FORMATION OF THE INDOLIZIDINE RING SYSTEM BY AN UNUSUAL BASE-INDUCED CYCLIZATION

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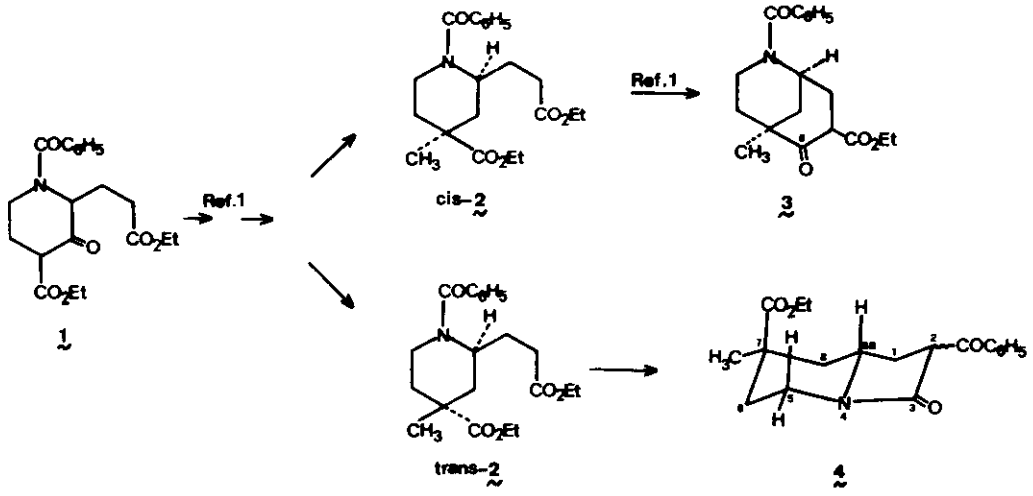
Abstract- The formation of the indolizidine ring system by base-induced cyclization of ethyl 1-benzoyl-2-piperidinepropionate derivative is described.

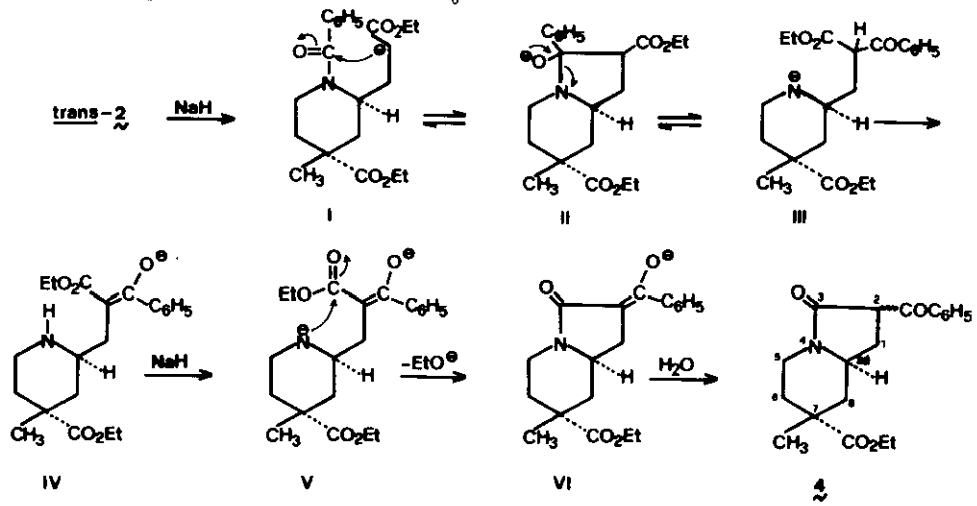
The acylation of an active methylene by an amide carbonyl group is a quite unusual process. An interesting reaction of this type leading to the indolizidine ring system takes place when ethyl 1-benzoyl-4-methyl-*t*-4-ethoxycarbonyl-*r*-2-piperidinepropionate (*trans*-2) was treated under Dieckmann reaction conditions.
Amido diesters 2 were obtained[1] from piperidone 1 in a three-step sequence (alkylation, thioketalization, and Raney nickel desulfurization), and their separation was achieved by fractional crystallization of the *trans* isomer (*trans*-2). The Dieckmann cyclization of the *cis* isomer to the functionalized 2-azabicyclo[3.3.1]nonane 3 has been previously reported.[1,2]



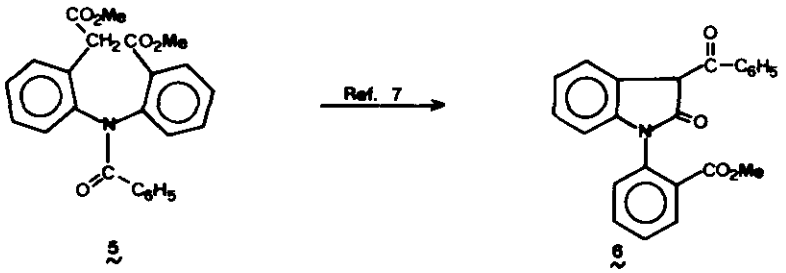
Treatment of *trans*-2 with excess sodium hydride gave ethyl (7*R**,8a*S**)-2-benzoyl-7-methyl-3-oxo-1,2,3,5,6,7,8,8a-octahydro-7-indolizinecarboxylate (4) in 50% yield as a mixture of C-2 epimers. Important characteristics in the ^{1}H nmr spectrum of 4 are: (i) signals for benzoyl, ethyl, and quaternary methyl groups, (ii) separate multiplets at δ3.63 and δ3.78 for the C_{8a}-H methine proton in each epimer, (iii) multiplets at δ4.52 and δ2.15-2.55 assignable to the C_2-H proton, placed in the α-position of two carbonyl groups, and to protons on the β-position of the piperidine ring, respectively, and (iv) signals due to the pyrrolidine methylene protons at ∿δ1.3 and δ1.80, the former masked with those of methyl groups. Finally, equatorial and axial protons of the N-CH_2 group appear at δ2.79 and δ4.04, respectively, the latter influenced by the amide carbonyl anisotropy effect as usual in similar lactams.[3] The stereochemical assignment of these protons was also inferred from their multiplicity.

The ^{13}C nmr spectrum (for full assignment see ref.4) are also remarkably similar for the two epimers of 4. The stereochemistry of the C-2 benzoyl substituent appears to have little effect upon the chemical shifts.

The formation of 4 can be accounted for in terms of intramolecular attack of carbanion I upon the amide carbonyl group since interaction with the C-4 piperidine ester group is not possible. The resulting intermediate II evolves to amidure III and then to the stable enolate IV by proton transfer. Irreversible abstraction of a second proton by sodium hydride gives dianion V. Finally, the amidure anion intramolecularly reacts with the ethoxycarbonyl group of the enolate β-keto ester in V to give the stable enolate VI. Its kinetic protonation[5] upon C-2 during the work-up leads to the epimeric indolizidines 4 in a nearly equimolecular ratio.



Another reaction of this type involving an N⟶C acyl transfer followed by lactamization is the cyclization of amido diester 5 in a process related to the Madelung indole synthesis.[6] Treatment of 5 with a slight excess of sodium methoxide gave oxindole 6 instead of the expected Dieckmann cyclization product.[7]



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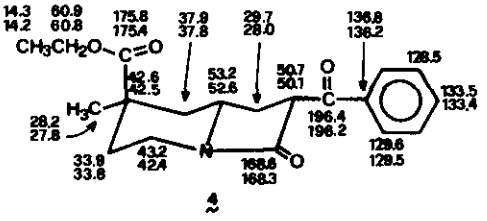
The formation of the indolizidine nucleus[8] described in this paper seems not to be general since piperidone 1, a compound closely related to *trans*-2, undergoes a Claisen intermolecular condensation process under similar basic conditions.[9]

EXPERIMENTAL

A sodium hydride oil dispersion (55%, 350 mg, 8 mmol) was suspended in anhydrous toluene (80 ml) under nitrogen and *trans*-2 (1 g, 2.66 mmol) in anhydrous toluene (20 ml) containing a few drops of ethanol was added dropwise with stirring at room temperature. The resulting mixture was refluxed with vigorous stirring for five hours. After evaporation, the residue was dissolved in 1N hydrochloric acid and extracted with ether. The organic extract was dried over anhydrous magnesium sulfate, filtered, and evaporated to give an oil which on chromatography (SiO_2, $CHCl_3$) afforded 440 mg (50% yield) of indolizidines 4:bp 240-250°C/0.1 mm Hg (oven temperature); ^{1}H nmr (200 MHz, $CDCl_3$): δ1.24 (s,3H,C_7-CH_3), 1.29 (t,3H,OCH_2CH_3), 1.2-1.4 (masked,1H,C_1-H), 1.80 (m,1H,C_1-H), 2.15-2.55 (m,4H,6- and 8-CH_2), 2.79 (m,1H,C_5-H_{ax}), 3.63 and 3.78 (2m,$W_{1/2}$=32 Hz,1/2H each,C_{8a}-H), 4.04 (m,1H,C_5-H_{eq}), 4.20 and 4.21 (2q,1H each,OCH_2), 4.52 (m,1H,C_2-H), 7.45-7.59 (m,3H,ArH), 8.07-8.15 (m,2H, ArH); ir ($CHCl_3$), 1720 (ester) and 1675-1690 cm^{-1} (ketone and lactam); mass spectrum, m/e (relative intensity), 329(M^+,7), 224(11), 215(4), 196(5), 150(24), 122 (17), 105(100). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.36; H, 7.15; N, 4.52.

REFERENCES AND NOTES

1. J. Bosch and J. Bonjoch, *J. Org. Chem.*, 1981, *46*, 1538.
2. For a review on the synthesis of 2-azabicyclo[3.3.1]nonanes, see: J. Bosch and J. Bonjoch, *Heterocycles*, 1980, *14*, 505.
3. a) F. Bohlmann and D. Schumann, *Tetrahedron Lett.*, 1965, 2435; b) H. E. Schoemaker, J. Dijkink, and W. N. Speckamp, *Tetrahedron*, 1978, *34*, 163.
4. The ^{13}C nmr spectral data ($CDCl_3$, ppm) of compounds 4 are summarized in the following structure



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For model compounds used in the assignments see: M. Shamma and D. M. Hindenlang, "Carbon-13 NMR Shift Assignments of Amines and Alkaloids", Plenum Press, New York, 1979.

5. It is well-known that protonation of delocalized carbanions and enolates occurs kinetically with approach of the proton donor from the less hindered side of the enolate moiety; see note 14 in H. E. Zimmerman and R. J. Pasteris, *J. Org. Chem.*, 1980, *45*, 4864.
6. R. K. Brown, "Synthesis of the Indole Nucleus" in "Indoles" Part I, ed. by W. J. Houlihan, John Wiley, New York, 1972, pp 385-396.
7. a) J. W. Schulenberg and S. Archer, *J. Am. Chem. Soc.*, 1961, *83*, 3091; b) J. W. Schulenberg, *J. Am. Chem. Soc.*, 1968, *90*, 7008.
8. For a review on indolizine chemistry see: J. F. Swinbourne, J. H. Hunt, and G. Klinkert, *Adv. Heterocycl. Chem.*, 1978, *23*, 103.
9. J. Bosch, J. Bonjoch, and J. Mis, *An. Quim.*, 1981, *77C*, 205.

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