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Synthesis of Methoxyonychine and Use of ^{1}H- and ^{13}C-Nuclear Magnetic Resonance Spectra for Structure Determination of Geometrical Isomers of Indan-1-one Oxime Derivatives

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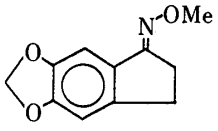
Synthesis of an alkaloid, methoxyonychine, was accomplished by an application of a synthetic method for constructing cycloalkenopyridines from oxime *O*-allyl ethers, and its structure was confirmed. During the course of the synthesis, the chemical shift differences of the signals of C_7-H and C_1, C_7, and C_{7a} in the ^{1}H- and ^{13}C-nuclear magnetic resonance spectra were employed for the stereostructure determination of *E*- and *Z*-isomers of oxime *O*-methyl and *O*-allyl ethers of indan-1-ones.

Keywords——alkaloid; methoxyonychine; geometrical isomer; *E*-form; *Z*-form; indan-1-one; oxime; rearrangement; thermolysis; X-ray analysis

Previously, we reported[1] a synthesis of the compound, 4-methyl-1-azafluoren-9-one (**1**), corresponding to the structure of onychine[2] (proposed by a Brazilian group) occurring in *Onychopetalum amazonicum* (Annonaceae). However, the spectroscopic properties of the synthetic compound were different from the reported data on onychine. Therefore, we also carried out a synthesis of the isomeric compound, 1-methyl-4-azafluoren-9-one (**2**) by application of the synthetic method for constructing cycloalkenopyridines from oxime *O*-allyl ethers of cycloalkanones. The isomer (**2**) exhibited identical spectroscopic properties with onychine. On the basis of this finding, we proposed that the structure of the alkaloid should be revised to **2**.[1]

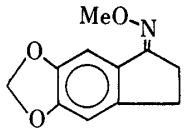
In 1986, Goulart and his co-workers reported[3] the isolation of methoxyonychine (**3**) from trunkwood of *Guatteriana dielsiana* and they maintained that the structure of this alkaloid is 6-methoxy-4-methyl-1-azafluoren-9-one (**3**) based on the previous structure of onychine. In 1987, Cavé and his co-researchers[4] mentioned that the structure of onychine is **2**, as we proposed. Very recently, Cavé *et al.* confirmed[5] that the structure of methoxyonychine is 6-methoxy-1-methyl-4-azafluoren-9-one (**4**) by synthesis using our method for constructing cycloalkenopyridines. These results prompted us to report the results of our synthesis of the alkaloid (**4**). This paper also deals with the use of ^{1}H- and ^{13}C-nuclear magnetic resonance (^{1}H and ^{13}C-NMR) spectra for structure elucidation of geometrical isomers of indan-1-one oxime derivatives.

Treatment of the indanone (**5**)[6] with the *O*-allylhydroxylamine (**6a**) in the usual way gave a mixture of the oximes of *E*- (**7a**) and *Z*-isomers (**7b**). Both isomers were easily separated by flash column chromatography. Reaction of the indanone (**5**) and the *O*-allylhydroxylamine (**6b**) gave also a mixture consisting of *E*- and *Z*-oxime (**17a** and **17b**) separable in the same way. The stereostructures of the isomers were confirmed by ^{1}H- and ^{13}C-NMR (*vide infra*). Each isomer was subjected to oxidative thermal rearrangement in a sealed glass tube at 180 °C (bath



11a

space group $P21/A$,
monoclinic
$a=7.220$, $b=20.647$, $c=6.641$ (Å)
alpha = 90.00, beta = 102.83, gamma = 90.00
$Z=4$, $D_{obs}=1.300$, $D_{cal}=1.412$,
number of reflections 1333
R-value = 0.046



11b

space group $PCAB$
orthorhombic
$a=7.678$, $b=13.827$, $c=18.630$ (Å)
alpha = 90.00, beta = 90.00, gamma = 90.00
$Z=8$, $D_{obs}=1.300$, $D_{cal}=1.378$
number of reflections 1173
R-value = 0.056

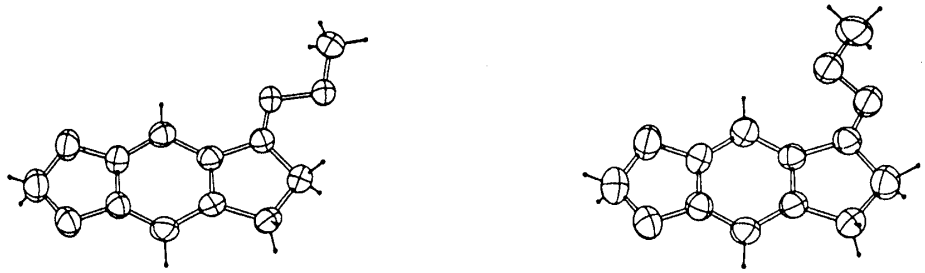
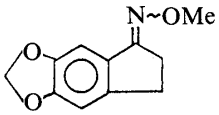
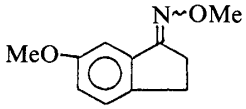
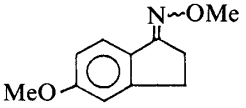
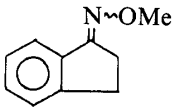
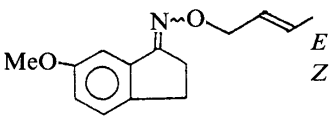
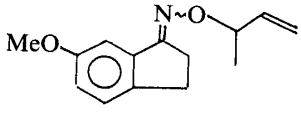


Fig. 1

TABLE I. Chemical Shifts of the Diagnostic Signals Available to Differentiate the *E*- and *Z*-Forms of the Oximes of 1-Indanones

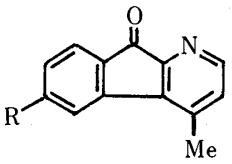
Compound	Form	C_1	Δ	C_2	Δ	C_7	Δ	C_{7a}	Δ	C_7-H	Δ
	*E* (**11a**)	162.29	3.21	28.47	−1.22	100.96	−4.29	129.06	2.06	7.25	−0.50
	Z (**11b**)	159.08		29.69		105.25		127.54		7.75	
	*E* (**14a**)	162.81	3.20	27.82	−1.93	104.08	−9.16	137.21	2.46	7.14	−0.70
	Z (**14b**)	159.61		29.75		113.24		134.75		7.84	
	*E* (**15a**)	162.16	0.21	28.66	−0.65	122.50	−8.02	128.93	1.85	7.59	−0.62
	Z (**15b**)	161.95		29.31		130.52		127.08		8.21	
	*E* (**16a**)	162.48	2.97	28.55	−0.49	121.53	−7.88	136.32	2.38	7.68	−0.64
	Z (**16b**)	159.51		29.04		129.41		133.94		8.32	
	*E* (**7a**)	162.67	3.07	27.85	−1.95	104.40	−9.16	137.51	2.60	7.12	−0.78
	Z (**7b**)	159.60		29.80		113.56		134.91		7.90	
	*E* (**17a**)	162.54	2.98	27.82	−1.93	104.46	−9.02	137.67	2.71	7.16	−0.78
	Z (**17b**)	159.56		29.75		113.48		134.96		7.94	

Δ-Values are differences between the chemical shifts of the *E*-form and the *Z*-form (chemical shifts of the *E*-forms minus those of the *Z*-forms).

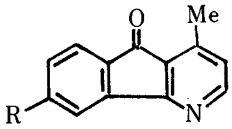
temperature), giving rise to a mixture consisting of α-methyl- (**8**) and γ-methylazafluorene (**9**) in almost 1 : 4 ratio in 30% yield. These azafluorenes were isolated in pure form by preparative thin layer chromatography (TLC), but were considerably air-sensitive: after storage for a few days, they turn to a mixture (TLC examination) showing a carbonyl band in the 1700 cm^{-1} region. Oxidation of the γ-methylazafluorene (**9**) with potassium permanganate in acetone furnished methoxyonychine (**4**) in good yield, the spectroscopic properties (^{1}H-NMR) of which were in good accord with the reported data, accomplishing the synthesis of the alkaloid.

Next, we focused our attention on the structure elucidation of the oximes obtained as the *E*- and *Z*-isomer. For this purpose, it was necessary to prepare an appropriate oxime of known structure as the standard specimen. Condensation of *O*-methylhydroxylamine and 5,6-methylenedioxyindan-1-one (**10**) gave the stereoisomeric oximes as crystals corresponding to *E*-(**11a**) (mp 120—123 °C) and *Z*-isomers (**11b**) (mp 87—88 °C). The structures of these oximes were established by X-ray crystallographic analysis. Crystal data and computer drawings of the structures are given in Fig. 1. ^{1}H- and ^{13}C-NMR data available for structure elucidation of *E*- and *Z*-oximes of indan-1-ones are summarized in Table I.

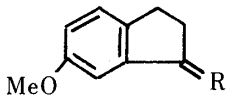
Levy and Nelson have reported[7] that ^{13}C-NMR examination is available to elucidate the structures of the geometrical isomers of oximes of aliphatic carbonyl compounds and benzaldehyde. From Table I, the chemical shifts of C_1 and C_2 are in agreement with Levy and Nelson's results. The signals of C_7 and C_7-H of *Z*-oximes show larger low field shifts than those of *E*-oximes in the case of the oximes of indan-1-ones, providing diagnostic signals to differentiate *E*- and *Z*-isomers.



1 : R=H
3 : R=OMe



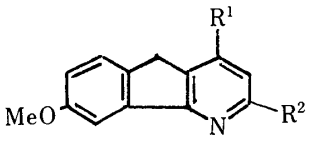
2 : R=H
4 : R=OMe



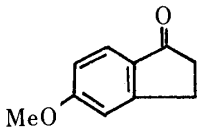
5 : R=O
7a : R=N-O- *E*-form
7b : R=N-O- *Z*-form
17a : R=N-O- *E*-form
17b : R=N-O- *Z*-form

H_2N-O-CH_2CH=CH-Me

6a



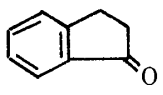
8 : R^1=H; R^2=Me
9 : R^1=Me; R^2=H



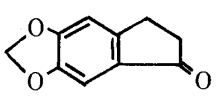
12

H_2N-O-CH(Me)-CH=CH_2

6b



13



10

Chart 1

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-408 infrared spectrophotometer. ^{1}H- and ^{13}C-NMR were taken on Hitachi R-600, Varian EM360, and JEOL FX-90Q spectrometers with tetramethylsilane as an internal standard in $CDCl_3$. Mass spectra (MS) were recorded with a JEOL JMS-01SG spectrometer. Preparative thin layer chromatography (TLC) was carried out on Kieselgel $60F_{254}$ (Merck) with appropriate solvents. Homogeneity and purity of the oily compounds were examined by TLC and ^{1}H-NMR spectroscopy.

6-Methoxyindan-1-one Oximes (7a, b)——A solution of 6-methoxyindanone (**5**) (3.5 g), the *O*-allylhydroxylamine hydrochloride (**6a**) (3.8 g) and sodium acetate (1.7 g) in EtOH (100 ml) was heated under reflux for 2 h and concentrated under reduced pressure to dryness to give a residue, which was suspended in water. The suspension was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with aqueous Na_2CO_3, dilute HCl and water, and dried ($MgSO_4$). Removal of the solvent gave a residue (2.04 g) which was subjected to flash column chromatography on silica gel in hexane–ether (15 : 1). The faster-running fruction gave the *E*-oxime (**7a**) (1.5 g) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1605 (C=N). MS *m/z*: 231 (M^+). Elution with the same solvent gave the *Z*-oxime (**7b**) (0.35 g) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1605 (C=N). MS *m/z*: 231 (M^+). Similar treatment of the indanone (**5**) with the *O*-allylhydroxylamine (**6b**) and the indanones (**5**, **10**, **12**, and **13**) with *O*-methylhydroxylamine gave the corresponding oximes (**17a**, **b**, **14a**, **b**, **11a**, **b**, **15a**, **b**, and **16a**, **b**) in good yields.

Thermolysis of the *E*-Oxime (7a)——*E*-oxime (**7a**) (0.33 g) was heated in a sealed glass tube (length 80 cm, diameter 2 cm) at 180 °C (bath temperature) for 24 h. After heating, the product was taken up in $CHCl_3$. The $CHCl_3$ solution was concentrated to dryness to leave an oil, which was thoroughly washed with Et_2O. The Et_2O solution was washed with dilute HCl, aqueous Na_2CO_3, and water and dried. Removal of the solvent gave a residue (0.12 g) which was subjected to preparative TLC on a silica gel plate to give the starting material (80 mg). The HCl washing was basified with K_2CO_3 and extracted with Et_2O. The Et_2O extract was washed with water, and dried. Removal of the solvent gave a residue (130 mg), which was chromatographed on a silica gel plate with hexane–ether (1 : 5). The faster-running zone gave the α-methylazafluorene (**8**) (19 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1612, 1579. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (3H, s), 3.74 (2H, s), 3.91 (3H, s), 6.98 (1H, dd, J=2.3, 8.7 Hz), 7.04 (1H, d, J=8 Hz), 7.43 (1H, d, J=8.7 Hz), 7.66 (1H, d, J=2.3 Hz), 7.68 (1H, d, J=8 Hz). The slower-running zone gave the γ-methylazafluorene (**9**) (74 mg), MS *m/z*: 211 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1608, 1577. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 3.70 (2H, s), 3.91 (3H, s), 6.98 (1H, dd, J=2.5, 8.3 Hz), 7.01 (1H, d, J=5.4 Hz), 7.45 (1H, d, J=8.3 Hz), 7.61 (1H, d, J=8.3 Hz), 7.61 (1H, d, J=2.5 Hz), 8.45 (1H, d, J=5.4 Hz). Both azafluorenes were sensitive to air to give a mixture showing a carbonyl band in the 1700 cm^{-1} region on storage. Thermolysis of **7b**, **17a**, and **17b** followed by the same work-up gave similar results.

6-Methoxyonychine (4)——A solution of the azafluorene (**9**) (100 mg) and potassium permanganate (300 mg) in acetone (5 ml) was stirred at room temperature for 2 h and diluted with EtOH (0.5 ml) and the whole was filtered. The filtrate was concentrated under reduced pressure to leave a residue, which crystallized from EtOH to give methoxyonychine (**4**) (85 mg) (mp 130—132 °C) (lit.[3] gum) which showed an identical ^{1}H-NMR spectrum to that reported for methoxy-onychine.

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