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Studies on Prostaglandins. II.[1,2] Synthesis of 4-Alkoxymethyl-2-norbornen-5-one and Its Oxidation Reaction with *m*-Chloroperbenzoic Acid

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4-Alkoxymethyl-5-chloro-5-cyano-2-norbornene (III) was produced by the Diels-Alder reaction using 5-alkoxymethyl-cyclopentadiene and α-chloroacrylonitrile in the presence of aqueous cupric boronfluoride. III was hydrolyzed to 4-alkoxymethyl-2-norbornen-5-one (V). When V was oxidized with *m*-chloroperbenzoic acid, the products were varied by differences of the reaction conditions. (3β-Methoxymethyl-3α-hydroxy-4-cyclopenten-1α-yl)-acetic acid lactone (IXa) was produced by the oxidation of 4-methoxymethyl-2-norbornen-5-one (Va) with *m*-chloroperbenzoic acid in the presence of aqueous sodium bicarbonate. IXa which was very unstable was easily rearranged to 5-methoxymethyl-3,3aβ,4,6aβ-tetrahydro-2H-cyclopenta[*b*]furan-2-one (Xa).

Prostaglandins (PGs) and their analogues have been studied with keenest interest in many laboratories. We have been also studied on the synthesis of PGs using a Corey's method[4] which was the most important and useful method for the purpose. This report describes on the preparation of 4-alkoxymethyl-2-norbornen-5-one derivatives (Va and Vb) which were found during the studies on the Corey's method and on the oxidation reaction of them using *m*-chloroperbenzoic acid (MCPB).

When 5-methoxymethyl-cyclopentadiene (Ia, R=H) was condensed with α-chloroacrylonitrile in the presence of anhydrous cupric boronfluoride according to the Corey's procedure, we found a small amount of 4-methoxymethyl-5-chloro-5-cyano-2-norbornene (IIIa, R=H) with 7-*syn*-methoxymethyl-5-chloro-5-cyano-2-norbornene (IIa, R=H)[4a,d] which was the purposive product. In this reaction, it was recognized that, if aqueous cupric boronfluoride instead of anhydrous cupric boronfluoride was used, IIIa was produced mainly. IIIa was hydrolyzed to 4-methoxymethyl-2-norbornen-5-one (Va, R=H) which was easily purified as a crystalline semicarbazone derivative. The analogous derivatives, IIIb and Vb, were also obtained by the same procedures starting from 5-benzyloxymethyl-cyclopentadiene (Ib, R=C_6H_5).

The oxidation reaction of Va using MCPB was very interesting, because, by differences of the reaction conditions, the Baeyer-Villiger oxidation of a ketone, the epoxidation of a double bond or both reactions were proceeded as shown below. When Va was oxidized with MCPB in dry methylene chloride at or below room temperature, 2,3-epoxy-4-methoxymethyl-

1) Part I: N. Inukai, H. Iwamoto, I. Yanagisawa, N. Nagano, T. Tamura, Y. Ishii, and M. Murakami, *Chem. Pharm. Bull.* (Tokyo), **24**, 2566 (1976).
2) This study was presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April, 1975.
3) Location: *No. 1-8, Azusawa-1-chome, Itabashi-ku, Tokyo.*
4) *a*) E.J. Corey, N.M. Weinshenker, T.K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969); *b*) E.J. Corey. T.K. Schaaf, W. Huber, U. Koelliker, and N.M. Weinshenker, *ibid.*, **92**, 397 (1970); *c*) E.J. Corey, R. Noyori, and T.K. Schaaf, *ibid.*, **92**, 2586 (1970); *d*) E.J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971); *e*) E.J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T.K. Schaaf, *ibid.*, **93**, 1490 (1971); *f*) E.J. Corey, T. Ravindranathan, and S. Terashima, *ibid.*, **93**, 4326 (1971); *g*) E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf, and R.K. Varma, *ibid.*, **93**, 1491 (1971).

bicyclo[2.2.1]heptan-5-one (VIIa, R=H) which was produced by the epoxidation was obtained as main product. If anhydrous sodium bicarbonate was suspended in the above reaction mixture, both the Baeyer-Villiger oxidation and the epoxidation were proceeded at the same time and 4,5-epoxi-3α-hydroxy-3β-methoxymethyl-1α-cyclopentylacetic acid lactone (VIIIa, R=H) was obtained. VIIIa was also obtained from VIIa by the same condition. Furthermore, if aqueous sodium bicarbonate instead of anhydrous sodium bicarbonate was added to the above reaction mixture, the Baeyer-Villiger oxidation was mainly occurred and (3α-hydroxy-3β-methoxymethyl-4-cyclopenten-1α-yl)acetic acid lactone (IXa, R=H) was produced with the high yields. IXa which was very unstable was easily rearranged to 5-methoxymethyl-3,3aβ,4,6aβ-tetrahydro-2H-cyclopenta[*b*]furan-2-one (Xa, R=H), when IXa was contacted with water or allowed to stand itself at room temperature. The analogous rearran-

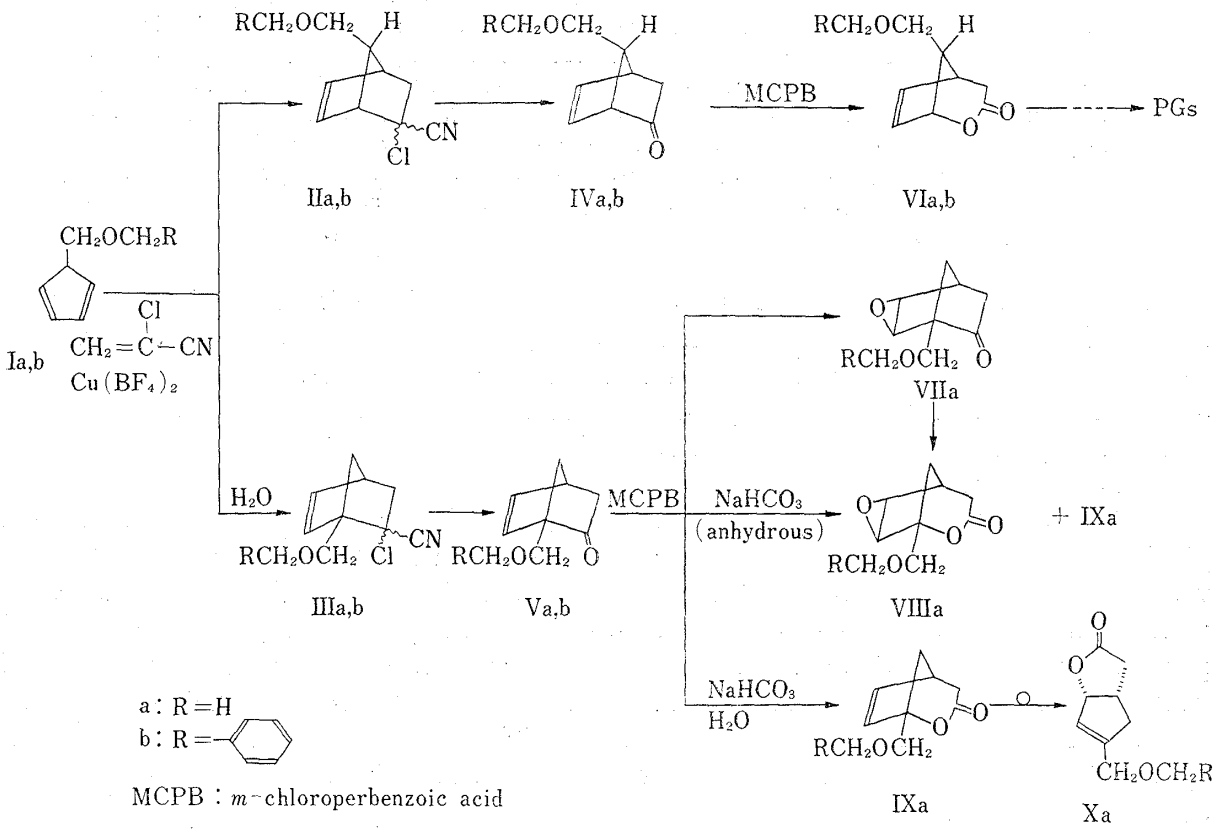

Chart 1

TABLE I

Condition		H_2O	MCPB[a]	$NaHCO_3$	Product (%)[b]			
Temp. °C	Time hr	±	moles	moles	VIIa	VIIIa	IXa	Va
0	18	−	2.5	−	91.1	1.8	−	7.5
−20	72	−	2	2	−	36.8	63.2	0.1
0	18	−	2	2	0.4	24.5	46.1	28.3
0	42	−	2	2	0.8	34.3	64.8	−
20	42	−	2	2	5.1	30.7	58.3	5.1
−20	93	+	2	2	−	5.1	83.3	11.5
0	20	+	1.6	1.6	−	5.7	94.3	−

a) MCPB: *m*-chloroperbenzoic acid
b) The yields were determined by the gas chromatographic analysis using a 6ft×0.125 in. column containing 10% silicon (UC W-98 and DC-710) at 120°.

gement reaction in the presence of acid was reported recently about bicyclo[2.2.1]hept-2-en-5-one (dehydronorcamphor)[5,6] and PGs-intermediate VI.[7,8]

These results were summarized in Chart 1 and Table I.

Experimental[9]

7-*syn*-Benzyloxymethyl-5-chloro-5-cyano-2-norbornene (IIb, R=C_6H_5)[4e,4f] and 4-Benzyloxymethyl-5-chloro-5-cyano-2-norbornene (IIIb, R=C_6H_5)——Anhydrous cupric boronfluoride (2.1 g) was added to a mixture of dry *t*-butanol (3.2 g) and α-chloroacrylonitrile (7.2 g). The blue colored solution obtained was cooled below 0° and the cold solution was added to a mixture of 5-benzyloxymethyl-cyclopentadiene (8.1 g)[4e,4f] freshly prepared and α-chloroacrylonitrile (8.0 g) which was precooled below −20°. The solution was allowed to stand for 3 days at 0—5°. The solution was concentrated under reduced pressure and the oily residue obtained was dissolved in ether. The ether solution was washed successively with 10% aqueous sodium tartarate and water saturated with sodium chloride, and dried over magnesium sulfate. The solvent was evaporated off and 18.9 g of the crude oily products which consisted of IIb and IIIb was obtained. The separation of IIb and IIIb and the purification were carried out by column chromatography on silica gel using a mixture of *n*-hexane and ethylacetate (8: 1) as an eluting solvent. 10.3 g (45.5%) of IIb and 0.8 g of IIIb were obtained. Mass Spectrum *m/e*: 273 (M^+). NMR of IIb (CCl_4) δ: 5.95 (1H, dd, J=6cps, HC=), 6.25 (1H, dd, J=6 cps, HC=), 3.32 (2H, d, J=7 cps, HC–C$\underline{H}_2$–O), 2.5 (1H, t, J=7 cps, HC–CH_2O–). NMR of IIIb (CCl_4) δ: 5.95 (1H, d, J=6 cps, HC–), 6.3 (1H, dd, J=6 cps, HC=), 2.9 (1H, broad, HC–), 3.96 (2H, s, –C–C$\underline{H}_2$O–).

4-Methoxymethyl-5-chloro-5-cyano-2-norbornene (IIIa, R=H) and *syn*-7-Methoxymethyl-5-chloro-5-cyano-2-norbornene (IIa, R=H)[4a,4d]——To a mixture of α-chloroacrylonitril (19 g) and a few drops of 45% aqueous cupric boronfluoride in dry tetrahydrofuran (THF) (10 ml), a solution of 5-methoxymethyl-cyclopentadiene (7.9 g)[4a,4d] freshly prepared in dry THF (5 ml) was added dropwise at −10° with stirring. The solution was stirred for 4 hr at this temperature and allowed to stand overnight in refrigerator. Chloroform (30 ml) was added to the reaction solution and the solution was washed twice with water and dried over magnesium sulfate. The solvent was evaporated off and the residual oil was distilled under reduced pressure. The yellowish oil (11.4 g) was obtained: bp 88—93° (0.5 mmHg). *Anal.* Calcd. for $C_{10}H_{12}NOCl$: C, 60.76; H, 6.12; N, 7.09; Cl, 7.94. Found: C, 60.61; H, 6.05; N, 7.32; Cl, 17.99.

The oil thus obtained was the mixture of IIa and IIIa and the productive ratio of IIa and IIIa was about 22%: 78%, when it was detected by the gas chromatographic analysis using a 6 ft × 0.125 in. column containing 10% silicone (UC W-98) at 120°. The separation of IIa and IIIa was carried out by column chromatography on silica gel as described above. NMR of IIa (CCl_4) δ: 6.0 (1H, dd, J=6 cps. HC=), 6.3 (1H, dd, J=6 cps, HC=), 2.5 (1H, t, J=7.5 cps, HC–CH_2O–), 3.3 (2H, ABq, –C$\underline{H}_2$OCH_3), 3.22 (3H, s, –CH_2OC$\underline{H}_3$). NMR of IIIa (CCl_4) δ: 5.95 (1H, d, J=6 cps, HC=), 6.35 (1H, dd, J=6 cps, HC=), 2.97 (1H, broad, HC–), 3.87 (2H, ABq, J=12 cps, –C$\underline{H}_2$OCH_3), 3.44 (3H, s, –CH_2OC$\underline{H}_3$).

4-Methoxymethyl-2-norbornen-5-one (Va, R=H)——To a solution of IIIa (8.6 g) in DMSO (26 ml), a solution of KOH (6.1 g) in water (5 ml) was added and the solution was stirred for 2 days at about 28°. Water (100 ml) was added to the reaction solution and the oil precipitated was extracted with ether. The extracted solution was washed with water and dried over sodium sulfate, and then concentrated under reduced pressure. The pale yellowish oil obtained was purified by distillation under reduced pressure: bp 50—54° (0.35 mmHg); yield 5.6 g (84%). NMR ($CHCl_3$) δ: 5.84 (1H, d, J=6 cps, HC=), 6.45 (1H, dd, J=6 cps, HC=), 3.12 (1H, broad, HC–), 3.61 (2H, s, –C$\underline{H}_2$OCH_3), 3.33 (3H, s, –CH_2OC$\underline{H}_3$). IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O). Semicarbazone of Va: mp 213—216°. *Anal.* Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.10; H, 7.35; N, 19.67.

4-Benzyloxymethyl-2-norbornen-5-one (Vb, R=C_6H_5)——Vb was obtained by the hydrolysis of IIIb according to the same procedure as described on Va. NMR (CCl_4) δ: 5.84 (1H, d, J=6 cps, HC=), 6.45 (1H, dd, J=6 cps, HC=), 3.05 (1H, broad, HC–), 3.69 (2H, s, –C–C$\underline{H}_2$O–). Semicarbazone of Vb: mp 160—171°.

2,3-Epoxy-4-methoxymethyl-bicyclo[2.2.1]heptan-5-one (VIIa, R=H)——A mixture of Va (50 mg) and MCPB (142 mg) in dry methylene chloride (2 ml) was allowed to stand overnight at 0°. The reaction solution was diluted with chloroform and washed successively with an aqueous solution saturated with sodium carbonate and water, and then dried over magnesium sulfate. The solvent was evaporated off and the residual oil obtained was purified by column chromatography on silica gel using ether as an eluting solvent; yield 44 mg (80%). Mass Spectrum *m/e*: 168 (M^+). NMR (CCl_4) δ: 2.93 (1H, d, J=4 cps, HC(O)—C$\underline{H}$), 3.34 (4H, –CH_2OC$\underline{H}_3$ and HC(O)—C$\underline{H}$). IR ν_{max}^{KBr} cm^{-1}: 1750 (C=O).

5) J. Meinwald, M.C. Seidel, and B.C. Cadoff, *J. Am. Chem. Soc.*, **80**, 6303 (1958).
6) J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, **82**, 5235 (1960).
7) Imperial Chemical Industries Ltd., Ger. Offen 2323454 (1973) [*C. A.*, **80**, 95369*r* (1974)].
8) H. Nakamoto, Japan Kokai 109381 (1974).
9) All melting points are not corrected.

4,5-Epoxy-3α-hydroxy-3β-methoxymethyl-1α-cyclopentylacetic Acid Lactone (VIIIa, R=H)——To a mixture of VIIa (100 mg) and MCPB (150 mg) in dry methylene chloride (3 ml), anhydrous sodium bicarbonate (75 mg) was suspended and stirred overnight at room temperature. Chloroform and aqueous sodium carbonate was added to the reaction mixture and shaken well. The organic layer was separated and washed with water, and then dried over magnesium sulfate. The solvent was evaporated off and the residual oil was purified by column chromatography on silica gel followed by distillation: bp 170° (bath temperature) (0.4 mmHg). IR cm^{-1}: $\nu_{C=O}$1760 (CCl_4). NMR (CCl_4) δ: 3.5 (2H, s, $\underline{H}C(O)C\underline{H}$). Mass Spectrum *m/e*: 184 (M^+).

(3β-Methoxymethyl-3α-hydroxy-4-cyclopenten-1α-yl)acetic Acid Lactone (IXa, R=H) and 5-Methoxymethyl-3,3aβ,4,6aβ-tetrahydro-2H-cyclopenta[*b*]furan-2-one (Xa, R=H)——A solution of MCPB (45.4 g) in chloroform (360 ml) was added portionwise to a solution of sodium bicarbonate (24 g) in water (90 ml) with stirring. After the evolution of CO_2 gas ceased, the mixture was cooled at −20°. To the cooled mixture, a solution of Va (20 g) in methylene chloride (270 ml) which was precooled at −20° was added with shaking. The mixture was allowed to stand for 93 hr at −20° in deepfreezer. The reaction mixture was washed 4 times with each 300 ml of ice-cooled 8.5% aqueous sodium carbonate and then ice-water. When the solvent was evaporated off below 5°, 22 g of the yellowish oil (IXa) was obtained. NMR of IXa δ: 6.07 (1H, d, J=6 cps, HC=), 6.38 (1H, dd, J=6 cps, HC=), 2.95 (1H, broad, HC–), 3.4 (3H, s, $-CH_2OC\underline{H}_3$), 3.62 (2H, s, $-C\underline{H}_2OCH_3$).

A solution of IXa in chloroform was shaken with water at room temperature for about 3 min. The organic layer was concentrated under reduced pressure and the residual oil (Xa) was purified by distillation: bp 110° (0.4 mmHg). Furthermore, IXa was gradually rearranged to Xa, when IXa itself was allowed to stand at room temperature. NMR of Xa δ: 5.72 (1H, broad, HC=), 5.4 (1H, broad, –CO–CH–), 3.95 (2H, $-C\underline{H}_2OCH_3$), 3.31 (3H, s, $-CH_2OC\underline{H}_3$). Mass Spectrum *m/e*: 168 (M^+). *Anal.* Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.60; H, 6.92.

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