2-AZABICYCLO[3.2.0]HEPTANE-3,4-DIONES (4): THERMAL REARRANGEMENT OF 3-ETHOXY-2-AZABICYCLO[3.2.0]HEPT-2-EN-4-ONES LEADING TO 2-ETHOXY-3,4-DIHYDROPYRIDINES [1]

Takehiro Sano* and Yoshie Horiguchi
Showa College of Pharmaceutical Sciences, Setagaya-Ku, Tokyo 154, Japan.
Yoshisuke Tsuda
Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920, Japan.

Thermolysis of 3-ethoxy-2-azabicyclo[3.2.0]hept-2-en-4-ones yielded 2-ethoxy-3,4-dihydropyridines, which is explained by [1,3] sigmatropic rearrangement followed by cheletropic elimination of CO.

We report here a thermal conversion of imidic esters of 2-azabicyclo[3.2.0]-heptane-3,4-diones (1 or 2) to 2-ethoxy-3,4-dihydropyridines (3) under relatively mild conditions, which we believe [1,3] sigmatropic shift of an azabicyclo[3.2.0]-heptene to an azabicyclo[2.2.1]heptene followed by cheletropic elimination of carbon monoxide.

The imidates (1 or 2) were prepared from 2-azabicyclo[3.2.0]heptane-3,4-diones on treatment with Meerwein reagent.[2]

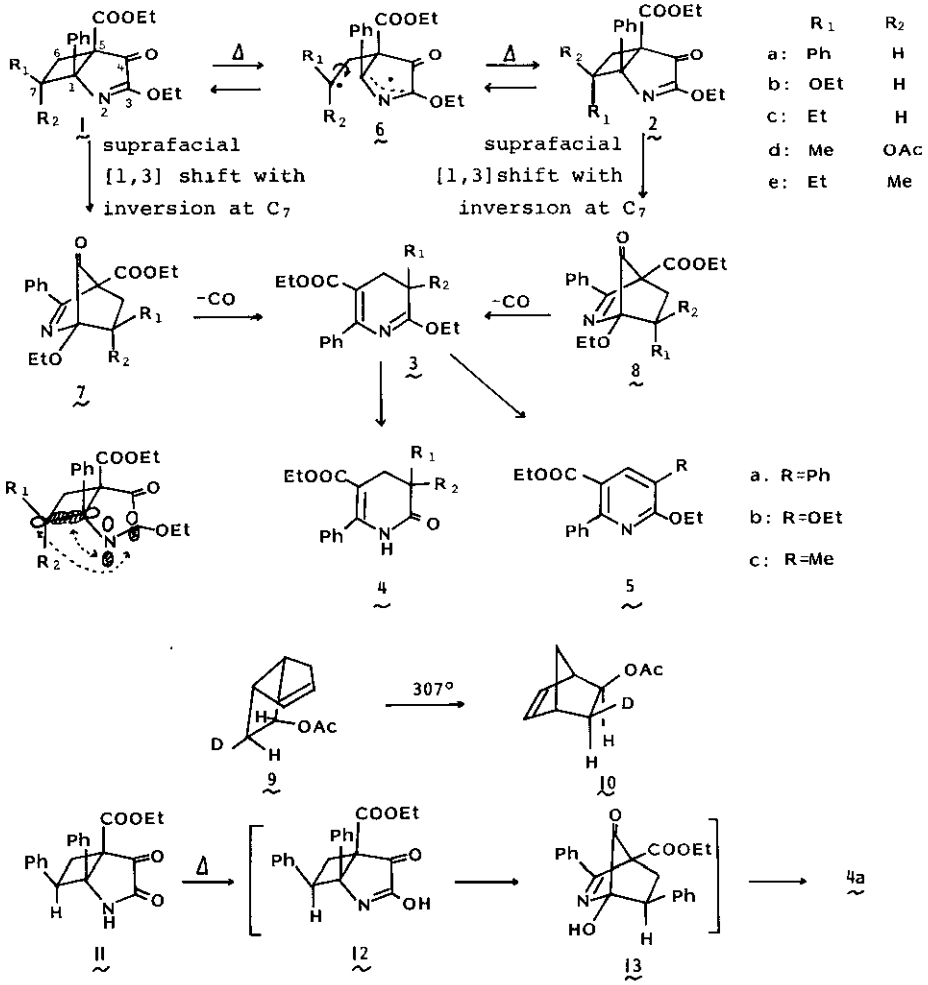
When 7-*exo*-phenyl derivative (1a) was heated in toluene at 120° for 4 hr, a gum was produced, the spectral data of which suggested that it is 2-ethoxy-5-ethoxycarbonyl-6-phenyl-3,4-dihydropyridine (3a).[3] Confirming this assignment, it gave the 3,4-dihydropyridone (4a)[4] (67% from 1a) on acid hydrolysis (5%HCl-THF, r.t.) and the 2-ethoxypyridine (5a)[5] (84% from 1a) on DDQ oxidation.

7-*Endo*-phenyl isomer (2a) was stable under the similar condition, but changed at 200° for 2 hr into the same dihydropyridine (3a) (80%).[3] The difference in reactivity due to orientational difference of C_7-substituent is attributable to retarding the [1,3] shift process by a 7-*endo* group. For thermally allowed suprafacial [1,3] sigmatropic shift with inversion of the configuration of the migrating center (C_7), movement of a 7-*endo* substituent would require higher activation energy than that of a 7-*exo* isomer due to increase of steric hindrance in a transition state.

The similar effect was observed in thermolysis of 7-ethoxy derivatives. Formation of the dihydropyridine (3b) (~75%)[3] at 200° from the *exo*-isomer (1b)

completed within 2 hr, but required 20 hr from the *endo*-isomer (2b).

7,7-Disubstituted derivatives also gave dihydropyridines, though forced conditions were required, as expected. Thus 7-Et-7-Me derivative (1e) gave the dihydropyridine (3e)[3] in 85% yield on heating at 200° for 20 hr. Both the 7-*exo*-Me-7-*endo*-OAc and 7-*exo*-OAc-7-*endo*-Me derivatives, (1d) and (2d), gave (200°, 16 hr) the same pyridine derivative (5c)[5] (47% from 1d, 29% from 2d), which is the product apparently due to thermal loss of acetic acid from the intermediary dihydropyridine (3d). Interestingly, the imidates recovered from the above reaction mixture (27% from 1d, 29% from 2d) were contaminated with the other stereoisomer (10% and 30%, respectively, as evidenced from the NMR spectra), indicating that epimerization of C_7-substituent was taking place.



The 7-*exo*-ethyl derivative (1c), did not produce the dihydropyridine (3c) on heating at 200° for 8 hr, but it instead epimerized to the 7-*endo*-ethyl isomer (2c) (60% yield), indicating that epimerization of C_7-substituent occures as another independent thermal process of the imidates. Since this thermal epimerization of a 7-*exo*-substituent to a thermodynamically more stable 7-*endo* isomer is likely to proceed through biradical intermediate (6) as already suggested in epimerization of 7-substituted-2-azabicyclo[3.2.0]heptane-3,4-diones,[6] all of the above evidence support that the smooth [1,3] shift from an *exo*-isomer proceeds in a concerted manner without through radical intermediate. In fact, no epimerization was observed during the migration of the *exo*-isomers, 1a and 1b. At high temperature homolytic cleavage of C_1-C_7 bond competitively occurs, which becomes predominant when the migration is slow (i.e. in 1c).

Among two consecutive steps in formation of dihydropyridines, [1,3] shift and cheletropic loss of CO, the first step is similar with the stereospecific [1,3] rearrangement of 9 to 10 reported by Berson.[7] Including this, reported thermal [1,3] shift such as vinylcyclopropanes to cyclopentenes[8-10], whether it is of concerted or of biradical pathway, generally requires high temperature (>250°). In contrast to those, our aza[1.3] shift is facilitated probably by presence of C_3-ethoxyl and C_1-phenyl groups, of course electron rich substituent at 7-*exo* position being another accelerating factor. Such lowering the activation energy of sigmatropic shift by substitution at a migrating terminus with an electron rich substituent has been reported.[11]

Direct formation of the dihydropyridone (4a)(10%) in thermolysis (200°, 2 hr) of a 2-azabicyclo[3.2.0]heptane-3,4-dione (11)[6] also suggests the participation of the lactim form (12) in the reaction, although the radical pathway can not be discarded in this case.[12]

Acknowlegements. One of the authors (T.S.) is grateful to financial support of a part of this work by a Grant-in-Aid (No 567369) for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Reference and Note

1. Dioxopyrrolines XVIII , Part XVII : T. Sano, Y. Horiguchi and Y. Tsuda, Heterocycles, 1981, 16, in press.
2. The imidates 1a and 2b were reported in ref. 1. Following new imidates gave satisfactory spectral data and micro-analyses.
1b: mp.100-102°, 1c: mp.94-95°, 1d: mp.81-83°, 1e: mp.100-105°, 2a:mp.122-127°

2c: mp.55-57°, 2d: mp.112-113°. For the stereochemistry, see ref. 6.

3. The dihydropyridines gave the following spectral data. The yield was calculated on hydrolysis to a dihydropyridone (see ref. 4).

3a; gum. IR(CH_2Cl_2): 1750, 1700(sh), 1685, 1620, 1600, 1580. UV $\lambda_{max}^{Dioxane}$ (ε): 222(13,000), 293(7,800). NMR($CDCl_3$): δ 0.90(3H, t, J=7 Hz), 1.27(3H, t, J=7 Hz), 3.00(1H, d, J=8 Hz), 3.02(1H, d, J=5 Hz), 3.70(1H, dd, J= 5 and 8 Hz), 3.93(2H, q, J=7 Hz), 4.33(2H, q, J=7 Hz), 7.0-7.4(10H, Ar-H).

3b; gum. IR(CH_2Cl_2): 1750, 1720, 1680, 1620. UV $\lambda_{max}^{Dioxane}$ (ε): 228(8,800), 288 (6,000). NMR($CDCl_3$): δ 0.87(3H, t, J=7 Hz), 1.08(3H, t, J=7 Hz), 1.23(3H, t, J=7 Hz), 2.81(1H, d, J=5 Hz) 2.91(1H, d, J=5 Hz), 3.63(2H, q, J=7 Hz), 3.93(1H, t, J=5 Hz), 4.00(2H, q, J=7 Hz), 4.36(2H, q, J=7 Hz), 7.1-7.4(5H, Ar-H).

3e; gum. IR(film): 1750, 1720, 1690, 1600. UV $\lambda_{max}^{Dioxane}$(ε): 294(5,600). NMR($CDCl_3$): δ 0.90(3H, t, J=7 Hz), 0.93(3H, t, J=7 Hz), 1.17(3H, s), 1.30 (3H, t, J=7 Hz), 1.50(2H, m), 2.53(2H, ABq, Δδ=23 Hz, J=17 Hz), 3.97(2H, q, J=7 Hz), 4.28(2H, q, J=7 Hz), 7.30(5H, m).

4. For 4a and 4b, see T. Sano, Y. Horiguchi, Y. Tsuda, and Y. Itatani, Heterocycles, 1978, 9, 161.

4e; mp.108-110°. IR(Nujol): 1690, 1660, 1630(sh). NMR($CDCl_3$): δ 0.90(6H, t, J=7 Hz), 1.18(3H, s), 1.63(2H, q, J=7 Hz), 2.65(2H, ABq, Δδ=20 Hz, J=18 Hz), 3.92(2H, q, J=7 Hz), 7.30(5H, b.s, Ar-H).

5. 5a; mp.102-103.5°. IR(Nujol): 1700, 1590. UV $\lambda_{max}^{Dioxane}$(ε):300(17,900). NMR($CDCl_3$): δ 1.09(3H, t, J=7 Hz), 1.40(3H, t, J=7 Hz), 4.18(2H, q, J=7 Hz), 4.57(2H, q, J=7 Hz), 7.36-7.70(10H, m, Ar-H), 8.13(1H, s, C_4-H).

5b; mp.65-66°. IR(Nujol): 1685, 1580. UV $\lambda_{max}^{Dioxane}$(ε): 288(12,700). NMR($CDCl_3$): δ 1.03(3H, t, J=7 Hz), 1.43(3H, t, J=7 Hz). 1.50(3H, t, J=7 Hz), 1.13(2H, q, J=7 Hz), 4.20(2H, q, J=7 Hz), 4.60(2H, q, J=7 Hz), 7.30(1H, s, C_4-H), 7.4-7.55(5H, m, Ar-H).

5c; colorless gum. IR(CH_2Cl_2): 1720, 1700, 1600. UV $\lambda_{max}^{Dioxane}$(ε): 281(11,030). NMR($CDCl_3$): δ 1.05(3H, t, J=7 Hz), 1.41(3H, t, J=7 Hz), 2.25(3H, s, CH_3), 4.12(2H, q, J=7 Hz), 4.50(2H, q, J=7 Hz), 7.2-7.6(5H, m, Ar-H), 7.87(1H, s, C_4-H).

6. a) T. Sano, Y. Horiguchi, and Y. Tsuda, Heterocycles, 1981, 16, in press (2-azabicyclo[3.2.0]heptane-3,4-dione (1)).

b) idem, ibid, in press (2-azabicyclo[3.2.0]heptane-3,4-dione (2)).

7. J.A. Berson and G.L. Nelson, J. Am. Chem. Soc., 1967, 89, 5503.

8. J.M. Simpson and H.G. Richey,Jr., Tetrahedron Lett., 1973, 2545.

9. H.G. Richey,Jr., and D.W. Shull, ibid, 1976, 575.

10. B.M. Trost, Y. Nishimura, K. Yamamoto, and S.S. McElvain, J. Am. Chem. Soc., 1979, 101, 1328.

11. a) D.A. Evans and D.J. Baillargeon, Tetrahedron Lett., 1978, 3319.

b) F. Scheidt and W. Kirmse, J. C. S. Chem. Comm., 1972, 716.

12. Y. Tsuda, M. Kaneda, Y. Itatani, T. Sano, Y. Horiguchi, and Y. Iitaka, Heterocycles, 1978, 9, 153.

Received, 9th February, 1981