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1-Indancarboxylic Acids. I. Electrophilic Substitution Reactions of 1-Indancarboxylic Acid and Synthesis of 6-Substituted 1-Indancarboxylic Acids as Potential Antiinflammatory Agents

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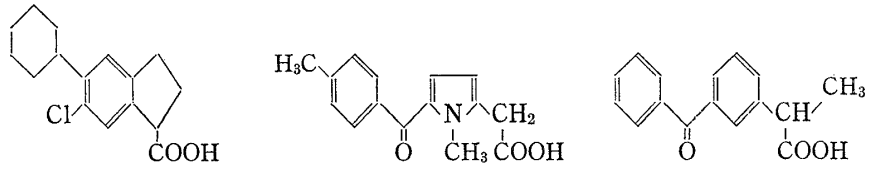
The relative reactivity in each position of 1-indancarboxylic acid (IV) toward electrophilic substitution reaction such as chlorination, bromination, acylation, sulfonation and nitration was examined and it was found that the 6-position is the most reactive. By these reactions, pharmacologically interesting *meta*-substituted phenylacetic acid derivatives were readily obtained. Electrophilic chlorination of IV followed by cycloalkylation provided an improved alternative synthetic method of antiinflammatory 6-chloro-5-cyclohexyl-1-indancarboxylic acid (TAI-284, I) and its analogs.

Keywords——antiinflammatory activity; 1-indancarboxylic acid; Friedel-Crafts reaction; chlorination; alkylation; acylation

A number of indan derivatives have been synthesized in expectation of pharmacological activities. However, very few compounds having practical use have been reported.[2] Recently we have reported the preparations of cyclic analogs of antiinflammatory *p*-alkylphenylacetic acids, 5-alkyl-1-indancarboxylic acids with the carboxyl group being held in an essentially rigid, out-of-plane conformation.[3] Among the compounds prepared, 6-chloro-5-cyclohexyl-1-indancarboxylic acid (I, TAI-284) was found to show the high antiinflammatory, analgesic and antipyretic activities. However, six-membered ring analogs of I, 1,2,3,4-tetrahydro-1-naphthoic acid derivatives, were reported to possess no such potent activity as that of the corresponding 1-indancarboxylic acid derivatives.[4] Therefore, 1-indancarboxylic acid seems to involve the essential conformation of the phenylacetic acids for exerting the antiinflammatory activity.

Recently some *meta*-substituted arylacetic acids, *e.g.* tolumetin (II)[5] and ketoprofen (III),[6] have also drawn attention as potent antiinflammatory agents. This fact led us to an expectation that a new antiinflammatory agent could be obtained by introducing an



I II III

Chart 1

1) Location: *17–85, Jusohonmachi-2-chome Yodogawa-ku, Osaka 532, Japan.*
2) C.R. Ganellin, *Advances in Drug Research*, **4**, 163 (1967).
3) *a*) S. Noguchi, S. Kishimoto, I. Minamida, M. Obayashi, and K. Kawakita, *Chem. Pharm. Bull.* (Tokyo), **19**, 646 (1971); *b*) S. Noguchi, S. Kishimoto, I. Minamida, and M. Obayashi, *ibid.*, **22**, 529 (1974).
4) P.F. Juby, W.R. Goodwin, T.W. Hudyma, and R.A. Partyka, *J. Med. Chem.*, **15**, 1306 (1972).
5) J.R. Carson, D.N. McKinsky, and S. Wong, *J. Med. Chem.*, **14**, 646 (1971).
6) L. Julou, J.C. Guyonnet, R. Ducrot, C. Garret, M.C. Bardone, G. Maignan, and J. Pasquet, *J. Pharmacol.* (Paris), **2**, 259 (1971).

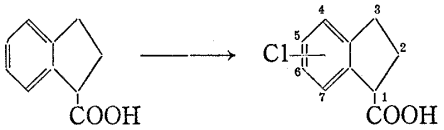
appropriate substituent at either of the 4- or 6-positions of 1-indancarboxylic acid (IV), which corresponds to the *meta*-position in phenylacetic acid. This paper describes the electrophilic substitution reactions of IV to give various 4- and 6-substituted derivatives as well as an alternative synthesis of I *via* 6-chloro-1-indancarboxylic acid (Vc).

Electrophilic substitution reactions of benzocyclenes such as indan and tetralin have received considerable attention with respect to their relative reactivities and the characteristic orientation in their aromatic rings, so-called "The Mills-Nixon Effect".[7] According to the Mills-Nixon effect, the electrophilic substitution reaction toward unsubstituted indan is expected to occur predominantly at the β-position,[8] while in unsubstituted tetralin a considerable amount of α-substitution may occur in addition to the β-substitution. However, information on the reaction of their 1-carboxylic acid derivatives has been limited. This fact prompted us to investigate the electrophilic substitution reactions of 1-indancarboxylic acid (IV). It should be mentioned that analogous studies on 1-indancarboxylic acid (IV) and its ester have been recently reported by Kirsch, *et al.*[9] independently of our work.

Chlorination

We have reported that 5-cyclohexyl-1-indancarboxylic acid is chlorinated at the 6-position with molecular chlorine in acetonitrile without catalyst to yield I with a high selectivity.[3b] It was found, however, that chlorination of IV under tha same condition afforded by-products in addition to the desired 6-chloro-1-indancarboxylic acid (Vc).[10] The nuclear magnetic resonance (NMR) spectrum of the mixture showed that the by-products bear chlorine at the 3-position. Since the formation of the by-products was suspected to be a result of a radical mechanism, it seemed preferable to employ a polar catalyst such as Lewis acid in order to direct the reaction to the ionic process. Therefore, the reactions were carried out with molec-

Table I. Chlorination of 1-Indancarboxylic Acid (IV)



IV V

Entry	Reagent	Solvent	Isomer ratio %[a] Va 4-Cl	Vb 5-Cl	Vc 6-Cl	Vd 7-Cl
1	Cl_2-$FeCl_3$	CH_3CN	8.4	1.9	89.2	0.5
2	Cl_2-$TiCl_4$	CH_3CN	11.7	3.3	83.5	1.5
3	Cl_2-$ZnCl_2$	CH_3CN	12.5	5.7	81.5	0.4
4	Cl_2-$SnCl_4$	CH_3CN	16.0	3.9	79.7	0.4
5	Cl_2-$FeCl_3$	$(CH_3)_2CHCN$	18.9	7.3	71.7	2.1
6	Cl_2-$TiCl_4$	CH_2Cl_2	33.5	3.0	62.8	0.7
7	NCS[b]	DMF[c]	7.8	14.5	77.0	0.7
8	$TiCl_4$-mCPBA[d]	CH_2Cl_2	36.9	3.8	53.2	6.0

a) Analysis, after treated with bis(trimethylsilyl)acetamide, by gas chromatography on a 4 m × 2.5 mm QF-1(3% on Chromosorb G) column at 150°.
b) N-Chlorosuccinimide.
c) Dimethylformamide.
d) *m*-Chloroperbenzoic acid.

7) G.W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, 1955, p. 479.
8) Positions in the aromatic ring of the benzocyclenes have been expressed for convenience by α for the position adjacent to the fused ring and β for other positions.
9) G. Kirsch, C. Rufer, F. Bahjmann, H. Simon, and E. Stiebing, *Ann. Chem.*, **1976**, 1914.
10) Kirsch, *et al.* have reported that Vc was obtained in 65% yield under the similar conditions.[9]

ular chlorine in the presence of various metal halides, with N-chlorosuccinimide (NCS) and with positive chlorine such as hypochlorous acid under the conditions described in the experimental part. The crude products obtained were led to the trimethylsilyl esters with bis(trimethylsilyl)acetamide and analyzed by means of gas chromatography to determine the relative reactivity of each position of the indan ring. The results are summarized in Table I.

As shown in Table I, the isomer distribution in the products considerably varied with the reaction conditions employed. However, a tendency deduced from the results is that the 6-position is the most reactive toward the electrophilic chlorination and the reactivity decreases in the order of 6-$\gg$ 4-$>$5- and 7-positions.

It is well known that the benzylic hydrogens in indan are favorably situated for hyperconjugative electron release.[11] Therefore, this effective hyperconjugation is considered to be one of the important factors for determing the orientation in electrophilic substitution of indan. Of the three benzylic hydrogens in 1-indancarboxylic acid (IV), one is located at C-1 which bears an electron withdrawing carboxyl group. Therefore, the hydrogen at C-1

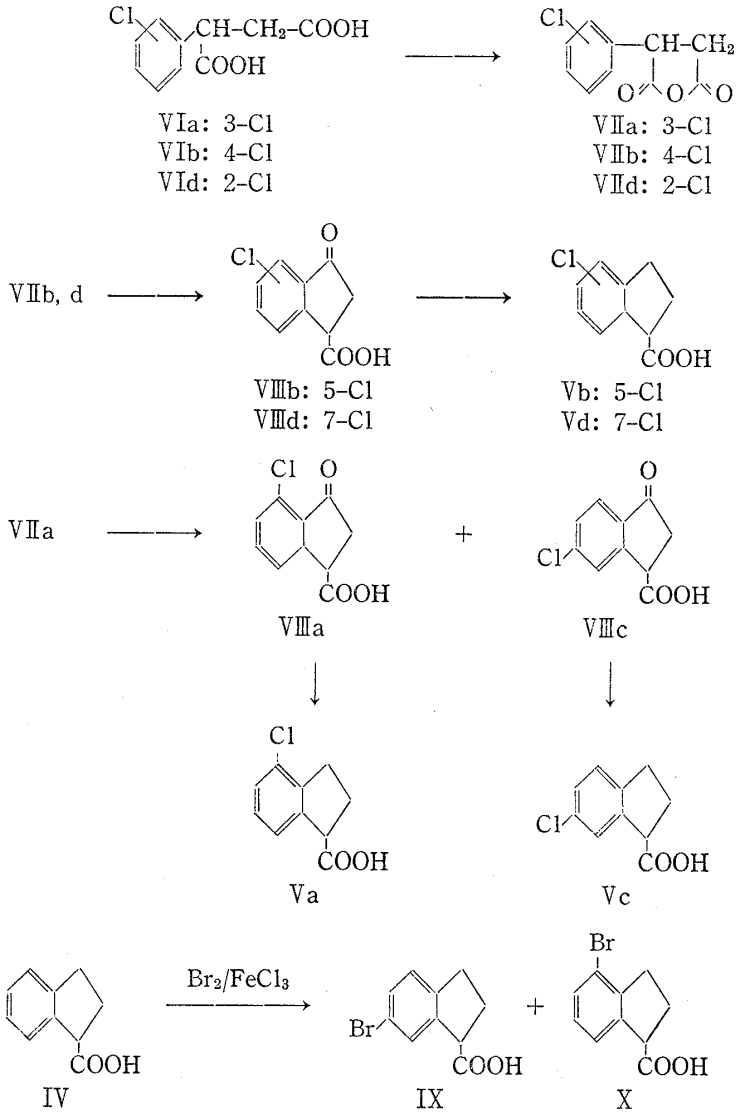


Chart 2

11) G. Baddeley and M. Gordon, *J. Chem. Soc.*, **1952**, 2190; G. Baddeley, J.W. Rasburn, and R. Rose, *ibid.*, **1958**, 3168.

seems to have less influence on the orientation. This tendency would be enhanced when the carboxyl group forms a complex with Lewis acid added as a catalyst.[12] As a result, the two hydrogens at C-3 mainly contribute to the determination of the orientation through the hyperconjugation, directing the electrophilic attack predominantly to the 6- (the *para* to C-3) and 4- (the *ortho* to C-3) positions. On the basis of these considerations, it seems to be reasonable that the 6-position of IV is the most reactive toward electrophilic chlorination.

The results in Table I also indicate that, in the chlorinations with molecular chlorine (entry 1—6), the use of ferric chloride is the most preferable among the metal chlorides with respect to the selectivity to give 6-chloro-1-indancarboxylic acid (Vc) and acetonitrile is significantly favorable as solvent. Under these conditions (entry 1), Vc was isolated in 57.5% yield. Chlorination with NCS (entry 7) gave a relatively large amount of 5-chloro-1-indancarboxylic acid (Vb) presumably because of the absence of Lewis acid. When titanium tetrachloride with *m*-chloroperbenzoic acid (*m*CPBA) (entry 8) was used, the selectivity of chlorination was poor probably owing to the relatively high reactivity of the chlorinating species, hypochlorous acid or its titanate ester.[13]

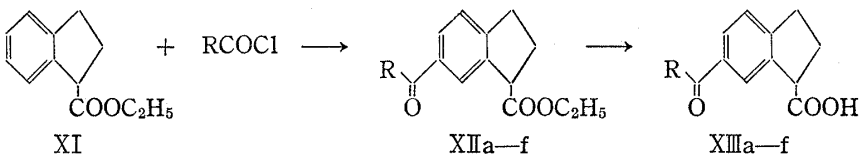
The authentic samples of 4-, 5-, 6- and 7-chloro-1-indancarboxylic acids (Va, b, c and d) used for gas chromatographic analysis were prepared as follows: (3-, 4- and 2-chlorophenyl)-succinic acids (VIa, b and d) were converted into the corresponding acid anhydrides (VIIa, b and d), which were cyclized with aluminum chloride to chloro-3-oxo-1-indancarboxylic acids (VIIIa, b, c and d). From (4- and 2-chlorophenyl)succinic anhydrides (VIIb and d), 5- and 7-chloro-3-oxo-1-indancarboxylic acids (VIIIb and d) were obtained, respectively. The cyclization of (3-chlorophenyl)succinic anhydride (VIIa), however, gave a mixture of isomeric products, 4-chloro-3-oxo-1-indancarboxylic acid (VIIIa) and 6-chloro-3-oxo-1-indancarboxylic acid (VIIIc), which were separated to each other by fractional recrystallization. Each isomer (VIIIa, b, c and d) was subjected to the Clemmensen reduction to afford Va, Vb, Vc and Vd, respectively.

Bromination

Bromination of IV with molecular bromine in the presence of ferric chloride afforded similar result to that found in the above chlorination, giving 6-bromo-1-indancarboxylic acid (IX) as the major product and 4-bromo-1-indancarboxylic acid (X) as the minor product. The structures of the products were determined by comparison of their NMR spectra with those of the analogous chlorides.

Acylation

Askam and Linnel reported that acetylation of ethyl 1-indancarboxylate (XI) with acetyl chloride gave the corresponding 6-acetyl derivative[14] although details were not described. We have reinvestigated the acetylation and confirmed, by means of gas chromatographic and



XI XIIa—f XIIIa—f

a: R=C_2H_5 d: R=iso-C_4H_9
b: R=C_3H_7 e: R=cyclopentyl
c: R=iso-C_3H_7 f: R=cyclohexyl

Chart 3

12) Y. Kishi, F. Nakatsubo, M. Aratani, T. Goto, S. Inoue, H. Kadoi, and S. Sugiura, *Tetrahedron Lett.*, **1970**, 5127.
13) G.K. Chip and J.S. Grossert, *Can. J. Chem.*, **50**, 1233 (1972).
14) V. Askam and W. Linnel, *J. Chem. Soc.*, **1954**, 4691.

NMR spectroscopic analyses, that the reaction occurred exclusively at the 6-position. It was also found that the reactions with other acyl chlorides similarly proceeded to afford 6-acyl derivatives (XII) as the major products. However, the formation of 4-acyl isomers as the minor products was observed with the increase of bulkiness of the acyl group as had been the cases with the acylations of alkylbenzene[15] and ethyl phenylacetate.[16] Ethyl 6-acyl-1-indancarboxylates (XII) thus obtained were hydrolyzed to the corresponding acid (XIII).

Chloroacetylation

Chloroacetylation of XI was carried out in the presence of aluminum chloride and the NMR spectrum of the crude product indicated that ethyl 6-chloroacetyl-1-indancarboxylate (XIV) was obtained exclusively. XIV was allowed to react with thiourea and thioacetamide to give the corresponding 6-aminothiazole and 6-methylthiazole derivatives (XV and XVI).

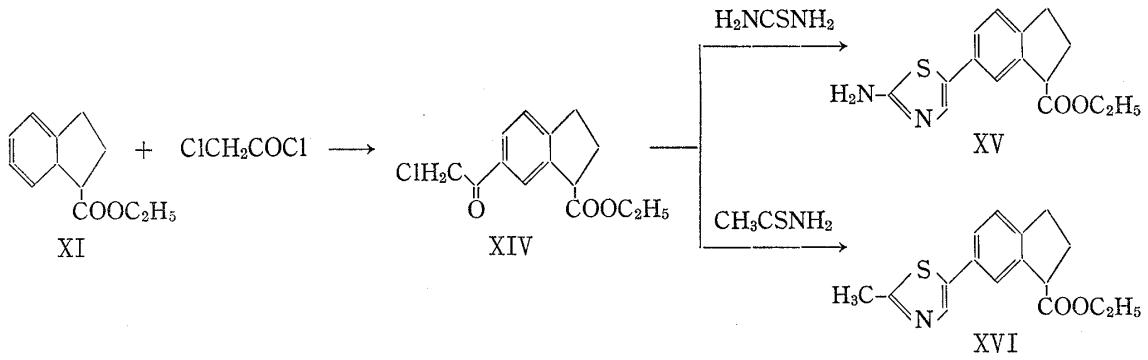


Chart 4

Sulfonation

Sulfonation of XI with chlorosulfonic acid afforded a single product, ethyl 6-chlorosulfonyl-1-indancarboxylate (XVIII), in a yield of 74%. Compound XVIII was converted to sulfonamide (XIX) by the reaction with ammonia.

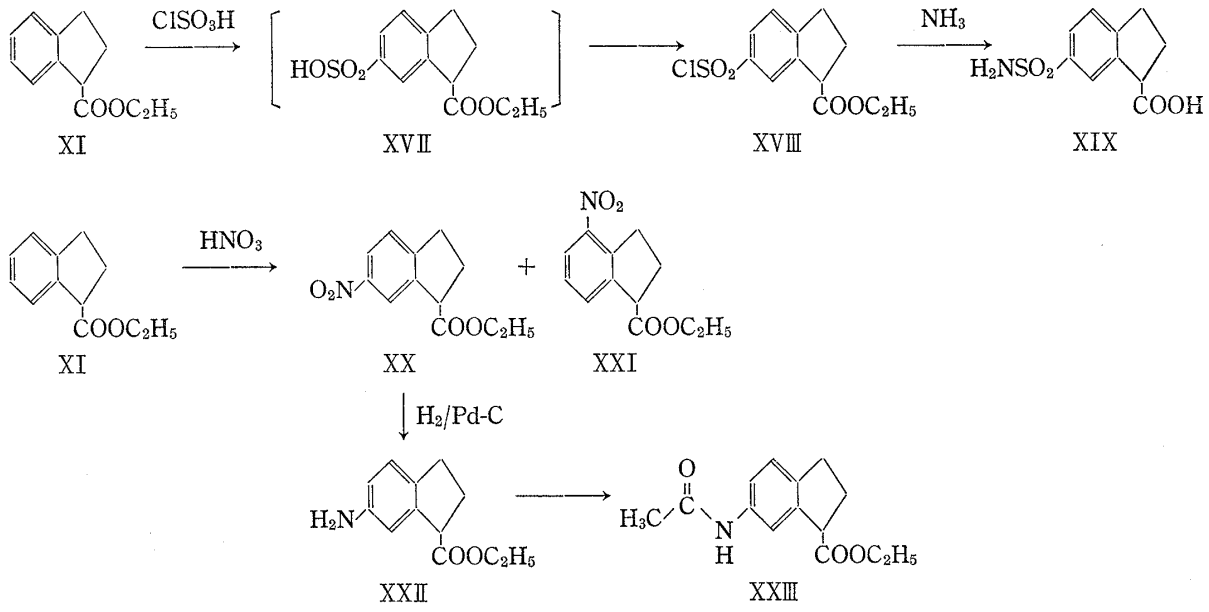


Chart 5

15) R.O.C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier Publishing Company, Amsterdam, London, New York, 1965, p. 181.
16) E.D. Morgan, *Tetrahedron*, **23**, 1735 (1967).

Nitration

Ethyl 1-indancarboxylate (XI) was nitrated with nitric acid in acetic anhydride at −5°. The NMR spectrum of the crude product showed two peaks due to the C-3 protons at 3.5 and 3.1 ppm, which were assigned to those of ethyl 4-nitro-1-indancarboxylate (XXI) and ethyl 6-nitro-1-indancarboxylate (XX), respectively. The integral intensity of those peaks suggested that the ratio of XXI and XX in the mixture was about 1: 2. The mixture, without purification, was led to the corresponding acetylamino derivatives by catalytic hydrogenation over palladium-carbon followed by treatment with acetic anhydride. On recrystallization of the mixture, only ethyl 6-acetylamino-1-indancarboxylate (XXIII), whose structure was determined by means of NMR spectroscopy, was isolated. A similar result was also reported by Kirsch, *et al.*[9]

From the above results, it is concluded that the electrophilic substitution reactions of 1-indancarboxylic acid (IV) or its ester (XI) take place predominantly at the 6-position. It is noteworthy from the standpoint of medicinal chemistry that the electrophilic substitution reactions of 1-indancarboxylic acid (IV) afforded its 6-substituted derivatives which incorporate a pharmaceutically interesting *meta*-substituted phenylacetic acid moiety.

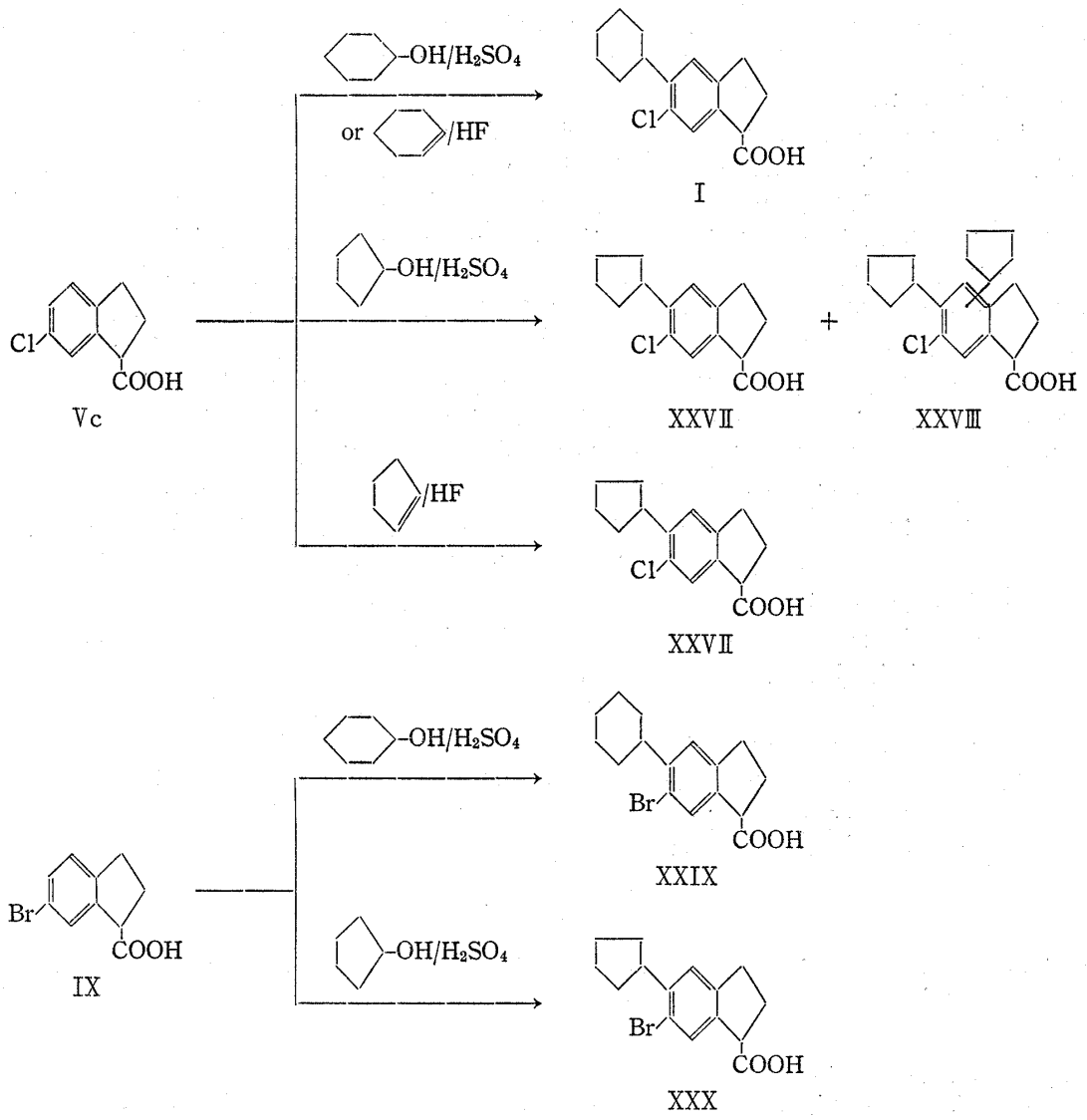


Chart 6

17) S.I. Sergieuskaya and N.P. Volynsky, *J. Gen. Chem. USSR*, **22**, 1035 (1952) [*C.A.*, **47**, 8053*a* (1953)].

Subsequently, some electrophilic substitution reactions of 1,2,3,4-tetrahydro-1-naphthoic acid (XXIV) were undertaken for the comparative study. Although the acetylation of ethyl 1,2,3,4-tetrahydro-1-naphthoate (XXV) gave ethyl 7-acetyl-1,2,3,4-tetrahydro-1-naphthoate (XXVI) as the main product, the chlorination of XXIV proceeded with less selectivity giving a mixture of chlorinated products, which could not be separated by fractional recrystallization. It has been reported by Sergieuskaya and Volynsky that the nitration of XXIV gave an about 1:1 mixture of 5- and 7-nitro derivatives.[17] Thus, the α-position in 1,2,3,4-tetrahydro-1-naphthoic acid (XXIV) seems to be more reactive toward electrophilic substitution reaction in contrast to the α-position of 1-indancarboxylic acid (IV).

Several methods have already been reported with respect to the synthesis of TAI-284(I), a potent antiinflammatory agent.[3,18] In all the methods, however, I was obtained *via* a number of steps starting from cyclohexylbenzene. We postulated that the process would be much simplified if a cyclohexyl group could be introduced selectively at the 5-position of the compound Vc.

Therefore, cyclohexylation of Vc was examined under a variety of conditions, *e.g.* cyclohexanol or cyclohene in strong acid such as sulfuric acid and hydrogen fluoride, and cyclohexyl chloride in the presence of a Lewis acid. Of these conditions, the treatment of Vc with cyclohexene in hydrogen fluoride or cyclohexanol in concentrated sulfuric acid was found to be effective for the conversion of Vc into I. Under these conditions, the cyclohexylation occurred predominantly at the 5-position. The result appears to be reasonable in view of the *ortho* and *para* directing property of the chlorine substituent along with the Mills-Nixon effect. Similarly, 6-bromo-1-indancarboxylic acid (IX) was converted into 6-bromo-5-cyclohexyl-1-indancarboxylic acid (XXIX)[3] by the reaction with cyclohexanol in concentrated sulfuric acid.

Cyclopentylation of Vc was also investigated under the similar conditions and somewhat different results were observed. Thus, when cyclopentylation was carried out using cyclopentene in hydrogen fluoride, 6-chloro-5-cyclopentyl-1-indancarboxylic acid (XXVII) was obtained as the sole product. However, the reaction of Vc with cyclopentanol in concentrated sulfuric acid gave, in addition to the desired product (XXVII), a considerable amount of by-product (XXVIII), which proved to be a mixture of 6-chloro-4,5-dicyclopentyl-1-indancarboxylic acid and 6-chloro-5,7-dicyclopentyl-1-indancarboxylic acid from the NMR spectrum. On the other hand, cyclopentylation of bromo analog (IX) gave solely 6-bromo-5-cyclopentyl-1-indancarboxylic acid (XXX) under the similar conditions, accompanied by no dicyclopentylated products such as XXVIII. This difference in the results of cyclopentylation of Vc and IX could be interpreted in terms of steric effects of halo-substituents. The bromine and cyclopentyl group in the compound XXX may bend away from each other, so the second cyclopentyl group is inhibited to approach the compound XXX.

Compounds synthesized in the present paper were tested for antiinflammatory activity using the carrageenin-induced foot edema method in rats.[19] Among them, XXVII and XXVIII showed approximately a half and a quarter antiinflammatory activity of I, respectively. 6-Acyl, thiazolyl and aminosulfonyl derivatives showed no significant activity.[20]

Benzoylation of IV is now under investigation and will be reported in a subsequent paper.

Experimental[21]

Chlorination of 1-Indancarboxylic Acid (IV) (Table I)——a) General Procedure for Entry 1—6; To a stirred, ice-cooled mixture of 0.81 g (5 mmol) of IV and 5 mmol of a catalyst ($FeCl_3$, $TiCl_4$, $ZnCl_2$ and $SnCl_4$)

18) P.F. Juby, W.R. Goodwin, T.W. Hudyma, and R.A. Partyka, *J. Med. Chem.*, **15**, 1297 (1972); Y. Sawa, T. Hattori, Y. Kawakami, S. Katsube, and A. Goto, *Yakugaku Zasshi*, **96**, 653 (1976).
19) C.A. Winter, E.A. Risley, and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
20) K. Kawai, S. Kuzuna, unpublished.
21) Melting points and boiling points were uncorrected. IR spectra were obtained with a Hitachi-215 spectrophotometer and NMR spectra with a Varian A-60 spectrometer using TMS as an internal standard.

in 5 ml of a solvent was added dropwise a solution of 0.53 g (7.5 mmol) of Cl_2 in 7 ml of a solvent. The mixture was stirred for 1.3 hr under cooling and then poured onto ice-water. The mixture was extracted with ether and the extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was treated with bis(trimethylsilyl)acetamide and submitted to the analysis with gas chromatography.

b) Entry 7: To a stirred, ice-cooled solution of 0.81 g (5 mmol) of IV in 10 ml of dimethylformamide was added 0.99 g (7.5 mmol) of N-chlorosuccinimide. The mixture was stirred for 1 hr at room temperature and then 6 hr at 50°. After cooling, the mixture was poured into water. The mixture was extracted with ether and the extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was treated with bis(trimethylsilyl)acetamide and then analyzed by gas chromatography.

c) Entry 8: The reaction was carried out in an atmosphere of nitrogen. To a stirred, ice-cooled solution of 0.81 g (5 mmol) of IV in 30 ml of CH_2Cl_2 was added 0.90 g (5 mmol) of $TiCl_4$. To the resulting mixture was added dropwise a solution of 0.87 g (5 mmol) of *m*-chloroperbenzoic acid in 5 ml of CH_2Cl_2 over a 20 minute period. The mixture was stirred for 5 hr at room temperature and then poured onto ice-water. The mixture was extracted with CH_2Cl_2 and the extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was treated with bis(trimethylsilyl)acetamide and submitted to the analysis with gas chromatography.

Preparation of (Chlorophenyl)succinic Anhydrides (VII)——A suspension of 22.9 g of (2-chlorophenyl)-succinic acid (VId)[22] in 150 ml of acetic anhydride was heated under reflux for 2 hr. After cooling, the solution was concentrated to dryness under reduced pressure. The residue was recrystallized from benzene to give 14 g (60.5%) of (2-chlorophenyl)succinic anhydride (VIId), mp 119—120°. *Anal.* Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35; Cl, 16.84. Found: C, 57.04; H, 3.36; Cl, 16.86. IR ν_{max}^{Nujol} cm^{-1}: 1860, 1780 (C=O).

By the similar procedures were prepared the following two derivatives: (3-Chlorophenyl)succinic anhydride (VIIa), bp 161° (0.5 mmHg). *Anal.* Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35; Cl, 16.84. Found: C, 57.06; H, 3.43; Cl, 16.85. IR ν_{max}^{Neat} cm^{-1}: 1865, 1790 (C=O). (4-Chlorophenyl)succinic anhydride (VIIb), mp 63—65° (from ether–hexane, 74%). *Anal.* Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35; Cl, 16.84. Found: C, 57.01; H, 3.17; Cl, 16.94. IR ν_{max}^{Nujol} cm^{-1}: 1860, 1780 (C=O).

Cyclization of (3-Chlorophenyl)succinic Anhydride (VIIa)——To a stirred, ice-cooled suspension of 30.4 g of pulverized anhydrous $AlCl_3$ in 140 ml of CH_2Cl_2 was added dropwise a solution of 16.0 g of VIIa in 70 ml of CH_2Cl_2 over 2-hr period. The mixture was stirred under cooling for 4 hr and then at room temperature for further 2 hr. To the stirred, ice-cooled reaction mixture was added dropwise 250 ml of dil. HCl. After standing for 12 hr at room temperature, $CHCl_3$ was added to the mixture, After shaking well, the resulting precipitate was collected by filtration, dissolved in AcOEt and then extracted twice with 5% aqueous Na_2CO_3. The extract was washed with ether and acidified with dil. HCl. The resulting precipitate was collected by filtration, dried and recrystallized from benzene to give 9.4 g (59%) of 6-chloro-3-oxo-1-indancarboxylic acid (VIIIc), mp 148—151°. *Anal.* Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35; Cl, 16.84. Found: C, 57.18; H, 3.16; Cl, 16.84. IR ν_{max}^{Nujol} cm^{-1}: 1730 (C=O), 1710 (C=O). NMR (in $CDCl_3$+d_6-DMSO) δ: 7.77 (1H, s, C_7–H), 7.69 (1H, d, J=8.5 Hz, C_4–H), 7.40 (1H, d, J=8.5 Hz, C_5–H), 4.25 (1H, q, C_1–H), 2.96 (2H, q, C_2–H). The CH_2Cl_2–$CHCl_3$ layer obtained above as the filtrate was washed with water and then extracted with 5% aqueous Na_2CO_3. The extract was washed with ether and acidified with dil. HCl. The resulting precipitate was extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from benzene to give 1.1 g of crystals, further recrystallization of which from AcOEt gave 0.58 g (3.6%) of 4-chloro-3-oxo-1-indancarboxylic acid (VIIIa), mp 171—174°. *Anal.* Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35; Cl, 16.84. Found: C, 57.16; H, 3.37; Cl, 16.48. IR ν_{max}^{Nujol} cm^{-1}: 1735 (C=O), 1700 (C=O). NMR (in d_6-DMSO) δ: 7.38—7.77 (3H, m, aromatic protons), 4.28 (1H, t, C_1–H), 2.90 (2H, d, C_2–H).

5-Chloro-3-oxo-1-indancarboxylic Acid (VIIIb)——To a stirred, ice-cooled suspension of 24 g of pulverized anhydrous $AlCl_3$ in 100 ml of CH_2Cl_2 was added dropwise a solution of 12.6 g of VIIb in 50 ml of CH_2Cl_2 over a 1-hr period. The mixture was stirred for 4 hr at room temperature and poured onto ice-water. The organic layer was separated and the aqueous layer was extracted with AcOEt. The organic layers were combined. After washing with water, the organic layer was extracted with 5% aqueous $NaHCO_3$. The extract was washed with ether and acidified with dil. HCl. The resulting precipitate was extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was crystallized from hexane to give 10.5 g (83%) of VIIIb. The analytical sample was obtained by further recrystallization from AcOEt, mp 150—153°. *Anal.* Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35; Cl, 16.84. Found: C, 56.88; H, 3.38; Cl, 17.01. IR ν_{max}^{Nujol} cm^{-1}: 1725 (C=O), 1705 (C=O). NMR (in d_6-DMSO) δ: 7.6—7.8 (3H, m, aromatic protons), 4.34 (1H, t, J=5 Hz, C_1–H), 2.95 (2H, d, J=5 Hz, C_2–H).

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7-Chloro-3-oxo-1-indancarboxylic Acid (VIIId)——To a stirred, ice-cooled suspension of 55 g of pulverized anhydrous $AlCl_3$ in 200 ml of CH_2Cl_2 was added dropwise a solution of 26 g of VIId in 300 ml of CH_2Cl_2 over a 15-minute period. The mixture was stirred for 4 hr at room temperature and then poured onto ice-water After standing overnight at room mperature, the resulting precipitate was collected by filtration and dried to give 16.2 g of VIIId as solid. The organic layer of the filtrate was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give further 6.0 g of VIIId (Total yield: 22.2 g, 85%). The analytical sample was obtained by recrystallization from 50% MeOH, mp 182—185°. *Anal.* Calcd. for $C_{10}H_7ClO_3$: C, 57.03; H, 3.35; Cl, 16.84. Found: C, 56.88; H, 3.39; Cl, 16.80. IR ν_{max}^{Nujol} cm^{-1}: 1740 (C=O), 1690 (C=O). NMR (in d_6-DMSO) δ: 7.40—7.72 (3H, m, aromatic protons), 4.33 (1H, dd, J=8 Hz, 3 Hz, C_1–H), 3.13 (1H, dd, J=19 Hz, 8 Hz, C_2–H), 2.74 (1H, dd, J=19 Hz, 3 Hz, C_2–H).

Chloro-1-indancarboxylic Acids (V)——a) From VIII: Zn-amalgam prepared from 5.0 g of Zn powder and 0.5 g of $HgCl_2$[3b] was added to a suspension of 2.1 g of VIIId in 10 ml of toluene and 8 ml of conc. HCl and the mixture was heated under reflux for 6 hr with stirring. After cooling and diluting with water, the reaction mixture was extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from cyclohexane to give 1.3 g (69%) of 7-chloro-1-indancarboxylic acid (Vd), mp 117—119°. *Anal.* Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; 18.03. Found: C, 61.18; H, 4.52; Cl, 18.07. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 7.12 (3H, s, aromatic protons), 4.12 (1H, t, J=6 Hz, C_1–H).

By the similar procedures were obtained the following compounds: 4-Chloro-1-indancarboxylic acid (Va), mp 114—117° (from hexane, 62%). *Anal.* Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 61.28; H, 4.59. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 7.05—7.38 (3H, m, aromatic protons), 4.08 (1H, t, J=6 Hz, C_1–H).

5-Chloro-1-indancarboxylic Acid (Vb): mp 75.5—77.5° (from petroleum ether, 56%). *Anal.* Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 61.00; H, 4.49; Cl, 17.93. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 7.32 (1H, d, J=8 Hz, C_7–H), 7.18 (1H, s, C_4–H), 7.12 (1H, d, J=8 Hz, C_6–H), 3.99 (1H, t, J=7 Hz, C_1–H).

6-Chloro-1-indancarboxylic Acid (Vc): mp 125—128° (from hexane, 56%). *Anal.* Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 60.85; H, 4.53; Cl, 17.97. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 7.38 (1H, s, C_7–H), 7.18 (1H, d, J=8 Hz, C_5–H), 7.08 (1H, d, J=8 Hz, C_4–H), 4.02 (1H, t, J=7 Hz, C_1–H).

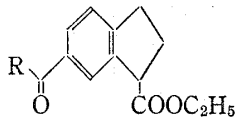
b) From IV: To a stirred, ice-cooled mixture of 16.2 g of IV and 16.2 g of $FeCl_3$ in 300 ml of acetonitrile was added dropwise a solution of 8.52 g of Cl_2 in 120 ml of acetonitrile. Stirring and cooling were continued for 4 hr. A solution of 2.13 g of Cl_2 in 30 ml of acetonitrile was further added dropwise to the reaction mixture. After stirring for additional 1.5 hr, the mixture was poured into 600 ml of 6% HCl. After removal of acetonitrile under reduced pressure, the mixture was extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from hexane to give 11.3 g (57.5%) of 6-chloro-1-indancarboxylic acid (Vc), mp 125—127°. The IR and NMR spectra of this compound were identical with those of an authentic sample obtained from VIIIc.

Bromination of 1-Indancarboxylic Acid (IV)——To a stirred, ice-cooled mixture of 8.1 g of IV and 8.1 g of $FeCl_3$ in 300 ml of CCl_4 was added dropwise a solution of 8.8 g of Br_2 in 100 ml of CH_2Cl_2 over a 1-hr period. The mixture was stirred for 3 hr under cooling and then further 1.5 hr at room temperature. The mixture was poured into 500 ml of 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 crystallized from hexane to give 5.2 g (45%) of 6-bromo-1-indancarboxylic acid (IX). The analytical sample was obtained by recrystallization from cyclohexane, mp 142—145°. *Anal.* Calcd. for $C_{10}H_9BrO_2$: C,49.81; H, 3.76; Br, 33.15. Found: C, 49.68; H, 3.62; Br, 33.12. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 7.57 (1H, s, C_7–H), 7.36 (1H, d, J=8 Hz, C_5–H), 7.08 (1H, d, J=8 Hz, C_4–H). The mother liquor was concentrated to dryness. The residue was recrystallized from hexane to give 4-bromo-1-indancarboxylic acid (X), mp 121—125°. *Anal.* Calcd. for $C_{10}H_9BrO_2$: C, 49.81; H, 3.76. Found: C, 49.44; H, 3.55. IR ν_{max}^{Nujol} cm^{-1}: 1715 (C=O). NMR (in $CDCl_3$) δ: 7.50—7.00 (3H, m, aromatic protons).

Ethyl 6-Acyl-1-indancarboxylates (XII) (Table II)——General Procedure: To a stirred, ice-cooled suspension of 5.3 g of pulverized anhydrous $AlCl_3$ and 3.8 g of ethyl 1-indancarboxylate (XI)[14] in 45 ml of CS_2 was added dropwise a solution of 0.04 mol of acyl chloride in 15 ml of CS_2. The mixture was stirred for 3.5 hr at room temperature and poured onto ice-water. The mixture was extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual oil was distilled to give XII.

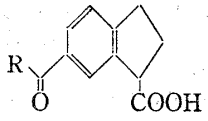
6-Acyl-1-indancarboxylic Acids (XIII) (Table III)——a) General Procedure: To 80 ml of conc. HCl was added 2.5 g of XII. The mixture was heated under reflux for 3 hr. After cooling, the mixture was extracted with ether. After washing with water, the ethereal layer was extracted with 1% aqueous NaOH. The aqueous 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 cyclohexane to give XIII. Compounds XIIIa—d were prepared by this method from the corresponding ethyl esters, XIIa—d.

Table II. Ethyl 6-Acyl-1-indancarboxylate (XIIa—f)



Compd. No.	R	bp (°C) (mmHg)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
XIIa	C_2H_5	141—144 (0.4)	77	$C_{15}H_{18}O_3$	73.14	7.37	72.96	7.40
XIIb	C_3H_7	142—144 (0.3)	52	$C_{16}H_{20}O_3$	73.82	7.74	74.32	7.58
XIIc	Iso-C_3H_7	136—138 (0.3)	46	$C_{16}H_{20}O_3$	73.82	7.74	73.97	7.78
XIId	Iso-C_4H_9	153—156 (0.8)	57	$C_{17}H_{22}O_3$	74.42	8.08	73.86	7.88
XIIe	Cyclopentyl	173—176 (0.3)	81	$C_{18}H_{22}O_3$	75.49	7.74	75.25	7.66
XIIf	Cyclohexyl	183—185 (0.2)	39	$C_{19}H_{24}O_3$	75.97	8.05	75.84	8.23

Table III. 6-Acyl-1-indancarboxylic Acids (XIIIa—f)



Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	Calcd. (Found) H	NMR (in $CDCl_3$) δ:
XIIIa	C_2H_5	112—113	44	$C_{13}H_{14}O_3$	71.54 (71.93)	6.47 (6.37)	7.98 (1H, s, C_7–H) 7.82 (1H, d, J=8 Hz, C_5–H) 7.28 (1H, d, J=8 Hz, C_4–H) 4.08 (1H, t, J=7 Hz, C_1–H)
XIIIb	C_3H_7	96— 98	75	$C_{14}H_{16}O_3$	72.39 (72.46)	6.94 (6.86)	7.98 (1H, s, C_7–H) 7.82 (1H, d, J=8 Hz, C_5–H) 7.28 (1H, d, J=8 Hz, C_4–H) 4.08 (1H, t, J=7.5 Hz, C_1–H)
XIIIc	Iso-C_3H_7	89— 91	80	$C_{14}H_{16}O_3$	72.39 (72.43)	6.94 (7.09)	7.97 (1H, s, C_7–H) 7.82 (1H, d, J=8 Hz, C_5–H) 7.28 (1H, d, J=8 Hz, C_4–H) 4.07 (1H, t, J=7 Hz, C_1–H)
XIIId	Iso-C_4H_9	95— 97	49	$C_{15}H_{18}O_3$	73.14 (73.30)	7.37 (7.38)	7.98 (1H, s, C_7–H) 7.82 (1H, d, J=8 Hz, C_5–H) 7.28 (1H, d, J=8 Hz, C_4–H) 4.09 (1H, t, J=7 Hz, C_1–H)
XIIIe	Cyclopentyl	71— 72	72	$C_{16}H_{18}O_3$	73.89 (74.11)	7.02 (7.02)	8.03 (1H, s, C_7–H) 7.88 (1H, d, J=8 Hz, C_5–H) 7.32 (1H, d, J=8 Hz, C_4–H) 4.10 (1H, t, J=7 Hz, C_1–H)
XIIIf	Cyclohexyl	94— 96	25	$C_{17}H_{20}O_3$	74.85 (74.99)	7.22 (7.40)	8.00 (1H, s, C_7–H) 7.85 (1H, d, J=8 Hz, C_5-H) 7.32 (1H, d, J=8 Hz, C_4- H) 4.10 (1H, t, J=7 Hz, C_1–H)

b) A mixture of 40 ml of EtOH, 33 ml of 1/2 N NaOH and 4.1 g of XII was refluxed for 30 min under nitrogen. After EtOH was evaporated under reduced pressure, the mixture was washed with ether and acidified with dil. HCl. The resulting precipitate was extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Recrystallization of the residue from hexane to give XIII. By this method, compounds XIIIe and XIIIf were prepared from XIIe and XIIf, respectively.

Ethyl 6-Chloroacetyl-1-indancarboxylate (XIV)——To a stirred, ice-cooled mixture of 3.8 g of XI and 5.3 g of pulverized anhydrous $AlCl_3$ in 20 ml of CS_2 was added dropwise 9.0 g of chloroacetyl chloride. The mixture was stirred for 2 hr at room temperature and then poured onto ice-water. The mixture was extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 5.3 g (100%) of XIV. No by-product was detected by means of NMR spectroscopy. NMR (in $CDCl_3$) δ: 8.00 (1H, s, C_7–H), 7.81 (1H, d, $J=8$ Hz, C_5–H), 7.31 (1H, d, $J=8$ Hz, C_4–H), 4.67 (2H, s, $-CH_2-Cl$), 4.08 (1H, t, $J=7$ Hz, C_1–H).

Ethyl 6-(2-Amino-4-thiazolyl)-1-indancarboxylate (XV)——A mixture of 1.3 g of XIV and 0.38 g of thiourea in 10 ml of EtOH was heated for 10 min under reflux. After cooling, the mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was washed with saturated aqueous $NaHCO_3$ and water, and dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure. The residue was recrystallized from benzene to give 0.83 g (59%) of XV as colorless granules, mp 140.5—141.5°. *Anal.* Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.47; H, 5.59; N, 9.72; S, 11.12. Found: C, 62.32; H, 5.59; N, 9.85; S, 10.89. IR ν_{max}^{Nujol} cm^{-1}: 3420 (N–H), 3325 (N–H), 1720 (C=O). NMR (in $CDCl_3$) δ: 7.76 (1H, s, C_7–H), 7.63 (1H, d, $J=8$ Hz, C_5–H), 7.13 (1H, d, $J=8$ Hz, C_4–H), 6.54 (1H, s, $C_{5'}$–H), 5.83 (2H, s, NH_2), 4.01 (1H, t, $J=7$ Hz, C_1–H).

Ethyl 6-(2-Methyl-4-thiazolyl)-1-indancarboxylate (XVI)——A mixture of 1.95 g of XIV and 0.67 g of thioacetamide in 25 ml of dry benzene was heated for 2 hr under reflux. After cooling, the mixture was poured into water and 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 eluent to give 0.72 g (34%) of XVI as an oil. *Anal.* Calcd. for $C_{16}H_{17}NO_2S$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.55; H, 5.93; N, 5.26. IR ν_{max}^{Neat} cm^{-1}: 1730 (C=O). NMR (in $CDCl_3$) δ: 7.83 (1H, s, C_7–H), 7.71 (1H, d, $J=8$ Hz, C_5–H), 7.19 (1H, s, $C_{5'}$–H), 7.12 (1H, d, $J=8$ Hz, C_4–H), 4.40 (3H, s, CH_3), 4.00 (1H, t, $J=7$ Hz, C_1–H).

Ethyl 6-Chlorosulfonyl-1-indancarboxylate (XVIII)——To stirred, ice-cooled 19.0 g of XI was added 30 ml of chlorosulfonic acid. The mixture was stirred for 4 hr at room temperature and poured onto ice-water. 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 chromatographed on silica gel using $CHCl_3$ as the eluent to give 21.4 g (74.1%) of XVIII as an oil. *Anal.* Calcd. for $C_{12}H_{13}ClO_4S$: C, 49.92; H, 4.54; Cl, 12.28; S, 11.10. Found: C, 49.95; H, 4.51; Cl, 12.24; S, 10.95. IR ν_{max}^{Neat} cm^{-1}: 1725 (C=O). NMR (in $CDCl_3$) δ: 8.06 (1H, s, C_7–H), 7.88 (1H, d, $J=8$ Hz, C_5–H), 7.45 (1H, d, $J=8$ Hz, C_4–H), 4.11 (1H, t, $J=8$ Hz, C_1–H).

6-Aminosulfonyl-1-indacarboxylic Acid (XIX)——A solution of 11.6 g of XVIII in 80 ml of benzene was heated with 120 ml of 28% aqueous NH_3 for 1.5 hr under reflux. After cooling, the organic layer was separated. The aqueous layer was washed with benzene and acidified with 50 ml of conc. HCl. The resulting precipitate was collected by filtration and recrystallized from water to give 1.53 g (15.9%) of XIX, mp 175—186°. *Anal.* Calcd. for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.60; N, 5.81. Found: C, 49.72; H, 4.54; N, 5.73. IR ν_{max}^{Nujol} cm^{-1}: 3370 (N–H), 3270 (N–H), 1710 (C=O). NMR (in d_6-DMSO) δ: 7.82 (1H, s, C_7–H), 7.67 (1H, d, $J=8$ Hz, C_5–H), 7.36 (1H, d, $J=8$ Hz, C_4–H), 7.22 (2H, s, NH_2), 4.03 (1H, t, $J=8$ Hz, C_1–H).

Nitration of Ethyl 1-Indancarboxylate (XI)——To a stirred solution of 1.5 g of XI in 20 ml of acetic anhydride was added at −5° a mixture of 4 ml of HNO_3 ($d=1.38$) and 8 ml of acetic anhydride. The mixture was stirred for 1.5 hr at −5° and then poured onto ice-water. The mixture was extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give 1.94 g of an oil, which proved to be a 2:1 mixture of ethyl 6-nitro-1-indancarboxylate (XX) and ethyl 4-nitro-1-indancarboxylate (XXI) from the NMR spectrum. NMR (in $CDCl_3$) δ: 7.3—8.3 (3H, m, aromatic protons), 4.0—4.5 (3H, m, C_1–H and $-C\underline{H}_2-CH_3$), 3.35—3.65 (2/3H, m, C_3–H of XXI), 2.90—3.30 (4/3H, m, C_3–H of XX), 2.3—2.7 (2H, m, C_2–H), 1.20—1.43 (3H, double triplet, CH_3).

Ethyl 6-Acetylamino-1-indancarboxylate (XXIII)——A solution of the above mixture of XX and XXI (1.6 g) in 50 ml of EtOH was catalytically hydrogenated over 5% Pd–C (0.3 g) under atmospheric pressure at room temperature until 520 ml of hydrogen was absorbed. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. To the residue were added 0.3 g of AcOK and 20 ml of acetic anhydride. The mixture was heated for 2 hr at 60°. After cooling, the mixture was poured into water 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 cyclohexane (1:1) to give 0.31 g of XXIII as colorless prisms, mp 124—125°. *Anal.* Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.18; H, 6.89; N, 5.64. IR ν_{max}^{Nujol} cm^{-1}: 3400 (NH), 1740 (C=O), 1660 (C=O). NMR (in $CDCl_3$) δ: 7.1—7.8 (3H, m, aromatic protons), 4.00 (1H, t, $J=7$ Hz, C_1–H), 2.10 (3H, s, $-CO-CH_3$).

Ethyl 7-Acetyl-1,2,3,4-tetrahydro-1-naphthoate (XXVI)——To a stirred, ice-cooled suspension of 4.0 g of pulverized anhydrous $AlCl_3$ and 2.0 g of ethyl 1,2,3,4-tetrahydro-1-naphthoate (XXV) in 40 ml of CS_2 was added dropwise a solution of 1.6 g of acetyl chloride in 10 ml of CS_2. The mixture was stirred for 1 hr at room temperature and poured onto ice-water. The mixture was extracted with $CHCl_3$. The extract was washed with water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give XXVI as an oil in an almost quantitative yield. No by-product was detected by means of NMR spectroscopy. NMR (in $CDCl_3$) δ: 7.90 (1H, s, C_8–H), 7.80 (1H, d, $J=8$ Hz, C_6–H), 7.25 (1H, d, $J=8$ Hz, C_5–H), 3.90 (1H, t, $J=4$ Hz, C_1–H).

6-Chloro-5-cyclohexyl-1-indancarboxylic Acid (I)——a) To a stirred solution of 5.9 g of Vc in 30 ml of conc. H_2SO_4 was added dropwise 8.2 ml of cyclohexanol over a 30-minute period at 25°. The mixture was stirred for 1 hr at the same temperature and then poured into water. The mixture was shaken with ether and the ethereal layer was extracted with 5% aqueous NaOH. The extract was acidified with dil. HCl and extracted with AcOEt. The extract was washed with 1% aqueous $NaHCO_3$ and then water, dried over anhydrous $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was recrystallized from hexane to give 3.41 g (40.7%) of I as colorless needles, mp 150—152° (lit.[3] 151—152°). The IR and NMR spectra of this compound were indentical with those of an authentic sample.[3]

b) Compound Vc (1.0 g) and 2.1 g of cyclohexene were dissolved in 20 ml of HF and the solution was kept at 20° for 3 hr with stirring. After evaporation of HF, to the residue was added ether. The ethereal solution was washed with water and then extracted with 5% aqueous NaOH. The extract was acidified with dil. HCl and extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from hexane to give 0.49 g (34.4%) of I as colorless needles, mp 150—152° (lit.[3] 151—152°). The IR and NMR spectra of this compound were identical with those of an authentic sample.[3]

6-Chloro-5-cyclopentyl-1-indancarboxylic Acid (XXVII)——A solution of Vc (0.4 g) and cyclopentene in 10 ml of HF was stirred for 2.5 hr under cooling with ice-water. After evaporation of HF, the residue was dissolved in ether. The ethereal solution was washed with water and then extracted with 4% aqueous NaOH. The extract was washed with ether, acidified with dil. HCl and extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from hexane to give 0.18 g (33%) of XXVII as colorless needles, mp 129—131°. *Anal.* Calcd. for $C_{15}H_{17}ClO_2$: C, 68.05; H, 6.47; Cl, 13.39. Found: C, 67.78; H, 6.43; Cl, 13.27. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 7.39 (1H, s, C_7–H), 7.15 (1H, s, C_4–H), 4.00 (1H, t, $J=7$ Hz, C_1–H).

Cyclopentylation of Vc with Cyclopentanol in Sulfuric Acid——To a stirred, ice-cooled solution of 0.5 g of Vc in 2.5 ml of conc. H_2SO_4 was added dropwise 0.7 ml of cyclopentanol. The mixture was stirred for 2 hr under ice-cooling and further 2 hr at room temperature, and then poured onto ice-water. The mixture was extracted with ether and the ethereal layer was extracted with 5% aqueous NaOH. The extract was washed with ether and acidified with dil. HCl. The mixture was extracted with ether. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel impregnated with 1% oxalic acid using benzene–AcOEt (5: 1) as the eluent. Evaporation of the first elution band gave 0.2 g of a mixture of 6-chloro-4,5-dicyclopentyl-1-indancarboxylic acid and 6-chloro-5,7-dicyclopentyl-1-indancarboxylic acid (XXVIII), mp 157—191°. *Anal.* Calcd. for $C_{20}H_{25}ClO_2$: C, 72.16; H, 7.57; Cl, 10.65. Found: C, 71.97; H, 7.65; Cl, 10.66. The subsequent fraction gave 0.14 g (21%) of XXVII, mp 129—131°. The IR and NMR spectra of this compound were identical with those of compound obtained above.

6-Bromo-5-cyclohexyl-1-indancarboxylic Acid (XXIX)——To a stirred, ice-cooled solution of 0.5 g of IX in 2.5 ml of conc. H_2SO_4 was added dropwise 0.7 ml of cyclohexanol. The mixture was stirred for 4 hr at 20° and then poured onto ice-water. The mixture was shaken with ether. The ethereal layer was washed with water and extracted with 5% aqueous NaOH. The extract was washed with ether and acidified with dil. HCl. The mixture was extracted with AcOEt. The extract was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from hexane to give 0.25 g (36%) of XXIX as colorless needles, mp 160—164° (lit.[3b] 160—164°). The IR and NMR spectra of this compound were identical with those of an authentic sample.[3b]

6-Bromo-5-cyclopentyl-1-indancarboxylic Acid (XXX)——To a stirred, ice-cooled solution of 0.5 g of IX in 2.5 ml of conc. H_2SO_4 was added dropwise 0.7 ml of cyclopentanol. The mixture was stirred for 4 hr at 20° and then poured onto ice-water. The mixture was extracted with ether. The ethereal layer was washed with water and extracted with 5% aqueous NaOH. The extract was washed with ether and acidified with dil. HCl. The mixture was 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 impregnated with 1% oxalic acid using benzene–AcOEt (5: 1) as the eluent to give 0.17 g (27%) of XXX as colorless needles, mp 145—147°. *Anal.* Calcd. for $C_{15}H_{17}BrO_2$: C, 58.28; H, 5.54; Br, 25.85. Found: C, 58.30; H, 5.51; Br, 25.91. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O). NMR (in $CDCl_3$) δ: 7.60 (1H, s, C_7–H), 7.15 (1H, s, C_4–H), 4.00 (1H, t, $J=7.5$ Hz, C_1–H).

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