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5-Substituted-1-indancarboxylic Acids as Potential Antiinflammatory Agents

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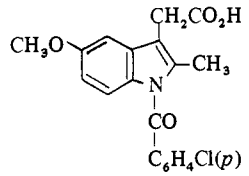
The preparation of a series of 5-substituted-1-indancarboxylic acids is described. These compounds are analogs of the active phenylacetic acids in which the carboxyl group is fixed conformationally. Racemic 5-isopropyl- and 5-cyclohexyl-1-indancarboxylic acid are active in suppressing carrageenin-induced paw edema in the rat and uv-induced erythema in the guinea pig. However, they appear less potent than indomethacin in these systems. None of the indancarboxylic acids significantly suppressed adjuvant-induced arthritis or promoted weight gain in the rat.

The reports on the utility of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid (**1**)[1] and *p*-isobutylphenylacetic acid (**2**)[2] as antiinflammatory agents stimulated an intense search for other such compounds within the heterocyclic and arylalkanoic acid series. The clinical utility of the former substance added impetus to this effort, and early investigations focused upon a series of indenacetic acids, as exemplified by the cis isomer **3**.[3] The activity of **3** indicated that the indomethacin-like potency was not restricted to indole derivatives, and the preparation of other arylacetic acids was undertaken. These investigations culminated in the preparation of a series of biphenylylacetic acids and *p*-alkyl- and *p*-cycloalkylphenylacetic acids.[4] One member of the last series, the dextrorotatory isomer of 2-(4-cyclohexyl-3-chlorophenyl)propionic acid (**4**), was reputed to be the most potent nonsteroidal antiinflammatory agent known at that time.[4]



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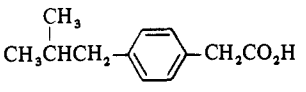

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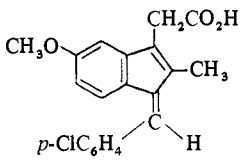

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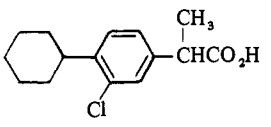

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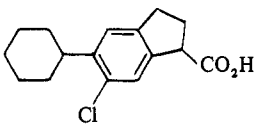
In view of our interest[5,6] in analogs of nonsteroidal antiinflammatory agents in which the carboxylic acid group is fixed conformationally, we have prepared certain 5-alkylindancarboxylic acids for testing as antiinflammatory agents. Independent of our efforts, two other laboratories have prepared the most apparent analog of this type, *i.e.*, 6-chloro-5-cyclohexylindan-1-carboxylic acid (**5**), and reported on its antiinflammatory properties.[7,8]

The 5-substituted-1-indancarboxylic acids **11** were prepared by Clemmensen reduction of the corresponding 3-indanone derivatives **10** (see Scheme I), which were obtained by Friedel-Crafts closure with hydrogen fluoride of a substituted phenylsuccinic acid **9**. The last substances were synthesized by a modification of the procedure of Baker and Lapworth.[9,10] Thus, allowing 4-biphenylylcarboxaldehyde (**6b**) and 4-cyclohexylbenzaldehyde (**6c**) to react with ethyl cyanoacetate gave the corresponding unsaturated esters **7**. Michael addition of cyanide to these α-cyanocinnamates and acid hydrolysis of the intermediate dinitriles gave the substituted succinic acids **9** in good yield. Considerable succinimide **8b** was formed in the preparation of 4-biphenylylsuccinic acid (**9b**). Application of this sequence to *p*-isopropylbenzaldehyde (**6a**) furnished 56% of acid **9a** without isolation of intermediates.



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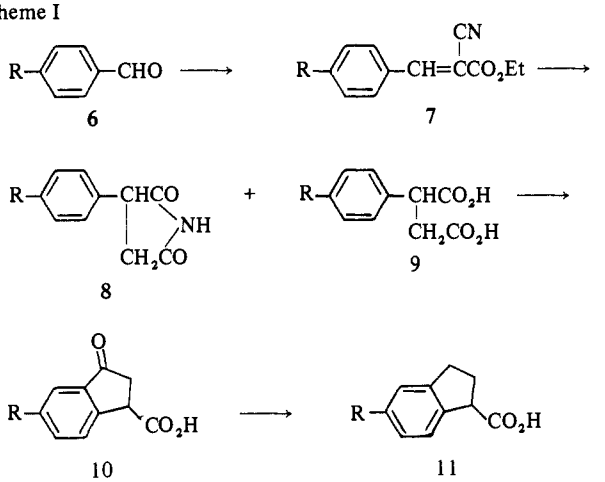
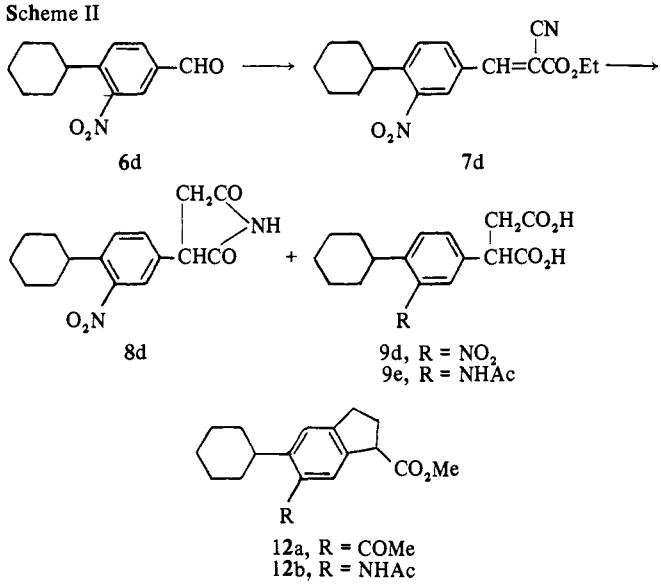
Scheme I



a, R = *i*-C_3H_7
b, R = C_6H_5
c, R = *c*-C_6H_{11}

Scheme II



Utilization of 4-cyclohexyl-3-nitrobenzaldehyde in this sequence was investigated as a method of synthesizing 6-substituted derivatives, *e.g.*, **5**. The required aldehyde was obtained by nitration of *p*-cyclohexylbenzaldehyde (**6c**), and conversion of the nitroaldehyde into the desired succinic acid **9d** was uneventful. Succinimide **8d** was a minor coproduct, however (see Scheme II). Since the nitrophenyl derivative **9d** was unsuitable for cyclization, it was converted into the acetamido derivative **9e** by a sequence encompassing hydrogenation, conversion to the diester, acetylation, and saponification. Direct acetylation of the reduction product was not successful. All attempts to effect cyclization of **9e** into the corresponding indanone failed. Treatment of **9e** with hydrogen fluoride or polyphosphoric acid and exposure of the acid chloride or anhydride derived from **9e** to aluminum chloride were among the methods investigated.

Electrophilic substitutions on 5-cyclohexyl-1-indancarboxylic acid (**11c**) did provide the desired 6-substituted derivatives. Chlorination of **11c** gave **5**, and acylation of the methyl ester of **11c** with acetyl chloride gave the acetyl derivative **12a**. The oxime of **12a** was rearranged into the acetamido derivative **12b** in the usual manner. The pattern of substitution in **5** and **12** was established by their nmr spectra (two single aryl proton resonances).

Table I. Effect of 5-Substituted-1-indancarboxylic Acids on Development of Carrageenin-Induced Rat Paw Edema[a]

Treatment	Dose,[b] mg/kg	No. of rats	Ratio control/treated edema	95% confidence limits
Controls		64		
Indomethacin (1)	250	32	2.9	(2.3–3.6)
	83	32	2.3	(1.8–2.9)
	27	32	2.2	(1.8–2.8)
	9	32	2.0	(1.6–2.5)
	3	32	1.5	(1.2–1.9)
5-Isopropyl-1-indancarboxylic acid (11a)	250	8	2.0	(1.3–3.1)
5-Cyclohexyl-1-indancarboxylic acid (11c)	250	8	1.8	(1.1–2.8)
6-Chloro-5-cyclohexyl-1-indancarboxylic acid (5)	250	4	1.3	(0.7–2.3)

[a] Determined by a modification of the method of Winter, *et al.*[11] [b] Measurements were made 5 hr after oral administration.

Table II. Effect of 5-Substituted-1-indancarboxylic Acids on Development of Uv-Induced Erythema in Guinea Pigs[a]

Treatment	Dose,[b] mg/kg	Score (avg) 1 hr	Score (avg) 4 hr	Dead animals/ total	Decision
Control		2.1	2.8	4/384	
Indomethacin (1)	250	0	1.0	1/20	A[c]
	125	0	1.3	0/12	A
	62.5	0	1.3	0/8	A
	31.3	0.1	1.9	0/8	A
	15.6	0	2.0	0/8	A
	7.8	0.6	2.3	0/8	A
	3.9	1.2	2.9	0/8	
5-Isopropyl-1-indancarboxylic acid (11a)	250	0.3	2.6	0/8	A
5-Cyclohexyl-1-indancarboxylic acid (11c)	250	0	1.8	0/8	A
6-Chloro-5-cyclohexyl-1-indancarboxylic acid (5)	250	0.2	1.8	0/8	A
	125	0	1.9	0/4	A

[a] Determined by a modification of the method of Winder, *et al.*[12] [b] Oral administration. [c] A = active (discriminant function analysis).

Biological Activity. The effects of racemic 5-isopropyl- (**11a**), 5-cyclohexyl- (**11c**), and 5-cyclohexyl-6-chloro-1-indancarboxylic acid (**5**) in suppressing carrageenin-induced paw edema and adjuvant-induced arthritis in the rat and uv erythema in the guinea pig were determined. The results are shown in Tables I–III; pooled data for indomethacin are also given. Compounds **11a** and **11c** significantly suppressed carrageenin-induced paw edema at 250 mg/kg (Table I); however, the low control/treated edema ratios suggest that these compounds are less potent than indomethacin. All compounds showed significant suppression of uv-induced erythema (Table II). However, none of the indancarboxylic acids showed significant suppression of adjuvant-induced arthritis or promoted rat weight gain (Table III). Indomethacin is significantly active in each respect. Our results also suggest that 5-cyclohexyl-6-chloro-1-indancarboxylic acid (**5**) is toxic at 6.3 mg/kg per day and indicate that this substance is less interesting than indomethacin, notwithstanding claims to the contrary.[8]

Our data indicate that the 5-alkyl-1-indancarboxylic acids, *e.g.*, **11a**, possess an effect similar to the 5-cycloalkyl derivatives in certain experimental antiinflammatory systems. Introduction of nuclear substituents into the latter compounds reduces their effectiveness.

Experimental Section

General. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Solutions were dried ($MgSO_4$) and concd under reduced pressure on a rotary evaporator. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The petr ether used was that fraction with bp 30–60°.

4-Cyclohexyl-3-nitrobenzaldehyde (6d). 4-Cyclohexylbenzaldehyde (3.74 g, 20 mmoles) was added dropwise over 30 min to a soln of 1.67 ml of fuming HNO_3 (*d* 1.5) in 12 ml of concd H_2SO_4 that was maintained at 5–10°. An orange solid separated, and the mixture was maintained at room temperature for 16 hr. The resulting dark soln was poured onto cracked ice, and the brown paste was collected by filtration and dissolved in Et_2O. This soln was washed successively with H_2O, 2% NaOH, and saline. The residue remaining after solvent removal crystallized from Et_2O–hexane to give 2.50 g (54%) of white crystals, mp 60–62°. Further recrystallizations from petr ether gave white crystals, mp 64–65°. *Anal.* ($C_{13}H_{15}NO_3$) C, H, N.

Preparation of Ethyl α-Cyano-4-substitutedcinnamates (7). A mixture of 18.22 g (0.10 mole) of 4-biphenylylcarboxaldehyde and 11.60 g (0.103 mole) of ethyl cyanoacetate in $CHCl_3$ was warmed to

Table III. Effect of 5-Substituted-1-indancarboxylic Acids on Adjuvant-Induced Arthritis in Rats[a]

Treatment	Oral dose, mg/kg	Ratio of dead to treated, 21 days	Mean weight gain,[b] g		% inhibition[b] of swelling (primary lesion)		% inhibition[b] of score (secondary lesion)	
			Day 14	Day 21	Day 14	Day 21	Day 14	Day 21
Normal rats		4/51	69*	110*				
Adjuvant controls		21/234	36	39	0	0	0	0
Indomethacin (1)	2	2/21	65*	68*	67*	36*	24*	22*
	1	3/21	54*	60*	64*	15	9	11
	0.5	0/12	47	45	44*	11	0	4
5-Isopropyl-1-indancarboxylic acid (11a)	50	0/3	25	15	0	0	22	14
5-Cyclohexyl-1-indancarboxylic acid (11c)	100	0/3	26	23	38	0	15	1
	50	0/6	22	31	43	9	20	8
6-Chloro-5-cyclohexyl-1-indancarboxylic acid (5)	50	6/6						
	25	3/3						
	12.5	3/3						
	6.3	3/3						
	3.1	1/5	34	28	22	33	22	4

[a]Determined by a modification of the procedure of Newbould.[13] [b]Significant difference from adjuvant controls indicated by *; $p < 0.05$ by t test.

Table IV. 5-Substituted-1-indancarboxylic Acids and Intermediates in Their Preparation

No.	Compound	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
7b	Ethyl 3-(4-biphenylyl)-2-cyanoacrylate	90	CH_2Cl_2–MeOH	131–133	$C_{18}H_{15}NO_2$	C, H, N
7c	Ethyl α-cyano-4-cyclohexylcinnamate	87	EtOH–heptane	73–74	$C_{18}H_{21}NO_2$	C, H, N
7d	Ethyl α-cyano-4-cyclohexyl-3-nitrocinnamate	73	Ether	112–113	$C_{18}H_{20}N_2O_4$	C, H, N
9a	(*p*-Cumenyl)succinic acid	56[a]	Acetone–hexane	186–189	$C_{13}H_{16}O_4$	C, H
8b	4-Biphenylylsuccinimide		MeOH	194–196	$C_{16}H_{13}NO_2$	H, N; C[b]
9b	4-Biphenylylsuccinic acid	72	Acetone–hexane	236–237	$C_{16}H_{14}O_4$	C, H
9c	(4-Cyclohexylphenyl)succinic acid	54	Ether–hexane	194–195	$C_{16}H_{20}O_4$	C, H
8d	(4-Cyclohexyl-3-nitrophenyl)succinimide	9	MeOH	230–233	$C_{16}H_{18}N_2O_4$	C, H, N
9d	(4-Cyclohexyl-3-nitrophenyl)succinic acid	57	Acetone–hexane	186–188	$C_{16}H_{19}NO_6$	C, H, N
9e	(3-Acetamido-4-cyclohexylphenyl)succinic acid	100	Acetone–hexane	224–226	$C_{18}H_{23}NO_5$	C, H, N
10b	5-Phenyl-3-oxo-1-indancarboxylic acid	13[c]	Acetone–hexane	182–184	$C_{16}H_{12}O_3$	C, H
10c	5-Cyclohexyl-3-oxo-1-indancarboxylic acid	50	Ether–hexane	120–122	$C_{16}H_{18}O_3$	C, H
11a	5-Isopropyl-1-indancarboxylic acid	62	Hexane	68–70	$C_{13}H_{16}O_2$	C, H
11b	5-Phenyl-1-indancarboxylic acid	93		145–146[d]	$C_{16}H_{14}O_2$	C, H
11c	5-Cyclohexyl-1-indancarboxylic acid	69	Ether–hexane	145–147	$C_{16}H_{20}O_2$	C, H

[a]Overall for three stages from *p*-isopropylbenzaldehyde. [b]C: calcd, 76.47; found, 77.05. [c]Isolated by partition chromatography on diatomaceous silica using a heptane–ethylene dichloride–MeOH–H_2O (75:25:17:4) system; the product was eluted at peak hold back volume 3.5 (V_m/V_s = 2.46). [d]Purified by sublimation at 100° (0.1 mm).

effect soln.[10] Piperidine (0.5 ml) was added, and a vigorous exotherm was noted. The reaction soln was stirred for 30 min, and the **ethyl 3-(4-biphenylyl)-2-cyanoacrylate (7b)** was isolated in the usual way. Characterization of this substance and other esters prepared by this general procedure is given in Table IV.

Preparation of the (Substitutedphenyl)succinic Acids (9). The following synthesis of **(4-cyclohexyl-3-nitrophenyl)succinic acid (9d)** illustrates the general procedure. A soln of 4.00 g (12.2 mmoles) of ethyl α-cyano-4-cyclohexyl-3-nitrocinnamate (7d) in 5 ml of THF was stirred for 18 hr in an argon atmosphere with a soln of 0.64 g (13 mmoles) of NaCN in 3 ml of H_2O. The THF was removed in a stream of argon, and the conc was diluted with H_2O and acidified with HCl. The aqueous layer was decanted from a brown paste, which was then heated at reflux temperature for 24 hr with 25 ml of 12 *N* HCl and 15 ml of H_2O. The cooled mixture was extracted successively with CH_2Cl_2 and ether. Concentration of the combined organic soln led to separation of 320 mg (9%) of **(4-cyclohexyl-3-nitrophenyl)succinimide (8d)**, mp 224–227°, before complete removal of the solvent. The solvent was removed from the filtrate, and the residue crystallized from Et_2O–hexane to give 2.20 g (57%) of the succinic acid, mp 178–180°. Characterization of the various succinimides and succinic acids is given in Table IV.

(3-Amino-4-cyclohexylphenyl)succinic Acid. Hydrogenation of a mixture of 780 mg (2.43 mmoles) of (4-cyclohexyl-3-nitrophenyl)-succinic acid (9d), 410 mg (4.90 mmoles) of $NaHCO_3$, and 100 mg of 10% Pd/C in 50 ml of H_2O was complete in 15 min. The mixture was filtered, and the filtrate was neutralized with HOAc to give 515 mg (73%) of crystals, mp 187–189°. The product was recrystallized from dilute MeOH to give crystals, mp 195–197°. *Anal.* ($C_{16}H_{21}NO_4$) C, H, N.

Diethyl (3-Acetamido-4-cyclohexylphenyl)succinate. A solution of 5.60 g (19.2 mmoles) of (3-amino-4-cyclohexylphenyl)succinic acid in 500 ml of EtOH was saturated with HCl and then heated at reflux temperature for 2 hr. The solvent was removed, and the residue was dissolved in Et_2O. This solution was washed with $NaHCO_3$ soln, and the solvent was removed. The residue was treated with 5 ml of HOAc and 10 ml of Ac_2O for 4 hr at room temperature. Dilution with H_2O gave 4.90 g (66%) of white powder, mp 122–125°. Material from a similar experiment was recrystallized from acetone–hexane to give crystals, mp 118–120°. *Anal.* ($C_{22}H_{31}NO_5$) C, H, N.

(3-Acetamido-4-cyclohexylphenyl)succinic Acid (9e). Hydrolysis of 4.36 g (11.2 mmoles) of diethyl (3-acetamido-4-cyclohexylphenyl)succinate was effected by stirring with a soln of 0.92 g (23 mmoles) of NaOH in dilute EtOH for 16 hr. Removal of the alcohol and acidification of the concentrate with 6 *N* HCl soln gave 3.80 g (100%) of white powder, the characterization of which is given in Table IV.

Preparation of 5-Substituted-3-oxo-1-indancarboxylic Acids. The method is illustrated by the following preparation of **5-cyclohexyl-3-oxo-1-indancarboxylic acid (10c)**. A mixture of 3.20 g (11.6 mmoles) of (4-cyclohexylphenyl)succinic acid and approximately 20 ml of liquid HF was allowed to stand at room temperature for 17 days. The HF was permitted to evaporate at the end of this period. The residue was dissolved in Et_2O, this soln was washed (H_2O, saline), and the solvent was removed. The residue was eluted from 60 g of silica gel with an Et_2O–CH_2Cl_2 (1:4) soln. Crystallization of the oil from acetone–hexane gave white crystals, mp 109–113°. The characterization of this substance is given in Table IV.

Preparation of the 5-Substituted-1-indancarboxylic Acids (11). Zinc amalgam was prepared by swirling 2.0 g of mossy zinc with 200 mg of $HgCl_2$, 0.1 ml of 37% HCl, and 3 ml of H_2O. The amalgam was washed with H_2O and transferred to a soln of 250 mg (0.9 mmole) of 5-cyclohexyl-3-oxo-1-indancarboxylic acid in 8 ml of HOAc and 10 ml of 37% HCl. The mixture was heated at reflux temperature for

16 hr, cooled, and diluted with H_2O. The precipitated solid was dissolved in Et_2O, and this solution was washed (H_2O) and evaporated. Crystallization of the residue from Et_2O–hexane gave **5-cyclohexyl-1-indancarboxylic acid (11c)**, the characterization of which is given in Table IV.

6-Chloro-5-cyclohexyl-1-indancarboxylic Acid (5). To a soln of 244 mg (1.0 mmole) of 5-cyclohexyl-1-indancarboxylic acid (11c) in 12 ml of MeCN was added a trace of sublimed $FeCl_3$ and then 0.74 ml of a soln of MeCN containing 71 mg of Cl_2. The soln was stirred at ambient temperature for 2.5 hr, and then diluted by dropwise addition of 11 ml of H_2O. The precipitated solid was collected as 150 mg (54%) of white crystals, mp 146–148°. Recrystallization from Et_2O–petr ether did not alter the melting point. Noguchi and his coworkers[8] record mp 151–152° and Juby and his collaborators[7] report mp 150.5–152.5°. The 4-chloro isomer has mp 120–123°.[8] *Anal.* ($C_{16}H_{19}ClO_2$) C, H, Cl.

Methyl 5-Cyclohexyl-1-indancarboxylate. To a stirred soln of 488 mg (2.0 mmoles) of 5-cyclohexyl-1-indancarboxylic acid in 10 ml of CH_2Cl_2 was added dropwise a soln of 360 mg of 3-methyl-1-*p*-tolyltriazine in 10 ml of CH_2Cl_2.[14] The soln was stirred at ambient temperature for 2 hr, diluted with 50 ml of Et_2O, and washed successively with 1 *N* HCl, H_2O, 1 *N* NaOH, and H_2O. The dried soln was evaporated, and the residual gum was crystallized from dilute MeOH affording 442 mg (85%) of white crystals, mp 45–47°. A sample recrystallized from dilute MeOH had mp 46–47°. *Anal.* ($C_{17}H_{22}O_2$) C, H.

Methyl 6-Acetyl-5-cyclohexyl-1-indancarboxylate (12a). To a soln of 258 mg (1.0 mmole) of methyl-5-cyclohexyl-1-indancarboxylate in 5 ml of CS_2 was added 0.09 ml of AcCl and 380 mg of $AlCl_3$. The mixture was stirred and heated under reflux for 2 hr and then evaporated. To the residue was added 30 ml of iced, dilute H_2SO_4, and the resulting gum was rubbed to a solid. The solid was crystallized from dilute MeOH to give 205 mg (69%) of white crystals, mp 72–73°. *Anal.* ($C_{19}H_{24}O_3$) C, H.

Methyl 6-Acetyl-5-cyclohexyl-1-indancarboxylate Oxime. To a soln of 100 mg (0.33 mmole) of methyl 6-acetyl-5-cyclohexyl-1-indancarboxylate in 5 ml of MeOH was added 62 mg of hydroxylamine hydrochloride and 0.066 ml of pyridine. The mixture was stirred and heated under reflux for 18 hr and then evaporated. The residue was partitioned between EtOAc and H_2O. The organic solution was washed with saline, dried, and evaporated. The residual gum was triturated with petr ether, and the resulting solid was collected to give 80 mg (76%) of white crystals, mp 136–140°. The 80 mg of crystals were recrystallized from dil MeOH to afford 56 mg of white needles, mp 142–143°. *Anal.* ($C_{19}H_{25}NO_3$) C, H, N.

Methyl 6-Acetamido-5-cyclohexyl-1-indancarboxylate (12b). To a stirred, ice-chilled soln of 1.15 g (3.65 mmoles) of methyl 6-acetyl-5-cyclohexyl-1-indancarboxylate oxime in 55 ml of Et_2O was added 1.15 g of PCl_5. The mixture was stirred at ambient temperature for 2 hr and then poured into 120 ml of ice H_2O. The Et_2O soln was separated and washed successively with 1 *N* HCl, H_2O, 1 *N* NaOH, and H_2O. The dried organic soln was evaporated under reduced pressure, and the residual gum was crystallized from Et_2O–petr ether affording, in two crops, 788 mg (68%) of white crystals, mp 167–169°. A sample of this material recrystallized from Et_2O–petr ether had mp 170–171°. *Anal.* ($C_{19}H_{25}NO_3$) C, H, N.

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Irreversible Enzyme Inhibitors. 194.†[1] Hydrophobic Bonding to Some Dehydrogenases by Substituted 5-Phenylethyl-4-hydroxyquinoline-3-carboxylic Acids

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Nineteen derivatives of 4-hydroxyquinoline-3-carboxylic acid bearing substituted phenylethyl groups at the 5 position and Cl at the 8 position were prepared as inhibitors of glutamate, glyceraldehyde-3-phosphate, lactate, and malate dehydrogenases. The 2,6-$Cl_2C_6H_3CH_2CH_2$- and the 2,4-$Cl_2C_6H_3CH_2CH_2$-substituted compounds (**20** and **22**) were the best inhibitors of malate dehydrogenase. Both were complexed 5000-fold more effectively than the parent compound and 20,000-fold more effectively than the substrate L-malate. The best inhibitor of glutamate dehydrogenase was the *o*-$C_6H_5C_6H_4CH_2CH_2$-substituted compound (**8**), being complexed 250-fold more effectively than the parent and 1000-fold more than the substrate L-glutamate.

In a previous paper of this series, the possible utility of inhibitors of glutamate, glyceraldehyde-3-phosphate, lactate, and malate dehydrogenases as target enzymes for the treatment of cancer cells in the resting phase (G_0) was discussed.[2] The study of hydrophobic bonding of derivatives of **1** with substituents at the 5, 6, 7, and 8 positions has shown good hydrophobic bonding to malate dehydrogenase by **2** and good to excellent bonding to three of the four enzymes by **3**, **4**, and **5**, the exception being glyceraldehyde-3-phosphate dehydrogenase.[3,4]

A series of 5-phenylethyl derivatives with the Cl at the 8 position (**3**) was extended to include several compounds bearing substituents on the 5-phenylethyl ring. The phenyl-

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