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Potential Antiinflammatory Agents. II.[1] Synthesis and Structure-Activity Relationships of 6-Chloro-5-cyclohexylindan-1-carboxylic Acid (TAI-284) and Related 5-Substituted Indan-1-carboxylic Acids[2]

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6-Chloro-5-cyclohexylindan-1-carboxylic acid (TAI-284) and related 5-substituted indan-1-carboxylic acids were prepared for the evaluation of antiinflammatory action. Among them, TAI-284 showed the most potent activity, comparable to that of indomethacin. The replacement of the cyclohexyl moiety at C–5 by other alkyl groups such as isobutyl or isopropyl, or the removal of the chlorine atom at C–6 resulted in a considerable reduction of the activities.

The resolution of TAI-284 was effected with quinine, and it was found that the antiinflammatory activity virtually resided in the dextro isomer, the absolute configuration of which was assigned the sinister series by the optical rotatory dispersion spectrum and X-ray crystarography.

Although antiinflammatory corticosteroids are dramatically effective in the treatment of rheumatoid arthritis and related diseases, they have serious hormonal side effects such as adaptive adrenal atrophy. Considerable efforts have been made to prepare more specific antiinflammatory steroids with little or no such hormonal side effects, but almost all of them have resulted in failure. On the other hand, many non-steroidal compounds have been explored as possible antiinflammatory agents. One of the most explored series is arylalkanoic acids, among which various *p*-alkylphenylacetic acids such as 4-isobutyl-α-methylphenylacetic acid[4] and 3-chloro-4-cyclohexyl-α-methylphenylacetic acid[5] were reported as potent antiinflammatory agents. In the course of our synthetic study of potential antiinflammatory agents, the synthesis and biological evaluation of indan-1-carboxylic acid derivatives were much attractive, because they were considered to have some structural similarity to corticosteroids[1,6] and also to be an analog of the active phenylacetic acids. Thus some 5-substituted indan-1-carboxylic acids were prepared. In our previous communication,[1,7] it was reported that 6-chloro-5-cyclohexylindan-1-carboxylic acid (TAI-284) (**1**) showed remarkable antiinflammatory, analgetic and antipyretic activities. The present paper describes the synthesis and structure-activity relationships of TAI-284 (**1**) and related 5-substituted indan-1-carboxylic acids.

The synthesis of **1** was accomplished by the procedures, as shown in Chart 1, starting with 3-chloro-4-cyclohexylphenylacetonitrile[1] (**2**). **2** was condensed successively with diethyl carbonate and ethyl bromoacetate, and subsequent alkaline hydrolysis gave 3-chloro-

1) Part I (preliminary communication): S. Noguchi, S. Kishimoto, I. Minamida, M. Obayashi, and K. Kawakita, *Chem. Pharm. Bull.* (Tokyo), **19**, 646 (1971).
2) A part of this work was presented at the 91st Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, April 1971.
3) Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*
4) S.S. Adams, E.E. Cliffe, B. Lessel, and J.S. Nicholson, *J. Pharm. Sci.*, **56**, 1686 (1967).
5) T.Y. Shen, C.P. Dorn, W.V. Ruyle, B.E. Witzel, C.H. Shunk, A.R. Matzuk, H. Schwam, R.L. Bugianesi, L. Bock, H.M. Lewis, G. Arth, and A.A. Patchett, 2nd Mid-Atlantic Regional Meeting of American Chemical Society, New York, Feb. 6–7, 1967; *Chem. Eng. News*, **45**, 10 (Feb. 13, 1967); T.Y. Shen, *Chim. Ther.*, **2**, 459 (1967).
6) C.R. Ganellin, *Advances in Drug Research*, **4**, 219 (1967).
7) K. Kawai, S. Kuzuna, S. Morimoto, H. Ishii, and N. Matsumoto, *Jap. J. Pharmacol.*, **21**, 621 (1971).

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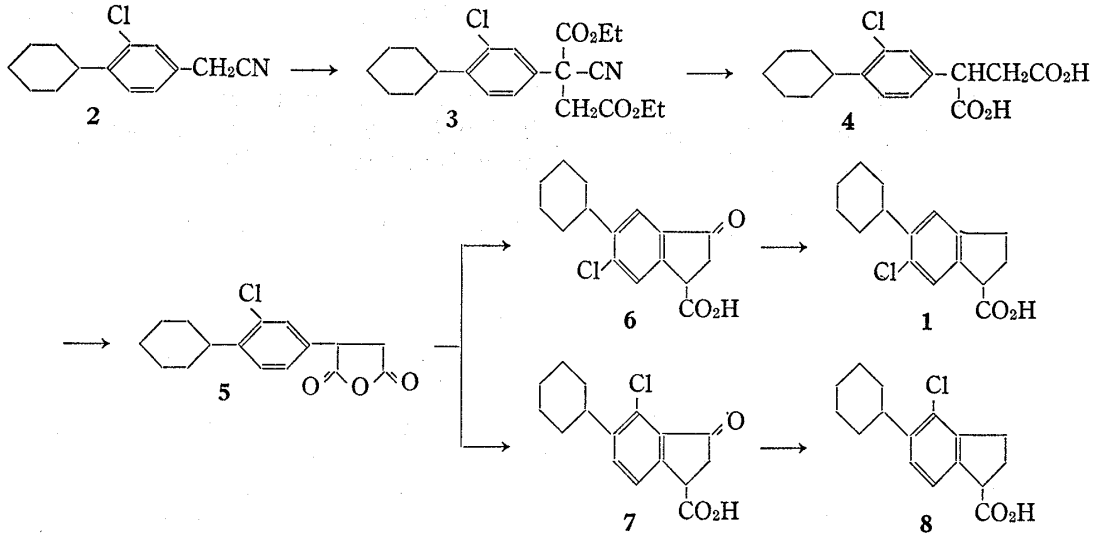

Chart 1

4-cyclohexylphenylsuccinic acid (**4**). **4** was converted to the anhydride (**5**) by heating with acetic anhydride. Cyclization of **5** was effected with aluminum chloride in methylene chloride to give 6-chloro-5-cyclohexyl-3-oxoindan-1-carboxylic acid (**6**). In addition to **6**, the isomeric 4-chloro-5-cyclohexyl-3-oxoindan-1-carboxylic acid (**7**) was simultaneously formed as a minor product. Clemmensen reduction of **6** gave the desired **1**, mp 151—152°, and the reduction of **7** gave 4-chloro-5-cyclohexylindan-1-carboxylic acid (**8**). In the nuclear magnetic resonance (NMR) spectra, **1** showed two singlets at δ 7.12 and 7.39 ppm due to the substantially uncoupled *para* aromatic protons at C-4 and C-7, while **8** a characteristic four line AB pattern centered at δ 7.20 ppm due to the coupling of *ortho* protons at C-6 and C-7. The mass spectrum of **1** showed two intense peaks at *m/e* 278 (M^+) and 233 (M^+—45, the base peak) formed by loss of the carboxyl group.

Intermediary phenylsuccinic acid (**4**) was alternatively prepared from 4-cyclohexylbenzaldehyde[8] (**9**) by a modification of the procedure of Baker and Lapworth,[9,10] as shown in Chart 2. **9** was chlorinated with chlorine in dichloroethane in the presence of aluminum chloride to give the 3-chloro derivative (**10**). Condensation of **10** with ethyl cyanoacetate, followed by addition of hydrogen cyanide and subsequent hydrolysis, gave **4**.

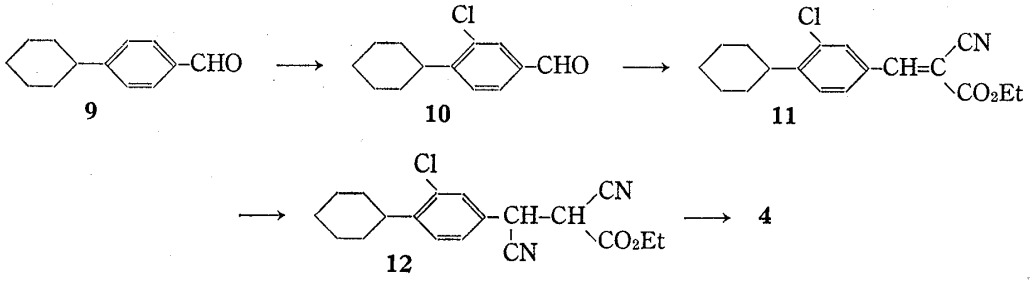

Chart 2

5-Cyclohexylindan-1-carboxylic acid (**13**), the dechloro derivative of **1**, was similarly prepared from 4-cyclohexylphenylacetonitrile *via* 4-cyclohexylphenylsuccinic acid. **1** was also obtained by the direct chlorination of **13**. This chlorination was effected with chlorine in appropriate solvents for aromatic chlorination in the presence of $FeCl_3$ as a catalyst. Inter-

8) D. Bodroux and R. Thomassin, *Compt. Rend.*, **205**, 991 (1937).
9) W. Baker and A. Lapworth, *J. Chem. Soc.*, **1925**, 560.
10) V. Askam and W.H. Linnell, *J. Chem. Soc.*, **1954**, 2435.

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estingly, when acetonitrile was used as the solvent, this reaction proceeded even in the absence of the catalyst and with more selectivity, giving **1** in about 80% yield. The 6-bromo analog, 6-bromo-5-cyclohexylindan-1-carboxylic acid (**14**), was prepared from **13** using bromine instead of chlorine.

Recently, independent of our research, Juby, *et al.*[11] have reported the preparation and antiinflammatory activity of some indan-1-carboxylic acids including compounds, **1** and **13**. They prepared **1** by treatment of **13**, which was led from **9** through the intermediary 4-cyclohexylphenylsuccinic acid, with N-chlorosuccinimide in DMF. Furthermore, Allen, *et al.*[12] have prepared **1** by chlorination of **13**, according to the procedure reported previously in our patent,[13] for a comparative study of biological activity.

6-Chloro-5-isopropylindan-1-carboxylic acid (**19d**) and 6-chloro-5-isobutylindan-1-carboxylic acid (**19c**), which are 5-alkyl analogs of **1**, were synthesized from *p*-isopropyl- or *p*-isobutyl-phenylacetonitrile (**15a, 15b**), respectively, by similar procedures, as shown in Chart 3.

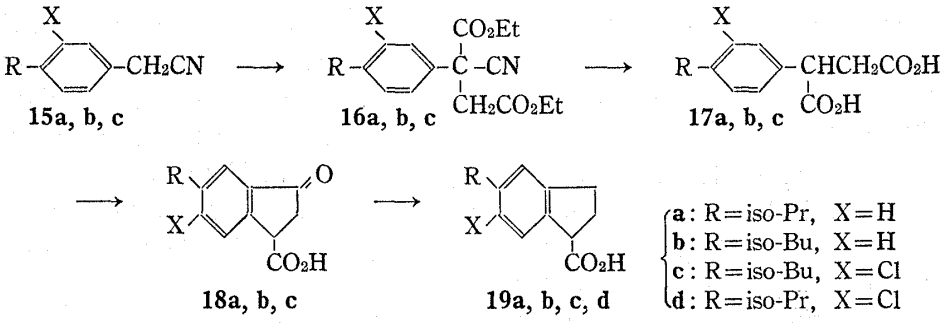

Chart 3

Antiinflammatory activity of indan-1-carboxylic acids prepared in this study is shown in Table I.[14] Among them, **1** showed the most potent activity.

Table I. Antiinflammatory Activity of 5-Substituted Indan-1-carboxylic Acids in Carrageenin Edema Test in Rats

	Antiinflammatory activity[14]
6-Chloro-5-cyclohexylindan-1-carboxylic acid (TAI-284) (**1**)	###
5-Cyclohexylindan-1-carboxylic acid (**13**)	##
6-Chloro-5-isobutylindan-1-carboxylic acid (**19c**)	+
6-Chloro-5-isopropylindan-1-carboxylic acid (**19d**)	+
6-Bromo-5-cyclohexylindan-1-carboxylic acid (**14**)	###
4-Chloro-5-cyclohexylindan-1-carboxylic acid (**8**)	±
Phenylbutazone	##
Indomethacin	###

1 possesses an asymmetric center at C-1, the position bearing a conformationally fixed carboxyl group. The racemic product was resolved *via* its quinine salt to give its enantiomers. Interestingly, it was found that the antiinflammatory activity[14] virtually resided in the dextro rotatory isomer, mp 130—135°, $[\alpha]_D$ +28.1°. The absolute configuration of *d*-TAI-284 was assigned the sinister form by comparing its optical rotatory dispersion (ORD) spectrum with that of (*S*)-(—)-indan-1-carboxylic acid reported by Brewster *et al.*,[15] as shown in Fig. 1. The ORD curve of *d*-TAI-284 was similar to that of (*S*)-(—)-indan-1-carboxylic acid, showing

11) P.F. Juby, W.R. Goodwin, T.W. Hudyma, and R.A. Partyka, *J. Med. Chem.*, **15**, 1297 (1972).
12) G.R. Allen, Jr., R. Littell, F.J. McEvoy, and A.E. Sloboda, *J. Med. Chem.*, **15**, 934 (1972).
13) S. Noguchi, S. Kishimoto, M. Obayashi, I. Minamida, and K. Kawai, Belg. Patent 750405 (1970).
14) K. Kawai, S. Kuzuna, unpublished.
15) J.H. Brewster and J.G. Buta, *J. Am. Chem. Soc.*, **88**, 2233 (1966).

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multiple Cotton effects in the region 250—275 mμ corresponding in fine structure to the ^1L_b absorption bands. The sodium salt of *d*-TAI-284 also showed a similar ORD curve to that of sodium (*S*)-(—)-indan-1-carboxylate. Finally, the sinister configuration of *d*-TAI-284 was confirmed by the X-ray crystallography.[16]

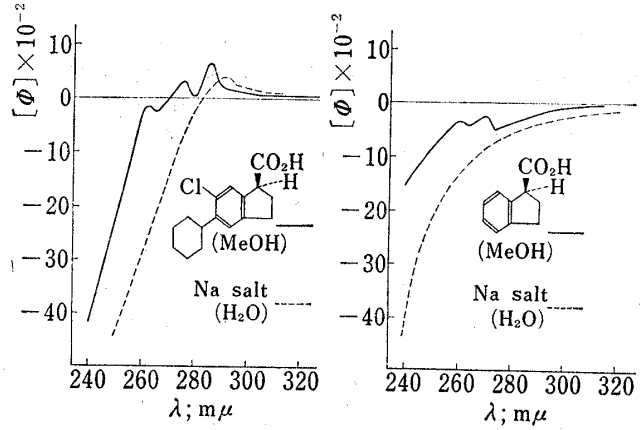

Fig. 1. ORD Curves of (*S*)-(+)-TAI-284 and (*S*)-(—)-Indan-1-carboxylic Acid

Structure-Activity Relationships

Racemic TAI-284 (**1**) showed remarkable antiinflammatory, analgetic and antipyretic activities comparable or even superior to those of indomethacin in various animal assays as shown in Table II.[7] In particular, it should be noted that the antipyretic activity of **1** was remarkable as compared with other hitherto known antipyretic drugs. Antiinflammatory activities of related compounds decreased in the following order, **1**≒**14**>**13**>**19c**≒**19d**>**8**, as shown in Table I. Thus, the presence and position of the halogen substituent seemed to be particularly important, since **13** and **8** exhibited much reduced activity while **14** was approximately equal to **1** in the activity. The structure specificity was also indicated by a considerable reduction in potency when the 5-cyclohexyl group was replaced by other alkyls such as isopropyl and isobutyl.

Table II. Comparative Antiinflammatory, Analgetic and Antipyretic Activities of Racemic TAI-284 (**1**) and Indomethacin (approximate relative potency: TAI-284=1)

Bioassay		(±) TAI-284	Indomethacin
Antiinflammatory activity	C.E.[a]	1	0.75
	G.P.[b]	1	2.08
	C.P.[c]	1	0.76
Analgetic activity	Randall-selitto	1	1
Antipyretic activity	Febrile rats	1	0.18
	Febrile rabbits	1	0.39
Toxicity (LD_{50})	mice (*p.o.*)	880mg/kg	25mg/kg
	rats (*p.o.*)	45	20

a) carrageenin edema
b) granuloma pouch
c) cotton pellet

Of both optical isomers of **1**, the antiinflammatory activity virtually resided in the dextro isomer having the sinister configuration at C-1. This is in good accord with other observations[17] that the antiinflammatory activity of α-methylarylacetic acids, such as α-methylated indomethacin analogs[18] or 3-chloro-4-cyclohexyl-α-methylphenylacetic acid,[5] is associated with the dextro rotatory isomer having the sinister configuration at the α-carbon. Interest-

16) K. Kamiya, K. Wada, and M. Nishikawa, unpublished. We thank Dr. Nishikawa of our laboratories for the X-ray analysis.
17) The only exception was observed in ibuprofen (4-isobutyl-α-methylphenylacetic acid). The two enantiomorphs have indicated no difference in the antiinflammatory potency in guinea pig ultraviolet erythema test.[4]
18) Merck and Co., Inc., Brit. Patent 957990 (1964) [*Chem. Abstr.*, **61**, 4319 (1964)].

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ingly, corticosteroids also have the similar configuration at C-17.[1] The configuration of the carboxyl group at C-1 of **1** may play an important role in the biological activity like the dihydroxyacetone side chain at C-17 of corticosteroids, perhaps by exerting influence on a stereospecific drug-receptor interaction. Recently, our biological group suggested that the difference in the biological activity of the enantiomers of **1** is in part due to different rate of metabolism which lead to different blood concentrations.[19]

Clinical evaluation of *dl*-TAI-284 (**1**) is now under progress in this country.

Experimental[20]

Preparation of 4-Substituted 3-Chlorophenylacetonitriles——These nitriles were prepared using a procedure similar to the one described for 3-chloro-4-cyclohexylphenylacetonitrile (**2**). To a stirred, ice-cooled mixture of 39.8 g of 4-cyclohexylphenylacetonitrile and 32.4 g of $FeCl_3$ in 100 ml of CCl_4 was added a solution of 14.2 g of Cl_2 in 230 ml of CCl_4 dropwise. Stirring and cooling were continued for 2 hr. A solution of 4.7 g of Cl_2 in 77 ml of CCl_4 was further added dropwise to the reaction mixture. After being stirred for additional 15 min, the reaction mixture was poured into 1 liter of 12% HCl. The CCl_4 layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic solution was washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residual oil was distilled to give **2** as a colorless oil (29.5 g, 61%, purity:[21] 75%), bp 155—168° (2.5 mmHg). Analytical sample was obtained by repeated distillation. *Anal.* Calcd. for $C_{14}H_{16}NCl$: C, 71.94; H, 6.90; N, 5.99; Cl, 15.17. Found: C, 72.04; H, 6.90; N, 5.74; Cl, 15.14. 3-Chloro-4-isobutylphenylacetonitrile (**15c**): bp 125—128° (3.4 mmHg) (70% yield, purity:[21] 72—79%). Analytical sample was obtained by repeated distillation. *Anal.* Calcd. for $C_{12}H_{14}NCl$: C, 69.39; H, 6.79; N, 6.74; Cl, 17.07. Found: C, 69.41; H, 6.63; N, 7.11; Cl, 17.25.

Preparation of Diethyl α-Cyano-α-(4-substituted phenyl)succinates——These succinates were prepared using a procedure similar to the one described for diethyl α-cyano-α-(3-chloro-4-cyclohexylphenyl)succinate (**3**). To a stirred suspension of 68 g of NaOEt (prepared from 23 g of metallic Na) in 100 ml of dry toluene was added dropwise a solution of 234 g of **2** in 400 ml of dry toluene, followed by 354 g of diethyl carbonate. The mixture was heated on an oil bath with stirring, and the resulting EtOH was distilled off as it was formed. During this reaction, the volume of the reaction mixture was maintained constant by means of adding dry toluene dropwise. After the temperature of the vapor had risen to 110—112°, the heating was stopped. To the cooled reaction mixture was added 167 g of ethyl bromoacetate, and the mixture was heated under reflux for 2 hr. After being cooled, the reaction mixture was poured onto ice-water and extracted with AcOEt. The extract was washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residual oil was distilled to give **3** as a colorless oil (299 g, 76%), bp 205—210° (0.5 mmHg). *Anal.* Calcd. for $C_{21}H_{26}O_4NCl$: C, 64.35; H, 6.69; N, 3.57. Found: C, 64.58; H, 6.81; N, 3.71. IR $\nu_{max}^{liq.}$ cm^{-1}: 2250 (CN), 1745 (C=O). Diethyl α-cyano-α-(4-cyclohexylphenyl)succinate: bp 198—201° (1.8 mmHg), mp 53—55° (89%). *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.35; H, 7.69; N, 4.03. IR $\nu_{max}^{liq.}$ cm^{-1}: 2260 (CN), 1750 (C=O). Diethyl α-cyano-α-(4-isopropylphenyl)succinate (**16a**): bp 159—160° (0.15 mmHg, 75.3%). *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.01; H, 7.50; N, 4.55. IR $\nu_{max}^{liq.}$ cm^{-1}: 2250 (CN), 1745 (C=O). Diethyl α-cyano-α-(4-isobutylphenyl)succinate (**16b**): bp 158—161° (0.2 mmHg, 71.5%). *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.18; H, 7.91; N, 4.36. IR $\nu_{max}^{liq.}$ cm^{-1}: 2260 (CN), 1740 (C=O). Diethyl α-cyano-α-(3-chloro-4-isobutylphenyl)succinate (**16c**): bp 190—194° (0.8 mmHg, 72.7%). *Anal.* Calcd. for $C_{19}H_{24}O_4NCl$: C, 62.37; H, 6.61; N, 3.83; Cl, 9.72. Found: C, 62.43; H, 6.56; N, 3.82; Cl, 9.69. IR $\nu_{max}^{liq.}$ cm^{-1}: 2250 (CN), 1740 (C=O).

3-Chloro-4-cyclohexylbenzaldehyde (10)——7.6 g of 4-cyclohexylbenzaldehyde (**9**) was added dropwise to 13.4 g of pulverized anhydrous $AlCl_3$ with vigorous stirring at 60°. The resulting molten complex[22] was dissolved in 120 ml of ethylene chloride, and the solution was cooled at −10°. Cl_2 was introduced to the cooled solution for 45 min with stirring. After being stirred for additional 1 hr, the reaction mixture was poured into dilute HCl. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated. The residual oil was distilled to give **10** as a colorless oil (5.6 g, 63%), bp 117—121° (0.3 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 1700 (C=O). NMR (in CCl_4) δ: 9.86 (1H, s, CHO), 7.3—7.7 (3H, m, aromatc protons), 2.9 (1H, m, C-1′ methine proton), 0.8—2.15 (10H, m, methylene protons).

19) S. Kuzuna, N. Matsumoto, T. Kometani, and K. Kawai: presented at the 42nd Kinki Regional Meeting of Japan Pharmacological Society, Kyoto, November 1972.

20) Melting and boiling points are uncorrected. Infrared (IR) spectra were obtained with a Hitachi-215 spectrophotometer and NMR spectra with a Varian A-60 spectrometer using TMS as internal standard.

21) This sample was contaminated with the 2-chloro isomer, and the purity was estimated on the basis of the NMR spectral data.

22) D.E. Person, H.W. Pope, W.W. Hargrove, and W.E. Stamper, *J. Org. Chem.*, 23, 1412 (1958).

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Ethyl α-Cyano-3-chloro-4-cyclohexylcinnamate (11)——To a mixture of 4.4 g of **10** and 2.3 g of ethyl cyanoacetate was added 0.2 ml of piperidine, followed by 10 ml of benzene. The mixture was heated under reflux for 10 min. The cooled reaction solution was mixed with 100 ml of ether and washed with dilute HCl and water successively. The organic solution was dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residual solid was recrystallized from 10 ml of MeOH to give **11** as colorless crystals (3.35 g, 53%), mp 107—110°. *Anal.* Calcd. for $C_{18}H_{20}O_2NCl$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.91; H, 6.33; N, 4.26. IR ν_{max}^{Nujol} cm^{-1}: 2240 (CN), 1730 (C=O).

Preparation of 4-Substituted Phenylsuccinic Acids——a) From Diethyl α-Cyano-α-(4-substituted phenyl)-succinates: The phenylsuccinic acids were prepared using a procedure similar to the one described for 3-chloro-4-cyclohexylphenylsuccinic acid (**4**). A solution of 299 g of **3** and 354 g of NaOH in 2 liters of ethylene glycol was heated under reflux for 8 hr. After being cooled, the reaction mixture was poured onto ice-water, acidified with dilute HCl, and extracted with AcOEt. The extract was washed with water, dried over anhydrous Na_2SO_4, and concentrated to dryness under reduced pressure. The residual solid was recrystallized from benzene to give **4** as colorless crystals (167 g, 71%), mp 175—177°. *Anal.* Calcd. for $C_{16}H_{19}O_4Cl$: C, 61.84; H, 6.16. Found: C, 62.13; H, 6.15. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1695 (C=O). 4-Cyclohexylphenylsuccinic acid:[11,12] mp 189—191° (CH_3CN, 70%). *Anal.* Calcd. for $C_{16}H_{20}O_4$: C, 69.56; H, 7.30. Found: C, 69.45; H, 7.30. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). 4-Isopropylphenylsuccinic acid[12] (**17a**): mp 178—180° (acetone–AcOEt, 93%). *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.87; H, 6.90. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). 4-Isobutylphenylsuccinic acid (**17b**): mp 151.5—154° (AcOEt, 71.2%). *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.95; H, 7.34. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). 3-Chloro-4-isobutylphenylsuccinic acid (**17c**): mp 99—101° (benzene, 70.3%). *Anal.* Calcd. for $C_{14}H_{17}O_4Cl$: C, 59.05; H, 6.02; Cl, 12.45. Found: C, 59.05; H, 6.03; Cl, 12.57. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O).

b) From Ethyl α-Cyanocinnamate: **4** was prepared from **11** as follows. To a solution of 12.5 g of **11** in 40 ml of EtOH was added dropwise a solution of 2.3 g of NaCN in 15 ml of water. The mixture was stirred for 4 hr at room temperature and then heated under reflux for 2 hr. After being cooled, the reaction solution was diluted with 400 ml of water and acidified with 6 ml of concentrated HCl. The precipitate was collected and added to 200 ml of concentrated HCl. The mixture was heated under reflux for 10 hr and allowed to cool. The precipitate was collected, washed with water, benzene, and petroleum ether successively, and dried to give **4** as colorless crystals. **4** thus obtained was identified with a sample prepared from **2** by the method a, by mixed melting point and comparison of their IR and NMR spectra.

Preparation of 4-Substituted Phenylsuccinic Anhydrides——These anhydrides were prepared using a procedure similar to the one described for 3-chloro-4-cyclohexylphenylsuccinic anhydride (**5**). A suspension of 116.8 g of **4** in 600 ml of acetic anhydride was heated under reflux for 4 hr. The cooled solution was concentrated to dryness under reduced pressure. The residual solid was washed with hexane–ether to give 103 g (94%) of **5**, which was recrystallized from ligroin to give colorless crystals, mp 119—121°. *Anal.* Calcd. for $C_{16}H_{17}O_3Cl$: C, 65.64; H, 5.85; Cl, 12.11. Found: C, 65.92; H, 5.85; Cl, 12.04. IR ν_{max}^{Nujol} cm^{-1}: 1870, 1785 (C=O). 4-Isopropylphenylsuccinic anhydride: mp 83.5—85° (petroleum benzine, 88%). *Anal.* Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.38; H, 6.41. IR ν_{max}^{Nujol} cm^{-1}: 1860, 1780 (C=O). 4-Isobutylphenylsuccinic anhydride: mp 44.5—45.5° (petroleum benzine–hexane, 88.1%). *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.40; H, 7.02. IR ν_{max}^{Nujol} cm^{-1}: 1860, 1780 (C=O). 3-Chloro-4-isobutylphenylsuccinic anhydride: mp 61—62° (ether–hexane, 32.7%). *Anal.* Calcd. for $C_{14}H_{15}O_3Cl$: C, 63.03; H, 5.67; Cl, 13.29. Found: C, 63.21; H, 5.57; Cl, 13.25. IR ν_{max}^{Nujol} cm^{-1}: 1870, 1790 (C=O).

Preparation of 5-Substituted 3-Oxoindan-1-carboxylic Acids——These indanones were prepared using a procedure similar to the one described for 6-chloro-5-cyclohexyl-3-oxoindan-1-carboxylic acid (**6**) and 4-chloro-5-cyclohexyl-3-oxoindan-1-carboxylic acid (**7**). A solution of 91.8 g of **5** in 500 ml of CH_2Cl_2 was added dropwise to a stirred, ice-cooled suspension of 92.4 g of pulverized anhydrous $AlCl_3$ in 700 ml of CH_2Cl_2.[23] The mixture was stirred with cooling for 4 hr and then at room temperature for 4 hr. To the stirred, cooled reaction mixture was added dropwise cooled dilute HCl. The organic layer was separated, dried over $MgSO_4$, and concentrated to dryness under reduced pressure. The residue was treated with 600 ml of hexane and 60 ml of ether. The resulting solid was collected, dried and recrystallized from benzene to give **6** as colorless crystals, mp 184—186° (33 g, 36%). *Anal.* Calcd. for $C_{16}H_{17}O_3Cl$: C, 65.64; H, 5.85; Cl, 12.11. Found: C, 65.64; H, 5.75; Cl, 12.13. IR ν_{max}^{Nujol} cm^{-1}: 1725, 1705 (C=O). From the mother liquor **7** was obtained as colorless crystals, mp 188—191° (1.1 g, 1.2%). *Anal.* Calcd. for $C_{16}H_{17}O_3Cl$: C, 65.64; H, 5.85; Cl, 12.11. Found: C, 65.50; H, 5.77; Cl, 12.23. IR ν_{max}^{Nujol} cm^{-1}: 1725 (C=O). 5-Isopropyl-3-oxoindan-1-carboxylic acid (**18a**): mp 102—104.5° (ether–petroleum ether, 90.1%). *Anal.* Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.64; H, 6.53. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1680 (C=O). 5-Isobutyl-3-oxoindan-1-carboxylic acid[12] (**18b**): mp 80.5—82° (benzene–petroleum benzine, 83.6%). *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.28; H, 7.02. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). 6-Chloro-5-isobutyl-3-oxoindan-1-carboxylic acid (**18c**): mp 148.5—149.5° (benzene–cyclohexane, 47.5%). *Anal.* Calcd. for $C_{14}H_{15}O_3Cl$: C, 63.03; H, 5.67; Cl, 13.29. Found: C, 63.13; H, 5.65; Cl, 13.28. IR ν_{max}^{Nujol} cm^{-1}: 1715, 1705 (C=O).

23) K. Mori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem.*, **27**, 27 (1963).

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Preparation of 5-Substituted Indan-1-carboxylic Acids——These indancarboxylic acids were prepared using a procedure similar to the one described for 6-chloro-5-cyclohexylindan-1-carboxylic acid (**1**). Zn amalgam was prepared by swirling 38 g of Zn powder with 3.8 g of $HgCl_2$, 1.9 ml of 35% HCl, and 57 ml of water. The amalgam was washed with water and transferred to a suspension of 21 g of **6** in 72 ml of toluene, 28 ml of water and 56 ml of 35% HCl.[24] The mixture was heated at reflux temperature for 16 hr with stirring, cooled, diluted with water, and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated to dryness under reduced pressure. The residual solid was recrystallized from 600 ml of hexane to give **1** as colorless needles, mp 151—152° (10.8 g, 54%). *Anal.* Calcd. for $C_{16}H_{19}O_2Cl$: C, 68.94; H, 6.87; Cl, 12.72. Found: C, 69.00; H, 6.84; Cl, 12.91. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O). NMR (in $CDCl_3$) δ: 7.39 (1H, s, C_7–H), 7.12 (1H, s, C_4–H), 3.98 (1H, t, C_1–H). 4-Chloro-5-cyclohexylindan-1-carboxylic acid (**8**): mp 120—123° (hexane, 66%). *Anal.* Calcd. for $C_{16}H_{19}O_2Cl$: C, 68.94; H, 6.87; Cl, 12.72. Found: C, 68.79; H, 6.96; Cl, 13.38. IR ν_{max}^{Nujol} cm^{-1}: 1715 (C=O). NMR (in $CDCl_3$) δ: 7.20 (2H, q, aromatic protons), 4.00 (1H, t, C_1–H). 5-Isopropylindan-1-carboxylic acid[12] (**19a**): mp 82—84° (hexane, 71.4%). *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.50; H, 8.03. IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O). 5-Isobutylindan-1-carboxylic acid (**19b**): mp 73—74° (hexane, 54.3%). *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.00; H, 8.38. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). 6-Chloro-5-isobutylindan-1-carboxylic acid (**19c**): mp 116—116.5° (petroleum benzine, 51.8%). *Anal.* Calcd. for $C_{14}H_{17}O_2Cl$: C, 66.52; H, 6.78; Cl, 14.03. Found: C, 66.46; H, 6.79; Cl, 14.19. IR ν_{max}^{Nujol} cm^{-1}: 1715 (C=O). NMR (in $CDCl_3$) δ: 7.41 (1H, s, C_7–H), 7.04 (1H, s, C_4–H), 4.02 (1H, t, C_1–H).

Halogenation of 5-Substituted Indan-1-carboxylic Acids——a) 6-Chloro-5-cyclohexylindan-1-carboxylic Acid (**1**): A solution of 0.8 g of Cl_2 in 20 ml of CH_3CN was added dropwise to a stirred, ice-cooled solution of 2.44 g of 5-cyclohexylindan-1-carboxylic acid (**13**) in 160 ml of CH_3CN. The mixture was stirred for 1 hr with cooling. A solution of 0.4 g of Cl_2 in 10 ml of CH_3CN was further added to the mixture, and the stirring was continued with cooling for 1 hr and then at 20° for 3 hr. The reaction mixture was concentrated to dryness under reduced pressure. The residual solid was recrystallized from 100 ml of hexane to give **1** as colorless needles, mp 151—152° (1.92 g, 68.8%).

b) 6-Chloro-5-isopropylindan-1-carboxylic Acid (**19d**) and 6-Chloro-5-isobutylindan-1-carboxylic Acid (**19c**): To a stirred, ice-cooled mixture of 7.0 g of **19a** and 5.56 g of $FeCl_3$ in 210 ml of CCl_4 was added dropwise a solution of 2.9 g of Cl_2 in 70 ml of CCl_4. The mixture was stirred for 2 hr with cooling and then poured into dilute HCl. The product was extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was treated with 50 ml of petroleum ether. The resulting solid was collected and recrystallized from 60 ml of hexane to give **19d** as colorless crystals, mp 121—124° (2.08 g, 25.4%). *Anal.* Calcd. for $C_{13}H_{15}O_2Cl$: C, 65.41; H, 6.33; Cl, 14.85. Found: C, 65.46; H, 6.19; Cl, 15.22. IR ν_{max}^{Nujol} cm^{-1}: 1715 (C=O). NMR (in $CDCl_3$) δ:7.38 (1H, s, C_7–H), 7.13 (1H, s, C_4–H), 3.98 (1H, t, C_1–H). According to the procedure similar to the one described above, **19c** was prepared from **19b**. **19c** thus obtained was identified with a sample prepared from **18c** by the Clemmensen reduction, by mixed melting point and comparison of their IR and NMR spectra.

c) 6-Bromo-5-cyclohexylindan-1-carboxylic Acid (**14**): To a stirred, ice-cooled mixture of 1.2 g of **13** and 0.8 g of $FeCl_3$ in 40 ml of CCl_4 was added dropwise 0.8 g of Br_2. The mixture was stirred for 2 hr with cooling, and then poured into dilute HCl. The CCl_4 layer was separated, dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residual solid was recrystallized from 100 ml of hexane to give **14** as colorless needles, mp 160—164° (0.6 g, 38%). *Anal.* Calcd. for $C_{16}H_{19}O_2Br$: C, 59.47; H, 5.93; Br, 24.73. Found: C, 59.55; H, 5.85; Br, 24.52. IR ν_{max}^{Nujol} cm^{-1}: 1715 (C=O). NMR (in $CDCl_3$) δ: 7.62 (1H, s, C_7–H), 7.14 (1H, s, C_4–H), 4.02 (1H, t, C_1–H).

Optical Resolution of TAI-284 (1)——a) (*R*)-(−)-6-Chloro-5-cyclohexylindan-1-carboxylic Acid: A suspension of 9.8 g of TAI-284 (**1**) and 5.6 g of quinine in 105 ml of acetone was warmed to give a clear solution. The solution was allowed to stand overnight at room temperature. The precipitate was collected, washed with acetone, and recrystallized from 600 ml of CH_3CN to give the quinine salt of (−)-TAI-284 as colorless crystals, mp 124—129°. This salt was dissolved in $CHCl_3$. The solution was washed with dilute HCl and water, dried over anhydrous Na_2SO_4, and concentrated to dryness under reduced pressure. The residual solid was recrystallized from 70 ml of hexane to give (*R*)-(−)-TAI-284 as colorless needles, mp 130—135° (1.4 g, 29%). *Anal.* Calcd. for $C_{16}H_{19}O_2Cl$: C, 68.94; H, 6.87; Cl, 12.72. Found: C, 68.73; H, 6.89; Cl, 12.84. $[\alpha]_D^{25}$: −28.3° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O).

b) (*S*)-(+)-6-Chloro-5-cyclohexylindan-1-carboxylic Acid: The mother liquor of the first isolation of the quinine salt of (−)-TAI-284 was concentrated to dryness under reduced pressure. The residual solid was dissolved in $CHCl_3$. The solution was washed with dilute HCl and water, dried over anhydrous Na_2SO_4, and concentrated to dryness under reduced pressure. The residual solid was recrystallized from hexane. The first crystals thus obtained were those of (±)-TAI-284. The second mother liquor was concentrated to dryness under reduced pressure. The residual solid also gave (±)-TAI-284 by recrystallization. The third mother liquor was worked up similarly, and this time (+)-TAI-284 was obtained as colorless crystals,

24) W.H. Linnel, D.W. Mathieson, and D.T. Modi, *J. Chem. Soc.*, **1953**, 3257.

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mp 130—135° (1.3 g, 27%). *Anal.* Calcd. for $C_{16}H_{19}O_2Cl$: C, 68.94; H, 6.87; Cl, 12.72. Found: C, 68.87; H, 6.97; Cl, 12.93. $[\alpha]_D^{25}$: +28.1° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O).

c) Sodium (*S*)-(+)-6-Chloro-5-cyclohexylindan-1-carboxylate: To a solution of 279 mg of (*S*)-(+)-TAI-284 in 10 ml of EtOH was added a solution of NaOEt (prepared from 23 mg of metallic Na) in EtOH, and the mixture was allowed to stand for 5 hr. The solution was concentrated to dryness under reduced pressure. The residual solid was treated with acetone. The resulting crystals were collected, washed with acetone and dried to give the sodium salt of (+)-TAI-284, the melting point of which was not clear. *Anal.* Calcd. for $C_{16}H_{18}O_2ClNa \cdot 1/2H_2O$: C, 62.04; H, 6.18. Found: C, 62.45; H, 6.24. $[\alpha]_D^{25}$:−14.5° (c=1, MeOH). Sodium salt of (−)-TAI-284 was prepared using the similar procedure. *Anal.* Calcd. for $C_{16}H_{18}O_2ClNa \cdot 1/2H_2O$: C, 62.04; H, 6.18. Found: C, 62.07; H, 6.20. $[\alpha]_D^{25}$: +13.8° (c=1, MeOH).

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