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Reactions of Indole Related Compounds. III.[1] (*E*) and (*Z*)-2-Oxoindolin-3-ethylidenes

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The reaction of 2-indolinone (I) with acetaldehyde was carried out in the presence of dimethylaniline and afforded the epimeric mixture of 2-oxoindolin-3-ethylidenes in good yield.

The epimeric 2-oxoindolin-3-ethylidenes were successfully separated to give pale yellow needles (II), mp 173—174° (15%) and bright yellow needles (III), mp 147—148.5° (38%).

The configurations of II and III were assigned *Z* and *E* respectively on the basis of their ^{1}H- and ^{13}C-NMR spectral data.

Keywords——2-indolinone; configuration; ^{1}H-NMR; ^{13}C-NMR

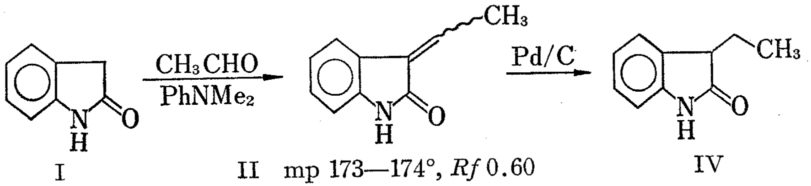
Although numerous reports are available on the chemistry of 2-indolinones,[3] and more paticularly, of 2-indolinones which contain α,β-unsaturated double bonds at C-3, relatively little is known about the stereoisomerism due to the trisubstituted double bond which many 2-oxoindolin-3-ylidenes have.[4]

Earlier, Kondo and co-workers[5] described the preparation and isolation of the isomeric 2-oxoindolin-3-ethylidenes, yellow needles, mp 164—169° (II) and orange-red needles, mp 143.5—145° (III). Since the isomeric 2-oxoindolin-3-ethylidenes gave 3-ethyl-2-indolinone (IV) on Pd/C reduction, they concluded that these isomers should be the stereoisomers due to the trisubstituted double bond at C-3. However, unfortunately the early workers had no tool for elucidating this stereochemical problem.

Our interest on the stereochemistry led us to elucidate the configuration of these isomeric 2-oxoindolin-3-ethylidenes.

Thus, 2-indolinone (I) was allowed to react with acetaldehyde in the presence of dimethylaniline as catalyst in a sealed tube on a steam bath for 13 hr according to the previously outlined procedure[5] to afford the epimeric mixture in *ca.* 70% yield.

Thin-layer chromatography (TLC) revealed this epimeric mixture as two spots (*Rf* 0.60 and 0.52, benzene–ethyl acetate 1:1) and the slower moving epimer as major component.



I

II mp 173—174°, *Rf* 0.60
III mp 147—148.5°, *Rf* 0.52

IV

Chart 1

(*E*)- and (*Z*)-2-Oxoindolin-3-ethylidenes were successfully separated by carefully repeated column chromatography over silica gel eluted with benzene–ethyl acetate and the yield of the epimeric 2-oxoindolin-3-ethylidenes obtained in this way was 53%.

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1) Part II: A. Kubo, T, Nakai, and T. Nozoye, *Heterocycles*, 4, 1675 (1976).

2) Location: *1-35-23 Nozawa, Setagaya, Tokyo, 154, Japan.*

3) R.L. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, pp. 341—392.

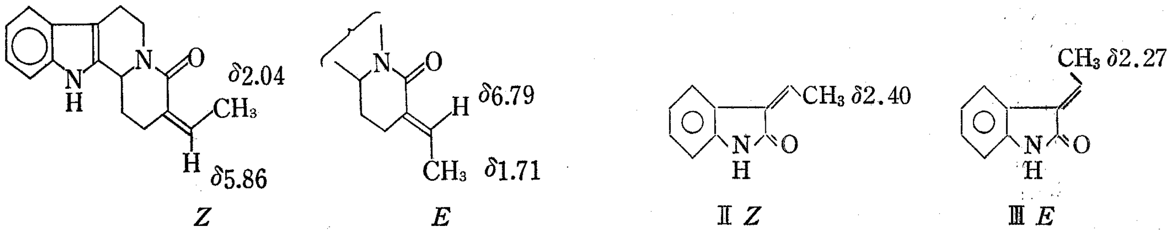
4) R.L. Autrey and F.C. Tahk, *Tetrahedron*, 23, 901 (1967); G. Tacconi and F. Marione, *Ric. Sci.*, 38, 1239 (1968) [*C.A.*, 71, 101641*f* (1969)].

5) H. Kondo, T. Nozoye, and M. Tobita, *Itsuu Kenkyusho Nempo*, 1, 32 (1950).

The one epimer (II) was obtained as pale yellow needles, mp 173—174°, $C_{10}H_9ON$, *Rf* 0.60, from benzene–ethyl acetate (9: 1) eluate in 15% yield and was confirmed identical with the yellow needles, mp 164—169°, described previously.[5] Whereas the other epimer (III) was obtained as bright yellow needles, mp 147—148.5°, $C_{10}H_9ON$, *Rf* 0.52, from benzene–ethyl acetate (9: 1—7: 3) eluate in 38% yield. The latter (III) was identified with the compound described as the orange-red needles, mp 143.5—145°,[5] which proved to be contaminated with a small amount of colored material.

Now, the *E* and *Z*-geometry of the epimeric 2-oxoindolin-3-ethylidenes were assigned on the basis of their proton nuclear magnetic resonance (^1H–NMR) spectral data.

Very recently, Winterfeldt, *et al.*[6] reported that the exocyclic vinyl proton in the α-methylene lactam systems was less shielded in the *Z* than in the *E* geometry because of a large paramagnetic anisotropy effect from lactam carbonyl group in the *cis* position and for the methyl group this anisotropy effect was reverse of that with the vinyl proton.



Z *E* II *Z* III *E*

Chart 2

Although the ^1H–NMR spectra (DMSO-d_6) of II and III did not allow an unambiguous assignment of the their α-vinyl protons because of overlapping with their aromatic proton signals, the methyl protons were clearly observed at δ 2.40 (d, J=8 Hz) (II) and δ 2.27 (d, J=8 Hz) (III) respectively.

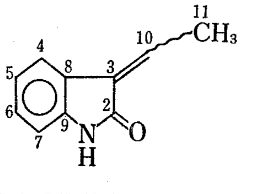
Since these values were fully consistent with Winterfeldt's observations, it was reasonable to conclude that the configurations of II and III were assigned *Z* and *E* respectively.

However, the small paramagnetic shift with respect to *E*-methyl group (δ 2.27) (III) was presumably due to the deshielding effect of benzene ring.

The increased availability of ^{13}C–NMR has enabled application of this technique to a variety of problems and for the determination of the geometrical isomers ^{13}C–NMR analysis proved to be a useful method.[7]

Therefore, in order to confirm the above assignments, it was decided to study the ^{13}C–NMR spectra of II and III.

Table I. ^{13}C-NMR Chemical Shifts (δ)[a] of II and III



	Number of carbon (off-resonance)									
	2(s)	3(s)	4(d)	5(d)	6(d)	7(d)	8(s)	9(s)	10(d)	11(q)
II(*Z*)	168.28	123.32	120.85	128.38	136.96	109.28	127.86	140.21	119.29	13.64
III(*E*)	167.89	122.28	121.24	128.77	135.66	109.54	128.77	142.03	123.58	14.81

a) in parts per million from TMS and measured in DMSO-d_6

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6) D. Thielke, J. Wegener, and E. Winterfeldt, *Chem. Ber.*, **108**, 1791 (1975).

The chemical shift assignments for II and III were made with the assistance of off-resonance decoupled spectra and are given in Table.

There is a general tendency for olefinic carbons in *Z* isomers to absorb at slightly higher fields than those in the *E* analogs.[7]

Thus we examined the differential shieldings between C-10 carbons in the II (*Z*) and III (*E*) isomers and the $\Delta\delta_C$ $(=\delta_C^Z-\delta_C^E)$ value was found to be −4.29 ppm.

This olefinic $\Delta\delta_C$ value clearly indicated that II should be assigned *Z* geometrical isomer and this assignment for II was consistent with that established by ^{1}H–NMR analysis.

As the result, this observation lends considerable support to the utility of ^{13}C–NMR as a method for making geometrical assignments.

Experimental

Melting points were determined on a Yanagimoto Micro-melting point Apparatus and recorded uncorrected. Ultraviolet absorption spectra were determined on a Jasco UVIDC-1 spectrometer and infrared absorption spectra were taken on a Jasco DS-701G spectrometer.

^{1}H-NMR spectra were determined on a Jeol PS-100 (100 MHz) NMR spectrometer and were recorded in δ value (ppm) from tetramethylsilane (TMS) as internal standard. Signal multiplicities were represented by s(singlet), d(doublet), t(triplet), q(quartet) and m(multiplet). Mass spectra were determined on a Jeol JMS-01SG-2 double focus mass spectrometer. ^{1}H-Noise decoupling and off-resonance ^{13}C-NMR spectra were taken with Jeol FX-60 FT-NMR spectrometer operating at 15.0 MHz and were recorded in δ value (ppm) from TMS. Column chromatography was effected using Merck silica gel 60 (70—230 mesh). TLC was performed on Merck Kieselgel 60, GF_{254} and solvent system used was benzene-ethyl acetate 1: 1.

(*Z*) and (*E*)-2-Oxoindolin-3-ethylidenes (II and III)

2-Indolinone (I) (6 g, 45 mM), acetaldehyde (8 g, 181 mM, freshly prepared from paraldehyde) and sodium sulfate (2.5 g) in dimethylaniline (35 ml) were heated in a sealed tube on a steam bath for 13 hr. After cooling, the reaction mixture was treated with water and then extracted with ether (60 ml). The extract was washed with with water and dried (Na_2SO_4). Evaporation of the solvent and dimethylaniline *in vacuo* gave a residue which was extracted with ether (100 ml). The etheral extract was washed with 10% HCl (×5) and water successively. The dried solvent was removed over *in vacuo* to give the crude product 5.73 g, which was chromatographed (C-1) over silica gel (170 g) by eluting with benzene–ethyl acetate (2: 1, 1: 1, 1: 2) to give the epimeric mixture 5.02 g (70%) and further chromatographed (C-2) on silica gel (150 g) to give II (*Z*) 503 mg from benzene–ethyl acetate (9; 1) eluate and II+III (*E*) 3.75 g from benzene–ethyl acetate (4: 1—3: 2) eluate. Chromatography (C-3) of the II+III mixture fraction (3.75 g, C-2) on silica gel (115 g) by eluting with benzene–ethyl acetate (9: 1) gave II (*Z*) 255 mg and II+III mixture 2.075 g. In addition, III rich fraction 1.377 g from ethyl acetate eluate was chromatographed (C-4,5,6) over silica gel to afford the pure III (*E*) 784 mg.

The combined II+III mixture fraction (2.35 g) was purified by silica gel chromatography (C-7, 80 g) by eluting with benzene–ethyl acetate (185: 15) to give II 307 mg, II+III mixture 513 mg and III 1.46 g. II+III mixture (513 mg) was further chromatographed (C-8,9) over silica gel by eluting with benzene–ethyl acetate (97: 3—95: 5) to give II 21 mg and III 418 mg respectively.

(*Z*)-2-Oxoindolin-3-ethylidene (II)——1.09 g (15%), pale yellow needles, mp 173—174° (from benzene). *Anal.* Calcd. for $C_{10}H_9ON$; C, 75.45; H, 5.70; N, 8.80. Found: C, 75.52; H, 5.75; N, 8.80. *Rf* 0.60; IR ν_{max}^{KBr} cm^{-1}: 1703, 1645, 1613. UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 252 (4.40, sh.), 254 (4.41), 260 (4.41), 292 (3.63), 355 (3.10); $\lambda_{min}^{95\%\ EtOH}$ nm (log ε): 230 (3.74), 257.5 (4.37), 273 (3.53), 323 (2.90); ^{1}H-NMR (DMSO-d_6) δ: 2.40 (d, J=8 Hz, 3H), 6.77—7.48 (m, 5H), 10.28 (s, 1H, NH). Mass Spectrum *m/e* (%): 159 (M$^+$, base), 144 (M−15, 72), 130 (M−29, 36).

(*E*)-2-Oxoindolin-3-ethylidene (III)——2.67 g (38%), bright yellow needles, mp 147—148.5° (from benzene); *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.45; H, 5.70; N, 8.80. Found: C,75.39; H, 5.76; N, 8.71. *Rf* 0.52. IR ν_{max}^{KBr} cm^{-1}: 1710, 1655, 1610. UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 247 (4.41), 250 (4.41, sh.), 257.5 (4.47), 288 (3.63), 355 (3.14). $\lambda_{min}^{95\%\ EtOH}$ nm (log ε): 227.5 (3.83), 253 (4.37), 268 (3.48), 317 (2.82). ^{1}H-NMR (DMSO-d_6) δ: 2.27 (d, J=8 Hz, 3H), 6.79—7.60 (m, 5H), 10.28 (s, 1H, NH). Mass Spectrum *m/e* (%): 159 (M$^+$, base), 144 (M−15,48), 130 (M−29,38).

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[7] J.B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, 1972, pp. 389—506; G.C. Levy and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, 1972.