CHEMISTRY LETTERS, pp. 1281-1282, 1978. Published by the Chemical Society of Japan

SYNTHESIS OF E- AND Z-ISOMERS OF 3-(α-THIOETHOXYMETHYLENE)OXINDOLE: CHARACTERIZATION AND RELATIVE STABILITY OF THE TWO ISOMERS[1]

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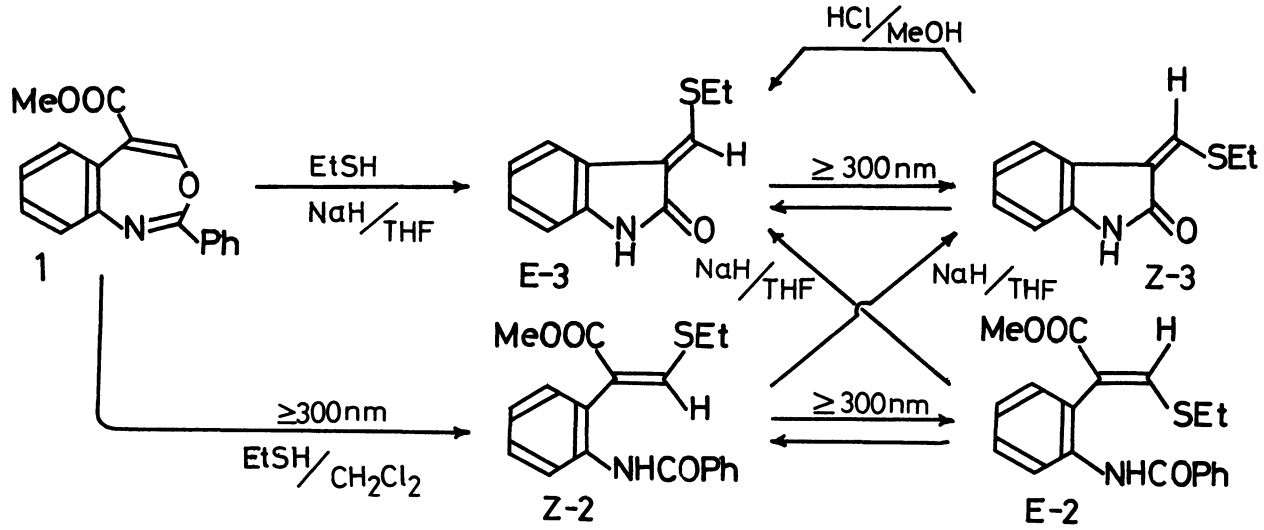
The E- and Z-isomers of 3-(α-thioethoxymethylene)oxindole have been synthesized for the first time and the verification that the E-isomer is more stable than the Z-isomer is provided experimentally.

Synthesis of α-methylene lactones has received considerable attention recently, because of interest in the anticancer properties of these substances.[2] However, all of the 3-(α-alkoxyalkylidene)oxindoles reported so far have the E-form irrespective to the method of their syntheses.[3] In this paper, we report the synthesis of both E- and Z-isomers of 3-(α-thioethoxymethylene)oxindole and demonstrate that the E-isomer is thermodynamically more stable than the Z-isomer.

Reaction of methyl 2-phenylbenz[d]-1,3-oxazepine 5-carboxylate (1)[4] with an excess of ethanethiol in THF in the presence of NaH at room temperature afforded stereoselectively the oxindole [E-3; mp 128-129.5°, λ_{max}^{MeOH} nm (log ε): 242.5 (4.09), 252 (4.10), 278, sh. (3.87), 284 (3.91), and 331 (4.22)] in 79% yield. Irradiation of E-3 with ≥300 nm rays in $CDCl_3$ in an NMR tube produced a photostationary mixture of this and the other isomer (Z-3) in a ratio of ca. 5:2 (judged from NMR spectroscopy). Chromatography on silica gel afforded the latter in a pure form which was obtained from a slightly less polar fraction than the original E-isomer [Z-3; mp 126-127.5°, λ_{max}^{MeOH} nm (log ε): 234.5 (3.82), 255 (3.85), 277 (4.09), 282 (4.11), and 334 (4.25)]. The NMR signals of both isomers are not very different, except for the olefinic protons: E-3 δ 7.83 (s); Z-3 δ 7.57 (s).[5] The olefinic proton in the E-isomer would only be deshielded by the carbonyl function, so leading to a resonance at lower field than the Z-isomer.

The configurational assignments of the two isomers were finally confirmed by the stereoselective synthesis of each isomer from 1. Thus, irradiation (≥300 nm) of 1 in CH_2Cl_2 in the presence of the thiol, until the consumption of 1 was complete, afforded the ring-opened addition products in 65% yield as a mixture of both Z- and E-isomers of methyl 3-thioethoxy-2-(2-benzamidophenyl)acrylate (2). Since E-Z isomerization of each addition product was more facile than the photo-addition reaction to 1, the isolation yield of each isomer was the same with the ratio (E:Z; ca. 2:1) in their photostationary state. However, by t.l.c. monitoring of the reaction, the Z-isomer is shown to be the primary product. The NMR spectra of both of the isomers distinguished their stereochemistry: the olefinic proton of E-2 (mp 109-111°, δ 8.03) appeared in a lower field than that (the signal was hidden in the ring proton signals: δ 7.1-7.6) of Z-2 (mp 115-117°). Each isomer was then transformed stereoselectively to the corresponding oxindoles (E-3 and Z-3) by treatment with NaH in THF.



From these observations, it became clear that the initial addition of the thiol to 1 under thermal conditions occurred stereoselectively to give E-2[6], which under these conditions was transformed to E-3, while the photo-addition of the thiol to 1 took the reverse stereochemical course. These results are in parallel with those obtained in the related alcohol addition reactions to 1 reported previously.[7]

A very important observation has been gained when we treat these two isomers (E-3 and Z-3) with 10% HCl in methanol. Thus, while the E-isomer was found to be stable, the Z-isomer was transformed quantitatively to the E-isomer (60°, 15 min).

The results demonstrate that the E-isomer (E-3) is thermodynamically more stable than the Z-isomer (Z-3) and support the conclusion that non-existence of the Z-isomer in the corresponding alkoxymethylene derivatives may be due to an intrinsic instability of that isomer under an ordinary condition as suggested in the previous paper.[1]

Acknowledgement. The authors thank the Ministry of Education, Japan, for Grant-in-Aid for Special Project Research: Chemical Research in Development and Utilization of Nitrogen-Organic Resources.

References and Notes

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3) See ref. 1 and the cited papers therein.
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5) All of the NMR spectra were measured in $CDCl_3$.
6) The reaction of 1 with the thiol in ether in the presence of triethylamine[7] resulted in an entire recovery of the starting material and none of the ring opened addition product (2) was obtained.
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(Received September 6, 1978)