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STRUCTURAL ELUCIDATION OF THE PYROLYSIS PRODUCTS OF 1,4-BENZOXAZINE DERIVATIVES[1]

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Abstract —— The thermal reaction of trimethyl 2,3-dihydro-6-chloro-2-oxo-4H-1,4-benzoxazine-$\Delta^{3,\gamma}$-aconitate afforded novel cyclization products. These compounds were characterized by spectral data and X-ray crystallographic analysis.

Recently, we have reported a facile synthesis of pyrido[1,2-a]quinoxalines (3) and pyrido[1,2-a]pyrazines (4) either by the pyrolysis or treatment with base of aconitate derivatives (1 and 2).[2] We have subsequently investigated this efficient intramolecular cyclization reaction with other aconitates (5 and 6)[3] which were easily prepared by the reaction of o-aminophenols and β-aminoalcohols with dimethyl acetylenedicarboxylate (DMAD), respectively. We describe here our results that expected cyclyzation product (7) was obtained either by the pyrolysis or treatment with Et_3N of 5 in good yields but instead of expected product (8), other novel products were obtained by the pyrolysis of 6.

A solution of trimethyl 2,3,5,6-tetrahydro-5,5-dimethyl-2-oxo-4H-1,4-oxazine-$\Delta^{3,\gamma}$-aconitate (5) in dry DMSO was refluxed for 1 h under nitrogen. Extraction of the reaction product with EtOAc followed by evaporation of the solvent provided a brownish oily solid which was purified by preparative TLC on silica gel to afford pure crystals (7, mp 203-205°C) in 69.9% yield.[4] The elemental analysis and the mass spectrum of 7 indicated that this pyrolysis resulted in the elimination of MeOH from 5. ^1H and ^{13}C NMR signals of 7 were very similar to those of previously prepared 4[2] to suggest that this material is similar cyclization product. Thus,

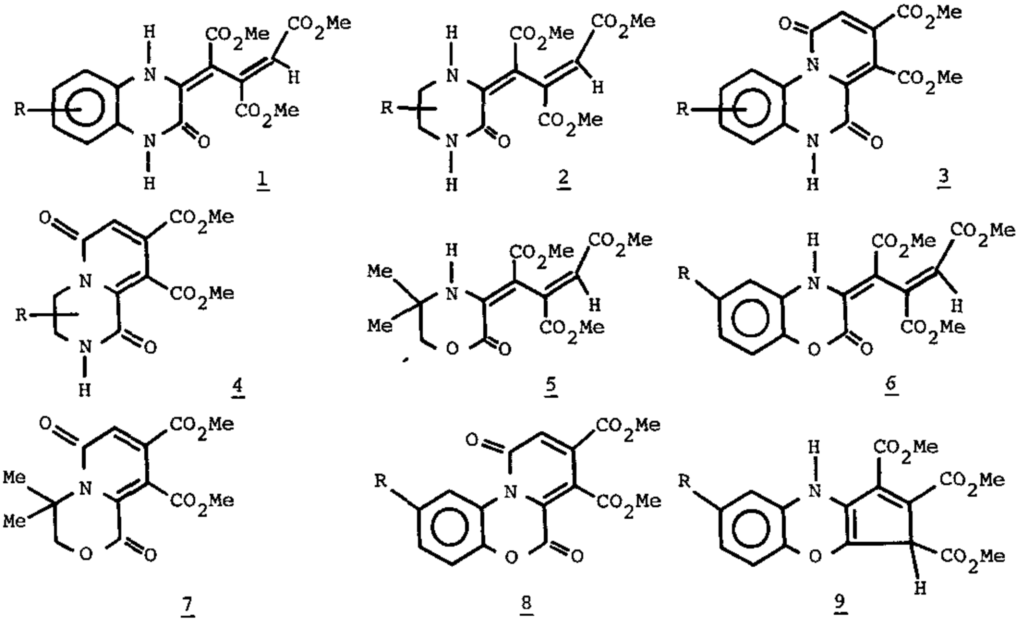


Chart 1

the structure of 7 was assigned to be dimethyl 3,4-dihydro-4,4-dimethylpyrido-[2,1-c]-1,4-oxazine-1,6-dioxo-8,9-dicarboxylate which was an expected product. This compound was also prepared by treatment with Et_3N of 5 in CH_2Cl_2 at room temperature in 84.7% yield.

Trimethyl 2,3-dihydro-6-chloro-2-oxo-4H-1,4-benzoxazine-$\Delta^{3,\gamma}$-aconitate (6, R = Cl) was pyrolysed in the same manner to that used for the preparation of 7 and the residue obtained after evaporation of the solvent was subjected to silica gel column chromatography. Two crystalline compounds could be isolated from the reaction mixture. Neither of them were expected cyclization product (8).

The major product (mp 239-241°C, 38.8% yield)[5] has an empirical formula $C_{17}H_{14}NO_7Cl$ which was derived from elemental and mass spectral analyses. This result shows that this product is a de-oxygen compound of the starting material (6, $C_{17}H_{14}NO_8Cl$). ^1H NMR of this material shows three methyl esters at δ 3.60, 3.68 and 3.70, three aromatic protons at δ 6.89-7.51 and an amino proton at δ 10.09. A vinyl proton signal at δ 6.95 observed in 6 (R = Cl) was disappeared and instead, a signal at δ 4.47 (s, 1H) appears. ^{13}C NMR spectrum has a signal at δ 49.60 which became doublet by single frequency off-resonance mode. These signals (δ 4.47 and δ 49.60) suggest the presence of a methine carbon having a methoxy-carbonyl group. The infrared spectrum displays the absence of absorption at

1769 cm^{-1} existed in 6 (R = Cl) exhibiting no presence of a lactone structure in the molecule. Taking into account the result of the pyrolysis of 5, the pyrolysis of 6 (R = Cl) might be assumed to proceed by the reaction mechanism concerning aromatic ring and side chain cyclized. Thus, the structure of this material was estimated as a novel tricyclic compound; trimethyl 2,3-cyclopenta-1',3'-dieno-6-chloro-1,4-benzoxazine-3',4',5'-tricarboxylate (9, R = Cl). The formation of 9 can be formulated as an electrocyclic reaction accompanying de-oxygen process as shown in chart 2. When 6 (R = H) was pyrolyzed, 9 (R = H) was obtained in 47.9% yield.

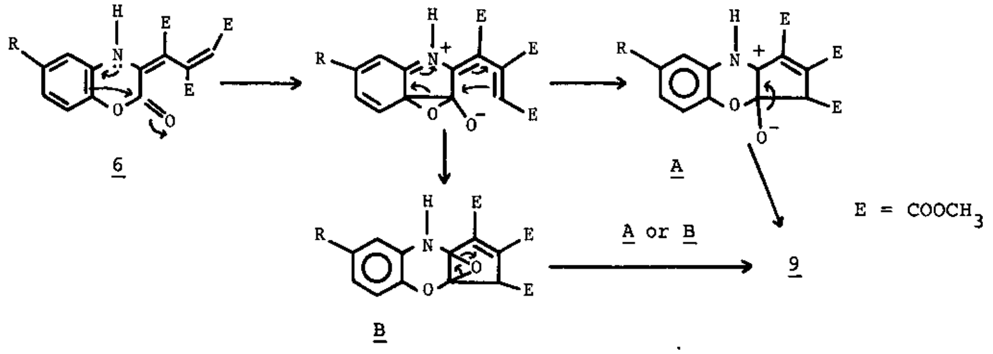


Chart 2

A small amount (3.44%) of the second product of the pyrolysis mixture was obtained as colourless fine prisms [10, mp 178°C, MS m/e = 305,307($\frac{M^+}{2}$)]. A novel structure of this compound was unequivocally determined by a crystallographic study. The crystal of 10 is a monoclinic (a = 8.5490Å, b = 9.3740Å, c = 7.6670Å, V = 613.61Å^3, Z = 1, α = 88.630°, β = 91.070°, γ = 92.400°, space group P$\bar{1}$). The reflexion data were collected on a Rigaku four-circle diffractometer using graphite monochromated Cu K radiation. Those reflexions having an intensity exceeding 3 tines of the corresponding standard deviations were collected, and 1724 reflexions out of 1984 reflexions were used as data. The structure was solved by the heavy-atom (Cl) method and refined by the block-diagonal least-squares method to a final R value

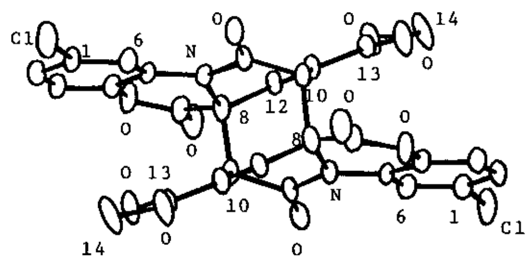
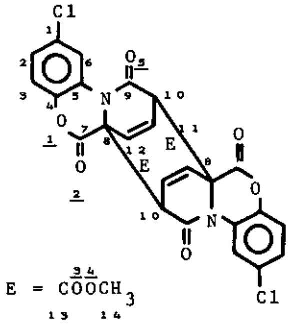


Fig. 1 The molecular structure of 10



of 0.074. In Fig. 1, the molecular structure of 10 and the atomic numbering system are shown. The bond lengths are shown in Table 1.

Table 1 *Bond lengths and their standard deviations in the parenthesis*

C(1) -Cl(1)=1.738(4)	C(5) - N(1)=1.429(5)	C(9) - N(1)=1.401(5)
C(1) - C(2)=1.375(6)	C(7) - C(8)=1.526(5)	C(9) - O(5)=1.201(5)
C(1) - C(6)=1.396(6)	C(7) - O(1)=1.344(5)	C(10)-C(11)=1.500(5)
C(2) - C(3)=1.378(6)	C(7) - O(2)=1.183(5)	C(11)-C(12)=1.330(6)
C(3) - C(4)=1.384(6)	C(8) -C(12)=1.529(6)	C(11)-C(13)=1.500(6)
C(4) - C(5)=1.381(5)	C(8) - N(1)=1.473(5)	C(13)- O(3)=1.200(5)
C(4) - O(1)=1.391(5)	*C(8) -C(10)=1.630(6)	C(13)- O(4)=1.318(5)
C(5) - C(6)=1.392(5)	C(9) -C(10)=1.530(5)	C(14)- O(4)=1.460(7)

* The bond length of C(8)-C(10) is longer than other C-C bond length to indicate that this bond is a connective part of the dimer.

The mechanism of the formation of this dimerization product is not clear until now. In conclusion, it was found that the pyrolysis or treatment with base of 5 afforded an expected material (7) in good yields but the pyrolysis of 6 (R = H, Cl) containing aromatic ring afforded unexpected reaction products whose structures were assigned to be 9 (R = H, Cl) and 10 (obtained only when R = Cl) by spectral data and X-ray analysis. The study of the unexpected results given by treatment with base of 6 is now in progress.

REFERENCES AND NOTES

1. Presented in part at 103th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 4-6, 1983.
2. N. Kawahara, T. Nakajima, T. Itoh and H. Ogura, Heterocycles, 1983, **20**, 1721.
3. N. Kawahara, T. Nakajima, T. Itoh H. Takayanagi and H. Ogura, Chem. Pharm. Bull., 1984, **32**, 1163.
4. 7: mp 203-205°C; MS m/e = 309(M^+); ^1H NMR(DMSO-d_6) δ 1.59(s,6H,C-CH_3),3.73(s,3H,O-CH_3),3.82(s,3H,O-CH_3),4.51(s,2H,-CH_2-),7.09(s,1H,=CH-).
5. 9 (R = Cl): MS m/e = 379,381(M^+); ^1H NMR(DMSO-d_6) δ 3.60(s,3H,O-CH_3),3.68(s,3H,O-CH_3),3.70(s,3H,O-CH_3),4.47(s,1H,-CH-),6.89-6.98(d,1H,aromatic),7.48-7.51(s,1H,aromatic),10.09(br,1H,-NH); ^{13}C NMR(DMSO-d_6) δ 49.61(d),51.02(q),51.51(q),52.14(q),98.53(s),107.64(s),116.22(d),117.93(d),122.19(d),126.45(s),128.45(s),138.88(s),141.65(s),152.87(s),161.59(s),163.34(s),169.58(s).
6. 9 (R = H): mp 235-238°C; MS m/e = 345(M^+); ^1H NMR($CDCl_3$) δ 3.75,3.79 and 3.83 (each s,9H,O-CH_3x3),4.60(s,1H,-CH-),6.80-7.20(m,4H,aromatic),8.45(br,1H,-NH).
7. *All the new compounds reported herein gave satisfactory elemental analyses.*

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