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Development of Ethyl 3,4-Dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylate, a New Prototype with Oral Antiallergy Activity[1]

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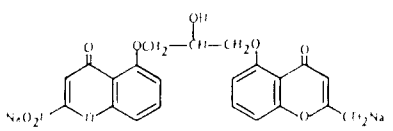
Structural modification of 3,4-dihydro-4-oxoquinazoline-2-carboxylic acid leading to ethyl 3,4-dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylate, a new prototype with oral antiallergy activity of the disodium cromoglycate type, is described. This prototype is 10 times more potent than disodium cromoglycate in the rat passive cutaneous anaphylaxis test. Structure activity studies indicate that a carboxylic acid moiety directly attached to the 2 position of the pyrimidine ring is most favorable for intravenous activity while esters of this acid are preferred for oral activity. The oral activity of ethyl 3,4-dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylate (ED_{50} = 3 mg/kg) places this ester among the more potent orally active antiallergy agents reported to date.

The discovery about a decade ago that inhalation of disodium cromoglycate (1, DSCG) provides protection



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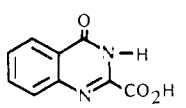
against antigen-induced seasonal allergic asthma[2] has stimulated considerable research seeking agents acting by a similar pharmacological mechanism.

Since DSCG is not absorbed orally this effort has focused on finding orally active agents. In the past few years a number of different chemical series have been reported to possess oral activity in the rat passive cutaneous anaphylaxis (PCA) procedure, a test capable of identifying antiallergy agents pharmacologically related to DSCG. Examples of these orally active series include xanthone-2-carboxylic acids,[3] 2-nitroindan-1,3-diones,[4] 3-(5-tetrazolyl)thioxanthone 10,10-dioxides,[5] 8-azapurinones,[6] 1,4,6,9-tetrahydro-4,6-dioxopyrido[3,2-*g*]quinoline-2,8-dicarboxylic acids,[7] cinnoline-3-propionic acids,[8] 2- and 3-substituted chromones,[9-12] and aryl oxamates.[13]

We wish to report the development of a novel prototype, ethyl 3,4-dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylate, which exhibits oral DSCG-type antiallergy activity. This compound was developed by successive molecular modification of the carbocyclic ring of 3,4-dihydro-4-oxoquinazoline-2-carboxylic acid (3), leading to



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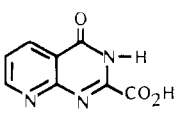

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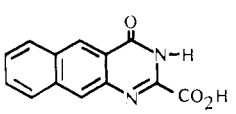

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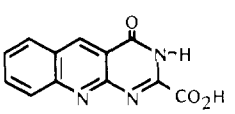

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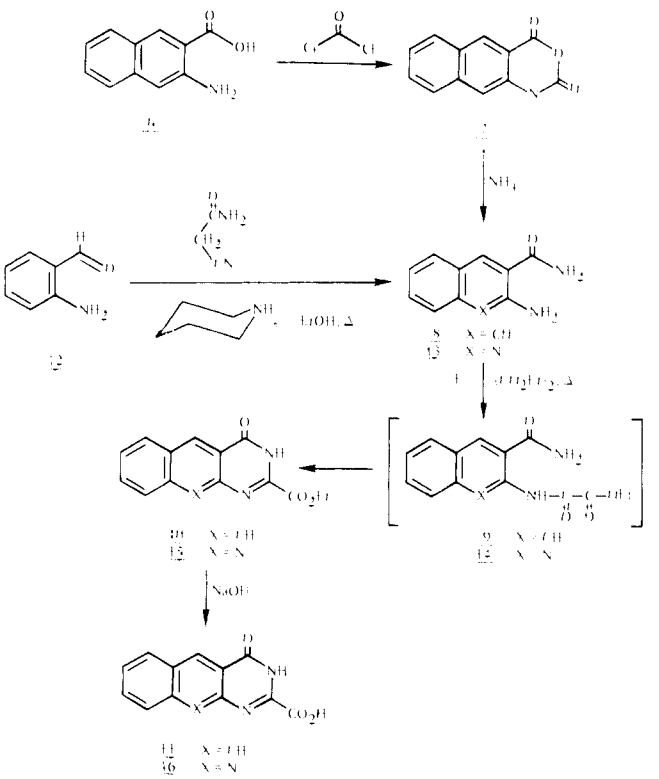
acids **5**, **11**, and then **16**. Initial attempts to increase potency by substitution of the carbocyclic ring of **3** were unsuccessful. However, either incorporation of a nitrogen atom into this ring or fusion of another ring onto **3**, affording **5** and **11**, respectively, did increase potency. A further, marked potency enhancement was achieved with compound **16** which incorporates both of these changes. More significantly, the ethyl ester of **16** displayed potent oral activity.

Scheme I. Synthesis of 3,4-Dihydro-4-oxobenzo[*g*]quinazoline-2-carboxylic Acids (X = CH) and 3,4-Dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylic Acids (X = N)



Chemistry. Although a few 3,4-dihydro-4-oxoquinazoline-2-carboxylic acids (**3**) have previously been reported in the literature,[14] this communication reports the first synthesis of 3,4-dihydro-4-oxopyrido[2,3-*d*]pyrimidine-2-carboxylic acids (**5**), 3,4-dihydro-4-oxobenzo[*g*]quinazoline-2-carboxylic acids (**11**), and 3,4-dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylic acids (**16**). Esters of these four series of 3,4-dihydro-4-oxopyrimi-

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dine-2-carboxylic acids were synthesized by reacting diethyl oxalate with the corresponding (*o*-aminoaryl)-carboxamides[14] (Scheme I). Synthesis of esters **10** and **15** resembles the preparation of 2-substituted pyrimido-[4,5-*b*]quinolin-3(4*H*)-ones reported by Taylor,[15] who employed acid anhydrides instead of diethyl oxalate to effect pyrimidine ring formation.

The new ethyl 3,4-dihydro-4-oxoquinazoline-2-carboxylates **2**a–**e** and their corresponding acids **3**a–**d** were prepared by methods analogous to those reported for the synthesis of the parent ester **2** and acid **3**.[14c] The requisite anthranilamide precursors for these esters were either known compounds[14,16] or prepared from available anthranilic acids via reaction of isatoic anhydrides with ammonia, a procedure well documented in the literature.[17] 2-Aminonicotinamide, the precursor for the pyridopyrimidine ester **4**, was prepared from 2-aminonicotinic acid by reaction of the acid chloride[18] with ammonia. 3-Aminonaphthalene-2-carboxamide (**8**), the precursor to **10**, was prepared from benzoisatoic anhydride (**7**), and 2-aminoquinoline-3-carboxamide[15] (**13**), the precursor for **15**, was prepared by condensation of 2-aminobenzaldehyde (**12**) with cyanoacetamide (Scheme I).

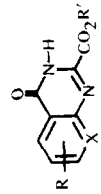
Hydrolysis of the fused pyrimidine-2-carboxylic acid esters **2**, **4**, **10**, and **15** with sodium hydroxide readily provided the corresponding acids **3**, **5**, **11**, and **16**, respectively (Scheme I).

Biological Results and Discussion. Biological evaluation was carried out in the rat passive cutaneous anaphylaxis procedure, a test generally employed for the identification and screening of antiallergy agents pharmacologically related to DSCG. The lead compound, **3**, displayed approximately one-tenth the potency of DSCG on intravenous administration but, like DSCG, had no significant oral activity. Substituent effects on the carbocyclic ring of 3,4-dihydro-4-oxoquinazoline-2-carboxylic acids **3**a–**d** and their corresponding esters **2**a–**e** were examined first in efforts to maximize potency. As shown in Table I, alkoxy, halo, nitro, and trifluoromethyl substitution (**2**a and **3**a,**b**) did not increase potency and other compounds (**2d**,**e** and **3c**,**d**) were inactive when tested at doses comparable to that of **3**.

Next examined were acid and ester prototypes of fused pyrimidines expected to differ in lipophilicity from the quinazolines. Introducing a heteroatom in the ring adjacent to the pyrimidine ring yielded pyrido[2,3-*d*]pyrimidine ethyl ester **4**, which exhibited about five times greater intravenous potency than **3**. This compound approaches the potency of DSCG but again lacked oral activity (Table I). A two- to threefold increase in potency was achieved by fusion of a benzene ring onto **3**, giving benzo[*g*]quinazoline **11** (Table II). The corresponding ethyl ester **10** was the first compound to demonstrate oral activity in this series, albeit at relatively high doses (100 mg/kg). The diminished activity of other 2-substituted benzo[*g*]quinazolin-4(3*H*)-ones (**17**–**19**) indicates that a carboxylic acid group attached directly to the pyrimidine ring is preferred for activity.

Potency was increased markedly with 3,4-dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylic acid **16**, which combines the structural features of **5** and **11**. This compound is approximately 100 times more potent than the original lead compound **3** and 10 times more potent than DSCG. The ethyl ester **15**, corresponding to **16**, displayed oral activity and was significantly more potent (ED_{50} = 3 mg/kg) than **10**. The fact that **15** and **16** are equipotent intravenously clearly shows that esterification facilitates oral absorption. Although this does not

Table I. Antiallergic 3,4-Dihydro-4-oxoquinazoline-2-carboxylic Acids and 3,4-Dihydro-4-oxopyrido[2,3-*d*]pyrimidine-2-carboxylic Acids



compd	R	X	R′	yield, %	mp, °C	solvent	formula	analyses	rat PCA: % protection at various doses (mg/kg iv)			
									1.0	3.0	10	30	50
1	DSCG								55	77	90	99[a]	
3	H	CH	H	55[b]	212–214		$C_9H_6N_2O_3$				52		
3a	6,7-$(MeO)_2$	CH	H	65	296–298 dec	aq HCl	$C_{11}H_{10}N_2O\cdot HCl$	C, H, N				69[a]	
2a	6,7-$(MeO)_2$	CH	Et	66	281–283	DEO[c]–EtOH	$C_{15}H_{14}N_2O_5$	C, H, N				80[a]	
3b	6-NO_2	CH	H	60	420 dec	aq HCl	$C_9H_5N_3O_5\cdot 1.5HCl$	H, N; C[d]				67	
3c	6,8-Br_2	CH	H	90	328 dec	aq HCl	$C_9H_4Br_2N_2O_3\cdot 1.5HCl$	H, N; C[e]					0[f]
3d	6-Cl, 8-CF_3	CH	H	85	320 dec	aq HCl	$C_{10}H_4ClF_3N_2O_3\cdot H_2O$	C, H			0		
2d	6-Cl, 8-CF_3	CH	Et	40	206–207	EtOH	$C_{12}H_8ClF_3N_2O_3$	C, H, N			0		
2e	6-MeO, 7-BzO	CH	Et	45	216–217	DEO[c]–EtOH	$C_{19}H_{18}N_2O_5$	C, H, N			14		
4	H	N	Et	30	190–192	C_6H_6–$C_nH_{1.4}$	$C_{11}N_9N_3O_3$	C, H, N	6	66	96[a]		

[a] Inactive at 100 mg/kg po. [b] Lit.[14c] mp 214–216 °C. [c] DEO is diethyl oxalate. [d] C: calcd, 37.29; found, 36.23. [e] C: calcd, 26.85; found, 26.28. [f] Tested ip.

Table II. Antiallergic 3,4-Dihydro-4-oxobenzo[g]quinazoline-2-carboxylic Acids, 3,4-Dihydro-4-oxopyrimido[4,5-b]quinoline-2-carboxylic Acids, and Related Compounds

compd	X	R′	yield, %	mp,[a] °C	solvent	formula[b]	rat PCA: % protection at various doses (mg/kg)							
							iv			po				
							0.1	1.0	3.0	10	1.0	3.0	10	30	100
11	CH	CO_2Na	68	340 dec	aq base	$C_{13}H_6NaN_2O_3 \cdot H_2O$		14	36	100					0
10	CH	CO_2Et	79	240–224	EtOH	$C_{15}H_{12}N_2O_3 \cdot 0.5H_2O$				27[c]					38
17	CH	H	70[d]	270–272		$C_{12}H_8N_2O$			31						
18	CH	CH_3	81[e]	320		$C_{13}H_{10}N_2O$			15						
19	CH	$(CH_2)_2CO_2H$	50	270–271		$C_{15}H_{12}N_2O_3$				7					
16	N	CO_2Na	73	345–347 dec	H_2O	$C_{12}H_5Na_2N_3O_3 \cdot 0.5H_2O$		92					0	57	96
15	N	CO_2Et	45	247–248	$CHCl_3$	$C_{14}H_{11}N_3O_3$	47	98			12	53	75	72	80
20	N	H	84[f]			$C_{11}H_7N_3O$			33	4					
21	N	OH	f	352–354		$C_{11}H_7N_3O$			41						
1	DSCG						14	55	77	90					

[a] Elemental analyses for new compounds are given in the Experimental Section. [b] Tested ip at 30 mg/kg. [c] See ref 23. [d] Lit.[24] mp 320 °C. [e] Lit.[15] mp 353.5–354.5 °C. [f] Lit.[15] mp > 320 °C.

Table III. Reported Oral Activity of Selected Antiallergy Agents

Compd	Structure	Oral ED_{50} (mg/kg) in PCA Procedure	Potency in the PCA Procedure Rel to DSCG=1	Active Oral Dose in Man	Ref
22		≤ 30		200 mg	5b
23		~ 1.0	25	2 mg/kg	4a,4c
24		~0.2	35-50		6
25		≤ 25-50	50		7
26		~ 4	< 1		8
27		15 5	0.19	4-6 mg	9b
28		2.0	~ 1		10c
29		2	4		12
30		25-200	≥ 1		13

universally hold, as evidenced by the lack of oral activity of compound **4**, it is consistent with reported oral compared to intravenous activity of acids and esters in other series.[13b] The importance of a 2-carboxylic acid moiety is again evidenced by the modest activity of compounds **20** and **21**.

Since our work was completed, Sellstadt[13] et al. reported a series of aryloxamic acid esters (compound **30**, Table III) that display modest DSCG-like activity by oral administration to rats. These oxamic acid derivatives can be visualized as the ring-opened form of our original lead compound **3**. We isolated the oxamate intermediate **14** in our pyrimido[4,5-*b*]quinoline series and found this compound to be equipotent with **15**.

Confirming a DSCG-like spectrum of pharmacological action, compound **15** was inactive against intradermal histamine injections in the rat PCA test at doses of 10 mg/kg iv or 100 mg/kg po, did not antagonize histamine-induced bronchoconstriction in conscious guinea pigs up to 100 mg/kg po, and had no significant activity against carrageenan-induced rat-foot edema at doses of 10 mg/kg po. This suggests that ethyl 3,4-dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylate, like DSCG, inhibits the release of the mediators of anaphylaxis.

The activity of some of the more potent, known orally active, antiallergy agents is summarized in Table III for comparison. Most of these agents (compounds **22**–**30**) have ED_{50} values in the PCA procedure ranging from 1 to 25 mg/kg and some of them (**22**, **23**, and **27**) are reported to have oral activity in clinical trials. With an ED_{50} of 3.0 mg/kg, the new prototype **15** compares favorably in oral potency in the PCA procedure with agents reported to date.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Analytical Department of Pfizer Inc. Where the analyses are indicated only by the symbols of the elements,

the analytical values were within ±0.4% of theoretical values. NMR and/or mass spectra were obtained on all compounds and were consistent with the structures. The NMR spectra were recorded on either a Varian A-60 or T-60 spectrometer and mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E spectrometer.

2-Aminonicotinamide. 2-Aminonicotinoyl chloride hydrochloride was prepared by reaction of 2-aminonicotinic acid (15.0 g, 0.11 mol) with PCl_5, according to methods described by Miescher and Kägi.[18] Over the period of 1 h, NH_3 was bubbled into a solution of the acid chloride in CH_3CN. After cooling, the mixture was diluted with H_2O and extracted with EtOAc. Concentration of the solvent yielded 8.16 g (55% based on the acid) of the desired amide: mp 196–198 °C (lit.[19] mp 199 °C).

Benzoisatoic Anhydride (7). 3-Amino-2-naphthoic acid (**6**; 25.0 g, 0.133 mol) was dissolved with warming in a mixture of H_2O (50 mL), HCl (50 mL), and dioxane (100 mL). Phosgene was passed into the solution with good stirring at a rate such that the temperature was held below 50 °C and bubbles of gas escaped slowly into an NH_3 scrubber attached to the reaction flask. After phosgene was passed into the mixture for 4 h, the residual phosgene was blown out by passing air through the mixture. The product was filtered, washed with cold H_2O, and dried to give 26.5 g (94%) of **7**: mp 390 °C dec.

3-Aminonaphthalene-2-carboxamide (8). Ammonia, NH_3, was intermittently bubbled into a suspension of benzoisatoic anhydride (**7**; 5.0 g, 2.25 mmol) and EtOH (80 mL) for a period of 2 days. The bright green solid which formed was filtered from the reaction mixture, dried, and then recrystallized from EtOH to yield 1.95 g (46%) of the title amide, mp 234–235 °C, which was used directly in the next step.

2-Aminoquinoline-3-carboxamide (13). This compound was prepared in 84% yield by condensation of 2-aminobenzaldehyde (**12**) with cyanoacetamide: mp 240–242 °C (lit.[20] mp 240 °C).

Ethyl 3,4-Dihydro-4-oxopyrido[2,3-*d*]pyrimidine-2-carboxylate (4). A mixture of diethyl oxalate (530 mg, 3.65 mmol) and 2-aminonicotinamide (500 mg, 3.65 mmol) was heated to reflux overnight. The mixture was then cooled in an ice bath, and the yellow solid which precipitated was filtered and recrystallized from C_6H_6–C_6H_{14} (1:1) to yield 196 mg (30%) of **4**: mp 190–192 °C. Anal. ($C_{10}H_9N_3O_3$) C, H, N.

Ethyl 3,4-Dihydro-4-oxobenzo[*g*]quinazoline-2-carboxylate (10). Diethyl oxalate (2.35 g, 16.1 mmol), NaOMe (10 mg), and 3-aminonaphthalene-2-carboxamide (**8**; 1.50 g, 8.05 mmol) were mixed together and heated to reflux for 2 days. The mixture was then cooled in an ice bath and the brown precipitate recovered by filtration. Recrystallization of the solid from EtOH gave 1.76 g (79%) of the desired ester: mp 240–242 °C. Anal. ($C_{13}H_{12}N_2O_3 \cdot 0.5H_2O$) H, N; C: calcd, 64.97; found, 65.44.

Ethyl 3,4-Dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylate (15). A mixture of 2-aminoquinoline-3-carboxamide (**13**; 25.0 g, 0.134 mol) and diethyl oxalate (500 mL) was heated to reflux for 4 h while the EtOH-H_2O which formed was distilled off. The reaction was then cooled to room temperature and the product filtered, washed with diethyl oxalate, and air-dried to give 22.6 g of a brownish green solid: mp 245–246 °C. This was purified by recrystallization, with decolorization, from hot $CHCl_3$ to yield 16.2 g (45%) of **15** as an off-white solid: mp 247–248 °C. Anal. ($C_{14}H_{11}N_3O_3$) C, H, N.

3,4-Dihydro-4-oxobenzo[*g*]quinazoline-2-carboxylic Acid (11). Ester **10** (1.05 g, 3.92 mmol) was added to 15% NaOH (20 mL) and the mixture refluxed for 2 days, then cooled to room temperature, and acidified to pH 2 with 10% HCl. After evaporation to dryness in vacuo, the residue was treated with MeOH–H_2O (1:1, 50 mL) and the suspension filtered to give 0.70 g of yellow crystals which was added to a saturated solution of $NaHCO_3$ (35 mL) and H_2O (20 mL). The mixture was stirred for 30 min and the yellow solid filtered and dried to yield 0.64 g (55%) of acid **11** as the disodium salt monohydrate: mp 340 °C dec. Anal. ($C_{13}H_6N_2O_3 \cdot 2Na \cdot H_2O$) C, H, N.

3,4-Dihydro-4-oxopyrimido[4,5-*b*]quinoline-2-carboxylic Acid (16). Ester **15** (5.0 g, 18.5 mmol) was added to 15% NaOH (200 mL) and the mixture stirred for 20 h at room temperature. The yellow solid which formed was filtered from the reaction mixture and dissolved in H_2O, and the solution was adjusted to pH 7 by slow addition of 10% HCl. The precipitate was filtered and triturated with MeOH, the slurry was filtered, and the resulting filter cake was washed with MeOH and dried to yield 4.0 g (73%) of **16** as the disodium salt hemihydrate: mp 245–347 °C dec. Anal. ($C_{12}H_5N_3O_3 \cdot Na_2 \cdot 0.5H_2O$) C, H, N.

Pharmacological Methods. Passive Cutaneous Anaphylaxis (PCA) Assay. The ability of agents to interfere with PCA reactions was measured in male Charles River Wistar rats, 170–210 g. Reaginic antiserum was prepared according to Mota,[21] using hen egg albumin and *Bordetella pertussis*, or according to Petillo and Smith,[22] using hen egg albumin and $Al(OH)_3$. A 0.1-mL portion of a dilution of reaginic antiserum sufficient to cause a 15-mm wheal at the time of challenge was injected intradermally (id) into the shaved skin of a normal rat's back; 48 h later drug or saline was injected intravenously, followed by 2.5 mg of Evan's blue dye and 5 mg of egg albumin in saline; immediately thereafter 60 μg of histamine dihydrochloride and 0.5 μg of serotonin creatinine sulfate were injected intradermally in 0.1-mL volumes at separate sites as checks for antihistaminic, antiserotinergic, and unspecific types of blockade. Thirty minutes later the animals were asphyxiated using chloroform, and the skin of the back was removed and reversed for observation. A score was assigned to each injection site equal to the product of the diameter of the site in millimeters and a grade of 0.5, 1, 2, 3, or 4 proportional to intensity of dye coloration. The scores for a given injection site were summed for each group of five or seven animals and compared to the saline-treated control. The difference was expressed as percent blockade. Each of the values in Tables I and II was derived from one group of animals with the exceptions of values for compound **15** and DSCG. Twenty groups of animals were used to generate the data for compound **15** and 88 groups were used for DSCG. Values less than 35% are insignificant. The method is easily reproducible in other laboratories as judged by the ED_{50} value of ~1 mg/kg reported by many for DSCG; at 1 mg/kg we observed 54.9 ± 3.8% inhibition, $n = 25$.

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Syntheses and Antiinflammatory Actions of 4,5,6,7-Tetrahydroindazole-5-carboxylic Acids

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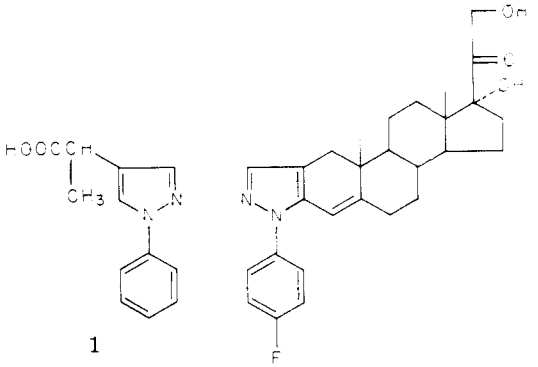
A novel series of 1-aryl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acids and 2-aryl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylic acids were synthesized via condensation between a phenylhydrazine and a 2-(hydroxymethylene)cyclohexanone-4-carboxylate, and the antiinflammatory activity was determined. In the carrageenan edema test, 1-aryl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acids exhibited fairly high antiinflammatory activity. However, the 2-aryl isomers were far less active than the former. The most active compound of the series was 1-phenyl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acid, which had an ED_{50} value of 3.5 mg/kg.

Antiinflammatory, analgesic, antipyretic, and antirheumatic activity has been reported for acidic pyrazole derivatives.[1,2] One of these derivatives, 2-(1-phenylpyrazol-4-yl)propionic acid (1),[1] has been shown to be

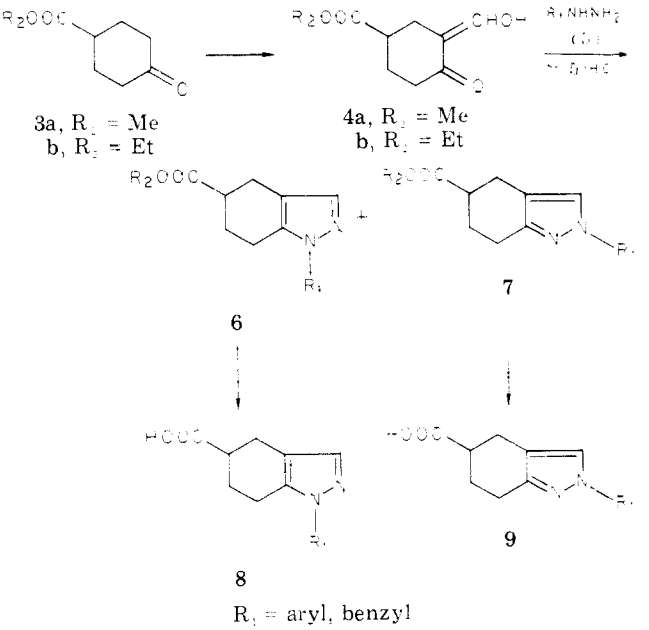


1 2

clinically active in the treatment of rheumatic disorders. In addition, it has been reported that pyrazole corticoids[3,4] are more active than parent corticoids. One of these derivatives, 17α,21-dihydroxy-20-oxopregn-4-eno[3,2-c]-2′-(4-fluorophenyl)pyrazole (**2**),[4] has been used clinically as a topical antiinflammatory agent. These reports led us to synthesize acidic 4,5,6,7-tetrahydroindazole-5-carboxylic acids and related compounds.

Chemistry. The novel 4,5,6,7-tetrahydroindazole-5-carboxylic acids and related compounds were synthesized by a modified Auwers's method[5] (Scheme I) and are collected in Table I. 2-(Hydroxymethylene)cyclohexanone-4-carboxylate (**4**) was obtained by formylation of cyclohexanone-4-carboxylate (**3**) under conditions using Ainsworth's method.[6] The appropriate substituted hydrazine **5** was cyclized with **4** to two isomers, 1-substituted 4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylate **6** and 2-substituted 4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylate **7**, which could be separated by column chromatography or fractional recrystallization. Hydrolysis of **6** and **7** af-

Scheme I



3a, R_2 = Me
b, R_2 = Et

4a, R_2 = Me
b, R_2 = Et

6 7

8 9

R_1 = aryl, benzyl

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