[Chem. Pharm. Bull. 26(4)1153—1161(1978)]

UDC 547.665.04.09 : 615.276.011.5.015.11

1-Indancarboxylic Acids. II.[1] Synthesis of 4- and 6-Aroyl-1-indancarboxylic Acids as Potential Antiinflammatory Agents

Tetsuya Aono, Yoshiaki Araki, Masayuki Imanishi, and Shunsaku Noguchi

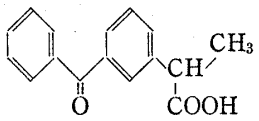
Central Research Division, Takeda Chemical Industries, Ltd.[2]

(Received September 8, 1977)

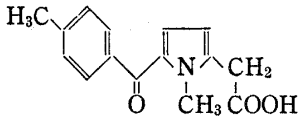
6-Aroyl-1-indancarboxylic acids (V) and isomeric 4-aroyl-1-indancarboxylic acids (XVIII) were prepared in an attempt to obtain information on the receptor sites of antiinflammatory aroylarylacetic acids. Compounds V were easily obtained by the Friedel-Crafts reaction of ethyl 1-indancarboxylate (III) and aroyl chloride. On the other hand, compounds XVIII were synthesized from 1-oxo-4-indancarboxylic acid (VIII) *via* the Friedel–Crafts reaction of 1-cyano-4-indancarbonyl chloride (XVI) and benzene or its derivative. Although compounds XVIII showed potent antiinflammatory activity, the activity of V was significantly weaker. The result suggests that locations and conformations of the functional groups in XVIII are considerably close to the actual conformation of a aroylarylacetic acid required for exerting antiinflammatory activity.

Keywords——antiinflammatory agent; aroyl-1-indancarboxylic acid; conformation; structure of receptor site; structure-activity relationship; deacylation of diarylketone

Recently some aroylarylacetic acids, exemplified by ketoprofen (I)[3] and tolumetin (II),[4] have been evaluated as new potent antiinflammatory agents. Little information, however, has been available with regard to their pharmacologically effective conformation. Assuming that derivatives of the aroylarylacetic acids with considerable conformational rigidity might be helpful for the elucidation of the favorable conformation for antiinflammatory activity, we have undertaken a study on the synthesis of 4- and 6-aroyl-1-indancarboxylic acids (XVIII and V) as well as the structure-activity relationship.



I



II

Chart 1

The reaction of ethyl 1-indancarboxylate (III) with benzoyl chloride in carbon disulfide in the presence of aluminum chloride followed by hydrolysis with aqueous sodium hydroxide gave a mixture of two isomers of benzoyl-1-indancarboxylic acid in 81% and 8% yields based on the gas chromatographic analysis. Judging from the reactivity of 1-indancarboxylic acid discussed in the previous paper,[1] the major and the minor products were presumed to be 6-benzoyl-1-indancarboxylic acid (Va) and 4-benzoyl-1-indancarboxylic acid (XVIIIa), respectively. The reaction of the mixture with thionyl chloride followed by treatment with ammonia yielded a mixture of amides as crystals. Upon recrystallization of the amides from ethanol, 6-benzoyl-1-indancarboxamide (VI) was preferentially crystallized. Hydrolysis of

1) Part I: T. Aono, S. Kishimoto, Y. Araki, and S. Noguchi, *Chem. Pharm. Bull.* (Tokyo), **25**, 3198 (1977).
2) Location: *17–85, Jusohonmachi-2-chome, Yodogawa-ku, Osaka 532, Japan.*
3) L. Julou, J.C. Guyonnet, R. Ducrot, C. Garret, M.C. Bardone, G. Maignan, and J. Pasquet, *J. Pharmacol.* (Paris), **2**, 259 (1971).
4) J.R. Carson, D.N. McKinstry, and S. Wong, *J. Med. Chem.*, **14**, 646 (1971).

VI with hydrochloric acid and recrystallization of the product from benzene-cyclohexane afforded Va as prisms, mp 95.5—96.5°.[5] By similar reactions, 6-(4-methylbenzoyl)- and 6-(4-chlorobenzoyl)-1-indancarboxylic acids (Vb and Vc) were obtained. In these cases, however, both compounds were readily crystallized from the reaction mixture without leading to the amides. The structure of Va, Vb and Vc was confirmed by the nuclear magnetic resonance (NMR) spectra. Thus, in the spectrum of Vb, the three aromatic protons of indan ring appeared at δ: 7.82 (1H, singlet), δ: 7.62 (1H, doublet, J=8 Hz) and δ: 7.26 (1H, doublet, J=8 Hz). This pattern, one singlet and one AB type, suggested that 4-methylbenzoyl group was introduced at either of the 5- and 6-positions. However, the large δ-value of the singlet peak was rationalized when it was assigned to the proton at the 7-position which situates between the carbonyl group at the 6-position and the carboxyl group at the 1-position.

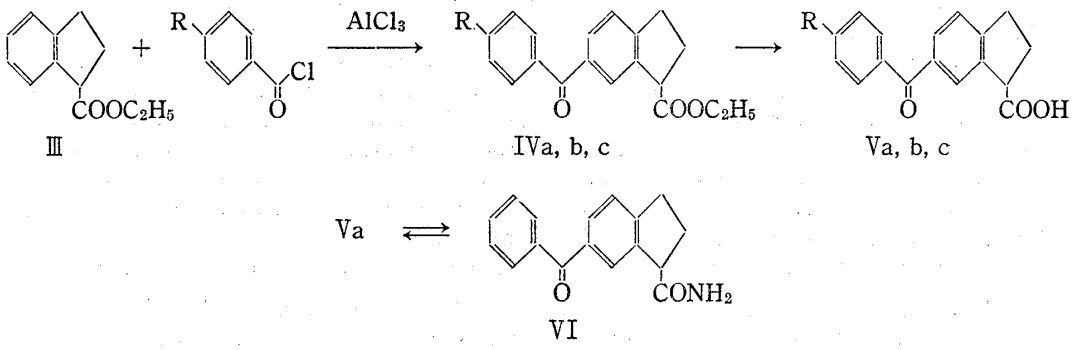


Chart 2

Since it seemed tedious to isolate 4-aroyl-1-indancarboxylic acid (XVIII), the minor component, from the above reaction mixture, attempts were made to synthesize XVIII by an alternative process. Thus, 1-oxo-4-indancarboxylic acid (VIII)[6] was chosen as the starting material with the intention to introduce the 4-aroyl group by the Friedel-Crafts reaction

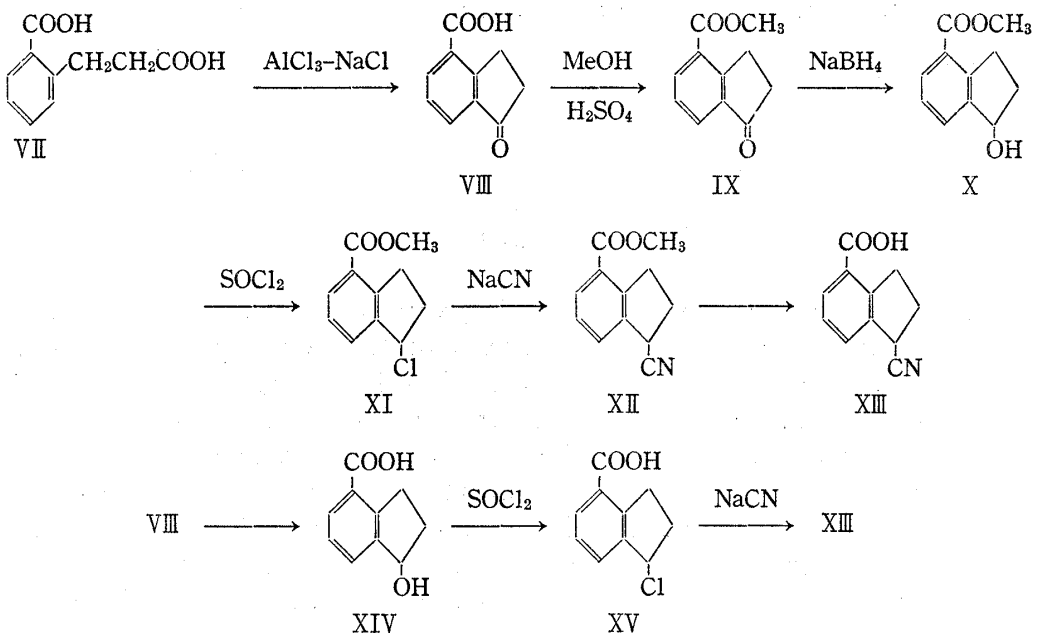


Chart 3

5) Resently Kirsch and his co-workers have obtained Va as an oil independently of our work. See G. Kirsch, C. Rufer, F. Bahjmann, H. Simon, and E. Stiebing, *Ann. Chem.*, **1976**, 1914.
6) H. Tomita, *Nippon Kagaku Zasshi*, **82**, 505 (1961).

with a benzene derivative. Although compound VIII had been prepared by the intramolecular cyclization of 3-(2-carboxyphenyl)propionic acid (VII) in polyphosphoric acid (PPA), the yield was reported to be as low as 17%.[6] However, our investigations revealed that the yield of VIII could be raised to 90% by melting VII with a mixture of aluminum chloride and sodium chloride[7] at around 160° for 2 hours. Compound VIII was esterified with methanol-sulfuric acid and the resulting methyl ester IX was reduced to methyl 1-hydroxy-4-indancarboxylate (X) with sodium borohydride in ethanol. Treatment of X with thionyl chloride in chloroform followed by the reaction with sodium cyanide in dimethyl sulfoxide (DMSO) gave methyl 1-cyano-4-indancarboxylate (XII) in 42% yield based on the starting material VIII. The cyano ester XII was hydrolyzed to 1-cyano-4-indancarboxylic acid (XIII) in 96% yield with aqueous sodium hydroxide. When these reactions were carried out without the esterification of VIII, *i.e. via* the pathway VIII→XIV→XV→XIII, the yield of XIII was appreciably lower (20% based on VIII) despite the shorter process.

Next subject was the conversion of the carboxyl group in XIII to an aroyl group. First, XIII was treated with thionyl chloride in chloroform to give acid chloride XVI, which was allowed to react with benzene in the presence of aluminum chloride under the condition of the Friedel–Crafts reaction. Work-up and column chromatography of the crude product on silica gel afforded 4-benzoyl-1-indancarbonitrile (XVIIa) in 75% yield, which was then hydrolyzed with 60% sulfuric acid to 4-benzoyl-1-indancarboxylic acid (XVIIIa), mp 101—103°.

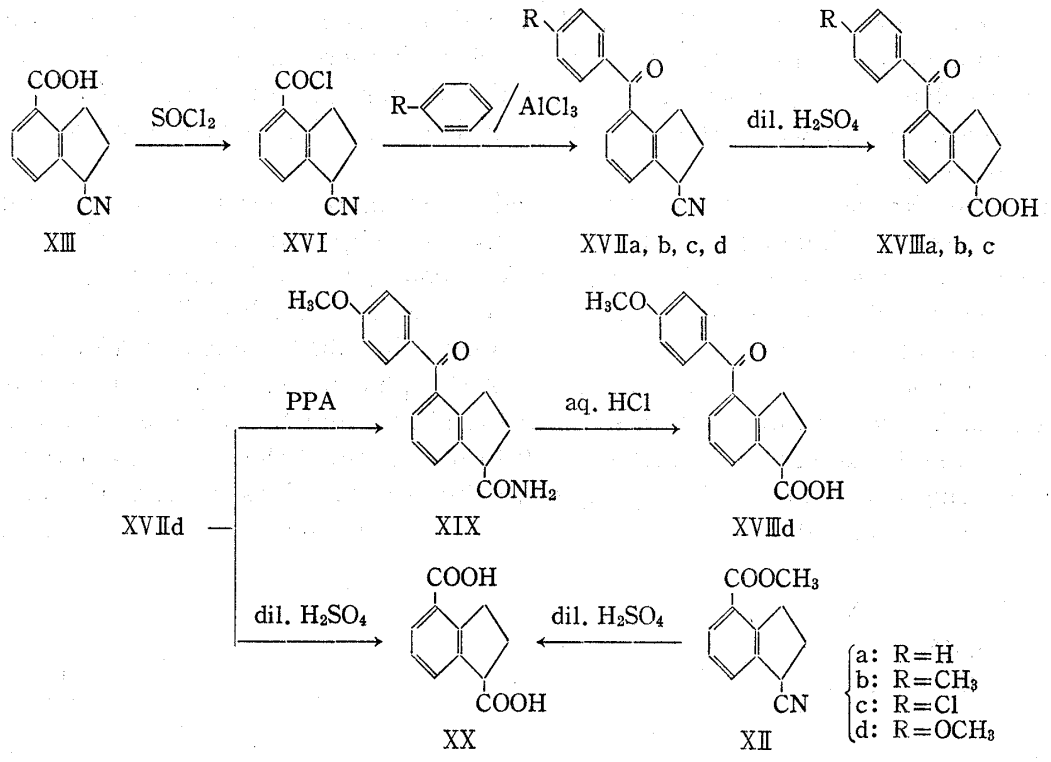


Chart 4

In a similar manner, toluene, chlorobenzene and anisole were allowed to react with XVI, since methyl, chlorine and methoxy groups are the first choice among the aromatic substituents according to the Topliss' operational scheme to find the most potent compound as early as possible.[8] In these Friedel-Crafts reactions, the yields of the 4-aroyl compounds (XVII) varied depending on the substituents on the benzene ring: The yield was higher (92.5%)

7) G. Baddeley and R. Williamson, *J. Chem. Soc.*, **1956**, 4647.
8) J.G. Topliss, *J. Med. Chem.*, **15**, 1006 (1972).

in the reaction with anisole in which the benzene ring was activated by an electron donating group and lower (18.2%) in chlorobenzene with an electron attracting group. 4-(4-Methyl and 4-chlorobenzoyl)-1-indancarbonitriles (XVIIb and XVIIc) were hydrolyzed with 60% sulfuric acid to the corresponding acids (XVIIIb and XVIIIc). The hydrolysis of 4-(4-methoxybenzoyl)-1-indancarbonitrile (XVIId), however, gave 1,4-indandicarboxylic acid (XX) as the sole product, whose structure was confirmed by identification with the compound obtained by the hydrolysis of the cyano ester XII. The formation of XX was interpreted by the deacylation reaction of XVIId or its carboxylic acid derivative (XVIIId). It is well known that deacylation of an aryl ketone occurs with strong acid when the electron density of the aromatic ring is enhanced or when the carbonyl group is sterically hindered.[9] The above case seemed to correspond to the former. Therefore, 4-(4-methoxybenzoyl)-1-indancarboxylic acid (XVIIId) was prepared by the hydrolysis of 4-(4-methoxybenzoyl)-1-indancarboxamide (XIX) which was obtained by treatment of XVIId with PPA.

Compounds synthesized in the present paper were tested for antiinflammatory activity using the carageenin-induced foot edema method in rats.[10] The antiinflammatory activity of 6-benzoyl-1-indancarboxylic acid (Va) was found to be relatively weak, as has been mentioned by Kirsch *et al.*,[5] but isomeric 4-benzoyl-1-indancarboxylic acid (XVIIIa) and its derivatives (XVIIIb—d) showed strong antiinflammatory activities.[11]

This result suggests that the benzoyl and the carboxyl groups in the 4-benzoyl derivatives (XVIIIa—d) are located at more favorable positions to be in contact with the receptor than those in the 6-benzoyl isomers (Va—c). It would be reasonable, therefore, to assume that other antiinflammatory aroylarylacetic acids such as ketoprofen (I) and tolumetin (II) also exhibit their pharmacological activities in a similar conformation to that of XVIIIa—d, that is, the conformation in which the benzoyl group is extended toward the opposite direction to the carboxyl group.

Since the ultraviolet spectra of XVIII and V are almost identical, the dihedral angles between benzene and indan ring in the both types of compounds seem to be comparable to each other. Moreover, the dihedral angle in V is considered to be almost equal to that of benzophenone which has been shown to be 56° by the X-ray analysis,[12] because little steric hindrance seems to exist in the compound V. Hence, the dihedral angle in XVIIIa—d is also thought to be about 56° in their stable forms. Although compounds Va—c may exist in two stable forms, *i.e. syn* and *anti* with respect to the phenyl and the indan groups, compounds XVIIIa—d would take predominantly the *anti*-form because of the steric interaction between the benzene ring and the methylene group of the 3-position. Consequently, the *anti*-form of XVIIIa—d is considered to be the active form of antiinflammatory aroylarylacetic acid.

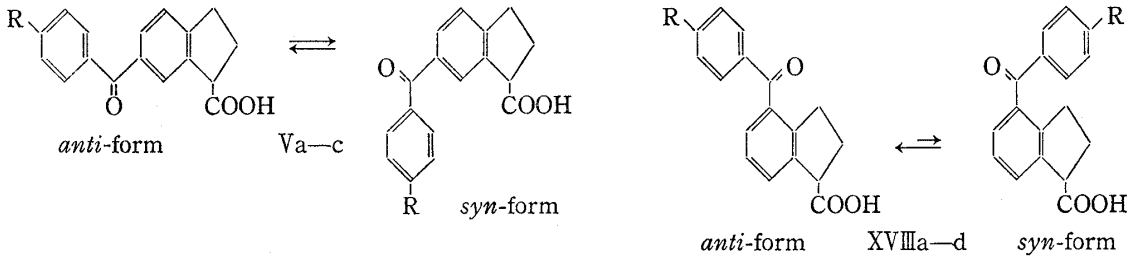


Chart 5. Conformational Equilibria of Va—c and XVIIIa—d

9) R.O.C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier Publishing Company, Amsterdam, London, New York, 1965, p. 231.
10) C.A. Winter, E.A. Risley, and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
11) On the first stage screening, XVIIIa—d exhibited the more potent activities than any of the non-steroidal antiinflammatory agents used in this country. Details are now under investigation and the results are to be published in the future.
12) E.B. Fleischer, N. Sung, and S. Hawkinson, *J. Phys. Chem.*, **72**, 4311 (1968).

This spatial arrangement of XVIIIa—d can substantially satisfy the requirements of the receptor site proposed by Shen,[13] which is nowadays called "prostaglandin synthetase anti-inflammatory receptor."[14]

Experimental[15]

Ethyl 6-Aroyl-1-indancarboxylate (IV)——a) To a stirred, ice-cooled mixture of 5.7 g of ethyl 1-indancarboxylate (III)[16] 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. After the addition was completed, the mixture was stirred for 4 hr under reflux. After cooling, the mixture was poured onto ice-water and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ and water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was distilled to give 7.1 g (80.5%) of ethyl 6-benzoyl-1-indancarboxylate (IVa) as an oil, bp 180—181° (0.2 mmHg). This product was used for the subsequent process without further purification. IR ν_{max}^{neat} cm^{-1}: 1740 (C=O), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.1—7.8 (8H, m, aromatic protons), 4.10 (2H, q, $J=7$ Hz, $-C\underline{H}_2-CH_3$), 4.05 (1H, t, $J=8$ Hz, C_1–H), 2.8—3.1 (2H, m, C_3–H), 2.3—2.7 (2H, m, C_2–H), 1.20 (3H, t, $J=7$ Hz, CH_3).

By the similar procedures was obtained the following compound: Ethyl 6-(4-methylbenzoyl)-1-indancarboxylate (IVb), bp 165—171° (0.5 mmHg). IR ν_{max}^{neat} cm^{-1}: 1730 (C=O), 1650 (C=O). NMR (in $CDCl_3$) δ: 7.77 (1H, s, C_7–H), 7.68 (2H, d, $J=8$ Hz, C_2'– and C_6'–H), 7.23 (2H, d, $J=8$ Hz, C_3'– and C_5'–H), 7.65 (1H, d, $J=8$ Hz, C_5–H), 7.28 (1H, d, $J=8$ Hz, C_4–H), 4.06 (1H, t, $J=8$ Hz, C_1–H), 2.9—3.1 (2H, m, C_3–H), 2.3—2.7 (2H, m, C_2–H), 1.25 (3H, t, $J=8$ Hz, CH_3).

b) To a stirred, ice-cooled mixture of 1.90 g of III and 9.0 g of pulverized anhydrous $AlCl_3$ in 30 ml of CS_2 was added dropwise a solution of 9.0 g of 4-chlorobenzoyl chloride in 10 ml of CS_2. After the addition was completed, the mixture was stirred for 2 hr at room temperature and for 2 hr under reflux. After cooling, the mixture was poured onto ice-water and extracted with CH_2Cl_2. 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 a mixture of benzene and AcOEt (5: 1) as the eluant to give 2.67 g (81%) of ethyl 6-(4-chlorobenzoyl)-1-indancarboxylate (IVc) as an oil. IR ν_{max}^{neat} cm^{-1}: 1730 (C=O), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.73 (2H, d, $J=8$ Hz, C_2'– and C_6'–H), 7.40 (2H, d, $J=8$ Hz, C_3'– and C_5'–H), 7.2—8.0 (3H, m, aromatic protons), 4.08 (1H, t, $J=8$ Hz, C_1–H), 2.9—3.3 (2H, m, C_3–H), 2.3—2.7 (2H, m, C_2–H), 4.20 (2H, q, $J=7$ Hz, $-C\underline{H}_2-CH_3$), 1.28 (3H, t, $J=7$ Hz, CH_3).

6-Benzoyl-1-indancarboxamide (VI)——A mixture of 2.0 g of IVa, 25 ml of EtOH and 25 ml of 4% aqueous NaOH was refluxed for 1 hr in an atmosphere of nitrogen. After cooling, EtOH was removed under reduced pressure and the resulting mixture was washed with ether, acidified with dilute 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 dissolved in 10 ml of thionyl chloride and the solution was heated under reflux for 1 hr. After removal of the excess of thionyl chloride, the residue was dissolved in 50 ml of ether and ammonia gas was admitted into the solution. After standing overnight, the precipitate was collected by filtration and recrystallized from EtOH to give 1.2 g (60%) of VI as colorless prisms, mp 195.5—197.0°. *Anal.* Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.96; H, 5.65; N, 5.28. IR ν_{max}^{Nujol} cm^{-1}: 3370 (N–H), 3300 (N–H), 3150 (N–H), 1660 (C=O), 1640 (C=O). NMR (in d_6-DMSO) δ: 7.3—7.8 (8H, m, aromatic protons), 6.96 (2H, s, NH), 3.94 (1H, t, $J=7$ Hz, C_1–H), 2.8—3.2 (2H, m, C_3–H), 2.1—2.5 (2H, m, C_2–H).

6-Aroyl-1-indancarboxylic Acids (V)——a) A suspension of 5.3 g of VI in 250 ml of conc. HCl was heated under reflux for 5 hr. After cooling, the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and then extracted with 1 N NaOH. The extract was washed with ether, acidified with dilute 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 cyclohexane and benzene (10: 3, v/v) to give 4.1 g (73%) of 6-benzoyl-1-indancarboxylic acid (Va) as colorless prisms, mp 95.5—96.5°. *Anal.* Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.32; H, 5.39. IR ν_{max}^{Nujol} cm^{-1}:

13) T.Y. Shen, "Topics in Medicinal Chemistry," Vol. 1, ed. by J.L. Rabinowitz and R.M. Myerson, John Wiley and Sons, Inc., New York, 1967, p. 53.
14) R.A. Scherrer, "Antiinflammatory Agents," Vol. 1, Academic Press, New York, San Francisco and London, 1974, p. 29.
15) Melting points and boiling points are not corrected. The IR spectra were measured with a Hitachi-215 spectrometer. The NMR spectra were obtained on a Varian HA-100 spectrometer using TMS as an internal standard. The UV spectra were measured with a Perkin-Elmer 450 UV-Visible NIR spectrophotometer.
16) V. Askam and W.H. Linnel, *J. Chem. Soc.*, **1954**, 4691.

1710 (C=O), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.2—7.9 (8H, m, aromatic protons), 4.10 (1H, t, J=7 Hz, C_1–H), 2.8—3.3 (2H, m, C_3–H), 2.3—2.7 (2H, m, C_2–H). UV λ_{max}^{EtOH} nm (ε): 260 (14600).

b) In an atmosphere of nitrogen, a mixture of 1.5 g of IVb, 30 ml of EtOH and 30 ml of 2% aqueous NaOH was heated under reflux for 1 hr. After cooling, EtOH was removed under reduced pressure and the resulting mixture was washed with ether, acidified with dilute 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 0.78 g (57%) of 6-(4-methylbenzoyl)-1-indancarboxylic acid (Vb) as colorless needles, mp 144.5—146.0°. *Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.74; H, 5.54. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 1645 (C=O). NMR (in $CDCl_3$) δ: 7.82 (1H, s, C_7–H), 7.62 (1H, d, J= 8 Hz, C_5–H), 7.26 (1H, d, J=8 Hz, C_4–H), 7.65 (2H, d, J=8 Hz, C_2'– and C_6'–H), 7.20 (2H, d, J=8 Hz, C_3'– and C_5'–H), 4.08 (1H, t, J=7 Hz, C_1–H), 2.8—3.3 (2H, m, C_3–H), 2.3—2.6 (2H, m, C_2–H), 2.40 (3H, s, CH_3). UV λ_{max}^{EtOH} nm (ε): 263 (18800).

By the similar procedures was obtained the following compound from IVc: 6-(4-Chlorobenzoyl)-1-indancarboxylic acid (Vc), mp 125—126° (colorless needles from benzene, 35%). *Anal.* Calcd. for $C_{17}H_{13}ClO_3$: C, 67.89; H, 4.36; Cl, 11.79. Found: C, 67.89; H, 4.36; Cl, 11.99. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 1655 (C=O). NMR (in $CDCl_3$) δ: 7.3—7.9 (7H, m, aromatic protons), 4.03 (1H, t, J=7 Hz, C_1–H), 2.9—3.3 (2H, m, C_3–H), 2.2—2.6 (2H, m, C_2–H). UV λ_{max}^{EtOH} nm (ε): 261 (18400).

1-Oxo-4-indancarboxylic Acid (VIII)——A mixture of 43 g of 3-(2-carboxyphenyl)propionic acid[17] (VII), 150 g of pulverized anhydrous $AlCl_3$ and 13.5 g of NaCl was heated for 2 hr at around 160° with occasional stirring. After cooling, the complex was decomposed with 300 ml of conc. HCl and 400 g of ice. The resulting precipitate was collected by filtration, washed with water and dried to give 35 g (90%) of VIII. The analytical sample was obtained by recrystallization from acetone, colorless plates, mp 225.5—227.5° (lit.[6] 225—226°). *Anal.* Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.11; H, 4.47. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1690 (C=O). NMR (in d_6-DMSO) δ: 8.17 (1H, dd, J=2 and 7 Hz, C_5–H), 7.79 (1H, dd, J=2 and 7 Hz, C_7–H), 7.14 (1H, t, J=7 Hz, C_6–H), 3.36–3.50 (2H, m, C_3–H), 2.48—2.75 (2H, m, C_2–H).

Methyl 1-Oxo-4-indancarboxylate (IX)——To 300 ml of MeOH were added 20 g of VIII and 20 ml of H_2SO_4. The mixture was heated under reflux for 5 hr and, after cooling, most of the MeOH was removed 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 recrystallized from a mixture of ether and hexane (1: 1) to give 21 g (97.5%) of IX. The analytical sample was obtained by further recrystallization from ether, colorless plates, mp 103—105° (lit.[6] 102—103°). *Anal.* Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.31; H, 5.21. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 8.25 (1H, dd, J=2 and 8 Hz, C_5–H), 7.92 (1H, dd, J=2 and 8 Hz, C_7–H), 7.43 (1H, t, J=8 Hz, C_6–H), 3.95 (3H, s, CH_3), 3.30—3.60 (2H, m, C_3–H), 2.56—2.86 (2H, m, C_2–H).

Methyl 1-Hydroxy-4-indancarboxylate (X)——To a stirred solution of 88 g of IX in 2 l of EtOH was added 9.0 g of sodium borohydride and the mixture was stirred for 9 hr at room temperature. Then 30 ml of acetone was added and the mixture was further stirred for 30 min. The mixture was concentrated under reduced pressure and to the residue was added dilute HCl. The residue was extracted with benzene. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated to dryness under reduced pressure to give 84 g (94.5%) of X. The analytical sample was obtained by recrystallization from a mixture of ether and petroleum ether (1.5: 1, v/v), colorless needles, mp 65—67°. *Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.40; H, 6.38. IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 1720 (C=O). NMR (in $CDCl_3$) δ: 7.85 (1H, dd, J=2 and 7 Hz, C_5–H), 7.50 (1H, dd, J=2 and 7 Hz, C_7–H), 7.21 (1H, t, J=7 Hz, C_6–H), 5.12 (1H, t, J=7 Hz, C_1–H), 3.82 (3H, s, CH_3), 2.85—3.52 (2H, m, C_3–H), 2.24—2.57 (1H, m, C_2–H), 1.70—2.03 (1H, m, C_2–H).

Methyl 1-Chloro-4-indancarboxylate (XI)——To a stirred, ice-cooled solution of 1.9 g of X in 2 ml of $CHCl_3$ was added 1 ml of thionyl chloride and the mixture was stirred for 1 hr under ice-cooling. The excess of thionyl chloride and $CHCl_3$ were removed under reduced pressure to give 2.1 g of XI as an oil. This product was used for the subsequent process without purification. IR ν_{max}^{neat} cm^{-1}: 1720 (C=O). NMR (in $CDCl_3$) δ: 7.92 (1H, dd, J=2 and 7 Hz, C_5–H), 7.61 (1H, dd, J=2 and 7 Hz, C_7–H), 7.30 (1H, t, J=7 Hz, C_6–H), 5.42 (1H, t, J=5 Hz, C_1–H), 3.90 (3H, s, CH_3), 3.3—3.6 (2H, m, C_3–H), 2.30—2.75 (2H, m, C_2–H).

Methyl 1-Cyano-4-indancarboxylate (XII)——To a solution of 100 g of XI in 530 ml of dimethyl sulfoxide (DMSO) was added 35.25 g of NaCN and the mixture was stirred at room temperature for 7 hr. After pouring into 3 l of water, the mixture was acidified with dilute 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 chromatographed on silica gel using $CHCl_3$ as the eluant to give 45 g (47%) of XII. The analytical sample was obtained by recrystallization from cyclohexane, colorless granules, mp 76.5—77.5°. *Anal.* Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.48; H, 5.51; N, 6.81. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N),

17) G.A. Page and D.S. Tarbell, "Org. Syntheses," Coll. Vol. 4, John Wiley & Sons, Inc., New York, London, 1963, p. 136.

1720 (C=O). NMR (in $CDCl_3$) δ: 7.93 (1H, dd, J=2 and 7 Hz, C_5–H), 7.58 (1H, dd, J=2 and 7 Hz, C_7–H), 7.30 (1H, t, J=7 Hz, C_6–H), 4.08 (1H, t, J=8 Hz, C_1–H), 3.85 (3H, s, CH_3), 2.66—3.04 (2H, m, C_3–H), 2.20—2.76 (2H, m, C_2–H).

1-Hydroxy-4-indancarboxylic Acid (XIV)——To a stirred, ice-cooled solution of 17.6 g of VIII in 100 ml of 4.4% aqueous NaOH was added 1.89 g of sodium borohydride and the mixture was stirred for 1 hr under ice-cooling and then for 2 hr at room temperature. The mixture was acidified with dilute HCl and kept in a refrigerator overnight. The resulting precipitate was collected by filtration and dried to give 16.5 g (92.7%) of XIV. The analytical sample was obtained by recrystallization from acetone, colorless granules, mp 174—176° (dec.). *Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.17; H, 5.41. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). NMR (in d_6-DMSO) δ: 7.80 (1H, dd, J=2 and 7 Hz, C_5–H), 7.49 (1H, dd, J=2 and 7 Hz, C_7–H), 7.21 (1H, t, J=7 Hz, C_6–H), 5.05 (1H, t, J=7 Hz, C_1–H), 2.6—3.5 (2H, m, C_3–H), 2.1—2.6 (1H, m, C_2–H), 1.6—2.0 (1H, m, C_2–H).

1-Chloro-4-indancarboxylic Acid (XV)——A mixture of 5.35 g of XIV, 15 ml of thionyl chloride and 30 ml of benzene was stirred at room temperature overnight. The excess of thionyl chloride and benzene were removed under reduced pressure. The residue was recrystallized from benzene to give 0.85 g (14.4%) of XV as colorless granules, mp 135.5—137.5°. *Anal.* Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 60.82; H, 4.68; Cl, 17.92. IR ν_{max}^{Nujol} cm^{-1}: 1685 (C=O). NMR (in d_6-DMSO) δ: 7.88 (1H, dd, J=2 and 7 Hz, C_5–H), 7.62 (1H, dd, J=2 and 7 Hz, C_7–H), 7.34 (1H, t, J=7 Hz, C_6–H), 5.58 (1H, dd, J=3 and 6 Hz, C_1–H), 3.2—3.4 (2H, m, C_3–H), 2.1—2.7 (2H, m, C_2–H).

1-Cyano-4-indancarboxylic Acid (XIII)——a) (From XII): To a mixture of 3.0 g of NaOH, 75 ml of water and 75 ml of MeOH was added 10 g of XII and the mixture was kept at 60° for 30 min with stirring. After cooling, the mixture was poured into 100 ml of 1 N-HCl and extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 9.0 g (96%) of XIII. The analytical sample was obtained by recrystallization from benzene, colorless granules, mp 206—208°. *Anal.* Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.59; H, 4.94; N, 7.39. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1690 (C=O). NMR (in d_6-DMSO) δ: 7.90 (1H, dd, J=2 and 8 Hz, C_5–H), 7.77 (1H, dd, J=2 and 8 Hz, C_7–H), 7.38 (1H, t, J=8 Hz, C_6–H), 4.47 (1H, t, J=8 Hz, C_1–H), 3.1—3.5 (2H, m, C_3–H), 2.0—2.9 (2H, m, C_2–H).

b) (From XV): A mixture of 1.78 g of XIV, 5 ml of thionyl chloride and 10 ml of benzene was stirred at room temperature for 2 hr and then concentrated under reduced pressure to give crude XV, which was dissolved in 15 ml of DMSO and to the mixture 1.96 g of NaCN was added. The mixture was stirred at room temperature overnight and poured into 150 ml of water. Insoluble materials were removed by filtration and the filtrate was acidified with 10 ml of conc. HCl. Resulting precipitate was collected by filtration, dried and recrystallized from benzene to give 0.56 g (23%) of XIII as colorless granules. The melting point and IR and NMR spectra were identical with those of a compound obtained in a).

4-Benzoyl-1-indancarbonitrile (XVIIa)——A suspension of 3.0 g of XIII in 35 ml of $CHCl_3$ and 35 ml of thionyl chloride was stirred at room temperature overnight. After the removal of $CHCl_3$ and the excess of thionyl chloride, 30 ml of benzene was added to the residue. To the stirred, ice-cooled solution was added 3.7 g of pulverized anhydrous $AlCl_3$ and the mixture was stirred for 15 min under ice-cooling and for 4 hr at room temperature. After pouring onto ice-dilute HCl, the mixture was 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 a mixture of benzene and AcOEt (80: 1, v/v) as the eluant to give 4.0 g (75%) of XVIIa as an oil. IR ν_{max}^{neat} cm^{-1}: 2230 (C≡N), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.3—7.9 (8H, m, aromatic protons), 4.20 (1H, t, J=8 Hz, C_1–H), 3.1—3.4 (2H, m, C_3–H), 2.3—2.7 (2H, m, C_2–H).

4-(4-Methylbenzoyl)-1-indancarbonitrile (XVIIb)——A suspension of 3.0 g of XIII in 35 ml of $CHCl_3$ and 35 ml of thionyl chloride was stirred at room temperature overnight. After the removal of $CHCl_3$ and the excess of thionyl chloride, 30 ml of toluene and 20 ml of CH_2Cl_2 were added to the residue. To the stirred, ice-cooled solution was added 3.8 g of pulverized anhydrous $AlCl_3$ and the mixture was stirred for 4 hr at room temperature. The mixture was poured onto ice-dilute 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 a mixture of benzene and AcOEt (80: 1, v/v) as the eluant to give 3.4 g (81%) of XVIIb as an oil. IR ν_{max}^{neat} cm^{-1}: 2230 (C≡N), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.2—7.8 (7H, m, aromatic protons), 4.20 (1H, t, J=8 Hz, C_1–H), 3.05—3.40 (2H, m, C_3–H), 2.45 (3H, s, CH_3), 2.3—2.7 (2H, m, C_2–H).

4-(4-Chlorobenzoyl)-1-indancarbonitrile (XVIIc)——A suspension of 3.0 g of XIII in 35 ml of $CHCl_3$ and 35 ml of thionyl chloride was stirred at room temperature overnight. After the removal of $CHCl_3$ and the excess of thionyl chloride, 50 ml of chlorobenzene was added to the residue. To the stirred, ice-cooled solution was added 3.0 g of pulverized anhydrous $AlCl_3$ and the mixture was stirred at 80° for 2.5 hr. The mixture was poured onto ice-dilute 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 0.82 g (18.2%) of XVIIc as an oil. IR ν_{max}^{neat} cm^{-1}: 2230 (C≡N), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.23—7.80 (7H, m, aromatic protons), 4.20 (1H, t, J=8 Hz, C_1–H), 3.1—3.4

(2H, m, C_3–H), 2.3—2.7 (2H, m, C_2–H).

4-(4-Methoxybenzoyl)-1-indancarbonitrile (XVIId)——A suspension of 5.0 g of XIII in 30 ml of $CHCl_3$ and 30 ml of thionyl chloride was stirred at room temperature overnight. After the removal of $CHCl_3$ and the excess of thionyl chloride, 40 ml of CH_2Cl_2 and 30 ml of anisole were added to the residue. To the stirred, ice-cooled solution was added 6.0 g of pulverized anhydrous $AlCl_3$ and the mixture was stirred for 3.5 hr at room temperature. The mixture was poured onto ice-dilute 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 chromatographed on silica gel using a mixture of benzene and AcOEt (40: 1, v/v) as the eluant followed by recrystallization from cyclohexane to give 6.85 g (92.5%) of XVIId as colorless granules, mp 115.5—117.5°. *Anal.* Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.80; H, 5.59; N, 4.77. IR ν_{max}^{Nujol} cm^{-1}: 2230 (C≡N), 1650 (C=O). NMR (in $CDCl_3$) δ: 7.10—7.70 (3H, m, aromatic protons), 7.75 (2H, d, J=8 Hz, C_2'– and C_6'–H), 6.91 (2H, d, J=8 Hz, C_3'– and C_5'–H), 4.18 (1H, t, J=8 Hz, C_1–H), 3.87 (3H, s, CH_3), 3.0—3.3 (2H, m, C_3–H), 2.3—2.7 (2H, m, C_2–H).

4-(4-Methoxybenzoyl)-1-indancarboxamide (XIX)——A suspension of 1.0 g of XVIId in 150 g of polyphosphoric acid was heated at around 120° for 40 min with occasional stirring and then 200 ml of water was added to it. The mixture was extracted with AcOEt and the extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 0.9 g (84%) of XIX. The analytical sample was obtained by recrystallization from benzene, colorless plates, mp 164—166°. *Anal.* Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.47. Found: C, 73.35; H, 5.85; N, 4.76. IR ν_{max}^{Nujol} cm^{-1}: 1665 (C=O), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.80 (2H, d, J=8 Hz, C_2'– and C_6'–H), 6.93 (2H, d, J=8 Hz, C_3'– and C_5'–H), 7.20—7.60 (3H, m, aromatic protons), 3.98 (1H, t, J=8 Hz, C_1–H), 3.88 (3H, s, CH_3), 2.9—3.3 (2H, m, C_3–H), 2.1—2.6 (2H, m, C_2–H).

4-Aroyl-1-indancarboxylic Acids (XVIII)——a) A suspension of 0.9 g of XVIIa in 20 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 100 ml of 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 dilute 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 cyclohexane (7: 20, v/v) to give 0.6 g (61.4%) of 4-benzoyl-1-indancarboxylic acid (XVIIIa) as colorless prisms, mp 101—103°. *Anal.* Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.54; H, 5.19. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 1670 (C=O). NMR (in $CDCl_3$) δ: 7.15—7.80 (8H, m, aromatic protons), 4.10 (1H, t, J=7 Hz, C_1–H), 3.04—3.33 (2H, m, C_3–H), 2.26—2.53 (2H, m, C_2–H). UV λ_{max}^{EtOH} nm (ε): 253 (16000).

By the similar procedures the following two compounds were obtained from XVIIb and XVIIc, respectively: 4-(4-Methylbenzoyl)-1-indancarboxylic Acid (XVIIIb), mp 132.5—134.5° (colorless needles from a mixture of benzene and cyclohexane (8: 25, v/v), 43%). *Anal.* Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.08; H, 5.63. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 1650 (C=O). NMR (in $CDCl_3$) δ: 7.65 (2H, d, J= 7 Hz, C_2'– and C_6'–H), 7.20 (2H, d, J=7 Hz, C_3'– and C_5'–H), 7.20—7.65 (3H, m, aromatic protons), 4.08 (1H, t, J=7 Hz, C_1–H), 3.00—3.35 (2H, m, C_3–H), 2.20—2.60 (2H, m, C_2–H), 2.40 (3H, s, CH_3). UV λ_{max}^{EtOH} nm (ε): 260 (18100).

4-(4-Chlorobenzoyl)-1-indancarboxylic acid (XVIIIc), mp 137.5—139.5° (colorless needles from a mixture of benzene and cyclohexane (3: 10), 53.5%). *Anal.* Calcd. for $C_{17}H_{13}ClO_3$: C, 67.89; H, 4.36; Cl, 11.79. Found: C, 67.75; H, 4.18; Cl, 11.89. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.16—7.70 (3H, m, aromatic protons), 7.68 (2H, d, J=8 Hz, C_2'– and C_6'–H), 7.38 (2H, d, J=8 Hz, C_3'– and C_5'–H), 4.09 (1H, t, J=7 Hz, C_1–H), 3.02—3.32 (2H, m, C_3–H), 2.26—2.50 (2H, m, C_2–H). UV λ_{max}^{EtOH} nm (ε): 260 (19500).

b) A suspension of 0.87 g of XIX in 140 ml of 20% HCl was heated under reflux for 7 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 dilute 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 cyclohexane (1: 2, v/v) to give 0.63 g (72%) of 4-(4-methoxybenzoyl)-1-indancarboxylic acid (XVIIId) as colorless granules, mp 137.5—138.5°. *Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.77; H, 5.22. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O), 1642 (C=O). NMR (in $CDCl_3$) δ: 7.76 (2H, d, J=8 Hz, C_2'– and C_6'–H), 6.90 (2H, d, J=8 Hz, C_3'– and C_5'–H), 7.15—7.60 (3H, m, aromatic protons), 4.11 (1H, t, J=7 Hz, C_1–H), 3.84 (3H, s, CH_3), 3.00—3.30 (2H, m, C_3–H), 2.28—2.50 (2H, m, C_2–H). UV λ_{max}^{EtOH} nm (ε): 288 (17250).

1,4-Indandicarboxylic Acid (XX)——a) (From XII) A suspension of 2.0 g of XII in 50 ml of 50 wt % H_2SO_4 was heated under reflux for 1.5 hr. After cooling, precipitate was collected by filtration, dried and recrystallized from acetone to give 1.0 g (49%) of XX as colorless prisms, mp 245.5—248.0°. *Anal.* Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.09; H, 4.73. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1690 (C=O). NMR (in d_6-DMSO) δ: 7.83 (1H, dd, J=2 and 7 Hz, C_5–H), 7.57 (1H, dd, J=2 and 7 Hz, C_7–H), 7.28 (1H, t, J= 7 Hz, C_6–H), 4.00 (1H, t, J=7 Hz, C_1–H), 3.00—3.48 (2H, m, C_3–H), 2.12—2.50 (2H, m, C_2–H).

b) (From XVIId) A suspension of 0.2 g of XVIId in 5 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 extracted with ether. The ethereal

layer was washed with water and extracted with 5% aqueous K_2CO_3. The extract was acidified with dilute HCl and extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 0.08 g (53%) of XX. The IR and NMR spectra were identical with those of an authentic sample obtained in a).

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