and the residual oil was chromatographed on silica gel. The fraction eluted with 3% MeOH–$CHCl_3$ was evaporated to dryness and the residue was recrystallized from AcOEt to give 0.25 g of **5a**.

Preparations of 5b—e——Compounds 3 (4.5 g) was chlorinated with $POCl_3$. The sulfonylchloride was dissolved in AcOEt (100 ml). The solution was treated with $MeNH_2$ (saturation), Me_2NH (saturation) and propylamine (20 ml) to give **5b** (1.4 g), **5c** (0.6 g) and **5d** (0.85 g), respectively.

Compound **5e** (0.5 g) was obtained from **8** (1.74 g) by the method described above.

Melting points, yields and the results of elemental analyses are given in the table.

Anticonvulsant Activity——All experiments were carried out in male mice of STD-ddr strain weighing 20—22 g. Diet and water were given *ad libitum* to animals until the time of experiment. All compounds were administered by gavage as a suspension of 0.5% tragacanth solution. Drugs were evaluated for ability to prevent the hindlimb tonic extensor component of MES induced by a 60-Hz, 25 mA current for 0.2 s, delivered through corneal electrodes 2 h after dosing. DE_{50} values were calulated by the method of Litchfield and Wilcoxon.(6)

Acknowledgment We are grateful to Dr. H. Nishimura, the director of these laboratories, for his encouragement throughout of this work and to Dr. T. Karasawa for helpful discussions.

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Ring Transformation of 5-Oxo-4-oxaspiro[2.3]hexanes

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1-Ethoxycarbonyl-5-oxo-4-oxaspiro[2.3]hexane (**3**), on treatment with sodio methyl acetoacetate in THF, was transformed into 3-hydroxy-4-ethoxycarbonyl-2-cyclopenten-1-one (**5**) in 82% yield. Reaction of compound **3** with malononitrile (**4a**) in the presence of sodium hydride in THF gave the cyclopentenone **5** and 2-amino-3-cyano-6-ethoxycarbonylethyl-4-pyrone (**6**) in 49% and 24% yields, respectively. Similarly, reaction of compound **3** with ethyl cyanoacetate (**4b**) afforded compound **5** and 2-amino-3-ethoxycarbonyl-6-(2-ethoxycarbonylethyl)-4-pyrone (**7**) in 63% and 19% yields, respectively.

Reaction of 1-dimethylphosphono-1-methyl-5-oxo-4-oxaspiro[2.3]hexane (**1c**) with **4a** and **4b** under similar conditions gave 2-amino-3-cyano-6-(2-dimethylphosphonopropyl)-4-pyrone (**10**) and 2-amino-3-ethoxycarbonyl-6-(2-dimethylphosphonopropyl)-4-pyrone (**11**) in 58% and 63% yields, respectively.

Keywords——ring transformation; 5-oxo-4-oxaspiro[2.3]hexanes; active methylene compounds; 2-cyclopentenones; 2-amino-4-pyrones

During the course of investigations of the addition reaction of carbenes to the oxo double bond of diketene to give 5-oxo-4-oxaspiro[2.3]hexanes,[1-4] we have observed a novel ring transformation of 1-aryl-1-dimethylphosphono-5-oxo-4-oxaspiro[2.3]hexanes (**1a, b**) prepared from diketene and dimethyl (diazoarylmethyl)phosphonate, on treatment with methyl acetoacetate in the presence of sodium hydride, to 4-aryl-4-dimethylphosphono-3-hydroxy-2-cyclo-

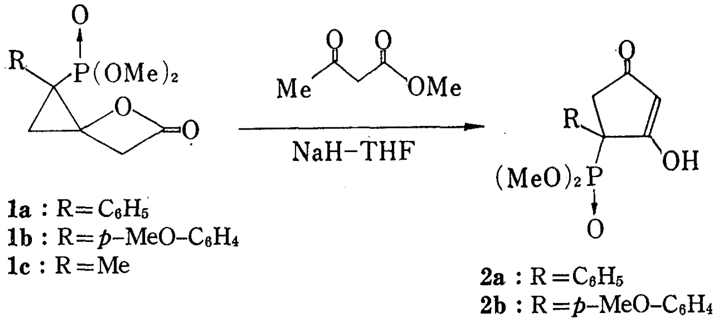


Chart 1

penten-1-ones (**2a**, **b**) in good yields.[5] The present paper reports a continuation of this study of the ring transformation of 5-oxo-4-oxaspiro[2.3]hexanes (**1c** and **3**) with methyl acetoacetate, malononitrile (**4a**), and ethyl cyanoacetate (**4b**) in the presence of sodium hydride.

Though the reaction of 1-dimethylphosphono-1-methyl-5-oxo-4-oxaspiro[2.3]hexane (**1c**) with methyl acetoacetate in the presence of sodium hydride did not give the cyclopentenone derivative corresponding to compound **2** (where R is methyl), reaction of 1-ethoxycarbonyl-5-oxo-4-oxaspiro[2.3]hexane (**3**) under the same conditions gave the cyclopentenone, 3-hydroxy-4-ethoxycarbonyl-2-cyclopenten-1-one (**5**), in 82% yield. Structural assignment was made as follows; elemental and mass spectral analyses indicated its empirical formula to be $C_8H_{10}O_4$, the same as that of the starting material **3**. The IR spectrum showed the presence of a cyclic 1,3-diketone (1670 and 1590 cm^{-1}) and an ester carbonyl (1730 cm^{-1}). The NMR spectrum indicated signals due to methylene protons (H_a and H_b; 2.80 ppm, 1H, dd, and 2.94 ppm, 1H, dd) and a methine proton (H_c; 3.63 ppm, 1H, dd).

Treatment of the cyclopentenone **5** with ethanol in the presence of conc. sulfuric acid as a catalyst gave the ethylated products, 3-ethoxy-5-ethoxycarbonyl-2-cyclopenten-1-one (**8**) and 3-ethoxy-4-ethoxycarbonyl-2-cyclopenten-1-one (**9**), in 49% and 24% yields, respectively. These structures were determined on the basis of the following observations; the signal due to

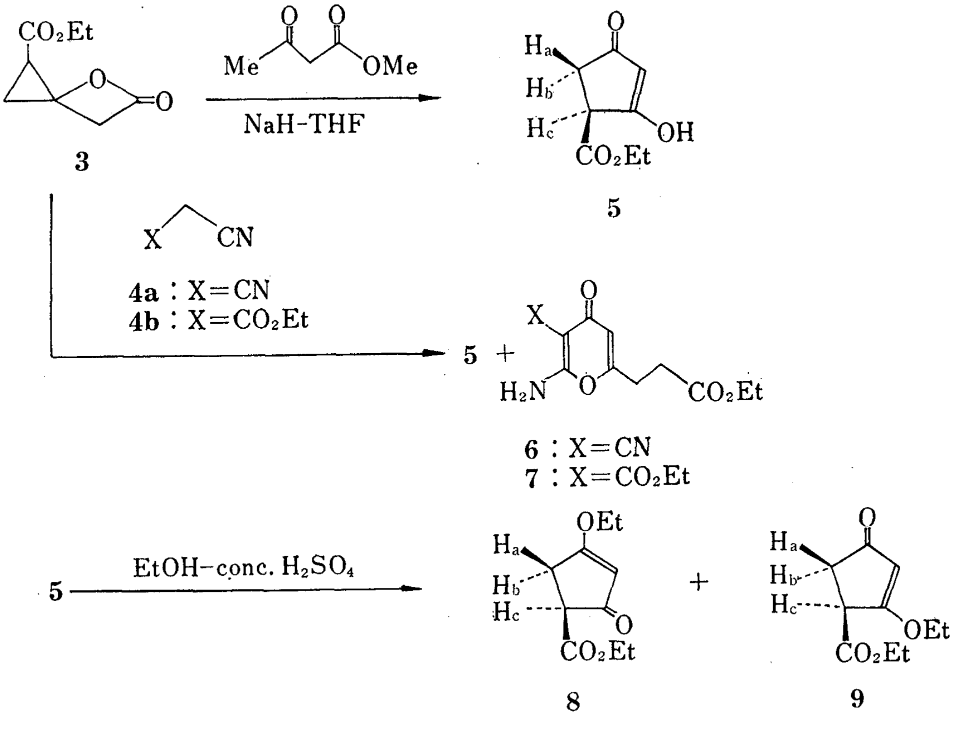


Chart 2

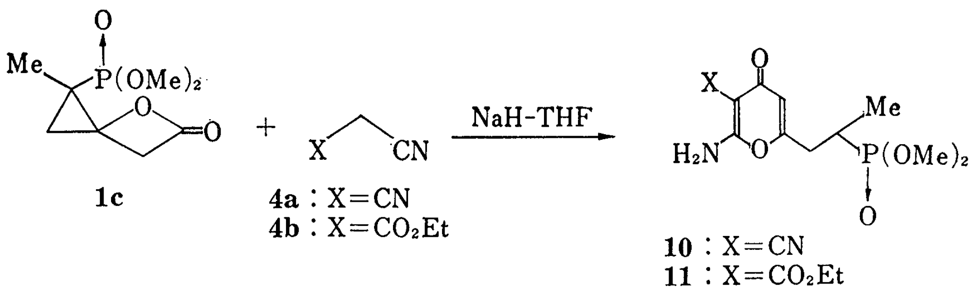


Chart 3

Table I. Reaction of 5-Oxo-4-oxaspiro[2.3]hexanes (**1c** and **3**) with Active Methylene Compounds

5-Oxo-4-oxaspiro-[2.3]hexane No.	5-Oxo-4-oxaspiro-[2.3]hexane g (mmol)	Active methylene compd. g (mmol)	Reaction temp. (°C)	Reaction time (h)	Product No.	Product Yield (%)	Product mp (°C)	Product Appearance (Recryst. solvent)
3	1.7(10)	Methyl Acetoacetate 1.16(10)	0	3	5	1.4(82)	72—73	Needles (Ether–hexane)
3	1.7(10)	**4a**	−15	6	6	1.0(43)	199	Needles (EtOAc)
		0.66(10)			5	0.5(30)	—	—
3	1.9(11)	**4b**	−15	12	7	0.6(19)	174	Needles (Benzene)
		1.27(11)			5	1.2(63)	—	—
1c	0.66(3)	**4a** 0.2 (3)	0	3	10	0.5(58)	215—216	Prisms (EtOH)
1c	0.66(3)	**4b** 0.35(3)	0	3	11	0.64(64)	117—118	Needles (Benzene)

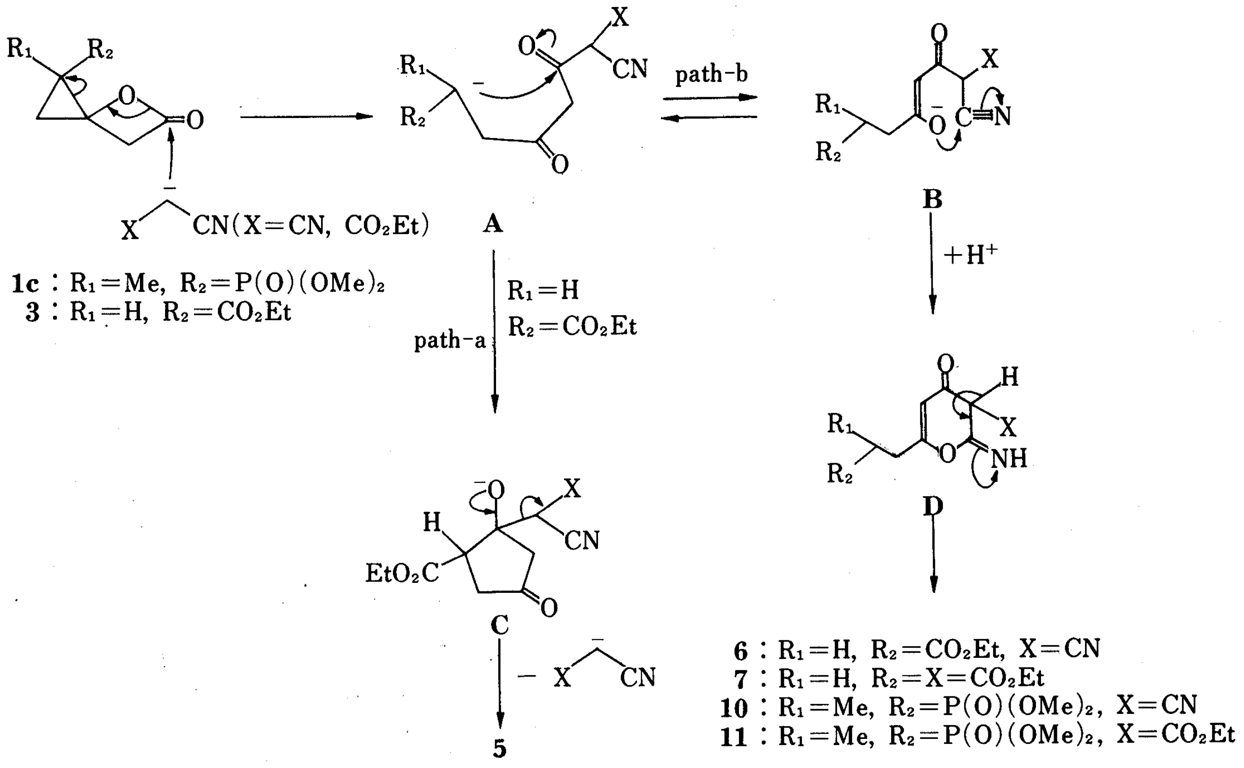
Table II. Physical and Analytical Data for 2-Cyclopentenones (**5**, **8**, and **9**)

Compd. No.	Formula	Analysis (%) Calcd (Found) C	Analysis (%) Calcd (Found) H	IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}	^{1}H NMR (CDCl$_3$) δ
5	$C_8H_{10}O_4$	56.46 (56.26	5.92 66.15)	3600—2400 (OH) 1730(C=O) 1670(C=O) 1590(C=C)	1.30 (3H, t, J=7.3 Hz, CH_3), 2.80 (1H, dd, J=18.0 Hz, J=6.6 Hz, Hb), 2.94 (1H, dd, J=18.0 Hz, J=3.7 Hz, Ha), 3.63 (1H, dd, J=6.6 Hz, J=3.7 Hz, Hc), 4.21 (2H, q, J=7.3 Hz, $OC\underline{H}_2CH_3$), 5.32 (1H, s, olefinic H), 9.75 (1H, br, OH)
8	$C_{10}H_{14}O_4$	60.59 (60.89	7.12 7.33)	1730(C=O) 1690(C=O) 1595(C=C)	1.30, 1.44 (each 3H, t, J=7.1 Hz, 2×CH_3), 2.80 (1H, ddd, J=17.6 Hz, J=7.5 Hz, J=1.4 Hz, $\underline{\mathrm{Hb}}$), 2.98 (1H, ddd, J=17.6 Hz, J=3.3 Hz, J=1.4 Hz, $\underline{\mathrm{Ha}}$), 3.50 (1H, dd, J=7.5 Hz, J=3.3 Hz, $\underline{\mathrm{Hc}}$), 4.08, 4.23 (each 2H, q, J=7.1 Hz, 2×$OC\underline{H}_2CH_3$), 5.24 (1H, t, J=1.4 Hz, olefinic H).
9	$C_{10}H_{14}O_4$	60.59 (60.74	7.12 7.40)	1730(C=O) 1695(C=O) 1595(C=C)	1.28, 1.41 (each 3H, t, J=7.2 Hz), 2.66 (2H, d, J=5.5 Hz, Ha and Hb), 3.70 (1H, dt, J= 5.5 Hz, J=1.4 Hz, Hc), 4.08, 4.21 (each 2H, q, J=7.2 Hz, 2×$OC\underline{H}_2CH_3$), 5.34 (1H, d, J=1.4 Hz, olefinic H)

TABLE III. Physical and Analytical Data for 2-Amino-4-pyrones (**6**, **7**, **10**, and **11**)

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	N	IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}	^{1}H NMR (CDCl$_3$) δ
6	$C_{11}H_{12}N_2O_4$	55.93 (56.07	5.12 5.09	11.86 11.66)	3340, 3160 (NH$_2$) 2440 (CN) 1730, 1670 (C=O) 1615 (C=C)	1.20 (3H, t, J=7.2 Hz, CH$_3$), 2.70 (4H, s), 4.10 (2H, q, J=7.2 Hz, OC$\underline{H}_2$CH$_3$), 5.91 (1H, s, olefinic H), 8.57 (2H, br, NH$_2$)$^{a)}$
7	$C_{13}H_{17}NO_6$	55.12 (55.01	6.05 6.05	4.95 5.07)	3520, 3320 (NH$_2$) 1735, 1690, 1665, (sh), 1635 (sh) (C=O), 1595 (C=C)	1.27, 1.39 (each 3H, t, J=7.0 Hz, 2×CH$_3$), 2.69 (4H, s), 4.19, 4.37 (each 2H, q, J=7.0 Hz, 2×OC$\underline{H}_2$CH$_3$), 5.93 (1H, s, olefinic H), 7.60 (2H, br, NH$_2$)
10	$C_{11}H_{15}N_2O_5P$	46.15 (45.73	5.24 5.30	9.79 9.91)	3280, 3140 (NH$_2$) 2440 (CN) 1665 (C=O) 1610 (C=C) 1235 (P=O) 1065, 1030 (POC)	1.08 (3H, dd, J=19.1 Hz, J=7.1 Hz, CH$_3$), 2.00—2.90 (3H, m), 3.66 (6H, d, J=10.5 Hz, 2×POCH$_3$), 5.98 (1H, s, olefinic H), 8.32 (2H, br, NH$_2$)$^{a)}$
11	$C_{13}H_{20}NO_7P\cdot 1/2H_2O$	45.61 (45.35	6.14 6.15	4.09 4.26)	3480, 3360 (NH$_2$) 1680, 1665 (sh) 1640 (sh) (C=O) 1600 (C=C) 1300 (P=O) 1070, 1040 (POC)	1.18 (3H, dd, J=18.3 Hz, J=7.1 Hz, CH$_3$), 1.38 (3H, t, J=7.2 Hz, CH$_3$), 2.10—3.00 (3H, m), 3.76 (6H, d, J=10.3 Hz, 2×POCH$_3$), 4.32 (2H, q, J=7.2 Hz, OC$\underline{H}_2$CH$_3$), 5.88 (1H, s, olefinic H), 7.86 (2H, br, NH$_2$)

a) In DMSO-d_6.



1c : R_1=Me, R_2=P(O)(OMe)$_2$
3 : R_1=H, R_2=CO$_2$Et

6 : R_1=H, R_2=CO$_2$Et, X=CN
7 : R_1=H, R_2=X=CO$_2$Et
10 : R_1=Me, R_2=P(O)(OMe)$_2$, X=CN
11 : R_1=Me, R_2=P(O)(OMe)$_2$, X=CO$_2$Et

Chart 4

an olefinic proton of **8** appeared as a triplet at 5.24 ppm, while that of **9** appeared as a doublet at 5.34 ppm.

Reaction of compound **3** with malononitrile (**4a**) in place of methyl acetoacetate afforded the cyclopentenone **5** and 2-amino-3-cyano-6-(2-ethoxycarbonylethyl)-4-pyrone (**6**) in 49% and 24% yields, respectively.

Similarly, reaction of compound **3** with ethyl cyanoacetate (**4b**) gave compound **5** and 2-amino-3-ethoxycarbonyl-6-(2-ethoxycarbonylethyl)-4-pyrone (**7**) in 63% and 19% yields, respectively.

Next, a similar reaction of 1-dimethylphosphono-1-methyl-5-oxo-4-oxaspiro[2.3]hexane (**1c**) was carried out. Though the cyclopentenone corresponding to the product **2** (where R is methyl) was not isolated, reaction with malononitrile (**4a**) and ethyl cyanoacetate (**4b**) gave 2-amino-3-cyano-6-(2-dimethylphosphonopropyl)-4-pyrone (**10**) and 2-amino-3-ethoxycarbonyl-6-(2-dimethylphosphonopropyl)-4-pyrone (**11**) in 58% and 63% yields, respectively. The results are summarized in Tables I, II, and III.

The mechanisms of formation of the cyclopentenone and the 4-pyrones can be elucidated as follows; nucleophilic attack of the carbanion of malononitrile (**4a**) or ethyl cyanoacetate (**4b**) at the β-lactone carbonyl of the spiro compound **1c** or **3** would give an intermediate **A**, cyclization of which along path-a gives the cyclopentenone **5** *via* an intermediate **C**. The enolic (or tautomeric) isomer **B** would cyclize to give the 4-pyrones **6**, **7**, **10**, and **11** *via* an intermediate **D**.

Experimental

IR spectra were taken on a JASCO IR spectrophotometer. NMR spectra were measured with a Hitachi R-20 instrument using tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi RMU-7L double focusing mass spectrometer. Melting points are uncorrected.

Reaction of the Spiro Compounds 1c and 3 with Active Methylene Compounds: General Procedure——A suspension of 60% dispersion of sodium hydride (equivalent mol) in THF (5 ml) was added to a solution of active methylene compound (3—11 mmol) in tetrahydrofuran (THF) (5 ml), and the mixture was stirred at -15°C. To this was added dropwise a solution of the spiro compound (equivalent mol) in THF (5 ml), and the whole was stirred at the same temperature for 3—12 h. The solvent was removed by distillation, and water was added to the residue to destroy the excess sodium hydride. The mixture was then extracted with chloroform (or ether). The water fraction was acidified with 10% hydrochloric acid, and the acidic solution was extracted with ethyl acetate. The ethyl acetate extract gave the product.

Reaction of 3 with Methyl Acetoacetate——Following the general procedure, compound **3** (1.7 g) was allowed to react with methyl acetoacetate (1.16 g). The ethyl acetate fraction was concentrated, and the oily residue was subjected to silica gel (30 g) column chromatography. Elution with chloroform afforded an oily product, to which a mixture of ether and hexane (1: 1) was added. The whole was kept at -20°C in a refrigerater to give a crystalline substance. Recrystallization from ether–hexane gave the product as needles. MS *m/e*: 170 (M^+).

Ethylation of the Cyclopentenone (5)——A catalytic amount (3 drops) of conc. sulfuric acid was added to a solution of compound **5** (0.35 g) in absolute ethanol (2 ml) and benzene (5 ml). The reaction mixture was refluxed for 6 h. The solvent was removed by distillation and water was added to the resulting residue. The mixture was extracted with ethyl acetate. The ethyl acetate fraction was dried, and concentrated to give an oily residue (0.4 g), which was subjected to silica gel (40 g) column chromatography. After eluting with 1 l of a mixture of hexane and chloroform (3: 1), elution was continued with a 1: 1 mixture of the same solvents to give the product **8**, bp 80—82°C (0.002 mmHg), 0.2 g (49%). Subsequent elution with chloroform gave the product **9**, bp 70—72°C (0.002 mmHg), 0.09 g (24%).

Reaction of Compound 3 with Malononitrile (4a)——Following the general procedure, compound **3** (1.7 g) was allowed to react with malononitrile (**4a**) (0.66 g). The ethyl acetate fraction was concentrated to give a crystalline residue, which was washed with a mixture of benzene and ethyl acetate (2: 1). The separated crystals were purified by recrystallization from ethyl acetate to give the 4-pyrone **6** as needles. Yield, 0.7 g (30%). The benzene–ethyl acetate soluble layer was concentrated to give an oily residue, which was subjected to silica gel (20 g) column chromatography using mixtures of chloroform and hexane (1: 5, 0.3 l and then 1: 1, 0.3 l). Subsequent elution with chloroform gave the product **6**, 0.3 g (13%). Elution was continued with chloroform to give the product **5**.

Reaction of 3 with Ethyl Cyanoacetate (4b)——Compound **3** (1.9 g) was allowed to react with ethyl cyanoacetate (**4b**) (1.27 g). Treatment of the reaction mixture in the manner described above gave an ethyl acetate solution, which was concentrated to give an oily residue (2.0 g). Purification by silica gel (20 g) column chromatography using a mixture of chloroform and hexane (1:1) gave the product **7**. Subsequent elution with ethyl acetate gave the product **5**.

Reaction of 1c with Malononitrile (**4a**)——Following the general procedure, compound **1c** (0.66 g) was allowed to react with malononitrile (0.2 g). The ethyl acetate fraction gave a residue, which was washed with ethyl acetate to give a crystalline substance (**10**).

Reaction of 1c with Ethyl Cyanoacetate——Compound **1c** (0.66 g) was allowed to react with ethyl cyanoacetate (0.35 g) according to the general procedure. A mixture of ether and pertoleum ether (1:3) was added to the ethyl acetate extract, and the whole was allowed to stand overnight in a refrigerater at −15°C to give a crystalline substance. Recrystallization from benzene gave the product **11**.

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Antitumor Activity of 3-Nitroso-2-oxazolidones

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2-Oxazolidones (Ia→f) were not effective against rat ascites hepatoma AH13 or mouse lymphoid leukemia, L1210. However, among 3-nitroso-2-oxazolidones (IIa→f), compounds IIa, IIb, IIc and IId were active against AH13, and compounds IIa, IIb and IIf were active against L1210. Cyclic N-nitrosocarbamates and N-nitrosoureas showed greater antitumor effects than the corresponding acyclic N-nitroso compounds.

Since the reaction of compounds IIa→f with 4-(*p*-nitrobenzyl)pyridine gave a purple color, their antitumor mechanism presumably involves alkylation, but there was no correlation between the antitumor activities and the color intensities.

Keywords——2-oxazolidones; cyclic carbamates; 3-nitroso-2-oxazolidones; acyclic nitroso carbamates; antitumor activity; AH13; L1210; alkylating activity; NBP reagent

Ethyl carbamate (urethan) had been used for the treatment of chronic myeloid leukemia and related blood disease.[1] Antitumor antibiotics, mitomycin C and bleomycins, which are clinically useful antitumor agents, also have a carbamate partial structure with other antitumor chemical functional groups. Antitumor plant components, maytansinoids, have a cyclic carbamate partial structure with other antitumor chemical functional groups. These findings prompted us to test the antitumor activities of 2-oxazolidones (I) as cyclic carbamates and their N-nitroso derivatives (II).

Some of 3-nitroso-2-oxazolidones (IIa→f) were active against rat ascites hepatoma AH13 and mouse lymphoid leukemia L1210. Their alkylating activities were shown to be involved in the antitumor mechanism.

As shown in Table I, 2-oxazolidones (Ia→f) were all inactive against AH13 and L1210.