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1-Indancarboxylic Acids. V.[1] Syntheses of Phenoxy- and (2-Thienylcarbonyl)-1-indancarboxylic Acids, New Antiinflammatory Agents

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Phenoxy-1-indancarboxylic acids (II and III) and (2-thienylcarbonyl)-1-indancarboxylic acids (V, VI and VII) were synthesized *via* the corresponding phenoxy- and (2-thienylcarbonyl)-1-indancarbonitriles (XII, XVII and XXIII). The relationship between the antiinflammatory activity and the stereochemical features of the substituents of the compounds synthesized was also discussed.

Keywords——antiinflammatory agent; diphenyliodonium chloride; Ullmann reaction; tosylmethyl isocyanide (TosMIC); receptor site for antiinflammatory agent

Previously we synthesized several benzoyl-1-indancarboxylic acid derivatives, among which 4-benzoyl-1-indancarboxylic acid (I) was found to exhibit strong antiinflammatory activity.[3,4] This together with the fact that the 6-benzoyl isomer of I showed significantly weaker activity than I suggested that situations of the functional groups in I, where the carboxyl group directs opposite to the benzoyl group and stands out of plane of the indan ring, might represent the essential conformation of a 2-(3-benzoylphenyl)propionic acid (ketoprofen)[5] molecule required for the interaction with the receptor site. In an attempt to further confirm this assumption, our work has been extended to the syntheses of similar indan derivatives related to two parent compounds, 2-(3-phenoxyphenyl)propionic acid (IV:

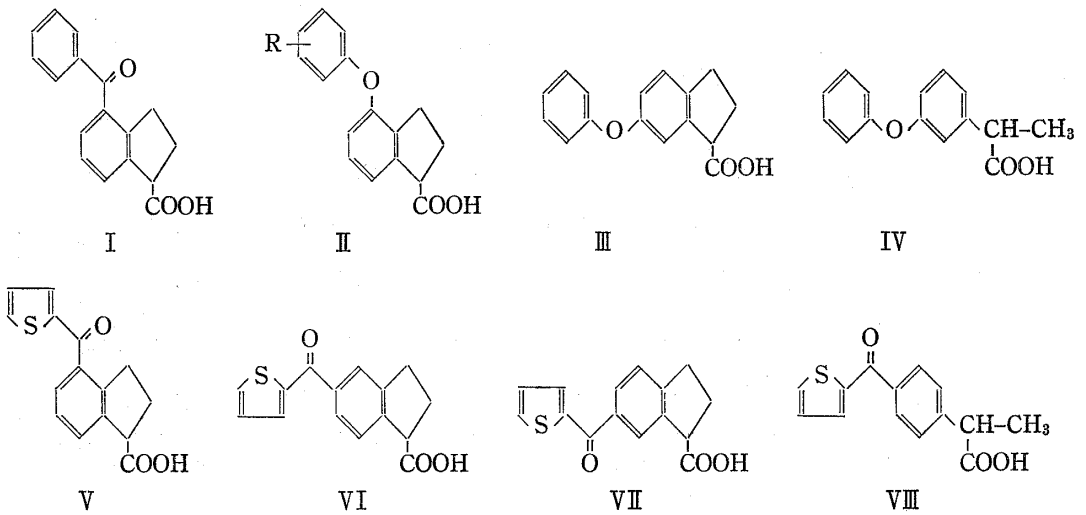


Chart 1

1) Part IV: T. Aono, S. Kishimoto, Y. Araki, and S. Noguchi, *Chem. Pharm. Bull.* (Tokyo), **26**, 1776 (1978).
2) Location: *17–85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan.*
3) T. Aono, Y. Araki, M. Imanishi, and S. Noguchi, *Chem. Pharm. Bull.* (Tokyo), **26**, 1153 (1978).
4) T. Aono, Y. Araki, K. Tanaka, M. Imanishi, and S. Noguchi, *Chem. Pharm. Bull.* (Tokyo), **26**, 1511 (1978).
5) L. Julou, J.C. Guyonnet, R. Ducrot, C. Garret, M.C. Bardone, G. Maignan, and J. Pasquet, *J. Pharmacol.* (Paris), **2**, 259 (1971).

fenoprofen)[6] and 2-[4-(2-thienylcarbonyl)phenyl]propionic acid (VIII: suprofen),[7] both of which have received evaluations as antiinflammatory agents.

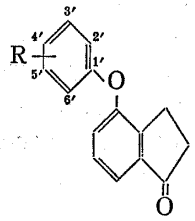
This paper deals with the syntheses of phenoxy-1-indancarboxylic acids (II and III[8]) and (2-thienylcarbonyl)-1-indancarboxylic acids (V, VI and VII[8]), which can be related to conformationally restricted derivatives of fenoprofen (IV) and suprofen (VIII), respectively.

Phenoxy-1-indancarboxylic Acids

The synthesis of 4-phenoxy-1-indancarboxylic acids (II) was achieved by the phenylation of 4-hydroxy-1-indanone (IX), followed by the conversion of the ketone into carboxylic acid by way of the nitrile. Two methods have hitherto been known for the practical conversion of a phenol into diphenyl ether: One is the reaction with a phenylating agent such as diphenyliodonium halide[9] and the other is the Ullmann reaction.

The reaction of IX with diphenyliodonium chloride (Xa) in water in the presence of sodium hydroxide under reflux afforded 4-phenoxy-1-indanone (XIa) in 42% yield. Similarly 6-phenoxy-1-indanone (XVI) was prepared by the reaction of 6-hydroxy-1-indanone (XV) with Xa and 4-(4-chlorophenoxy)-1-indanone (XIb) was obtained by use of 4,4′-dichlorodiphenyliodonium chloride (Xb). This method, however, proved to be inappropriate for the synthesis of a variety of substituted phenoxy derivatives because the preparation of the corresponding substituted diphenyliodonium halides often met with failure. Moreover decomposition of the iodonium salts, which occurred under the reaction condition to a considerable

Table I. 4-Phenoxy-1-indanones (XIa—f)



Compd. No.	Substituent R-	Method[a]	mp (°C)	Rec.[b] sol.	Yield (%)	Formula	Analysis (%) Found (Calcd.) C	H	Cl
XIa	H	A	80.5—82.0	C	42	$C_{15}H_{12}O_2$	80.33 (80.69)	5.39 (5.47)	
		B			41				
XIb	4′-Cl	A	60.0—61.0	C-H	43	$C_{15}H_{11}ClO_2$	69.64 (69.34)	4.29 (4.10)	13.71 (13.73)
XIc	4′-CH_3	B	93.5—94.5	C	28	$C_{16}H_{14}O_2$	80.64 (80.91)	5.92 (5.78)	
XId	3′-CF_3	B	102.5—104.0	C	31	$C_{16}H_{11}F_3O_2$	65.75 (65.77)	3.79 (3.72)	
XIe	3′-Cl	B	116.5—118.0	C-H	45	$C_{15}H_{11}ClO_2$	69.64 (69.57)	4.29 (4.03)	13.71 (13.54)
XIf	3′-CH_3	B	115.5—116.5	C	38	$C_{16}H_{14}O_2$	80.64 (80.55)	5.92 (5.96)	

a) A: phenylation with diphenyliodonium chlorides, B: phenylation by the Ullmann reaction.
b) Recrystallization solvent, C: cyclohexane, H: hexane.

6) R.C. Nickander, R.J. Kraay, and W.S. Marshall, *Fed. Proc.*, **30**, 563 (1971).
7) P.G.H. Van Daele, J.M. Boey, V.K. Sipido, M.F.L. De Bruyn, and P.A.J. Janssen, *Arzneim.-Forsch.*, **25**, 1495 (1975).
8) The syntheses of III and VII have recently been reported by Kirsch, *et al.* independently of our work. See G. Kirsch, C. Rufer, F. Bahjmann, H. Simon, and E. Stiebing, *Ann. Chem.*, **1976**, 1914.
9) J.R. Crowder, E.E. Glover, M.F. Grundon, and H.X. Kaempfen, *J. Chem. Soc.*, **1963**, 4578.

extent, was obviously responsible for the unsatisfactory yields of the products in the above reactions.

On the other hand, the Ullmann reaction of IX with bromobenzene under a variety of conditions revealed that XIa was obtained in 41% yield when the mixture of IX and bromo-

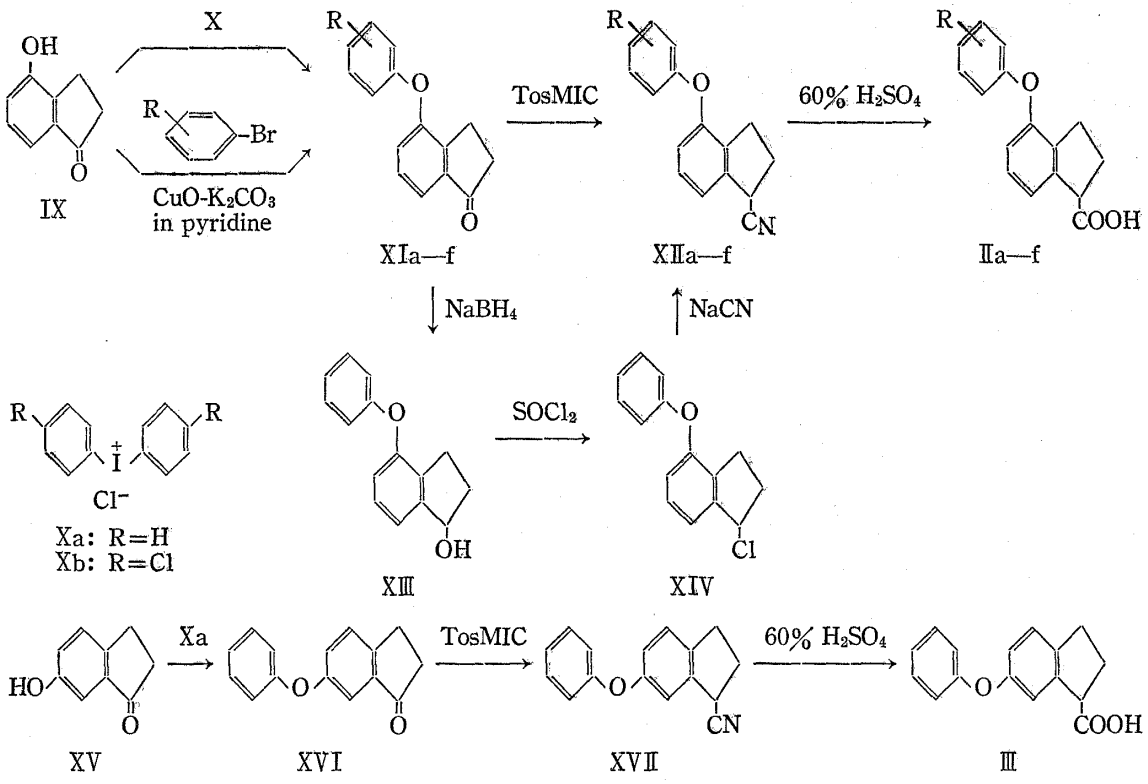
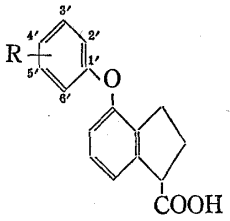


Chart 1

TABLE II. 4-Phenoxy-1-indancarboxylic Acids (II)



Compd. No.	Substituent R-	mp (°C)	Rec.[a] solv.	Yield (%)	Formula	Analysis (%) Found (Calcd.) C	H	Cl
IIa	H	97.0—98.0	C	70	$C_{16}H_{14}O_3$	75.60 (75.57)	5.48 (5.55)	
IIb	4′-Cl	131.0—133.0	C	41	$C_{16}H_{13}ClO_3$	66.56 (66.34)	4.54 (4.61)	12.28 (12.69)
IIc	4′-CH_3	117.5—119.5	C	46	$C_{17}H_{16}O_3$	76.10 (76.00)	6.01 (6.06)	
IId	3′-CF_3	78.0—79.5	H	66	$C_{17}H_{13}F_3O_3$	63.35 (33.52)	4.06 (3.96)	
IIe	3′-Cl	108.5—109.5	C	53	$C_{16}H_{13}ClO_3$	66.56 (66.58)	4.54 (4.40)	12.28 (12.20)
IIf	3′-CH_3	103.5—104.5	C	41	$C_{17}H_{16}O_3$	76.10 (76.12)	6.01 (5.94)	

a) Recrystallization solvent, C: cyclohexane, H: hexane.

benzene was refluxed in pyridine under nitrogen using copper (II) oxide-potassium carbonate as the catalyst.[10] In this way several 4-phenoxy-1-indanones (XIc—f) were obtained. Although the yields were also rather unsatisfactory (28—45%), this method seemed to have an advantage over the phenylation with diphenyliodonium halides in the accessibility of the reagents. Phenoxy-1-indanones prepared by these two methods are summarized in Table I.

The conversion of the phenoxy-1-indanones into the corresponding carboxylic acids was performed by use of tosylmethyl isocyanide (TosMIC). Thus, phenoxy-1-indanones (XI and XVI) were allowed to react with TosMIC in dimethoxyethane in the presence of sodium ethoxide to give phenoxy-1-indancarbonitriles (XII and XVII), which were hydrolyzed with 60% sulfuric acid to afford the aimed phenoxy-1-indancarboxylic acids (II and III). 4-Phenoxy-1-indancarbonitrile (XIIa) was also obtained stepwise from XIa by sodium borohydride reduction affording indanol (XIII), treatment with thionyl chloride to give the chloride (XIV) and the reaction with sodium cyanide. 4-Phenoxy-1-indancarboxylic acids thus prepared are listed in Table II.

(2-Thienylcarbonyl)-1-indancarboxylic Acids

In view of the structure-activity relationships of a series of substituted benzoyl-1-indancarboxylic acids discussed in our preceding papers,[1,3] it became of interest to replace the phenyl group of the benzoyl moiety in those compounds by a thienyl group, since a thienyl group has been considered bioisosteric[11] with a phenyl group. Therefore, we hava undertaken the synthesis of 4-, 5- and 6-(2-thienylcarbony)-1-indancarboxylic acids (V, VI and VII), which can be regarded as conformationally rigid derivatives of suprofen (VIII).

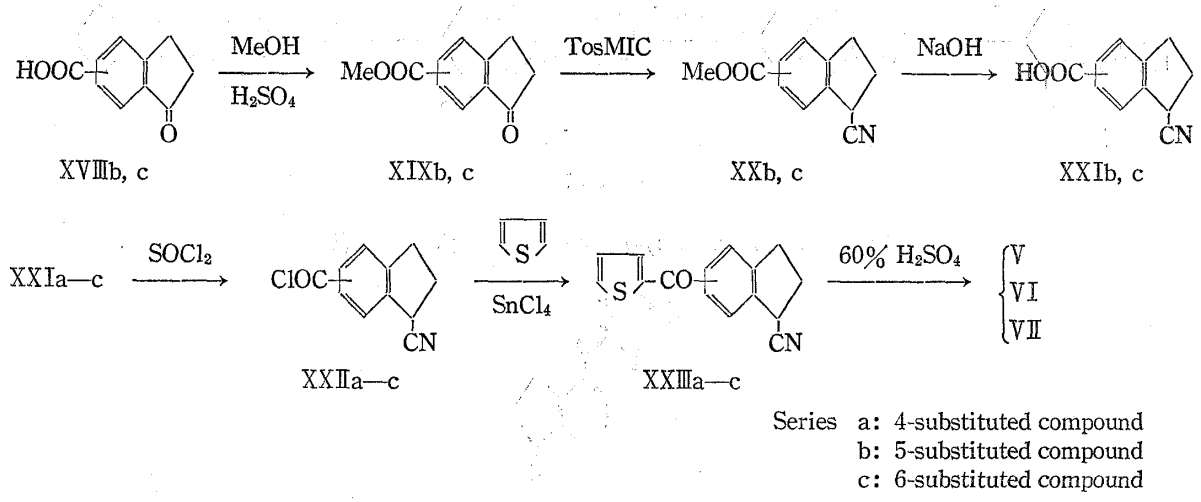


Chart 3

The synthesis of V, VI and VII was carried out by way of the corresponding 1-cyanoindancarboxylic acids (XXIa, b, c), in a similar way to the case of the synthesis of benzoyl-1-indancarboxylic acids.[3] Thus, 1-oxo-5-indancarboxylic acid (XVIIIb)[12] was led to methyl 1-oxo-5-indancarboxylate (XIXb) by the esterification with methanol and sulfuric acid. The reaction of XIXb with TosMIC afforded methyl 1-cyano-5-indancarboxylate (XXb), which was hydrolyzed to XXIb. Similarly XXIc was prepared from 1-oxo-6-indancarboxylic acid.[13] The preparation of XXIa has been described in a previous paper.[3] 1-Cyanoindancarboxylic acids (XXIa, b, c) were converted to the corresponding acid chlorides (XXIIa, b, c) with

10) M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. Pharm. Bull.* (Tokyo), **13**, 1341 (1965).
11) E.J. Ariëns, "Drug Design," Vol. 1, ed by E.J. Ariëns, Academic Press, New York and London, 1971, p. 241.
12) N.L. Allinger and E.S. Jones, *J. Org. Chem.*, **27**, 70 (1962).
13) G. Baddeley and R. Willamson, *J. Chem. Soc.*, **1956**, 4647.

thionyl chloride, which were then allowed to react with thiophene in the presence of stannic chloride to give (2-thienylcarbonyl)-1-indancarbonitriles (XXIIIa, b, c). When aluminium chloride was used as the catalyst in place of stannic chloride, the decomposition of thiophene occurred to a considerable extent. The nitriles (XXIIIa, b, c) were hydrolyzed to the aimed compounds (V, VI and VII) by treatment with 60% sulfuric acid.

Compounds prepared in this study were tested for antiinflammatory activity using the carrageenin-induced foot edema method in rats.[14] In both the phenoxy and thienylcarbonyl series, the 4-substituted derivatives (II and V) showed more potent activities than the corresponding 5- and 6-substituted ones.[15] Especially the activity of V was the best among the compounds in the present study. These results are consistent with that for a series of benzoyl-1-indancarboxylic acids[3] and afford further support for the hypothesis that 4-substituted 1-indancarboxylic acid would substantially satisfy the structural requirements of the receptor site for antiinflammatory phenylacetic acids.[3]

Experimental[16]

4-Phenoxy-1-indanones (XI) (Table I)——a) Phenylation with Diphenyliodonium Chlorides (X): To a stirred mixture of 4-hydroxy-1-indanone (IX)[17] (7.4 g), NaOH (2.0 g) and water (150 ml) was added diphenyliodonium chloride (Xa)[18] (16.8 g) and the resulting mixture was stirred under reflux for 3 hr. After cooling, the mixture was acidified with conc. HCl and extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ as the eluant to give 4-phenoxy-1-indanone (XIa). IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in $CDCl_3$) δ: 6.9—7.5 (8H, m, aromatic protons), 2.9—3.1 (2H, m, C_3–H), 2.5—2.7 (2H, m, C_2–H). By this method 4-(4-chlorophenoxy)-1-indanone (XIb) was obtained from IX and 4,4′-dichlorodiphenyliodonium chloride (Xb).[19]

b) Phenylation by the Ullmann Reaction: To a stirred solution of IX (15 g) in dry pyridine (100 ml) was added bromobenzene (31 g) and K_2CO_3 (14 g), and the mixture was heated under nitrogen. When the reflux started, CuO (10 g) was added to the mixture and the resulting mixture was refluxed for 8.5 hr with stirring under nitrogen. After cooling, the mixture was diluted with a mixture of MeOH (50 ml) and benzene (100 ml), and the insoluble material was filtered off. The filtrate was diluted with water and extracted with benzene. The extract was washed with dil. HCl and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ as the eluant to give 4-phenoxy-1-indanone (XIa). The IR and NMR spectra were identical with those of the compound obtained in a). By this method, 4-(substituted phenoxy)-1-indanones (XIc—f) were prepared from IX and the corresponding bromobenzene derivatives.

4-Phenoxy-1-indanol (XIII)——To a stirred ice-cooled solution of XIa (9 g) in MeOH (180 ml) was added $NaBH_4$ (1.1 g) by portions. After stirring for 2 hr at room temperature, MeOH was removed under reduced pressure. The residue was dissolved in AcOEt. The AcOEt layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give XIII as an oil 9.2 g (100%). *Anal.* Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.44; H, 6.13. IR ν_{max}^{neat} cm^{-1}: 3350 (OH). NMR (in $CDCl_3$) δ: 6.8—7.4 (8H, m, aromatic protons), 5.20 (1H, t, J=6 Hz, C_1–H), 2.6—3.1 (2H, m, C_3–H), 1.8—2.5 (2H, m, C_2–H).

1-Chloro-4-phenoxyindan (XIV)——To a stirred ice-cooled solution of XIII (9.1 g) in CH_2Cl_2 (170 ml) was added dropwise a solution of $SOCl_2$ (6.3 g) in CH_2Cl_2 (5 ml) over a 5-minute period and the mixture was stirred for 1 hr at room temperature. The solvent and the excess of $SOCl_2$ were evaporated under reduced pressure to give XIV as an oil (9.8 g), which was used for the subsequent reaction without further purification. NMR (in $CDCl_3$) δ: 6.8—7.4 (8H, m, aromatic protons), 5.43 (1H, t, J=6 Hz, C_1–H), 2.8—3.2 (2H, m, C_3–H), 2.2—2.7 (2H, m, C_2–H).

14) C.A. Winter, E.A. Risley, and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
15) K. Kawai, unpublished.
16) Melting points are not corrected. The IR spectra were measured with a Hitachi-215 spectrometer. NMR spectra were recorded with a Varian HA-100 or T-60 spectrometer using Me_4Si as an internal standard.
17) J.A. Dominguez, J. Sandler, and L.M.I. Zavala, *Rev. Soc. Quim. Mex.*, **11**, 39 (1967) [*C.A.*, **67**, 53901j (1967)].
18) F.M. Beringer, E.J. Geering, I. Kuntz, and H. Mausner, *J. Phys. Chem.*, **60**, 141 (1956).
19) F.M. Beringer, R.A. Falk, M. Karniol, I. Lillien, G. Masullo, M. Mausaner, and E. Sommer, *J. Am. Chem. Soc.*, **81**, 342 (1959).

6-Phenoxy-1-indanone (XVI)——a) To a stirred mixture of 6-hydroxy-1-indanone (XV)[20] (7.4 g), NaOH (2.0 g) and water (150 ml) was added Xa (16.8 g) and the resulting mixture was stirred under reflux for 3 hr. After cooling, the mixture was acidified with conc. HCl and extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ as the eluant and recrystallized from cyclohexane to give 4.4 g (39%) of XVI, mp 53.0—54.5°. *Anal.* Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39. Found: C, 80.14; H, 5.25. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in $CDCl_3$) δ: 6.9—7.4 (8H, m, aromatic protons), 2.9—3.1 (2H, m, C_3–H), 2.6—2.8 (2H, m, C_2–H).

b) To a stirred solution of XV (7.5 g) in dry pyridine (50 ml) were added bromobenzene (15.5 g) and K_2CO_3 (7 g) and the mixture was heated under nitrogen. When the reflux started, CuO (5 g) was added to the mixture and the resulting mixture was refluxed for 7 hr with stirring under nitrogen. After cooling the mixture was diluted with MeOH (30 ml) and benzene (50 ml) and the insoluble material was filtered off. The filtrate was diluted with water and extracted with benzene. The extract was washed with dil. HCl and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel using $CHCl_3$ as the eluant to give 3.0 g (26%) of XVI. The IR and NMR spectra of this compound were identical with those of the compound obtained in a).

4-Phenoxy-1-indancarbonitriles (XII)——a) To a stirred, ice-cooled mixture of XIa (3.4 g) and tosylmethyl isocyanide (TosMIC) (4.4 g) in dimethoxyethane (DME) (50 ml) was added dropwise a solution of NaOEt (1.5 g) in EtOH (10 ml) and DME (35 ml) over a 30-minute period. After the addition was completed, the mixture was stirred for 4 hr at room temperature. After cooling, the mixture was diluted with dil. HCl and 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 $CHCl_3$ as the eluant to give 1.6 g (46%) of 4-phenoxy-1-indancarbonitrile (XIIa) as an oil. *Anal.* Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.75. Found: C, 81.50; H, 5.46; N, 5.79. IR ν_{max}^{neat} cm^{-1}: 2230 (C≡N). NMR (in $CDCl_3$) δ: 6.9—7.5 (8H, m, aromatic protons), 4.10 (1H, t, J=8 Hz, C_1–H), 2.8—3.2 (2H, m, C_3–H), 2.2—2.6 (2H, m, C_2–H). By the similar procedures compounds XIIb, XIId and XIIe were obtained as oils in 40, 34 and 47% yields, respectively. These oily products were used for the subsequent hydrolysis without further purification. Compounds XIIc and XIIf were obtained as crystals. 4-(4-Methylphenoxy)-1-indancarbonitrile (XIIc): mp 69—70° (from hexane-cyclohexane, 47%). *Anal.* Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.22; H, 5.91; N, 5.74. 4-(3-Methylphenoxy)-1-indancarbonitrile (XIIf): mp 56—57° (from hexane, 42%). *Anal.* Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.87; H, 5.84; N, 5.61.

b) To a stirred suspension of NaCN (2.7 g) in dimethylformamide (DMF) (375 ml) was added a solution of XIV (9.8 g) in DMF (75 ml) under nitrogen. After stirring for 6 hr at 50°, the mixture was poured into water and 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 to give 5.3 g (58%) of XIIa. The IR and NMR spectra of this compound were identical with those of the compound obtained in a).

6-Phenoxy-1-indancarbonitrile (XVII)——To a stirred, ice-cooled mixture of XVI (6.0 g) and TosMIC (7.8 g) in DME (85 ml) was added dropwise a solution of NaOEt (2.7 g) in EtOH (17 ml) and DME (60 ml) over a 30-minute period. After the addition was completed, the mixture was stirred for 4 hr at room temperature. After cooling, the mixture was diluted with dil. HCl and 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 $CHCl_3$ as the eluant to give 3.0 g (47%) of XVII as an oil. This compound was used for the subsequent hydrolysis without further purification. IR ν_{max}^{neat} cm^{-1}: 2230 (C≡N). NMR (in $CDCl_3$) δ: 6.8—7.5 (8H, m, aromatic protons), 3.98 (1H, t, J=8 Hz, C_1–H), 2.8—3.1 (2H, m, C_3–H), 2.2—2.7 (2H, m, C_2–H).

4-Phenoxy-1-indancarboxylic Acids (II) (Table II)——General Procedure: A suspension of XII (2.0 g) in 60 wt % H_2SO_4 (40 ml) was heated under reflux for 2.5 hr in an atmosphere of nitrogen. After cooling, the mixture was diluted with water (50 ml) 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 II.

6-Phenoxy-1-indancarboxylic Acid (III)——A suspension of XVII (2.9 g) in 60 wt % H_2SO_4 (50 ml) was heated under reflux for 2.5 hr in an atmosphere of nitrogen. After cooling, the mixture was diluted with 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 from cyclohexane to give 1.4 g (46%) of III, mp 75.5—77.5°. *Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.35; H, 5.25. IR ν_{max}^{Nujol} cm^{-1}: 1695 (C=O). NMR (in $CDCl_3$) δ: 6.7—7.3 (8H, m, aromatic protons), 3.98 (1H, t, J=8 Hz, C_1–H), 2.8—3.2 (2H, m, C_3–H), 2.3—2.7 (2H, m, C_2–H).

20) J. Sam, U.S. Patent 2820817 [*C.A.*, **52**, 10197a (1958)].

Methyl 1-Oxoindancarboxylate (XIX)——To 250 ml of MeOH were added H_2SO_4 (10 ml) and 1-oxo-5-indancarboxylic acid (XVIIIb) (6.7 g). The mixture was heated under reflux for 8 hr and, after cooling, MeOH was removed by evaporation under reduced pressure. To the residue was added water and the mixture was extracted with AcOEt. The extract was washed with aqueous $NaHCO_3$ and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from MeOH to give 5.0 g (70%) of methyl 1-oxo-5-indancarboxylate (XIXb), mp 115.0—117.0°. *Anal.* Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.40; H, 5.38. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1700 (C=O). NMR (in $CDCl_3$) δ: 8.18 (1H, s, C_4–H), 8.10 (1H, d, J=8 Hz, C_6–H), 7.81 (1H, d, J=8 Hz, C_7–H), 3.98 (3H, s, CH_3), 3.1—3.4 (2H, m, C_3–H), 2.6—2.9 (2H, m, C_2–H). By the similar procedures methyl 1-oxo-6-indancarboxylate (XIXc) was obtained from 1-oxo-6-indancarboxylic acid (XVIIIc), mp 118.0—120.0° (from cyclohexane, 72%). *Anal.* Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.55; H, 5.46. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O), 1705 (C=O). NMR (in $CDCl_3$) δ: 8.52 (1H, d, J=8 Hz, C_5–H), 8.35 (1H, s, C_7–H), 8.22 (1H, d, J=8 Hz, C_4–H), 3.94 (3H, s, CH_3), 3.1—3.4 (2H, m, C_3–H), 2.6—2.9 (2H, m, C_2–H).

Methyl 1-Cyanoindancarboxylate (XX)——To a stirred, ice-cooled mixture of XIXb (0.76 g) and TosMIC (1.17 g) in DME (20 ml) was added dropwise a 28 wt % solution of NaOMe in MeOH (1.15 g) diluted with DME (6 ml) over a 30-minute period. After the addition was completed, the mixture was stirred for 2 hr under ice-cooling and then for 5 hr at room temperature. After cooling, the mixture was diluted 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 chromatographed on silica gel using a mixture of benzene and AcOEt (100: 3) as the eluant and recrystallized from isopropyl ether to give 0.3 g (36%) of methyl 1-cyano-5-indancarboxylate (XXb), mp 75.0—76.0°. *Anal.* Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.98. Found: C, 71.73; H, 5.56; N, 6.90. IR ν_{max}^{Nujol} cm^{-1}: 2235 (C≡N), 1725 (C=O). NMR (in $CDCl_3$) δ: 8.03 (1H, d, J=8 Hz, C_6–H), 7.96 (1H, s, C_4–H), 7.50 (1H, d, J=8 Hz, C_7–H), 4.14 (1H, t, J=8 Hz, C_1–H), 3.90 (3H, s, CH_3), 2.9—3.3 (2H, m, C_3–H), 2.3—2.8 (2H, m, C_2–H). By the similar procedures methyl 1-cyano-6-indancarboxylate (XXc) was obtained from XIXc as an oil in 24% yield. *Anal.* Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.62; H, 5.63; N, 6.99. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1720 (C=O). NMR (in $CDCl_3$) δ: 8.10 (1H, s, C_7–H), 8.00 (1H, d, J=8 Hz, C_5–H), 7.34 (1H, d, J=8 Hz, C_4–H), 4.15 (1H, t, J=8 Hz, C_1–H), 3.94 (3H, s, CH_3), 2.9—3.3 (2H, m, C_3–H), 2.3—2.7 (2H, m, C_2–H).

1-Cyanoindancarboxylic Acids (XXI)——To a mixture of NaOH (87 mg), MeOH (5 ml) and water (5 ml) was added XXb (0.3 g) and the mixture was stirred for 5 hr at room temperature. After MeOH was removed under reduced pressure, the mixture was diluted with water. The insoluble material was filtered off and the filtrate was acidified with dil. HCl. After standing overnight, the resulting precipitate was collected by filtration, dried over P_2O_5 and recrystallized from acetone to give 0.22 g (83%) of 1-cyano-5-indancarboxylic acid (XXIb), mp 203.5—204.5°. *Anal.* Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.58; H, 4.86; N, 7.73. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1690 (C=O). NMR (in d_6-DMSO) δ: 7.90 (1H, d, J=8 Hz, C_6–H), 7.88 (1H, s, C_4–H), 7.52 (1H, d, J=8 Hz, C_7–H), 4.52 (1H, t, J=8 Hz, C_1–H), 2.9—3.2 (2H, m, C_3–H), 2.1—2.8 (2H, m, C_2–H). By the similar procedures 1-cyano-6-indancarboxylic acid (XXIc) was obtained from XXc, mp 188.0—191.0° (from benzene, 80%). *Anal.* Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.72; H, 4.66; N, 7.34. IR ν_{max}^{Nujol} cm^{-1}: 2240 (C≡N), 1680 (C=O). NMR (in d_6-DMSO) δ: 7.90 (1H, s, C_7–H), 7.83 (1H, d, J=8 Hz, C_6–H), 7.37 (1H, d, J=8 Hz, C_4–H), 4.47 (1H, t, J=8 Hz, C_1–H), 2.9—3.4 (2H, m, C_3–H), 2.2—2.7 (2H, m, C_2–H).

(2-Thienylcarbonyl)-1-indancarbonitriles (XXIII)——A suspension of 1-cyano-4-indancarboxylic acid (XXIa)[3] (2.5 g) in $CHCl_3$ (40 ml) and $SOCl_2$ (25 g) was stirred overnight at room temperature. Evaporation of $CHCl_3$ and excess $SOCl_2$ under reduced pressure gave 1-cyano-4-indancarbonyl chloride (XXIIa) as a yellow oil, which was taken up in CH_2Cl_2 (10 ml) and added to a stirred mixture of thiophene (1.2 g), $SnCl_4$ (3.5 g) and CH_2Cl_2 (15 ml) at −15°. After stirring for 1.5 hr at −15° and further 1 hr at room temperature, the mixture was poured onto ice-dil. HCl and extracted with CH_2Cl_2. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica gel using a mixture of benzene and AcOEt (100: 1) as the eluant gave 2.6 g (77%) of 4-(2-thienylcarbonyl)-1-indancarbonitrile (XXIIIa) as a pale yellow oil. This product was used for the subsequent hydrolysis without further purification. IR ν_{max}^{neat} cm^{-1}: 2230 (C≡N), 1630 (C=O). NMR (in $CDCl_3$) δ: 7.1—8.0 (6H, m, aromatic protons), 4.15 (1H, t, J=7 Hz, C_1–H), 3.1—3.4 (2H, m, C_3–H), 2.2—2.7 (2H, m, C_2–H). By the similar procedures the following two compounds were obtained from the corresponding acids (XXI). 5-(2-Thienylcarbonyl)-1-indancarbonitrile (XXIIIb): pale yellow oil, 22%. IR ν_{max}^{neat} cm^{-1}: 2240 (C≡N), 1630 (C=O). NMR (in $CDCl_3$) δ: 7.1—8.0 (6H, m, aromatic protons), 4.27 (1H, t, J=8 Hz, C_1–H), 2.9—3.3 (2H, m, C_3–H), 2.2—2.8 (2H, m, C_2–H). 6-(2-Thienylcarbonyl)-1-indancarbonitrile (XXIIIc): pale yellow oil, 48%. IR ν_{max}^{neat} cm^{-1}: 2240 (C≡N), 1630 (C=O). NMR (in $CDCl_3$) δ: 7.1—8.0 (6H, m, aromatic protons), 4.23 (1H, t, J=8 Hz, C_1–H), 3.0—3.3 (2H, m, C_3–H), 2.3—2.8 (2H, m, C_2–H).

(2-Thienylcarbonyl)-1-indancarboxylic Acids (V, VI and VII)——A suspension of XXIIIa (2.5 g) in 60 wt % H_2SO_4 (20 ml) was heated under reflux in an atmosphere of argon. After cooling, the mixture was diluted with water and extracted with benzene. The benzene layer was washed with water and then extracted with 5% aqueous K_2CO_3. The extract was acidified with 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 recrystallized from a mixture of benzene and cyclohexane (1:2) to give 2.0 g (71%) of 4-(2-thienylcarbonyl)-1-indancarboxylic acid (V), mp 121.5—123.5°. *Anal.* Calcd. for $C_{15}H_{12}O_3S$: C, 66.15; H, 4.44. Found: C, 66.36; H, 4.40. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 1630 (C=O). NMR (in $CDCl_3$) δ: 7.0—7.8 (6H, m, aromatic protons), 4.12 (1H, t, $J=8$ Hz, C_1–H), 3.1—3.4 (2H,m, C_3–H), 2.2—2.6 (2H, m, C_2–H). By the similar procedures the following two compounds were obtained from the corresponding carbonitriles (XXIII). 5-(2-Thienylcarbonyl)-1-indancarboxylic acid (VI): mp 127.0—129.0° [from a mixture of benzene and cyclohexane (1:2), 56%]. *Anal.* Calcd. for $C_{15}H_{12}O_3S$: C, 66.15; H, 4.44. Found: C, 66.35; H, 4.57. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 1630 (C=O). NMR (in $CDCl_3$) δ: 7.1—7.8 (6H, m, aromatic protons), 4.15 (1H, t, $J=8$ Hz, C_1–H), 2.8—3.3 (2H, m, C_3–H), 2.3—2.6 (2H, m, C_2–H). 6-(2-Thienylcarbonyl)-1-indancarboxylic acid (VII): mp 132.0—134.0° [from a mixture of benzene and cyclohexane (1:2), 63%] (lit.[8] 130°). *Anal.* Calcd. for $C_{15}H_{12}O_3S$: C, 66.15; H, 4.44. Found: C, 66.03; H, 4.49. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 1630 (C=O). NMR (in $CDCl_3$) δ: 7.0—7.9 (6H, m, aromatic protons), 4.10 (1H, t, $J=8$ Hz, C_1–H), 2.9—3.4 (2H, m, C_3–H), 2.2—2.7 (2H, m, C_2–H).

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