Bull. Chem. Soc. Jpn., 70, 2777—2780 (1997)

Ring Expansion and Ring Contraction Observed in Isopropenyldihydrofuran Derivatives

Seiji Yamaguchi,* Yoshihiko Sugioka, Yuzoh Kitagawa, Yoshinori Matsumoto, Hajime Yokoyama, and Yoshiro Hirai

Department of Chemistry, Faculty of Science, Toyama University, Gofuku 3190, Toyama 930

(Received June 6, 1997)

An intramolecular anhydride formation in 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylic acid caused a new ring expansion to give 4,7-dihydro-6-methyloxepin-2,3-dicarboxylic anhydride (**2b**). An aminolysis of **2b** with benzylamine gave a mixture of two isomeric carboxamides, *N*-benzyl-4,7-dihydro-6-methyloxepin-2-carboxamide and *trans*-1-(benzyloxamoyl)-2-isopropenylcyclopropane. Also, the ring expansion and ring contraction are discussed.

During the course of our studies concerning naturally occurring 2-isopropenyl-2,3-dihydrobenzofuran and 2,5-dihydro-3-methyl-1-benzoxepin derivatives, diethyl 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylate (**1a**)[1] and 4,7-dihydro-6-methyloxepin-3-carbaldehyde (**2a**)[2] were prepared by cyclization of diethyl α-oxosuccinate or dimethyl malonate with (*E*)-1,4-dibromo-2-methyl-2-butene (Chart 1). In this paper we discuss a new ring expansion and a subsequent ring contraction, observed there.

An intramolecular anhydride conversion of five-membered 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylic acid (**1b**),[1] prepared from **1a**, was attempted by refluxing with acetic anhydride and a crystalline anhydride **2b**, mp 84—85 °C, was obtained as the product (Chart 2). The crystalline product **2b** showed the usual properties of intramolecular anhydrides, showing no reaction with an ethereal solution of diazomethane, being insoluble in cold water, being soluble in an aqueous solution of sodium hydrogencarbonate, and being recoverable by acidification of the resulting solution. Furthermore, the mass spectrum showed a molecular ion at *m/z* 180, and the IR spectrum showed two carbonyl bands at 1760 and 1850 cm^{-1}. However, the ^1H NMR spectrum showed no ABX pattern typical of five-membered 2-isopropenyl-2,3-dihydrofuran derivatives,[1] and showed a new pattern similar to seven-membered 4,7-dihydro-6-methyloxepin-3-carbonyl derivatives.[2] Thus, the structure of the anhydride **2b** was assigned to seven-membered 4,7-dihydro-6-methyloxepin-2,3-dicarboxylic anhydride.

The ring expansion observed here might be explained as follows. The anhydride conversion of **1b** once might give unstable five-membered 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylic anhydride (**1c**), which was immediately converted to seven-membered oxepindicarboxylic anhydride **2b**, via **A**, to release the ring strain.[3] The expansions with acetic anhydride were studied under several conditions; the results are summarized in Table 1. No ring expansion was observed at room temperature, and some ring expansions were observed at the refluxing temperature. The thermal decomposition of **2b** might be implied, because a longer refluxing reduced the yield. The thermal stability of **2b** was studied based on the ^1H NMR spectra. In heating DMSO-d_6 solutions of **2b** at several temperatures, the intensity of the

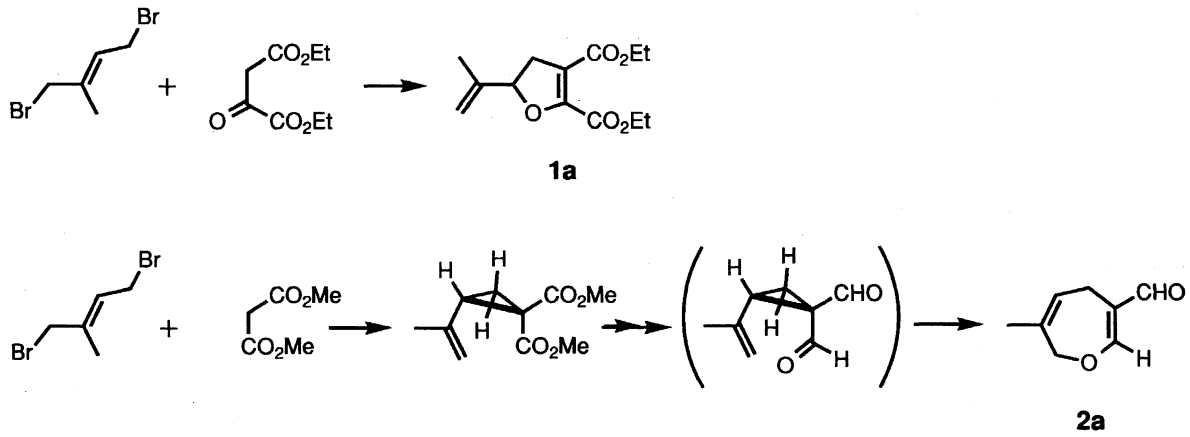

Chart 1.

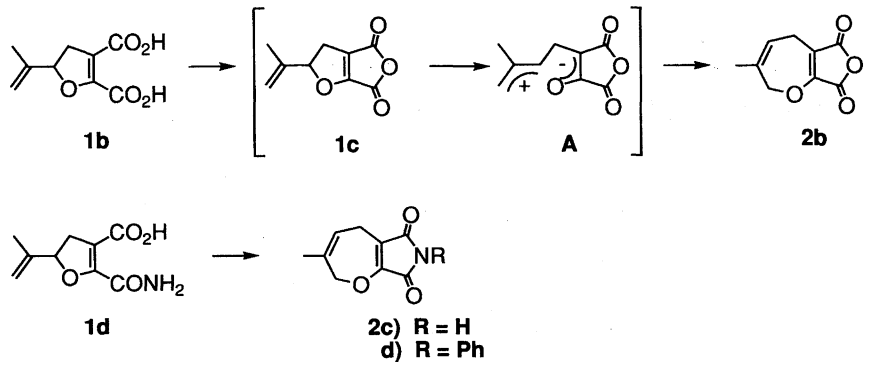

Chart 2.

Table 1. Ring Expansions of **1b** with Acetic Anhydride or Thionyl Chloride

Reagent	Reaction temperature	Reaction time	Yield of **2b**
		h	%
Excess acetic anhydride	Room temperature	24	0
Excess acetic anhydride	Refluxing temperature	1.5	22
Excess acetic anhydride	Refluxing temperature	3	22
Excess acetic anhydride	Refluxing temperature	6	Trace
Excess acetic anhydride	75 °C	10	47
Excess thionyl chloride	Room temperature	24	11
Excess thionyl chloride	Refluxing temperature	1	15
2 Mol equiv thionyl chloride in dry benzene	Refluxing temperature	24	11
2 Mol equiv thionyl chloride in dry pyridine	Room temperature	24	0

signals was followed at regular time intervals; the results are summarized in Table 2. Oxepindicarboxylic anhydride **2b** was almost stable under 75 °C. The conversion was then performed at 75 °C, and the best yield of 47% was obtained after 10 h. A similar anhydride conversion of **1b** with thionyl chloride also gave **2b**; these are also summarized in Table 1. A ring expansion with thionyl chloride was observed even at room temperature, showing that thionyl chloride is more reactive than acetic anhydride. However, in every ring expansion with thionyl chloride, the yields of **2b** were very low, and also the use of pyridine was unsuccessful. These results might show that product **2b** was reactive with hydrogen chloride gas and pyridine. An intramolecular imide formation of 2-carbamoyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylic acid **1d**[1] by treating with thionyl chloride also gave a corresponding seven-membered 4,7-dihydro-6-methyloxepin-2,3-dicarboximide (**2c**).

In our previous paper,[1] ammonolysis and some aminolyses of diethyl 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylate **1a** were discussed. Thus, a similar ammonolysis and some aminolyses of **2b** were studied. Although an ammonolysis of **2b** by bubbling anhydrous ammonia gas into the benzene solution once formed colorless precipitates, the precipitates regenerated the starting **2b** by acidification.[4] An aminolysis of **2b** with benzylamine in refluxing benzene gave a mixture of two isomeric carboxamide, a crystalline carboxamide **2e**, mp 88—89.5 °C, and an oily carboxamide **3a** (Chart 3). Both carboxamides showed NH bands at 3345 cm^{-1} (**2e**) and 3370 cm^{-1} (**3a**) in the IR spectra, and, in the mass spectra, both molecular ions (*m/z* 243) suggested decarboxylation. In the ^1H NMR spectrum, the crystalline carboxamide **2e** showed a similar pattern to oxepindicarboxylic anhydride **2b**, but also showed a new triplet ($J = 5$ Hz) at 6.2 ppm assigned to a new olefinic 3-H. The structure of **2e** was thus assigned to *N*-benzyl-4,7-dihydro-6-methyloxepin-2-carboxamide. The ^1H NMR spectrum of the oily carboxamide **3a** showed a quite different pattern from the original, but was similar to a pattern typical to isopropenylcyclopropane derivatives;[2] the coupling constant (4 Hz) in $J_{1,2}$ suggested the trans configuration.[5] The structure of **3a** was assigned to *trans*-1-(benzyloxamoyl)-2-isopropenylcyclopropane.

Table 2. Residual ^1H NMR Signals of the DMSO-d_6 Solution of **2b**

Temperature/°C	0 h[a]	1 h	3 h	5 h
60	100%	95%	90%	85%
75	100%	90%	70%	45%
90	100%	50%	5%	0%
105	100%	5%	0%	—

a) Standard intensities.

The ring contraction might be explained as follows. A nucleophilic attack of benzylamine occurred preferentially on the 2-carbonyl group to give 2-(benzylcarbamoyl)-4,7-dihydro-6-methyloxepin-3-carboxylic acid **2f**, because the 3-carbonyl group was deactivated by conjugation with the lone-paired electrons on a furan ring oxygen through a C=C

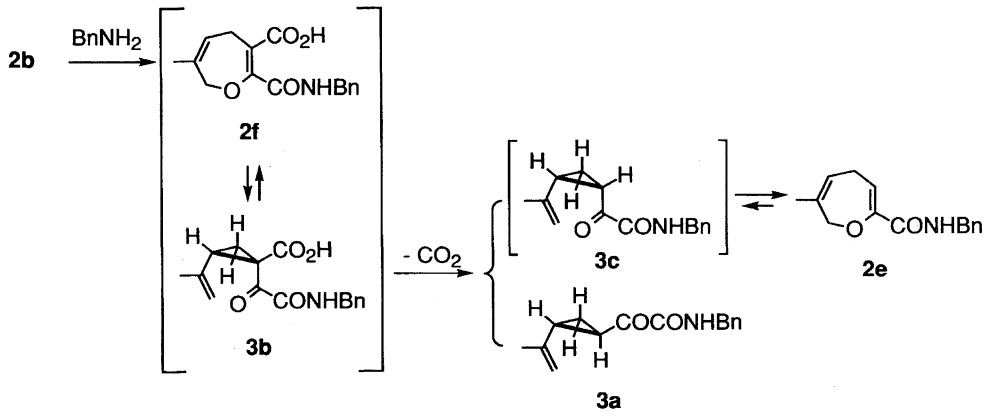

Chart 3.

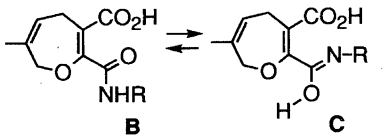

Chart 4.

bond.[1] The resulting 2-(benzylcarbamoyl) 3-carboxylic acid **2f** might be interconverted 1-(benzyloxamoyl)-*t*-2-isopropenylcyclopropane-*r*-1-carboxylic acid **3b**. The β-oxo carboxylic acid **3b** was decarboxylated to give a mixture of two isomeric 1-(benzyloxamoyl)-2-isopropenyl-cyclopropanes, **3a** and **3c**. The *cis* isomer **3c** was converted to the corresponding seven-membered **2c** to reduce the dipole repulsion of α-dicarbonyls; the *trans* isomer **3a** might remain. Aminolysis of **2b** with aniline was studied similarly, but interestingly showed neither decarboxylation nor ring contraction, and gave seven-membered 4,7-dihydro-6-methyl-*N*-phenyloxepin-2,3-dicarboximide **2d**. The reason why aminolysis with aniline caused neither decarboxylation nor ring contraction remains to be studied (Chart 4).[6]

Experimental

The melting points were measured on a Yanagimoto Micro Melting Point Apparatus, and are uncorrected. Infra-red spectra were recorded on a JASCO WS/IR-7300 spectrometer in liquid films or KBr disks. ^{1}H NMR spectra were recorded on a JEOL PMX-60Si, FX-90Q, or JNM A400 NMR spectrometer in $CDCl_3$ solutions, and abbreviated for multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; dq, double quartet; td, triple doublet; qt, quadruple triplet; ddd, double double doublet; br, broad. Mass spectra were measured on a JEOL JMS-OISG-2 mass spectrometer.

Conversion of 5-Isopropenyl-4,5-dihydrofuran-2,3-dicarboxylic Acid (1b) to 4,7-Dihydro-6-methyloxepin-2,3-dicarboxylic Anhydride (2b). With Acetic Anhydride: 5-Isopropenyl-4,5-dihydrofuran-2,3-dicarboxylic acid (**1b**)[1] (1.5 g, 7.7 mmol). was treated with acetic anhydride (500 ml) at 75 °C for 10 h. Under cooling, the mixture was concentrated under reduced pressure, and the residual oil was diluted with ether. After the formed dark precipitates were removed by filtration, the filtrate was concentrated again under reduced pressure. The residue was chromatographed on a silica-gel column, and the fractions eluted with benzene were crystallized in ether- hexane to give 4,7-dihydro-6-methyloxepin-2,3-dicarboxylic anhydride (**2b**), mp 84—85 °C, as colorless crystals.

2b; IR 1850 and 1760 cm^{-1} (CO). ^{1}H NMR δ = 1.9 (3H, br s, 6-Me), 3.2 (2H, br d, J = 6 Hz, 4-H), 4.8 (2H, s, 7-H), 6.0 (1H, br t, J = 6 Hz, 5-H). MS *m/z* 180 (M^+). Found: C, 59.87; H, 4.48%. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48%. Similar conversions of **1b** with acetic anhydride were also studied under several different conditions; the results are summarized in Table 1.

With Thionyl Chloride: 5-Isopropenyl-4,5-dihydrofuran-2,3-dicarboxylic acid (**1b**) (0.97 g, 4.9 mmol) was treated with thionyl chloride (50 g) and the mixture was refluxed for 1 h. Under cooling, the mixture was concentrated under reduced pressure, and the residual oil was treated with cold water and extracted with ether. After the formed dark precipitates were removed by filtration, the ethereal filtrate was washed with a saturated aqueous solution of sodium chloride. After removing the ether under reduced pressure, the residue was chromatographed on a silica-gel column. The fractions eluted with benzene gave **2b** by crystallization.

Similar conversions of **1b** with thionyl chloride were also studied under several different conditions; the results are summarized in Table 1.

Conversion of 2-Carbamoyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylic Acid (1d) to 4,7-Dihydro-6-methyloxepin-2,3-dicarboximide (2c). 2-Carbamoyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylic acid (**1c**)[1] (420 mg, 2.1 mmol) was treated with thionyl chloride (10 g), and the mixture was stirred for 30 min. The mixture was concentrated under reduced pressure, and the residual oil was diluted with benzene. The benzene solution was washed with a saturated aqueous solution of sodium hydrogencarbonate. After removing the benzene under reduced pressure, the residue was chromatographed on a silica-gel column. The fractions eluted with benzene–chloroform (8 : 2) gave **2c** (190 mg, 50%), mp 131—132 °C, as colorless crystals.

2c; IR 3230 (NH), 1780, and 1730 cm^{-1} (CO). ^{1}H NMR δ = 1.9 (3H, q, J = 2 Hz, 6-Me), 3.1 (2H, dq, J = 6 and 2 Hz, 4-H), 4.8 (2H, s, 7-H), 6.0 (1H, td, J = 6 and 2 Hz, 5-H), 7.0 (1H, br s, NH). MS *m/z* 179 (M^+), 136 (M^+−CHNO). High MS Found: M^+, *m/z* 179.0598. Calcd for $C_9H_9NO_3$: M, 179.0583.

Aminolysis of Oxepindicarboxylic Anhydride 2b with Benzylamine. To a solutionon of **2b** (0.80 g, 4.4 mmol) in dry benzene (30 ml) was added benzylamine (2.1 g, 20 mmol), and the mixture was refluxed for 1 h. After cooling, the mixture was diluted with ether and the ether layer was washed with 1% hydrochloric acid and a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. After removing the ether, the oily residue was chromatographed on a silica-gel column. The fractions eluted with benzene gave *trans*-1-(benzyloxamoyl)-2-isopropenylcyclopropane (**3a**) (0.18 g, 17%) as an oil. The fractions eluted with benzene–chloroform was crystallized from ether–hexane to give *N*-

benzyl-4,7-dihydro-6-methyloxepin-2-carboxamide (**2e**) (0.10 g, 9.4%), mp 88—89.5 °C, as colorless crystals.

3a; IR 3370 (NH) and 1680 cm^{-1} (CONH). ^1H NMR $\delta = 1.40$ (1H, ddd, $J = 4$, 7, and 8 Hz, 3-H_A), 1.50 (1H, ddd, $J = 4$, 5, and 8 Hz, 3-H_B), 1.68 (3H, br s, Me), 2.15 (1H, ddd, $J = 4$, 7, and 8 Hz, 2-H), 3.20 (1H, ddd, $J = 4$, 5, and 8 Hz, 1-H), 4.50 (2H, d, $J = 6$ Hz, CH_2Ph), 4.85 (2H, br s, $-C{=}CH_2$), 7.30 (5H, s, –Ph). MS *m/z* 243 (M^+). High MS Found: M^+, *m/z* 243.1258. Calcd for $C_{15}H_{17}NO_2$: M, 243.1260.

2e; IR 3345 (NH) and 1645 cm^{-1} (CONH). ^1H NMR $\delta = 1.75$ (3H, br s, 6-Me), 3.00 (2H, br t, $J = 5$ Hz, 4-H), 4.45 (2H, s, 7-H), 4.50 (1H, d, $J = 6$ Hz, CH_2Ph), 5.60 (H, br t, $J = 5$ Hz, 5-H), 6.20 (1H, t, $J = 5$ Hz, 3-H), 7.00 (1H, br t, $J = 6$ Hz, NH), 7.30 (5H, s, –Ph). MS *m/z* 243 (M^+). High MS Found: M^+, *m/z* 243.1248. Calcd for $C_{15}H_{17}NO_2$: M, 243.1260.

Aminolysis of Oxepindicarboxylic Anhydride 2b with Aniline. To a solutionon of **2b** (589 mg, 3.26 mmol) in dry benzene (30 ml) was added aniline (1.62 g, 17.4 mmol), and the mixture was refluxed for 1 h. After cooling, the mixture was diluted with benzene and the benzene layer was washed with 1% hydrochloric acid and a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. After removing the benzene, the oily residue was chromatographed on a silica-gel column. The fractions eluted with benzene was crystallized from ether–hexane to give 4,7-dihydro-6-methyl-*N*-phenyloxepin-2,3-dicarboximide (**2d**) (54 mg, 7%), mp 124.5—125.5 °C, as colorless crystals.

2d; IR 1770 and 1700 cm^{-1} (CO). ^1H NMR $\delta = 1.9$ (3H, q, $J = 2$ Hz, 6-Me), 3.2 (2H, dq, $J = 6$ and 2 Hz, 4-H), 4.8 (2H, s, 7-H), 6.0 (H, qt, $J = 2$ and 6 Hz, 5-H), 7.4 (5H, br s, –Ph). MS *m/z* 255 (M^+), 227 ($M^+ - CO$). High MS Found: M^+, *m/z* 255.0890. Calcd for $C_{15}H_{13}NO_3$: M, 255.0893.

References

1) S. Yamaguchi, Y. Sugioka, M. Ishida, H. Yokoyama, and Y. Hirai, *J. Heterocycl. Chem.*, **34**, in press (1997).

2) S. Yamaguchi, A. Arisawa, N. Katoh, H. Yokoyama, and Y. Hirai, *Bull. Chem. Soc. Jpn.*, **70**, 2215 (1997).

3) The ring strain had been implied in our previous studies;[1] aminolysis of diethyl ester **1a** with benzylamine gave the corresponding dicarboxamide instead of the corresponding cyclic imide. This might be due to the strain of bicyclo[3.3.0]oct-4(8)-ene ring systems.

4) The precipitates were insoluble in ether, and the structure was supposed to ammonium 2-carbamoyl-4,7-dihydro-6-methyloxepin-3-carboxylate.

5) W. Brugel showed $J_{1,2}$ of both stereoisomers of methyl 2-vinylcyclopropane-1-carboxylate, and assigned 8.5 Hz to cis coupling and 4 Hz to the trans coupling. ("Handbook of NMR Parameters," Heyden and Son, Inc., London (1981), Vol. 1, p. 255).

6) These might be due to the properties of 2-carbamoyl-4,7-dihydro-6-methyloxepin-3-carboxylic acid **B**. Ammonia and benzylamine were enough basic to form the salts with **B**, and the salt of benzylcarbamoyl acid caused thermal decarboxylation to give **2e** and **3a**. While, aniline was not so basic, and phenylcarbamoyl acid **B** was interconvered with *N*-phenylcarboximidic acid **C**, and the electron-rich nitrogen in **C** might attack the carboxyl to afford **2d**.