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# Opitical Resolution and Determination of Absolute Configuration of 2-(2-Isopropylindan-5-yl)propionic Acid

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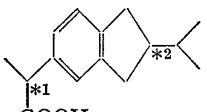
The optical resolution and the determination of the absolute configuration of the four possible stereoisomers of the anti-inflammatory agent, 2-(2-isopropylindan-5-yl)propionic acid (I), are described.

**Keywords**——anti-inflammatory; optical resolution; indanpropionic acid; absolute configuration; diastereomer; ORD

Considerable differences in biological activity are often observed between enantiomorphic pairs.[2a] Such differences have been observed with the anti-inflammatory phenylpropionic acid derivatives.[2b]



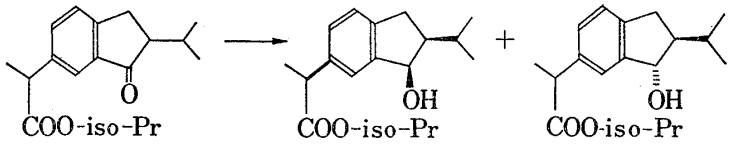

I

Chart 1

The compound 2-(2-isopropylindan-5-yl)propionic acid[3] (I) has shown to possess significant anti-inflammatory activity.[3a] Compound I has two asymmetric carbon atoms (2-position of propionic acid (*1) and 2-position of indan nucleus (*2); see Chart 1) separated by a distance of about seven angstroms.

According to Dreiding models, it appears that I is a nearly symmetric molecule; consequently it would be difficult to separate its optical isomers.

In order to facilitate the separation of diastereomers the key intermediate, 2-(1-hydroxy-2-isopropylindan-6-yl)propionic acid (VI), was synthesized. $NaBH_4$ reduction of isopropyl 2-(2-isopropylindan-1-on-6-yl)propionate (II)[3a] gave two products, *cis*- and *trans*-isopropyl 2-(1-hydroxy-2-isopropylindan-6-yl)propionate (III and IV) in 50 and 32% yield respectively.




II III IV

| | III | IV |
|---|---|---|
| $NaBH_4$ | 50 | 32 |
| $Al(iso\text{-}PrO)_3$ | 48 | 30 |
| $Li(s\text{-}Bu)_3BH$ | 65 | 0% |

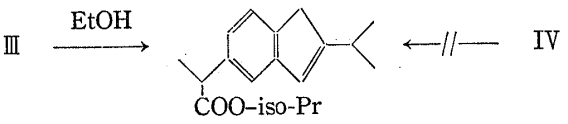
Chart 2

1) Location: *2–58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo.*

2) *a*) A.F. Cary in "Medicinal Chemistry," 3rd ed., ed. by A. Burger, Wiley Interscience, New York, 1970, p. 81; *b*) *d*-Compound is more active than *l*-isomer; T.Y. Shen, *Angew. Chem. Int. Ed. Engl.*, **11**, 460 (1972); J.S. Kaltenbronn, *J. Med. Chem.*, **16**, 490 (1973); S. Noguchi, S. Kishimoto, I. Minamida, and M. Obayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 529 (1974); Z.N. Gaut, H. Baruth, L.O. Randall, C. Ashley, and J.R. Paulsrud, *Prostaglandines*, **10**, 59 (1975); S.S. Adams, P. Bresloff, and C.G. Mason, *J. Pharm. Pharmac.*, **28**, 256 (1976).

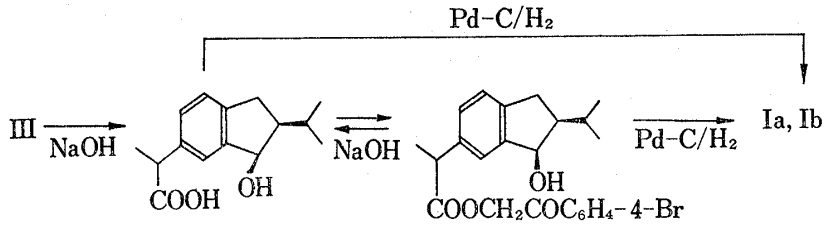
3) *a*) Sankyo Co., Ltd. German Patent Application (laying-open data), 2501459 (21st August 1975); *b*) Sandoz AG., *ibid.*, 2449928 (5th July 1975); *c*) Hexachimie S.A., *ibid.*, 2504689 (14th August 1975). Optically active compounds were not reported.

Almost the same result was obtained by the Meerwein-Ponndorf-Verley reduction of II. On the other hand, reduction of II using lithium tri-sec-butylborohydride[4] gave *cis*, III, stereoselectively. The elemental analysis of III and IV agreed with an empirical formula $C_{18}H_{26}O_3$. The mass spectrum of IV showed molecular peak ($M^+$=290) and base peak (230), but compound III only showed a very weak molecular peak. Compounds III and IV displayed a new methin signal at 5.03 ppm ($J$=5 Hz) and 5.00 ppm ($J$=6 Hz), respectively, in the nuclear magnetic resonance (NMR). In the presence of 0.2 M of $Eu(DPM)_3$, the methyl signal of the isopropyl group at 2-position of compound III was shifted 0.83 ppm lower and appeared as a double of doublets which may indicate hindered rotation. In contrast, $Eu(DPM)_3$ shifted the methyl signal of IV 0.88 ppm lower and it appeared as a sharp doublet. Compound III gave the dehydration product isopropyl 2-(2-isopropylinden-5-yl)propionate (V), in 10% yield, when allowed to stand in ethanol for 2 days at room temperature. Compound IV, however, was recovered unchanged under the conditions employed. From these data, compounds III and IV were assigned as the *cis*- and *trans*- alcohols, respectively. Hydrolysis of III with one equivalent of sodium hydroxide in ethanol yielded *cis*-2-(1-hydroxy-2-isopropylindan-6-yl)propionic acid (VI) (mp 134—135°). Esterification with 4-bromophenacylbromide and sodium hydride in dimethyl formamide afforded 4-bromophenacyl 2-(1-hydroxy-2-isopropylindan-6-yl)propionate (VII). High pressure liquid chromatography (HPLC) of




V

Chart 3




VIa, VIb VIIa, VIIb

Chart 4

VII showed two very close peaks[5], VIIa (mp 114—115°) and VIIb (mp 86—87°), which were isolated by preparative HPLC. The diastereomers, VIIa and VIIb, were assigned their structures on the basis of the following data and an elemental analysis ($C_{23}H_{25}BrO_4$). The infrared (IR) spectra of both VIIa and VIIb showed a hydroxy band at 3550 $cm^{-1}$, a carbonyl absorption at 1700 $cm^{-1}$ and an ester group at 1730 $cm^{-1}$. The NMR spectra showed no differences between VIIa and VIIb and supported their assigned structures. Although hydrogenolysis of VIIa with Pd-carbon at 5 atm.[6] of hydrogen gave the expected Ia in poor yield (20%), the compound, VIa, was obtained by saponification of VIIa using one equivalent of sodium hydroxide in ethanol at room temperature[7] afforded the desired diastereomer Ia (mp 77—84°) in good yield (75%). Likewise, another diastereomer, Ib (mp 76—83°), was synthesized from VIIb. A mixed melting point of Ia and Ib (67—81°) assured the daistereo-

4) H.C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **94**, 7159 (1972).
5) Likewise HPLC analysis of 4-bromophenacylester of IV showed two very close peaks, XVIIa (mp 120—122°) and XVIIb (mp 109—110°).
6) G.C. Stelakatos, A. Paganou, and L. Zervas, *J. Chem. Soc.* (*C*), 1191 (1966).
7) Reesterification of VIa gave VIIa as sole product, which means compound VIa retains same configuration as VIIa.

meric relationship of Ia and Ib.[8] Because of the facile dehydration of VIa, hydrogenolysis of VIa would expected to pass through the intermediate compound, 2-(2-isopropylinden-5-yl)propionic acid (VIII). To determine the reaction path, VIa was reduced catalyticaly under deuterium in monodeuteroethanol. The NMR spectrum of the product exhibited no

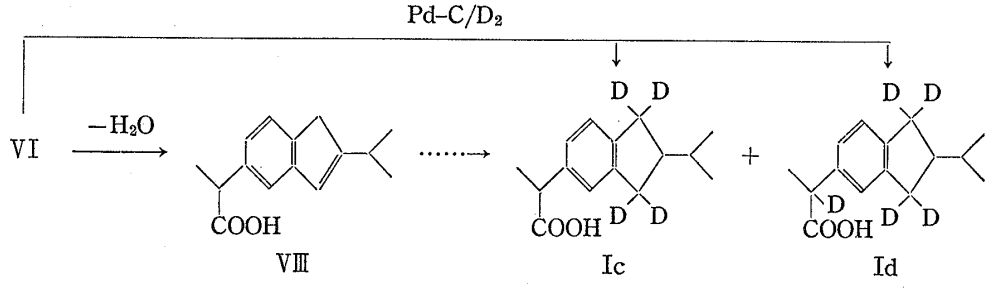



Chart 5

benzyl proton peak around 2.5 ppm, a half amount of methin proton at 3.76 ppm as a quartet ($J$=7 Hz), a half amount of methyl proton at 1.50 ppm as a doublet ($J$=7 Hz), a half amount of methyl proton at 1.55 ppm as a singlet and a methin proton at 2.2 ppm as a broad doublet ($J$=7 Hz). These results showed that the deuterium reduction product is a mixture of 2-(2-isopropyl-1,1,3,3-tetradeuteroindan-5-yl)propionic acid (Ic) and 2-deutero-2-(2-isopropyl-1,1,3,3-tetradeuteroindan-5-yl)propionic acid (Id) as depicted in Chart 5. Proton noise decoupled $^{13}C$ spectrum supported this structure. The benzylic carbon at 37.2 and 37.3 ppm disappeared and the intensity of another benzylic carbon at 45.1 ppm was depressed. From these facts, it was clear that deuterium atoms exchanged with the benzyl methane protons at C-1 and C-3 and not C-2. On the other hand, deuterogenolysis of *trans*-2-(1-hydroxy-2-isopropylindan-6-yl)propionic acid (IX) also gave the same mixture of Ic and Id. From these results, it is implied that deuterogenolysis might have occurred directly, that is, the benzylic hydroxy was exchanged with deuterium, and was not reduced after dehydration.

Ia thus obtained was treated with thionyl chloride, followed by *d*-1-phenylethylamine to afford two kinds of amides, *d*-N-(1-phenylethyl)-2-(2-isopropylindan-5-yl)propion amide (Xa) (mp 101—102°, $[\alpha]_D$=+68.4° (EtOH)) and *d*-N-(1-phenylethyl)-2-(2-isopropylindan-5-yl)propion amide (XIa) (mp 105—107°, $[\alpha]_D$=+33.6° (EtOH)), which were separated by preparative HPLC. Hydrolysis of Xa with conc. HCl and AcOH gave partially racemized I

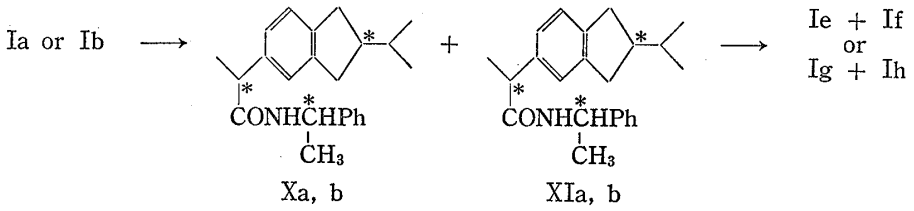



Chart 6

($[\alpha]_D$=+30°). Therefore, cleavage of the amide bond of Xa was performed by diazotization with $N_2O_4$ followed by decomposition in $CCl_4$.[9] Purification of the mixture on a silica gel column gave the desired Ie (mp 62—24°, $[\alpha]_D^{20}$=+54.6° (EtOH)). Similary, If (mp 62—64°, $[\alpha]_D^{20}$=−53.5° (EtOH)) was obtained from XIa. Using the same reaction conditions diastereomer, Ib, afforded Ig (mp 61—63°, $[\alpha]_D^{20}$=+54.1° (EtOH)) and Ih (mp 61—63°, $[\alpha]_D^{20}$=−53.9° (EtOH)) *via* Xb (mp 103—104°, $[\alpha]_D$=+71.3° (EtOH)) and XIb (mp 93—94°, $[\alpha]_D$=+34.8° (EtOH)). Mixed melting points of the enantiomers, Xa and XIb or Xb and XIa,

8) Racemate of I melted at 87—89°.
9) G. Haas and V. Prelog, *Helv. Chim. Acta.* **52**, 1202 (1969).

were depressed. There were no detectable differences in the ORD curves of Xa and XIb or Xb and XIa.

The desirable four isomers thus obtained satisfied an elemental analysis for $C_{15}H_{20}O_2$. The structure of these four isomers was supported by the NMR, mass and IR, but there were no differences between all of them. The NMR spectrum, even in a presence of optically active shift reagent, or the X-ray powder diffraction patterns did not show detectable differences. Mixed melting point of Ie and Ig melted at 60—62°, and If and Ih melted at 60—62°. The ORD measurements were carried out in order to determine the configuration of each compound. If and Ih had the same positive cotton effect ($[\phi]_{238}=+4100°$(MeOH)) which assured *S*-configuration of carbon (*1) of 2-indanylpropionic acid[10], and Ie and Ig showed negative cotton effect ($[\phi]_{238}=-4100°$ (MeOH)) which meant *R*-configuration. No differences between the enantiomers If and Ih or Ie and Ig suggested that they might be relatively symmetrical molecules.

To assign the configuration of the other asymmetric carbon (*2), I was transformed to 2,5-diisopropylindan (XII), which possesses only one asymmetric carbon. An ether solution

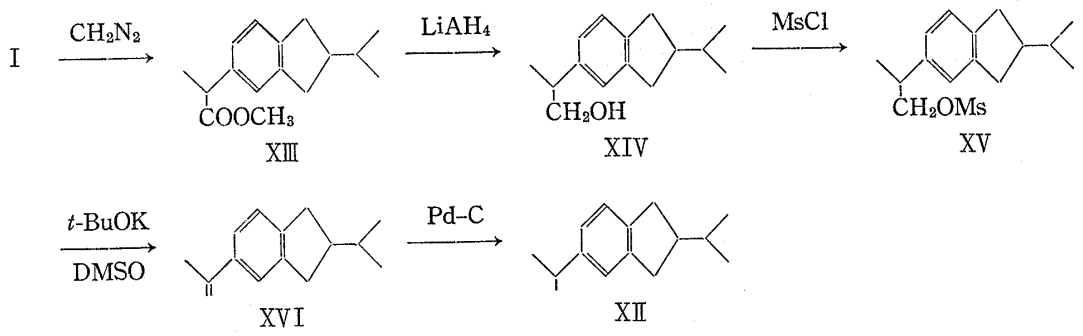



Chart 7

of I and diazomethane gave methyl 2-(2-isopropylindan-5-yl)propionate (XIII) quantitatively and subsequently lithium aluminium hydride reduction of XIII yielded 2-(2-isopropylindan-5-yl)propanol (XIV). Mesylation of XIV using methanesulfonyl chloride in pyridine at 0° produced 2-(2-isopropylindan-5-yl)propyl methanesulfonate (XV) in 90% yield. Elimination of the mesyl group was performed with potassium *t*-butoxide in dimethylsulfoxide at 180° for 1 hr to yield 5-isopropenyl-2-isopropylindan (XVI) in 80% yield. Catalytic hydrogenation of XVI with Pd-carbon in ethanol gave the desired XII in 85% yield.

Compounds Ie or Ig yielded XIIa which showed a very weak plan rotatory dispersion ($[\phi]_{300}=+5°$(MeOH)), and compounds If or Ih yielded XIIb having weak negative in ORD ($[\phi]_{300}=-5°$(MeOH)).

In this manner, the interrelationships of four optical isomers were made clear. The X-ray crystallographic study of Xa was carried[11] out in order to determine the absolute configuration of the carbon at the 2-position of indan nucleus (*2). From these results the compound derived from Xa was assigned to be ((*R*)-2-(*R*)-2-isopropylindan-5-yl)propionic acid. The absolute configuration of other three compounds (Ie, Ig and Ih) were concluded to be *S*,*S* for Ie, *R*,*S* for Ig, and *S*,*R* for Ih, respectively. (*S*,*R* correspond to*1, *2).

These compounds are currently being tested for biological activity.

10) G. Barth, W. Voelter, H.S. Mosher, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **92**, 875 (1970).
11) *a*) Absolute configuration were decided by using *d*-amine with *R*-configuration,[12] *b*) S. Naruto, T. Hata, and C. Tamura; manuscript in preparation.
12) J.C. Craig, R.P.K. Chan, and S.K. Roy, *Tetrahedron*, **23**, 3573 (1967).

## Experimental

Melting points were determined with a Büchi melting points apparatus and are uncorrected. IR spectra were determined on a Hitachi EPI-G3 greating IR spectrometer and mass spectra were recorded on a JEOL's JMS-01S spectrometer. Proton NMR spectra were measured with either Varian T-60 or HA-100 and carbon NMR spectra were determined on a Varian XL-100-15 spectrometer. High pressure liquid chromatography was performed on a Waters ALC-401 with microporasil for analysis and 10 ft. × 3/8 in. silica gel column for preparation. UV spectra were recorded on a Hitachi 365 spectrometer. Optical rotation were measured on a Perkin-Elmer 241 spectrometer and ORD spectra were recorded on a JASCO J-20 spectrometer. All organic extracts were dried over anhydrous sodium sulfate.

**$NaBH_4$ Reduction of Isopropyl 2-(2-Isopropylindan-1-on-6-yl)propionate (II)**——A solution of 23 g of II and 3.6 g of $NaBH_4$ in 350 ml of isopropyl alcohol was refluxed for 3 hr. The reaction mixture was treated with cold dil. HCl, extracted with ether, and concentrated under reduced pressure, affording 22 g of yellow oil. The crude product was chromatographed on 30 g of silica gel and eluted with $CH_2Cl_2$–EtOAc to give 20 g of an oil. The oil was separated by preparative HPLC with 15% EtOAc–*n*-hexane. The first fraction afforded 11.6 g (50%) of colourless oil of III. *Anal.* Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.21; H, 8.81. NMR $\delta^{CDCl_3}$: 1.02 (3H, d, $J$=6 Hz), 1.10 (9H, d, $J$=7 Hz), 1.47 (3H, d, $J$=7 Hz), 1.7—2.2 (2H, m), 2.7—3.0 (2H, m), 3.73 (1H, q, $J$=7 Hz), 5.01 (1H, sep, $J$=6 Hz), 5.03 (1H, d, $J$=5 Hz), 7.28 (2H, bs), 7.42 (1H, bs). IR $\nu_{max}^{neat}$ $cm^{-1}$: 3450, 1735. MS *m/e*: 290 ($M^+$, weak), 283, 247, 204 (base). The second fraction gave 7.4 g (32%) of IV. *Anal.* Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.17; H, 8.91. NMR $\delta^{CDCl_3}$: 0.99 (3H, d, $J$=6 Hz), 1.08 (3H, d, $J$=7 Hz), 1.10 (6H, d, $J$=7 Hz), 1.49 (3H, d, $J$=7 Hz), 1.8—3.3 (4H, m), 3.73 (1H, q, $J$=7 Hz), 5.00 (1H, d, $J$=6 Hz), 5.01 (1H, sep, $J$=6 Hz), 7.22 (2H, bs), 7.36 (1H, bs). IR $\nu_{max}^{neat}$ $cm^{-1}$: 3430, 1735. MS *m/e*: 290 ($M^+$), 204 (base).

**Meerwein-Ponndorf-Verley Reduction of II**——Aluminium isopropoxide (3 g) and 2 g of II were dissolved in 250 ml of absolute isopropyl alcohol and refluxed for 50 hr. The reaction mixture was concentrated *in vacuo* and treated with dil. HCl and extracted with ether. Ether extract was separated by preparative HPLC to afforded 0.97 g (48%) of III and 0.6 g (30%) of IV.

**Lithium tri-sec-Butylborohydride Reduction of II**——To a solution of 2 g of II in 10 ml of absolute THF cooled to −78° under nitrogen was added dropwise 16 ml of lithium tri-sec-butylborohydride (0.5 M THF solution). After 2 hr at 0°, the reaction mixture was quenched by the addition of 80 ml of 0.1 N HCl and extracted with ether. The solvent was removed under reduced pressure to leave an oily residue which was purified with column chromatography to give 1.2 g of III.

***cis*-2-(1-Hydroxy-2-isopropylindan-6-yl)propionic Acid (VI)**——A solution of 2.0 g of III and 0.3 g of NaOH in 30 ml of MeOH was standing 12 hr at room temperature. The solvent was removed *in vacuo* and acidified with dil. HCl. Precipitate was recrystallized from EtOAc–*n*-hexane to give colourless prisms of VI, 1.35 g (79%), mp 135—138°. *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.81; H, 8.12. NMR $\delta^{CDCl_3}$: 1.00 (3H, d, $J$=6 Hz), 1.09 (3H, d, $J$=6 Hz), 1.46 (3H, d, $J$=7 Hz), 1.6—2.1 (2H, m), 2.4—3.1 (2H, m), 3.66 (1H, q, $J$=7 Hz), 4.95 (1H, d, $J$=5 Hz), 6.0 (2H, bs, –OH), 7.18 (2H, s), 7.25 (1H, s). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3230, 1680. MS *m/e*: 234 (base), 206, 190, 171, 161.

***trans*-2-(1-Hydroxy-2-isopropylindan-6-yl)propionic Acid (XVII)**——Compound IV (2.0 g) was conducted with reaction mentioned above to produce 1.28 g (75%) of XVII, mp 107—108°. *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.79; H, 8.02. NMR $\delta^{CDCl_3}$: 0.95 (3H, d, $J$=6 Hz), 1.06 (3H, d, $J$=6 Hz), 1.46 (3H, d, $J$=7 Hz), 1.5—3.2 (4H, m), 3.70 (1H, q, $J$=7 Hz), 4.92 (1H, d, $J$=6 Hz), 6.2 (2H, bs, –OH), 7.12 (2H, s), 7.27 (1H, s). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3370, 1695. MS *m/e*: 248 ($M^+$, base), 230, 205, 175.

**4-Bromophenacyl 2-(1-Hydroxy-2-isopropylindan-6-yl)propionate (VII)**——To a stirred suspension of 1.15 g of 50% NaH dispersion (washed with hexane prior to use) in 50 ml of DMF was added dropwise a solution of 4.96 g of VI in 10 ml of DMF at 0°. After addition was completed, the reaction mixture was warmed to 40° for 2 hr. The solution was cooled to 0° and treated with a solution of 6.1 g of 4-bromophenacylbromide in 10 ml of DMF. The resulting mixture was again warmed to 40° and stirred for 0.5 hr. The reaction mixture was quenched by the addition of water and extracted with EtOAc. The EtOAc layer was extracted with 30 ml of 5% $NaHCO_3$ solution and aq. layer was acidified with dil. HCl to afford 1.2 g of starting material, VI (24%). The EtOAc layer was concentrated *in vacuo* and chromatographed on 60 g of silica gel. Elution with $CH_2Cl_2$–EtOAc afforded 6.6 g of VII (74%) which was conducted with preparative HPLC to give 2.6 g (29%) of VIIa and 2.6 g (29%) of VIIb. Recrystallization of VIIa from $CH_2Cl_2$–*n*-hexane gave colourless leaflets melted at 114—115°. *Anal.* Calcd. for $C_{23}H_{25}BrO_4$: C, 62.02; H, 5.65; Br, 17.94. Found: C, 62.05; H, 5.63; Br, 17.83. NMR $\delta^{CDCl_3}$: 1.00 (3H, d, $J$=6 Hz), 1.08 (3H, d, $J$=6 Hz), 1.50 (3H, d, $J$=7 Hz), 1.6—2.1 (2H, m), 1.98 (1H, s, –OH), 2.4—3.1 (2H, m), 3.82 (1H, q, $J$=7 Hz), 4.92 (1H, d, $J$=5 Hz), 5.10 (2H, s), 7.13 (2H, s), 7.30 (1H, s), 7.50 (2H, d, $J$=9 Hz), 7.60 (2H, d, $J$=9 Hz). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3470, 1735, 1700. MS *m/e*: 446, 444 ($M^+$), 428, 426, 413, 411, 247 (base). VIIb was obtained as colourless small prisms, mp 86—87°. *Anal.* Calcd. for $C_{23}H_{25}BrO_4$: C, 62.02; H, 5.65; Br, 17.94. Found: C, 61.81; H, 5.43; Br, 17.77. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3560, 1725, 1695. NMR and mass spectra were identical with that of VIIa.

**Saponification of VIIa**——A solution of 2.0 g of VIIa and 0.18 g of NaOH in 20 ml of MeOH was standing 24 hr at room temperature. MeOH was evaporated *in vacuo* and residual oil was dissolved in 10 ml of water. The aqueous layer was extracted with ether and resulting solution was acidified with dil. HCl. The resulting precipitate was collected and recrystallized from *n*-hexane to give 0.9 g (86%) of VIa, mp 114—115°. *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.62; H, 7.91. NMR, IR and mass spectra of VIa were identical with that of VI. Under the same condition, VIIb gave 81% of VIb as colourless prisms, mp 86—87°. *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.43; H, 8.32. NMR, IR and mass spectra of VIb were identical with that of VI.

**Reduction of VIa**——A solution of 1.34 g of VIa in 100 ml of ethanol was hydrogenated over 1.0 g of Pd-carbon at 5 atm. for 14 hr. After filtration and evaporation under reduced pressure, a residual oil was chromatographed on 10 g of silica gel. Elution with $CH_2Cl_2$–EtOAc gave Ia (0.96 g, 77%), mp 77 —84°. *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.48; H, 8.59. NMR $\delta^{CDCl_3}$: 0.95 (6H, d, $J$=6 Hz), 1.45 (3H, d, $J$=7 Hz), 1.5—3.1 (6H, m), 3.73 (1H, q, $J$=7 Hz), 7.10 (3H, s), 9.7 (1H, s, –OH). $^{13}$C NMR ($CDCl_3$): 18.3, 21.3, 33.5, 37.3, 37.5, 45.1, 48.3, 123.3, 124.2, 124.3, 137.5, 143.0, 144.3, 180.4 ppm. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 2900, 1710. MS *m/e*: 232 ($M^+$), 188 (base). UV $\lambda_{max}^{MeOH}$ nm ($\varepsilon$): 263.5 (980), 271.0 (1470), 277.2 (1750).

**Reduction of VIb**——Compound VIb (1.0 g) was reduced with the procedure mentioned above to produce 0.62 g of Ib (66%), mp 76—83°. *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.64; H, 8.52. NMR, IR and UV spectra of Ib were identical with that of Ia.

**Reduction of VI under Deuterium**——A solution of 1.0 g of VI in 30 ml of EtOD was deuterated over 1.0 g of Pd-carbon at 5 atm. for 24 hr. After filtration, solvent was removed *in vacuo*. Residual solid was chromatographed on 3 g of silica gel to afford 0.52 g of crystal, mp 79—84°, which was a mixture of Ic and Id (1: 1). NMR $\delta^{CDCl_3}$: 0.95 (6H, d, $J$=6 Hz), 1.45 (1.5H, d, $J$=7 Hz), 1.44 (1.5H, s), 1.70 (1H, m), 2.13 (1H, d, $J$=7 Hz), 3.73 (0.5H, q, $J$=7 Hz), 7.10 (3H, s). $^{13}$C NMR ($CDCl_3$): 18.2, 18.3, 21.3, 33.4, 45.3, 48.0, 123.5, 124.5, 125.5, 137.7, 143.1, 144.5, 181.2 ppm. Reduction of XVII under the same condition gave same mixture of Ic and Id.

***d*-N-(1-Phenylethyl) Amide (Xa and XIa) of Ia**——A solution of 0.96 g of Ia in 10 ml of $SOCl_2$ was stirred for 1 hr at 40° and excess $SOCl_2$ was removed *in vacuo*. The residual oil was dissolved in 5 ml of benzene, and was added to a solution of 2 g of *d*-1-phenylethylamine in 30 ml of benzene under ice-bath. After 1 hr, the reaction mixture was treated with 20 ml of 0.5 N HCl and benzene layer was separated and washed with 20 ml of 5% $NaHCO_3$ solution. The benzene solution was washed with saturated brine solution and concentrated *in vacuo*. The residual solid was dissolved in $CHCl_3$ and conducted with preparative HPLC (eluted with 15% EtOAc–15% $CHCl_3$–70% *n*-hexane) to afford 496 mg of Xa and 501 mg of XIa. Compound Xa was recrystallized from *n*-hexane to produce colourless fleaks, mp 101—102°. *Anal.* Calcd. for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.18. Found: C, 82.28; H, 8.78; N, 4.01. NMR $\delta^{CDCl_3}$: 0.95 (6H, d, $J$=6 Hz), 1.33 (3H, d, $J$=7 Hz), 1.43 (3H, d, $J$=7 Hz), 1.5—3.1 (6H, m), 3.43 (1H, q, $J$=7 Hz), 5.06 (1H, q, $J$=7 Hz), 5.5 (1H, bs, –NH), 7.00 (2H, s), 7.16 (6H, bs). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3300, 1630. UV $\lambda_{max}^{MeOH}$ nm ($\varepsilon$): 262.7 (1220), 270.4 (1630), 276.9 (1870). ORD ($c$=0.224, EtOH) [$\alpha$] (nm): +66.4° (589), +243.9° (365). Recrystallization of XIb from *n*-hexane gave prisms, mp 105—107°. *Anal.* Calcd. for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.18. Found: C, 82.09; H, 8.70; N, 3.97. IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3250, 1630. UV $\lambda_{max}^{MeOH}$ nm ($\varepsilon$): 262.8 (1160), 270.6 (1530), 277.0 (1750). ORD ($c$=0.239, EtOH) [$\alpha$] (nm): +32.7° (589), +131.5° (365).

***d*-N-(1-Phenylethyl) Amide (Xb and XIb) of Ib**——600 mg of Ib was reacted with the same procedure mentioned above to give 320 mg of Xb and 265 mg of XIb. Recrystallization of Xb from *n*-hexane yielded colourless amorphous melted at 103—105°. *Anal.* Calcd. for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.18. Found: C, 82.31; H, 8.75; N, 3.99. ORD ($c$=0.175, EtOH) [$\alpha$] (nm): +68.2° (589), +253.3 (365). IR and NMR spectra of Xb were identical with that of Xa. XIb was obtained as small prisms by the recrystallization from *n*-hexane, mp 93—94°. *Anal.* Calcd. for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.18. Found: C, 82.60; H, 8.69; N, 4.00. ORD ($c$=0.099, EtOH) [$\alpha$] (nm): +33.4° (589), +132.6° (365). IR and NMR spectra of XIb was identical with that of XIa. Mixed melting points of Xa and Xb was 101—105° and XIa and XIb was 96—105°.

**Amide Bond Cleavage of Xa, Xb, XIa and XIb (Ie, If, Ig and Ih)**——To a stirred suspension of 3.5 g of AcONa in 15 ml of $CCl_4$ at −78° was treated with 2 ml of $N_2O_4$ (1.5 M $CCl_4$ solution). After 1 hr, a stirred yellow suspension was treated dropwise with 500 mg of Xa in 4 ml of $CCl_4$ at 0° and kept for 24 hr. The reaction mixture was diluted with 30 ml of water and $CCl_4$ layer was separated. Aqueous layer was extracted with ether and combined organic solvents were removed *in vacuo*. Resulting oil was dissolved in 25 ml of $CCl_4$ and refluxed for 1 hr. $CCl_4$ was evaporated and chromatographed on 2 g of silica gel to produce 260 mg (75%) of Ie which was recrystallized from *n*-hexane to afford prisms, mp 62—64°. *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.36; H, 8.63. ORD ($c$=0.293, EtOH) [$\alpha$]$^{20}$ (nm): +53.6° (389), +4100° (238). Other three amide, XIa, Xb and XIb, were treated with the same procedure to give corresponding acids, If, Ig and Ih, respectively. If, mp 62—64°, *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.62; H, 8.55. ORD ($c$=0.203, EtOH) [$\alpha$]$^{20}$ (nm): −53.5° (589), −4100 (238). Ig, mp 61—63°, *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.36; H, 8.55. ORD ($c$=0.208, EtOH) [$\alpha$]$^{20}$ (nm): +54.1° (589), +4100° (238). Ih, mp 61—63°, *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.67; H,

8.63. ORD ($c$=0.260, EtOH) $[\alpha]^{20}$ (nm): −53.9° (589), −4100° (238). IR, NMR and mass spectra of four compounds were identical with that of Ia.

**Methyl 2-(2-Isopropylindan-5-yl)propionate (XIII)**——To a solution of 170 mg of I in 5 ml of ether was added ether solution of diazomethane under ice-bath. The solvent was removed under reduced pressure leaving an oil which was chromatographed on 2 g of silica gel. Elution with $CH_2Cl_2$ gave the colourless oil of XIII (169 mg, 94%). *Anal.* Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H 9.00. Found: C, 78.23; H, 9.11. NMR $\delta^{CDCl_3}$: 0.93 (6H, d, $J$=6 Hz), 1.40 (3H, d, $J$=7 Hz), 1.5—3.1 (6H, m), 3.60 (3H, s), 3.65 (1H, q, $J$=7 Hz), 6.96 (3H, s). IR $\nu_{max}^{neat}$ $cm^{-1}$: 1730.

**2-(2-Isopropylindan-5-yl)propanol (XIV)**——A suspension of $LiAlH_4$ (120 mg) and XIII (169 mg) in 10 ml of ether was heated under reflux for 1 hr. The reaction mixture was quenched with 0.3 ml of water and filtrate was concentrated *in vacuo*. Resulting oil was chromatographed on silica gel to afford 140 mg of XIV (94%), mp 44—46°. *Anal.* Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.38; H, 9.99. NMR $\delta^{CDCl_3}$: 0.96 (6H, d, $J$=6 Hz), 1.23 (3H, d, $J$=7 Hz), 1.58 (1H, s, –OH), 1.5—3.2 (7H, m), 3.66 (2H, d, $J$=7 Hz), 7.05 (3H, m). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3300.

**2-(2-Isopropylindan-5-yl)propyl methanesulfonate (XV)**——To a well stirred mixture of 127 mg of XIV and 1.2 ml of pyridine under ice-bath was added 0.2 g of methanesulfonylchloride. After 1 hr, reaction mixture was quenched by the addition of 20 ml of water and extracted with ether. Extract was washed with 2 ml of dil. HCl and solvent was removed *in vacuo*. Resulting oil was purified with 1 g of silica gel chromatography to give 142 mg (82%) of XV. NMR $\delta^{CDCl_3}$: 0.98 (6H, d, $J$=6 Hz), 1.35 (3H, d, $J$=7 Hz), 1.4—3.3 (6H, m), 2.82 (3H, s), 4.14 (1H, q, $J$=7 Hz), 7.03 (3H, s).

**5-Isopropenyl-2-isopropylindan (XVI)**——A solution of 142 mg of XV in 1.5 ml of DMSO was treated 0.2 g of *t*-BuOK at room temperature for 1 hr. The reaction mixture was treated with 20 ml of water and extracted with ether. Ether extract was chromatographed on silica gel to produce 88 mg (92%) of XVI as oil. *Anal.* Calcd. for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.73; H, 9.89. NMR $\delta^{CDCl_3}$: 0.93 (6H, d, $J$= 6 Hz) 1.4—3.3 (6H, m), 2.10 (3H, s), 5.00 (1H, m), 5.30 (1H, bs), 7.15 (3H, m). UV $\lambda_{max}^{EtOH}$ nm ($\varepsilon$): 248 (11700).

**2,5-Diisopropylindan (XII)**——A solution of 88 mg of XVI in 5 ml of EtOH was catalyticaly hydrogenated over 30 mg of 10% Pd-carbon for 1 hr. Filtrate was condenced *in vacuo* and residual oil was purified with chromatography of silica gel to give 75 mg of oil of XII. XIIa, *Anal.* Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.79; H, 10.77. NMR $\delta^{CDCl_3}$: 0.97 (6H, d, $J$=6 Hz), 1.24 (6H, d, $J$=6 Hz), 1.4—3.3 (6H, m), 7.12 (3H, m). UV $\lambda_{max}^{MeOH}$ nm ($\varepsilon$): 263.5 (1060), 271.3 (1620), 277.2 (1890). ORD ($c$=2.1×$10^{-4}$, MeOH) [$\alpha$] (nm): +5° (300) (through). XIIb, *Anal.* Calcd. for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.98; H, 10.87. ORD ($c$=1.9×$10^{-4}$, MeOH) [$\alpha$] (nm): −5° (300) (through). NMR and UV spectra of XIIb were identical with that of XIIa.

**Isopropyl 2-(2-Isopropylinden-5-yl)propionate (V)**——A solution of 1.0 g of III in 20 ml of EtOH was standing 2 days at room temperature. The solvent was removed *in vacuo* and residual oil was chromatographed on silica gel to afford 93 mg (10%) of V and 850 mg of staring material, III. *Anal.* Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.21; H, 8.76. NMR $\delta^{CDCl_3}$: 0.96 (6H, d, $J$=6 Hz), 1.22 (6H, d, $J$=6 Hz), 1.52 (3H, d, $J$=7 Hz), 2.6—3.1 (1H, m), 3.36 (2H, s), 3.81 (1H, q, $J$=7 Hz), 5.00 (1H, sep, $J$=6 Hz), 6.60 (1H, s), 7.0—7.5 (3H, m).