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Potential Antiinflammatory Agents. III.[1] Syntheses of 1-Substituted 6-Chloro-5-cyclohexylindans as Related Compounds of 6-Chloro-5-cyclohexylindan-1-carboxylic Acid (TAI-284)

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Some 1-substituted 6-chloro-5-cyclohexylindans: 6-chloro-5-cyclohexyl-1-hydroxymethylcarbonylindan (**5**), 1-acetyl-6-chloro-5-cyclohexyl-1-indanol (**10**), 5-[(6-chloro-5-cyclohexylindan)-1-yl]tetrazole (**13**) and 6-chloro-5-cyclohexyl-1-methylindan-1-carboxylic acid (**14**), were prepared as related compounds of 6-chloro-5-cyclohexylindan-1-carboxylic acid (TAI-284) (**1**), a potent nonsteroidal antiinflammatory agent. During this work an interesting rearrangement from the acetate (**4**) of **5** to 3-acetyl-5-chloro-6-cyclohexylindene (**6**) by acetic acid treatment was discovered and the mechanism of this reaction was proposed.

In the previous communications,[1,3,4] the synthesis and antiinflammatory activities of 6-chloro-5-cyclohexylindan-1-carboxylic acid (TAI-284) (**1**) and related 5-substituted indan-1-carboxylic acids have been reported. Although **1** exhibited a potent antiinflammatory activity, the replacement of cyclohexyl moiety at C-5 by other alkyl groups such as isopropyl or isobutyl, or the removal of the chlorine atom at C-6 resulted in considerable reduction of the activities.[1] However, it is also attractive to vary the carboxyl moiety at C-1 to other pharmaceutically interesting groups. Therefore, synthesis of some 1-substituted 6-chloro-5-cyclohexylindans was attempted. The present paper describes the syntheses of 1-hydroxyacetyl, 1-acetyl-1-hydroxy and 1-tetrazolyl analogs and 1-methylated derivative of **1**.

1 bears certain structural similarity to antiinflammatory corticosteroids, if the carboxyl group at C-1 and chlorine atom at C-6 are considered to represent the corticoidal dihydroxyacetone side chain and 11β-hydroxyl group, respectively, which are essential for the activity. It was therefore of interest to modify the carboxyl group of **1** for an even closer resemblance to the corticoidal side chain. So syntheses of 6-chloro-5-cyclohexyl-1-hydroxyacetylindan (**5**) and 1-acetyl-6-chloro-5-cyclohexylindan-1-ol (**10**) were attempted.

5 was synthesized from the corresponding carboxylic acid (**1**) by the method of Steiger and Reichstein,[5,6] as shown in Chart 1.

The acid chloride (**2**) derived from **1** was converted to the diazoketone (**3**) by reaction with diazomethane. Treatment of **3** with acetic acid and subsequent alkaline hydrolysis gave the desired 1-hydroxyacetyl analog (**5**). **5** was considerably unstable and decomposed gradually to an oily substance on standing at room temperature.

Under the same consideration, Juby, *et al.*[7] have independently prepared both 5-cyclohexyl-1-hydroxyacetylindan and its 6-hydroxy derivative and reported that the 1-hydroxy-

1) Part II: S. Noguchi, S. Kishimoto, I. Minamida, and M. Obayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 529 (1974).
2) Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*
3) S. Noguchi, S. Kishimoto, I. Minamida, M. Obayashi, and K. Kawakita, *Chem. Pharm. Bull.* (Tokyo), **19**, 646 (1971).
4) K. Kawai, S. Kuzuna, S. Morimoto, H. Ishii, and N. Matsumoto, *Jap. J. Pharmacol.*, **21**, 621 (1971).
5) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).
6) W.H. Linnell, D.W. Mathieson, and G. Williams, *Nature*, **167**, 237 (1951).
7) P.F. Juby, T.W. Hudyma, and R.A. Partyka, *J. Med. Chem.*, **15**, 120 (1972).

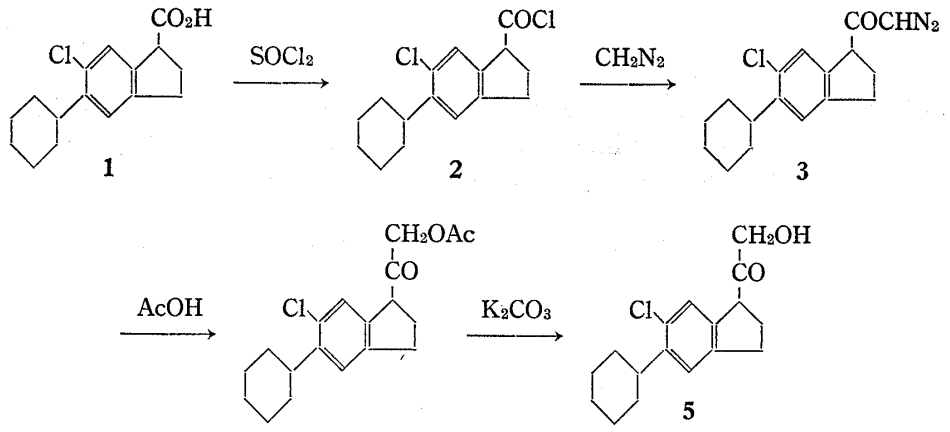


Chart 1

acetylindan compounds were considerably less active than the corresponding carboxyl compounds. **5** prepared in this study was also less potent than **1.**

Interestingly, when intermediary **4** was heated in acetic acid for a long time, 3-acetylindene derivative (**6**) was isolated quantitatively. The structure of **6** was confirmed by the ultraviolet (UV), infrared (IR) and nuclear magnetic resonance (NMR) spectra[8]: UV 238 mμ (ε=15000); IR 1671 cm^{-1} (CO); NMR 2.47 (3H, singlet, CH_3CO), 3.50 (2H, doublet, J=2.1 Hz, CH_2 at C-1), 7.30 (1H, triplet, J=2.1 Hz, CH at C-2), 7.36 and 8.17 ppm (1H each, singlet, aromatic protons at C-4 and C-7). The following mechanism is proposed for the formation of **6** from **4** (Chart 2):

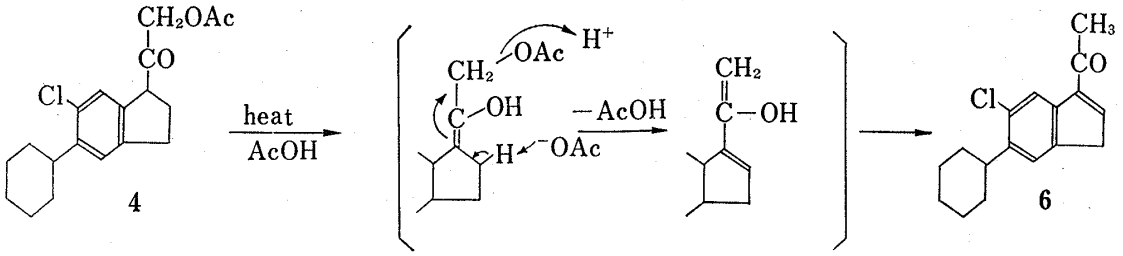


Chart 2

The synthesis of **10** was accomplished by the procedures shown in Chart 3, starting with **1.** **1** was heated with acetic anhydride in pyridine under conditions of decarboxylative acetylation[9] to give an expected enol acetate (**8**), which was obtained as a mixed product with intermediary 1-acetylindan derivative (**7**) and isolated by chromatography. **8** was subjected to the epoxidation with *m*-chloroperbenzoic acid followed by alkaline hydrolysis, according to the general method of Gallagher[10] in preparing 17α-hydroxypregnan-20-ones, to give the desired product (**10**).

Replacement of a carboxyl by a comparably acidic 5-tetrazolyl group in a biologically active carboxylic acid has sometimes resulted in retention of activity or in an improvement in potency.[11] Thus, **1** was converted to the corresponding tetrazolyl analog (**13**) *via* sodium azide treatment of the carbonitrile (**12**), which was obtained by dehydration of the carboxamide derivative (**11**) with P_2O_5, as shown in Chart 4.

8) W. Uhde and K. Hartke, *Chem. Ber.*, **103**, 2675 (1970).
9) J.A. King and F.H. McMillan, *J. Am. Chem. Soc.*, **73**, 4911 (1951); W. Wunderlich, *Arch. Pharm.*, **286**, 512 (1953); H.D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91 (1928).
10) T.H. Kritchivsky and T.F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).
11) P.F. Juby, T.W. Hudyma, and M. Brown, *J. Med. Chem.*, **11**, 111 (1968); P.F. Juby and T.W. Hudyma, *ibid.*, **12**, 396 (1969); Merck and Co., Inc., Bel. Pat. 727012 (1969).

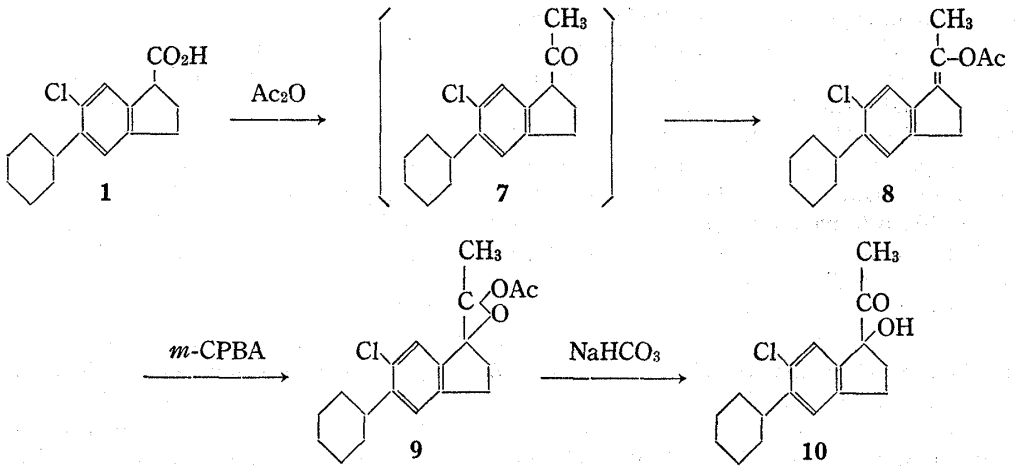


Chart 3

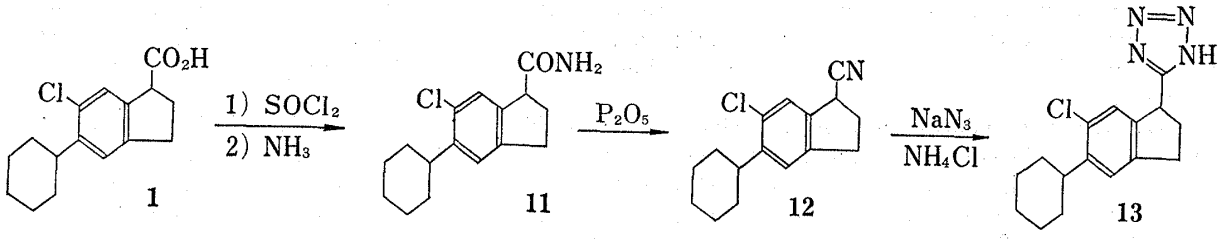
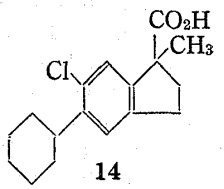


Chart 4

1-Methylated derivative (**14**) of **1** was prepared by treatment of the methyl ester of **1** with methyl iodide in DMSO in the presence of sodium hydride, followed by subsequent hydrolysis.

Compounds synthesized in the present paper were tested orally for antiinflammatory activity using the carrageenin-induced foot edema method in rats.[12] All of the compounds, however, were less active than **1**.[13]



Experimental[14]

6-Chloro-5-cyclohexyl-1-diazomethylcarbonylindan (3)——A mixture of 1.9 g of 6-chloro-5-cyclohexylindan-1-carboxylic acid (1) and 5 ml of $SOCl_2$ was refluxed for 1 hr. The reaction solution was concentrated under reduced pressure to give 2.2 g of the crude acid chloride (2). Without further purification, the acid chloride was dissolved in 6 ml of ether and treated with a solution of CH_2N_2 in ether. After decomposition of the excess of CH_2N_2 with AcOH, the solution was concentrated to dryness under reduced pressure to give a residual solid, which was recrystallized from hexane to give 1.5 g (73%) of 3 as yellow crystals, mp 70—71°. *Anal.* Calcd. for $C_{17}H_{19}ON_2Cl$: C, 67.43; H, 6.32; N, 9.25; Cl, 11.71. Found: C, 67.72; H, 6.37; N, 9.04; Cl, 11.80. IR ν_{max}^{Nujol} cm^{-1}: 1632 (C=O), 2270 (CHN_2). NMR ($CDCl_3$) δ: 3.95 (1H, br. t, J=7 Hz, C_1–H), 5.24 (1H, s, CHN_2), 7.16, 7.23 (1H each, s, aromatic protons at C_4 and C_7).

1-Acetoxymethylcarbonyl-6-chloro-5-cyclohexylindan (4)——A solution of 1.3 g of 3 in 5 ml of AcOH was heated on a water bath for 3 hr and then concentrated to dryness under reduced pressure. The residue was extracted into benzene. The benzene solution was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized from hexane to give 1.0 g (87%) of 4, mp 114—115°. *Anal.* Calcd. for $C_{19}H_{23}O_3Cl$: C, 68.15; H, 6.92; Cl, 10.59. Found: C, 67.91; H, 6.92; Cl, 10.09. IR ν_{max}^{Nujol} cm^{-1}: 1758 (CH_3CO), 1722 ($COCH_2$). NMR ($CDCl_3$) δ: 2.15 (3H, s, CH_3CO), 4.10 (1H, br. t, J= 7 Hz, C_1–H), 4.78 (2H, s, $COCH_2O$), 3.16, 3.25 (1H, each, s, aromatic protons at C_4 and C_7).

12) C.A. Winter, E.A. Risley, and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
13) K. Kawai, unpublished.
14) All melting points are uncorrected. IR spectra were obtained with a Hitachi-215 spectrophotometer and NMR spectra with a Varian A-60 spectrometer using TMS as internal standard. UV spectra were taken with a Perkin-Elmer 450 spectrophotometer.

6-Chloro-5-cyclohexyl-1-hydroxymethylcarbonylindan (5)——A mixture of 942 mg of **4** and 380 mg of K_2CO_3 in 3 ml of H_2O and 25 ml of MeOH was stirred for 2 hr at room temperature under nitrogen atmosphere. The reaction mixture was concentrated to dryness. The residue was extracted with ether. The extracts were washed with H_2O, dried over Na_2SO_4 and concentrated. The oily residue was chromatographed on silica gel with $CHCl_3$–acetone (9:1) to give 462 mg (50%) of oily **5**. The structure of **5** was confirmed by the following spectral data: IR ν_{max}^{Nujol} cm^{-1}: 3440 (OH), 1720 (C=O). NMR ($CDCl_3$) δ: 4.35 (2H, s, $COCH_2O$), 4.05 (1H, br. t, J=7 Hz, C_1-H), 7.14, 7.18 (1H each, s, aromatic protons at C_4 and C_7).

3-Acetyl-5-chloro-6-cyclohexylindene (6)——A solution of 500 mg of **4** in 5 ml of AcOH was refluxed for 20 hr and then concentrated to dryness under reduced pressure. The residual solid was recrystallized from hexane to give 363 mg (89%) of **6**, mp 112—114°. *Anal.* Calcd. for $C_{17}H_{19}OCl$: C, 74.30; H, 6.93. Found: C, 74.22; H, 7.02. IR ν_{max}^{Nujol} cm^{-1}: 1671 (C=O). NMR ($CDCl_3$) δ: 2.47 (3H, s, CH_3CO), 7.30 (1H, t, J=2.1 Hz, C_2–H), 3.50 (2H, d, J=2.1 Hz, C_1–H), 7.36, 8.18 (1H each, s, aromatic protons at C_4 and C_7).[8]

1-Acetyl-6-chloro-5-cyclohexylindan (7) and 1-(1-Acetoxyethylidene)-6-chloro-5-cyclohexylindan (8)——A mixture of 3.6 g of **1**, 30 ml of Ac_2O and 30 ml of pyridine was stirred for 8 hr at 80°. The reaction mixture was concentrated under reduced pressure to dryness. The residue was chromatographed on silica gel with benzene to give 0.42 g (12%) of **7** and 1.40 g (34%) of **8** respectively. **7** thus obtained exhibited mp 105—106°. *Anal.* Calcd. for $C_{17}H_{21}OCl$: C, 69.73; H, 7.25; Cl, 12.11. Found: C, 69.48; H, 7.37; Cl, 12.23. IR ν_{max}^{Nujol} cm^{-1}: 1707 (C=O). NMR (CCl_4) δ: 2.13 (3H, s, CH_3), 3.92 (1H, q, C_1–H), 7.05, 7.20 (1H each, s, aromatic protons at C_4 and C_7). Analytical sample of **8** was obtained by recrystallization from MeOH, mp 76—84°. *Anal.* Calcd. for $C_{19}H_{23}O_2Cl$: C, 71.57; H, 7.27; Cl, 11.12. Found: C, 71.26; H, 7.37; Cl, 11.18. IR ν_{max}^{Nujol} cm^{-1}: 1750 (CH_3CO). The NMR spectrum of **8** thus obtained indicated the sample was a mixture of *E* and *Z* isomers.

1-(1-Acetoxyethylidene)-6-chloro-5-cyclohexylindan Oxide (9)——To a solution of 319 mg of **8** in 10 ml of benzene was added 220 mg of *m*-chloroperbenzoic acid. The mixture was stirred for 1 hr at room temperature. The reaction solution was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with benzene to give 260 mg (78%) of **9**, which was recrystallized from hexane, mp 138—139°. *Anal.* Calcd. for $C_{19}H_{23}O_3Cl$: C, 68.15; H, 6.92; Cl, 10.58. Found: C, 68.19; H, 6.82; Cl, 10.38. IR ν_{max}^{Nujol} cm^{-1}: 1712, 1727. NMR (CCl_4) δ: 2.04 (6H, s, CH_3 and CH_3CO), 3.00 (4H, m, methylene protons at C_2 and C_3), 7.12, 7.18 (1H each, s, aromatic protons at C_4 and C_7).

1-Acetyl-6-chloro-5-cyclohexyl-1-indanol (10)——A mixture of 200 mg of **9**, 10 ml of 0.2 M aqueous solution of $NaHCO_3$ and 50 ml of MeOH was refluxed for 1 hr. The reaction solution was concentrated to dryness under reduced pressure. The residue was extracted into $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over Na_2SO_4 and concentrated to give a residual solid, which was recrystallized from cyclohexane to give 128 mg (73%) of **10**, mp 91—92°. *Anal.* Calcd. for $C_{17}H_{21}O_2Cl$: C, 69.73; H, 7.22; Cl, 12.12. Found: C, 69.80; H, 7.19; Cl, 12.22. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 3440 (OH). NMR (CCl_4) δ: 2.00 (3H, s, CH_3CO), 4.32 (1H, br. s, OH), 7.02, 7.20 (1H each, s, aromatic protons at C_4 and C_7).

6-Chloro-5-cyclohexylindan-1-carboxamide (11)——To a solution of liq. NH_3 in ether was added a solution of 13.5 g of **2**, which was prepared by treatment of **1** with $SOCl_2$, in 20 ml of benzene. The resulting precipitates were collected and recrystallized from MeOH to give 11.8 g (87%) of **11**, mp 184—185°. *Anal.* Calcd. for $C_{16}H_{18}ONCl$: C, 69.18; H, 7.26; N, 5.06; Cl, 12.76. Found: C, 68.95; H, 7.19; N, 5.19; Cl, 12.54. IR ν_{max}^{Nujol} cm^{-1}: 1650 ($CONH_2$), 3200, 3380 (NH_2). NMR (d_6-DMSO) δ: 3.81 (1H, br. t, J=7 Hz, C_1–H), 7.17, 7.26 (1H each, s, aromatic protons at C_4 and C_7).

6-Chloro-5-cyclohexylindan-1-carbonitrile (12)——A mixture of 1.8 g of **11** and 1.0 g of P_2O_5 was heated for 2 hr at 200—210° under N_2 atmosphere. After being cooled, the reaction mixture was poured into H_2O and extracted with ether. The extracts were washed with H_2O, treated with charcoal, dried over Na_2SO_4 and concentrated. The residual solid was recrystallized from hexane to give 0.8 g (48%) of **12**, mp 102—103°. *Anal.* Calcd. for $C_{16}H_{18}NCl$: C, 73.92; H, 6.98; N, 5.39. Found: C, 74.12; H, 7.18; N, 5.46. IR ν_{max}^{Nujol} cm^{-1}: 2230 (CN). NMR (CCl_4) δ: 3.94 (1H, br. t, J=8 Hz, C_1–H), 7.10, 7.34 (1H each, s, aromatic protons at C_4 and C_7).

5-[(6-Chloro-5-cyclohexylindan)-1-yl]tetrazole (13)——A mixture of 0.6 g of **12**, 0.22 g of NaN_3, 0.18 g of NH_4Cl and 7 ml of DMF was stirred for 20 hr at 120° under N_2 atmosphere. The cooled reaction mixture was poured onto ice-water and extracted with ether. The ether solution was washed with H_2O and then extracted with 10% aqueous NaOH. The alkaline extracts were washed with ether, treated with charcoal and acidified with conc. HCl. The resulting precipitates were collected, washed with H_2O, dried and recrystallized from MeOH to give 170 mg (24%) of **13**, mp 245—248°. *Anal.* Calcd. for $C_{16}H_{19}N_4Cl$: C, 63.46; H, 6.32; N, 18.50. Found: C, 63.72; H, 6.36; N, 18.64. IR ν_{max}^{Nujol} cm^{-1}: 1580, 2500—2800 (tetrazole). NMR (d_6-DMSO) δ: 4.76 (1H, br. t, J=8 Hz, C_1–H), 7.16, 7.30 (1H each, s, aromatic protons at C_4 and C_7), 7.62 (1H, br. s, NH).

6-Chloro-5-cyclohexyl-1-methylindan-1-carboxylic Acid (14)——To a solution of 1.59 g of methyl 6-chloro-5-cyclohexylindan-1-carboxylate, prepared by treatment of the acid chloride (**2**) with MeOH using standard procedure, and 1.00 g of CH_3I in 10 ml of DMSO was added 0.16 g of NaH with stirring under N_2 atmosphere. After being allowed to stand overnight at room temperature, the reaction mixture was poured onto ice-water and extracted with ether. The ether solution was washed with H_2O, dried over Na_2-

SO_4 and concentrated to give 1.35 g of the crude methyl ester of 14. To the crude ester was added a solution of 0.5 g of NaOH in 10 ml of EtOH and 10 ml of H_2O. The mixture was refluxed for 5 hr under N_2 atmosphere and then poured onto ice-water. The alkaline aqueous solution was washed with ether and acidified with conc. HCl. The precipitates were collected, washed with H_2O, dried and recrystallized from hexane to give 0.75 g (47%) of **14**, mp 186—187°. *Anal.* Calcd. for $C_{17}H_{21}O_2Cl$: C, 69.73; H, 7.30; Cl, 12.11. Found: C, 69.69; H, 7.16; Cl, 12.76. IR ν_{max}^{Nujol} cm^{-1}: 1700 (COOH). NMR ($CDCl_3$) δ: 1.52 (3H, s, CH_3), 7.12, 7.31 (1H each, s, aromatic protons at C_4 and C_7), 11.20 (1H, br. s, COOH).

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