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RING CLOSURE REACTION AND MECHANISM OF 3-ALKOXY-2-(2-BENZAMIDOPHENYL)-ACRYLATES TO 3-(α-ALKOXYMETHYLENE)OXINDOLES[1]

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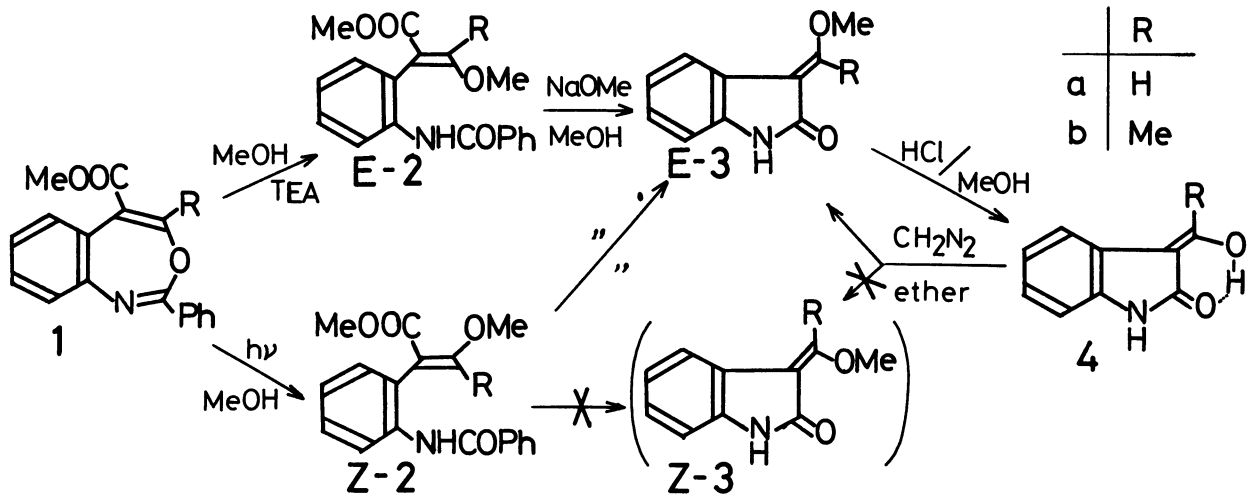
Treatment of the E- and Z-isomers of methyl 3-methoxy-2-(2-benzamidophenyl)acrylate with sodium methoxide in methanol affords the E-isomer of 3-(α-methoxymethylene)oxindole as a common product. A plausible mechanism of the reaction involving 1-benzoyl-3-dimethoxymethyloxindole as a key intermediate is proposed.

In the previous paper,[2] we reported that while irradiation of methyl 2-phenylbenz[d]-1,3-oxazepine 5-carboxylate (1a)[3] in methanol afforded the Z-isomer of methyl 3-methoxy-2-(2-amidophenyl)acrylate (Z-2a), thermal reaction of methanol with 1a in the presence of triethylamine gave the E-isomer (E-2a) and proposed the mechanisms accounting for the observed selectivities.

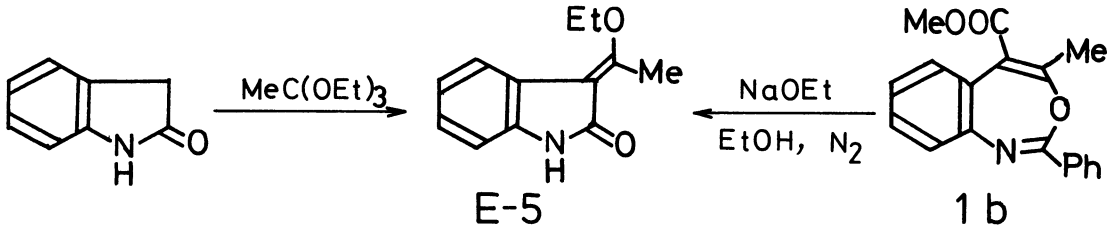
We now report ring closure reactions of both isomers (E- and Z-2a) caused by the action of sodium methoxide affording the E-isomer of 3-(α-methoxymethylene)oxindole (E-3a) as a common product, together with their mechanism and application to the related compounds.

Treatment of E-2a in methanol containing sodium methoxide at room temperature under nitrogen for 5 hr afforded E-3a (78%), mp 195-196°. The same oxindole was also obtained in 76% yield from Z-2a under the same condition. A careful examination of each reaction mixture showed that the other isomer (Z-3a) was not formed even in a trace amount. As expected from the stereoselective formation of E-2a in methanol in the presence of triethylamine, the oxazepine (1a) also gave E-3a under the same condition. Though the product (E-3a) was identified with 3-(α-methoxymethylene)oxindole prepared by the diazomethane-methylation of 3-formyloxindole (4a), the configuration around the methylene moiety of the latter species has remained to be clarified.[4] The attempted isomerization of E-3a to the other isomer was unsuc-

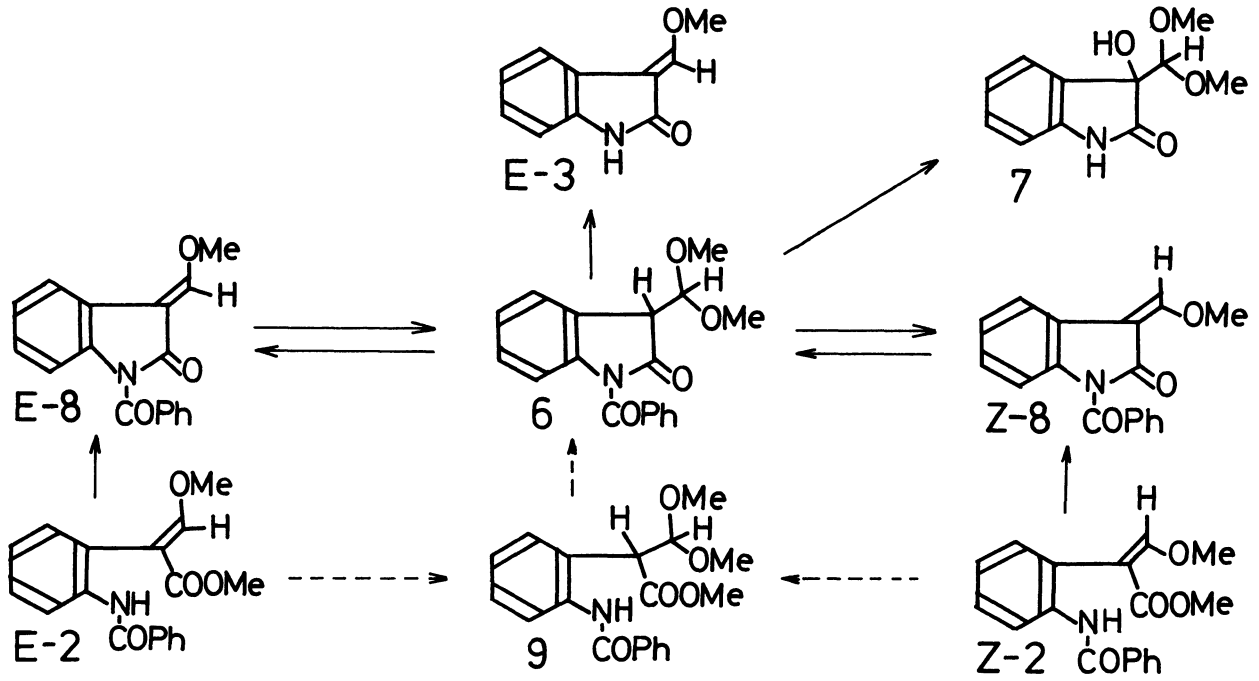


cessful due to its facile hydrolysis to 4a in methanol in the presence of 10% HCl[5] and its photostability.[6]

Quite recently, Korte et al.[7] concluded that 3-(α-ethoxyethylidene)oxindole (E-5) obtained from the reaction of the orthocarboxylic acid ester with oxindole had the E-configuration by NMR spectroscopy using shift reagents. Since their conclusion was further supported by X-ray crystallographic analysis of the related methylene lactones[8] and hence definitely reliable, we have prepared the same compound (mp 223-225°) from 1b by the reaction with sodium ethoxide in ethanol. As a result, an identity of both samples was confirmed by mixed melting point determination as well as spectral comparison.[9] Therefore, it now become evident that the oxindoles prepared in the present method have the E-configuration.



Our results are consistent with the premise that the formation of E-3a from both E-2a and Z-2a occurs through a common intermediate which then affords the final product (E-3a) by thermodynamically controlled reaction. The fact that both isomers of 2a when treated with sodium ethoxide in ethanol afforded the corresponding E-isomer [Et instead of Me in the formula E-3a: mp 131.5-132.5°; δ of the olefinic proton: 7.53 ($CDCl_3$)] suggested that the intermediate in the above transformation should be a 3-dialkoxymethyloxindole (e.g. 6). Intermediacy of 6 in the above reactions was further supported by the formation of 3-(dimethoxymethyl)dioxindole [7: mp 205-207°, δ(DMSO-d_6): 3.18 (3H, s), 3.53 (3H, s), 4.38 (1H, s),



5.99 (s, OH), 6.6-7.4 (4H, m), 9.95 (s, NH)] when the ring closure reactions of 1a and E-2a were carried out under an ordinary atmosphere. It is well known that the oxindoles, mono-substituted at the 3-position, undergo air oxidation (especially readily in a basic medium) to yield the corresponding dioxindoles.[10] Taking all of the above results into consideration, the entire mechanism for the ring closure reaction of 2 can be formulated as shown above. The mechanism of the formation of the key intermediate (6) is either that the ring closure to the oxindoles (8) occurs first followed by the Michael addition of methanol or the Michael addition precedes the ring closure reaction.[11,12]

An exclusive formation of E-3a in the above reactions together with the fact that all of the 3-type compounds prepared so far have the E-configuration seems to indicate an intrinsic instability of the Z-isomer relative to the E-isomer. Hence, we may conclude that the Z-isomer of the type 3 and 5 would be too unstable to be isolated under an ordinary condition. This conclusion seems to be supported if we consider complete stereoselective formation of the E-isomer from 3-formyl (as verified presently) or 3-acyloxindoles by diazomethane,[7] because these oxindoles are known to exist in the Z-configuration due to the intramolecular hydrogen bonding as shown in the formula 4.

Finally, it should be noted that the present method has provided a new synthetic route to the oxindoles of the type 3 and 5 starting from an appropriate quinoline 4-carboxylic acid.

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References and Notes

1) Part V of "Studies on the Oxazepine Derivatives." The following papers constitute Part I-IV of this series: a) Part I: S. Yamada and C. Kaneko, Rept. Inst. Med. Engi. Tokyo Medico-Dental Univ., 3, 75 (1965); b) Part II: M. Ishikawa, C. Kaneko, I. Yokoe, and S. Yamada, Tetrahedron, 25, 295 (1969); Part III: S. Yamada, M. Ishikawa, and C. Kaneko, Chem. Commun., 1972, 1093; d) Part IV: S. Yamada, M. Ishikawa, and C. Kaneko, Chem. Pharm. Bull., 23, 2818 (1975).

2) M. Somei, R. Kitamura, H. Fujii, K. Hashiba, S. Kawai, and C. Kaneko, Chem. Commun., 1977, 899.

3) R. Kitamura, H. Fujii, K. Hashiba, M. Somei, and C. Kaneko, Tetrahedron Lett., 1977, 2911.

4) a) E. Wenkert, N. K. Bhattacharrya, T. L. Reid, and T. E. Stevens, J. Am. Chem. Soc., 78, 797 (1956); b) L. Horner, Ann., 548, 117 (1941).

5) The thio-analogs of Z-3a isomerized completely to the E-isomer in methanol containing HCl; see Part VI of this series: C. Kaneko, S. Kawai, and M. Somei, Chem. Lett., subsequent communication.

6) Both E-2a and Z-2a as well as their thio-analogs reached the photostationary states composed of both isomers by irradiation ($\geq$300 nm).[2,5]

7) H. Wolfers, U. Kraatz, and F. Korte, Chem. Ber., 109, 1061 (1976).

8) O. L. Chapman, C. L. McIntosh, and J. C. Clardy, Chem. Commun., 1971, 384.

9) We thank Prof. Korte (München University) for sending us the sample of the E-isomer of 3-(α-ethoxyethylidene)oxindole (E-5).

10) a) P. Aeberli and W. J. Houlihan, J. Org. Chem., 33, 1640 (1968); b) E. C. Kendall and A. E. Osterberg, J. Am. Chem. Soc., 49, 2047 (1927); c) P. L. Julian and J. Pikl, J. Am. Chem. Soc., 57, 539 (1935).

11) In a hope to obtain Z-3a, we have treated Z-2a with sodium hydride in THF. However, no identifiable product was obtained.

12) A very slow addition of methanol to either E-2a or Z-2a giving 9 (mp 144-146°) was observed by the treatment with methanol containing triethylamine. The structure of 9 was determined from its NMR spectrum; $\delta(CDCl_3)$: 3.38 (3H, s), 3.52 (3H, s), 3.70 (3H, s), 4.14 (1H, d, J=7.0 Hz), 4.98 (1H, d, J=7.0), 7.2-7.6 (8H, m), 7.99 (1H, d, J=7.0), 9.42 (1H, br. s, the signal disappeared by the addition of D_2O).

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