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

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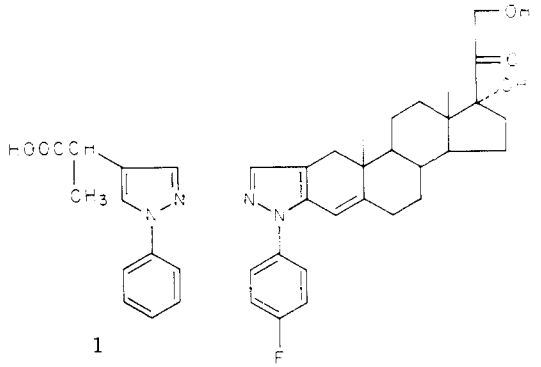
A novel series of 1-aryl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acids and 2-aryl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylic acids were synthesized via condensation between a phenylhydrazine and a 2-(hydroxymethylene)cyclohexanone-4-carboxylate, and the antiinflammatory activity was determined. 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

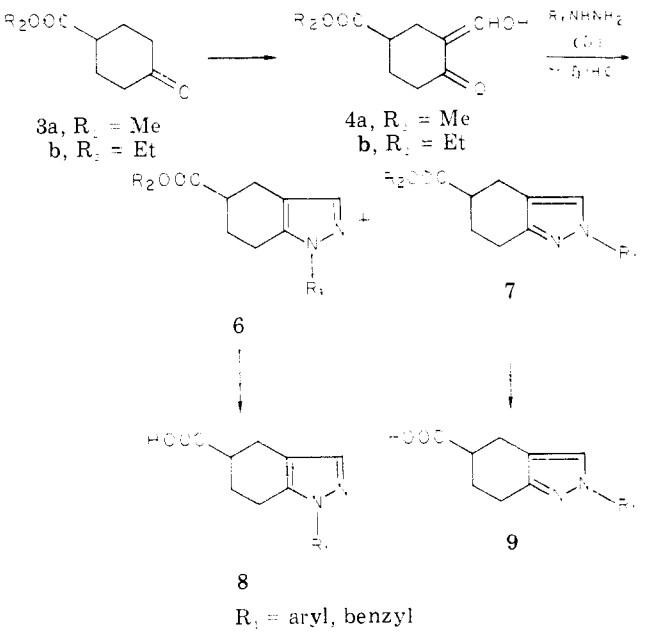


1 2

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

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

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-

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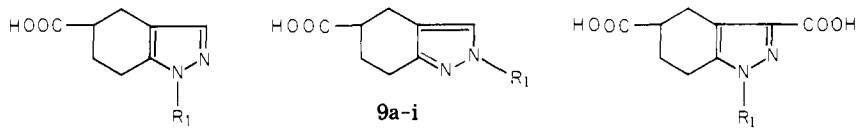
Table I. Physical Properties and Pharmacological Activities of 4,5,6,7-Tetrahydroindazole-5-carboxylic Acid Derivatives

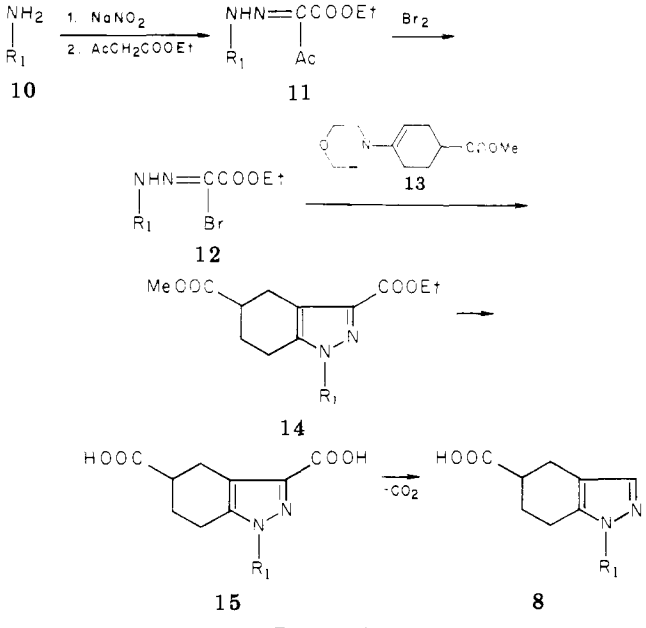


8a-m 9a-i 15a-d

compd no.	R_1	yield,[a] %	mp, °C	recrystn solvent	formula[b]	inhibitory act. on carrageenan paw edema: dose, mg/kg po	inhibitory act. on carrageenan paw edema: % inhibn[c]
8a	C_6H_5	85.7	181-182	Me_2CO	$C_{14}H_{14}N_2O_2$	10	72.6***
						2.5	40.6**
8b	4-ClC_6H_4	77.2	192.5-194	MeOH	$C_{14}H_{13}N_2O_2Cl$	25	60.0***
						10	39.4**
8c	3-FC_6H_4	62.5	157-158	EtOH-*n*-hexane	$C_{14}H_{13}N_2O_2F$	25	38.2*
8d	4-MeC_6H_4	55.7	177-178.5	EtOH-*n*-hexane	$C_{15}H_{16}N_2O_2$	25	38.7*
8e	2-MeC_6H_4	74.0	171-172	EtOH-*n*-hexane	$C_{15}H_{16}N_2O_2$	25	0
8f	4-$MeOC_6H_4$	80.5	167-170	EtOH-*n*-hexane	$C_{15}H_{16}N_2O_3$	25	9.8
8g	4-HOC_6H_4	86.2[d]	263-265	MeOH	$C_{14}H_{14}N_2O_3$	100	14.7
8h	3-$CF_3C_6H_4$	57.6	145-146.5	*i*-PrOH-EtOH	$C_{15}H_{13}N_2O_2F_3$	25	35.6*
8i	2-C_5H_4N	73.8	163-164	EtOH-*n*-hexane	$C_{13}H_{13}N_3O_2$	25	57.9**
8j	4-C_5H_4N	51.5	263-264	MeOH	$C_{13}H_{13}N_3O_2$	25	13.4
8k	1-$C_{10}H_7$[f]	58.4	171.5-172.5	EtOH	$C_{18}H_{16}N_2O_2$	25	13.1
8l	$C_6H_5CH_2$	87.9	160-161	MeOH	$C_{15}H_{16}N_2O_2$	25	15.9
8m	4-$C_6H_5CH_2$-OC_6H_4	92.5	168-169	MeOH	$C_{21}H_{20}N_2O_3$	NT[e]	
9a	C_6H_5	74.1	165.5-167	EtOH-*n*-hexane	$C_{14}H_{14}N_2O_2$	100	36.4*
9b	4-ClC_6H_4	81.0	203-204	EtOH	$C_{14}H_{13}N_2O_2Cl$	100	17.9
9c	4-MeC_6H_4	75.0	199.5-200.5	MeOH	$C_{15}H_{16}N_2O_2$	100	10.8
9d	2-MeC_6H_4	75.4	152-154	EtOH-*n*-hexane	$C_{15}H_{16}N_2O_2$	100	38.0*
9e	4-$MeOC_6H_4$	90.0	173-174	MeOH	$C_{15}H_{16}N_2O_3$	100	6.0
9f	3-$CF_3C_6H_4$	59.0	128-129.5	*i*-PrOH-*n*-hexane	$C_{15}H_{13}N_2O_2F_3$	100	14.8
9g	2-C_5H_4N	89.8	171-172	Me_2CO	$C_{13}H_{13}N_3O_2$	100	11.5
9h	1-$C_{10}H_7$	70.4	192-193	EtOH-*n*-hexane	$C_{18}H_{16}N_2O_2$	25	0
9i	$C_6H_5CH_2$	67.9	181.5-183	MeOH	$C_{15}H_{16}N_2O_2$	100	3.7
15a	C_6H_5	84.5	277 dec	dioxane	$C_{14}H_{14}N_2O_4$	100	0
15b	4-ClC_6H_4	97.0	278 dec	MeOH	$C_{15}H_{13}N_2O_4Cl$	100	0
15c	4-MeC_6H_4	quant	266 dec	dioxane	$C_{16}H_{16}N_2O_4$	100	0
15d	3-$CF_3C_6H_4$	quant	263 dec	dioxane	$C_{16}H_{13}N_2O_4F_3$	100	0
phenylbutazone						50	43.4**
indomethacin						3	35.5*

[a] The yield from hydrolysis of the ester. [b] All new compounds were analyzed for C, H, and N. [c] Significant difference from control: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. [d] The yield from the catalytic hydrogenation of the benzyl compound. [e] NT = not tested. [f] Naphthyl.

Scheme II

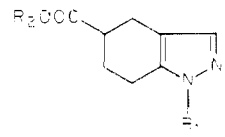


R_1 = aryl

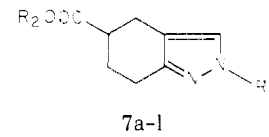
forded 1-substituted 4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acid **8** and 2-substituted 4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylic acid **9**, respectively. In the case of cyclization, the use of free base **5** (method A) preferentially gave **7**. However, when **5** was used as an HCl salt (method B), the main product was **6** with only a trace of **7**. The structure of **8** was confirmed by preparing **8** according to Scheme II (method C). Incidentally, the structure of the other isomer could be confirmed as **7**. Ethyl α-bromoglyoxylate substituted hydrazone **12** was prepared from aniline derivatives **10** under conditions using Sharp's method.[7] **12** was cyclized with methyl 1-morpholinocyclohexene-4-carboxylate (**13**) to methyl 1-substituted 3-carbethoxy-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylate (**14**) according to a modified method.[8] Alkaline hydrolysis of **14** afforded 1-substituted 4,5,6,7-tetrahydro-1*H*-indazole-3,5-dicarboxylic acid (**15**), which was converted into **8** by decarboxylation. The physical properties of **8** obtained as shown in Scheme II were identical with those obtained via Scheme I. The physical properties of intermediates **6**, **7**, and **14** are shown in Table II.

Pharmacology and Structure-Activity Relationships. The test compounds were first subjected to the

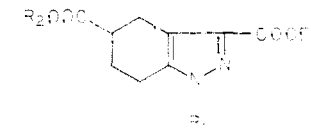
Table II. Intermediates for Table I



6a-o



7a-l



14a-d

compd no.	R_1	R_2	method	yield, %	mp, °C	recrystn solvent	formula[a]
6a	C_6H_5	Et	A	14.4	61-62	EtOH-*n*-hexane	$C_{16}H_{14}N_2O_2$
			B	88.9			
6b	C_6H_5	Me	B	71.7	108-109	MeOH	$C_{14}H_{16}N_2O_2$
6c	4-ClC_6H_4	Et	A	31.3	180-185 (0.15)[b]		$C_{16}H_{13}N_2O_2Cl$
			B	37.8			
6d	4-ClC_6H_4	Me	B	52.9	95-96.5	MeOH	$C_{15}H_{13}N_2O_2Cl$
6e	4-MeC_6H_4	Et	A	9.3	56.5-58	*n*-hexane	$C_{17}H_{16}N_2O_2$
			B	32.0			
6f	3-$CF_3C_6H_4$	Et	A	32.0	130-156 (0.1)[b]		$C_{17}H_{13}N_2O_2F_3$
6g	4-$MeOC_6H_4$	Et	A	8.1	67.5-69	EtOH-*n*-hexane	$C_{17}H_{16}N_2O_3$
6h	2-MeC_6H_4	Et	A	14.4	120-138 (0.12)[b]		$C_{17}H_{16}N_2O_2$
6i	3-FC_6H_4	Et	B	65.5	163-180 (0.2)[b]		$C_{16}H_{13}N_2O_2F$
6j	2-C_5H_4N	Et	B	49.8	75-76	EtOH	$C_{15}H_{13}N_3O_2$
6k	2-C_5H_4N	Me	B	35.1	165-180 (0.015)[b]		$C_{14}H_{11}N_3O_2$
6l	4-C_5H_4N	Et	B	59.0	83-85	Et_2O	$C_{15}H_{13}N_3O_2$
6m	1-$C_{10}H_7$	Et	B	36.8	140-186 (0.1)[b]		$C_{20}H_{16}N_2O_2$
6n	$C_6H_5CH_2$	Et	B	53.8	167-169[c]	EtOH-Et_2O	$C_{17}H_{17}N_2O_2Cl$[c]
6o	4-$C_6H_5CH_2OC_6H_4$	Me	B	17.1	88-89	EtOH	$C_{24}H_{22}N_2O_3$
7a	C_6H_5	Et	A	40.7	93-94.5	EtOH-*n*-hexane	$C_{16}H_{14}N_2O_2$
			B	9.9			
7b	C_6H_5	Me	B	3.0	122-123	MeOH	$C_{14}H_{12}N_2O_2$
7c	4-ClC_6H_4	Et	A	52.6	145-146	EtOH	$C_{16}H_{13}N_2O_2Cl$
			B	3.0			
7d	4-ClC_6H_4	Me	B	4.2	180-181	MeOH	$C_{14}H_{11}N_2O_2Cl$
7e	4-MeC_6H_4	Et	A	45.8	99-100.5	EtOH-*n*-hexane	$C_{17}H_{16}N_2O_2$
			B	2.0			
7f	3-$CF_3C_6H_4$	Et	A	31.6	116-117	EtOH	$C_{17}H_{13}N_2O_2F_3$
7g	4-$MeOC_6H_4$	Et	A	57.6	90-91.5	EtOH-*n*-hexane	$C_{17}H_{16}N_2O_3$
7h	2-MeC_6H_4	Et	A	30.4	140-158 (0.18)[b]		$C_{17}H_{16}N_2O_2$
7i	3-FC_6H_4	Et	B	2.4	123-124	EtOH	$C_{16}H_{13}N_2O_2F$
7j	2-C_5H_4N	Et	B	10.5	58-59	EtOH-*n*-hexane	$C_{15}H_{13}N_3O_2$
7k	1-$C_{10}H_7$	Et	B	4.3	140-180 (0.1)[b]		$C_{20}H_{16}N_2O_2$
7l	$C_6H_5CH_2$	Et	B	3.4	150-176 (0.09)[b]		$C_{17}H_{16}N_2O_2$
14a	C_6H_5	Me	C	68.5	109-110	Me_2CO-Et_2O	$C_{14}H_{20}N_2O_4$
14b	4-ClC_6H_4	Me	C	72.0	154-155	Me_2CO	$C_{14}H_{19}N_2O_4Cl$
14c	4-MeC_6H_4	Me	C	76.0	121-122	Me_2CO	$C_{15}H_{22}N_2O_4$
14d	3-$CF_3C_6H_4$	Me	C	49.6	72-73	Me_2CO-*n*-hexane	$C_{15}H_{19}N_2O_4F_3$

[a] All new compounds were analyzed for C, H, and N except 6c,f,h,i,k,m and 7h,k,l. [b] Boiling point. [c] Hydrochloride.

Table III. Pharmacological Activities (po) of 8a,b and Some Reference Drugs

compd	ED_{50}, mg/kg: inhibitory effects on carrageenan paw edema	therapeutic effects on established adjuvant arthritis	analgesic effects on acetic acid writhing	ulcerogenic effects, MUD,[a] mg/kg
8a	3.5 (1.9-6.3)[b]	1.5 (1.0-2.3)	4.7 (2.8-8.0)	20 (13-38)
8b	17 (7-30)	6.4 (4.9-9.0)	7.0 (3.7-13)	70 (37-110)
indomethacin	3.8 (2.1-6.8)	0.3 (0.1-0.7)	6.3 (3.7-11)	5.6 (2.8-9.0)
flufenamic acid	20 (11-38)	5.1 (2.4-10)	160 (119-216)	50 (23-85)
phenylbutazone	78 (39-156)	12 (6.3-23)	810 (450-1458)	90 (47-200)

[a] MUD = minimum ulcerogenic dose. [b] Figures in parentheses indicate 95% confidence limits.

carrageenan edema test according to the method of Winter.[9] The compounds, as a suspension in 0.5% CMC, were administered orally to rats in doses of 100 and/or 25 mg/kg. One hour later, 0.05 mL of a 1% solution of carrageenan was injected into the hind paw. Seven animals were used to test each dose. In Table I, the inhibitory activities on carrageenan paw edema are expressed as a percent inhibition, along with the activities of the standard compounds, phenylbutazone and indomethacin.

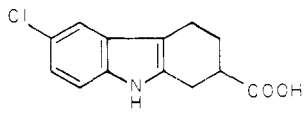
Compound **8a** revealed an activity almost equal to that of indomethacin. However, in general, substituents such as halogen, Me, OMe, CF_3, and OH groups in the phenyl ring of **8** reduced the activity of the parent compound. The reduction in the activity was marked, especially in the case of the 2-Me, 4-OMe, and 4-OH analogues. Furthermore, introduction of 2-C_5H_4N (2-pyridyl), 4-C_5H_4N, $C_6H_5CH_2$, and 1-$C_{10}H_7$ (1-naphthyl) in place of the phenyl ring showed lower activity than that of **8a**. Interestingly, 2-substituted 4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acids **9a**–**i** were less active than 1-substituted 4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acids **8a**–**l** in general. In addition, 1-substituted 4,5,6,7-tetrahydro-1*H*-indazole-3,5-dicarboxylic acids **15a**–**d** were inactive even at a dose of 100 mg/kg po. Two compounds, **8a** and **8b**, were

selected for further pharmacological tests. The results obtained are shown in Table III. The ED_{50} values were obtained from the dose–response curve in the carrageenan edema assay as described above. The activity of **8a** was equal to that of indomethacin, while **8b** revealed an activity almost equal to that of flufenamic acid.

The therapeutic test in rats with established adjuvant arthritis was carried out using the method of Newbould.[10] The compounds were administered orally once a day for 14 days starting at the 14th day after adjuvant inoculation. The effects of treatment were assessed by measurements of foot swelling (volume). Inhibitory effects were expressed as ED_{50} values estimated from the dose–response curve of the tested compounds. In this assay, **8a** had one-fifth lower activity than indomethacin. **8b** was less active than flufenamic acid but more active than phenylbutazone. As for analgesic activity measured according to the acetic acid writhing method of Koster (10 male mice at each dose),[11] **8a** and **8b** were comparable to indomethacin.

In addition, the induction of gastric lesions was tested using the modified method of Lumachi,[12] as described in the Experimental Section. **8a** was less active than indomethacin but more active than flufenamic acid. **8b** was less potent than flufenamic acid.

Differing from arylacetic acids which have been well reported as antiinflammatory drugs, **8a** and **8b** are "tied back" arylpropionic acids, among which 1,2,3,4-tetrahydrocarbazole-2-carboxylic acids[13]—for instance, 6-chloro-1,2,3,4-tetrahydrocarbazole-2-carboxylic acid



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(**16**)—are known and are the first, highly potent compounds. Further studies are in progress and the data will be published in succeeding papers.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on a JASCO DS-403G spectrophotometer, and NMR spectra were determined on a JEOL C-60H (60 MHz) spectrometer in $CDCl_3$ (unless otherwise noted) with added Me_4Si. UV spectra were determined on a Hitachi EPS 2 spectrophotometer. Where the analyses are indicated only by the symbols of the elements, the analytical results were within ±0.4% of theoretical values.

Ethyl 2-(Hydroxymethylene)cyclohexanone-4-carboxylate (4b). A mixture of Na (7.65 g, 0.333 mol), dry Et_2O (1 L), ethyl cyclohexanone-4-carboxylate[14] (**3b**; 50 g, 0.294 mol), and HCOOEt (35.6 g, 0.480 mol) was placed in a 2-L, three-necked flask equipped with a stirrer, stopper, and vent tube. The reaction was initiated by the addition of EtOH (2.5 mL) to the stirred mixture, which was then placed in a cold-water bath. Stirring was continued for 6 h. EtOH (7.5 mL) was added, and the mixture was stirred for 3 h. After the addition of H_2O (70 mL), the mixture was shaken in a 1-L separatory funnel. The Et_2O layer was washed with H_2O (15 mL), and the combined aqueous extracts were washed with Et_2O (30 mL). The aqueous layer was acidified with 6 N HCl (50 mL), and the mixture was extracted three times with Et_2O (100 mL). The ether solution was washed with saturated NaCl solution (10 mL), dried with Na_2SO_4, and fractionally distilled to afford a pale yellow oil, **4b**: 19.8 g, 34.0%; bp 75–95 °C (0.1 mm); NMR δ 1.22 (t, J = 8 Hz, 3 H, CH_3), 4.08 (q, J = 8 Hz, 2 H, CH_2Me), 8.6 (s, 1 H, =CHO); IR 1730 cm^{-1} (COOEt).

Similarly, **methyl 2-(hydroxymethylene)cyclohexanone-4-carboxylate (4a)** was also obtained from methyl cyclohexanone-4-carboxylate (**3a**) and HCOOMe by treatment with NaOMe or 50% NaH: bp 110–115 °C (2 mm); yield 33.0%.

Method A. Ethyl 1-Phenyl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylate (6a) and Ethyl 2-Phenyl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylate (7a). A mixture of **4b** (4.7 g, 0.024 mol) and phenylhydrazine (3.2 g, 0.03 mol) in EtOH (180 mL) was refluxed for 6 h and concentrated to dryness in vacuo. The residue was separated on alumina chromatography using C_6H_6. The first eluate afforded a white solid which was crystallized from EtOH–n-C_6H_{14}, yielding **7a**: 2.61 g, 40.7%; colorless needles; mp 93–94.5 °C; UV λ_{max} (MeOH) 268 nm (log ϵ 4.28); IR 1725 cm^{-1} (COOEt); NMR δ 1.18 (t, J = 8 Hz, 3 H, CH_3), 4.04 (q, J = 8 Hz, 2 H, CH_2Me). Anal. ($C_{16}H_{18}N_2O_2$) C, H, N. The second eluate afforded **6a** (0.92 g, 14.4%) as colorless plates from EtOH–n-C_6H_{14}: mp 61–62 °C; UV λ_{max} (MeOH) 250 nm (log ϵ 4.13); IR 1729 cm^{-1} (COOEt); NMR δ 1.20 (t, J = 8 Hz, 3 H, CH_3), 4.04 (q, J = 8 Hz, 2 H, CH_2Me). Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

Method B. Methyl 1-(4-Chlorophenyl)-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylate (6d) and Methyl 2-(4-Chlorophenyl)-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylate (7d). A mixture of **4a** (1.44 g, 0.008 mol) and (4-chlorophenyl)hydrazine hydrochloride (1.04 g, 0.008 mol) in MeOH (23 mL) was stirred at 45–50 °C for 6 h and evaporated under reduced pressure. The residue was separated by alumina chromatography using C_6H_6. The first eluate afforded a white solid which was crystallized from MeOH, yielding **7d**: 95 mg, 4.2%; colorless needles; mp 180–181 °C; UV λ_{max} (MeOH) 274 nm (log ϵ 4.37); IR 1725 cm^{-1} (COOMe); NMR δ 3.55 (s, 3 H, CH_3). Anal. ($C_{15}H_{15}N_2O_2Cl$) C, H, N. The second eluate afforded **6d** (1.2 g, 52.9%) as colorless needles from MeOH: mp 95–96.5 °C; UV λ_{max} (MeOH) 256 nm (log ϵ 4.19); IR 1735 cm^{-1} (COOMe); NMR δ 3.70 (s, 3 H, CH_3). Anal. ($C_{15}H_{15}N_2O_2Cl$) C, H, N.

1-Phenyl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic Acid (8a). A solution of **6a** (2.42 g, 0.009 mol) and 10% NaOH (8.8 mL) in MeOH (45 mL) was refluxed for 1.5 h. The reaction mixture was concentrated and the residue was diluted with H_2O and washed ($CHCl_3$). The aqueous layer was acidified with HCl. The resulting precipitate was collected and crystallized from Me_2CO to yield a colorless prism of **8a**: 1.68 g, 85.7%; mp 181–182 °C; IR 1715 cm^{-1} (COOH). Anal. ($C_{14}H_{14}N_2O_2$) C, H, N.

1-(4-Hydroxyphenyl)-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic Acid (8g). A mixture of **4a** (30.1 g, 0.163 mol), [4-(benzyloxy)phenyl]hydrazine[15] (32 g, 0.149 mol), and concentrated HCl (15.5 mL) in MeOH (500 mL) was stirred at 48–52 °C for 6 h and evaporated under reduced pressure. The residue was diluted with H_2O, made basic with Na_2CO_3, and extracted with $CHCl_3$, and the washed and dried extract was concentrated. The dark brown, oily residue (35 g) was separated by silica gel chromatography using $CHCl_3$, and the eluate afforded a solid which was crystallized from EtOH, yielding methyl 1-[4-(benzyloxy)phenyl]-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylate (**6o**): 9.22 g, 17.1%; colorless, fine needles; mp 88–89 °C. Anal. ($C_{22}H_{22}N_2O_3$) C, H, N.

A solution of **6o** (9.0 g, 0.025 mol) and NaOH (1.2 g) in 90% aqueous MeOH was refluxed for 2 h. The reaction mixture was concentrated, and the residue was diluted with H_2O and washed ($CHCl_3$). The aqueous layer was acidified with HCl. The resulting precipitate was collected and crystallized from EtOH to yield colorless plates of 1-[4-(benzyloxy)phenyl]-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acid (**8m**): 8.04 g, 92.5%; mp 168–169 °C. Anal. ($C_{21}H_{20}N_2O_3$) C, H, N.

A solution of **8m** (7.95 g, 0.023 mol) and 5% NaOH (20 mL) in MeOH (150 mL) was hydrogenated over 5% Pd/C (1.5 g) at room temperature for 1 h. The mixture was filtered, evaporated, and acidified with HCl. The resulting precipitate was collected and crystallized from MeOH to yield a colorless prism of **8g**: 5.3 g, 90.2%; mp 263–265 °C. Anal. ($C_{14}H_{14}N_2O_3$) C, H, N.

Ethyl 2,3-Dioxobutanoate 2-(4-Chlorophenyl)hydrazone (11b, R_1 = 4-ClC_6H_4). 4-Chloroaniline (38.4 g, 0.3 mol) was dissolved by heating in H_2O (150 mL) containing concentrated HCl (75 mL). The resulting hot solution was poured onto ice and the amine hydrochloride precipitated. A solution of $NaNO_2$ (20.7 g, 0.3 mol) in H_2O (38 mL) was added to this mixture, and the resulting diazonium solution was added rapidly to a solution of ethyl acetoacetate (39 g, 0.3 mol) in EtOH (225 mL) and ice water (1.5 L) containing AcONa (75 g, 0.9 mol). The reaction mixture immediately thickened as the product precipitated out of solution. After the mixture was stirred for 2.5 h the yellow solid was removed by filtration and washed with H_2O. Recrystallization from EtOH yielded **11b**: 73 g, 91%; mp 81–84 °C.

Ethyl 2,3-dioxobutanoate 2-phenylhydrazone (11a, R_1 = C_6H_5): mp 61–64 °C; 65%.

Ethyl 2,3-dioxobutanoate 2-(4-tolyl)hydrazone (11c, R_1 = 4-MeC_6H_4): mp 61–65 °C; 68%.

Ethyl 2,3-dioxobutanoate 2-[3-(trifluoromethyl)phenyl]hydrazone (11d, R_1 = 3-$CF_3C_6H_4$): mp 69–71 °C; 80%.

Ethyl α-Bromoglyoxylate (4-Chlorophenyl)hydrazone (12b, R_1 = 4-ClC_6H_4). 11b (48.4 g, 0.18 mol) was added to a mixture of AcOH (400 mL) and Ac_2O (132 mL) containing AcONa (36 g, 0.44 mol), and the temperature was lowered to 0 °C. To this was added over 1 h Br_2 (9.2 mL, 0.18 mol) dissolved in AcOH (120 mL). After the mixture was stirred for 1 h, the product was precipitated by pouring the reaction mixture into ice–water (1.3 L). After filtration and thorough washing, recrystallization from Me_2CO–H_2O yielded 12b: 48.5 g, 88%; mp 133–135 °C.

Ethyl α-bromoglyoxylate phenylhydrazone (12a, R_1 = C_6H_5): mp 82–83 °C; 75%.

Ethyl α-bromoglyoxylate 4-tolylhydrazone (12c, R_1 = 4-MeC_6H_4): mp 89.5–90.5 °C; 61%.

Ethyl α-bromoglyoxylate [3-(trifluoromethyl)phenyl]hydrazone (12d, R_1 = 3-$CF_3C_6H_4$): mp 130–131 °C; 78%.

Methyl 1-Morpholinocyclohexene-4-carboxylate (13). A mixture of 3a (31.2 g, 0.2 mol), morpholine (26.2 g, 0.3 mol), and *p*-TsOH (50 mg) in C_6H_6 (100 mL) was refluxed for 8 h in a flask fitted with a water separator. The benzene was evaporated off in vacuo, and the residue was distilled to afford a pale yellow oil, 13: 38.1 g, 84.5%; bp 158 °C (3 mm). Anal. ($C_{12}H_{19}NO_3$) C, H, N.

Method C. Methyl 3-Carbethoxy-1-(4-chlorophenyl)-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylate (14b, R_1 = 4-ClC_6H_4). To a stirred solution of 12b (3.65 g, 0.012 mol) and 13 (2.7 g, 0.012 mol) in C_6H_6 (30 mL), Et_3N (1.82 g, 0.018 mol) in C_6H_6 (3 mL) was added dropwise over a period of 5 min at 0 °C. Stirring was continued for another 1.5 h and the mixture was allowed to stand overnight at room temperature. The resulting precipitate was filtered and washed with C_6H_6 (50 mL). The benzene solution was washed with 10% HCl (50 mL × 2) and H_2O, dried with Na_2SO_4, and evaporated to give a red-yellow solid. Recrystallization from Me_2CO gave colorless, fine needles of 14b: 3.13 g, 72%; mp 154–155 °C; NMR δ 1.37 (t, *J* = 7 Hz, 3 H, $OCCH_3$), 3.68 (s, 3 H, OCH_3), 4.37 (q, *J* = 7 Hz, 2 H, OCH_2Me). Anal. ($C_{18}H_{19}N_2O_4Cl$) C, H, N.

1-(4-Chlorophenyl)-4,5,6,7-tetrahydro-1*H*-indazole-3,5-dicarboxylic Acid (15b, R_1 = 4-ClC_6H_4). A solution of 14b (4.0 g, 0.011 mol) and 10% NaOH (9 mL) in MeOH (50 mL) was refluxed for 2.5 h. The reaction mixture was concentrated and the residue was dissolved in H_2O. The aqueous solution was acidified with HCl. The resulting precipitate was collected and crystallized from MeOH to yield a colorless prism of 15b: 3.3 g, 97%; mp 278 °C dec; IR 1709 (COOH), 1684 cm^{-1} (COOH). Anal. ($C_{15}H_{13}N_2O_4Cl$) C, H, N.

Decarboxylation of 15b. 15b (100 mg, 0.31 mmol) was heated at 300–315 °C for 5 min in an oil bath; it decomposed with the evolution of CO_2. After being cooled, the residue was crystallized from MeOH to yield a colorless prism of 8b: 70 mg, 81%; mp 192.5–194 °C.

Ulcerogenic Activity Testing. The compounds were suspended in 0.2% carboxymethylcellulose and administered orally to seven male rats at each dose. For each compound at least five doses were administered. Animals used as controls were given 0.2% carboxymethylcellulose only. The animals were sacrificed 24 h after treatment. Then the stomach was opened and the number of gastric lesions (hemorrhage, erosion, and ulcer) was examined under blind conditions. The number of gastric lesions in control animals was less than two lesions. Therefore, MUD (minimum ulcerogenic dose), which was the dose required to induce two lesions in gastric mucosa, was calculated graphically.

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