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1-Indancarboxylic Acids. III.[1] Chemical Modifications of Antiinflammatory 4-Aroyl-1-indancarboxylic Acids

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For elucidating the receptor site of antiinflammatory arylacetic acids, some modifications were made on 4-aroyl-1-indancarboxylic acids (Ia—d) which have potent antiinflammatory activities. Modifications were introduced on the characteristic parts of I and 1-methylated derivatives (VIII), tetralin analogs (XVIII) and benzyl analogs (XXX) of I were prepared. However, these compounds showed weaker activities than the parent compound I. The result suggests that 1-indancarboxylic acid is the pharmacologically effective derivative of arylacetic acid.

Keywords——antiinflammatory agents; 1-indancarboxylic acid derivatives; 1,2,3,4-tetrahydro-1-naphthoic acid derivatives; receptor site of arylacetic acids; intramolecular cyclization

In the course of our synthetic study of potential antiinflammatory agents, we have synthesized a number of 1-indancarboxylic acid derivatives,[1,3] among which 4-aroyl-1-indancarboxylic acids (I) exhibited particularly potent antiinflammatory activities while the activities of isomeric 6-aroyl-1-indancarboxylic acids (II) were weak.[1] The relationships between the activities and the semi-rigid structure of I and II have provided us with a useful information concerning the spatial requirement of the receptor for antiinflammatory agents. The results seemed to suggest that the locations of functional groups in I might also represent the pharmacologically active conformation of ketoprofen.[4]

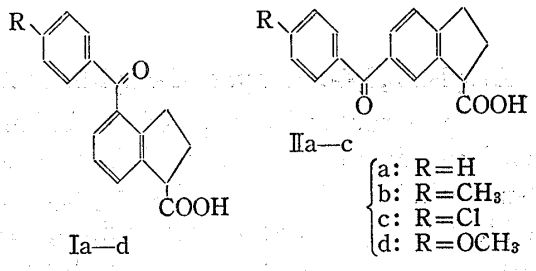


Chart 1

In order to elucidate the structure required for antiinflammatory activity in more detail, we have undertaken the syntheses of some analogs of I in which the spatial structure of I is partially perturbed. The present paper describes the syntheses of 4-aroyl-1-methyl-1-indancarboxylic acids (VIII), 5- and 7-aroyl-1,2,3,4-tetrahydro-1-naphthoic acids (XVIII and XXI), 4-arylmethyl-1-indancarboxylic acids (XXX) and the related compounds.

4-Aroyl-1-methyl-1-indancarboxylic Acids (VIII)

Although the introduction of a methyl group into the 1-position of I will little affect the conformation of the indan ring and the situation of the carboxyl and aroyl groups, this methyl group brings about a considerable steric effect on one side of the indan plane opposite to the carboxyl group. If a flat surface is essential for the interaction with the receptor site

1) Part II: T. Aono, Y. Araki, M. Imanishi, and S. Noguchi, *Chem. Pharm. Bull.* (Tokyo), **26**, 1153 (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) L. Julou, J.C. Guyonnet, R. Ducrot, C. Garret, M.C. Bardone, G. Maignan, and J. Pasquet, *J. Pharmacol.* (Paris), **2**, 259 (1971).

of the antiinflammatory agents as has been pointed out by Juby, *et al.*,[5] the introduction of the methyl group would reduce the antiinflammatory activity of I.

Based on these speculations, the synthesis of 4-aroyl-1-methyl-1-indancarboxylic acids (VIII) was undertaken employing the procedures shown in Chart 2. Thus, methyl 1-cyano-4-indancarboxylate (III)[1] was methylated with methyl iodide in the presence of sodium hydride in dimethyl sulfoxide (DMSO) to give methyl 1-cyano-1-methyl-4-indancarboxylate (IV). Hydrolysis of the ester (IV) with aqueous sodium hydroxide gave the carboxylic acid (V), which was treated with thionyl chloride to afford the acid chloride (VI). VI was allowed to react with benzene or its derivatives in the presence of aluminum chloride to give 4-aroyl-1-methyl-1-indancarbonitriles (VII). The Friedel-Crafts reaction of VI to VII proceeded smoothly in relatively better yields than in similar reactions in the synthesis of I.[1] In the latter case, side reactions due to the presence of an active hydrogen at C-1 was probably responsible for the low yield. Compounds VII were led to the corresponding VIII by the hydrolysis with 60% sulfuric acid.

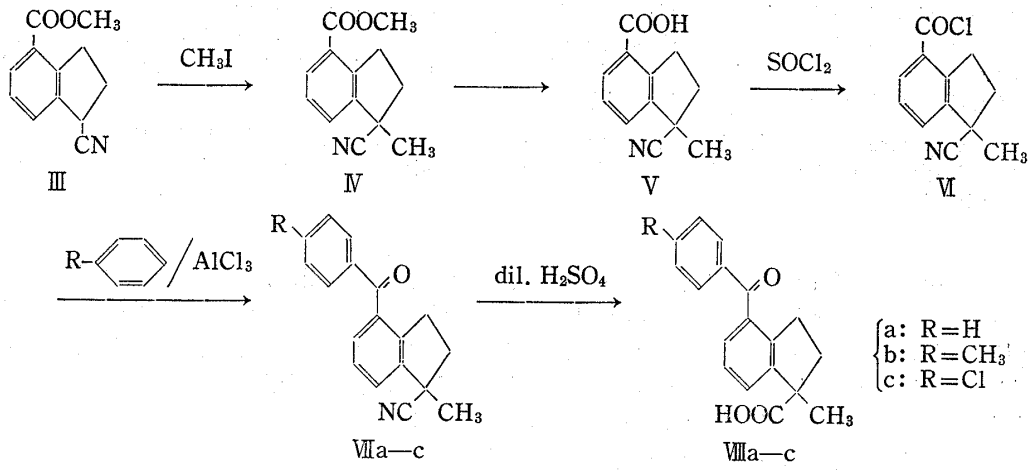


Chart 2

5-Aroyl-1,2,3,4-tetrahydro-1-naphthoic Acids (XVIII)

The structural change of the indan ring of I into a tetralin ring results in considerable conformational change around the carboxyl group. The carboxyl group of 1,2,3,4-tetrahydro-1-naphthoic acid is not held so rigidly out-of-plane of the benzene ring as in 1-indancarboxylic acid, existing in two conformations, pseudoaxial and pseudoequatorial. Since the pseudoequatorial conformation is generally more stable than the pseudoaxial,[6] the carboxyl group of XVIII is considered to occupy the pseudoequatorial position and to stay almost coplanar with the benzene ring. In addition, all the carbon atoms of the fused alicyclic ring are not coplanar with the benzene ring, although the situation of the aroyl group at the 5-position may not be so different from that of indan derivatives (I).

It was also of interest, therefore, to synthesize XVIII and investigate its activity. 4-(2-Carboxyphenyl)butyric acid (IX) obtained according to the Johnson's method[7] was melted together with a mixture of aluminum chloride and sodium chloride to give 5-oxo-5,6,7,8-tetrahydro-1-naphthoic acid (X) in 74% yield. Esterification of X to ethyl ester (XI) by treatment with ethanol-sulfuric acid followed by reduction with sodium borohydride afforded ethyl 5-hydroxy-5,6,7,8-tetrahydro-1-naphthoate (XII). After conversion of the alcohol (XII) to the chloride (XIII) with thionyl chloride, XIII was allowed to react with sodium cyanide

5) P.F. Juby, W.R. Goodwin, T.W. Hudyma, and R.A. Partyka, *J. Med. Chem.*, **15**, 1297 (1972).
6) E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., New York, 1962, p. 239.
7) *a*) W.S. Johnson and W.E. Shelberg, *J. Am. Chem. Soc.*, **67**, 1745 (1945); *b*) *Idem, ibid.*, **67**, 1754 (1945).

in DMSO at 50° according to the method reported in the previous paper.[1] In this case, however, the formation of a considerable amount of XI was detected by gas chromatography, in addition to the desired cyano ester (XIV). Assuming that the chloride (XIII) would be susceptible to oxidation by oxygen in DMSO, the reaction was carried out in a nitrogen atmosphere. Under this condition, no keto ester (XI) was formed and XIV was obtained in 69% yield. Therefore, the combination of DMSO and oxygen may be an effective oxidant toward chlorotetralin (XIII) as has been seen in the oxidation of epoxide in DMSO in the presence of air.[8] Compound XIV was hydrolyzed with aqueous sodium hydroxide to 5-cyano-5,6,7,8-tetrahydro-1-naphthoic acid (XV), which was converted to acid chloride (XVI) with thionyl chloride in chloroform. The Friedel-Crafts reaction of XVI with benzene or its derivatives gave 5-aroyl-1,2,3,4-tetrahydro-1-naphthonitriles (XVII), hydrolysis of which with 60% sulfuric acid afforded the corresponding 5-aroyl-1,2,3,4-tetrahydro-1-naphthoic acids(XVIII).

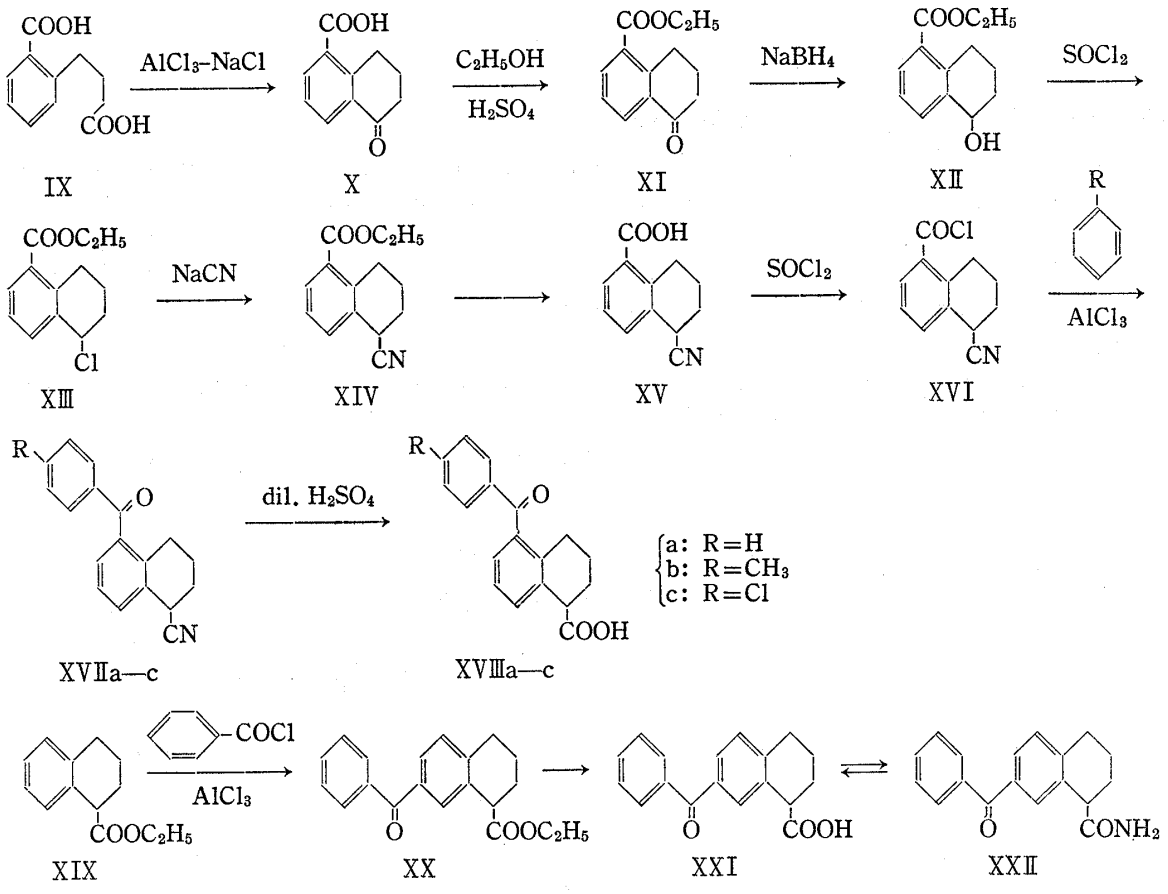


Chart 3

Subsequently, isomeric 7-benzoyl-1,2,3,4-tetrahydro-1-naphthoic acid (XXI), which is also a *meta*-benzoylphenylacetic acid derivative, was synthesized for the comparison of the antiinflammatory activity with that of XVIII. Thus, ethyl 1,2,3,4-tetrahydro-1-naphthoate (XIX) was subjected to the Friedel-Crafts reaction with benzoyl chloride and the product, which consisted mainly of ethyl 7-benzoyl-1,2,3,4-tetrahydro-1-naphthoate (XX) contaminated with a minor amount of the 5-benzoyl isomer, was hydrolyzed with aqueous sodium hydroxide to the corresponding naphthoic acids. For the purpose of purification, the crude acids were converted to crystalline amides *via* the acid chlorides. Acid hydrolysis of pure 7-benzoyl-1,2,3,4-tetrahydro-1-naphthamide (XXII), which was obtained by recrystallization of the mixture of amides from benzene, and recrystallization of the product from a mixture of benzene

8) T. Tsuji, *Tetrahedron Lett.*, **1966**, 2413.

and cyclohexane (1: 2) gave XXI as prisms, mp 85.5—86.5°.

In the ultraviolet spectra of I, II, XVIII and XXI, which are listed in Table I, no significant difference was observed in their maxium absorption intensities and their wave length, suggesting that the dihedral angles between the aroyl groups and the indan or tetralin rings are not so different from each other.

Table I. UV Spectra of Ia—c, IIa—c, XVIIIa—c and XXI

Compd. No.	λ_{max}^{EtOH} nm (ε)	Compd. No.	λ_{max}^{EtOH} nm (ε)
Ia	253 (16000) a)	IIc	261 (18400) a)
Ib	260 (18100) a)	XVIIIa	250 (15000)
Ic	260 (19500) a)	XVIIIb	260 (17700)
IIa	260 (14600) a)	XVIIIc	258 (19500)
IIb	263 (18800) a)	XXI	261 (15500)

a) Data from the reference 1).

4-Arylmethyl-1-indancarboxylic Acids (XXX)

As has been discussed in the previous paper,[1] the benzophenone moiety of I is considered to be fixed to a specific conformation because of the conjugation of the carbonyl group with the benzene rings. That conformation seems to be one of the requisites for the potent anti-inflammatory activity of I. If the benzoyl group in I was replaced by a benzyl group, the conjugated system would be broken and the phenyl group might take a different conformation from that of I.

The synthesis of 4-arylmethyl-1-indancarboxylic acids (XXX) was carried out as shown in Chart 4. 3-[2-(Arylmethyl)phenyl]propionic acids (XXVI), prepared from *o*-(arylmethyl)-benzyl bromide (XXIII)[9] by the malonic ester synthesis *via* compounds XXIV and XXV,

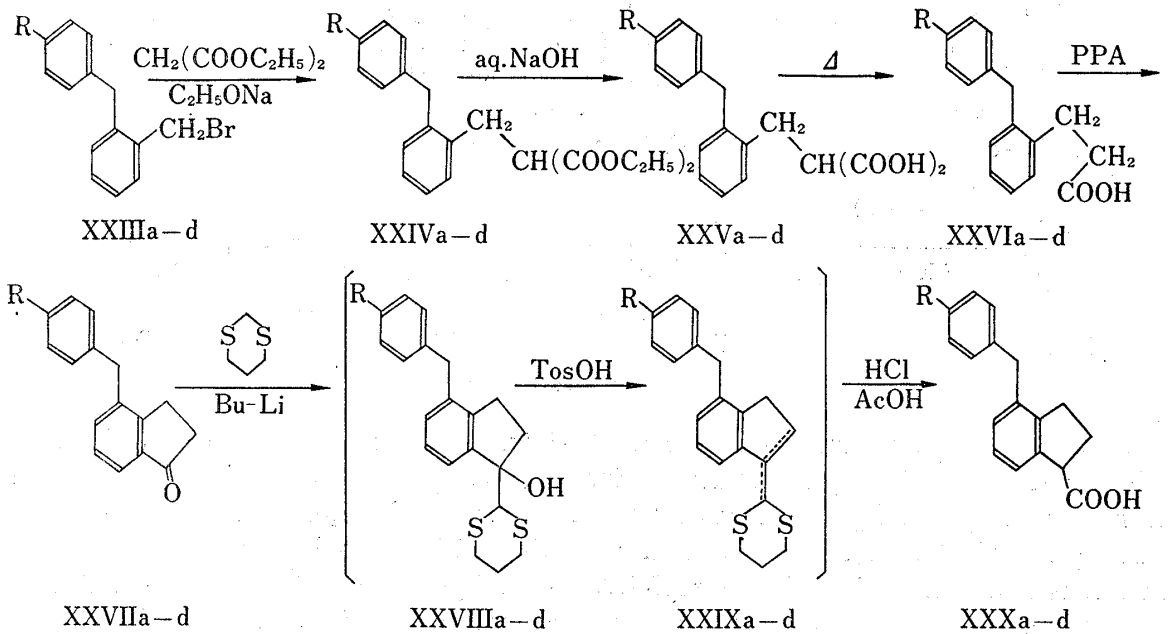
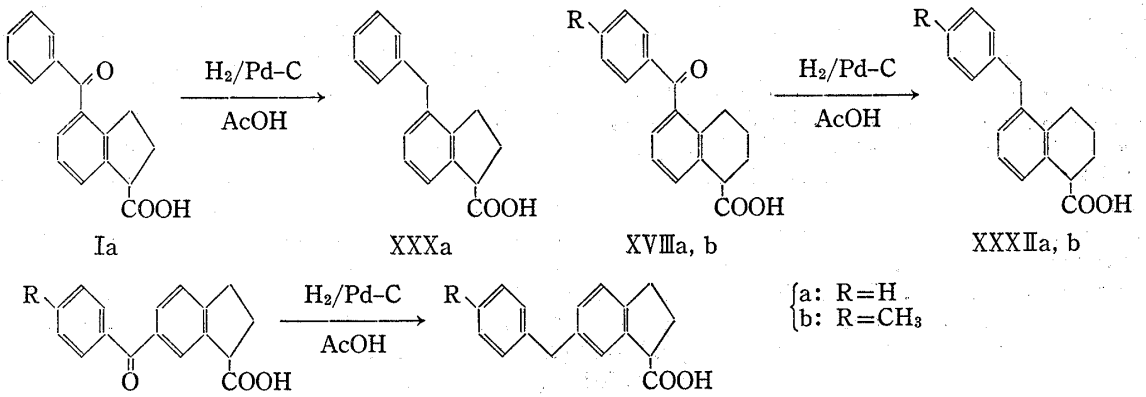


Chart 4

9) *a*) J. Fouché, J.C. Blondel, R. Horclois, C. James, A. Léger, and G. Poiget, *Bull. Soc. Chim. Fr.*, **1972**, 3113; *b*) F.J. Villani, U.S. Patent 3409640 (1968) [*C.A.*, **70**, 68009*k* (1969)].

were cyclized with polyphosphoric acid at around 150° to give 4-(arylmethyl)-1-indanones (XXVII) in 41—77% yields. 4-(4-Chlorobenzyl)-1-indanone (XXVIIc) was also obtained *via* acid chloride of XXVIc in 71% yield. Indanones (XXVII) thus obtained were converted to the corresponding acids (XXX) with 1,3-dithiane according to the procedure reported by Juby, *et al.*[5]

On the other hand, as shown in Chart 5, it was found that XXXa and isomeric 6-arylmethyl-1-indancarboxylic acids (XXXIa and XXXIb) were also obtained directly from the corresponding aroyl derivatives (Ia, IIa and IIb, respectively) by hydrogenation over palladium-carbon in acetic acid. Similarly 5-arylmethyl-1,2,3,4-tetrahydro-1-naphthoic acids (XXXII) were prepared from XVIII.



Ia XXXa XVIIIa, b XXXIIa, b

IIa, b XXXIa, b

Chart 5

Biological Results and Discussions

The above studies have achieved the chemical modifications of 4-aroyl-1-indancarboxylic acids (I) especially with respect to its three characteristic parts, namely the plane of indan ring, the carboxyl group fixed out-of-plane and the aroyl group fixed by the conjugated system.

The antiinflammatory activity of the compounds prepared in this study was tested using the carrageein induced foot edema method in rats.[10] All the compounds, however, proved to be less active than the parent compounds (I), although they still sustained considerable activities. The result indicates that none of the analogs prepared in this study can fully satisfy the structural requirements of the receptor site which are satisfied by the parent compound (I). The fact that modifications on 1-indancarboxylic acid moiety as in VIII and XVIII markedly reduced the activity suggests that the stereochemistry of 1-indancarboxylic acid is suited for the antiinflammatory activity. The reduction of the activity by the conversion of benzoyl group of I into benzyl group also suggests that the carbonyl group of the benzophenone moiety may play its role by fixing the benzene ring to a proper dihedral angle. When the activities of the two benzyl derivatives were compared, 4-benzyl-1-indancarboxylic acid (XXXa) was more active than 6-benzyl-1-inadcarboxylic acid (XXXIa) consistently with the result for I and II,[1] indicating that the substituent at the 4-position is more important than that at the 6-position for the antiinflammatory activity.

Experimental[11]

Methyl 1-Cyano-1-methyl-4-indancarboxylate (IV)——To a suspension of 1.6 g of NaH in 100 ml of dry DMSO was added a solution of 5.4 g of methyl 1-cyano-4-indancarboxylate (III)[1] in 60 ml of dry DMSO

10) C.A. Winter, E.A. Risley, and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
11) Melting points and boiling points are not corrected. The infra red (IR) spectra were measured with a Hitachi-215 spectrometer. The nuclear magnetic resonance (NMR) spectra were obtained on a Varian HA-100 spectrometer using tetramethyl silane (TMS) as an internal standard. The ultraviolet (UV) spectra were measured with a Perkin-Elmer 450 UV-Visible NIR spectrophotometer.

and the mixture was stirred for 1.5 hr at room temperature. After cooling with ice-water, 28 g of methyl iodide was added dropwise over a 30 minute period and the mixture was stirred for 2 hr at room temperature. The mixture was poured into water, acidified with dil. HCl and extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 5.6 g (100%) of IV as a colorless solid. The analytical sample was obtained by recrystallization from cyclohexane, colorless needles, mp 74—76°. *Anal.* Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.46; H, 6.16; N, 6.49. IR ν_{max}^{Nujol} cm^{-1}: 2225 (C≡N), 1705 (C=O). NMR (in $CDCl_3$) δ: 7.94 (1H, dd, J=2 and 7 Hz, C_5–H), 7.55 (1H, dd, J=2 and 7 Hz, C_7–H), 7.32 (1H, t, J=7 Hz, C_6–H), 3.86 (3H, s, OCH_3). 3.30—3.48 (2H, m, C_3–H), 2.50—2.78 (1H, m, C_2–H), 2.03—2.30 (1H, m, C_2–H), 1.62 (1H, s, CH_3).

1-Cyano-1-methyl-4-indancarboxylic Acid (V)——To a solution of 1.8 g of NaOH in 90 ml of 50% EtOH was added 5.6 g of IV and the mixture was stirred for 4 hr at 55°. After cooling, the mixture was poured into water, acidified with dil. HCl and then extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 5.0 g (92.6%) of V as a colorless solid. The analytical sample was obtained by recrystallization from benzene, mp 145—147°. *Anal.* Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.53; H, 5.48; N, 6.88. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1680 (C=O). NMR (in $CDCl_3$) δ: 8.10 (1H, dd, J=2 and 7 Hz, C_5–H), 7.70 (1H, dd, J=2 and 7 Hz, C_7–H), 7.41 (1H, t, J=7 Hz, C_6–H), 3.40—3.66 (2H, m, C_3–H), 2.00—2.98 (2H, m, C_2–H), 1.66 (3H, s, CH_3).

4-Benzoyl-1-methyl-1-indancarbonitrile (VIIa)——A suspension of 2.1 g of V in 42 ml of thionyl chloride was stirred for 4 hr at room temperature. After the removal of the excess of thionyl chloride, to the residue were added 35 ml of benzene, 35 ml of CS_2 and 3.5 g of pulverized anhydrous $AlCl_3$ and the mixture was stirred for 30 min at room temperature and 2 hr at 55°. After cooling, the mixture was poured onto ice-water 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 2.5 g (99%) of VIIa as an oil. IR ν_{max}^{neat} cm^{-1}: 2225 (C≡N), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.3—7.8 (8H, m, aromatic protons), 3.1—3.4 (2H, m, C_3–H), 2.0—3.0 (2H, m, C_2–H), 1.70 (3H, s, CH_3).

4-(4-Methylbenzoyl)-1-methyl-1-indancarbonitrile (VIIb)——A suspension of 1.2 g of V in 24 ml of thionyl chloride was stirred for 4 hr at room temperature. After the removal of the excess of thionyl chloride, to the residue were added 40 ml of toluene and 2.4 g of pulverized anhydrous $AlCl_3$ and the mixture was stirred for 30 min at room temperature and then 2 hr at 60°. After cooling, the mixture was poured onto ice-water and extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 1.6 g (97.5%) of VIIb as an oil. This product was used for the subsequent process without purification. IR ν_{max}^{neat} cm^{-1}: 2225 (C≡N), 1660 (C=O).

4-(4-Chlorobenzoyl)-1-methyl-1-indancarbonitrile (VIIc)——A suspension of 1.2 g of V in 24 ml of thionyl chloride was stirred for 4 hr at room temperature. After the removal of the excess of thionyl chloride, to the residue were added 40 ml of chlorobenzene and 2.4 g of pulverized anhydrous $AlCl_3$ and the mixture was stirred for 30 min at room temperature and then 2 hr at 70—80°. After cooling, the mixture was poured onto ice-water 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 1.7 g (96.4%) of VIIc as an oil. IR ν_{max}^{neat} cm^{-1}: 2225 (C≡N), 1660 (C=O), NMR (in $CDCl_3$) δ: 7.3—7.9 (7H, m, aromatic protons), 3.1—3.4 (2H, m, C_3–H), 2.0—3.0 (2H, m, C_2–H), 1.70 (3H, s, CH_3).

4-Aroyl-1-methyl-1-indancarboxylic Acids (VIII)——A mixture of 2.5 g of VIIa and 60 ml of 60 wt% H_2SO_4 was heated under reflux for 3.5 hr in an atmosphere of nitrogen. After cooling, the mixture was diluted with water and extracted with ether. The ethereal layer was extracted with 5% aqueous K_2CO_3. The extract was acidified 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 recrystallized from a mixture of benzene and hexane (4: 10) to give 1.5 g (55.8%) of 4-benzoyl-1-methyl-1-indancarboxylic acid (VIIIa) as colorless prisms, mp 100—103°. *Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.03; H, 5.89; IR ν_{max}^{Nujol} cm^{-1}: 1725 (C=O), 1630 (C=O), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (C=O), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.15—7.80 (8H, m, aromatic protons), 3.04—3.20 (2H, m, C_3–H), 2.58—2.84 (1H, m, C_2–H), 1.80—2.10 (1H, m, C_2–H), 1.57 (3H, s, CH_3).

By the similar procedures were obtained the following two compounds: 4-(4-Methylbenzoyl)-1-methyl-1-indancarboxylic acid (VIIIb), mp 99—101° [colorless needles from benzene–hexane (4: 15), 52.6%]. *Anal.* Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.79; H, 6.24. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O), 1650 (C=O). NMR (in $CDCl_3$) δ: 7.65 (2H, d, J=8 Hz, $C_{2'}$– and $C_{6'}$–H), 7.22—7.50 (3H, m, aromatic protons), 7.20 (2H, d, J=8 Hz, $C_{3'}$– and $C_{5'}$–H), 3.00—3.17 (2H, m, C_3–H), 2.56—2.82 (1H, m, C_2–H), 1.79—2.08 (1H, m, C_2–H), 2.38 (3H, s, $C_{4'}$–CH_3), 1.56 (3H, s, C_1–CH_3).

4-(4-Chlorobenzoyl)-1-methyl-1-indancarboxylic Acid (VIIIc) mp 146.5—149.5° [colorless needles from ether–petroleum ether (1: 3), 66.3%]. *Anal.* Calcd. for $C_{18}H_{15}ClO_3$: C, 68.68; H, 4.80; Cl, 11.26. Found: C, 68.70; H, 4.89; Cl, 11.43. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O), 1650 (C=O), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (C=O), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.2—7.7 (3H, m, aromatic protons), 7.69 (2H, d, J=8 Hz, $C_{2'}$– and $C_{6'}$–H), 7.39 (2H, d, J=8 Hz, $C_{3'}$– and $C_{5'}$–H), 3.04—3.20 (2H, m, C_3–H), 2.56—2.85 (1H, m, C_2–H), 1.80—2.10 (1H, m, C_2–H), 1.58 (3H, s, CH_3).

5,6,7,8-Tetrahydro-5-oxo-1-naphthoic Acid (X)——A mixture of 31.2 g of 4-(2-carboxyphenyl)butyric

acid (IX),[7b] 100 g of pulverized anhydrous $AlCl_3$ and 8.8 g of NaCl was heated at around 160° for 2 hr. After cooling, the complex was decomposed with 30 ml of conc. HCl and 400 g of ice. The precipitate was collected by filtration and washed with water. The solid was dissolved in aqueous K_2CO_3. After treatment with decoloring carbon, the solution was acidified with conc. HCl and the precipitate was collected by filtration, washed with water and dried to give 21.1 g (74%) of X. The analytical sample was obtained by recrystallization from acetone, prisms, mp 200.5—206.5°. *Anal.* Calcd. for $C_{11}H_{10}O_3$: C, 69.47; H, 5.30. Found: C, 69.48; H, 5.38. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O), 1665 (C=O). NMR (in d_6-DMSO) δ: 8.07 (1H, dd, J=1 and 8 Hz, C_2–H), 7.99 (1H, dd, J=1 and 8 Hz, C_4–H), 7.39 (1H, t, J=8 Hz, C_3–H), 3.23 (2H, t, J=6 Hz, C_6–H), 2.49—2.72 (2H, m, C_8–H), 1.89—2.18 (2H, m, C_7–H).

Ethyl 5,6,7,8-Tetrahydro-5-oxo-1-naphthoate (XI)——A mixture of 19.0 g of X and 20 ml of conc. H_2SO_4 in 200 ml of EtOH was heated under reflux for 6.5 hr. After cooling, most of the EtOH was evaporated under reduced pressure. To the residue was added water and the mixture was extracted with $CHCl_3$. The extract was washed with saturated aqueous $NaHCO_3$ 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 19.4 g (88.9%) of XI. The analytical sample was obtained by recrystallization from EtOH, prisms, 41—43°. *Anal.* Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.63; H, 6.27. IR ν_{max}^{Nujol} cm^{-1}: 1720 (C=O), 1690 (C=O). NMR (in $CDCl_3$) δ: 8.21 (1H, dd, J=2 and 8 Hz, C_2–H), 8.02 (1H, dd, J=2 and 8 Hz, C_4–H), 7.33 (1H, t, J=8 Hz, C_3–H), 3.30 (2H, t, J=6 Hz, C_6–H), 2.57—2.76 (2H, m, C_8–H), 1.96—2.05 (2H, m, C_7–H).

Ethyl 5-Hydroxy-5,6,7,8-tetrahydro-1-naphthoate (XII)——To a stirred, ice-cooled solution of 6.55 g of XI in 120 ml of EtOH was added 0.57 g of $NaBH_4$ and the mixture was stirred for 3 hr at room temperature. After standing overnight, 2 ml of acetone was added to the mixture and it was then stirred for 1 hr. Most of the EtOH was evaporated under reduced pressure and to the residue dil. HCl was added. The mixture was extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 6.4 g (96.4%) of XII as an oil. *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.85; H, 7.41. IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1715 (C=O). NMR (in $CDCl_3$) δ: 7.72 (1H, dd, J=1.5 and 8 Hz, C_2–H), 7.58 (1H, dd, J=1.5 and 8 Hz, C_4–H), 7.21 (1H, t, J=8 Hz, C_3–H), 4.74 (1H, t, J=4.5 Hz, C_5–H), 2.91—3.13 (2H, m, C_8–H), 2.72 (1H, s, OH), 1.68—2.08 (4H, m, C_6– and C_7–H).

Ethyl 5-Chloro-5,6,7,8-tetrahydro-1-naphthoate (XIII)——To a stirred, ice-cooled solution of 4.41 g of XII in 4 ml of $CHCl_3$ was added 2 ml of thionyl chloride and the mixture was stirred for 4 hr under ice-cooling. After the removal of the excess of thionyl chloride and $CHCl_3$, benzene was added to the residue and evaporated under reduced pressure to remove thionyl chloride completely. This procedure was repeated 3 times to give 4.77 g (100%) of XIII as an oil. *Anal.* Calcd. for $C_{13}H_{15}ClO_2$: C, 65.41; H, 6.33. Found: C, 65.63; H, 6.36. IR ν_{max}^{neat} cm^{-1}: 1720 (C=O). NMR (in $CDCl_3$) δ: 7.74 (1H, dd, J=1.5 and 8 Hz, C_2–H), 7.46 (1H, dd, J=1.5 and 8 Hz, C_4–H), 7.19 (1H, t, J=8 Hz, C_3–H), 5.30 (1H, t, J=3 Hz, C_5–H), 2.65—3.43 (2H, m, C_8–H), 1.62—2.45 (4H, m, C_6– and C_7–H).

Ethyl 5-Cyano-5,6,7,8-tetrahydro-1-naphthoate (XIV)——To a stirred solution of 4.77 g of XIII in 44 ml of DMSO was added 2 g of NaCN in an atmosphere of nitrogen. The mixture was stirred for 3 hr at 50° and then poured into water. The mixture was acidified 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 benzene as the eluant to give 3.18 g (69.3%) of XIV as a colorless oil. *Anal.* Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.28; H, 6.62; N, 6.07. IR ν_{max}^{neat} cm^{-1}: 2240 (C≡N), 1720 (C=O). NMR (in $CDCl_3$) δ: 7.77 (1H, dd, J=1.5 and 8 Hz, C_2–H), 7.50 (1H, dd, J=1.5 and 8 Hz, C_4–H), 7.23 (1H, t, J=8 Hz, C_3–H), 4.00 (1H, t, J=6 Hz, C_5–H), 3.01—3.31 (2H, m, C_8–H), 1.61—2.24 (4H, m, C_6– and C_7–H).

5-Cyano-5,6,7,8-tetrahydro-1-naphthoic Acid (XV)——A mixture of 9.6 g of XIV and 2.5 g of NaOH in 180 ml of 50% EtOH was heated at 50° for 3 hr with occasional stirring. After cooling, EtOH was removed under reduced pressure and the residue was diluted with water. The mixture was washed with ether, 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 benzene to give 6.5 g (77%) of XV as colorless prisms, mp 177—179°. *Anal.* Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.88; H, 5.44; N, 6.88. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1690 (C=O). NMR (in d_6-DMSO) δ: 12.54 (1H, br. s, COOH), 7.71 (1H, dd, J=2 and 8 Hz, C_2–H), 7.30 (1H, dd, J=2 and 8 Hz, C_4–H), 7.28 (1H, t, J=8 Hz, C_3–H), 4.36 (1H, t, J=6 Hz, C_5–H), 2.94—3.15 (2H, m, C_8–H), 1.73—2.17 (4H, m, C_6– and C_7–H).

5-Aroyl-1,2,3,4-tetrahydro-1-naphthonitriles (XVII)——A suspension of 2.0 g of XV in 12 ml of $CHCl_3$ and 45 ml of thionyl chloride was stirred for 12 hr at room temperature. After the removal of the excess of thionyl chloride and $CHCl_3$, to the residue were added 20 ml of benzene and 2.0 g of pulverized anhydrous $AlCl_3$ with ice-cooling. The mixture was stirred for 6.5 hr at 40°. After cooling, the mixture was poured into 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 $CHCl_3$ as the eluant and recrystallized from hexane to give 1.6 g (61.6%) of 5-benzoyl-1,2,3,4-tetrahydro-1-naphthonitrile (XVIIa) as granules, mp 91.5—93.5°. *Anal.* Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found:

C, 82.84; H, 5.60; N, 5.42. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.16—7.83 (8H, m, aromatic protons), 4.03 (1H, t, J=7 Hz, C_1–H), 2.75 (2H, t, J=6 Hz, C_4–H), 1.59—2.24 (4H, m, C_2– and C_3–H). UV λ_{max}^{EtOH} nm (ε): 250 (15500).

By the similar procedures were obtained the following two compounds: 5-(4-Methylbenzoyl)-1,2,3,4-tetrahydro-1-naphthonitrile (XVIIb), mp 72—73° (from hexane, 54%). *Anal.* Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.71; H, 6.20; N, 4.90. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1655 (C=O). NMR (in $CDCl_3$) δ: 7.10—7.73 (7H, m, aromatic protons), 4.01 (1H, t, J=6 Hz, C_1–H), 2.74 (2H, t, J=7 Hz, C_4–H), 2.40 (3H, s, CH_3), 1.61—2.26 (4H, m, C_2– and C_3–H). UV λ_{max}^{EtOH} nm (ε): 260 (16700).

5-(4-Chlorobenzoyl)-1,2,3,4-tetrahydro-1-naphthonitrile (XVIIc): mp 97—99° (from hexane, 39%). *Anal.* Calcd. for $C_{18}H_{14}ClNO$: C, 73.10; H, 4.77; Cl, 11.99; N, 4.74. Found: C, 73.05; H, 4.77; Cl, 12.07; N, 4.75. IR ν_{max}^{Nujol} cm^{-1}: 2220 (C≡N), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.13—7.79 (7H, m, aromatic protons), 4.03 (1H, t, J=6 Hz, C_1–H), 2.74 (2H, t, J=6 Hz, C_4–H), 1.56—2.26 (4H, m, C_2– and C_3–H). UV λ_{max}^{EtOH} nm (ε): 259 (19200).

5-Aroyl-1,2,3,4-tetrahydro-1-naphthoic Acids (XVIII)——A suspension of 1.5 g of XVIIa in 60 ml of 60% H_2SO_4 was heated under reflux for 5.5 hr. 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 benzene to give 1.0 g (61.3%) of 5-benzoyl-1,2,3,4-tetrahydro-1-naphthoic acid (XVIIIa) as prisms, mp 164—165°. *Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.01; H, 5.74. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O), 1670 (C=O). NMR (in $CDCl_3$) δ: 10.3 (1H, s, COOH), 7.11—7.85 (8H, m, aromatic protons), 3.91 (1H, t, J=5 Hz, C_1–H), 2.73 (2H, t, J=6 Hz, C_4–H), 1.69—2.21 (4H, m, C_2– and C_3–H). UV λ_{max}^{EtOH} nm (ε): 250 (15000).

By the similar procedures were obtained the following compounds: 5-(4-Methylbenzoyl)-1,2,3,4-tetrahydro-1-naphthoic acid (XVIIIb), mp 102—103° (needles from cyclohexane, 79.6%). *Anal.* Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.24; H, 6.04. IR ν_{max}^{Nujol} cm^{-1}: 1695 (C=O), 1655 (C=O). NMR (in $CDCl_3$) δ: 11.05 (1H, s, COOH), 7.07—7.76 (7H, m, aromatic protons), 3.90 (1H, t, J=7 Hz, C_1–H), 2.69 (2H, t, J=6 Hz, C_4–H), 2.38 (3H, s, CH_3), 1.65—2.25 (4H, m, C_2– and C_3–H). UV λ_{max}^{EtOH} nm (ε): 260 (17700).

5-(4-Chlorobenzoyl)-1,2,3,4-tetrahydro-1-naphthoic acid (XVIIIc), mp 152.5—153.5° [needles from benzene–hexane (2: 3), 86.1%]. *Anal.* Calcd. for $C_{18}H_{15}ClO_3$: C, 68.68; H, 4.80; Cl, 11.27. Found: C, 68.72; H, 4.76; Cl, 11.28. IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O), 1670 (C=O). NMR (in $CDCl_3$) δ: 10.4 (1H, s, COOH), 7.10—7.80 (7H, m, aromatic protons), 3.91 (1H, t, J=5 Hz, C_1–H), 2.71 (2H, t, J=7 Hz, C_4–H), 1.68—2.27 (4H, m, C_2– and C_3–H). UV λ_{max}^{EtOH} nm (ε): 258 (19500).

The Friedel-Crafts Reaction of Ethyl 1,2,3,4-Tetrahydro-1-naphthoate (XIX) with Benzoyl Chloride—— To a stirred, ice-cooled mixture of 6.0 g of XIX[12] and 27 g of pulverized anhydrous $AlCl_3$ in 90 ml of CS_2 was added dropwise a solution of 21 g of benzoyl chloride in 30 ml of CS_2 and the mixture was stirred for 30 min with ice-cooling and then 3.5 hr under reflux. After cooling, the mixture was poured onto ice-water and extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was distilled to give 6.2 g of an oil, bp 150—154° (0.1 mmHg), IR ν_{max}^{neat} cm^{-1}: 1720 (C=O), 1660 (C=O), which consisted mainly of ethyl 7-benzoyl-1,2,3,4-tetrahydro-1-naphthoate (XX). This product was used for the subsequent process without further purification.

7-Benzoyl-1,2,3,4-tetrahydro-1-naphthamide (XXII)——A mixture of 2.0 g of the above product and 1.0 g of NaOH in 60 ml of 50% EtOH was refluxed for 2 hr. After cooling, EtOH was removed under reduced pressure. The mixture was washed with ether, 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 to give 1.8 g of residue. The residue was dissolved in 20 ml of thionyl chloride and stood overnight. After the removal of the excess of thionyl chloride, to the residue were added 10 ml of benzene and 20 ml of 28% aqueous NH_3 and the mixture was stirred for 10 min at room temperature. Resulting precipitate was collected by filtration, dried and recrystallized from benzene to give 1.0 g of XXII as colorless granules, mp 175—176.5°. *Anal.* Calcd. for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.21; H, 5.98; N, 4.92. IR ν_{max}^{Nujol} cm^{-1}: 3370 (NH), 3300 (NH), 3200 (NH), 1660 (C=O). NMR (in d_6-DMSO) δ: 7.16—7.75 (8H, m, aromatic protons), 6.97 (2H, br. s, NH_2), 3.68 (1H, t, J=7 Hz, C_1–H), 2.80 (2H, t, J=6 Hz, C_4–H), 1.6—2.2 (4H, m, C_2– and C_3–H).

7-Benzoyl-1,2,3,4-tetrahydro-1-naphthoic Acid (XXI)——A suspension of 2.8 g of XXII in 125 ml of conc. HCl was refluxed for 5 hr. After cooling, the mixture was extracted with $CHCl_3$ and the $CHCl_3$ layer was extracted with 1% aqueous NaOH. The extract was washed with ether, acidified with dil. HCl and then 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 cyclohexane (1: 2) to give 1.6 g (58%) of XXI as colorless prisms, mp 85.5—86.5°. *Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.11; H, 5.45. IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O), 1655 (C=O). NMR (in $CDCl_3$) δ: 7.1—7.8 (8H, m,

12) M. Inaba and T. Mitsui, *Bull. Agr. Chem. Soc. Japan*, **20**, 42 (1956).

aromatic protons), 3.85 (1H, t, J=5 Hz, C_1–H), 2.85 (2H, t, J=6 Hz, C_4–H), 1.7—2.4 (4H, m, C_2– and C_3–H).

Diethyl [2-(Arylmethyl)benzyl]malonates (XXIV)——To a solution of EtONa in EtOH (prepared from 11.5 g of metallic Na and 250 ml of dry EtOH) was added 160 g of diethyl malonate and the mixture was refluxed for 5 min. After cooling, to the solution was added a solution of 130.5 g of *o*-benzylbenzyl bromide[9a] in 100 ml of benzene over a 10 minute period and then the mixture was refluxed for 2.5 hr. After cooling, the mixture was concentrated under reduced pressure. To the residue was added water and the mixture was extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was distilled to give 115.4 g (91%) of diethyl (2-benzylbenzyl)-malonate (XXIVa) as an oil, bp 174—180° (0.06 mmHg). *Anal.* Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.31; H, 7.08. IR ν_{max}^{neat} cm^{-1}: 1740 (C=O). NMR (in $CDCl_3$) δ: 7.0—7.2 (9H, m, aromatic protons), 4.01 (2H, s, Ar–CH_2–Ar), 4.07 (4H, q, J=7 Hz, –$C\underline{H}_2$–CH_3), 3.0—3.4 (3H, m, –$C\underline{H}_2$–$C\underline{H}$<), 1.18 (6H, t, J=7 Hz, CH_3).

By the similar procedures were obtained the following three compounds from the corresponding *o*-(4-substituted benzyl)benzyl bromides (XXIIIb—d):[9] Diethyl [2-(4-methylbenzyl)benzyl]malonate (XXIVb), 90%, bp 170—175° (0.2 mmHg). *Anal.* Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.31; H, 7.60. IR ν_{max}^{neat} cm^{-1}: 1735 (C=O). NMR (in $CDCl_3$) δ: 7.08 (4H, s, aromatic protons), 6.96 (4H, s, aromatic protons), 4.10 (4H, q, J=8 Hz, –$C\underline{H}_2$–CH_3), 4.00 (2H, s, Ar–CH_2–Ar), 3.1—3.6 (3H, m, –$C\underline{H}_2$–$C\underline{H}$<), 2.27 (3H, s, CH_3), 1.18 (6H, t, J=8 Hz, CH_3).

Diethyl [2-(4-chlorobenzyl)benzyl]malonate (XXIVc), 79%, bp 175—185° (0.2 mmHg). *Anal.* Calcd. for $C_{21}H_{23}ClO_4$: C, 67.28; H, 6.18; Cl, 9.46. Found: C, 67.46; H, 6.20; Cl, 9.38. IR ν_{max}^{neat} cm^{-1}: 1740 (C=O). NMR (in $CDCl_3$) δ: 6.9—7.4 (8H, m, aromatic protons), 4.14 (4H, q, J=8 Hz, –$C\underline{H}_2$–CH_3), 4.05 (2H, s, Ar–CH_2–Ar), 3.1—3.8 (3H, m, –$C\underline{H}_2$–$C\underline{H}$<), 1.17 (6H, t, J=8 Hz, CH_3).

Diethyl [2-(4-methoxybenzyl)benzyl]malonate (XXIVd), 86%, bp 170—175° (0.15 mmHg). *Anal.* Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.30; H, 7.15. IR ν_{max}^{neat} cm^{-1}: 1745 (C=O). NMR (in $CDCl_3$) δ: 6.6—7.1 (8H, m, aromatic protons), 4.10 (4H, q, J=8 Hz, –$C\underline{H}_2$–CH_3), 3.98 (2H, s, Ar–CH_2–Ar), 3.70 (3H, s, OCH_3), 3.1—3.6 (3H, m, –$C\underline{H}_2$–$C\underline{H}$<), 1.18 (6H, t, J=8 Hz, CH_2–$C\underline{H}_3$).

3-[2-(Arylmethyl)phenyl]propionic Acids (XXVI)——To a solution of 99 g of KOH in 100 ml of water was added 155 g of XXIVa over a 20 minute period and the mixture was stirred for 3 hr at 95°. After cooling, the mixture was diluted with 50 ml of water, acidified with conc. HCl and extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude (2-benzylbenzyl)malonic acid (XXVa) as the residue, which was heated for 3 hr at 140°. After cooling, the resulting solid was recrystallized from hexane to give 99 g (90%) of 3-(2-benzylphenyl)propionic acid (XXVIa) as colorless needles, mp 85—87° (lit.[13] 85—87°). *Anal.* Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.31; H, 6.40. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 6.98—7.25 (9H, m, aromatic protons), 3.95 (2H, s, Ar–CH_2–Ar), 2.87 (2H, t, J=8 Hz, Ar–$C\underline{H}_2$–CH_2–), 2.79 (2H, t, J=7 Hz, –$C\underline{H}_2$–COOH).

By the similar procedures were obtained the following compounds from the corresponding diesters (XXIVb—d): 3-[2-(4-Methylbenzyl)phenyl]propionic acid (XXVIb), mp 94—96° (from hexane, 74%). *Anal.* Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.20; H, 7.23. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in $CDCl_3$) δ: 7.2—7.9 (4H, m, aromatic protons), 7.0 (4H, s, aromatic protons), 4.0 (2H, s, Ar–CH_2–Ar), 2.3—3.1 (4H, m, CH_2–CH_2), 2.29 (3H, s, CH_3).

3-[2-(4-Chlorobenzyl)phenyl]propionic acid (XXVIc), mp 107—109° (from cyclohexane, 86%). *Anal.* Calcd. for $C_{16}H_{15}ClO_2$: C, 69.94; H, 5.50; Cl, 12.91. Found: C, 69.99; H, 5.35; Cl, 12.91. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in $CDCl_3$) δ: 6.9—7.4 (8H, m, aromatic protons), 3.98 (2H, s, Ar–CH_2–Ar), 2.3—3.1 (4H, m, CH_2–CH_2–).

3-[2-(4-Methoxybenzyl)phenyl]propionic acid (XXVId), mp 86—89°. (from cyclohexane, 88%). *Anal.* Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.80; H, 6.50. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in $CDCl_3$) δ: 6.6—7.1 (8H, m, aromatic protons), 3.94 (2H, s, Ar–CH_2–Ar), 3.70 (3H, s, OCH_3) 2.3—3.2 (4H, m, CH_2–CH_2).

4-(Arylmethyl)-1-indanones (XXVII)——a) A suspension of 30 g of XXVIa in 1500 g of polyphosphoric acid (PPA) was stirred for 4 hr at 120°. After cooling, the mixture was poured into water and extracted with benzene. The extract was washed with 5% aqueous NaOH and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was distilled to give 21.5 g (77%) of 4-benzyl-1-indanone (XXVIIa), bp 156—160° (0.2 mmHg) [lit.[13] 140° (0.01 mmHg)]. Recrystallization from cyclohexane gave needles, mp 71—73°. *Anal.* Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.40; H, 6.19. IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O). NMR (in $CDCl_3$) δ: 7.02—7.36 (7H, m, aromatic protons), 7.59 (1H, dd, J=2 and 6 Hz, C_7–H), 3.99 (2H, s, Ar–CH_2–Ar), 2.86—2.98 (2H, m, C_3–H), 2.52—2.65 (2H, m, C_2–H).

By the similar procedures were obtained the following compounds from the corresponding acids (XXVIb—d): 4-(4-Methylbenzyl)-1-indanone (XXVIIb), mp 102—105° (from cyclohexane, 72%). *Anal.* Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.66; H, 6.72. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ:

13) C. van der Stelt, P.S. Hofman, and W. Th. Nauta, *Rec. Trav. Chim. Pays-Bas*, **84**, 633 (1965).

7.2—7.8 (3H, m, aromatic protons), 7.06 (4H, s, aromatic protons), 4.00 (2H, s, Ar–CH_2–Ar), 2.5—3.1 (4H, m, C_2– and C_3–H), 2.31 (3H, s, CH_3).

4-(4-Chlorobenzyl)-1-indanone (XXVIIc), mp 87—88° (from cyclohexane, 41%). *Anal.* Calcd. for $C_{16}H_{13}ClO$: C, 74.85; H, 5.10; Cl, 13.81. Found: C, 74.82; H, 4.89; Cl, 13.91. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in $CDCl_3$) δ: 7.0—7.8 (7H, m, aromatic protons), 4.03 (2H, s, Ar–CH_2–Ar), 2.5—3.2 (4H, m, C_2– and C_3–H).

4-(4-Methoxybenzyl)-1-indanone (XXVIId), mp 82—84° (from cyclohexane, 59%). *Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.88; H, 6.41. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in $CDCl_3$) δ: 6.7—7.8 (7H, m, aromatic protons), 3.96 (2H, s, Ar–CH_2–Ar), 3.75 (3H, s, CH_3), 2.5—3.1 (4H, m, C_2– and C_3–H).

b) A mixture of 5.0 g of XXVIc and 10 ml of thionyl chloride in 30 ml of $CHCl_3$ was refluxed for 1 hr and, after cooling, $CHCl_3$ and thionyl chloride were removed under reduced pressure. To the residue were added 150 ml of CS_2 and 5.0 g of pulverized anhydrous $AlCl_3$ and the mixture was stirred for 5 hr at room temperature. The mixture was poured onto ice-water and the organic layer was separated. The organic layer was washed with 5% aqueous Na_2CO_3 and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel using benzene–AcOEt (40: 1) as the eluant to give 3.26 g (71%) of XXVIIc. The IR and NMR spectra were identical with those of the compound obtained above.

4-(Arylmethyl)-1-indancarboxylic Acids (XXX)——a) A solution of *n*-BuLi in hexane (24.5 ml, 20% solution) was added over a 7 minute period to a stirred, cooled (−40°) solution of 5.25 g of dithiane in 50 ml of dry THF in an atmosphere of nitrogen. After the solution was stirred for 1 hr at −15° and 3 hr at −5°, a solution of 7.77 g of XXVIIa in 140 ml of dry THF was added over a 1.5 hr period at −5°. The mixture was stirred for 20 hr at −5—0° and then concentrated under reduced pressure. To the residue was added 100 ml of 1 N HCl and the mixture was extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 15.5 g of crude XXVIIIa as the residue. To the residue were added 1.0 g of *p*-toluenesulfonic acid and 250 ml of dry benzene and the mixture was refluxed for 1 hr removing water azeotropically. After the removal of benzene under reduced pressure, to the residue were added 70 ml of conc. HCl and 210 ml of acetic acid and the mixture was refluxed for 3 hr. After cooling, the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and then extracted with 5% aqueous K_2CO_3. The extract was acidified with dil. HCl and extracted with CH_2Cl_2. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from cyclohexane to give 3.0 g (34%) of 4-benzyl-1-indancarboxylic acid (XXXa) as needles, mp 119.5—121.0°. *Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.11; H, 6.29. IR ν_{max}^{Nujol} cm^{-1}: 1705 (C=O). NMR (in $CDCl_3$) δ: 6.9—7.3 (8H, m, aromatic protons), 3.91 (2H, s, Ar–CH_2–Ar), 4.02 (1H, t, J=8 Hz, C_1–H), 2.7—3.2 (2H, m, C_3–H), 2.2—2.6 (2H, m, C_2–H).

By the similar procedures were obtained the following compounds from the corresponding indanones (XXVIIb—d): 4-(4-Methylbenzyl)-1-indancarboxylic acid (XXXb), mp 125—127° (from cyclohexane, 17%). *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.04; H, 6.60. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 10.6 (1H, s, COOH), 7.0 (4H, s, aromatic protons), 6.9—7.4 (3H, m, aromatic protons), 4.10 (1H, t, J=8 Hz, C_1–H), 3.9 (2H, s, Ar–CH_2–Ar), 2.3 (3H, s, CH_3), 2.2—3.2 (4H, m, C_2– and C_3–H).

4-(4-Chlorobenzyl)-1-indancarboxylic acid (XXXc), mp 127—129° (from cyclohexane, 31.5%). *Anal.* Calcd. for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27; Cl, 12.37. Found: C, 71.36; H, 5.53; Cl, 12.32. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 11.2 (1H, s, COOH), 6.8—7.5 (7H, m, aromatic protons), 4.07 (1H, t, J= 8 Hz, C_1–H), 3.88 (2H, s, Ar–CH_2–Ar), 2.1—3.2 (4H, m, C_2– and C_3–H).

4-(4-Methoxybenzyl)-1-indancarboxylic acid (XXXd), mp 109.5—111.5° (from cyclohexane, 18.5%). *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 76.54; H, 6.43. Found: C, 76.60; H, 6.51. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 12.5 (1H, s, COOH), 6.7—7.5 (7H, m, aromatic protons), 4.1 (1H, t, J=8 Hz, C_1–H), 3.86 (2H, s, Ar–CH_2–Ar), 3.74 (3H, s, CH_3), 2.1—3.1 (4H, m, C_2– and C_3–H).

b) A solution of 3.0 g of 4-benzoyl-1-indancarboxylic acid (Ia) in 50 ml of acetic acid was catalytically hydrogenated over 10% Pd–C (0.5 g) under atmospheric pressure at 80° until 450 ml of hydrogen was absorbed. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was recrystallized from cyclohexane to give 1.7 g (60%) of 4-benzyl-1-indancarboxylic acid (XXXa) as needles. The IR and NMR spectra were identical with those of the compound obtained above.

6-Arylmethyl-1-indancarboxylic Acids (XXXI)——A solution of 13.37 g of 6-benzoyl-1-indancarboxylic acid (IIa) in 80 ml of acetic acid was catalytically hydrogenated over 5% Pd–C (3.0 g) under atmospheric pressure at 80° until 2.5 l of hydrogen was absorbed. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was recrystallized from cyclohexane to give 10.5 g (83%) of 6-benzyl-1-indancarboxylic acid (XXXIa) as needles, mp 115—118°. *Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.01; H, 6.35. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 10.4 (1H, s, COOH), 6.8—7.4 (8H, m, aromatic protons), 3.98 (1H, t, J=8 Hz, C_1–H), 3.91 (2H, s, Ar–CH_2–Ar), 2.1—3.2 (4H, m, C_2– and C_3–H).

By the similar procedure was obtained 6-(4-methylbenzyl)-1-indancarboxylic acid (XXXIb), mp 98—100° [from cyclohexane-hexane (1: 5), 32%]. *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C,

81.40; H, 6.65. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in $CDCl_3$) δ: 8.00 (4H, s, aromatic protons), 7.22 (1H, s, C_7–H), 7.08 (1H, d, J=8 Hz, C_5–H), 6.98 (1H, d, J=8 Hz, C_4–H), 3.96 (1H, t, J=7 Hz, C_1–H), 2.8—3.2 (2H, m, C_3–H), 2.15—2.50 (2H, m, C_2–H), 2.23 (3H, s, CH_3).

5-Arylmethyl-1,2,3,4-tetrahydro-1-naphthoic Acids (XXXII)——By the similar procedures described about XXXI were obtained the following compounds: 5-Benzyl-1,2,3,4-tetrahydro-1-naphthoic acid (XXXIIa), mp 124—126° [from cyclohexane–hexane (1: 2), 53.4%]. *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: 81.19; H, 6.75. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). NMR (in $CDCl_3$) δ: 10.8 (1H, s, COOH), 6.90—7.39 (8H, m, aromatic protons), 3.92 (2H, s, Ar–CH_2–Ar), 3.84 (1H, t, J=7 Hz, C_1–H), 2.50—2.70 (2H, m, C_4–H), 1.66—2.28 (4H, m, C_2– and C_3–H).

5-(4-Methylbenzyl)-1,2,3,4-tetrahydro-1-naphthoic acid (XXXIIb), mp 134—135° (from cyclohexane, 66%). *Anal.* Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.23; H, 7.06. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). NMR (in $CDCl_3$) δ: 10.3 (1H, s, COOH), 6.89—7.14 (7H, m, aromatic protons), 3.87 (2H, s, Ar–CH_2–Ar), 3.84 (1H, t, J=7 Hz, C_1–H), 2.50—2.72 (2H, m, C_4–H), 2.27 (3H, s, CH_3), 1.62—2.22 (4H, m, C_2– and C_3–H).

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