2-AZABICYCLO[3.2.0]HEPTANE-3,4-DIONES (1)[1].
A NOVEL EPIMERIZATION REACTION OF C_7-SUBSTITUENTS.

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

On treatment with bases, 7,7-disubstituted and 7-substituted 2-azabicyclo[3.2.0]heptane-3,4-diones rapidly epimerized at C_7 to give a thermodynamically more stable isomer (7-*endo* isomer in the cases of mono-substituted compounds) predominantly, then changed into dihydroaza-tropolones. The mechanism of this novel epimerization reaction was suggested as a homolytic cleavage and recombination of C_1-C_7 bond, which may be of a thermal process accelerated by formation of an anion on the adjacent nitrogen.

Previously[2], we reported that 2-azabicyclo[3.2.0]heptane-3,4-diones (B), the photo-cycloadducts of the dioxopyrroline (A) with olefins, isomerized to the dihydroazatropolones (C) on treatment with NEt_3 or DBU in benzene solution. We now found that 7-substituted derivatives easily epimerize at C_7 on the same treatment, and that this epimerization reaction is faster than the ring opening to the dihydro-azatropolones. The epimerization was observed even for 7,7-disubstituted derivatives.

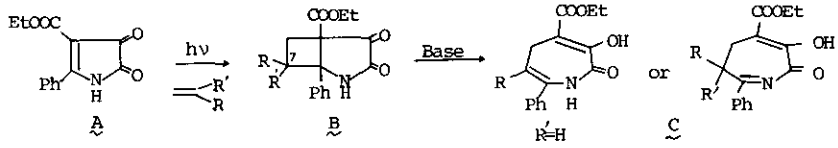


chart 1

Treatment of 7α-acetoxy-7β-methyl-2-azabicyclo[3.2.0]heptane-3,4-dione (1)[3,4], the major photo-cycloadduct of A and isopropenyl acetate, with 10%NEt_3-benzene at 80° for 2 hr gave a 3:5 mixture of 1 and new isomer (2), mp.181-184°.[5] The same treatment of the isomer (2) again gave a mixture of 1 and 2 in ratio of about 1:2. On further treatment, either compound gave the dihydroazatropolone (3), mp.131-134°[5] (40%, after 10 hr). Treatment of either 1 or 2 with DBU furnished 3 (67%, at r.t 40 hr). The above results when corroborated with the IR and NMR spectra of 2

established that it is the 7-epimer of 1, 7β-acetoxy-7α-methyl derivative[4].

The time-dependent product ratio analysis (Fig 1) by the NMR spectra of the reaction mixture from both the isomers clearly indicated that 1 and 2 are in rapid equilibrium which is faster than the formation of the dihydroazatropolone (3), thus excluding the possibility that the epimerization took place by ring closure of 3. Actually, 3 was not affected at all under the same base treatment. Kinetic treatment of the curves with computer simulation[6] gave the rate constants, k's, shown in chart 2, which indicates that the equilibrium constant K between 1 and 2 is 1.54, and that the formation of dihydroazatropolone (3) from 1 is ca. 300 times faster than from 2.

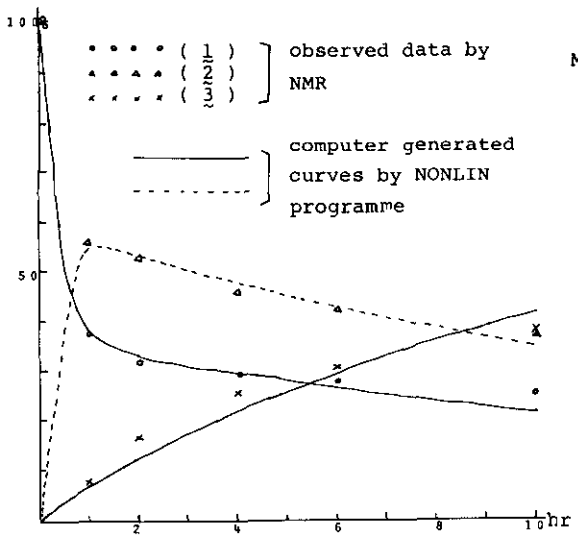
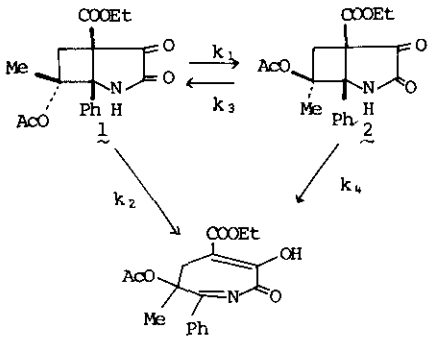


Fig 1 Time-dependent product analysis



k_1 = 1.9 hr^{-1}

k_2 = 0.14 hr^{-1}

k_3 = 1.2 hr^{-1}

k_4 = 0.4×10^{-3} hr^{-1}

chart 2

The same epimerization was also observed for the 7-ethyl-7-methyl derivative (4)[5], which on treatment with 10% NEt_3 in benzene at 80° gave a 1:1 mixture of the stereoisomers 4 and 5 as evidenced from NMR methyl peaks of the reaction mixture (δ 1.07 and 0.98), although chromatographic separation of the two isomers was failed. On prolonged heating, the mixture was gradually deteriorated[7], during which time the ratio of the two epimers was kept almost constant.

Epimerization of 7-monosubstituted derivatives gave further information. When 7-*exo*-phenyl isomer (6)[3], the major photo-adduct of A and styrene, was heated with 10% NEt_3 in benzene at 80° for 1.5 hr, it easily epimerized to give exclusively the 7-*endo*-phenyl isomer (7), mp.193-196°, which was identified with the minor product[3] obtained from photo-cyclization of A and styrene (NMR and IR comparisons).

Apparently there should be a large difference in the thermodynamic stability between the 7-*exo*-isomer (6) and the 7-*endo*-isomer (7) in this case, the severe steric interactions caused by three cis-arranged substituents (Ph, Ph, $COOC_2H_5$) on a cyclobutane ring in the *exo*-isomer (6) making it less stable. Prolonged heating of 6 under the same basic conditions produced the dihydroazatropolone (8) as reported already[2]. Similar base treatment of the 7-*endo*-phenyl isomer (7) directly gave 8. At any stage of this transformation the *exo*-isomer (6) was not detected in the reaction mixture. Time-dependent product ratio analysis from 6 again showed that the epimerization of C_7-substituent took place before ring expansion to the dihydroazatropolone (8).

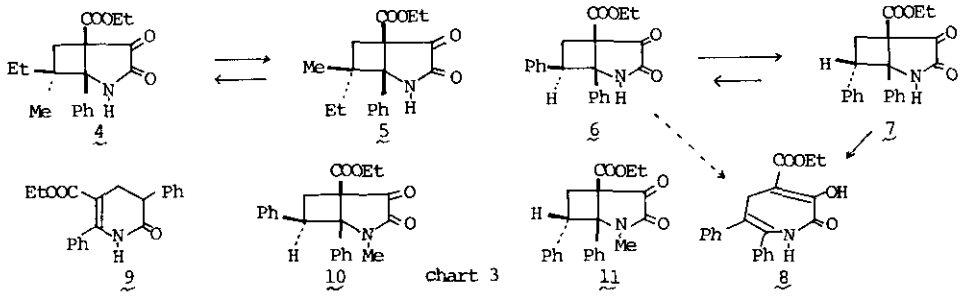


chart 3

The following result suggests that the above epimerization reaction might be of a thermal process. On heating 1 in xylene at 200°(sealed tube) for 2 hr without base, it gave a 1:1 mixture of 1 and 2.

We therefore consider that this epimerization reaction proceeds through homolytic cleavage of the C_1-C_7 bond and its recombination. However, the reaction appears to be accelerated by presence of a base. In fact, 6 was not affected at

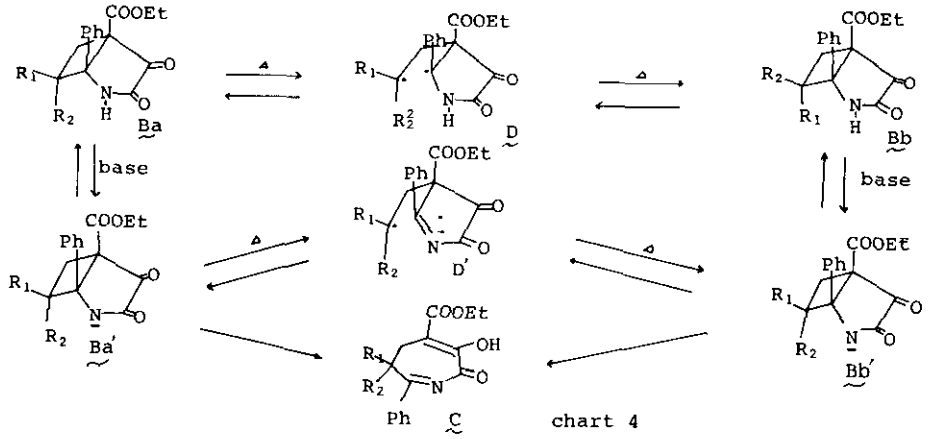


chart 4

all on heating in toluene (120°) or in CH_3CN (80°) for 24 hr without base. Heating of 6 at 200°(2 hr) resulted in dissociation of the compound giving rise to the dioxopyrroline (A), together with the dihydropyridone (9)[8]. Probably formation of an anion on the nitrogen will greatly facilitate the homolytic cleavage of C_1-C_7 bond, which is adjacent to the anion, producing an anion radical (D'). Supporting this consideration, both the isomers of N-methyl derivatives, 10[9] and 11[9] were found to be stable on heating with base (80°). The effect of nitrogen anion in promoting the carbon-carbon bond homolysis is very similar to the weaking effect of oxygen anion on adjacent bond strengths, reported by Evans[10].

References and Notes

1. Dioxopyrrolines XV. Part XIV: Y. Tsuda, Y. Sakai, and T. Sano, Heterocycles, in press.
2. T. Sano, Y. Horiguchi, and Y. Tsuda, Heterocycles, 1979, 12, 1427.
3. T. Sano and Y. Tsuda, Heterocycles, 1976, 4, 1229.
4. The stereochemistry of 1 and 2 at C_7-substituents is discussed in the following paper and established as shown here.
5. Physical data. 2: IR; 1780, 1750, 1730 cm^{-1}. NMR($CDCl_3$); δ 0.60(3H, t, J=7 Hz), 1.50(3H, s, CH_3), 1.73(3H, s, OAc), 2.37(1H, d, J=14 Hz), 3.45(1H, d, J=14 Hz), 3.70(2H, q, J=7 Hz). 3: IR; 1760, 1725, 1665, 1630 cm^{-1}. NMR($CDCl_3$); δ 1.37(3H, t, J=8 Hz), 1.77(3H, s, CH_3), 2.03(3H, s, OAc), 2.77(1H, d, J=18 Hz), 3.33(1H, d, J=18 Hz), 4.37(2H, q, J=8 Hz). 4: prepared by photo-cycloaddition of A and isoprene followed by hydrogenation. mp.119-122°. IR; 1770, 1730, 1690 cm^{-1}. NMR($CDCl_3$); δ 0.57(3H, t, J=7 Hz), 0.90(3H, t, J=7 Hz), 1.07(3H, s, CH_3), 1.1-1.5(2H, m), 1.95(1H, d, J=13 Hz), 2.92(1H, d, J=13 Hz), 4.03(2H, q, J=7 Hz). The stereochemistry is tentative.
6. The authors are indebted to Prof. A. Tsuji, Kanazawa University, for this treatment.
7. The dihydroazatropolone was not produced even on treatment with DBU. The equilibrium of 4 and 5 was only observed.
8. T. Sano, Y. Horiguchi, Y. Tsuda, and Y. Itatani, Heterocycles, 1978, 9, 161. This must be formed by 1,3-shift through the lactim form followed by cheletropic elimination of CO. cf. Y. Tsuda, M. Kaneta, Y. Itatani, T. Sano, Y. Horiguchi, and Y. Iitaka, Heterocycles, 1978, 9, 153.
9. Prepared by photo-cycloaddition of N-methyl-3-ethoxycarbonyl-2-phenyl-Δ^2-pyrroline-4,5-dione and styrene. 10 (major): mp.180-182°. IR; 1763, 1730, 1710, 1600 cm^{-1}. NMR($CDCl_3$); δ 0.73(3H, t, J=7 Hz), 2.63(1H, dd, J=8 Hz, 12 Hz, H-6), 3.30(3H, s, N-CH_3), 3.3-4.0(4H, $COOCH_2CH_3$, H-6, H-7). 11 (minor): mp. 185-187°. IR; 1768, 1730, 1710 cm^{-1}. NMR($CDCl_3$); δ 0.80(3H, t, J=7 Hz), 2.15 (3H, s, N-CH_3), 2.57(1H, dd, J=9 Hz, 14 Hz, H-6), 3.33(1H, dd, J=9 Hz, 14 Hz, H-6), 3.80(2H, qd, J=7 Hz, 2Hz), 4.97(1H, t, J=9 Hz, H-7).
10. D. A. Evans and D. J. Baillargeon, Tetrahedron Lett., 1978, 3319.

Received, 20th November, 1980