THERMAL REACTIONS OF 1,4-BENZOXAZINE DERIVATIVES II[1]

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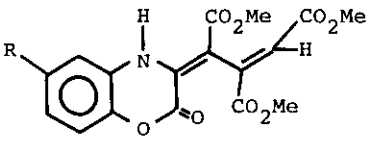
Abstract ——— The pyrolysis or treatment with base of aconitate derivatives (1a-c) afforded expected cyclization products (4a-c) whose structural elucidation was based on spectral data.

Recently, it was reported from our laboratory[1] that pyrolysis of benzoxazine derivative (1a) yielded a novel tricyclic compound (2a) and dimerization compound (3a) whereas did not yield an expected pyrido[2,1-c]-1,4-benzoxazine (4a). We have subsequently investigated this thermal reaction and could obtain the expected pyrido compound (4a) and a new compound (5a) which is assumed to be an intermediate of the formation of 3a. We wish to describe here the results of continued thermal reaction.

A solution of trimethyl 6-chloro-2,3-dihydro-2-oxo-4H-1,4-benzoxazine-$\Delta^{3,\gamma}$-aconitate (1a, R = Cl)[2] in dry DMSO was refluxed under nitrogen for 30 min to be a shorter time than that of the previous pyrolysis. The starting material was still recognized on thin layer chromathography of the reaction mixture.

The residual brownish oil obtained after evaporation of the solvent, was subjected to silica gel column chromatography. Five crystalline compounds other than 1a could be isolated from the reaction mixture. In addition to the compounds (2a and 3a) which were already obtained by previous pyrolysis[1], three new crystalline compounds were obtained. The first product (4a, 11.9 %)[3] of the pyrolysis of 1a has an empirical formula $C_{16}H_{10}NO_7Cl$ which was derived from elemental and mass spectral analyses. This indicates that this compound is a de-MeOH compound of 1a. ^{1}H-NMR spectrum of 4a shows two methyl esters at δ 3.95 (s) and δ 4.00 (s), two aromatic



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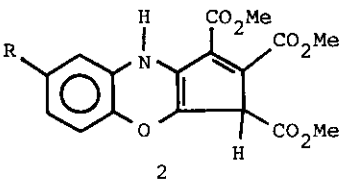

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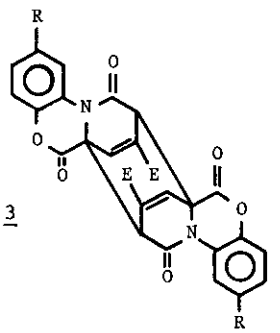

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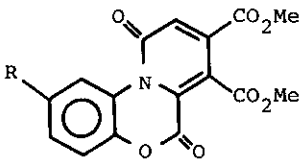

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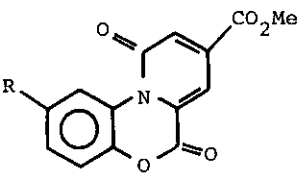

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a : R = Cl

b : R = H

c : R = Me

E = CO_2Me

Chart 1

protons at δ 7.19-7.46 (m) and a vinyl proton at δ 7.61 (s). Moreover, one of aromatic protons at δ 9.28 (d, J = 2.2 Hz) is observed at a very low magnetic field. This low field resonance suggests that this material is the expected intramolecular cyclization compound. Thus, the structure of 4a was assigned to be dimethyl 2-chloro-6,10-dioxopyrido[2,1-c]-1,4-benzoxazine-7,8-dicarboxylate (4a, R = Cl). The second product (5a, 4.1 %)[4] of the pyrolysis mixture was recrystallized from $CHCl_3$ to afford pale yellow needles [5a, mp 176-178°C, $C_{14}H_8NO_5Cl$, MS m/z 305, 307 (M^+)]. This compound has two vinyl protons at δ 7.59 (d) and δ 8.01 (d) which are coupled to each other and the coupling constant is 1.95 Hz. This value is presumed to be a meta coupling value. On the other hand, one aromatic proton [δ 9.51 (d)] resonances at a very low magnetic field. These data suggest that this compound (5a) is a de-methoxycarbonyl compound of 4a, and hence, the structure of 5a was elucidated to be methyl 2-chloro-6,10-dioxopyrido[2,1-c]-1,4-benzoxazine-8-carboxylate (5a, R = Cl). This compound can be estimated to be an intermediate of the formation of dimerization compound (3a) by pyrolysis of 1a. The structure of a small amount (1.9 %) of the last product of the pyrolysis mixture was not clear until now.[5] Compound (1b, R = H)[2] was pyrolyzed in the same manner to that used to 1a and the residue obtained after evaporation of the solvent was subjected to silica gel column chromatography. Only two crystalline compounds could be isolated from the reaction mixture. The deoxygenated compound (2b)[6] was obtained in 69.9 %

yield. Another product (6.1 %) was assigned to be the pyrido compound (4b).[7] When 1c (R = Me)[2] was pyrolyzed in the same manner, 2c and 4c were obtained in 62.4 % and 7.4 % yields, respectively.[8] The results mentioned above shows that the alternative reaction was observed only when chlorine was substituted on aromatic ring. The pyrido[2,1-c]-1,4-benzoxazines (4a-c) were also prepared as the minor products by treatment with Et_3N of 1a-c in CH_2Cl_2 at room temperature.[9]
Next a solution of 4b in DMF was heated under reflux for 7 h to give an almost

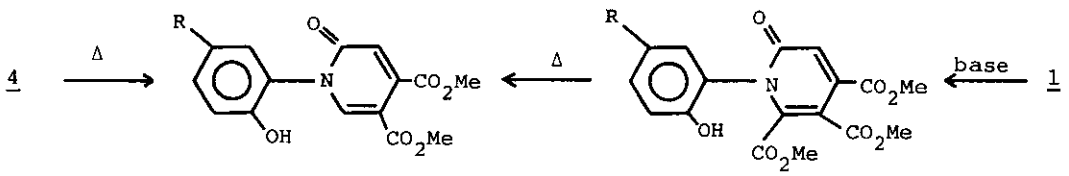
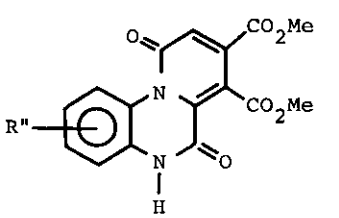


Chart 2

single product on TLC. No desired compounds such as 3b or 5b were obtained and a new product [mp 223-224°C, MS m/z 303 (M^+), $C_{15}H_{13}NO_6$] was obtained in 79.3 % yield. The ^{1}H-NMR spectrum of this compound shows the presence of two methyl esters at δ 3.72 (s) and δ 3.82 (s), two isolated vinyl protons at δ 6.63 (s) and δ 8.15 (s), four aromatic protons at δ 6.80-7.50 (m), and a hydroxy proton at δ 10.19 (s). These results suggest that this material is a ring-opened compound of the starting material (4b). Thus, the structure of this compound was assigned to be dimethyl 1-(o-hydroxyphenyl)-2-pyridone-4,5-dicarboxylate (6b).[10] Compound (6b) was also prepared as the sole product by heating of a solution of 7b in DMF which was prepared as a major product by treatment with base of 1b.[9] In this thermal reaction (reflux in DMF) of other pyrido compounds (8, 9 or 10), the starting materials were completely recovered. In conclusion, it may be noted that only the compound (4) containing benzoxazine ring system in the molecule are extremely sensitive to



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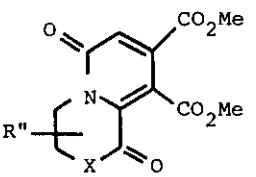

9 X = NH

10 X = O

Chart 3

heating in comparison with other pyrido compounds (8, 9 or 10) and the ring-opening reaction occurred. Furthermore, the lactone structure of 4 is easily opened by several nucleophiles and studies on these reactions are now in progress.

REFERENCES AND NOTES

1) Part I : N. Kawahara, T. Nakajima, T. Itoh, H. Takayanagi, and H. Ogura, Heterocycles, 1984, 22, 1729.
Presented in part at 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, April 3-5, 1985.

2) N. Kawahara, T. Nakajima, T. Itoh, H. Takayanagi, and H. Ogura, Chem. Pharm. Bull., 1984, 32, 1163.

3) 4a: mp 203-204°C; MS m/z 363, 365 (M^+); ^{13}C-NMR ($CDCl_3$) δ 53.46(q), 53.65(q), 118.42(d), 120.07(s), 121.24(d), 122.51(s), 126.84(s), 129.13(d), 130.64(s), 130.79(d), 136.93(s), 139.81(s), 153.01(s), 159.64(s), 162.32(s), 164.90(s).

4) 5a: ^{1}H-NMR ($CDCl_3$) δ 4.00(3H,s,OCH_3), 7.25(1H,d,J=8.11Hz, aromatic), 7.40(1H, dd,J=8.11Hz and J=2.44Hz, aromatic), 7.59(1H,d,J=1.95Hz,=CH-), 8.01(1H,d,J= 1.95Hz,=CH-), 9.51(1H,d,J=2.44Hz, aromatic); ^{13}C-NMR ($CDCl_3$) δ 53.41(q), 111.98 (d), 118.56(d), 121.39(d), 123.09(s), 128.79(d), 128.98(s), 130.26(d), 130.69 (s), 138.29(s), 139.95(s), 154.13(s), 161.01(s), 163.20(s).

5) mp 251-252°C; MS m/z 335, 337 (M^+); ^{1}H-NMR ($CDCl_3$) δ 3.82(3H,s), 3.86(3H,s), 7.48(2H,s), 8.56(2H,s), 8.97(1H,s).

6) 2b: mp 235-238°C; m/z 345 (M^+); ^{1}H-NMR ($CDCl_3$) δ 3.75, 3.79 and 3.83(each 3H,s, 3xOCH_3), 4.60(1H,s,-CH-), 6.80-7.20(4H,m, aromatic), 8.45(1H,br,-NH-); ^{13}C-NMR ($CDCl_3$) δ 49.90(d), 51.36(q), 51.70(q), 52.58(q), 97.85(s), 108.18(s), 115.49(d), 117.54(d), 123.24(d), 124.21(s), 125.04(d), 140.93(s), 144.09(s), 153.50(s), 162.51(s), 165.24(s), 170.31(s).

7) 4b: mp 205-206°C; MS m/z 329 (M^+); ^{1}H-NMR ($CDCl_3$) δ 3.95 and 3.99(each 3H,s, 3xOCH_3), 7.27-7.38(3H,m, aromatic), 7.58(1H,s,=CH-), 9.15(1H,m, aromatic); ^{13}C-NMR ($CDCl_3$) δ 53.41(q), 53.55(q), 117.44(d), 121.19(d), 121.97(s), 125.33(d), 129.13(d), 130.69(d), 136.69(s), 141.17(s), 153.54(s), 159.78(s), 162.46(s), 165.19(s).

8) 2c: mp 242-244°C; MS m/z 359 (M^+); ^{1}H-NMR ($CDCl_3$) δ 2.28(3H,s,C-CH_3), 3.75, 3.77 and 3.81(each 3H,s,3xOCH_3), 4.57(1H,s,-CH-), 6.64-7.10(3H,m, aromatic), 8.37(1H, br,-NH-). 4c: mp 201-202°C; MS m/z 343 (M^+); ^{1}H-NMR ($CDCl_3$) δ 2.42(3H,s,C-CH_3), 3.95 and 4.00(each 3H,s,3xOCH_3), 7.19-7.26(2H,br, aromatic), 7.60(1H,s,=CH-),

8.99(1H,br, aromatic); ^{13}C-NMR ($CDCl_3$) δ 21.44(q), 53.41(q), 53.55(q), 117.05 (d), 119.68(s), 121.14(d), 121.63(s), 127.43(s), 129.76(d), 130.54(d), 135.42 (s), 136.64(s), 139.12(s), 153.69(s), 159.84(s), 162.57(s), 165.24(s).

9) N. Kawahara, T. Nakajima, T. Itoh, and H. Ogura, Synthesis, 1985, in press.

10) 6b: ^{13}C-NMR (DMSO-d_6) δ 52.63(q), 53.21(q), 106.23(s), 116.90(d), 118.61(d), 119.68(d), 127.04(s), 128.65(d), 130.89(d), 144.19(s), 146.29(d), 152.13(s), 160.71(s), 163.59(s), 166.51(s).

11) Satisfactory elemental analyses were obtained for all compounds reported herein.

12) NMR spectra were measured on a JNM-FX100 spectrometer (JEOL) and MS spectra were taken by direct insertion method with 9000B (Shimadzu).

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