Communications to the Editor

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RING TRANSFORMATION OF AN ISOXAZOLINE-1-OXIDE. A NOVEL TRANSFORMATION PRODUCT, DIMETHYL 7-CHLORO-3a,4-DIHYDRO-5aH-BENZOFURO[3,3a-d]ISOXAZOLE-3,4-DICARBOXYLATE [1)]

Shonosuke Zen,*,[a] Kiyobumi Takahashi,[a] Eisuke Kaji,[a] Hikaru Nakamura,[b] and Yoichi Iitaka[b]

School of Pharmaceutical Sciences, Kitasato University,[a] Shirokane, Minato-ku, Tokyo 108, Japan and Faculty of Pharmaceutical Sciences, Tokyo University,[b] Hongo, Bunkyo-ku, Tokyo 113, Japan

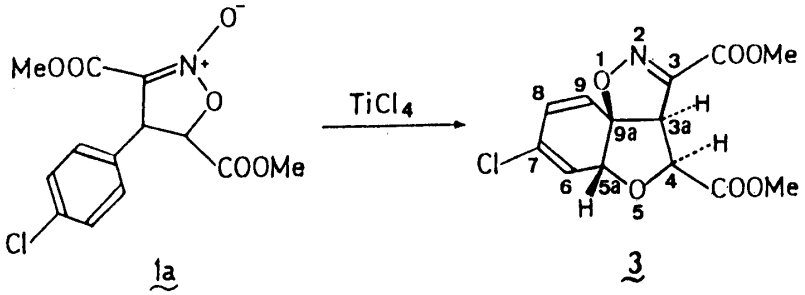
4-p-Chlorophenyl-3,5-bis(methoxycarbonyl)isoxazoline-1-oxide reacted with excess titanium tetrachloride in dichloromethane to yield a novel fused heterocycle, dimethyl 7-chloro-3a,4-dihydro-5aH-benzofuro-[3,3a-d]isoxazole-3,4-dicarboxylate in good yield. The result of this structural determination by single crystal X-ray analysis is reported.

KEYWORDS——isoxazoline-1-oxide; 3a,4-dihydro-5aH-benzofuro-[3,3a-d]isoxazole; titanium tetrachloride; ring transformation; X-ray analysis

We are currently interested in studying the reactivity of isoxazoline-1-oxide, a cyclic nitronic ester corresponding to the lactone in the carboxylic acid series. In our previous paper,[2)] 3,5-bis(methoxycarbonyl)-4-phenylisoxazoline-1-oxide[3)] (1) was transformed into methyl α-hydroxy-2-methoxycarbonyl-3H-indole-1-oxide-3-acetate (2) by the reaction with boron trifluoride etherate.

We wish to report here a new type of ring transformation of 4-p-chlorophenyl-3,5-bis(methoxycarbonyl)isoxazoline-1-oxide[4)] (1a) into 7-chloro-3a,4-dihydro-5aH-benzofuro[3,3a-d]isoxazole-3,4-dicarboxylate (3) by action of titanium tetrachloride as shown in Chart-1. Compound 3 was obtained as follows: 1a was reacted with four-fold excess of titanium tetrachloride in dichloromethane at 0°C for 30 min. The reaction mixture was quenched with 10% aqueous sodium carbonate and extracted with

chloroform. The products[5] were isolated by column chromatography on silica gel (chloroform/ethyl acetate 4:1) in the usual way. The compound 3 was given as colorless needles, mp 107-108°C (ether) in 81% yield. IR νmax cm^{-1} (KBr): 1750 and 1710 (ester C=O), 1590 (C=N). ^{1}H-NMR (δ in $CDCl_3$, 100 MHz): 3.71 and 3.85 (each 3H,s,ester Me), 4.21 (1H,d,H-3a,$J_{3a,4}$=7 Hz), 4.68 (1H,d,H-4,$J_{4,3a}$=7 Hz), 5.29 (1H,m,H-5a), 5.98 (3H,m,H-6,8,9). ^{13}C-NMR (δ in $CDCl_3$, 67.8 MHz): 52.5 and 52.8 (q,ester Me), 63.5 (d,C-3a), 78.1 (d,C-4), 84.4 (d,C-5a), 96.6 (s,C-9a), 121.5, 126.4, and 128.0 (each d,C-6,8,9), 130.7 (s,C-7), 149.4 (s,C-3), 160.3 (s, 3-ester C=O), 168.5 (s,5-ester C=O). UV λmax (in MeOH) nm (log ε): 222 (3.76), 246 (3.82). MS (m/z): 313 and 315 (M^+). Anal. Calcd for $C_{13}H_{12}NO_6Cl$: C, 49.77; H, 3.86; N, 4.46; Cl, 11.30. Found: C, 49.47; H, 3.82; N, 4.38; Cl, 11.54. and the corresponding diamide[6] of 3 prepared with NH_3/NH_4Cl, mp 292°C (dec.) (DMSO/ chloroform) in 86% yield.



1a 3

Chart 1

The structural determination of 3 by single crystal X-ray analysis resulted as follows: A crystal of approximate dimensions of 0.3 X 0.12 X 0.03 mm was mounted on the philips PW 1100 diffractometer. The unit cell parameters and the intensity data were collected by graphite monochromated CuKα radiation. Crystal data were: Dimethyl 7-chloro-3a,4-dihydro-5aH-benzofuro[3,3a-d]isoxazole-3,4-dicarboxylate, $C_{13}H_{12}NO_6Cl$ MW=313.7. Triclinic, space group $P\bar{1}$, Z=2, D_{cal}=1.532 gcm^{-3}, μ for CuKα= 27.8 cm^{-1}.

a=10.633(5), b=12.349(6), c=5.807(3) Å,

α=87.91(5), ß=102.36(5), γ=113.80(6)°, V=680.4 $Å^3$.

Of the total of 2939 reflections within the 2θ range of 6° through 156°, 2208 were measured as above the 2σ(I) level and were used for the structure determination. Approximate atomic coordinates were obtained by the direct method using MULTAN program[7] and subsequently they were refined by the block-diagonal-matrix least-squares method. The final R value was 0.054 including all the twelve hydrogen atoms.[8]

Fig.1 shows the stereo-structure of the molecule drawn by ORTEP program.[9] The numbering of the atoms is illustrated in Fig.2. It is seen that the isoxazole ring adopts a planar conformation and the carboxymethyl group is nearly coplanar with the ring. This is due to the conjugation of the two double bonds, C(3)=N(2) and C(10)=O(11) with C(3)-C(10). The oxolane ring, on the other hand, takes a distorted envelope conformation with the flag-pole atom at O(5), and the carboxymethyl group is attached to C(4) in equatorial direction with the carboxyl plane perpendicular to C(3a)-C(4)-O(5) plane. Therefore, the structure of 3 is represented as Fig. 2.

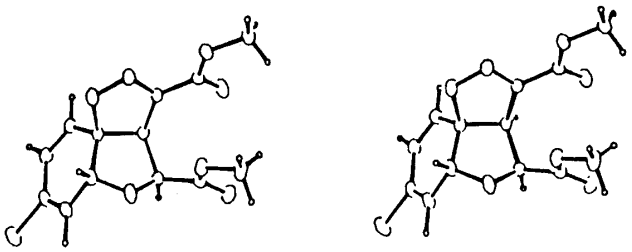


Fig. 1. Stereoscopic View of 3

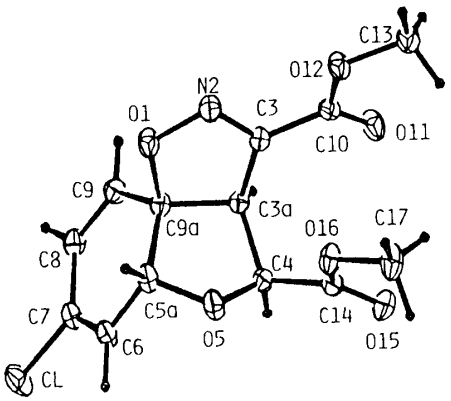


Fig. 2. A Perspective Drawing of 3 and Numbering of Atoms

A further detailed study and also a reaction mechanism on the ring transformation are now in progress.

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REFERENCES AND NOTES

1) Part II of a series of publications titled "Synthetic Reactions of Isoxazoline-1-oxide." Presented at the 15th Congress of Heterocyclic Chemistry, Sendai 1982: The Abstract p. 17; Heterocycles, 20, 119 (1983), (Part I: Ref. 2).

2) E. Kaji and S. Zen, Heterocycles, 13, 187 (1979).

3) E. Kaji and S. Zen, Chem. Pharm. Bull. 28, 479 (1980).

4) Mp. 147-147.5°C (methanol) colorless needles; IR (KBr) cm^{-1}: 1730 (ester C=O), 1625 (C=N), ^{1}H-NMR (δ in $CDCl_3$, 100 MHz): 3.78 and 3.92 (each 3H,s,ester Me), 4.87 (1H,d,H-4), 4.95 (1H,d,H-5), 7.28 (4H,m,C_6H_4), MS (m/z): 313 and 315 (M^+), Anal. Calcd for $C_{13}H_{12}NO_6Cl$: C, 49.78; H, 3.86; N, 4.66; Cl, 11.30. Found: C, 49.70; H, 3.75; N, 4.21; Cl, 11.21. ; prepared analogously by the method of Ref. 3.

5) From these, the corresponding 2a was also isolated as yellow syrup as a by-product in 8% yield. 2a: methyl α-hydroxy-6-chloro-2-methoxycarbonyl-3H-indole-1-oxide-3-acetate; MS (m/z): 313 and 315 (M^+), 296 and 298 (M^+-17); and the corresponding p-nitrobenzoyl derivative (2a'): mp. 68-70°C (dec.) (ether/petroleum ether); ^{1}H-NMR (δ in $CDCl_3$, 100 MHz): 3.77 and 3.90 (each 3H,s,ester ester Me), 4.73 (1H,d,$J_{3,\alpha}$=3 Hz,H-3), 5.19 (1H,d,$J_{3,\alpha}$=3 Hz,H-α), 7.18 (3H,m, H-4,5,7), 8.06 and 8.24 (each 2H,d,J=9 Hz,C_6H_4), MS (m/z): 462 and 464 (M^+), Anal. Calcd for $C_{20}H_{15}N_2O_9Cl$: C, 51.91; H, 3.27; N, 6.05; Cl, 7.66. Found: C, 52.21; H, 3.53; N, 5.73; Cl, 8.01.

6) IR νmax (KBr) cm^{-1}: 3380 (NH), 1675 (amide C=O), Anal. Calcd for $C_{11}H_{10}N_3O_4Cl$: C, 46.58; H, 3.55; N, 14.81; Cl, 12.50. Found: C, 46.77; H, 3.41; N, 14.52; Cl, 12.70.

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8) The list of Fo and Fc may be obtained from the author (H. N.) upon request.

9) C. K. Johnson, ORTEP. Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenessee, U.S.A. (1970).

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