the isoelectronics of azulene. The 1*H*-isomer is the novel isoelectronic of azulene (pseudoazulenes) with the nitrogen atom at ring junction. They also constitute the novel skeleton of pyrrolo[1,2-*b*]pyrazole. Their chemical behaviors are best expressed by the meso-ionic forms such as (**5**).

REFERENCES AND NOTES

1) a) R. Mayer, *Angew. Chem.*, **69**, 481 (1958). The first report to refer pseudoazulene; b) Treibs, W W. Schroth, H. Lichtmann and F. Fischer, *Justus Liebigs Ann. Chem.*, **642**, 97 (1961); c) D. L. Leave, J. Smolicz and W. H. Stafford, *J. Chem. Soc.*, **1962**, 740; d) G. V. Boyd and D. Hewson, *J. Chem. Soc. (C)*, **1968**, 2959; e) K. Hartke and W. Uhde, *Chem. Ber.*, **103**, 2667 (1970).

2) This alcohol was derived from 3-hydroxy-2-phenyl-3H-pyrazolo[1,5-a]indole (J-K. Shen and H. Katayama, *Chem. Lett.*, **1992**, 451) by the oxidation with DDQ and the reduction with lithium aluminum hydride.

3) H. Katayama, M. Sakurada, W. H. H. Herath, N. Takatsu and J-K. Shen, *Chem. Pharm. Bull.*, in press.

4) The two sets of lone pairs on adjacent nitrogen atoms of 1H-isomer can not contribute to form the π-electron systems of pseudoazulene [J. Elguero and R. M. Claramunt, *Adv. Heterocycl. Chem.*, **22**, 183 (1978); H. H. Elnagdi, M. R. H. Elmoghayer, and K. U. Sadek, *Adv. Heterocycl. Chem.*, **48**, 223 (1990)]. But the introduction of meso-ionic form [W. D. Ollis and C. A. Ramsden, *Adv. Heterocycl. Chem.*, **19**, 1 (1976)] allows for these nitrogen lone pairs to constitute the isoelectronic form of azulene.

(Received July 16, 1992)