THE INTRAMOLECULAR CYCLOADDITION REACTION OF o-CINNAMYLOXYBENZYLIDENE-(METHOXYCARBONYL)PHENYLMETHYLAMINES

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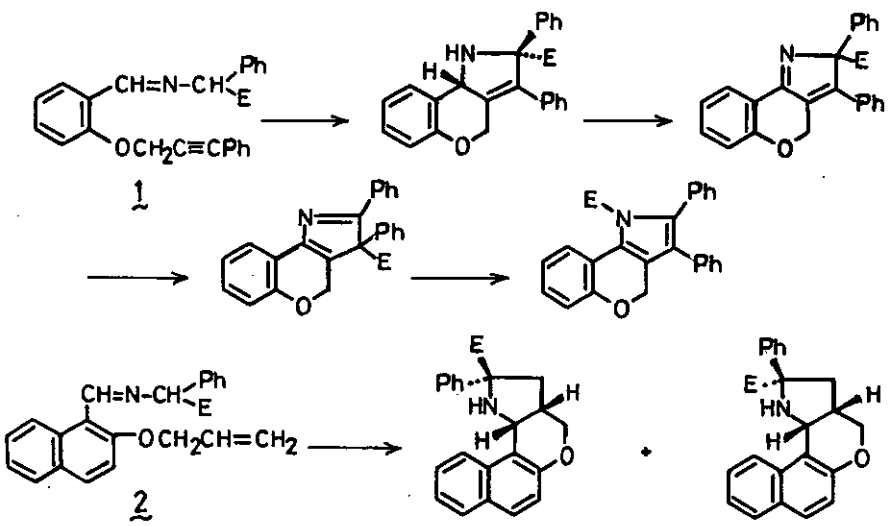
Abstract —— o-Cinnamyloxybenzylidene(methoxycarbonyl)phenylmethylamines undergo an intramolecular cycloaddition via their 1,3-dipolar tautomers to the alkenyl group, affording three stereoisomeric cycloadducts.

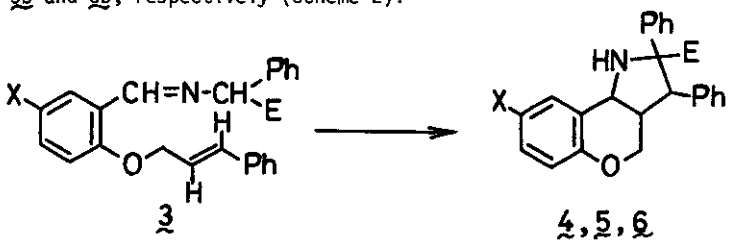
Recently, o-propargyloxybenzylideneamine 1 was found to undergo a thermal intramolecular cycloaddition via its 1,3-dipolar tautomer, azomethine ylide dipole, to the alkynyl group, and on further heating the initial cycloadduct was converted to dehydrogenated compounds with concurrent migration of the methoxycarbonyl group[1]. At the nearly same time, Grigg et al.[2] have demonstrated the analogous intramolecular cycloaddition of imine 2 leading to the formation of two stereoisomeric cycloadducts (Scheme 1). A recent publication[3] reporting on the sterochemistry of intermolecular cyclo-



Scheme 1

additions of imines of α-amino acid esters prompts us to report our findings concerning intramolecular cycloaddition of o-cinnamyloxybenzylidene(methoxycarbonyl)phenylmethylamines 3.

A solution of imine 3a or 3b[4] in xylene was refluxed for 3 h, and then chromatography (SiO_2, hexane-benzene (2:3)) of the reaction mixture afforded a mixture of three stereoisomeric cycloadducts 4a, 5a and 6a, or 4b, 5b and 6b, respectively (Scheme 2).



3 → 4, 5, 6

a: X=H; b: X=Br; E=COOMe

4a (31%), 5a (32%), 6a (13%)

4b (26%), 5b (30%), 6b (15%)

Scheme 2

4a: colorless prisms; mp 166-167°C; IR (KBr) 3350, 1725 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (1H, broad, NH), 2.90 (1H, dddd, H_b, J=9.5, 7.5, 3.0, 3.0 Hz), 3.30 (3H, s), 3.90, 4.08 (each 1H, dd, J=11.5, 3.0 Hz), 4.35 (1H, d, H_c, J=9.5 Hz), 4.78 (1H, d, H_a, J=7.5 Hz), 6.78-7.32 (14H, m); MS m/e 385 (M^+).

5a: colorless prisms; mp 87.5-89.5°C; IR (KBr)[5] 3380, 3330, 1725, 1708 cm^{-1}; NMR ($CDCl_3$) δ 2.16 (1H, broad, NH), 2.94 (1H, dddd, H_b, J=7.5, 7.5, 6.5, 4.0 Hz), 3.10 (3H, s), 3.63 (1H, d, H_c, J=7.5 Hz), 3.70 (1H, dd, J=11.0, 6.5 Hz), 4.02 (1H, dd, J=11.0, 4.0 Hz), 4.86 (1H, d, H_a, J=7.5 Hz), 6.70-7.57 (14H, m); MS m/e 385 (M^+).

6a: colorless prisms; mp 160-161°C; IR (KBr) 3300, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.70 (1H, broad, NH), 2.48 (1H, dddd, H_b, J=12.0, 11.0, 10.0, 4.8 Hz), 3.30 (3H, s), 3.50 (1H, d, H_c, J=12.0 Hz), 3.65 (1H, d, H_a, J=11.0 Hz), 4.02 (1H, dd, J=10.0, 10.0 Hz), 4.10 (1H, dd, J=10.0, 4.8 Hz), 6.75-8.0 (14H, m); MS m/e 385 (M^+).

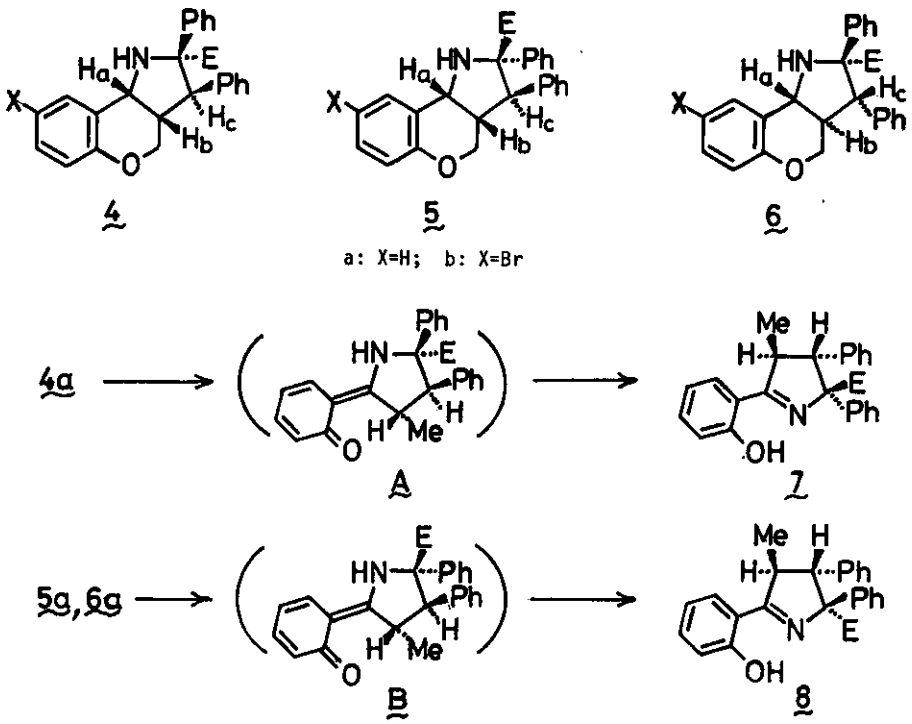
4b: colorless prisms; mp 193-194°C; IR (KBr) 3370, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (1H, dddd, H_b, J=9.5, 7.5, 3.0, 3.0 Hz), 3.20 (1H, broad, NH), 3.34 (3H, s), 3.95, 4.06 (each 1H, dd, J=11.5, 3.0 Hz), 4.34 (1H, d, H_c, J=9.5 Hz), 4.72 (1H, d, H_a, J=7.5 Hz), 6.68-7.42 (13H, m).

5b: colorless prisms; mp 101-102°C; IR (KBr)[6] 3400, 3340, 1730, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.16 (1H, broad, NH), 2.94 (1H, dddd, H_b, J=7.5, 7.5, 6.5, 4.0 Hz), 3.10 (3H, s), 3.63 (1H, d, H_c, J=7.5 Hz), 3.70 (1H, dd, J=11.0, 6.5 Hz), 4.02 (1H, dd, J=11.0, 4.0 Hz), 4.86 (1H, d, H_a, J=7.5 Hz), 6.70-7.57 (13H, m).

6b: colorless prisms; mp 203-205°C; IR (KBr) 3300, 1725 cm^{-1}; NMR ($CDCl_3$) δ 2.70 (1H, broad, NH), 2.48 (1H, dddd, H_b, J=12.0, 11.0, 10.0, 4.8 Hz), 3.30 (3H, s), 3.50 (1H, d, H_c, J=12.0 Hz), 3.65 (1H, d, H_a, J=11.0 Hz), 4.02 (1H, dd, J=10.0, 10.0 Hz), 4.10 (1H, dd, J=10.0, 4.8 Hz), 6.75-8.0

(13H, m).

It is generally difficult to infer the stereochemistry between 3- and 4-positions of pyrrolidine rings on the basis of values of coupling constants $J_{3,4}$[7]. However, it is reasonable to assume that the hydrogens H_b and H_c in all products are trans, because it is known that intermolecular cycloadditions to imines of α-amino acid esters proceed via a concerted fashion and are stereospecific[8]. As shown in NMR data, the coupling constants (each J=7.5 Hz) of the ring junction protons H_a and H_b of 4a, 4b, and 5a, 5b suggested cis fused ring systems, whereas those (both J=11.0 Hz) of 6a and 6b indicated trans ones[9]. It is thus possible to conclude that 4a, 4b, and 5a, 5b have the H_a, H_b-cis and H_b, H_c-trans configurations, and 6a and 6b have the H_a, H_b-trans and H_b, H_c-trans ones.



Scheme 3

Configurations of 2- and 3-positions in pyrrolidine moieties in all products were assumed on the basis of NMR data of compounds derived from 4a, 5a, and 6a. It is known that cyclic ethers such as tetrahydropyrans undergo catalytic ring cleavage with Pd-C at high temperature to give the corresponding aldehydes or ketones[10]. When a solution of 4a in decalin was refluxed with 5% Pd-C, 2-(o-hydroxyphenyl)-3-methyl-4,5-diphenyl-5-methoxycarbonyl-1-pyrroline 7, mp 169-170°C, was obtained in 95% yield. On the other hand, a similar treatment of 5a and 6a afforded the same product 8, mp 181-182°C, which was a stereoisomer of 7, in 53 and 47% yields respectively. On the basis of

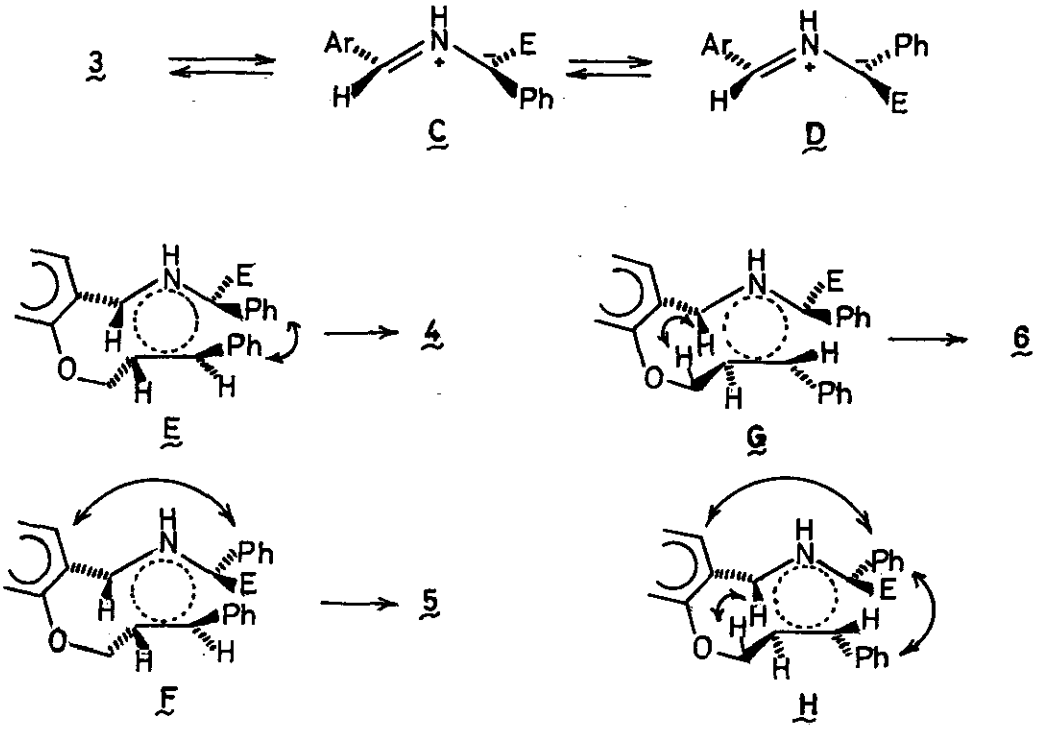
comparison of NMR data, the stereochemistry of 7 and 8 was assigned. The signals of methyl, methoxycarbonyl and 4-methine in 8 appeared at higher fields than those in 7 respectively, because of anisotropy effects of the 4- and 5-phenyl groups. It is thus concluded that 7 has 3-methyl, 4-phenyl-trans and 4-phenyl, 5-phenyl-cis configurations, whereas 8 has 3-methyl, 4-phenyl-trans and 4-phenyl, 5-phenyl-trans ones. The formation of 7 and 8 can be interpreted as arising from A and B respectively (Scheme 3).

7: pale greenish yellow prisms; IR (KBr) 3200-2300, 1730, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (3H, d, CH_3, J=7.0 Hz), 3.73 (3H, s, OCH_3), 3.79 (1H, m, 3-H), 4.30 (1H, d, 4-H, J=3.0 Hz), 6.70-7.63 (14H, m), 14.92 (1H, broad, OH); MS m/e 385 (M^+).

8: pale greenish yellow prisms; IR (KBr) 3600-2400, 1740, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (3H, d, CH_3, J=7.0 Hz), 3.19 (3H, s, OCH_3), 3.75 (1H, m, 3-H), 3.79 (1H, pseudo s, 4-H), 6.80-7.90 (14H, m), 14.96 (1H, broad, OH); MS m/e 385 (M^+).

On the basis of above observations, the stereochemistry of initial cycloadducts 4, 5, and 6 was assigned as shown in Scheme 3. The suggested structures for 4b, 5b, and 6b were finally confirmed by their X-ray diffraction studies[11].

The formation of 4, 5 and 6 from 3 can be interpreted as follows (Scheme 4). The intramolecular



Scheme 4

cycloaddition proceeds via a 1,3-dipolar cycloaddition involving a prototropic equilibrium of 3 with its 1,3-dipolar tautomer, azomethine ylide. The formation of 4 and 5 indicates that stereomutation (C ⇌ D) of the 1,3-dipole occurs. Such a stereomutation has been also reported in intermolecular cycloadditions of analogous imines to less reactive dipolarophiles[3]. However, inspection of the Dreiding models indicated that C is more preferable than D, because D suffers much higher van der Waals strain.

In the transition state E leading to 4, the 1,3-dipole moiety has a preferable geometry but there is a steric interaction between two phenyl groups. On the other hand, the transition state F for 5 has an unfavored geometry in the 1,3-dipole moiety. It seems reasonable to assume that E and F are energetically almost equivalent, because of comparable yields of 4 and 5. The minor product 6 forms via the transition state G in which there is a significant steric interaction between the azomethine hydrogen and methylene. It is thought that the fourth cycloadduct via the transition state H is not formed because H has significant steric interactions as shown in Scheme 4.

The present work was partially supported by Grant-in-Aid for Scientific Research from the Ministry of Education (No. 555345), to which authors' thanks are due.

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4. All compounds in this paper gave satisfactory elemental analyses. Imines 3 were prepared by the reaction of the corresponding o-cinnamyloxybenzaldehyde with glycine ester.
   3a: colorless prisms; mp 98-98.5°C; IR (KBr) 1740, 1630 cm^{-1}; NMR ($CDCl_3$) δ 3.66 (3H, s), 4.65 (2H, d, J=5.0 Hz), 5.17 (1H, s, ≥CH), 6.28 (1H, dd, H_2C-CH=, J=5.0, 16.0 Hz), 6.66 (1H, d, =CH-Ph, J=16.0 Hz), 6.75-7.55 (13H, m), 8.11 (1H, m), 8.81 (1H, s, N=CH).
   3b: colorless prisms; mp 100-101°C; IR (KBr) 1740, 1630 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (3H, s), 4.73 (2H, d, J=5.0 Hz), 5.24 (1H, s, ≥CH), 6.35 (1H, dd, H_2C-CH=, J=5.0, 16.0 Hz), 6.75 (1H, d, =CH-Ph, J=16.0 Hz), 6.86 (1H, d), 7.3-7.7 (11H, m), 8.32 (1H, m), 8.82 (1H, s, N=CH).
5. IR in nujol: 3400, 1725 cm^{-1}.
6. IR in CCl_4: 3370, 1730 cm^{-1}.
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11. The results will be published eleswhere.

Received, 26th May, 1981