stirred at r.t. for 3 hr. The reaction mixture was evaporated and the resulting residue was treated with 5% Na_2CO_3 aq. (1800 ml) and extracted twice with ether (500 ml). The ether extract was dried (Na_2SO_4) and evaporated. The residue was purified by vacuum distillation to give III (33.6 g, 24.5%) as colorless oil, bp 78—86° (18—20 mmHg). *Anal.* Calcd. for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.40; H, 10.69.

2-Ethoxy-5-propyl-1-pyrroline (XVI)——A solution of triethyloxonium tetrafluoroborate (114 g) and XIII (63.5 g) in anhyd. CH_2Cl_2 (100 ml) was stirred at r.t. for 24 hr. To the mixture, 20% K_2CO_3 aq. (400 ml) was added with stirring and the mixture was extracted with ether, and the resulting extract was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by vacuum distillation to give XVI (75.0 g, 97%) as colorless oil, bp 55—56° (0.9 mmHg).

2-Ethoxy-3,4,5,6-tetrahydropyridine (XVII)——According to the method of Pilotti, *et al.*[9] XVII was obtained as colorless oil, bp 64—66° (22 mmHg) (Yield: 81.5%).

Oudenone (I)——A mixture of II (3.0 g) and III (12.5 g) was heated in an oil bath at 95—100° for 6 hr and low boiling fraction was distilled off. The resulting residue was purified by column chromatography ($CHCl_3$–MeOH=10:1) te give I as colorless plates, which was identified by comparison of its IR and NMR spectra ($CDCl_3$) with those of an authentic sample obtained by the method of Ohno, *et al.*[6] In this reaction, the additions of Ac_2O and anhyd. $ZnCl_2$, which are usually employed in the condensations of orthoesters with active methylene compounds,[17] did not affect the reaction time and yield of I.

Other compds. in Table I were also prepared from materials A and B by the similar procedures.

Acknowledgement The authors are grateful to Drs. S. Tatsuoka, E. Ohmura, T. Masuda and S. Yurugi for their encouragements throughout this work.

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Studies on the Syntheses of Heterocyclic Compounds containing Benzopyrone. I. Syntheses of Cycloalkenochromones

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Cycloalkenochromones (IV) were prepared from salicylaldehyde methoxymethyl ether and cycloalkanones *via* aldol condensation.

Keywords——cycloalkenochromones; salicylaldehyde methoxymethyl ether; cycloalkanones; Aldol condensation; CrO_3-acetone oxidation; heterocyclic compounds containing benzopyrone

Chromones have been prepared by many investigators, some of the more important synthetic methods being: condensation of phenol with ethyl acetoacetate in the presence of phosphorus pentoxide (Simonis reaction),[2] condensation of ethylacetate[3] or diethyl oxalate[4]

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[1] Location: *1-1 Keyaki-Dai, Sakado, Saitama.*

[2] *a*) E. Petschek and H. Simonis, *Ber.*, **46**, 2014 (1913); *b*) S. Sethna and R. Phadke, "Org. Reactions," Vol. 7, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1953, p. 1.

[3] T.A. Geissman, *J. Am. Chem. Soc.*, **73**, 3514 (1951).

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with acetophenone, and condensation of aldehyde[5] or acid chloride[6] or acid anhydride[7] with enamines. We prepared chromones by mild aldol condensation[8] according to the synthetic route outlined in Chart 1. This method has the advantages that the starting materials are readily available and inexpensive and the few steps involved are simple.

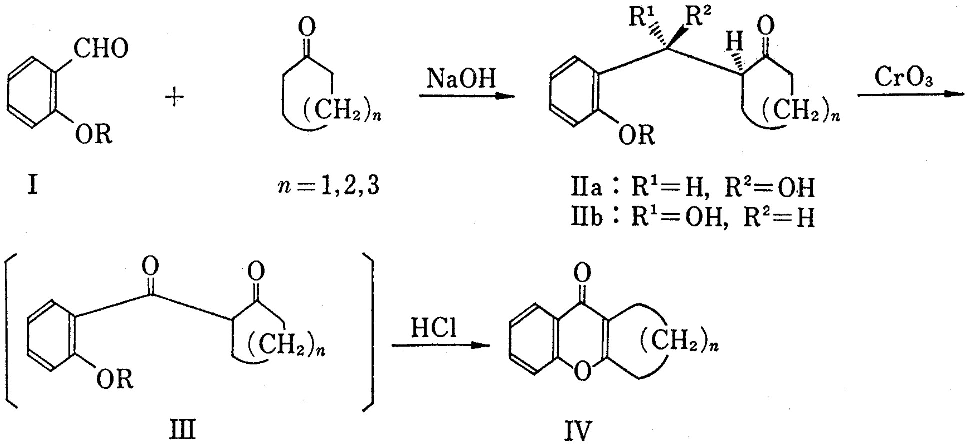

Chart 1

Salicylaldehyde methoxymethyl ether (I; R=CH_2OCH_3)[9] was condensed with cyclohexanone by the method reported by Billimoria[10] to yield α-hydroxybenzylcyclohexanones (IIa and IIb; R=CH_2OCH_3). The alcohols were obtained in lower yield when the reaction was carried out with tetrahydropyranyl ether (I; R=THP), while salicylaldehyde (I; R=H) or its acetate (I; R=Ac) gave no aldol condensation product. The two isomeric alcohols, IIa and IIb were separated by column chromatography, and their configurational assignments were made on the basis of their infrared (IR) absorption and proton magnetic resonance (PMR) spectra. The stretching frequencies of the hydroxyl groups in the IR spectra of IIa ($n=2$) and IIb ($n=2$), were not affected by the concentrations of materials (3×10^{-2} M, 6×10^{-4} M, 3×10^{-4} M in CCl_4), indicating the presence of intramolecular hydrogen bonding. The PMR spectra of IIa ($n=2$) and IIb ($n=2$) showed signals of benzylic methylene protons, coupled with methyne protons, at δ 5.72 (d, $J=3$ Hz) and 5.40 (d, $J=8$ Hz), respectively. In the conformation fixed with intramolecular hydrogen bonding (Fig. 1), the observed values can be reasonably explained by supposing that the coupling constants between the benzylic methylene proton and methyne proton are 3 Hz in II′a, and 8 Hz in II′b. The other possible conformation (i) for IIa seems less likely because of the two steric interactions between the phenyl group and the carbonyl and methylene groups, and because of the electrostatic interaction between the phenyl and carbonyl groups. Compound (IIa; $n=2$) formed colorless crystals and was recrystallized from n-hexane, whereas IIb ($n=2$) was an oil and was reconverted to the starting materials *via retro*-aldol condensation on heating or treatment under the conditions for gas chromatography. In the case of $n=3$, but not $n=1$, the epimeric alcohols, IIa and IIb, were separated.

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5) *a*) L.A. Paquette, *Tetrahedron Lett.*, **1965**, 1291; *b*) L. A.Paquette and H. Stucki, *J. Org. Chem.*, **31**, 1232 (1966).
6) M. Uchiyama, M. Ohhashi, and M. Matsui, *Agr. Biol. Chem.*, **30**, 1145 (1966).
7) G.V. Boyd, D. Hewson, and R.A. Newberry, *J. Chem. Soc.* (*C*), **1969**, 935.
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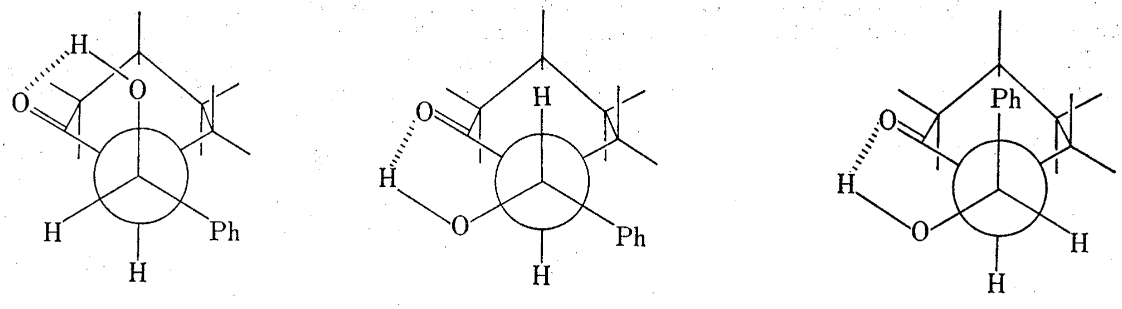
10) J.D. Billimoria, *J. Chem. Soc.*, **1955**, 1126.



II′a II′b i

Ph=phenyl

Fig. 1

Compound (II) was converted to III by oxidation with Collins reagent[11] or with CrO_3–acetone. On treatment of III with hydrochloric acid, the corresponding chromones (IV) were obtained and shown to be identical with authentic samples[7,12,13] (mp, IR). Further physical data (Mass, UV, PMR) are given in the experimental part. The yields of IV from salicylaldehyde methoxymethyl ether (I) were 15% (n=1), 82% (n=2) and 49% (n=3).

Experimental

Melting points were determined with a Mitamura one visual field micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO–DS–701–G spectrophotometer, using 0.1, 0.5, 10, 20 mm NaCl cells, and a Hitachi Model 215 spectrophotometer. UV spectra were recorded with a Hitachi Model 200–10 spectrophotometer, mass spectra with a Shimazu LKB–9000 mass spectrometer, and PMR spectra with a JEOL C–60HL spectrometer with tetramethylsilane as internal reference in $CDCl_3$. Extracts were dried over anhyd. Na_2SO_4. Column chromatographies were carried out on silica gel (Mallinckrodt) using a mixture of $CHCl_3$ and MeOH as eluent.

2-(*o*-Methoxymethoxy-α-hydroxybenzyl)cycloalkanones——Cycloalkanone (5 mmol) and salicylaldehyde methoxymethyl ether (I; $R=CH_2OCH_3$, 5 mmol) were suspended in H_2O (20 ml), and NaOH (5 mmol) in H_2O (5 ml) was added dropwise. The mixture was stirred at room temperature for 4 hr, and extracted with $CHCl_3$. The extract was dried and distilled and the residue was subjected to chromatography to give 2-(*o*-methoxymethoxy-α-hydroxybenzyl)cycloalkanone. The following compounds were obtained.

2-(*o*-Methoxymethoxy-α-hydroxybenzyl)cyclopentanone (II; $R=CH_2OCH_3$, $n=1$); Yield: 470 mg (38%). IR ν_{max}^{film} cm^{-1}: 3450 (OH), 1730 (C=O).

2-(*o*-Methoxymethoxy-α-hydroxybenzyl)cyclohexanone (II; $R=CH_2OCH_3$, $n=2$); Yield: 1.30 g (98%). *threo*-Form (IIa; $R=CH_2OCH_3$, $n=2$); mp 83° (from *n*-hexane). *Anal.* Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.36; H, 7.72. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3580 (OH), 1698 (C=O). PMR δ: 5.72 (d, $J=3$ Hz, Ph-C$\underline{H}$(OH)), 5.29 (s, $OC\underline{H}_2OCH_3$), 3.50 (s, $OCH_2OC\underline{H}_3$). *erythro*-Form (IIb; $R=CH_2OCH_3$, $n=2$); IR ν_{max}^{film} cm^{-1}: 3520 (OH), 1700 (C=O). PMR δ; 5.40 (d, $J=8$ Hz, Ph-C$\underline{H}$(OH)), 5.25 (s, $OC\underline{H}_2OCH_3$), 3.53 (s, $OCH_2OC\underline{H}_3$).

2-(*o*-Methoxymethoxy-α-hydroxybenzyl)cycloheptnone (II; $R=CH_2OCH_3$, $n=3$); Yield: 1.02 g (73%). *threo*-Form (IIa; $R=CH_2OCH_3$, $n=3$); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3540 (OH), 1960 (C=O). PMR δ: 5.55 (d, J=3 Hz, Ph-C$\underline{H}$(OH)), 5.29 (s, $OC\underline{H}_2OCH_3$), 3.53 (s, $OCH_2OC\underline{H}_3$). *erythro*-Form (IIb; $R=CH_2OCH_3$, $n=3$); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500 (OH), 1690 (C=O). PMR δ: 5.31 (d, $J=6$ Hz, Ph-C$\underline{H}$(OH)), 5.27 (s, $OC\underline{H}_2OCH_3$), 3.52 (s, $OCH_2OC\underline{H}_3$).

2-(*o*-Methoxymethoxybenzoyl)cycloalkanones. CrO_3–Acetone Oxidation——A mixture of equal amount of the keto-alcohol (II) and CrO_3 in 20 parts of acetone was stirred for 1 hr at room temperature. The reaction mixture was poured into 5 volumes of H_2O and extracted with ether. The extract was dried and distilled, and the residue was subjected to chromatography to give the diketone.

2-(*o*-Methoxymethoxybenzoyl)cyclopentanone (III; $R=CH_2OCH_3$, $n=1$); Yield: 206 mg (44%) from II ($R=CH_2OCH_3$, $n=1$, 470 mg). IR ν_{max}^{film} cm^{-1}: 1690 (C=O).

2-(*o*-Methoxymethoxybenzoyl)cyclohexanone (III; $R=CH_2OCH_3$, $n=2$); Yield: 186 mg (93%) from *threo*-alcohol (IIa; $R=CH_2OCH_3$, $n=2$, 200 mg). IR ν_{max}^{film} cm^{-1}: 1685 (C=O).

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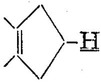
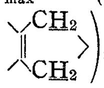
[11] J.C. Collins, W.W. Hess, and F.J. Frank, *Tetrahedron Lett.*, **1968**, 3363.

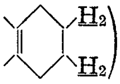
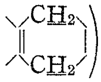
[12] M. Miyano, *J. Am. Chem. Soc.*, **87**, 3958 (1965).

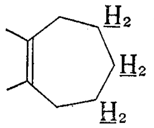
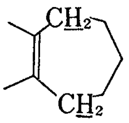
[13] H.I. Hall and S.G.P. Plant, *J. Chem. Soc.*, **1933**, 232.

2-(*o*-Methoxymethoxybenzoyl)cycloheptanone (III; R=CH_2OCH_3, *n*=3); Yield: 170 mg (73%) from *erythro*-alcohol (IIb; R=CH_2OCH_3, *n*=3, 230 mg). IR ν_{max}^{film} cm^{-1}: 1678 (C=O).

Chromones——A solution of the diketone (III) in conc. HCl-AcOH (3: 5) was heated at 60—70° for 1 hr. The reaction mixture was cooled and poured into 3 volumes of H_2O, and extracted with $CHCl_3$. The extract was dried and distilled, and the residue was subjected to chromatography. Cycloalkenochromone (IV) was eluted as the first fraction and recrystallized from pet. ether.

2,3-Dihydro-benzo[*b*]cyclopenta[*e*]pyran-9(1H)-one (IV; *n*=1); Yield: 123 mg (89%) from the diketone (III; R=CH_2OCH_3, *n*=1, 206 mg). mp 113.5—115.5°. *Anal.* Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.40; H, 5.62. UV λ_{max}^{EtOH} nm (ε): 227 (22900), 270 (6500), 294 (7100), 301 (7200). PMR δ: 1.9—2.4 (m, ), 2.8—3.2 (m, ), 7.37—7.72 (m, 6-, 7-, 8-H), 8.35 (d d, 5-H). MS *m/e* (relative in.): 186 (M^+) (72.9), 185 (100), 121 (14.3), 92 (11.4), 65 (11.4).

1,2,3,4-Tetrahydro-xanthen-9-one (IV; *n*=2); Yield: 95 mg (90%) from the diketone (III; R=CH_2OCH_3, *n*=2, 140 mg). mp 91—92°. *Anal.* Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.83; H, 5.99. UV λ_{max}^{EtOH} nm (ε): 228 (27400), 269 (7300), 297 (8200), 304 (8300). PMR δ: 1.7—2.1 (m, ), 2.5—2.9 (m, ), 7.29—7.93 (m, 6-, 7-, 8-H), 8.33 (d d, 5-H). MS *m/e* (relative in.): 200 (M^+) (100), 199 (97.6), 185 (64.8), 121 (26.4), 92 (20.8), 65 (13.6).

7,8,9,10-Tetrahydro-benzo[*b*]cyclohepta[*e*]pyran-11(6H)-one (IV; *n*=3); Yield: 35 mg (90%) from the diketone (III; R=CH_2OCH_3, *n*=3, 50 mg). mp 79—80°. *Anal.* Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.61; H, 6.63. UV ν_{max}^{EtOH} nm (ε): 230 (24300), 272 (4600), 297 (6900), 305 (7000). PMR δ: 1.5—2.2 (m, ), 2.7—3.1 (m, ), 7.28—7.90 (m, 2-, 3-, 4-H), 8.31 (d d, 1-H). MS *m/e* (relative in.): 214 (M^+) (69.4), 213 (19.4), 199 (38.9), 186 (83.3), 185 (100), 121 (22.2), 92 (19.4), 65 (19.4).