Carboxyarylindoles as Nonsteroidal Antiinflammatory Agents

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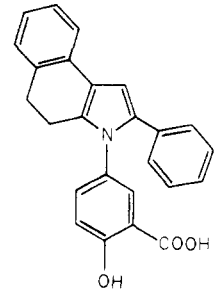
An extensive series of carboxyarylindoles has been evaluated for antiinflammatory activity in the carrageenin paw edema assay. The requirements for optimal antiinflammatory activity in this series are relatively specific: a central pyrrole nucleus with (a) a 3-carboxy-4-hydroxyphenyl moiety substituted directly on the nitrogen, (b) a 2-phenyl group (R_2) with a substituent of low electronegativity, (c) absence of a substituent in the 3 position (R_3), and (d) a system fused across the 4,5 positions (X), which is lipophilic, quasiplanar, and does not interact sterically with the *N*-phenyl group. One derivative, 3-(3-carboxy-4-hydroxyphenyl)-2-phenyl-4,5-dihydro-3*H*-benz[*e*]indole (42), has been selected for further study.

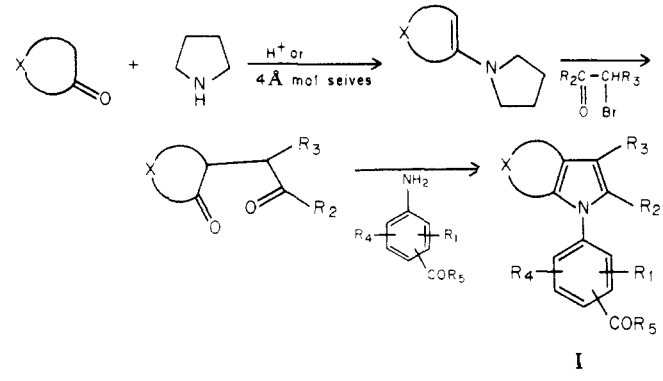
Although examples of nonsteroidal antiinflammatory agents are abundant in the medicinal literature of the past decade, the search continues for more effective compounds. This ongoing search has been stimulated in part by the somewhat disappointing clinical results from many of the "second generation" arylacetic acids, which in animal models had demonstrated potencies of the order of indomethacin with vastly improved gastric tolerance. The potency of many of these compounds in man has, however, been considerably less than expected from the animal models, leading to smaller clinical gains in therapeutic ratio in comparison with indomethacin.

While many laboratories continue to pursue the ultimate arylacetic acid or have sought nonacidic antiinflammatory agents, we have been of the conviction that investigation of acidic moieties other than arylacetic acids could most profitably lead to effective agents with improved therapeutic ratios. Bearing this in mind along with the practical admonitions of Sternbach[1] regarding the search for new drugs, we selected a series of carboxyarylindoles for study. This communication presents the synthesis and primary pharmacological evaluation of representative members of this series of compounds, the culmination of which has been the selection of 3-(3-carboxy-4-hydroxyphenyl)-2-phenyl-4,5-dihydro-3*H*-benz[*e*]indole (**42**) for further study.



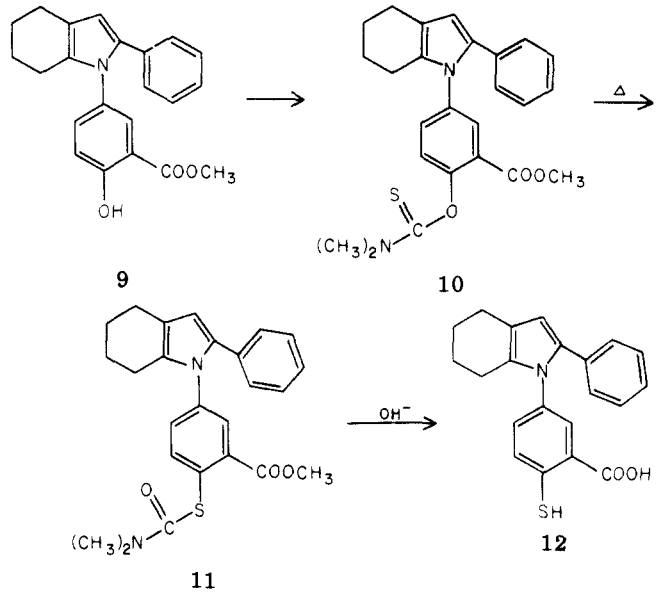
42

Scheme I



I

Scheme II



Chemistry. The primary route utilized in the preparation of the desired carboxyarylindoles is illustrated in Scheme I. Condensation of an α-halo ketone with an enamine[2,13] in either toluene[3] (procedure A) or DMF (procedure B) afforded a 1,4-diketone in moderate to good yield. In many cases the milder DMF procedure gave better yields of purer products. A majority of the diketones (Table II) were characterized only by NMR and ir spectra and subsequently condensed with appropriately substituted anilines in refluxing glacial acetic acid[4] (procedure C) to afford the requisite carboxyarylindoles.

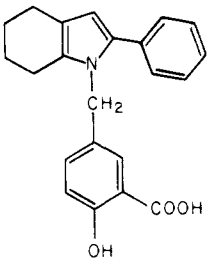
The syntheses of several derivatives, which lie outside the scope of the general method outlined in Scheme I, are worthy of special mention. The mercapto analog **12** initially resisted synthesis by a number of conventional methods. It was ultimately obtained in good yield, however, utilizing the elegant method of Newman[5] for the conversion of phenols to thiols (Scheme II). Thus the phenolic ester **9** was converted in good yield to the *O*-*N*,*N*-dimethylthiocarbamate **10**, which was pyrolized cleanly at 220–230° in excellent yield to the *S*-*N*,*N*-dimethylthiocarbamate **11**. Careful base hydrolysis under nitrogen afforded the desired thiol **12**.

The cyano congener **28** also presented special problems. The precursor diketone, 4-cyano-α-(2-oxocyclohexyl)-acetophenone, was obtained in good yield via a modification[6] of the Rosenmund–von Braun reaction as applied to **59**. However, condensation of this diketone with 5-aminosalicylic acid in the usual manner provided **28** in

very low yield; dehydration of the diketone to the corresponding furan appeared to be the significant competing side reaction, as was also the case in the synthesis of the nitro analog **29**. Compound **28** was ultimately provided in acceptable yield by direct application of the modified Rosenmund–von Braun reaction to 2-(4-bromophenyl)-1-(3-carboxy-4-hydroxyphenyl)-4,5,6,7-tetrahydroindole (**23**).

Structure–Activity Relationships. In order to rapidly assess the medicinal potential of the proposed compounds, several dozen widely varied examples (I) were prepared. The influence on activity of –COOH positional isomerism, the distance of the –COOH group from the ring (and the nature of intervening groups), and the constitution of X, R_2, and R_3 were among variants studied. It soon became apparent that of the initial compounds prepared, the only one displaying an interesting level of antiinflammatory activity was **1**. This compound was then chosen as a lead to be developed by further selected structural modification.

Maintaining the basic structure of **1**, the effect of additional substituents (R_1, R_4) in the *N*-phenyl ring was examined. Introduction of a 4-OH group (**2**) resulted in a marked enhancement of activity accompanied by low gastric irritation liability. Similar high levels of activity were also found when $-OCOCH_3$ (**4**) or –SH (**12**) was introduced into the 4 position; the activity was of lesser interest as other moieties (**5–8**, **10**, **11**) were substituted in place of the 4-OH. The specificity of this 3-COOH-4-OH arrangement for a high level of activity in this series is illustrated by the relatively low order of activity of the isomeric 4-COOH-3-OH derivative **3**. The importance of a "free" carboxyl group in the 3 position of the *N*-phenyl group is demonstrated by the lesser activities of amide (**13**) and ester (**9–11**) analogs. Introduction of additional substituents (**14–17**) into the 3-carboxy-4-hydroxyphenyl moiety resulted in a lowering of potency; insertion of a methylene group between this ring and the pyrrole nitrogen (**53**) virtually abolished antiinflammatory activity.



53

The effect of variations in R_2 was next examined while holding the preferred 3-carboxy-4-hydroxy configuration in the *N*-phenyl ring. Various alkyl groups were evaluated as the R_2 substituent, with the finding that activity in all cases was of a lower order than when R_2 is phenyl; the *tert*-butyl derivative **32** most closely approached the high order of activity of the phenyl congeners.

Having established the desirability of an aromatic R_2 moiety, an effort was made to determine the influence of substituents on the antiinflammatory activity. The selection of the substituents examined was such that a relatively wide range of electronic and hydrophobic properties was represented. In several cases (**18**, **20**, **22**, **31**) the substituted derivatives approached or equaled the potency of the unsubstituted analog **2**, but in most cases (**19**, **21**, **23–29**) the activity was of a lower order. In general, it appears that for a given substituent (CH_3O, for example), activity follows the pattern para ≥ ortho ≫ meta; a Hansch $\sigma-\pi$ correlation (personal communication, E. Druckrey, Hoechst AG, Frankfurt, W. Germany) suggests further that for best effect, a substituent should have a Hammett σ value close to zero.

A study of heterocyclic R_2 replacements for phenyl was also undertaken. The 2-thienyl congener **30** is illustrative that little was gained in this approach.

R_3 was also varied from the initial H (**2**) with no improvements in activity. Of various alkyl and aryl derivatives, only the phenyl analog **33** demonstrated an interesting level of potency.

The examination of variants of the group X for effects on activity proved both interesting and fruitful. Contraction (**35**) or expansion (**36**) of the fused cyclohexane ring of **2** afforded analogs of somewhat lesser activity and increased toxicity (LD_{50}, rat). Introduction of a keto function α to the β-pyrrole carbon (**37**) caused a marked lowering of activity; interestingly, a similar modification at R_3 (**34**) provided analogous results. Substitution of various small groupings (**38**, **39**) on the cyclohexyl ring of **2** led to retention of good activity, while larger, bulkier substituents (**40**) resulted in lower potency. Fusion of a benzene ring to the cyclohexane ring of **2** so as to form a 4,5-dihydrobenz[*g*]indole (**41**) also resulted in a less active derivative. In stark contrast, fusion of the benzene ring so as to form a 4,5-dihydrobenz[*e*]indole (**42**) resulted in improved activity over the parent **2**, as well as beneficial changes in the GI toxicity (rat) and distribution profiles. (Detailed pharmacology of this compound will be the subject of a separate communication.) Introduction of substituents into the fused benzene ring (**43**, **44**) as well as contraction to the indeno[2,1-*b*]pyrrole (**45**) offered no improvement in activity. As had previously been established with compound **2**, esters of **42** (**46**, **47**) were of lesser activity in the acute tests, while the activity of the acetate **48** more closely approached that of **42**. Fully aromatized derivatives (**49–51**) showed no appreciable changes in activity or toxicity from their saturated precursors (**42**, **2**, **40**).

In summary then, it would appear that for optimal antiinflammatory activity in this series, the requirements are relatively specific: a central pyrrole nucleus with (a) a 3-carboxy-4-hydroxyphenyl moiety substituted directly on the nitrogen, (b) a 2-phenyl group (R_2) with a substituent of low electronegativity, (c) absence of a substituent in the 3 position (R_3), and (d) a system fused across the 4,5 positions (X) which is lipophilic, quasiplanar, and does not interact sterically with the *N*-phenyl group.

Experimental Section

Pharmacology. The test for antiinflammatory activity was adapted from the rat paw edema test of Winter et al.[7]

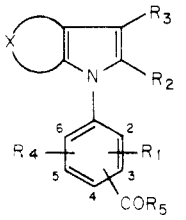
Groups of eight fasted male Wistar strain rats were given experimental drugs or placebo orally at 200 mg/kg as a saline–Tween 80 suspension (10 ml/kg). Thirty minutes later, 0.1 cc of 1% carrageenin in distilled water was injected subcutaneously into the plantar surface of the left hind paw and the paw volume was measured by displacement in a mercury bath. Three hours later, paw volume was measured again. The mean increase in paw volume was compared between placebo and drug-treated groups for calculations of percent inhibition.

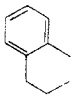
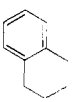
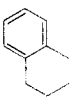
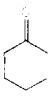
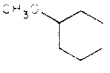
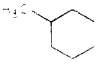
Results are given in Table I. Inhibition values of ≥20% indicate statistically significant activity.

ED_{50} values were determined by regression analysis of percent inhibition data obtained as above for at least four different dose levels.

Chemistry. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were performed by Micro-Tech Labs., Skokie, Ill. Where analyses are reported by the symbols of the elements, results were within

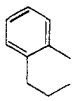
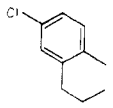
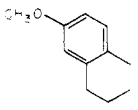
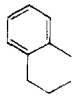
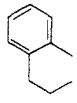
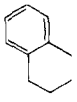
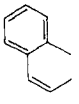
Table I. Carboxyarylindoles and Derivatives



No.	X	R_1	R_2	R_3	R_4	R_5[a]
1	$-(CH_2)_4-$	H	C_6H_5	H	H	OH (3)
2	$-(CH_2)_4-$	4-OH	C_6H_5	H	H	OH (3)
3	$-(CH_2)_4-$	3-OH	C_6H_5	H	H	OH (4)
4	$-(CH_2)_4-$	$4-OCOCH_3$	C_6H_5	H	H	OH (3)
5	$-(CH_2)_4-$	$4-CH_3O$	C_6H_5	H	H	OH (3)
6	$-(CH_2)_4-$	$4-NHCOCH_3$	C_6H_5	H	H	OH (3)
7	$-(CH_2)_4-$	$4-NH_2$	C_6H_5	H	H	OH (3)
8	$-(CH_2)_4-$	4-Cl	C_6H_5	H	H	OH (3)
9	$-(CH_2)_4-$	4-OH	C_6H_5	H	H	OCH_3 (3)
10	$-(CH_2)_4-$	$4-OC(=S)N(CH_3)_2$	C_6H_5	H	H	OCH_3 (3)
11	$-(CH_2)_4-$	$4-SC(=O)N(CH_3)_2$	C_6H_5	H	H	OCH_3 (3)
12	$-(CH_2)_4-$	4-SH	C_6H_5	H	H	OH (3)
13		4-OH	C_6H_5	H	H	NHC_2H_5 (3)
14	$-(CH_2)_4-$	4-OH	C_6H_5	H	6-CF_3	OH (3)
15	$-(CH_2)_4-$	4-OH	C_6H_5	H	5-Br	OH (3)
16	$-(CH_2)_4-$	4-OH	C_6H_5	H	5-Cl	OH (3)
17	$-(CH_2)_4-$	4-OH	C_6H_5	H	$5-CH_3CONH$	OH (3)
18	$-(CH_2)_4-$	4-OH	$4-CH_3OC_6H_4$	H	H	OH (3)
19	$-(CH_2)_4-$	4-OH	$3-CH_3OC_6H_4$	H	H	OH (3)
20	$-(CH_2)_4-$	4-OH	$2-CH_3OC_6H_4$	H	H	OH (3)
21	$-(CH_2)_4-$	4-OH	$4-CH_3C_6H_4$	H	H	OH (3)
22	$-(CH_2)_4-$	4-OH	$4-FC_6H_4$	H	H	OH (3)
23	$-(CH_2)_4-$	4-OH	$4-BrC_6H_4$	H	H	OH (3)
24	$-(CH_2)_4-$	4-OH	$4-ClC_6H_4$	H	H	OH (3)
25	$-(CH_2)_4-$	4-OH	$3,4-ClC_6H_3$	H	H	OH (3)
26	$-(CH_2)_4-$	4-OH	$4-HOC_6H_4$	H	H	OH (3)
27	$-(CH_2)_4-$	4-OH	$3-CF_3C_6H_4$	H	H	OH (3)
28	$-(CH_2)_4-$	4-OH	$4-CNC_6H_4$	H	H	OH (3)
29	$-(CH_2)_4-$	4-OH	$4-NO_2C_6H_4$	H	H	OH (3)
30	$-(CH_2)_4-$	4-OH		H	H	OH (3)
31	$-(CH_2)_4-$	4-OH	$4-C_6H_5C_6H_4$	H	H	OH (3)
32		4-OH	$(CH_3)_3C$	H	H	OH (3)
33	$-(CH_2)_4-$	4-OH	C_6H_5	C_6H_5	H	OH (3)
34		4-OH	C_6H_5	CH_3CO	H	OH (3)
35	$-(CH_2)_3-$	4-OH	C_6H_5	H	H	OH (3)
36	$-(CH_2)_5-$	4-OH	C_6H_5	H	H	OH (3)
37		4-OH	C_6H_5	H	H	OH (3)
38		4-OH	C_6H_5	H	H	OH (3)
39		4-OH	C_6H_5	H	H	OH (3)
40		4-OH	C_6H_5	H	H	OH (3)

Mp, °C[b]	% yield[c]	Method[d]	Recrystn[f] solvent	Emp formula	Analyses[g]	CPE[h] screen	ED_{50} (95% confidence limits), mg/kg
191-193	36	C	E	$C_{21}H_{19}NO_2$	C, H, N	++	
209-211	60	C	E-W	$C_{21}H_{19}NO_3$	C, H, N	++++++	87 (56-135)[w]
193-195	7	C	B-E	$C_{21}H_{19}NO_3$	C, H, N	+	
155-162	11	*e*	AA	$C_{23}H_{21}NO_4$	C, H, N	+++++	
179-181 dec	51	*d*	AN	$C_{22}H_{21}NO_3$	H, N; C[i]	++++	
192-194 dec	47	C	AN	$C_{23}H_{22}N_2O_3$	C, H, N	+++	
205.5-206.5 dec	23	*d*	E-W	$C_{21}H_{20}N_2O_2$	C, H, N	++++	
210-212	44	C	AN	$C_{21}H_{18}ClNO_2$	H, N; C[j]	++++	
141-142	60	*d*	M	$C_{22}H_{21}NO_3$	C, H, N	+	
163-164	65	*d*	M	$C_{25}H_{26}N_2O_3S$	C, H, N	+	
140-141	77	*d*	D	$C_{25}H_{26}N_2O_3S$	C, H, N	+	
186-188	54	*d*	AA	$C_{21}H_{19}NO_2S$	C, H, N	+++++	
175-176	56	*d*	H	$C_{27}H_{24}N_2O_2$	C, H, N	+	
188-190 dec	39	C	AA	$C_{22}H_{18}F_3NO_3$	C, H, N	+	
209-210 dec	46	C	AN	$C_{21}H_{18}BrNO_3$	C, H, N	+	
223-225 dec	77	C	AN	$C_{21}H_{18}ClNO_3$	C, H, N	+	
232-234 dec	57	C	AA	$C_{23}H_{22}N_2O_4$	C, H, N	+	
219-221 dec	40	C	E	$C_{22}H_{21}NO_4$	C, H, N	+++++	173 (72-415)[w]
175-177 dec	65	C	AA	$C_{22}H_{21}NO_4$	C, H, N	++	
212-214 dec		C	E	$C_{22}H_{21}NO_4$	H, N; C[k]	+++++	
212.5-214.5 dec	66	C	AN	$C_{22}H_{21}NO_3$	C, H, N	+++	
239-240 dec	37	C	AA	$C_{21}H_{18}FNO_3$	H, F, N; C[l]	++++++	88 (86-88)[w]
231-232 dec	19	C	AA	$C_{21}H_{18}BrNO_3$	C, H, Br, N	++++	
242-243 dec	48	C	E	$C_{21}H_{18}ClNO_3$	C, H, Cl, N	++++	
210-211	97	C	AN	$C_{21}H_{17}Cl_2NO_3$	C, H, Cl, N	+	
217-219 dec	37	C	AN	$C_{21}H_{19}NO_4$	C, H, N	++	
223-225 dec	47	C	I-W	$C_{22}H_{18}F_3NO_3$	C, H, N	++	
242-244 dec	23	*d*	AA	$C_{22}H_{18}N_2O_3$	H, N; C[m]	+	
241-242	7	C	AN	$C_{21}H_{18}N_2O_5$	C, H, N	+++	
211-213	30	C	AN	$C_{19}H_{17}NO_3S$	C, H, N	+++	
192-194 dec	22	C	AA	$C_{27}H_{23}NO_3$	H, N; C[n]	+++++	162 (142-189)[w]
258-260 dec	46	C	AN	$C_{23}H_{23}NO_3$	C, H, N	++++	
246-247	50	C	AN	$C_{27}H_{23}NO_3$	C, H, N	+++	
223-226 dec	18	*d*	E-W	$C_{27}H_{21}NO_4$	C, H, N	+	
198-199 dec	30	C	AA	$C_{20}H_{17}NO_3$	C, H, N	++++	
238-239 dec	59	C	E	$C_{22}H_{21}NO_3$	C, H, N	+++++	
262-263.5 dec	68	C	M	$C_{21}H_{17}NO_4$	C, H, N	+	
207-210 dec	62	C	AN	$C_{22}H_{21}NO_4$	C, H, N	++++	
213-215	57	C	AN	$C_{22}H_{21}NO_2$	C, H, N	++++	
260-262	69	C	AN	$C_{25}H_{27}NO_3$	C, H, N	+	

Table I (*Continued*)

No.	X	R_1	R_2	R_3	R_4	R_5[a]
41		4-OH	C_6H_5	H	H	OH (3)
42		4-OH	C_6H_5	H	H	OH (3)
43		4-OH	C_6H_5	H	H	OH (3)
44		4-OH	C_6H_5	H	H	OH (3)
45		4-OH	C_6H_5	H	H	OH (3)
46		4-OH	C_6H_5	H	H	OCH_3 (3)
47		4-OH	C_6H_5	H	H	OC_2H_5 (3)
48		4-$OCOCH_3$	C_6H_5	H	H	OH (3)
49		4-OH	C_6H_5	H	H	OH (3)
50		4-OH	C_6H_5	H	H	OH (3)
51		4-OH	C_6H_5	H	H	OH (3)
Aspirin						

[a] Number in parentheses indicates position of attachment of carboxyl moiety to *N*-phenyl ring. [b] Uncorrected; dec = with decomposition. [c] Yield of analytically pure material; no efforts were made to optimize yields. [d] Refer to Experimental Section. [e] Prepared from 2 in the same manner as compound 48. [f] AA = HOAc; AN = MeCN; B = benzene; C = cyclohexane; D = Et_2O, E = EtOH; H = hexane; I = 2-propanol; M = MeOH; P = petroleum ether; W = H_2O; X = xylene. [g] Elements shown, unless otherwise indicated, analyzed correctly to ±0.4% of calculated values. [h] CPE = carrageenin paw edema (rat), percent inhibition of edema at 200 mg/kg po; + = 0-19, ++ = 20-29, +++ = 30-39; ++++ = 40-49, +++++ = 50-

±0.4% of calculated values. The structures of all compounds are supported by their ir (Perkin-Elmer 457) and NMR (JEOL C60HL) spectra. The symbols "(NMR, ir)" following a compound indicate that the structure was determined by these methods alone.

The following known intermediates were prepared according to the cited literature references: α-bromo-3,4-dichloroacetophenone,[8] α-bromo-4-hydroxyacetophenone,[9] α-bromo-3-trifluoromethylacetophenone,[10] α-bromo-2-acetylthiophene,[11] α-bromo-α-phenylacetophenone,[9,12] 1-pyrrolidino-1-cycloheptene,[13] 1-pyrrolidino-4-*tert*-butyl-1-cyclohexene,[14] 6-methoxy-2-tetralone,[15] 1-(3,4-dihydro-6-methoxy-2-naphthyl)pyrrolidine,[16] pyrrolidino-2-indene,[17] α-(2-oxocyclohexyl)acetophenone,[3] α-(5-methoxy-2-oxo-1-cyclohexyl)acetophenone,[4] α-(2-oxocyclopentyl)acetophenone,[18] 3-hydroxy-2-phenacyl-2-cyclohexen-1-one,[19] 5-amino-3-chlorosalicylic acid,[20] 5-amino-3-bromosalicylic acid,[20] 2-acetamido-5-aminobenzoic acid,[21] and 5-amino-4-trifluoromethylsalicylic acid.[22]

Procedure A. To a refluxing solution of enamine (100 mmol) in dry toluene (50 ml) was added dropwise under N_2 a solution of an appropriate α-bromo ketone (100 mmol) in dry toluene (65 ml). After refluxing for 6 hr, water (50 ml) was added and the reflux continued for 4 hr. Upon cooling, the layers were separated; the toluene layer was washed with water, dried (Na_2SO_4), and evaporated in vacuo to afford the crude 1,4-diketone (Table II).

Procedure B. A solution of an appropriate α-bromo ketone (20 mmol) in dry DMF (100 ml) was added over 30 min at 25° to a stirred solution of enamine (20 mmol) in DMF (150 ml) under N_2. After stirring ca. 6 hr at room temperature, water (100 ml) was added. The resulting mixture was stirred overnight, poured into water, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried (Na_2SO_4), and evaporated in vacuo to give the crude 1,4-diketone (Table II).

Procedure C. A mixture of the appropriate 1,4-diketone (60 mmol) and substituted aminobenzoic acid (60 mmol) in glacial HOAc (60 ml) was refluxed under N_2 for 2 hr. The crude product normally precipitated upon cooling; in some cases addition of water was necessary to cause precipitation. The product was collected and recrystallized as indicated in Table I.

1-Pyrrolidino-4-methyl-1-cyclohexene. This compound was obtained in 98% yield from 4-methylcyclohexanone using the general procedure of Stork[2] (NMR, ir).

Mp, °C[b]	% yield[c]	Method[d]	Recrystn[f] solvent	Emp formula	Analyses[g]	CPE[h] screen	ED_{50} (95% confidence limits), mg/kg
245-247 dec	22	C	B-C	$C_{25}H_{19}NO_3$	C, H, N	+	
223-225 dec	68	C	AA	$C_{25}H_{19}NO_3$	C, H, N	++++++	125 (116-137)[w] 66 (60-74)[y]
249-251	59	C	AN	$C_{25}H_{18}ClNO_3$	C, H, N	+++++	
233-234	67	C	AN	$C_{26}H_{21}NO_4$	H, N; C[o]	+++++	164 (140-200)[x]
201-205 dec	55	C	AA	$C_{24}H_{17}NO_3 \cdot CH_3COOH$	H, N; C[p]	+++	
164.5-165.5	91	q	AN	$C_{26}H_{21}NO_3$	C, H, N	+++	
134-135	51	q	E	$C_{27}H_{23}NO_3$	C, H, N	+	
194-196 dec	91	d	E	$C_{27}H_{21}NO_4$	C, H, N	+++++	75 (64-87)[y]
241.5-242.5	48	d	X	$C_{25}H_{17}NO_3$	H, N; C[r]	++++++	105 (71-186)[w] 69 (69-75)[x]
213.5-214.5	50	s	AA	$C_{21}H_{15}NO_3$	H, N; C[t]	++++++	
271-273 dec	82	u	AN	$C_{25}H_{23}NO_3$	H, N; C[v]	+	
						++++++	140[w]

59; ++++++ = >60. [i] C: calcd, 76.06; found, 75.34. [j] C: calcd, 71.69; found, 71.13. [k] C: calcd, 72.73; found, 72.08. [l] C: calcd, 71.79; found, 70.83. [m] C: calcd, 73.73; found, 72.89. [n] C: calcd, 79.20; found, 79.63. [o] C: c calcd, 75.90; found, 76.43. [p] Analysis performed on a thoroughly dried, unsolvated sample; HOAc content determined by NMR analysis. [q] Prepared from 42 in the same manner as 9. [r] C: calcd, 79.14; found, 79.76. [s] Prepared from 2 in the same manner as 49. [t] C: calcd, 76.58; found, 77.09. [u] Prepared from 40 in the same manner as 49. [v] C: calcd, 77.90; found, 78.42. [w] 30-min pretreatment time. [x] 60-min pretreatment time. [y] 120-min pretreatment time.

1-(3,4-Dihydro-6-chloro-2-naphthyl)pyrrolidine. This compound was prepared from 6-chloro-2-tetralone[23] using the general method of Taguchi.[13] Trituration of the crude solid with petroleum ether afforded 68% of the desired product, mp 116–119° (NMR, ir).

2-Phenacyl-1-tetralone.[24] This compound was prepared from 1-(3,4-dihydro-1-naphthyl)pyrrolidine[25] by method A. The crude diketone (87%) was recrystallized from hexane to afford the analytical sample, mp 87–88° (lit.[24] 90.5–91.5°, EtOH) (NMR, ir).

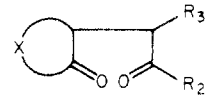
3-Acetamido-5-aminosalicylic Acid. A mixture of 3-acetamido-5-nitrosalicylic acid[20] (15 g, 63 mmol), 80% ethanol (700 ml), concentrated HCl (6 ml), and 5% Pd/C (1.5 g) was hydrogenated at 50 psi in a Parr apparatus for 30 min at 25°. The catalyst was filtered, the solvent removed in vacuo, the residue dissolved in water, and the pH adjusted to ca. 6 with 10% Na_2CO_3 solution. The resulting suspension was filtered to afford 9.6 g (73%) of product, mp 261–262° dec (NMR, ir).

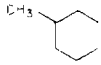
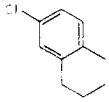
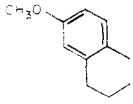
1-(3-Carboxy-4-methoxyphenyl)-2-phenyl-4,5,6,7-tetrahydroindole (5). To a well-stirred mixture of 2 (5.9 g, 18 mmol), powdered KOH (2.5 g, 44 mmol), and acetone (50 ml) was added dropwise at room temperature a solution of dimethyl sulfate (5.3 g, 42 mmol) in acetone (15 ml). After stirring for 3 hr, the solvent was removed in vacuo and the residue partitioned between water and EtOAc. The layers were separated; the EtOAc layer was washed with 5% $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated in vacuo to yield 6.3 g of an amber oil. The oil was dissolved in a mixture of 60% MeOH (70 ml) and KOH (2.1 g, 38 mmol) and refluxed for 2 hr. Dilution with water followed by acidification (HCl) afforded 5.2 g (84%) of crude solid. Crystallization from CH_3CN gave 3.6 g (51%) of pure product, mp 179–181° dec.

1-(4-Amino-3-carboxyphenyl)-2-phenyl-4,5,6,7-tetrahydroindole (7). A mixture of 6 (4.0 g, 11 mmol), 80% ethanol (60 ml), and concentrated HCl (2 ml) was refluxed for 4 hr under N_2. The resulting solution was concentrated in vacuo and diluted with water and the pH adjusted to ca. 4. Filtration afforded 2.9 g (82%) of product. Crystallization several times from 75% ethanol afforded 0.83 g (23%) of pure product, mp 205.5–206.5° dec.

1-(4-Hydroxy-3-methoxycarbonylphenyl)-2-phenyl-

Table II. Novel 1,4-Diketones



No.	X	R_2	R_3	Mp or bp (mm),[a] °C	% yield[b]	Crystn solvent[c]	Method[d]	Emp formula	Analyses[e]
54	$-(CH_2)_4-$	4-$CH_3OC_6H_4-$	H	98-99	84	P	A	$C_{15}H_{18}O_3$	NMR, ir
55	$-(CH_2)_4-$	3-$CH_3OC_6H_4-$	H	178-182 (0.15)	58		A	$C_{15}H_{18}O_3$	NMR, ir
56	$-(CH_2)_4-$	2-$CH_3OC_6H_4-$	H		55		A	$C_{15}H_{18}O_3$	NMR, ir
57	$-(CH_2)_4-$	4-$CH_3C_6H_4-$	H	161-165 (0.2)	53		B	$C_{15}H_{18}O_2$	NMR, ir
58	$-(CH_2)_4-$	4-FC_6H_4-	H		64		A	$C_{14}H_{15}FO_2$	NMR, ir
59	$-(CH_2)_4-$	4-BrC_6H_4-	H	78-80	37	C-E	A	$C_{14}H_{15}BrO_2$	C, H
60	$-(CH_2)_4-$	4-ClC_6H_4-	H	56-58	72	P-D	A	$C_{14}H_{15}ClO_2$	NMR, ir
61	$-(CH_2)_4-$	3,4-$Cl_2C_6H_3-$	H	78-79	60	E	B	$C_{14}H_{14}Cl_2O_2$	NMR, ir
62	$-(CH_2)_4-$	4-HOC_6H_4-	H	120-125	61	AN-D	B	$C_{14}H_{16}O_3$	NMR, ir
63	$-(CH_2)_4-$	3-$CF_3C_6H_4-$	H	137-138 (0.075)	42		A	$C_{15}H_{15}F_3O_2$	NMR, ir
64	$-(CH_2)_4-$	4-$NO_2C_6H_4-$	H	61-63	89	E	B	$C_{14}H_{15}NO_4$	NMR, ir
65	$-(CH_2)_4-$		H		40		B	$C_{12}H_{14}O_2S$	NMR, ir
66	$-(CH_2)_4-$	4-C_6H_5-C_6H_4-	H	108-112	45		A	$C_{20}H_{20}O_2$	NMR, ir
67		$(CH_3)_3C-$	H	149-151 (0.07)	64		B	$C_{16}H_{20}O_2$	NMR, ir
68	$-(CH_2)_4-$	C_6H_5	C_6H_5		85	E	B	$C_{20}H_{20}O_2$	NMR, ir
69		C_6H_5	H		74		B	$C_{15}H_{18}O_2$	NMR, ir
70		C_6H_5	H	127-129	39	E	B	$C_{18}H_{24}O_2$	NMR, ir
71		C_6H_5	H		90		B	$C_{18}H_{15}ClO_2$	NMR, ir
72		C_6H_5	H	55-59	72	P-D	B	$C_{19}H_{18}O_3$	NMR, ir
73		C_6H_5	H	79-81	84	M	B	$C_{18}H_{16}O_2$	C, H
74		C_6H_5	H		45		B	$C_{17}H_{14}O_2$	NMR, ir
75	$-(CH_2)_5-$	C_6H_5	H	42-44	25	P-D	B	$C_{15}H_{18}O_2$	NMR, ir

[a] Uncorrected. [b] Crude yield; no effort was made to optimize yields. [c] See footnote *f*, Table I. [d] See Experimental Section. [e] The symbols "NMR, ir" indicate that structure determination was by these methods alone; where analyses are indicated by the symbols of the elements, results were within ±0.4% of calculated values.

4,5,6,7-tetrahydroindole (9). A solution of **2** (25 g, 75 mmol) in HCl saturated MeOH (750 ml) was refluxed for 18 hr. Cooling followed by filtration afforded 19.6 g (75%) of a white solid, which upon recrystallization from MeOH yielded 15.3 g (60%) of pure product, mp 141-142°.

1-(4-*O*-*N*,*N*-Dimethylthiocarbamyl-3-methoxycarbonylphenyl)-2-phenyl-4,5,6,7-tetrahydroindole (10). A mixture of **9** (3.5 g, 10 mmol), 1,4-diazabicyclo[2.2.2]octane (3.4 g, 30 mmol), *N*,*N*-dimethylthiocarbamoyl chloride (3.7 g, 30 mmol), and DMF (20 ml) was heated at 50–60° for 2.5 hr. The resulting solution was poured into water and extracted with benzene. The benzene extracts were washed with dilute HCl solution and water, dried (Na_2SO_4), and evaporated in vacuo. Crystallization of the residue from MeOH afforded 2.8 g (65%) of product, mp 163–164°.

1-(4-*S*-*N*,*N*-Dimethylthiocarbamyl-3-methoxycarbonylphenyl)-2-phenyl-4,5,6,7-tetrahydroindole (11). Compound **10** (9.0 g, 21 mmol) was pyrolyzed at 220–230° for 2 hr under N_2 to yield, after trituration with 2-propanol, 6.9 g (77%) of crude product. Crystallization from ether afforded 5.1 g (56%) of white crystals, mp 140–141°.

1-(3-Carboxy-4-mercaptophenyl)-2-phenyl-4,5,6,7-tetrahydroindole (12). A mixture of **11** (3.7 g, 8.5 mmol), KOH (2.4 g, 43 mmol), MeOH (35 ml), and water (10 ml) was refluxed under N_2 for 3 hr. Dilution with water, followed by acidification (HCl), afforded 2.5 g (84%) of solid. Crystallization from HOAc yielded 1.6 g (54%) of pure product, mp 186–188°.

3-(3-*N*-Ethylcarbamoyl-4-hydroxyphenyl)-2-phenyl-4,5-dihydro-3*H*-benz[*e*]indole (13). A mixture of **46** (5 g, 12.7 mmol), ethylamine (70 ml), and water (30 ml) was stirred at room temperature overnight, diluted with water, and acidified to pH 2 (HCl). The resulting solid was collected and crystallized from *n*-hexane to yield 2.9 g (56%) of pure product, mp 175–176°.

1-(3-Carboxy-4-hydroxyphenyl)-2-(4-cyanophenyl)-4,5,6,7-tetrahydroindole (28). A mixture of **23** (6.2 g, 15 mmol), cuprous cyanide (1.6 g, 18 mmol), and DMF (10 ml) was refluxed under nitrogen for 6 hr and then poured into a mixture of NaCN (3 g) and water (9 ml). After stirring for 5 min, additional water (46 ml) was added. Stirring was continued for 10 min, whereupon the pH was adjusted (HCl) to ca. 1–2. The solid which precipitated was collected and crystallized twice (HOAc) to afford 1.2 g (23%) of the desired product, mp 242–244° dec.

1-Acetyl-3-(3-carboxy-4-hydroxyphenyl)-2-phenyl-4,5-

dihydro-3*H*-benz[*e*]indole (34). A mixture of **42** (1.3 g, 3.3 mmol), Ac_2O (1 ml, ~10 mmol), HOAc (10 ml), and *p*-toluenesulfonic acid (100 mg) was stirred at room temperature under N_2 for 6 days. The resulting solid (900 mg) was triturated with MeOH (50 ml) and filtered. Evaporation of the solvent in vacuo followed by crystallization of the residue from 50% EtOH afforded 250 mg (18%) of product, mp 223–226° dec.

3-(4-Acetoxy-3-carboxyphenyl)-2-phenyl-4,5-dihydro-3*H*-benz[*e*]indole (48). A solution of **42** (26.2 g, 69.2 mmol) in Ac_2O (204.2 g, 2 mol) was heated at 75° for 4 hr. After cooling to room temperature, water (34 g, 1.9 mol) was added and the mixture stirred overnight. Filtration afforded 26.7 g (91%) of pure product, mp 194–196°.

3-(3-Carboxy-4-hydroxyphenyl)-2-phenyl-3*H*-benz[*e*]indole (49). A solution of **42** (7.6 g, 20 mmol) in xylene (350 ml) was refluxed with 10% Pd/C (9.1 g) under N_2 for 24 hr. The catalyst was filtered and washed with 150 ml of hot xylene. The combined xylene filtrates were concentrated to 135 ml and cooled. Filtration and subsequent recrystallization from xylene afforded 3.6 g (48%) of yellow crystals, mp 241.5–242.5°.

1-(4-Hydroxy-3-methoxycarbonylbenzyl)-2-phenyl-4,5,-6,7-tetrahydroindole (52). This compound was prepared from 4-hydroxy-3-methoxycarbonylbenzylamine[26] and α-(2-oxocyclohexyl)acetophenone[3] using general procedure C in 58% yield, oil (NMR, ir).

1-(3-Carboxy-4-hydroxybenzyl)-2-phenyl-4,5,6,7-tetrahydroindole (53). A mixture of **52** (3.2 g, 8.8 mmol), KOH (2.5 g, 44 mmol), MeOH (35 ml), and water (10 ml) was refluxed for 2.5 hr. Dilution with water and acidification (HCl) yielded a crude solid, which on crystallization from MeOH–hexane afforded 1.9 g (63%) of pure product, mp 152.5–154°. Anal. ($C_{22}H_{21}NO_3$) C, H, N.

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Notes

Synthesis and Some Biological Activities of the Tyrosine-8 Analog of Substance P[1]

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[Tyr[8]]-substance P, an undecapeptide having the structure Arg-Pro-Lys-Pro-Gln-Gln-Phe-Tyr-Gly-Leu-Met-NH_2, has been synthesized by the solid-phase technique on a Beckman automatic peptide synthesizer, appropriately purified and biologically characterized. At twice the dosage, [Tyr[8]]-substance P showed the same biological activity response as synthetic substance P for stimulation of contraction of the isolated guinea pig ileum and for decrease in the systemic blood pressure of dogs. On the dog's blood pressure, no qualitative differences were observed, but on the isolated gut, the Tyr[8] analog gave a more gradual increase in the muscle tone than synthetic substance P. [Tyr[8]]-substance P released, in vitro, the luteinizing and follicle-stimulating hormones at a very high dosage but did not release growth hormone, prolactin, or thyrotropin.

The existence of the undecapeptide substance P, having the structure Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2, has been demonstrated in several mammalian tissues.[2-7] Recently, determinations with a radioimmunoassay technique have confirmed the presence of substance P-like material in tissue extracts from the