

- (13) Dr. A. Fürst of F. Hoffmann-La Roche and Co., A. G., personal communication.  
 (14) The British Drug House Ltd., Belgian Patent 622,955; *Chem. Abstr.*, **60**, 9336a (1964).  
 (15) R. Wiechert and F. Neumann, *Arzneim.-Forsch.*, **15**, 244 (1965).  
 (16) F. Hoffmann-La Roche and Co., A.G., South African Patent 6804457; *Chem. Abstr.*, **72**, 21840 (1970).  
 (17) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *J. Amer. Chem. Soc.*, **81**, 3485 (1959).  
 (18) A. Boris, L. De Martino, and T. Trmal, *Acta Endocrinol.*, **63**, 476 (1970).  
 (19) R. van Strik, "Quantitative Methods in Pharmacology," H. de Jonge, Ed., North Holland Publishing Co., Amsterdam, 1961, p 88.  
 (20) Th. J. de Boer and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **73**, 229 (1964).

## Antiinflammatory Activity of Some Indan-1-carboxylic Acids and Related Compounds

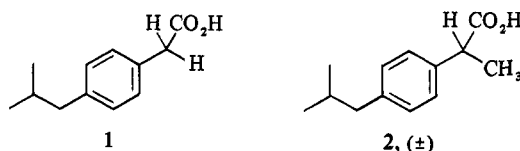
P. F. Juby,\* W. R. Goodwin, T. W. Hudyma, and R. A. Partyka

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201. Received May 31, 1972

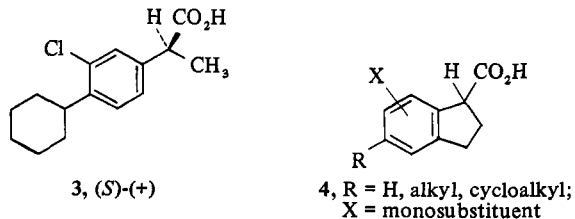
A series of indan-1-carboxylic acids and derivatives was prepared as potential antiinflammatory agents. Many of the indan compounds showed potent antiinflammatory activity when tested orally in the rat. Structure-activity relationships are discussed, and a resemblance is noted between structural requirements for these antiinflammatory agents and for certain plant growth regulators.

Of all the chemical classes that have been examined in recent years for potential nonsteroidal antiinflammatory agents, none has received wider attention than the aryl- and heteroarylalkanoic acids.<sup>1</sup> Features of a typical molecule which are important for activity include a carboxyl group separated by one or more carbon atoms from a flat, aromatic nucleus which is further substituted by a large lipophilic group.

Of particular interest have been the arylacetic acids. From lead compounds such as ibufenac<sup>2</sup> (1) have come ibuprofen<sup>3</sup> (2) and (*S*)-(+)-3-chloro-4-cyclohexyl- $\alpha$ -methylphenylacetic acid<sup>4</sup> (3). In this paper we now describe the synthesis of some indan-1-carboxylic acids (4) and related compounds, some of which have been found to exhibit potent antiinflammatory activity in the rat. Since our initial disclosure<sup>5</sup> of this work, papers have appeared<sup>6</sup> which confirm the antiinflammatory properties of 6-chloro-5-cyclohexylindan-1-carboxylic acid (17).

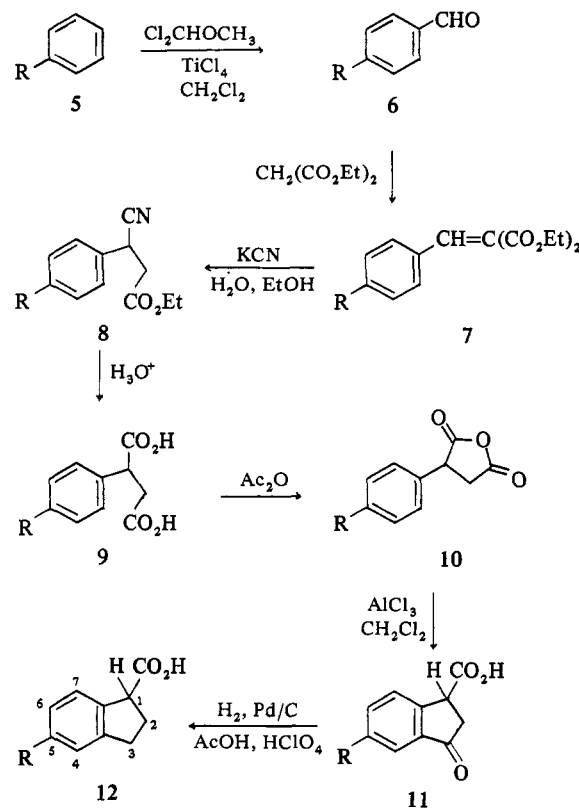


**Chemistry.** Our initial goal was to prepare 5-H-, 5-alkyl-, and 5-cycloalkylindan-1-carboxylic acids having the general structure 12. This was accomplished as outlined in Scheme I, and the compounds prepared are listed in Tables I-VI.



A more efficient, alternative synthesis (Scheme II) was developed for the 5-cyclohexyl compound 12e. 5-Cyclohexyl-1-indanone (15) was prepared from cyclohexylbenzene (13) and  $\beta$ -chloropropionyl chloride (14) by a method similar to the one described by Hart and Tebbe<sup>7</sup> for the preparation of 1-indanone. The indanone 15 was converted to 12e via the intermediate 16, an approach based on a general

Scheme I



procedure for the conversion of ketones to acids using 1,3-dithiane.<sup>8</sup> The overall yield from 13 to 12e was 37%.

Optimal antiinflammatory activity (see Structure-Activity Relationships) was found for the 5-cyclohexyl compound 12e which was selected for further modification. The 6-chloro derivative 17 (Table VI) was obtained by treatment of 12e with NCS in DMF.<sup>9</sup> The nmr spectrum of the monochloro product showed singlets at  $\delta$  7.20 (1 H) and 7.50

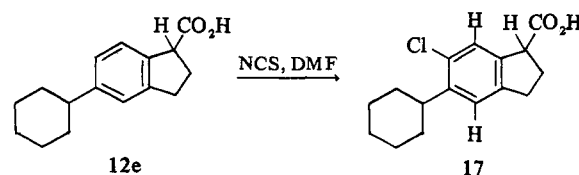
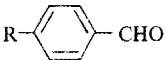


Table I. *p*-Alkylbenzaldehydes

					
No.	R	Bp (mm), °C	Yield, %	Formula	Analyses
6c	<i>i</i> -Bu <sup>a</sup>	48-50 (0.03)	60	C <sub>11</sub> H <sub>14</sub> O	C, H
6d	Cyclopentyl <sup>b</sup>	80-83 (0.03)	26	C <sub>12</sub> H <sub>14</sub> O	C, H
6f	Cycloheptyl <sup>c</sup>	117-117.5 (0.1)	40	C <sub>14</sub> H <sub>18</sub> O	C, H

<sup>a</sup>Nmr indicated para:ortho (7:3). <sup>b</sup>Nmr and glc indicated para:ortho (17:3). <sup>c</sup>Glc indicated para:ortho (8:1).

Table II. Diethyl *p*-Alkylbenzylidenemalonates

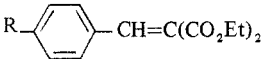
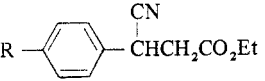
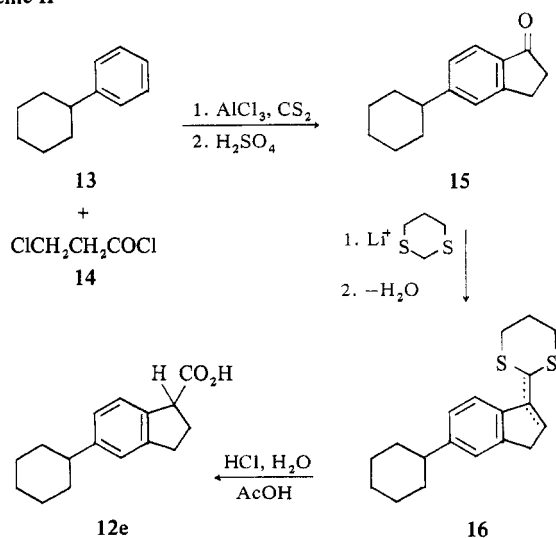
					
No.	R	Bp (mm), °C	Yield, %	Formula	Analyses
7b	<i>i</i> -Pr	130-135 (0.01)	92	C <sub>17</sub> H <sub>22</sub> O <sub>4</sub>	C, H
7c	<i>i</i> -Bu	128-129 (0.008)	74	C <sub>18</sub> H <sub>24</sub> O <sub>4</sub>	C, H
7d	Cyclopentyl	156-158 (0.01)	76	C <sub>19</sub> H <sub>24</sub> O <sub>4</sub>	C, H
7e	Cyclohexyl	172-174 (0.01)	71	C <sub>20</sub> H <sub>26</sub> O <sub>4</sub>	C, H
7f	Cycloheptyl	186 (0.03)	74	C <sub>21</sub> H <sub>28</sub> O <sub>4</sub>	C, H

Table III. Ethyl 3-Cyano-3-(*p*-alkylphenyl)propionates

					
No.	R	Bp (mm), °C	Yield, %	Formula	Analyses
8b	<i>i</i> -Pr	115-117 (0.01)	62	C <sub>15</sub> H <sub>19</sub> NO <sub>2</sub>	C, H, N
8c	<i>i</i> -Bu	125-128 (0.04)	52	C <sub>16</sub> H <sub>21</sub> NO <sub>2</sub>	C, H, N
8d	Cyclopentyl	139-140 (0.01)	66	C <sub>17</sub> H <sub>21</sub> NO <sub>2</sub>	C, H, N
8e	Cyclohexyl	160-161 (0.15)	54	C <sub>18</sub> H <sub>23</sub> NO <sub>2</sub>	C, H, N
8f	Cycloheptyl	164-166 (0.01)	75	C <sub>19</sub> H <sub>25</sub> NO <sub>2</sub>	C, H, N

Scheme II



ppm (1 H) indicating a para orientation for the aromatic hydrogen atoms.

Further nuclear substitution (see Table VI) of **12e** was obtained *via* direct nitration as outlined in Scheme III. Since only one (**19**) of the two nitro derivatives **18** and **19** could be isolated in a pure state, the position of each nitro group was inferred from an examination of the nmr spectra of the corresponding amino compounds. The spectrum of the 4-amino derivative **22** showed a pair of doublets ( $J = 8$  Hz) centered at  $\delta$  6.52 (1 H) and 6.83 ppm (1 H),

indicating an ortho orientation for the aromatic protons. The spectrum of the 6-amino derivative **23** showed a pair of singlets at  $\delta$  6.83 (1 H) and 7.05 ppm (1 H).

The position isomer **30** (Table VI) of **12e** was obtained *via* the sequence outline in Scheme IV.

Modifications were made on the cyclopentene ring of **12e** as outlined in Scheme V. The intermediate keto acid **11e** was reduced to a mixture of the *cis* and *trans* alcohols **31**. One isomer, **31a**, predominated (94%) and was purified. The other isomer **31b** could only be obtained contaminated with about 20% of **31a**. We were not able to assign structures to the isomers, the properties of which are shown in Table VI. The mixture of alcohols was dehydrated to the indene-1-carboxylic acid **32** (Table VII) by refluxing in toluene with TsOH for 5 min. Compound **32** was isomerized to the indene-3-carboxylic acid **33** (Table VII) either by refluxing with TsOH in toluene for 7 hr or by treatment with  $\text{CDCl}_3$ -DMSO- $d_6$  (1:1) at room temperature for 18 min.

Esters (**34-39**) of **12e** were prepared from the corresponding acid chloride by standard procedures and are listed in Table VI.

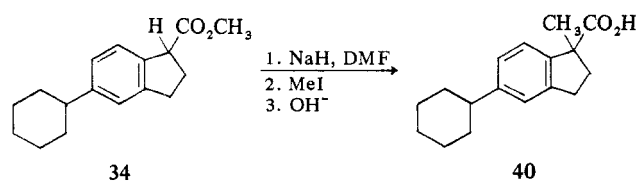


Table IV. *p*-Alkylphenylsuccinic Acids

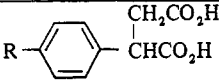
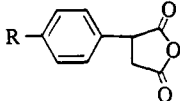
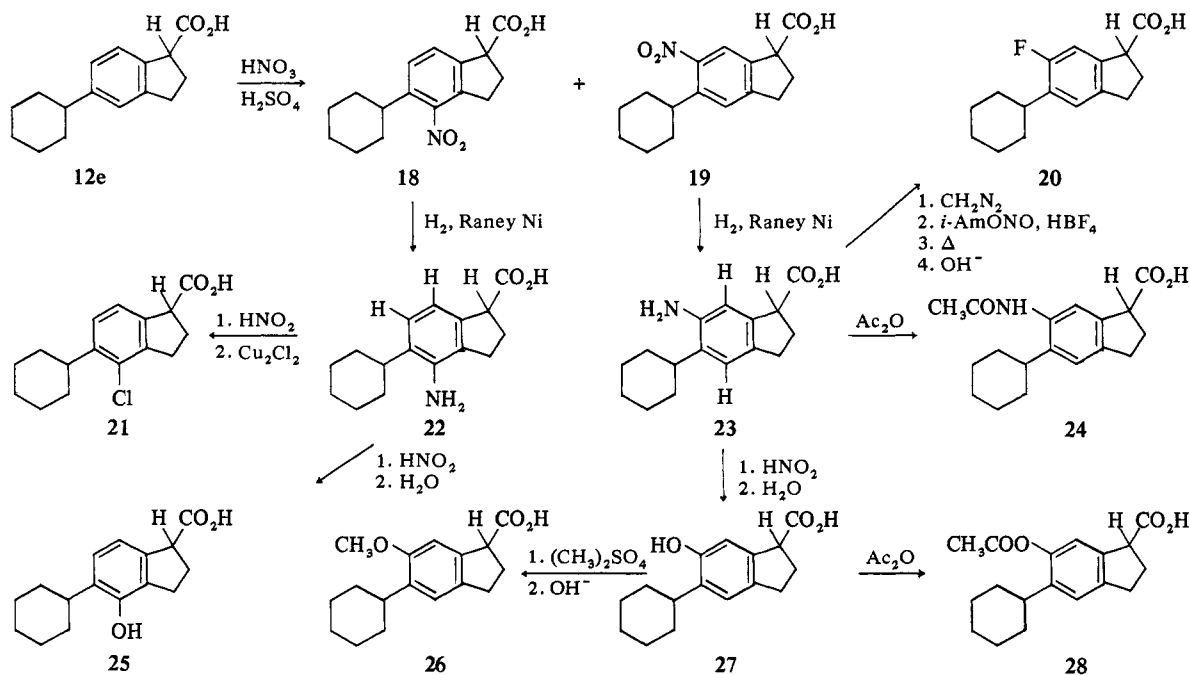
						
No.	R	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
9b	<i>i</i> -Pr	183–184	EtOAc	32	C <sub>13</sub> H <sub>16</sub> O <sub>4</sub>	C, H
9c	<i>i</i> -Bu	154–56	C <sub>6</sub> H <sub>6</sub>	42	C <sub>14</sub> H <sub>18</sub> O <sub>4</sub>	C, H
9d	Cyclopentyl	180–181.5	EtOAc-petr ether	76	C <sub>15</sub> H <sub>18</sub> O <sub>4</sub>	C, H
9e	Cyclohexyl	188–189	EtOAc	67	C <sub>16</sub> H <sub>20</sub> O <sub>4</sub>	C, H
9f	Cycloheptyl	157–158.5	EtOAc-petr ether	68	C <sub>17</sub> H <sub>22</sub> O <sub>4</sub>	C, H

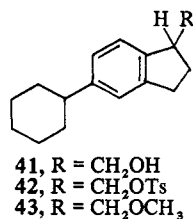
Table V. *p*-Alkylphenylsuccinic Anhydrides

						
No.	R	Mp or bp (mm), °C	Recrystn solvent	Yield, %	Formula	Analyses
10b	<i>i</i> -Pr	83–84.5	Cyclohexane	98	C <sub>13</sub> H <sub>14</sub> O <sub>3</sub>	C, H
10c	<i>i</i> -Bu	156–158 (0.1)	Cyclohexane	89	C <sub>14</sub> H <sub>16</sub> O <sub>3</sub>	C, H
10d	Cyclopentyl	101–102.5	Cyclohexane	77	C <sub>15</sub> H <sub>18</sub> O <sub>3</sub>	C, H
10e	Cyclohexyl	117–118.5	Cyclohexane	94	C <sub>16</sub> H <sub>18</sub> O <sub>3</sub>	C, H
10f	Cycloheptyl	138.5–140	Methylcyclohexane	91	C <sub>17</sub> H <sub>20</sub> O <sub>3</sub>	C, H

Scheme III



An  $\alpha$ -methyl derivative (40, Table VIII) of 12e was prepared by treatment of the methyl ester (34) of 12e with NaH followed by MeI, with subsequent hydrolysis.



The corresponding carbinol 41 and its derivatives 42 and 43 were obtained from 12e by standard procedures (see Table VIII).

Scheme IV

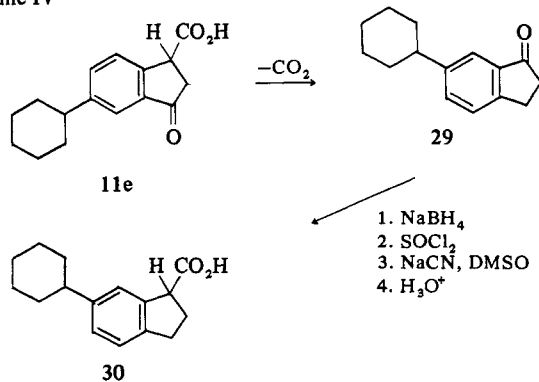


Table VI. Indan-1-carboxylic Acids and Esters

No.	Isomer <sup>a</sup>	R	X	Y	Z	R'	Mp or bp (mm), °C	Recrystn solvent <sup>b</sup>	Yield, %	Formula	Analyses	Anti- inflam ED <sub>50</sub> , mg/kg	LD <sub>50</sub> , mg/kg
11a		H	H	H	O	H	116.5-118	C <sub>6</sub> H <sub>6</sub>	28	C <sub>10</sub> H <sub>8</sub> O <sub>3</sub>	c	>128	
11b		<i>i</i> -Pr	H	H	O	H	103.5-104.5	C <sub>6</sub> H <sub>6</sub> -Skelly B <sup>d</sup>	60	C <sub>13</sub> H <sub>14</sub> O <sub>3</sub>	C, H	128	
11c		<i>i</i> -Bu	H	H	O	H	80-81	Cyclohexane	92	C <sub>14</sub> H <sub>16</sub> O <sub>3</sub>	C, H	>128	
11d		Cyclopentyl	H	H	O	H	116-118.5	Toluene	71	C <sub>15</sub> H <sub>18</sub> O <sub>3</sub>	C, H	128	
11e		Cyclohexyl	H	H	O	H	117-118	Cyclohexane	92	C <sub>16</sub> H <sub>18</sub> O <sub>3</sub>	C, H	128	
11f		Cycloheptyl	H	H	O	H	131.5-133	Cyclohexane	50	C <sub>17</sub> H <sub>20</sub> O <sub>3</sub>	C, H	128	
12a		H	H	H	H <sub>2</sub>	H	56-57	<i>n</i> -Pentane	85	C <sub>10</sub> H <sub>10</sub> O <sub>2</sub>	c	>128	
12b		<i>i</i> -Pr	H	H	H <sub>2</sub>	H	82.5-84	Petr ether	75	C <sub>13</sub> H <sub>16</sub> O <sub>2</sub>	C, H	64	
12c		<i>i</i> -Bu	H	H	H <sub>2</sub>	H	74-75	<i>n</i> -Pentane	62	C <sub>14</sub> H <sub>18</sub> O <sub>2</sub>	C, H	>128	
12d		Cyclopentyl	H	H	H <sub>2</sub>	H	111-113.5	Methylcyclohexane	84	C <sub>15</sub> H <sub>18</sub> O <sub>2</sub>	C, H	28	
12e		Cyclohexyl	H	H	H <sub>2</sub>	H	147-148	Skelly B <sup>d</sup>	99	C <sub>16</sub> H <sub>20</sub> O <sub>2</sub>	C, H	3.7	287
48	(+)	Cyclohexyl	H	H	H <sub>2</sub>	H	108-109.5	Petr ether	37 <sup>f</sup>	C <sub>16</sub> H <sub>20</sub> O <sub>2</sub>	C, H	128	
47	(-)	Cyclohexyl	H	H	H <sub>2</sub>	H	108-109.5	Petr ether	30 <sup>f</sup>	C <sub>16</sub> H <sub>20</sub> O <sub>2</sub>	C, H	2.1	254
12f		Cycloheptyl	H	H	H <sub>2</sub>	H	117.5-118.5	Petr ether	76	C <sub>17</sub> H <sub>22</sub> O <sub>2</sub>	C, H	10	
22		Cyclohexyl	H	NH <sub>2</sub>	H <sub>2</sub>	H	178-180 dec	EtOAc	16	C <sub>16</sub> H <sub>21</sub> NO <sub>2</sub>	C, H, N	64	
21		Cyclohexyl	H	Cl	H <sub>2</sub>	H	127-128	Petr ether	33	C <sub>16</sub> H <sub>19</sub> ClO <sub>2</sub>	C, H, Cl	128	
25		Cyclohexyl	H	OH	H <sub>2</sub>	H	155-157	C <sub>6</sub> H <sub>6</sub>	41	C <sub>16</sub> H <sub>20</sub> O <sub>3</sub>	C, H	>128	
17		Cyclohexyl	Cl	H	H <sub>2</sub>	H	150.5-152.5	Petr ether	59	C <sub>16</sub> H <sub>19</sub> ClO <sub>2</sub>	C, H, Cl	1.2	41
50	(+)	Cyclohexyl	Cl	H	H <sub>2</sub>	H	135-136	Petr ether	15 <sup>f</sup>	C <sub>16</sub> H <sub>19</sub> ClO <sub>2</sub>	C, H, Cl	0.85	35
49	(-)	Cyclohexyl	Cl	H	H <sub>2</sub>	H	134-135	Petr ether	34	C <sub>16</sub> H <sub>19</sub> ClO <sub>2</sub>	C, H, Cl	20	
19		Cyclohexyl	NO <sub>2</sub>	H	H <sub>2</sub>	H	150-151	Petr ether	32	C <sub>16</sub> H <sub>19</sub> NO <sub>4</sub>	C, H, N	4	54
23		Cyclohexyl	NH <sub>2</sub>	H	H <sub>2</sub>	H	90-91 dec	g	9	C <sub>16</sub> H <sub>21</sub> NO <sub>2</sub>	C, H, N	>128	
24		Cyclohexyl	AcNH	H	H <sub>2</sub>	H	199.5-202	EtOAc	54	C <sub>18</sub> H <sub>23</sub> NO <sub>3</sub>	C, H, N	8.5	450
20		Cyclohexyl	F	H	H <sub>2</sub>	H	143-145.5	EtOH-H <sub>2</sub> O	44	C <sub>16</sub> H <sub>19</sub> FO <sub>2</sub>	C, H	6.2	
27		Cyclohexyl	OH	H	H <sub>2</sub>	H	159.5-161	C <sub>6</sub> H <sub>6</sub>	34	C <sub>16</sub> H <sub>20</sub> O <sub>3</sub>	C, H	16.5	
26		Cyclohexyl	MeO	H	H <sub>2</sub>	H	167.5-169	Cyclohexane	87	C <sub>17</sub> H <sub>22</sub> O <sub>3</sub>	C, H	32	
28		Cyclohexyl	AcO	H	H <sub>2</sub>	H	189-191	Cyclohexane	73	C <sub>18</sub> H <sub>22</sub> O <sub>4</sub>	C, H	128	
30		H	Cyclohexyl	H	H <sub>2</sub>	H	95.5-96.5	Skelly B <sup>d</sup>	26	C <sub>16</sub> H <sub>20</sub> O <sub>2</sub>	C, H	64	
31a		Cyclohexyl	H	H	H, OH	H	163.5-165	EtOH-H <sub>2</sub> O	57	C <sub>16</sub> H <sub>20</sub> O <sub>3</sub>	C, H	64	
31b		Cyclohexyl	H	H	H, OH	H	120-155	h	h	C <sub>16</sub> H <sub>20</sub> O <sub>3</sub>	C, H	3	410
34		Cyclohexyl	H	H	H <sub>2</sub>	Me	46.5-48	MeOH	96	C <sub>17</sub> H <sub>22</sub> O <sub>2</sub>	C, H	2.9	254
52	(-)	Cyclohexyl	H	H	H <sub>2</sub>	Me	150 (0.1)		88	C <sub>17</sub> H <sub>22</sub> O <sub>2</sub>	C, H	6	371
35		Cyclohexyl	H	H	H <sub>2</sub>	Et	141.5-142		76	C <sub>18</sub> H <sub>24</sub> O <sub>2</sub>	C, H		
							(0.02)						
36		Cyclohexyl	H	H	H <sub>2</sub>	Me <sub>3</sub> C	<i>i</i>		59	C <sub>20</sub> H <sub>28</sub> O <sub>2</sub>	C, H	50	
37		Cyclohexyl	H	H	H <sub>2</sub>	Me(CH <sub>2</sub> ) <sub>9</sub>	184-188		73	C <sub>26</sub> H <sub>40</sub> O <sub>2</sub>	C, H	64	
							(0.02)						
38		Cyclohexyl	H	H	H <sub>2</sub>	Me <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> ·HCl	148-150	EtOAc	87	C <sub>20</sub> H <sub>29</sub> NO <sub>2</sub> ·HCl	C, H, N	14	
39		Cyclohexyl	H	H	H <sub>2</sub>	MeN(CH <sub>2</sub> ) <sub>2</sub> ·HCl	207-210	MeNO <sub>2</sub>	90	C <sub>22</sub> H <sub>31</sub> NO <sub>2</sub> ·HCl	C, H, Cl, N	17	572

<sup>a</sup>All compds are racemic unless otherwise indicated. <sup>b</sup>Final solvent. <sup>c</sup>Ref 26. <sup>d</sup>Skellysolve B. <sup>e</sup>See ref 18c. <sup>f</sup>Based on racemate. <sup>g</sup>Crystd from MeCN with solvent of crystn. This was removed by dissolving in C<sub>6</sub>H<sub>6</sub> and stripping. The reported mp and analytical data were obtained on the residue. <sup>h</sup>See Experimental Section. <sup>i</sup>Oil, purified by column chromatography.

Table VII. Cyclohexylindenecarboxylic Acids

No.	Structure	Anti-inflam ED <sub>30</sub> , mg/kg
32		64
33		64

Scheme V

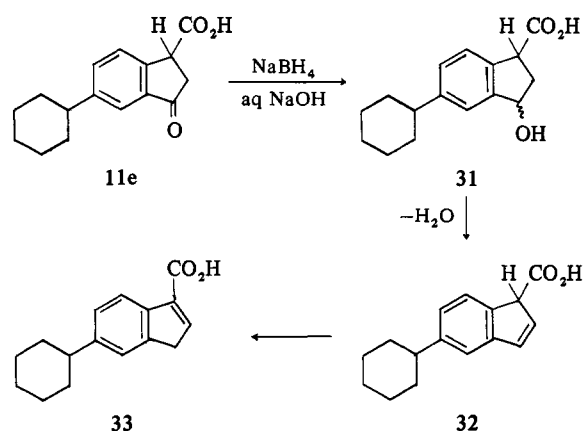


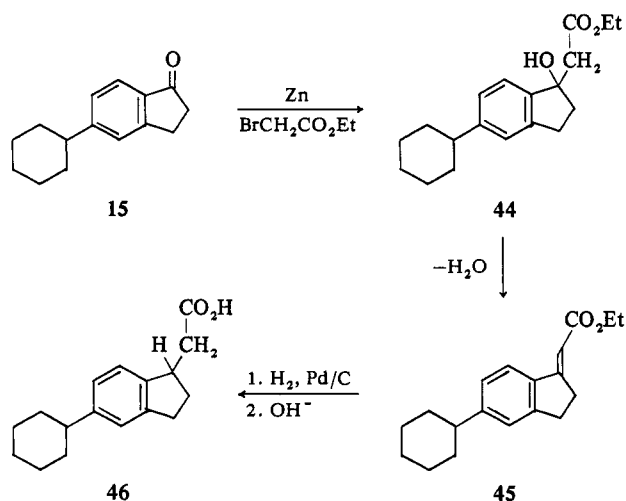
Table VIII. Miscellaneous 5-Cyclohexylindans

No.	Isomer <sup>a</sup>	Y	R	Mp or bp (mm), °C	Recrystn solvent <sup>b</sup>	Yield, %	Formula	Analyses	Antiinflamm ED <sub>30</sub> , mg/kg	LD <sub>50</sub> , mg/kg
Alcohols and Derivatives										
41		CH <sub>2</sub> OH	H	52-54	<i>n</i> -Pentane	93	C <sub>16</sub> H <sub>22</sub> O	C, H	5.0	295
54	(+)	CH <sub>2</sub> OH	H	50-52	<i>n</i> -Pentane	87	C <sub>16</sub> H <sub>22</sub> O	C, H	26	300
53	(-)	CH <sub>2</sub> OH	H	52-52	<i>n</i> -Pentane	97	C <sub>16</sub> H <sub>22</sub> O	C, H	2.0	165
42		CH <sub>2</sub> OTs	H	87-88.5	Petr ether	65	C <sub>23</sub> H <sub>28</sub> O <sub>3</sub> S	C, H, S	>128	
43		CH <sub>2</sub> OMe	H	100-114 (0.04)		85	C <sub>17</sub> H <sub>24</sub> O	C, H	>128	
Carboxylic Acids										
40		CO <sub>2</sub> H	Me	162-164	Skelly B <sup>c</sup>	23	C <sub>17</sub> H <sub>22</sub> O <sub>2</sub>	C, H	>128	
46		CH <sub>2</sub> CO <sub>2</sub> H	H	111-113	Petr ether	84	C <sub>17</sub> H <sub>22</sub> O <sub>2</sub>	C, H	128	

<sup>a</sup>All compds are racemic unless otherwise indicated. <sup>b</sup>Final solvent. <sup>c</sup>Skellysolve B.

A Reformatsky reaction on the indanone **15** was used as the initial step in a synthesis (Scheme VI) of the homolog **46** (Table VIII) of **12e**.

Scheme VI

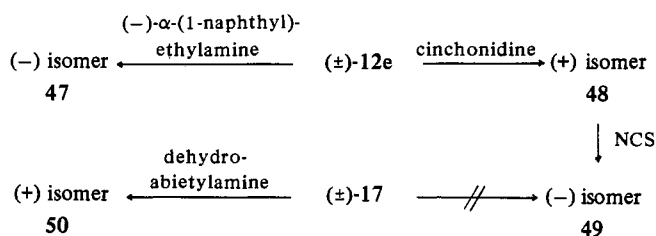


All the indan-1-carboxylic acids have an asymmetric carbon atom at position 1. The (+) and (-) isomers (Table VI) of both (±)-5-cyclohexylindan-1-carboxylic acid (**12e**) and (±)-6-chloro-5-cyclohexylindan-1-carboxylic acid (**17**) were isolated using the resolving agents as indicated in Scheme VII. We were unable to isolate the (-) isomer of **17** directly.

It should be noted that the absolute stereochemistry about position 1 of **47** and **50** is the same even though the signs of rotation are opposite at the wavelengths employed.

In terms of shape and sign, the ORD curve of (-)-5-cyclohexylindan-1-carboxylic acid (**47**) resembles the mirror image of the curve from (1*R*)-(+)-indan-1-carboxylic acid<sup>10</sup>

Scheme VII

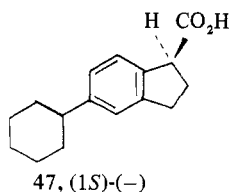
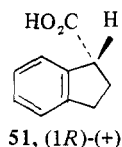


(**51**). Thus, the *S* configuration has been assigned to **47**.

Finally, the methyl ester (**52**, Table VI) of **47** and the corresponding carbinols (**53** and **54**, Table VIII) of **47** and **48** were prepared by standard procedures.

**Pharmacology.** All compounds containing the indan nucleus were tested orally for antiinflammatory activity using the carrageenin-induced foot edema method in the fasted rat.<sup>11</sup> The results, expressed as the doses which inhibited 30% of the edema (ED<sub>30</sub>), are recorded in Tables VI-VIII.<sup>†</sup> Phenylbutazone had an ED<sub>30</sub> of 20 mg/kg and

<sup>†</sup>The ED<sub>30</sub> was determined from a dose-response curve for which five animals per dose were used.



indomethacin an  $ED_{50}$  of 1.0 mg/kg in this assay. The oral  $LD_{50}$  in the rat was determined for a number of the compounds in 10-day, single dose studies (Tables VI and VIII). Deaths invariably resulted from gastrointestinal lesions.

**Structure-Activity Relationships.** Indan-1-carboxylic acid (**12a**) showed no significant antiinflammatory activity. Substitution at position 5 of the indan nucleus with open-chain aliphatic groups produced **12b** with weak activity. Substitution at position 5 with cycloalkyl groups (**12d-12f**) resulted in marked improvement, with optimum activity being shown by the 5-cyclohexyl derivative **12e**. The 6-cyclohexyl isomer (**30**) of **12e** showed weak activity.

The effect of nuclear substitution of **12e** depends mostly on the position of substitution and not on the nature of the substituent. With the exceptions of the acetamido, methoxy, and acetoxy groups (**24**, **26**, and **28**), incorporation of a variety of both electron-withdrawing and -releasing groups at position 6 gave products (**17**, **19**, **20**, **23**, and **27**) with improved or comparable activity. The most potent of these products is **17** with an  $ED_{50}$  of 1.2 mg/kg. Unlike the case of the open-chain phenylacetic acids, positions 6 and 4 are not equivalent, and substitution at the latter position lowered activity considerably (**21**, **22**, and **25**).

The 3-keto and 3-hydroxy analogs (**11e**, **31a**, and **31b**) and the indene analogs (**32** and **33**) of **12e** showed only weak activity. It should be noted that the carboxyl group of **33** lies in the plane of the benzene ring, and that **32** was readily isomerized to **33**. Substitution of a methyl group at position 1 of **12e** destroyed activity (**40**).

The corresponding alcohol **41** showed comparable activity to **12e**. The methyl ester (**34**) of **12e** showed comparable activity, but activity fell off for increasingly complex alkyl and alkylaminoalkyl esters (**35-39**).

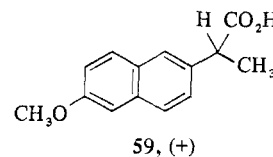
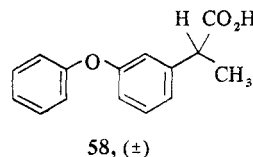
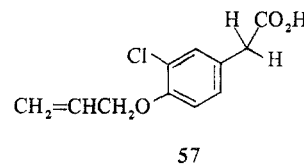
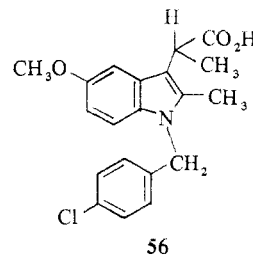
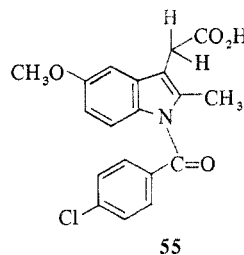
Optimum activity in the arylalkanoic acids is usually observed for compounds with one carbon atom separating the carboxyl group from the aromatic nucleus. Not unexpectedly, then, the homolog (**46**) of **12e** showed greatly reduced activity. Relatively weak antiinflammatory activity has also been observed for 5-(*p*-methoxyphenyl)indan-2-carboxylic acid.<sup>12</sup>

Most of the activity of both **17** and **12e** resides in the isomer with the *S* configuration at position 1. The most active compound in the series is (1*S*)-(+)-6-chloro-5-cyclohexylindan-1-carboxylic acid (**50**) which had an  $ED_{50}$  of 0.85 mg/kg and an  $LD_{50}$  of 35 mg/kg. A slightly less potent compound, but one with a more favorable therapeutic ratio, is (1*S*)-(-)-5-cyclohexylindan-1-carboxylic acid (**47**) which had an  $ED_{50}$  of 2.1 mg/kg and an  $LD_{50}$  of 254 mg/kg. This latter compound, BL-2365, is now in clinical trial.<sup>‡</sup>

The structure-activity relationships which we have outlined above allow us to define at least six structural requirements which are necessary for optimal activity in the indan series: (1) a carboxyl group separated by one carbon atom from a flat aromatic nucleus, (2) the carboxyl group deviating considerably from the plane of the nucleus, (3) a

free hydrogen atom at position 1; this may be a steric requirement, leaving one side of the cyclopentene ring relatively flat, (4) the *S* configuration at position 1 for those compounds with an asymmetric center, (5) optional substitution at position 6 by a small group, preferably chlorine, and (6) a cyclohexane ring para to the acetic acid residue.

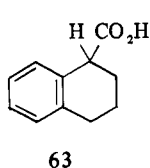
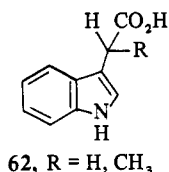
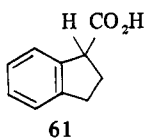
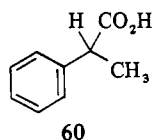
Most of these requirements also apply to many of the antiinflammatory aryl- and heteroarylalkanoic acids. The potent compounds such as **3**, indomethacin<sup>13</sup> (**55**), the  $\alpha$ -methyl benzyl analog of indomethacin<sup>14</sup> (**56**), alclofenac<sup>15</sup> (**57**), ibuprofen<sup>3</sup> (**2**), fenoprofen<sup>16</sup> (**58**), and naproxen<sup>17</sup> (**59**) are all acetic acid derivatives. The carboxyl group of these compounds is free to rotate, but at the antiinflam-



matory receptor(s) it may adopt a conformation out of the plane of the nucleus. All the above compounds have at least one free hydrogen  $\alpha$  to the carboxyl group. The activity of those compounds containing an asymmetric center is either equally divided between (+) and (-) isomers (**2** and **58**) or resides mostly in one isomer (**3**, **56**, and **59**). Where the absolute stereochemistry has been determined (**3** and **56**) the more active isomer is of the *S* configuration. The more complex the molecule, the greater is the likelihood that the receptor(s) will only be able to accommodate one isomer. For those compounds containing a para-substituted phenylacetic acid, substitution with chlorine at a position meta to the acetic acid side chain results in compounds with increased potency (**3** and **57**). The least demanding requirement, apart from the nucleus, is the nature and position of the large, lipophilic groups attached to the nucleus, although most can be positioned approximately opposite to the acetic acid side chain. For hydrocarbons directly attached to a benzene ring, the para position is preferred.

It is of interest to note that most of the requirements listed for these acidic antiinflammatory agents are the same requirements that have been observed<sup>18</sup> for plant growth regulators of the type **60-63**. Shen<sup>19</sup> has already remarked on the identity of the absolute stereochemistry about the asymmetric center of the more active isomers of both classes of compounds in the arylacetic acid series. Drain, *et al.*,<sup>20</sup> have also alluded to a superficial resemblance. The major difference in requirements concerns the substitution of the aromatic nucleus. The growth regulators do not re-

<sup>‡</sup>A more detailed account of the pharmacology of this compound will be reported elsewhere.



quire a large lipophilic substituent, and instead are often either unsubstituted or substituted with one or more small groups such as chlorine. At this point, we do not necessarily imply a similar mode of action for the two classes of compounds, although the molecular receptors may well be quite similar. We intend to elaborate further on these similarities in a subsequent paper on tetrahydro-1-naphthoic acids.

## Experimental Section<sup>§</sup>

***p*-Alkylbenzaldehydes.** The aldehydes (Table I) were prep'd by a method similar to that described for mesitaldehyde.<sup>21</sup>

**Diethyl *p*-Alkylbenzylidenemalonates.** The malonates (Table II) were prep'd by a method similar to that outlined for diethyl *p*-cyclohexylbenzylidenemalonate (7e) as follows. A soln of *p*-cyclohexylbenzaldehyde<sup>22</sup> (9.4 g, 0.05 mole), diethyl malonate (8.01 g, 0.05 mole), piperidine (0.5 g), and glacial AcOH (0.33 g) in C<sub>6</sub>H<sub>6</sub> (25 ml) was heated under reflux for 18 hr. H<sub>2</sub>O was removed as it was formed. The cooled soln was diluted with C<sub>6</sub>H<sub>6</sub>, washed (H<sub>2</sub>O, 1 N HCl, H<sub>2</sub>O, satd aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residual oil was distd to give 7e (11.7 g), bp 172–174° (0.01 mm).

**Ethyl 3-Cyano-3-(*p*-alkylphenyl)propionates.** The propionates (Table III) were prep'd using a procedure<sup>23</sup> similar to the one described for ethyl 3-cyano-3-(*p*-cyclohexylphenyl)propionate (8e) as follows. A soln of KCN (1.8 g, 0.028 mole) in H<sub>2</sub>O (4.5 ml) was added to a soln of 7e (9.0 g, 0.027 mole) in EtOH (90 ml). The stirred mixt was heated by means of an oil bath maintained at 70° for 20 hr. The mixt was allowed to cool. The ppt was removed by filtration. The filtrate was acidified (1.5 ml of 10% HCl) and concentrated. The residue was partitioned between CHCl<sub>3</sub> and H<sub>2</sub>O. The CHCl<sub>3</sub> layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residual oil was distd to give 8e (4.2 g), bp 160–161° (0.15 mm).

***p*-Alkylphenylsuccinic Acids.** The acids (Table IV) were prepared by a method similar to that described for *p*-cyclohexylphenylsuccinic acid (9e) as follows. A mixt of 8e (3.0 g), glacial AcOH (10 ml), and concentrated HCl (10 ml) was heated under reflux for 3 hr. A crystal solid separated from the reaction mixt which was allowed to cool slowly. The solid (1.95 g) was recrystallized from EtOH–H<sub>2</sub>O, followed by EtOAc, to give 9e, mp 188–189°.

***p*-Alkylphenylsuccinic Anhydrides.** The anhydrides (Table V) were prep'd by a method similar to that described for *p*-cyclohexylphenylsuccinic anhydride (10e) as follows. A mixt of 9e (10 g) and Ac<sub>2</sub>O (50 ml) was heated under reflux for 1.25 hr. The cooled soln was concentrated and the residue recrystallized from cyclohexane to give 10e (8.8 g) as colorless crystals, mp 117–118.5°.

**(±)-5-Alkyl-3-oxoindan-1-carboxylic Acids.** The keto acids 11b–11f (Table VI) were prep'd using a procedure similar to the one described for 5-cyclohexyl-3-oxoindan-1-carboxylic acid (11e) as follows. A soln of 10e (33.0 g, 0.128 mole) in CH<sub>2</sub>Cl<sub>2</sub> (400 ml)

was added dropwise to a stirred, cooled (ice-H<sub>2</sub>O) suspension of AlCl<sub>3</sub> (37.4 g, 0.281 mole) in CH<sub>2</sub>Cl<sub>2</sub> (400 ml). The mixt was stirred with cooling for 1 hr and then at room temp for 24 hr. The mixt was concentrated and the residue triturated with ice-H<sub>2</sub>O (500 ml) and concd HCl (30 ml). The gummy suspension was stirred for 36 hr at room temp. The resulting solid was collected, dried, and recrystallized from cyclohexane to give 11e (30.4 g) as off-white crystals, mp 117–118°.

**(±)-5-Alkylindan-1-carboxylic Acids.** The acids 12b–12f (Table VI) were prep'd by a method similar to that described for 5-cyclohexylindan-1-carboxylic acid (12e) as follows. A soln of 11e (9.0 g) in glacial AcOH (150 ml) containing 60% HClO<sub>4</sub> (2 ml) and 10% Pd/C (2 g) was shaken with H<sub>2</sub> at 3.5 kg/cm<sup>2</sup> until no further H<sub>2</sub> was absorbed. The mixt was filtered and anhydrous NaOAc (2.5 g) was added to the filtrate. The soln was reduced to dryness. Several portions of toluene were added to the residue, and the mixt was concentrated after each addition. The residue was partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The ether layer was washed (H<sub>2</sub>O, saturated aqueous NaCl) and dried (Na<sub>2</sub>SO<sub>4</sub>). The soln was concd and the residue recrystd from Skellysolve B to give 12e (8.4 g) as buff crystals, mp 145–147°.

**Alternative Synthesis of 12e. 5-Cyclohexyl-1-indanone (15).** A soln of ClCH<sub>2</sub>CH<sub>2</sub>COCl (13.33 g, 0.105 mole) and cyclohexylbenzene (16.03 g, 0.1 mole) in CS<sub>2</sub> (25 ml) was added dropwise with stirring over a period of 15 min to a cooled (ice-H<sub>2</sub>O) suspension of AlCl<sub>3</sub> (16.0 g, 0.12 mole) in CS<sub>2</sub> (60 ml).<sup>7</sup> The mixt was stirred at room temp for 3 hr and concentrated and then H<sub>2</sub>SO<sub>4</sub> (250 ml, sp gr 1.84) was added slowly with stirring and cooling (ice-H<sub>2</sub>O) to the residual oil. The mixt was stirred at room temp for 15 min and then heated by means of an oil bath, the temp of which was slowly raised to 100° and maintained at this temp for 2 hr. The mixt was allowed to stand at room temp for 15 hr and was then poured onto ice (1 kg). The mixt was extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O soln was washed (H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, satd aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was recrystallized from *n*-pentane (charcoal) to give 15 (14.7 g, 69%) as yellow crystals, mp 75–76.5°. Recrystallization from *n*-pentane (charcoal) gave 15 as off-white crystals, mp 75.5–77°. *Anal.* (C<sub>15</sub>H<sub>18</sub>O) C, H.

**Dithiane Intermediate 16.** A soln of *n*-BuLi in hexane (30 ml of 1.6 M, 0.048 mole of *n*-BuLi) was added over a period of 15 min to a cooled (–25°) soln of 1,3-dithiane (6.0 g, 0.05 mole) in THF (66 ml) under N<sub>2</sub>.<sup>8</sup> The soln was allowed to warm to –15° and was then stirred at this temp for 2 hr. The temp of the soln was adjusted to –2° over 30 min, when a soln of 15 (8.6 g, 0.04 mole) in THF (215 ml) was added over a period of 1 hr while the temp of the soln was maintained at 0°. The soln was allowed to stand at 0° for 20 hr. The solvents were removed, and the residue was partitioned between Et<sub>2</sub>O and 5% aqueous HCl. The Et<sub>2</sub>O layer was washed (5% HCl, H<sub>2</sub>O, saturated aqueous NaCl) and concentrated to an orange oil (15.6 g). A soln of the oil and TsOH·H<sub>2</sub>O (1.6 g) in C<sub>6</sub>H<sub>6</sub> (200 ml) was heated under reflux for 30 min, with continuous removal of the H<sub>2</sub>O formed. The cooled soln was washed (H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give 16 (13.7 g) as a brown oil.

**(±)-5-Cyclohexylindan-1-carboxylic Acid (12e).** A mixt of 16 (13.7 g), glacial AcOH (210 ml), and concentrated HCl (70 ml) was heated under reflux for 2 hr. The cooled mixt was concentrated. Several portions of toluene were added to the residue and the mixt concentrated after each addition. A CH<sub>2</sub>Cl<sub>2</sub> soln of the residue was washed with H<sub>2</sub>O until the washings were neutral. The soln was then exhaustively extracted with 5% aqueous K<sub>2</sub>CO<sub>3</sub>. The carbonate soln was washed (CH<sub>2</sub>Cl<sub>2</sub>), treated with charcoal, and filtered, and the filtrate acidified with concentrated HCl. The ppt was recrystallized from Skellysolve B to give 12e (5.2 g, 37% based on cyclohexylbenzene), mp 145–146°.

**(±)-6-Chloro-5-cyclohexylindan-1-carboxylic Acid (17).** NCS (8.2 g, 0.0614 mole) was added to a stirred, cooled (ice-H<sub>2</sub>O) soln of 12e (10.0 g, 0.0409 mole) in DMF (82 ml).<sup>9</sup> The soln was stirred for 15 min at 0°, 30 min at 25°, 9 hr at 50°, followed by 8 hr at 25°. The soln was diluted with H<sub>2</sub>O (400 ml) and stirred until the ppt turned granular. The crude product was collected, washed (H<sub>2</sub>O), dried, and recrystallized from Skellysolve B (charcoal) to give 17 (6.65 g), mp 149–150°. The product was recryst twice from Skellysolve B to give 17 as colorless crystals: mp 150.5–152.5°; nmr (CDCl<sub>3</sub>) δ 7.20 (s, 1 H) and 7.50 ppm (s, 1 H).

**Nitration of (±)-5-Cyclohexylindan-1-carboxylic Acid (12e).** (±)-5-Cyclohexyl-6-nitroindan-1-carboxylic Acid (19). A mixt of concentrated H<sub>2</sub>SO<sub>4</sub> (670 g) and concentrated HNO<sub>3</sub> (42 g of 70%, 0.466 mole of HNO<sub>3</sub>) was added dropwise with stirring to a cooled

<sup>§</sup>Satisfactory nmr and ir spectra were obtained for all compounds. Nmr spectra were obtained using a Varian Associates Model A-60 spectrometer. Chemical shifts (δ) were measured downfield from TMS. Where analyses are indicated only by symbols of the elements, results obtained for these elements were within ±0.4% of the theoretical values. Silicic acid used in chromatography was Mallinckrodt SilicAR, 100–200 mesh, CC-4 or CC-7 as indicated. Melting points are uncorrected.

(ice-H<sub>2</sub>O) mixt of **12e** (100 g, 0.409 mole) in MeNO<sub>2</sub> (1260 ml) over a period of 70 min. The soln was stirred for 2 hr with cooling, followed by 2.5 hr at 25°. The mixt was poured onto ice. The mixt was extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O ext was washed (H<sub>2</sub>O, aqueous NaOAc, H<sub>2</sub>O, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was recrystallized from MeNO<sub>2</sub> to give a tan solid (48.7 g), mp 102–112°. Recrystallization from C<sub>6</sub>H<sub>6</sub>-Skellysolve B gave tan crystals (38 g), mp 112–115°. A portion of the product was chromatographed on silicic acid (CC-4) with toluene-Me<sub>2</sub>CO (30:1). The product was recrystd from C<sub>6</sub>H<sub>6</sub>-Skellysolve B to give 19 as pale yellow crystals, mp 118–120°, resolidifying and melting at 150–151°. The (±)-4-nitro isomer (**18**) could not be isolated.

(±)-4-Amino-5-cyclohexylindan-1-carboxylic Acid (**22**). A crude mixt of 4-nitro (**18**) and 6-nitro (**19**) products obtained as described above from **12e** (100 g) was dissolved in 95% EtOH (250 ml) and hydrogenated at 3.5 kg/cm<sup>2</sup> using Raney Ni. The catalyst was removed by filtration and the filtrate concentrated to leave a residue which was crystallized from EtOH-H<sub>2</sub>O to give **22** (17 g), mp 165–171°. Two recrystallizations from EtOAc gave **22** as pale yellow crystals: mp 178–180° dec; nmr (CDCl<sub>3</sub>) δ 6.52 (d, 1 H, *J* = 6 Hz) and 6.83 ppm (d, 1 H, *J* = 6 Hz).

(±)-6-Amino-5-cyclohexylindan-1-carboxylic Acid (**23**). A dark solid (22 g) crystallized from the EtOH-H<sub>2</sub>O mother liquors of **22** over a period of 2 weeks. The solid was recrystallized from 95% EtOH to give **23** (9.1 g). The product was recrystallized from MeCN (see Table VI): mp 90–91° dec; nmr (CDCl<sub>3</sub>) δ 6.83 (s, 1 H) and 7.05 ppm (s, 1 H).

(±)-4-Chloro-5-cyclohexylindan-1-carboxylic Acid (**21**) and (±)-5-Cyclohexyl-4-hydroxyindan-1-carboxylic Acid (**25**). A soln of NaNO<sub>2</sub> (1.46 g, 0.0212 mole) in H<sub>2</sub>O (7 ml) was added over a period of 25 min to a cooled (ice-NaCl), stirred mixt of **22** (5.0 g, 0.0193 mole) in concentrated HCl (30 ml) and H<sub>2</sub>O (30 ml). The resulting mixt was added to a stirred, cooled soln of Cu<sub>2</sub>Cl<sub>2</sub> (2.3 g, 0.0232 mole) in concentrated HCl (30 ml) and H<sub>2</sub>O (30 ml). Stirring and cooling were continued for 50 min, then the mixt was warmed to 25°. The mixt was extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O soln was washed (H<sub>2</sub>O, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residual oil (4.28 g) was chromatographed on silicic acid (CC-4) with C<sub>6</sub>H<sub>6</sub>-Me<sub>2</sub>CO (20:1). The 4-chloro compd **21** (1.76 g) was eluted first from the column and was recrystd from petr ether to give the product as off-white crystals, mp 127–128°. The 4-hydroxy compd **25** (2.03 g) was eluted second and was recrystallized from C<sub>6</sub>H<sub>6</sub> followed by methylcyclohexane to give the product as off-white crystals, mp 155–157°.

(±)-6-Acetamido-5-cyclohexylindan-1-carboxylic Acid (**24**). NaOAc·3H<sub>2</sub>O (1.5 g, 0.0115 mole) was added to a stirred, cooled (ice-H<sub>2</sub>O) mixt of **23** (2.5 g, 0.00965 mole) in 1 *N* HCl (11.5 ml, 0.0115 mole) containing Ac<sub>2</sub>O (1.15 ml, 0.0122 mole). The mixt was treated with H<sub>2</sub>O and Et<sub>2</sub>O, and the Et<sub>2</sub>O layer concentrated to give an off-white solid which was recrystallized from EtOAc to give colorless crystals (1.56 g), mp 198–200°. The product was recrystallized twice from EtOAc to give **24**, mp 199.5–202°.

(±)-5-Cyclohexyl-6-fluoroindan-1-carboxylic Acid (**20**). A suspension of **23** (10.0 g, 0.0386 mole) in Et<sub>2</sub>O (70 ml) was treated with an excess of CH<sub>2</sub>N<sub>2</sub> in Et<sub>2</sub>O. The soln was filtered and the filtrate concentrated to give the methyl ester as an oil. HBF<sub>4</sub> (21.0 g of 49%, 0.116 mole) was added to a soln of the ester in EtOH (10 ml). To the cooled (ice-H<sub>2</sub>O) soln was added *i*-AmONO (5.0 g, 0.0425 mole). The mixt was allowed to stand at 0° for 0.5 hr. The soln was dild with Et<sub>2</sub>O (150 ml) and kept at –10° for 20 hr. The solid diazonium fluoroborate (9.0 g) was collected and dried. A suspension of the diazonium salt in Skellysolve C (100 ml) was heated under reflux for 0.5 hr. The mixt was filtered while still warm and the filtrate concd to give the methyl ester of **20** (6.2 g). A mixt of this crude ester, 1 *N* NaOH (50 ml), and 95% EtOH (20 ml) was heated under reflux for 0.5 hr. The hot soln was treated with charcoal and filtered. The cooled filtrate was acidified with 1 *N* HCl and the ppt extracted into Et<sub>2</sub>O. The Et<sub>2</sub>O soln was washed (H<sub>2</sub>O, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was recrystallized from Skellysolve B to give pale yellow crystals (4.4 g), mp 137–141°. The product was chromatographed on silicic acid (CC-4) with toluene-Me<sub>2</sub>CO (25:1) and finally recrystallized from EtOH-H<sub>2</sub>O to give **20** (3.5 g) as pale yellow crystals, mp 143–145.5°.

(±)-5-Cyclohexyl-6-hydroxyindan-1-carboxylic Acid (**27**). A mixt of **23** (5.80 g, 0.0224 mole), H<sub>2</sub>O (50 ml), and concentrated HCl (50 ml) was cooled to 0° and treated, with stirring, over a period of 45 min with NaNO<sub>2</sub> (1.70 g, 0.0246 mole) in H<sub>2</sub>O (5 ml). Stirring was continued for 15 min at 25° followed by 8 min at 80–90°. The mixt was cooled and extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O soln was washed (H<sub>2</sub>O, saturated aqueous NaCl) and concn-

trated. The residual gum was chromatographed on silicic acid (CC-4) with toluene-Me<sub>2</sub>CO (20:1). The product was recrystallized from C<sub>6</sub>H<sub>6</sub>-Skellysolve B to give **27** (2.0 g), mp 159–160°.

(±)-5-Cyclohexyl-6-methoxyindan-1-carboxylic Acid (**26**). A mixt of **27** (4.02 g, 0.0154 mole), Me<sub>2</sub>SO<sub>4</sub> (4.29 g, 0.034 mole), and K<sub>2</sub>CO<sub>3</sub> (8.55 g, 0.0618 mole) in Me<sub>2</sub>CO (45 ml) containing 10% KOH in MeOH (1 ml) was heated under reflux for 4 hr and then allowed to stand at 25° for 17 hr. The mixt was filtered and the filtrate concentrated. The residual oil (5.6 g) was chromatographed on silicic acid (CC-7) with toluene. A mixt of the product (3.3 g), 1 *N* NaOH (25 ml), and 95% EtOH (6 ml) was heated under reflux for 35 min. The cooled soln was acidified with dil HCl. The ppt was recrystallized from cyclohexane to give **26** (2.72 g) as pale yellow crystals, mp 167.5–169°.

(±)-6-Acetoxy-5-cyclohexylindan-1-carboxylic Acid (**28**). Ac<sub>2</sub>O (3.8 ml, 0.0401 mole) was added to a cooled (ice-H<sub>2</sub>O), stirred soln of **27** (7.79 g, 0.0299 mole) in 5 *N* NaOH (14.9 ml, 0.0745 mole), and H<sub>2</sub>O (20 ml) containing ice (50 g). After 3 min, the mixt was acidified with concentrated HCl, and the ppt was collected, washed (H<sub>2</sub>O), and dried. The product was recrystallized from cyclohexane to give **28** (6.6 g), mp 188–190°.

6-Cyclohexyl-indanone (**29**). A soln of keto acid **11e** (40 g) in C<sub>6</sub>H<sub>5</sub>NMe<sub>2</sub> (88 g) was heated for 7 hr at 160–180° with good stirring and a N<sub>2</sub> sweep. The soln was cooled (ice-H<sub>2</sub>O), acidified with concentrated HCl, and extracted with Et<sub>2</sub>O. The ethereal soln was washed (dil HCl, H<sub>2</sub>O, saturated aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was treated with charcoal in MeOH, filtered and concentrated. The residue was crystallized from Skellysolve B to give **29** (13.4 g, 40%), mp 85–86° (lit.<sup>24</sup> mp 87°).

(±)-6-Cyclohexyl-1-hydroxyindan. A suspension of **29** (15.4 g, 0.07 mole) in EtOH (250 ml) was cooled (ice-H<sub>2</sub>O) and treated with NaBH<sub>4</sub> (3.0 g, 0.08 mole) in portions. The mixt was stirred with cooling for 1 hr, then for 3 hr at room temp. Me<sub>2</sub>CO (12 ml) was added while keeping the temp below 15° and the mixt was stirred for 0.5 hr at room temp and then concentrated with addition of H<sub>2</sub>O. The mixt was acidified with concentrated HCl and extracted with Et<sub>2</sub>O. The ethereal soln was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was crystallized from Skellysolve B to give the product (13.7 g, 88%), mp 101–102°. Recrystallization from Skellysolve B gave analytical material, mp 101–102°. *Anal.* (C<sub>13</sub>H<sub>20</sub>O) C, H.

(±)-6-Cyclohexyl-1-cyanoindan. A soln of 6-cyclohexyl-1-hydroxyindan (2.0 g, 0.009 mole) and SOCl<sub>2</sub> (1.3 g, 0.011 mole) in CHCl<sub>3</sub> (20 ml) was refluxed for 1 hr, cooled, and concentrated. C<sub>6</sub>H<sub>6</sub> was added to the residue and the soln concentrated. A soln of the residue and NaCN (0.8 g, 0.016 mole) in DMSO (20 ml) was heated at 40° for 17 hr. The soln was cooled and poured into H<sub>2</sub>O (150 ml) and the soln exhaustively extracted with EtOAc. The combined exts were washed (H<sub>2</sub>O, satd aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), treated with charcoal, filtered, and concentrated. A portion (0.9 g) of the crude nitrile was chromatographed on silicic acid (CC-7) with *n*-pentane-toluene (5:1). The product was crystallized from *n*-pentane to give material (0.12 g) with mp 64–67°. Recrystallization from *n*-pentane gave analytical material, mp 65–66.5°. *Anal.* (C<sub>16</sub>H<sub>19</sub>N) C, H, N.

(±)-6-Cyclohexylindan-1-carboxylic Acid (**30**). A mixt of crude 6-cyclohexyl-1-cyanoindan (5.1 g, 0.023 mole), glacial AcOH (38 ml), and concentrated HCl (38 ml) was refluxed for 5 hr, cooled, and concentrated. The residue was dissolved in toluene and again concentrated. A soln of the residue in Et<sub>2</sub>O was washed with H<sub>2</sub>O then extracted with 5% aqueous K<sub>2</sub>CO<sub>3</sub>. The alk soln was washed with Et<sub>2</sub>O then acidified with concentrated HCl. The mixt was extracted with Et<sub>2</sub>O and the ethereal soln washed (H<sub>2</sub>O, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. A soln of the residue in MeOH was treated with charcoal, filtered, and concentrated. The residue was crystallized from *n*-pentane to give **30** (1.4 g), mp 95–97°. Recrystallization from Skellysolve B gave analytical material, mp 95.5–96.5°.

(±)-5-Cyclohexyl-3-hydroxyindan-1-carboxylic Acids (**31**). NaBH<sub>4</sub> (3.09 g, 0.0817 mole) was added to a cooled (ice-H<sub>2</sub>O), stirred soln of **11e** (15.48 g, 0.06 mole) in 0.5 *N* NaOH (163.2 ml, 0.0816 mole). The mixt was stirred for 1 hr at 0° and then for 2 hr at room temp. The cooled (ice-H<sub>2</sub>O) mixt was layered with Et<sub>2</sub>O (800 ml) and acidified to pH 2 with 1 *N* HCl. The Et<sub>2</sub>O layer was washed (H<sub>2</sub>O, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residual solid (14.9 g, 94% of **31a** by glc) was recrystallized from EtOH-H<sub>2</sub>O to give **31a** (8.9 g), mp 162.5–164°. Recrystallization from EtOH-H<sub>2</sub>O gave **31a** as colorless crystals, mp 163.5–165°. A second crop of material (3.5 g) was obtained from the mother liquors of the first recrystallization and was shown to be mainly **31a**. The mother liquors from this second crop were



concentrated to leave an off-white solid (0.55 g) which could not be further purified. This solid, mp 120–155°, was shown by glc to contain 19% of **31a** and 81% of the other isomer, **31b**.

(±)-5-Cyclohexylindene-1-carboxylic Acid (**32**). A soln of **31a** (5.58 g) and TsOH·H<sub>2</sub>O (0.75 g) in toluene (400 ml) was heated under reflux for 5 min. The cooled soln was washed (H<sub>2</sub>O), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was recrystallized from Skellysolve B (charcoal) to give **32** (3.0 g, 58%), mp 139.5–142°. Recrystallization from Skellysolve B gave colorless crystals: mp 140–142°; nmr [CDCl<sub>3</sub> (0.3 ml) + DMSO-*d*<sub>6</sub> (1 drop)] δ 4.38 ppm (m, 1 H, >CH-CO<sub>2</sub>H). Anal. (C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>) C, H.

6-Cyclohexylindene-3-carboxylic Acid (**33**). Method A. A soln of **31a** (7.75 g) and TsOH·H<sub>2</sub>O (1.0 g) in toluene (500 ml) was heated under reflux for 7 hr. The cooled soln was washed (H<sub>2</sub>O), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was crystallized (charcoal) from cyclohexane to give **33** (3.7 g, 51%) as yellow crystals, mp 178–181°. Two recrystallizations from cyclohexane gave buff crystals: mp 181–182.5°; nmr [CDCl<sub>3</sub> (0.3 ml) + DMSO-*d*<sub>6</sub> (1 drop)] δ 3.46 ppm (m, 2 H, -CH<sub>2</sub>-C=). Anal. (C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>) C, H.

Method B. Compd **32** (50 mg) readily isomerized to **33** at room temp in a mixt of CDCl<sub>3</sub> (0.15 ml) and DMSO-*d*<sub>6</sub> (0.15 ml). Bond migration, which was monitored by nmr, was essentially complete after 18 min. No attempt was made to isolate the product.

Racemic Esters. The methyl ester **34** (Table VI) was prepared by the treatment of **12e** with CH<sub>3</sub>N<sub>2</sub> in Et<sub>2</sub>O. The ethyl ester **35** (Table VI) was prepared by treatment of **12e** with EtOH and HCl gas. Esters **36–39** (Table VI) were prepared by treatment of the corresponding acid chloride with the appropriate alcohol using standard procedures.

(±)-5-Cyclohexyl-1-methylindan-1-carboxylic Acid (**40**). A soln of **34** (5.0 g, 0.0193 mole) in DMF (10 ml) was added to a cooled (ice-H<sub>2</sub>O), stirred mixt of NaH (0.80 g of a 61.1% NaH dispersion in mineral oil, 0.0203 mole of NaH) in DMF (5 ml). Stirring was continued for 0.5 hr at 25°, 0.5 hr at 50°, and 1 hr at 70–110° when H<sub>2</sub> evolution ceased. Diglyme (25 ml) followed by MeI (5.68 g, 0.04 mole) was added to the cooled (ice-H<sub>2</sub>O) soln. The mixt was stirred for 1 hr at 0° and 65 hr at 25°. The mixt was concentrated and the residue partitioned between Et<sub>2</sub>O and H<sub>2</sub>O. The Et<sub>2</sub>O soln was washed (H<sub>2</sub>O, satd aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. A mixt of the residual oil (5.49 g) in 95% EtOH (75 ml) and H<sub>2</sub>O (50 ml) containing NaOH (5.0 g) was heated under reflux for 2 hr. Most of the EtOH was removed and H<sub>2</sub>O (50 ml) added. The soln was washed (Et<sub>2</sub>O) and acidified with concentrated HCl to give a ppt (4.68 g) which was crystallized from Skellysolve B to give pale yellow crystals (3.14 g), mp 127–155°. The product was chromatographed on silicic acid (CC-4) with toluene to give **40** (1.17 g). Recrystallization from Skellysolve B gave colorless crystals, mp 162–164°.

(±)-5-Cyclohexylindan-1-methanol (**41**). A soln of **12e** (10.0 g, 0.0408 mole) in Et<sub>2</sub>O (100 ml) was added carefully to a stirred cooled (ice-H<sub>2</sub>O) mixt of LAH (3.0 g, 0.0816 mole) in Et<sub>2</sub>O (50 ml). The mixt was heated under reflux for 3 hr. The cooled mixt was treated with H<sub>2</sub>O (100 ml), followed by concentrated HCl (25 ml). The Et<sub>2</sub>O layer was washed (10% HCl, H<sub>2</sub>O, 1 N NaOH, H<sub>2</sub>O, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residual oil was crystallized from *n*-pentane to give **41** (8.73 g) as colorless crystals, mp 49–53°. Two recrystallizations from *n*-pentane gave colorless crystals, mp 52–53.5°.

The tosylate (**42**) was prepared by treatment of **41** with TsCl in pyridine. The methyl ether (**43**) was prepared by treatment of **41** with CH<sub>3</sub>N<sub>2</sub> and HBF<sub>4</sub> in Et<sub>2</sub>O.<sup>25</sup>

Ethyl 5-Cyclohexylindanylidene-1-acetate (**45**). A soln of **15** (15 g, 0.07 mole) and BrCH<sub>2</sub>CO<sub>2</sub>Et (14.1 g, 0.0845 mole) in C<sub>6</sub>H<sub>6</sub> (50 ml) was added to a stirred, heated (70°) mixt of granular Zn (5.5 g, 0.0843 g-atom) in C<sub>6</sub>H<sub>6</sub> (10 ml) during 35 min. The mixt was then heated under reflux for 1 hr. The cooled mixt was stirred with 10% H<sub>2</sub>SO<sub>4</sub> for 30 min. The C<sub>6</sub>H<sub>6</sub> layer was washed (H<sub>2</sub>O, saturated aqueous NaCl) and concentrated to leave the crude hydroxy ester **44** (23.4 g). A soln of **44** (23.4 g) in C<sub>6</sub>H<sub>6</sub> (125 ml) containing TsOH·H<sub>2</sub>O (1.5 g) was heated under reflux for 35 min. The cooled soln was washed (H<sub>2</sub>O, aqueous NaHCO<sub>3</sub>, H<sub>2</sub>O), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue (20 g) was recrystallized from *n*-pentane to give **45** (8.28 g, 42% from **15**) as yellow crystals, mp 74–76°. Recrystallization from *n*-pentane gave the analytical sample: mp 76–78°; ir (KBr) 1700 cm<sup>-1</sup> (α, β-unsaturated ester C=O). Anal. (C<sub>19</sub>H<sub>24</sub>O<sub>2</sub>) C, H.

(±)-5-Cyclohexylindan-1-acetic Acid (**46**). A soln of **45** (3.0 g) in 95% EtOH (100 ml) containing 10% Pd/C (0.8 g) was shaken with H<sub>2</sub> (3.5 kg/cm<sup>2</sup>) until H<sub>2</sub> uptake ceased. The mixt was filtered and the filtrate concentrated. A mixt of the residual ester (2.98 g),

95% EtOH (20 ml), and 3 N NaOH (17 ml) was heated under reflux for 2 hr. The soln was diluted with H<sub>2</sub>O (50 ml) and most of the EtOH removed. The aqueous soln was treated with charcoal and filtered. The filtrate was acidified (concentrated HCl) and the ppt (2.7 g) recrystallized from petr ether (bp 37–47°) to give **46** (2.3 g), mp 111–113°.

(1S)-(-)-5-Cyclohexylindan-1-carboxylic Acid (**47**). A soln of (-)-α-(1-naphthyl)ethylamine (1.76 g, 0.0103 mole) in MeCN (2 ml) was added to a boiling soln of **12e** (5.0 g, 0.0205 mole) in MeCN (250 ml). The soln was allowed to cool slowly and stand at 25° for 3 hr. The crystalline product was collected and recrystallized twice from MeCN to give the salt (3.0 g), mp 163–164.5°. The salt was partitioned between EtOAc (20 ml) and 0.5 N HCl (20 ml). The EtOAc layer was washed (1 N HCl, H<sub>2</sub>O, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue (1.68 g), mp 108–110°, was recrystallized from petr ether (bp 39–50°) to give **47** (1.51 g) as colorless crystals: mp 108–110°; [α]<sub>D</sub><sup>25</sup> -9.69° (c 2, EtOH) and [α]<sub>D</sub><sup>25</sup> -44.76° (c 2, EtOH); ORD (c 0.4, MeOH), 24°, [α]<sub>D</sub><sup>450</sup> -30°, [α]<sub>D</sub><sup>350</sup> -70°, [α]<sub>D</sub><sup>310</sup> -120°, [α]<sub>D</sub><sup>276</sup> -280° (trough), [α]<sub>D</sub><sup>268</sup> -100° (peak), [α]<sub>D</sub><sup>257</sup> -380° (shoulder), and [α]<sub>D</sub><sup>250</sup> -590°.

(1R)-(+)-5-Cyclohexylindan-1-carboxylic Acid (**48**). A soln of **12e** (15.0 g, 0.0614 mole) and cinchonidine (9.05 g, 0.0307 mole) in EtOH (700 ml) was boiled down to a vol of 300 ml. The mixt was allowed to cool slowly and was left for 20 hr at 25°. The mixt was filtered to yield the salt (13.0 g), mp 212–212.5°. The salt was recrystallized from EtOH to give a product (11.8 g), mp 217.5–219°, which was partitioned between Et<sub>2</sub>O (500 ml) and 10% HCl (250 ml). The Et<sub>2</sub>O layer was washed (10% HCl, H<sub>2</sub>O, satd aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give **48** (5.0 g), mp 108–110°. Two recrystallizations from petr ether (bp 39–50°) gave colorless needles: mp 108–109.5°; [α]<sub>D</sub><sup>25</sup> +9.60° (c 2, EtOH) and [α]<sub>D</sub><sup>25</sup> +44.8° (c 2, EtOH).

(1R)-(-)-6-Chloro-5-cyclohexylindan-1-carboxylic Acid (**49**). A soln of **48** (8.0 g, 0.0328 mole) and NCS (6.52 g, 0.049 mole) in DMF (66 ml) was heated at about 50° for 9 hr followed by 32° for 10 hr.<sup>9</sup> The soln was poured into H<sub>2</sub>O (280 ml), and the mixt triturated with ice cooling. The solid was collected, dried, and recrystallized from Skellysolve B (charcoal) to give colorless crystals (3.12 g), mp 127–130°. Two recrystallizations from petr ether (bp 30–60°) gave **49** as colorless crystals: mp 134–135°; [α]<sub>D</sub><sup>25</sup> -28.2° (c 2, EtOH) and [α]<sub>D</sub><sup>25</sup> -87.5° (c 2, EtOH).

(1S)-(+)-6-Chloro-5-cyclohexylindan-1-carboxylic Acid (**50**). A soln of **47** (20.0 g, 0.0719 mole) and dehydroabietylamine (10.22 g, 0.03595 mole) in EtOH (700 ml) was boiled down to about 380 ml. The mixt was allowed to cool slowly and left for 20 hr at 25°. The solid (16.3 g), mp 188–190°, was collected and recrystallized from MeOH-H<sub>2</sub>O (20:1) to give the salt (11.0 g), mp 192–194°. Recrystallization from MeOH gave colorless crystals (7.4 g), mp 194–195.5°. The salt was partitioned between Et<sub>2</sub>O and 1 N HCl. The Et<sub>2</sub>O layer was washed (1 N HCl, H<sub>2</sub>O, saturated aqueous NaCl), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give **50** (3.5 g) as colorless crystals, mp 133–134°. Recrystallization from Skellysolve B gave colorless needles (3.0 g): mp 135–136°; [α]<sub>D</sub><sup>25</sup> +28.7° (c 2, EtOH) and [α]<sub>D</sub><sup>25</sup> +87.7° (c 2, EtOH).

Methyl (-)-5-Cyclohexylindan-1-carboxylate (**52**, Table VI) was prep'd by treatment of **47** with CH<sub>3</sub>N<sub>2</sub> in Et<sub>2</sub>O. The distilled product had [α]<sub>D</sub><sup>25</sup> -0.93° and [α]<sub>D</sub><sup>25</sup> -12.4° (c 4.9, C<sub>6</sub>H<sub>6</sub>).

(-)-5-Cyclohexylindan-1-methanol (**53**) and (+)-5-cyclohexylindan-1-methanol (**54**) (Table VIII) were prep'd from **47** and **48**, respectively, by reduction with LAH as in a manner similar to that described for **41**.

Acknowledgments. The authors are indebted to Dr. Max E. Bierwagen and Dr. A. W. Pircio for permission to quote the pharmacological data, to Mr. R. B. Babel and Mr. M. Brown for the preparation of intermediates, and to the analytical and spectroscopic groups for their services.

## References

- (1) *Annu. Rep. Med. Chem.*, 1965–1970, Chapters on "Non-steroidal Antiinflammatory Agents" (1966–1971).
- (2) S. S. Adams, P. Hebborn, and J. S. Nicholson, *J. Pharm. Pharmacol.*, **20**, 305 (1968).
- (3) S. S. Adams, K. F. McCullough, and J. S. Nicholson, *Arch. Int. Pharmacodyn.*, **178**, 115 (1969).
- (4) T. Y. Shen, *Chim. Ther.*, **2**, 459 (1967).
- (5) P. F. Juby, T. W. Hudyma, and R. A. Partyka, *Ger. Offen.* 2,004,038 (1970); *Chem. Abstr.*, **73**, 352 (1970).
- (6) (a) S. Noguchi, S. Kishimoto, I. Minamida, M. Obayashi, and

- K. Kawakita, *Chem. Pharm. Bull.*, **19**, 646 (1971); (b) K. Kawai, S. Kuzuma, S. Morimoto, H. Ishii, and N. Matsumoto, *Jap. J. Pharmacol.*, **21**, 621 (1971).
- (7) R. T. Hart and R. F. Tebbe, *J. Amer. Chem. Soc.*, **72**, 3286 (1950).
- (8) (a) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965); (b) D. Seebach, *Synthesis*, **1**, 17 (1969).
- (9) W. B. Wright, Jr., *J. Med. Chem.*, **11**, 1161 (1968).
- (10) J. H. Brewster and J. G. Buta, *J. Amer. Chem. Soc.*, **88**, 2233 (1966).
- (11) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
- (12) M. Minssen-Guetté, M. Dvolaitzky, and J. Jacques, *Bull. Soc. Chim. Fr.*, 2111 (1968).
- (13) C. A. Winter, E. A. Risley, and G. W. Nuss, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **22**, 543 (1963).
- (14) T. Y. Shen, *Int. Symp. Non-Steroidal Anti-Inflammatory Drugs, Proc.*, **1964**, 13 (1965).
- (15) G. Lambelin, J. Roba, C. Gillet, and N. P. Buu-Hoi, *Arzneim.-Forsch.*, **20**, 610 (1970).
- (16) R. C. Nickander, R. J. Kraay, and W. S. Marshall, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **30**, 563 (1971).
- (17) I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, and J. H. Fried, *J. Med. Chem.*, **13**, 203 (1970).
- (18) (a) J. B. Koepfli, K. V. Thimann, and F. W. Went, *J. Biol. Chem.*, **122**, 763 (1938); (b) B. Sjöberg, *Ark. Kemi*, **13**, 1 (1958); (c) A. Fredga, *Chem. Ber.*, **89**, 322 (1956); (d) B. Åberg, *Kgl. Lantbruks-Hoegsk. Ann.*, **24**, 375 (1958); (e) B. Sjöberg, *Ark. Kemi*, **12**, 251 (1958); (f) N. N. Mel'nikov, R. Kh. Turetskaya, Yu. A. Baskakov, A. N. Boyarkin, and M. S. Kuznetsova, *Dokl. Akad. Nauk SSSR*, **89**, 953 (1953); (g) H. Veldstra and C. Van de Westeringh, *Recl. Trav. Chim. Pays-Bas*, **70**, 1113 (1951); (h) R. A. Heacock, R. L. Wain, and F. Wightman, *Ann. App. Biol.*, **46**, 352 (1958).
- (19) T. Y. Shen, *Annu. Rep. Med. Chem.*, **1966**, Chapter 21 (1967).
- (20) D. J. Drain, M. J. Daly, B. Davy, M. Horlington, J. G. B. Howes, J. M. Scruton, and R. A. Selway, *J. Pharm. Pharmacol.*, **22**, 684 (1970).
- (21) A. Rieche, H. Gross, and E. Höft, *Org. Syn.*, **47**, 1 (1967).
- (22) D. Bodroux and R. Thomassin, *C. R. Acad. Sci.*, **205**, 991 (1937).
- (23) C. F. H. Allen and H. B. Johnson, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 804.
- (24) N. P. Buu-Hoi, P. Cagniant, and Ch. Mentzer, *Bull. Soc. Chim. Fr.*, **11**, 127 (1944).
- (25) M. Neeman, M. C. Caseiro, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, **6**, 36 (1959).
- (26) W. Baker and W. G. Leeds, *J. Chem. Soc.*, 974 (1948).

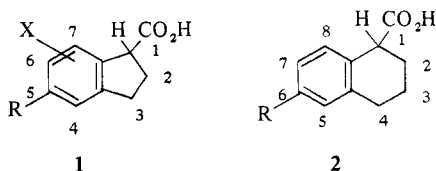
## Antiinflammatory Activity and Structure-Activity Relationships of Some 1,2,3,4-Tetrahydro-1-naphthoic Acids and Related Compounds

P. F. Juby,\* W. R. Goodwin, T. W. Hudyma, and R. A. Partyka

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201. Received May 31, 1972

6-Substituted 1,2,3,4-tetrahydro-1-naphthoic acids and related compounds were prepared as potential antiinflammatory agents. A few of the compounds showed moderate antiinflammatory activity when tested orally in the rat. The effect of the geometry of the fused alicyclic ring on activity is discussed and a resemblance noted between structural requirements for arylacetic acid type antiinflammatory agents and certain plant growth regulators.

In a previous paper<sup>1</sup> we described some indan-1-carboxylic acids (**1**, R = alkyl, cycloalkyl; X = monosubstituent) with potent antiinflammatory activity. We have now prepared some 1,2,3,4-tetrahydro-1-naphthoic acids (**2**, R = alkyl, cycloalkyl, phenyl) and related compounds.<sup>2,7</sup> Whereas the indan compounds contain a conformationally fixed car-

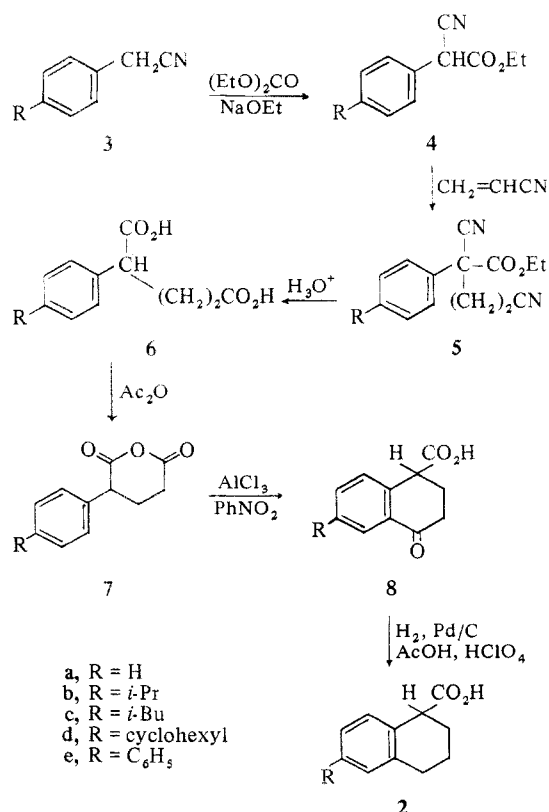


boxyl group attached to a fairly rigid system, the tetrahydro-naphthoic acids contain a carboxyl group which is only partially restrained by the larger, more flexible cyclohexene ring. The consequences of this flexibility are discussed. Some conclusions are drawn which are used to elaborate on observed similarities between the structural requirements of some acidic antiinflammatory agents and certain plant growth regulators.<sup>1</sup>

**Chemistry.** Compounds of type **2** were prepared as outlined in Scheme I. These products were not resolved into their optical antipodes. Intermediates and products are listed in Tables I-VI.

Dehydro analogs (**10**, **13**, **14**, and **15**) of **2d** were obtained as outlined in Scheme II (see Table VII). The two isomers

Scheme I



\*A Ciba group has recently reported on some similar compounds with antiinflammatory and analgetic activity.<sup>3</sup>