[Chem. Pharm. Bull. 26(6)1776—1785(1978)]

UDC 547.665.04.09 : 615.276.011.5

1-Indancarboxylic Acids. IV.[1] A Convenient Synthesis of Antiinflammatory 4-Aroyl-1-indancarboxylic Acids and Their Absolute Configurations

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(Received November 9, 1977)

Antiinflammatory 4-aroyl-1-indancarboxylic acids (I) were synthesized from the corresponding 4-aroyl-1-indanones (XI) by the one-carbon homologation reaction using *p*-toluenesulfonylmethylisocyanide (TosMIC, II) *via* 4-aroyl-1-indancarbonitriles (XIV). Among them, three compounds (Ia, b and c) were resolved into their enantiomers and it was found that the antiinflammatory activity virtually resides in the *levo* isomers, the absolute configurations of which were assigned the sinister series by the optical rotatory dispersion spectra.

Keywords——antiinflammatory agents; optical resolution; ORD; absolute configuration; one-carbon homologation

During the course of our investigations in search for a new non-steroidal antiinflammatory agent, we have synthesized a variety of 1-indancarboxylic acids and 1,2,3,4-tetrahydro-1-naphthoic acid derivatives, among which 4-aroyl-1-indancarboxylic acids (Ia—d) showed potent antiinflammatory activities.[1,3,4] The result prompted us to establish a more convenient route to 4-aroyl-1-indancarboxylic acids (I). It was also of interest to resolve I derivatives into each optical isomers and compare their activities in connection with the receptor analysis for antiinflammatory agents. The present paper deals with the improved synthetic method of I and the determination of their absolute configurations.

Improved Synthesis of 4-Aroyl-1-indancarboxylic Acids

1-Indancarboxylic acids have been prepared by cyclization of phenylsuccinic anhydrides followed by reduction[5] or by hydrolysis of 1-indancarbonitriles.[6] The former method, however, does not seem to be useful for the preparation of 4-substituted derivatives since they are obtained as only minor products from the corresponding (3-substituted phenyl)-succinic anhydrides.[3] 1-Indancarbonitriles, on the other hand, have been prepared by three steps from the corresponding 1-indanones, *i.e.* reduction to alcohol, halogenation and substitution with cyanide.[6] We assumed that a direct conversion of 1-indanone derivative to the corresponding 1-indancarboxylic acid or its equivalents would provide a simpler and general synthetic method of 1-indancarboxylic acid derivatives.

Although the formation of cyanohydrin has been known as a classical method for one-carbon homologation of carbonyl group, it has been shown that 1-indanone scarcely forms its cyanohydrin under the usual conditions.[7] Among the several reagents which have recently

1) Part III: T. Aono, Y. Araki, K. Tanaka, M. Imanishi, and S. Noguchi, *Chem. Pharm. Bull.* (Tokyo), **26**, 1511 (1978).
2) Location: *17–85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan.*
3) T. Aono, S. Kishimoto, Y. Araki, and S. Noguchi, *Chem. Pharm. Bull.* (Tokyo), **25**, 3198 (1977).
4) T. Aono, Y. Araki, M. Imanishi, and S. Noguchi, *Chem. Pharm. Bull.* (Tokyo), **26**, 1153 (1978).
5) K. Mori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem.* (Tokyo), **27**, 27 (1963).
6) Y. Sawa, T. Hattori, Y. Kawakami, S. Katsube, and A. Goto, *Yakugaku Zasshi*, **96**, 653 (1976).
7) P.A. Crooks and R. Szyndler, *Chem. Ind.* (London), **1973**, 1111.

been developed for that purpose,[8] 1,3-dithiane,[9] methyl methylthiomethyl sulfoxide (FAMSO),[10] toluenesulfonylmethylisocyanide (TosMIC, II)[11] and diethyl *tert*-butoxy(cyano)-methylphosphonate[8] seemed to be applicable to conjugated ketonic compounds. Although the application of 1,3-dithiane to the synthesis of 1-indancarboxylic acid derivatives have already been reported,[1,12] this method would not be appropriate for the present purpose, since 1,3-dithiane has been reported to react also with benzophenone under the similar conditions.[9] FAMSO was also excluded for the same reason.[10]

Accordingly, we investigated the application of TosMIC (II) to the synthesis of I. The synthesis and the utility of TosMIC (II) have been investigated by two groups.[11] Employing Leusen's procedure,[11a] 1-indanone (III) was allowed to react with TosMIC in the presence of sodium ethoxide to afford 1-indancarbonitrile (IV) in 55% yield. Under the similar condition, 4-benzyl-1-indanone (V) was converted to 4-benzyl-1-indancarbonitrile (VI), while the reaction of methyl 1-oxo-4-indancarboxylate (VII) afforded ethyl 1-cyano-4-indancarboxylate (VIII) due to the simultaneous transesterification. It was found, however, that benzophenone (IX) did not react with TosMIC under the same condition. These results suggested that 4-aroyl-1-indanone (XI) would be converted to 4-aroyl-1-indancarbonitrile (XIV) by the reaction with TosMIC leaving 4-aroyl group unchanged. Compound XIV was expected to be hydrolyzed into 4-aroyl-1-indancarboxylic acid (I) by the method already reported.[4]

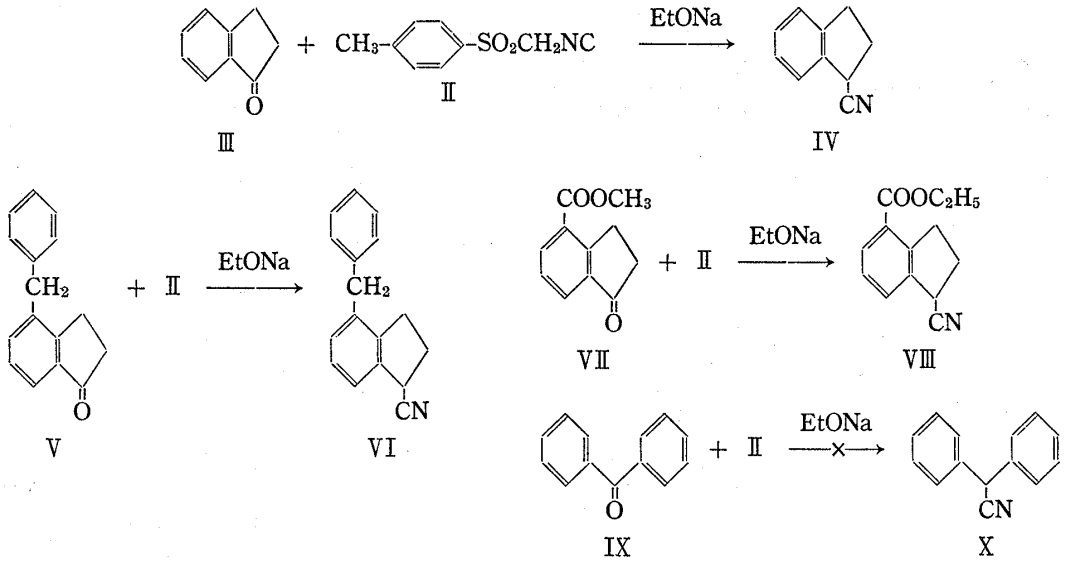


Chart 1

After these preliminary experiments, the synthesis of 4-aroyl-1-indanone (XI) was carried out by the Friedel–Crafts reaction of a benzene derivative with 1-oxo-4-indancarboxyl chloride (XIII) which was readily obtained by the reaction of 1-oxo-4-indancarboxylic acid (XII) with phosphorous pentachloride. By this method, a variety of 4-aroyl-1-indanones (XIa—c, e—k) were obtained.

8) S.E. Dinizo, R.W. Freerksen, W.E. Pabst, and D.S. Watt, *J. Am. Chem. Soc.*, **99**, 182 (1977) and the references cited therein.
9) E.J. Corey and D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **4**, 1075 (1965); D. Seebach, *Synthesis*, **1**, 17 (1969).
10) K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1972**, 2681.
11) *a*) O.H. Oldenziel and A.M. van Leusen, *Synthetic Communications*, **2**, 281 (1972); *idem*, *Tetrahedron Lett.*, **1973**, 1357; *b*) U. Schöllkopf and R. Schröder, *Angew. Chem. Int. Ed. Engl.*, **12**, 407 (1973) and the references cited therein.
12) P.F. Juby, W.R. Goodwin, T.W. Hudyma, and R.A. Partyka, *J. Med. Chem.*, **15**, 1297 (1972).

4-Aroyl-1-indanones (XI) thus obtained were subjected to the reaction with TosMIC under the conditions described above. As expected from the above experiments, only the carbonyl group of the indan ring reacted with TosMIC to afford 4-aroyl-1-indancarbonitriles (XIVa—c, e—k). The nitriles (XIVa—c) thus obtained were identified by comparing their infrared and nuclear magnetic resonance (NMR) spectra with those of compounds obtained by an alternative method[4] and the newly obtained nitriles (XIVe—j) were hydrolyzed to the corresponding 4-aroyl-1-indancarboxylic acids (Ie—j) under the conditions described in a previous paper.[4] The hydrolysis of 4-(2,4,6-trimethylbenzoyl)-1-indancarbonitrile (XIVk), however, resulted in the cleavage to give 1,4-indandicarboxylic acid (XV) and mesitylene. Previously a similar cleavage was observed in the hydrolysis of 4-(4-methoxybenzoyl)-1-indancarbonitrile, which was explained by the increased electron density of the benzoyl group by the methoxy group.[4] The cleavage of XIVk, however, is probably attributed to the steric hindrance of the carbonyl group by the 2′- and 6′-methyl groups.[13] The distortion at the aroyl moiety in XIVk is obvious from the spectral data described below. The synthesis of 4-(2,4,6-trimethylbenzoyl)-1-indancarboxylic acid (Ik), therefore, was achieved stepwise, *i.e.* conversion of XIVk to acid amide (XVI) by treatment with polyphosphoric acid followed by hydrolysis with hydrochloric acid. The 4-aroyl-1-indancarboxylic acids (I) are listed in Table I together with their ultraviolet (UV) and NMR spectral data.

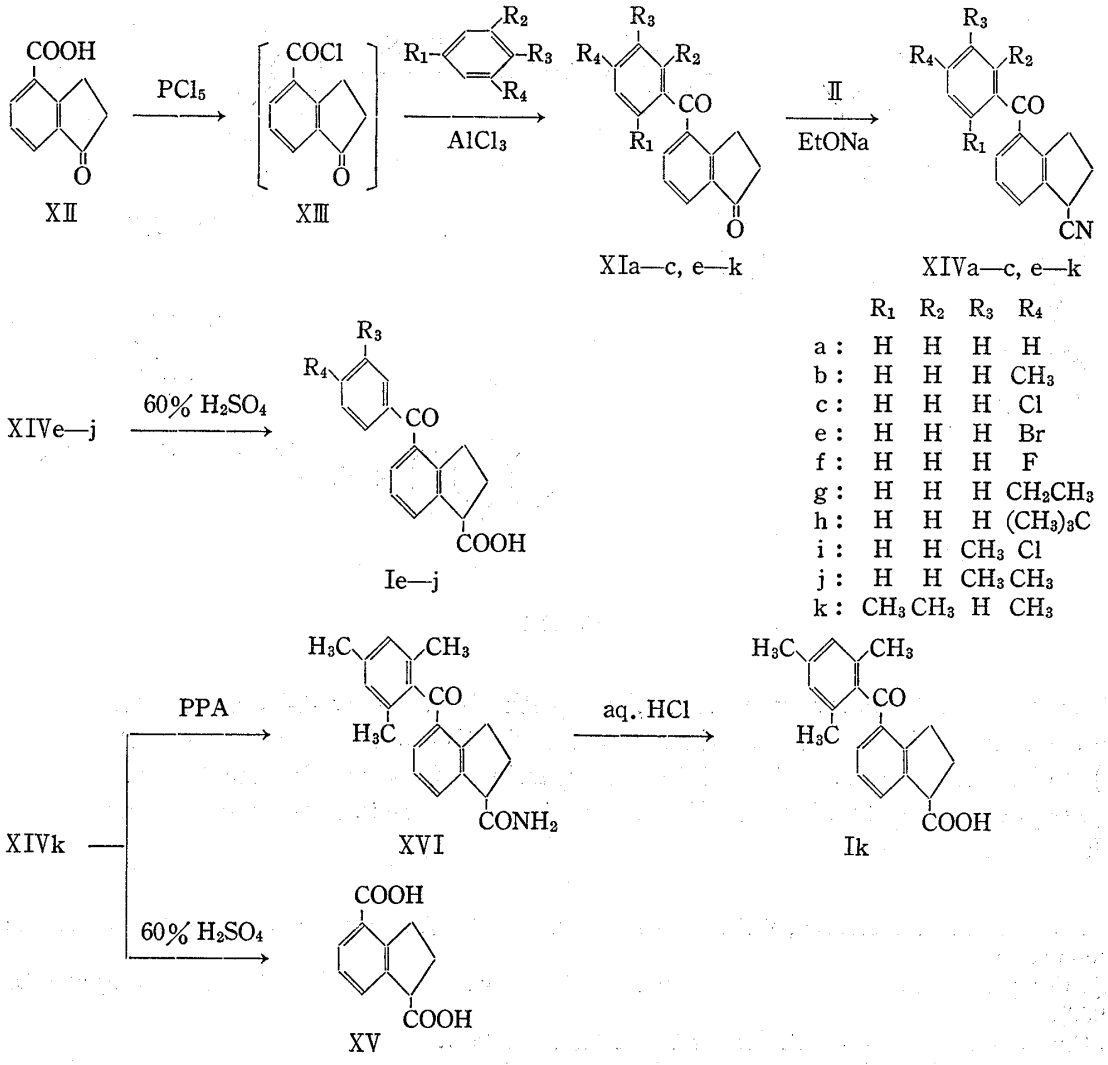
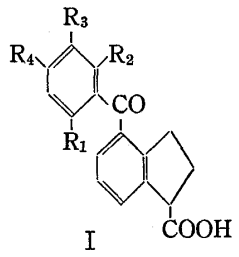


Chart 2

13) W.M. Schubert, *J. Am. Chem. Soc.*, **71**, 2639 (1949).

Table I. Deshielding Effect of the Carbonyl Group and Ultraviolet Absorption Spectra of 4-Aroyl-1-indancarboxylic Acids (I)



I

Compd. No.	Substituent				δ-Values of protons at the 3-position[a]	UV absorption max. nm(ε)[b]
	R_1	R_2	R_3	R_4		
Ia[c]	H	H	H	H	3.04—3.33	253(16000)
Ib[c]	H	H	H	CH_3	3.02—3.35	260(18100)
Ic[c]	H	H	H	Cl	3.02—3.32	260(19500)
Id[c]	H	H	H	OCH_3	3.00—3.30	288(17300)
Ie	H	H	H	Br	3.02—3.32	262(20800)
If	H	H	H	F	3.02—3.30	254(15600)
Ig	H	H	H	CH_3CH_2	3.00—3.30	261(18200)
Ih	H	H	H	$(CH_3)_3C$	3.02—3.30	261(19600)
Ii	H	H	CH_3	Cl	3.02—3.30	261(18400)
Ij	H	H	CH_3	CH_3	2.98—3.30	263(16600)
Ik	CH_3	CH_3	H	CH_3	3.26—3.50	252(14500)

a) Downfield value from TMS used as an internal reference standard.
b) All the spectra were measured in ethanol.
c) Data described in the previous paper, reference 4.

As is clear from Table I, the δ-value (3.26—3.50) of the protons at C-3 of Ik is apparently larger than those (3.02—3.35) of others. This observation suggests that the carbonyl group of Ik lies more closely to the plane of indan ring than in others, affecting the δ-value of the C-3 protons through the anisotropy and the hydrogen bond. As in the case of tri-*ortho*-substituted benzophenone,[14] mesitylene ring of Ik is considered to exist preferentially in a conformation with approximately right angle to the plane of the carbonyl and indan ring, while in the rest of derivatives the aroyl group would be nearly coplanar with the carbonyl group. This interpretation is consistent with the data of UV spectra, that is, the shift of the absorption maximum of Ik to shorter wavelength in addition to the decrease of the absorption intensity. These data reflect that the conjugation between the indan ring and the mesitylene ring is sterically inhibited.

Absolute Configuration of 4-Aroyl-1-indancarboxylic Acids

4-Aroyl-1-indancarboxylic acids (I) have an asymmetric carbon atom at the 1-position, bearing a conformationally fixed carboxyl group which is essential for the antiinflammatory activity.[1] To elucidate the relationship between activity and stereochemical structure, efforts were made to resolve Ia, Ib and Ic into each optical antipodes. Thus, *dl*-4-benzoyl-1-indancarboxylic acid (Ia)[4] was resolved *via* the cinchonidine salt to give *l*-Ia, $[\alpha]_D$ −66.4°, and *d*-Ia, $[\alpha]_D$ +66.4°, both as oils. Each optical isomer was converted to crystalline 4-benzoyl-1-indancarboxamides, *l*-XVII, $[\alpha]_D$ −114.5°, mp 168—169°, and *d*-XVII, $[\alpha]_D$ +114.7°, mp 168—169°, by treatment with thionyl chloride and ammonia. 4-(4-Methylbenzoyl)-1-indancarboxylic acid (Ib)[4] was resolved into *l*-Ib, $[\alpha]_D$ −70.8°, mp 113.5—115.5°, and *d*-Ib, $[\alpha]_D$ +64.3°, mp 110.5—114.0°, by use of their cinchonine and *l*-α-phenylethylamine salts, respec-

14) K. Maruyama, *Bull. Chem. Soc. Jpn.*, **39**, 2772 (1966); N.E. Alexandrou, *J. Chem. Soc. C*, **1969**, 536; E.J. Moriconi, W.F. O'Connor, and W.F. Forbes, *J. Am. Chem. Soc.*, **84**, 3928 (1962).

tively. Similarly, 4-(4-chlorobenzoyl)-1-indancarboxylic acid (Ic)[4] was resolved into *l*-Ic, $[\alpha]_D$ −66.9°, mp 121—122°, and *d*-Ic, $[\alpha]_D$ +65°, mp 121—122°.

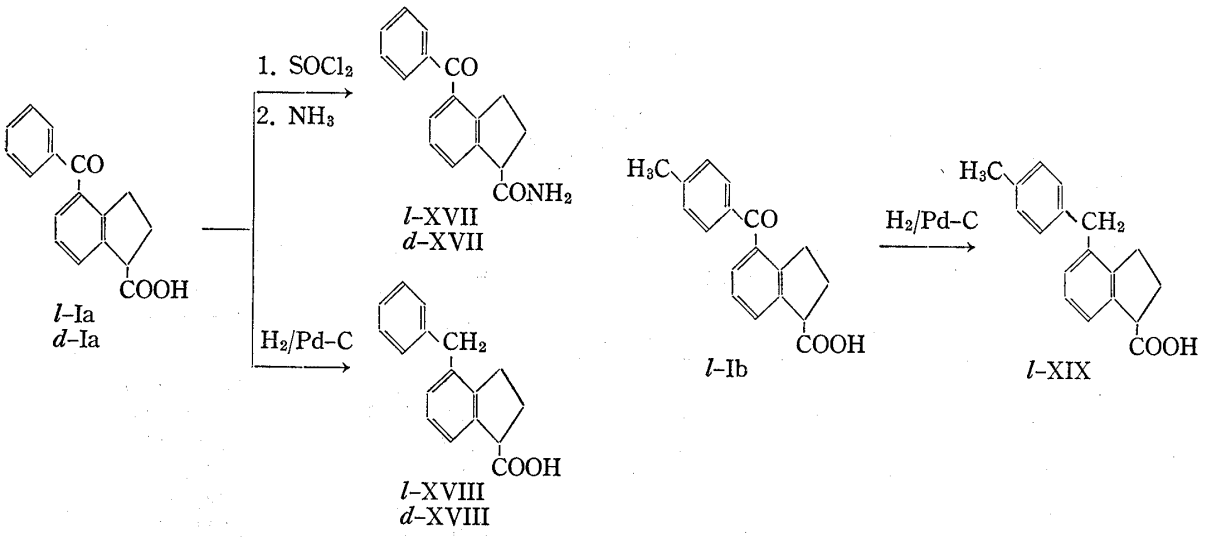


Chart 3

In an attempt to determine their absolute configurations, the optical rotatory dispersion (ORD) spectra of the optically active I were measured. However, their spectra proved to be too complicated to compare with those of the reference compounds such as *l*-1-indancarboxylic acid[15] and *d*-6-chloro-5-cyclohexyl-1-indancarboxylic acid,[16] whose absolute configurations had been established. Therefore, *l*-Ia and *d*-Ia were led to each 4-benzyl-1-indancarboxylic acid, *l*-XVIII, $[\alpha]_D$ −48.4°, mp 78—80°, and *d*-XVIII, $[\alpha]_D$ +49.2°, mp 77—79°, by hydrogenation over palladium-carbon in acetic acid. Similarly *l*-4-(4-methylbenzyl)-1-indancarboxylic acid (*l*-XIX), $[\alpha]_D$ −47.2°, mp 100.5—103.5°, was obtained from *l*-Ib. The ORD spectra of these benzyl derivatives (XVIII and XIX) were much simpler than those of the corresponding benzoyl derivatives (Ia and Ib). It was found that the ORD curves of *l*-XVIII and *l*-XIX were similar to those of (*S*)-*l*-1-indancarboxylic acid[15] and (*S*)-*d*-6-chloro-5-cyclohexyl-1-indancarboxylic acid,[16a] showing multiple Cotton effects in the region 260—280 nm corresponding in fine structure to the ^1L_b absorption band. Consequently, configurations at the 1-position of *l*-XVIII and *l*-XIX were established to be the sinister configurations and hence it became apparent that *l*-Ia and *l*-Ib have (*S*)-configurations. From the similarity of the ORD curve of *l*-Ic to those of *l*-Ia and *l*-Ib, *l*-Ic was also shown to have (*S*)-configuration.

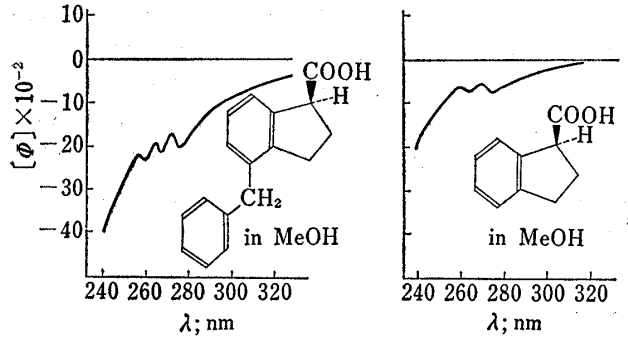


Fig. 1. ORD Curves of (*S*)-*l*-4-Benzyl-1-indancarboxylic Acid (XVIII) and (*S*)-*l*-1-Indancarboxylic Acid

The antiinflammatory activity of these optical isomers (Ia—c) was determined using the carrageenin-induced foot edema method in rats.[17] It was found that *l*-isomers have more potent activities than the corresponding *d*-isomers. The results indicate that the antiinflam-

15) J.H. Brewster and J.G. Buta, *J. Am. Chem. Soc.*, **88**, 2233 (1966).
16) *a*) S. Noguchi, S. Kishimoto, I. Minamida, and M. Obayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 529 (1974); *b*) K. Kamiya, Y. Wada, and M. Nishikawa, *ibid.*, **23**, 1589 (1975).
17) Details are to de published by K. Kawai *et al.* in the near future.

matory activity virtually resides in the isomers with (*S*)-configuration in agreement with the results of 6-chloro-5-cyclohexyl-1-indancarboxylic acid,[16a] 2-(3-chloro-4-cyclohexylphenyl)propionic acid,[18] 2-(4-biphenyl)propionic acid[18] and indomethacin analogs.[18]

Experimental[19]

1-Indancarbonitrile (IV)——To a stirred, ice-cooled mixture of 0.53 g of 1-indanone (III) and 1.2 g of *p*-toluenesulfonylmethylisocyanide (TosMIC, II)[11a] in 15 ml of dimethoxyethane (DME) was added dropwise a solution of 0.41 g of EtONa in 3 ml of EtOH and 6 ml of DME over a 30-minute period. The mixture was stirred for 40 min under cooling and 2.5 hr at room temperature. After cooling with ice-water, the mixture was diluted with water and then extracted with pentane. The extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 0.33 g (58%) of IV as an oil, the IR and NMR spectra of which were identical with those of the sample prepared from 1-indancarboxamide by dehydration with P_2O_5.[20] IR ν_{max}^{Neat} cm^{-1}: 2250 (C≡N). NMR (in $CDCl_3$) δ: 7.1—7.5 (4H, m, aromatic protons), 4.03 (1H, t, J=8 Hz, C_1–H), 2.83—3.17 (2H, m, C_3–H), 2.27—2.67 (2H, m, C_2–H).

4-Benzyl-1-indancarbonitrile (VI)——To a stirred, ice-cooled mixture of 4.0 g of 4-benzyl-1-indanone (V)[1] and 5.3 g of TosMIC (II) in 68 ml of DME was added dropwise a solution of 1.85 g of EtONa in 13.5 ml of EtOH and 27 ml of DME over a 50-minute period. The mixture was stirred for 1 hr under cooling and 4 hr at room temperature. After cooling with ice-water, the mixture was diluted with water and then extracted with benzene. The extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel using benzene as the eluant and recrystallized from hexane to give 1.93 g (46%) of VI, mp 43.0—44.5°. *Anal.* Calcd. for $C_{17}H_{15}N$: C, 87.53; H, 6.48; N, 6.01. Found: C, 87.44; H, 6.51; N, 5.67. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N). NMR (in $CDCl_3$) δ: 7.0—7.4 (8H, m, aromatic protons), 4.04 (1H, t, J=7 Hz, C_1–H), 3.87 (2H, s, Ar–CH_2–Ar), 2.69—3.00 (2H, m, C_3–H), 2.24—2.56 (2H, m, C_2–H).

Ethyl 1-Cyano-4-indancarboxylate (VIII)——To a stirred, ice-cooled mixture of 0.76 g of methyl 1-oxo-4-indancarboxylate (VII)[4] and 1.2 g of TosMIC (II) in 15 ml of DME was added dropwise a solution of 0.41 g of EtONa in 3 ml of EtOH and 6 ml of DME over a 30-minute period. The mixture was stirred for 1 hr under cooling and 5.5 hr at room temperature. After cooling with ice-water, the mixture was diluted with water and then extracted with benzene. The extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silicagel using a mixture of benzene and AcOEt (50: 1) as the eluant and recrystallized from cyclohexane to give 0.32 g (37%) of VIII, mp 93—95°. *Anal.* Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.54; H, 5.93; N, 6.55. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1690 (C=O). NMR (in $CDCl_3$) δ: 8.00 (1H, d, J=8 Hz, C_5–H), 7.47 (1H, t, J=8 Hz, C_6–H), 7.30 (1H, d, J=8 Hz, C_7–H), 4.37 (2H, q, J=7 Hz, –$C\underline{H}_2$–CH_3), 4.10 (1H, t, J=8 Hz, C_1–H), 3.56—3.67 (2H, m, C_3–H), 2.33—2.70 (2H, m, C_2–H), 1.40 (3H, t, J=7 Hz, CH_3).

4-Aroyl-1-indanone (XI) (Table II)——General Procedure: To a stirred, ice-cooled suspension of 17.6 g of 1-oxo-4-indancarboxylic acid (XII)[4] in 200 ml of benzene or substituted benzene (toluene, chlorobenzene, bromobenzene, fluorobenzene, ethylbenzene, *tert*-butylbenzene, *o*-chlorotoluene, *o*-xylene and mesitylene) was added 23 g of phosphorous pentachloride. The mixture was stirred for 3 hr at room temperature. To the mixture, cooled with ice-water, was added 40 g of pulverized anhydrous $AlCl_3$. The mixture was stirred for 1 hr at room temperature and then 2 hr at 50—70°. After cooling, the mixture was poured onto ice-dil. HCl and extracted with benzene. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel using benzene as the eluant and recrystallized to give XI.

4-Aroyl-1-indancarbonitrile (XIV)——General Procedure: To a stirred, ice-cooled mixture of 0.035 mol of 4-aroyl-1-indanone (XI) and 10 g of TosMIC (II) in 120 ml of DME was added a solution of 3.5 g of EtONa in 24 ml of EtOH and 48 ml of DME over a 30-minute period. The mixture was stirred for 30 min under cooling and 3 hr at room temperature. After cooling, the mixture was diluted with 800 ml of water and acidified with dil. HCl. The mixture was extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel using a mixture of benzene and AcOEt (50: 1) as the eluant to give XIV.

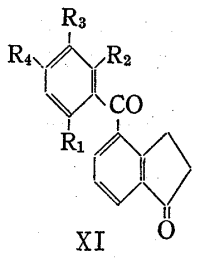
Compounds XIVa, XIVb, XIVf, XIVh, XIVi and XIVj were obtained as oils in 50, 45, 28, 46, 53 and 29% yields, respectively. These oily products were used for the subsequent hydrolysis without further

18) T.Y. Shen, *Angew. Chem. Int. Ed. Engl.*, **11**, 460 (1972).

19) Melting points are not corrected. The infrared (IR) spectra were measured with a Hitachi-215 spectrometer. The NMR spectra were obtained on a Varian HA-100 spectrometer using tetramethylsilane (TMS) as an internal standard. The UV spectra were measured with a Perkin-Elmer 450 UV-Visible NIR spectrophotometer. The optical rotations were measured with a Perkin-Elmer 141 polarimeter. The ORD spectra were measured with a Jasco ORD/UV-5 spectropolarimeter.

20) S. Noguchi, M. Obayashi, S. Kishimoto, and M. Imanishi, *Chem. Pharm. Bull.* (Tokyo), **22**, 537 (1974).

Table II. 4-Aroyl-1-indanone (XI)

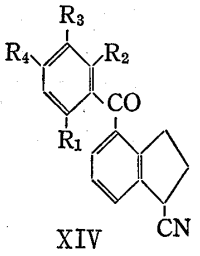


XI

Compd. No.	Substituent R_1	R_2	R_3	R_4	mp (°C)	Rec.[a] solv.	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	Cl or Br
XIa	H	H	H	H	87.0—89.0	C	61	$C_{16}H_{12}O_2$	81.34 (81.26	5.12 5.03)	
XIb	H	H	H	CH_3	105.0—108.0	C	45	$C_{17}H_{14}O_2$	81.58 (81.59	5.64 5.56)	
XIc	H	H	H	Cl	145.0—146.0	B-C (1:1)	55	$C_{16}H_{11}ClO_2$	70.98 (70.98	4.10 4.25)	Cl, 13.10 (13.04)
XIe	H	H	H	Br	154.0—155.0	B-C (1:1)	38	$C_{16}H_{11}BrO_2$	60.97 (61.28	3.52 3.58)	Br, 25.36 (25.52)
XIf	H	H	H	F	93.5—94.5	$CHCl_3$	28	$C_{16}H_{11}FO_2$	75.58 (75.40	4.36 4.23)	
XIg	H	H	H	CH_2CH_3	81.5—83.5	C	45	$C_{18}H_{16}O_2$	81.79 (81.86	6.10 6.07)	
XIh	H	H	H	$(CH_3)_3C$	Oil		59	$C_{20}H_{20}O_2$	82.15 (82.31	6.89 6.87)	
XIi	H	H	CH_3	Cl	88.5—90.5	B-C (3:20)	41	$C_{17}H_{13}ClO_2$	71.70 (71.98	4.60 4.49)	Cl, 12.45 (12.02)
XIj	H	H	CH_3	CH_3	114.5—116.0	C	70	$C_{18}H_{16}O_2$	81.79 (81.90	6.10 6.09)	
XIk	CH_3CH_3	H		CH_3	159.5—161.5	B-C (1:2)	54	$C_{19}H_{18}O_2$	81.98 (81.95	6.52 6.74)	

a) B: benzene, C: cyclohexane.

Table III. 4-Aroyl-1-indancarbonitriles (XIV)



XIV

Compd. No.	Substituent R_1	R_2	R_3	R_4	mp (°C)	Rec.[a] solv.	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	Br
XIVc[b]	H	H	H	Cl	116.0—118.0	B-C (1:10)	55	$C_{17}H_{12}ClNO$	72.49 (72.11	4.30 4.25	4.97 4.87)	
XIVe	H	H	H	Br	114.0—116.0	B-C (3:2)	37	$C_{17}H_{12}BrNO$	62.59 (62.69	3.71 3.55	4.29 4.32	24.50 24.36)
XIVg	H	H	H	CH_2CH_3	70.5—72.0	C-H (1:1)	41	$C_{19}H_{17}NO$	82.88 (82.76	6.22 6.13	5.09 5.00)	
XIVk	CH_3CH_3	H		CH_3	133.5—135.0	C	50	$C_{20}H_{19}NO$	83.01 (83.32	6.62 6.64	4.84 4.91)	

a) B: benzene, C: cyclohexane, H: hexane.
b) In the previous paper, XIVc was obtained as an iol, reference 4.

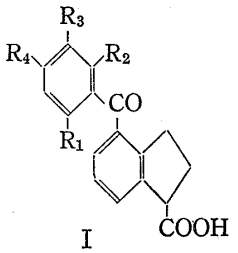
purification. Compounds XIVc, XIVe, XIVg and XIVk were obtained as crystals and their melting points and the data of elemental analyses were listed in Table III.

4-(2,4,6-Trimethylbenzoyl)-1-indancarboxamide (XVI)——A suspension of 0.2 g of XIVk in 40 g of polyphosphoric acid was heated at 100° for 1 hr with occasional stirring. After cooling, the mixture was diluted with 50 ml of water and extracted with AcOEt. The extract was washed with 5% aqueous Na_2CO_3 and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from EtOH to give 0.14 g (66%) of XVI as colorless prisms, mp 196—198°. *Anal.* Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.12; H, 7.00; N, 4.38. IR ν_{max}^{Nujol} cm^{-1}: 3410 (NH), 3175 (NH), 1680 (C=O), 1650 (C=O).

4-Aroyl-1-indancarboxylic Acid (I) (Table IV)——a) General Procedure: A suspension of 3.0 g of XIV in 60 ml of 60 wt% H_2SO_4 was heated under reflux for 3.3 hr in an atmosphere of nitrogen. After cooling, the mixture was poured into water and extracted with ether. The ethereal layer was washed with water and then extracted with 5% aqueous K_2CO_3. The extract was acidified with dil. HCl and extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized to give I. Compounds Ie—j were prepared by this method from corresponding carbonitriles (XIV).

b) A suspension of 0.84 g of XVI in 80 ml of conc. HCl and 20 ml of dioxane was heated under reflux for 5 hr in an atmosphere of nitrogen. After cooling, the mixture was extracted with ether. The ethereal layer was washed with water and extracted with 5% aqueous K_2CO_3. The extract was acidified with dil. HCl and extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from a mixture of benzene and hexane (1:1) to give 4-(2,4,6-trimethylbenzoyl)-1-indancarboxylic acid (Ik).

TABLE IV. 4-Aroyl-1-indancarboxylic Acids (I)



I

Compd. No.	Substituent				mp (°C)	Rec.[a] solv.	Yield (%)	Formula	Analysis (%) Calcd. (Found)		
	R_1	R_2	R_3	R_4					C	H	Cl or Br
Ie	H	H	H	Br	147.5—149.0	B-C (1:1)	76	$C_{17}H_{13}BrO_3$	59.15 (59.32	3.80 3.61)	Br, 23.15 (22.96)
If	H	H	H	F	109.0—110.0	B-C (3:20)	67	$C_{17}H_{13}FO_3$	71.82 (71.78	4.61 4.61)	
Ig	H	H	H	CH_2CH_3	93.0—94.5	C	45	$C_{19}H_{18}O_3$	77.53 (77.44	6.16 5.99)	
Ih	H	H	H	$(CH_3)_3C$	139.0—141.0	B-PE (1:1)	64	$C_{21}H_{22}O_3$	78.23 (78.24	6.88 6.96)	
Ii	H	H	CH_3	Cl	116.0—117.0	B-C (3:20)	67	$C_{18}H_{15}ClO_3$	68.68 (68.79	4.80 4.99)	Cl, 11.27 (11.53)
Ij	H	H	CH_3	CH_3	137.0—139.0	B-C (3:10)	47	$C_{19}H_{18}O_3$	77.53 (77.62	6.16 6.12)	
Ik	CH_3	CH_3	H	CH_3	191.5—193.0	B-H (1:1)	51	$C_{20}H_{20}O_3$	77.90 (77.90	6.54 6.80)	

a) B: benzene, C: cyclohexane, PE: petroleum ether, H: hexane.

1,4-Indandicarboxylic Acid (XV)——A suspension of 1.55 g of XIVk in 50 ml of 60 wt% H_2SO_4 was heated under reflux for 2.5 hr. After cooling, the mixture was diluted with water and extracted with ether. The ethereal layer was washed with water and extracted with 5% aqueous K_2CO_3. The extract was acidified with dil. HCl and then extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from acetone to give 0.63 g of XV as colorless prisms, mp 247.5—249° (lit.[4] 245.5—248.0°). The IR and NMR spectra were identical with those of the authentic sample.[4]

Optical Resolution of 4-Benzoyl-1-indancarboxylic Acid (Ia)——a) (*S*)-*l*-Ia: A suspension of 3.20 g of Ia and 1.76 g of cinchonidine in 60 ml of acetone was warmed to give a clear solution. The solution was allowed to stand overnight at room temperature. The resulting precipitate was collected by filtration and recrystallized twice from acetone to give 1.17 g (34%) of the cinchonidine salt of (*S*)-*l*-Ia as colorless crystals, mp 189—192°. *Anal.* Calcd. for $C_{36}H_{36}N_2O_4$: C, 77.12; H, 6.47; N, 5.00. Found: C, 77.18; H, 6.28; N, 4.91. $[\alpha]_D^{22}$ −132.2° (c=1, $CHCl_3$). This salt (1.15 g) was dissolved in 115 ml of $CHCl_3$. The solution was washed twice with 50 ml of 1 N HCl and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give (*S*)-*l*-Ia as an oil in a quantitative yield. *Anal.* Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.45; H, 5.37. $[\alpha]_D^{22}$ −66.4° (c=1, MeOH). The NMR spectrum was identical with that of the racemic compound.[4]

b) (*R*)-*d*-Ia: The mother liquor of the crude cinchonidine salt of *l*-Ia in a) was concentrated under reduced pressure. The residue and 1.70 g of cinchonidine were dissolved in 120 ml of CH_3CN by warming. The clear solution was allowed to stand overnight at room temperature. The precipitate was collected and recrystallized three times from CH_3CN to give 1.23 g (35%) of the cinchonidine salt of (*R*)-*d*-Ia as colorless crystals, mp 179—182°. *Anal.* Calcd. for $C_{36}H_{36}N_2O_4$: C, 77.12; H, 6.47; N, 5.00. Found: C, 77.15; H, 6.42; N, 4.72. $[\alpha]_D^{22}$ +11.2° (c=1, $CHCl_3$). Treatment of this salt with 1 N HCl in the similar manner to a) gave (*R*)-*d*-Ia as an oil in a quantitative yield. *Anal.* Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.53; H, 5.30. $[\alpha]_D^{22}$ +66.4° (c=1, MeOH). The NMR spectrum was identical with that of the racemic compound.[4]

Optical Resolution of 4-(4-Methylbenzoyl)-1-indancarboxylic Acid (Ib)——a) (*S*)-*l*-Ib: A suspension of 14.0 g of Ib and 7.4 g of cinchonine in 500 ml of CH_3CN was warmed to give a clear solution. The resulting solution was allowed to stand overnight at room temperature. The precipitate was collected by filtration and recrystallized from 2.2 l of CH_3CN to give 10.5 g (73%) of the cinchonine salt of (*S*)-*l*-Ib as colorless crystals, mp 195.0—197.0°. *Anal.* Calcd. for $C_{37}H_{38}N_2O_4$: C, 77.32; H, 6.67; N, 4.87. Found: C, 77.28; H, 6.62; N, 4.94. $[\alpha]_D^{23}$ +31.7° (c=1, $CHCl_3$). This salt (10.0 g) was dissolved in 200 ml of benzene. The solution was washed twice with 100 ml of 1 N HCl and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from a mixture of benzene and cyclohexane (3: 8) to give 4.25 g (87%) of (*S*)-*l*-Ib, mp 113.5—115.5°. *Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.08; H, 5.65. $[\alpha]_D^{23}$ −70.8° (c=1, MeOH). The NMR spectrum was identical with that of the racemic compound.[4]

b) (*R*)-*d*-Ib: The mother liquor of the crude cinchonine salt of *l*-Ib in a) was concentrated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$. The solution was washed with 1 N HCl and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved with 3.0 g of *l*-α-phenylethylamine in 400 ml of CH_3CN by warming. The solution was allowed to stand overnight. The resulting precipitate was collected by filtration and recrystallized twice from CH_3CN to give 5.6 g (56%) of the *l*-α-phenylethylamine salt of (*R*)-*d*-Ib as colorless needles, mp 149.0—150.0°. *Anal.* Calcd. for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.82; H, 6.68; N, 3.56. $[\alpha]_D^{23}$ +65.8° (c=1, $CHCl_3$). From this salt (*R*)-*d*-Ib was obtained by the similar procedures to that described in a), mp 110.5—114.0° [79%, recrystallized from a mixture of benzene and cyclohexane (3: 8)]. *Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.20; H, 5.66. $[\alpha]_D^{23}$ +64.3° (c=1, MeOH). The NMR spectrum was identical with that of the racemic compound.[4]

Optical Resolution of 4-(4-Chlorobenzoyl)-1-indancarboxylic Acid (Ic)——a) (*S*)-*l*-Ic: A suspension of 3.1 g of Ic and 1.5 g of cinchonine in 100 ml of acetone was warmed to give a clear solution. The solution was allowed to stand overnight in a refrigerator. The resulting precipitate was collected by filtration and recrystallized from CH_3CN to give 1.7 g (56%) of the cinchonine salt of (*S*)-*l*-Ic as colorless crystals, mp 190.0—192.0°. *Anal.* Calcd. for $C_{36}H_{34}ClN_2O_4$: C, 72.78; H, 5.77; N, 4.72. Found: C, 72.51; H, 5.92; N, 4.72. $[\alpha]_D^{23}$ +32.9° (c=1, $CHCl_3$). This salt was dissolved in 170 ml of $CHCl_3$. The solution was washed with 1 N HCl and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from a mixture of benzene and cyclohexane (1: 4) to give 0.60 g (70%) of (*S*)-*l*-Ic, mp 121—122°. *Anal.* Calcd. for $C_{17}H_{13}ClO_3$: C, 67.89; H, 4.36. Found: C, 67.96; H, 4.09. $[\alpha]_D^{24}$ −66.9° (c=1, MeOH). The NMR spectrum was identical with that of the racemic compound.[4]

b) (*R*)-*d*-Ic: The mother liquor of the crude cinchonine salt of *l*-Ic in a) was concentrated to dryness under reduced pressure. The residue was dissolved in 50 ml of CH_3CN. The solution was allowed to stand for 10 days and the resulting precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was dissolved in 150 ml of $CHCl_3$. The solution was washed with 1 N HCl and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved with 0.6 g of *l*-α-phenylethylamine in 80 ml of CH_3CN and the solution was allowed to stand overnight. The resulting precipitate was collected and recrystallized five times from CH_3CN to give 0.78 g (37%) of the *l*-α-phenylethylamine salt of (*R*)-*d*-Ic as colorless crystals, mp 148—150°. *Anal.* Calcd. for $C_{25}H_{24}ClNO_3$: C, 71.17; H, 5.73; N, 3.32. Found: C, 71.24; H, 5.67; N, 3.50. $[\alpha]_D^{24}$ +62.2° (c=1, $CHCl_3$). From this salt (*R*)-*d*-Ic was obtained by the similar procedures to that described in a), mp 121—122° [32%, recrystallized from a mixture of benzene and cyclohexane (1: 4)]. *Anal.* Calcd. for $C_{17}H_{13}ClO_3$: C, 67.89; H, 4.36. Found: C, 68.08; H, 4.17. $[\alpha]_D^{24}$ +65.0° (c=1, MeOH). The NMR spectrum was identical with that of the

racemic compound.[4]

(*S*)-*l*- and (*R*)-*d*-4-Benzoyl-1-indancarboxamides (XVII)——A mixture of 0.2 g of (*S*)-*l*-Ia and 1 ml of thionyl chloride in 10 ml of benzene was heated under reflux for 1 hr. After cooling, the mixture was concentrated under reduced pressure. The residue was dissolved in 10 ml of benzene and to the solution was added 0.5 ml of 30% NH_4OH. After stirred for 2 hr, the mixture was diluted with water and extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from benzene to give 0.07 g (35%) of (*S*)-*l*-XVII as colorless crystals, mp 168—169°. *Anal.* Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.09; H, 5.70; N, 5.36. $[\alpha]_D^{22}$ −114.5° (*c*=1, MeOH).

By the similar procedures (*R*)-*d*-XVII was obtained from (*R*)-*d*-Ia, mp 168—169° (from benzene). *Anal.* Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.66; H, 5.69; N, 5.69. $[\alpha]_D^{22}$ +114.7° (*c*=1, MeOH).

(*S*)-*l*- and (*R*)-*d*-4-Benzyl-1-indancarboxylic Acids (XVIII)——A solution of 0.3 g of (*S*)-*l*-Ia in 20 ml of AcOH was catalytically hydrogenated over 5% Pd-C (0.2 g) under atmospheric pressure at 80°. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was recrystallized from a mixture of hexane and cyclohexane (1: 1) to give 0.04 g of (*S*)-*l*-XVIII as colorless crystals, mp 78—80°. *Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.69; H, 6.44. $[\alpha]_D^{22}$ −48.4° (*c*=1, MeOH). The NMR spectrum was identical with that of the racemic compound.[1]

By the similar procedures (*R*)-*d*-XVIII was obtained from (*R*)-*d*-Ia, mp 77—79°. *Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.75; H, 6.45. $[\alpha]_D^{22}$ +49.2° (*c*=1, MeOH). The NMR spectrum was identical with that of the racemic compound.[1]

(*S*)-*l*-4-(4-Methylbenzyl)-1-indancarboxylic Acid (XIX)——A solution of 0.5 g of (*S*)-*l*-Ib in 20 ml of AcOH was catalytically hydrogenated over 5% Pd-C (0.2 g) under atmospheric pressure at 80°. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was recrystallized from cyclohexane to give 0.3 g (65%) of (*S*)-*l*-XIX as colorless crystals, mp 100.5—103.5°. *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.08; H, 6.71. $[\alpha]_D^{25}$ −47.2° (*c*=1, MeOH). The NMR spectrum was identical with that of the racemic compound.[1]

Acknowledgement The authors wish to thank Drs. E. Ohmura and K. Morita of this Division for their encouragement and useful discussion throughout this work.