SYNTHESES OF METHYL 3-ALKYL-2-(2-BENZAMIDOPHENYL)ACRYLATES AND THEIR RING CLOSURE TO INDOLINE OR OXINDOLE DERIVATIVES[1]

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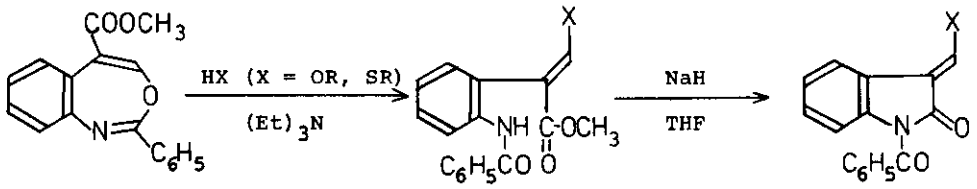
Abstract — Syntheses of methyl 3-dialkoxycarbonylmethyl- and -(α,α-dialkoxycarbonylethyl)-2-(2-benzamidophenyl)acrylates from methyl 2-phenyl-3,1-benzoxazepine-5-carboxylate were reported. Treatment of these two kinds of acrylates with base afforded entirely different products. Thus, while the former afforded 2,3-disubstituted indoline, the latter gave the oxindole, exclusively. The stereochemistries of the products as well as the mechanisms for these ring closure reactions are discussed.

In our earlier communications,[1-3] we reported the reactions of methyl 2-phenyl-3,1-benzoxazepine-5-carboxylate (1) with various heteronucleophiles (OR^- and SR^-) affording E-isomers (2) of methyl 2-(2-benzamidophenyl)acrylate having these nucleophiles at the 3-position, together with their ring closure to oxindoles (3) under basic conditions.



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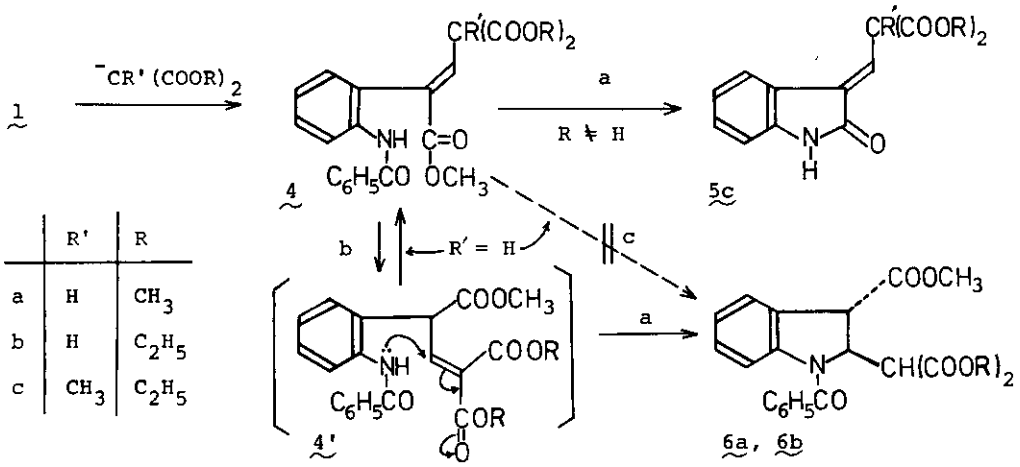
Here, we report the formation of corresponding ring-opened addition products (4) from the same oxazepine (1) by the use of carbanions such as malonate ion and their subsequent ring closure to either oxindole (5) or indoline derivatives (6), depending upon the presence or absence of the substituent on the malonate ion. Treatment of 1 in tetrahydrofuran with 3.0 mol equivalents of dimethyl- or diethylmalonate in the presence of NaH afforded, added to the indolines[4] (6a: oil and 6b: mp 113-114.5°, in ca. 40%), the expected ring-opened addition products (4a: mp 57-

58.5° and 4b: oil, in ca. 45-50%).[5] None of the oxindole derivatives were obtained in these reactions. 2,3-trans-Configuration in these indolines was established by a smaller coupling constant (ca. 3 Hz) between these two protons.[6] Structures of the ring-opened adducts (4a,b) were determined as in the following. At first, UV spectra of the adducts were quite close to those of 2 (e.g., λ_{max} nm (log ε) of 4a: 222 sh (4.23) and 260 (3.99) and that of 2 (X = OCH_3): 226 (4.38) and 252 sh (4.22)) and this fact indicated strongly that the double bond in 4a,b is in the conjugated position with the phenyl ring. Based on this assumption, the ^{1}H-nmr assignment is easily carried out; e.g., δ of 4a: 3.58 (6H, bs, 2 x CH_3), 3.69 (3H, s, CH_3), 4.08 (1H, d, J=11.0 Hz: C<u>H</u>$(COOCH_3)_2$), 7.22 (d, J=11.0 Hz: the olefinic proton), 7.0-8.1 (m, 9H, the ring protons) and 8.22 (1H, bs, N<u>H</u>).

The estabilshed structure of the ring opened adducts (4a,b) seemed to suggest that direct endocyclization (----→ in the scheme) of 4a,b afforded the final products (6a,b). However, this simple mechanism for the ring closure is doubtful when we consider the fact that none of the product expected from endocyclic ring closure was obtained from 2 under comparable basic conditions.[1-3] Furthermore, since double bond shifts are possible for 4a,b, an alternative pathway involving the base catalyzed double bond shifts to the deconjugated olefin (4') and subsequent exocyclic ring closure to 6a,b seems more attractive.

In order to exclude the direct endocyclization pathway from 4a,b to 6a,b, we treated 1 with diethyl methylmalonate in tetrahydrofuran in the presence of NaH. By the usual work-up after complete consumption of 1 (ca. 20 min at room temperature), the addition product (4c, oil; λ_{max} nm: 223 sh and 260 sh, and the spectrum is quite close with those of 4a,b) was obtained in 16.5%, together with 51.5% of the oxindole (5c, mp 125-126.5°). Heating of 5c at 100° in C_6D_6 in a sealed tube gave an equilibration mixture of the E- and Z-isomers (ratio: ca. 3:2). The reaction was followed nmr spectroscopically and the ratio of both isomers is easily determined from the olefinic and side-chain methyl signals [δ of E-isomer (5c): 7.93 and 1.76, and that of Z-isomer: 7.55 and 1.95]. The stereospecific formation of 5c (the E-isomer) from 4c in the above reaction showed chemically that 4c also had E-configuration at the olefinic moiety.[7] By the same base treatment, the adduct (4c) gave the oxindole (5c) in a quantitative yield and none of the indoline (6c) was obtained. Thus, it now becomes evident that cyclization of the adduct (4c) proceeds only in an exocyclic manner, and hence, the adduct (4c) affords directly oxindole (5c), while the adducts of the type 4a,b give the indolines (6a,b) via the double bond shifted isomers



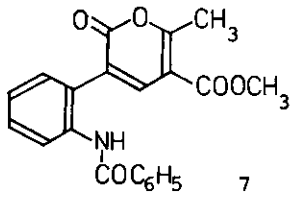
	R'	R
a	H	CH_3
b	H	C_2H_5
c	CH_3	C_2H_5

a) base catalyzed exocyclic ring closure
b) base catalyzed double bond shift
c) base catalyzed endocyclic ring closure

Scheme 1

(4'a,b).

Treatment of 1 with methyl acetoacetate instead of malonates under the same conditions afforded the α-pyrone (7, mp 165-166°) in 45% yield. The formation of 7 should obviously be occurred via Z-isomer of the corresponding ring-opened adduct and indicated that minor equilibration from E- to Z-isomer is existing under basic conditions.



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The present results indicated clearly that exocyclic ring closure is much easier path than endocyclic one in the formation of 5-membered ring and are in complete accordance with the proposal made by Baldwin.[8]

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REFERENCES AND NOTES

1. Part XI of the series entitled as "Studies on Oxazepine Derivatives". Part X, C. Kaneko, H. Fujii, S. Kawai, K. Hashiba, Y. Karasawa, R. Hayashi, and M. Somei, Chem. Pharm. Bull.(Tokyo), 1980, 28, in press.
2. C. Kaneko, H. Fujii, S. Kawai, and M. Somei, Chemistry Lett., 1978, 1277.
3. C. Kaneko, S. Kawai, and M. Somei, Chemistry Lett., 1978, 1281.

4. Satisfactory analyses, mass, and spectroscopic data were obtained for all new compounds described. Unless otherwise noted, $CDCl_3$ (nmr) and methanol (UV) were used as solvents. Melting points are uncorrected.

5. The reaction proceeded within several minutes at room temperature. The longer reaction time caused the increasement of 6a,b with concomitant decreasement of 4a,b. This tells clearly that the latter is the precursor of the former in these reactions.

6. The nmr of 6a; δ: 3.26, 3.71, and 3.78 (each s, 3H, CH_3), 4.30 (d, J=4.8 Hz, $C\underline{H}(COOCH_3)_2$), 4.38 (d, J=2.8 Hz, H-3), 5.62 (d-d, H-2), and 6.4-7.6 (m, 9H, ring protons). The assignments of the signals of 6a,b were confirmed from the comparison with the nmr of methyl 2-dicyanomethyl-1-benzoylindoline-3-carboxylate (mp 124-125.5°) obtained from 1 and dicyanomalonate under comparable conditions. The nmr of the latter indoline; δ: 4.28 (d, J=3.2 Hz, H-3), 5.10 (d, J=4.4 Hz, $C\underline{H}(CN)_2$), 5.52 (d-d, H-2). The complete analyses of ^{1}H-nmr spectra of 4,5, and 6 will be reported in a full paper.

7. The chemical shift (in δ) of the olefinic proton of 4c appeared at 7.53 (s), and the value is quite close to those of 4a,b (4a: 7.22 and 4b: 7.24). This fact showed that 4a and 4b have also E-configuration at the olefinic moiety.

8. The so-called Baldwin's rule, see: J.E. Baldwin, Chem. Commun., 1976, 734, 738; J.E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R.C. Thomas, Chem. Commun., 1976, 736; J.E. Baldwin and L.I. Kruse, Chem. Commun., 1977, 233; J.E. Baldwin, R.C. Thomas, L.I. Kruse, and L. Silberman, J. Org. Chem., 1977, 42, 3846.

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