Biochemical Screening. Cytosol Preparation and Incubation. Cytosols were prepared by centrifuging homogenates obtained from the organs of the species indicated in Table I and incubated with the corresponding radioligand (Table II); i.e., 5 nM [^{3}H]estradiol was incubated for 2 h at 0 °C with mouse uterus cytosol to label the estrogen receptor, 2.5 nM [^{3}H]R 5020 was incubated for 24 h at 0 °C with rabbit uterus cytosol to label the progestin receptor, 2.5 nM [^{3}H]R 1881 was incubated for 2 h at 0 °C with rat prostate cytosol to label the androgen receptor, 5 nM [^{3}H]dexamethasone was incubated for 4 h at 0 °C with rat liver cytosol to label the glucocorticoid receptor, and 2.5 nM [^{3}H]aldosterone was incubated for 30 min at 25 °C with rat kidney homogenates, which was then centrifuged at 800g for 10 min at 0 °C to label the mineralocorticoid receptor. All incubations were performed in the absence and in the presence of 0 to 2500 nM unlabeled competing steroids.

Bound Steroid Measurement. A 100-μL aliquot of incubated cytosol was stirred for 10 min at 0–4 °C with 100 μL of DCC (0.625% Dextran 80000–1.25% charcoal Norit A) in a microtiter plate and then centrifuged for 10 min at 800g. The radioactivity of a 100-μL supernatant sample was measured.

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Synthesis and Analgesic Activity of Some 5-(4-Hydroxyphenyl)-2-azabicyclo[3.2.1]octanes

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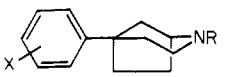
A representative series of 5-(4-hydroxyphenyl)-2-azabicyclo[3.2.1]octanes was synthesized and evaluated in vitro, as well as in vivo, as potential analgetic agents. In general, moderate to good activity (19 twice as active as morphine) was observed in the phenylquinone writhing assay (PQW), while only marginal activity was detected by the tail-flick method. Compounds 19 and 18, being the most active in the PQW model, also demonstrated weak binding affinity for the opiate receptors labeled by [^{3}H]naloxone in rat brain homogenates.

In a previous publication[1] from this laboratory, we described the synthesis and analgesic activity of a series of 5-(3-hydroxyphenyl)-2-azabicyclo[3.2.1]octane derivatives (I), some of which displayed a mixed agonist–antagonist



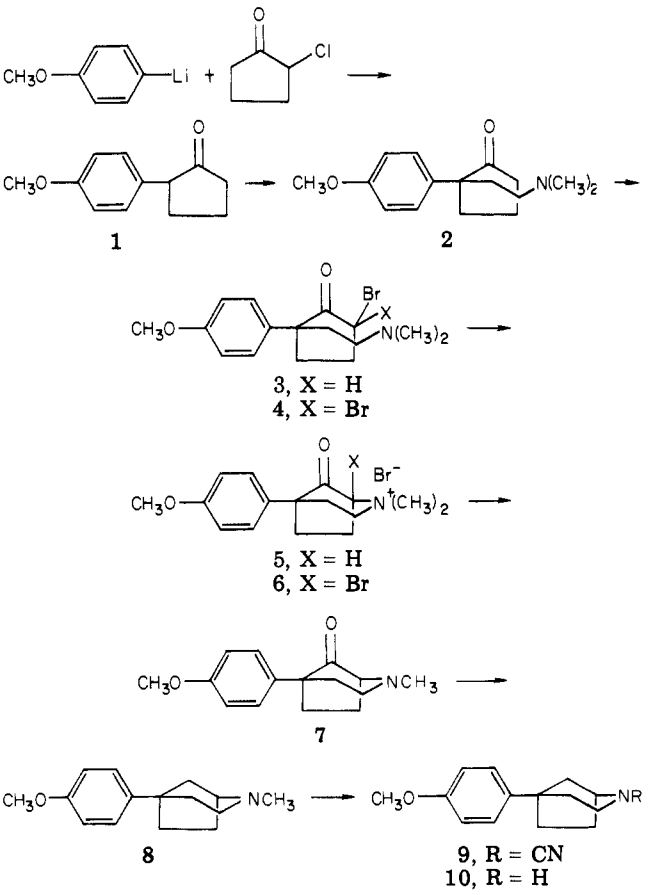
I, X = 3-OH
II, X = 4-OH

profile with a potency range comparable to that of morphine. Structure–activity studies of these compounds centered mostly upon the modification of N-substituents, and it was also demonstrated that analogues bearing a 3-hydroxy substituent on the aromatic nucleus were much more active than their 3-methoxy counterparts when other structural parameters were held at optimum.

Although the activity-enhancing effect of a free phenolic hydroxy group located meta to the quarternary carbon is widely recognized for many classes of centrally mediated (polycyclic) analgesics,[2a,b] evidence supporting a similar conclusion has yet to be documented for bicyclic strong analgetics, which possess not only a greater degree of conformational flexibility but also markedly different spatial relationships between the basic nitrogen and the aromatic ring. In this article we report the synthesis and biological activity of a number of 5-(4-hydroxyphenyl)-2-azabicyclo[3.2.1]octanes (II).

Chemistry. The title compounds **15–20** were synthesized by previously published routes.[1] 2-Chlorocyclopentanone reacted with 4-methoxyphenyllithium at −50 °C to give a mixture of chlorohydrins, which underwent a "one-pot" thermal rearrangement to afford 1 in high purity. Alkylation of 1 with β-(dimethylamino)ethyl

Scheme I



1, 2, 3, X = H, 4, X = Br, 5, X = H, 6, X = Br, 7, 8, 9, R = CN, 10, R = H

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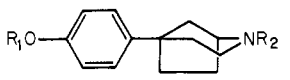
Table I. 5-(4-Hydroxyphenyl)-2-azabicyclo[3.2.1]octanes and Derivatives[a]



no.	R_1	R_2	start. material	method	mp, °C	yield,[b] %	recrystn[c] solv	formula	anal.
8	CH_3	CH_3	7		188-190	78	C-E	$C_{15}H_{21}NO\cdot HBr$	C, H, Br, N
10	CH_3	H	9		237-239	86	C-E	$C_{14}H_{19}NO\cdot HBr$	C, H, Br, N
11	CH_3	n-C_3H_7	10	A	174-176	77	A-C-E	$C_{17}H_{25}NO\cdot HBr$	C, H, Br, N
12	CH_3	$(CH_2)_2C_6H_5$	10	C	235-237	51	A-C-E	$C_{22}H_{27}NO\cdot HBr$	C, H, Br, N
13	CH_3	$(CH_2)_3C(=O)C_6H_4$-4-F	10	A	186-189	78	A-C-E	$C_{24}H_{28}FNO_2\cdot HBr$	C, H, Br, F, N
14	c-$C_3H_5C(=O)$	C(=O)-c-C_3H_5	15	D	112-114	85	D	$C_{21}H_{25}NO_3$	C, H, N
15	H	H	9	B	257-259	88	B-C	$C_{13}H_{17}NO\cdot HBr$	C, H, Br, N
16	H	CH_3	7	B	214-216	73	A-C-E	$C_{14}H_{19}NO\cdot HBr$	C, H, Br, N
17	H	n-C_3H_7	11	B	237-239	90	C-E	$C_{16}H_{23}NO\cdot HBr$	C, H, Br, N
18	H	$(CH_2)_2C_6H_5$	12	B	271-273	92	A-C-E	$C_{21}H_{25}NO\cdot HBr$	C, H, Br, N
19	H	$(CH_2)_3C(=O)C_6H_4$-4-F	13	B	244-245	91	A-C-E	$C_{23}H_{26}FNO_2\cdot HBr$	C, H, Br, F, N
20	H	CH_2-c-C_3H_5	14	E	236-238	84	C-E	$C_{17}H_{23}NO\cdot HBr$	C, H, Br, N

[a] All compounds exhibited IR, ^1H NMR, and MS spectra consistent with the structure. [b] Isolated yield; no efforts were made to optimize these yields. [c] A = acetone; B = ethanol; C = ethyl ether; D = hexane; E = methanol.

chloride and potassium *tert*-butoxide yielded **2** as the major product, along with a small amount of an amino ether resulting from O-alkylation (Scheme I).

Bromination of **2** in refluxing glacial acetic acid gave predominately the dibromo compound **4**, whereas in an aprotic solvent at low temperature (0 °C) only the monobrominated product **3** was isolated. Under mildly basic conditions, **3** and **4** underwent a facile ring closure to give bicyclo quaternary salts **5** and **6**, respectively, in fair to excellent yields. Degradation of **5** to the corresponding amino ketone **7** was carried out thermally, and the latter was converted to the deoxy derivative **8** by Wolff–Kishner reduction. Treatment of **8** with cyanogen bromide gave a crystalline cyanamide, **9**, which was readily hydrolyzed to the secondary amine **10**. For the preparation of target compounds **16**, **17**, and **19**, compound **10** was alkylated with an appropriate halide (method A), followed by O-demethylation with 48% hydrobromic acid (method B). The *N*-phenethyl precursor (**12**) was prepared by acylating **10** with phenylacetyl chloride and reduction of the resultant amide with lithium aluminum hydride (method C). For the synthesis of acid-sensitive cyclopropylmethyl analogue **20**, **10** was first converted to **15** (method B), and then bisacylation of **15** with cyclopropylcarbonyl chloride yielded the amido ester **14**, which was subsequently reduced to **20** with lithium aluminum hydride (method E).

Biological Results. As shown in Table II, the in vivo analgesic activity was assessed by measuring the inhibition of phenyl-*p*-quinone-induced writhing (PQW)[1,3] and the delay in response to noxious heat stimuli in mice (D'Amour–Smith tail-flick method).[1,4,5] The in vitro binding constants for opiate receptors were determined by measuring the inhibition of stereospecific binding of [^3H]naloxone in rat brain homogenates.[6]

Table II. Biological Activity of 5-(4-Hydroxyphenyl)-2-azabicyclo[3.2.1]octanes

compd[a]	analgesic act.:[b] ED_{50}, mg/kg sc PQW writhing	tail flick	inhibn of [^3H]naloxone binding:[d,e] IC_{50}, nM
16	10.8 (7.2-21.9)	>25	7290
17	3.7 (3.2-4.4)	>25	6980
18	2.5 (2.2-2.7)	>25	340
19[c]	0.27 (0.20-0.36)	>25	268
20	3.0 (2.6-3.4)	>25	2780
pentazocine	2.4 (2.1-2.9)	14.6 (7.4-24.4)	46
morphine	0.68 (0.65-0.72)	3.8 (1.7-9.5)	11

[a] All compounds were tested as racemic hydrobromides. [b] The vehicle control used in both analgesic tests consists of distilled water and a few drops of Tween 80. [c] Marked overt effects were observed. [d] Brains from three to four rats were pooled and dissected rapidly; the homogenates were assayed at dilutions for which specific receptor binding was linear with protein concentration (1-3 mg/mL). [e] Six concentrations of the test drug (10^{-9} to 10^{-4} M) were incubated with 5 nM [^3H]naloxone (8.2 Ci/mmol); the IC_{50} values are the means of at least three separate determinations.

In the PQW assay, the *N*-methyl analogue (**16**) was found to be equipotent to its isomer in the 5-(3-hydroxy-

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(4) F. D'Amour and D. Smith, *J. Pharmacol. Exp. Ther.*, **72**, 74 (1941).
(5) G. Hayashi and A. E. Takemori, *Eur. J. Pharmacol.*, **16**, 63 (1971).
(6) C. B. Pert and S. H. Snyder, *Science*, **179**, 1011 (1973).

phenyl)-2-azabicyclo[3.2.1]octane series, being approximately one-fifteenth as active as morphine.[1] Lengthening the *N*-alkyl terminal from a one-carbon moiety to a three-carbon chain (**17**) augmented the activity by a factor of 3, whereas the replacement of *N*-methyl with a phenethyl group resulted in a fourfold enhancement of potency. The latter increase, though significant, was much less than the 15-fold difference arising from a similar structural change in the 3-hydroxyphenyl series. Somewhat surprisingly, the cyclopropylmethyl analogue (**20**), despite its moderate agonist activity, was virtually devoid of antagonistic properties, as measured by the morphine mania assay.[1] Among the several title compounds tested, the most active congener was the butyrophenone analogue (**19**), which was more than twice as active as morphine in the antiwrithing model. This compound, however, manifested a strong CNS depressant component, as evidenced by ataxia, hypothermia, and a marked decrease in spontaneous motor activity. Similar overt effects were also observed for its methoxy derivative (**13**).

In the tail-flick assay, which, in general, is more sensitive to pure agonist activity, compounds **15–20** were at best marginally active. It is interesting to note, however, that a qualitative correlation seems to exist between the antiwrithing potencies and the in vitro binding constants for the opiate receptors: compounds **19** and **18**, being the most active congeners in the PQW assay, were also most effective in displacing stereospecifically bound [^{3}H]naloxone from rat brain homogenates.

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457) and ^{1}H NMR (Jeolco C6OHL) (tetramethylsilane) spectra. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectral data were determined with a Finnigan Model 4000 GC–MS equipped with a INCOS data system. Where analyses were indicated by symbols of the elements, the analytical results obtained for those elements (performed by Micro-Tech Laboratories, Skokie, Ill.) were within 0.4% of theoretical values.

2-(4-Methoxyphenyl)cyclopentanone (1). To a cold (−50 °C) stirred solution of 112 g (0.6 mol) of *p*-bromoanisole in 380 mL of anhydrous THF was added dropwise 258 mL of 2.2 M *n*-butyllithium in hexane (Alfa Chemical Co.) under nitrogen. After 2 h, a solution of 70.8 g (0.6 mol) of 2-chlorocyclopentanone in 50 mL of THF was slowly added during 20 min, and the mixture was stirred for 1 h at −50 °C and then overnight at room temperature. Xylene (800 mL) was added, and the low-boiling THF was distilled off until the internal temperature reached 100 °C. After 16 h at reflux, the cooled reaction mixture was treated with chilled 1 N HCl, filtered, and separated. The organic layer was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Fractionation of the crude product in vacuo yielded, as the main fraction, 52 g (46%) of **1**: bp 125–128 °C (0.2 mmHg); IR ($CHCl_3$) 1750 cm^{-1}; MS *m/e* 190 (M^+). Anal. ($C_{12}H_{14}O_2$) C, H.

2-(4-Methoxyphenyl)-2-[2-(dimethylamino)ethyl]cyclopentanone Hydrobromide (2). A solution of 28.5 g (0.15 mol) of **1** in 30 mL of 1,2-dimethoxyethane (DME) was added dropwise to a well-stirred slurry of 17.1 g (0.15 mol) of potassium *tert*-butoxide (Aldrich Chemical Co.) in 300 mL of DME. The reddish brown solution was stirred at room temperature for 30 min before 16.2 g (0.15 mol) of freshly distilled β-(dimethylamino)ethyl chloride was added during 5–10 min. Stirring was continued at reflux under nitrogen for an additional 20 h. The cooled mixture was quenched with water, the organic material was extracted into ether, and the combined ether solution was shaken with a large excess of 1 N HCl. The acidic solution was warmed briefly on a steam bath to give, upon ether extraction, 6.7 g of **1**, recoverd from cleavage of the O-alkylated product. The aqueous layer was then basified with ammonia, and the precipitated oil was dried (K_2CO_3) in ether. The crude product was distilled at 140–143 °C (0.25 mmHg) to give 19.2 g of a pale yellowish liquid, which was converted to a crystalline hydrobromide, **2**, with ethereal HBr. Recrystallization of the crude salt from acetone–ether gave 22.5 g (44%) of prisms, mp 157–159 °C. Anal. ($C_{16}H_{24}BrNO_2$) C, H, Br, N.

5-Bromo-2-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)cyclopentanone Hydrobromide (3). A solution of **2** (1.71 g, 5 mmol) in 15 mL of $CHCl_3$ was cooled to 0 °C, and to it was added dropwise a solution of 0.8 g (5 mmol) of bromine in 15 mL of the same solvent. The solution was stirred under nitrogen overnight and concentrated at 50 °C to a glassy residue. Trituration with 10 mL of acetone–ethyl acetate (1:10, v/v) afforded, upon cooling and scratching, 1.9 g (90%) of microscopic granules, mp 142–144 °C. Recrystallization of the crude product from acetone–ethyl acetate raised the melting point to 146–147 °C. Anal. ($C_{16}H_{23}Br_2NO_2$) C, H, Br, N.

5,5-Dibromo-2-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)cyclopentanone Hydrobromide (4). A mixture of **2** (2.74 g, 8.0 mmol) in 10 mL of glacial acetic acid was heated at reflux to form a clear solution. To this was added dropwise a solution of 1.6 g (10 mmol) of bromine in 10 mL of glacial acetic acid over a period of 30 min. After the solution stirred at room temperature overnight, 40 mL of anhydrous ether was added to bring about precipitation of the salt, and the crude product was recrystallized from methanol–acetone–ether to give 2.2 g (55%) of microscopic granules, mp 164–165 °C. Anal. ($C_{16}H_{22}Br_3NO_2$) C, H, N.

5-(4-Methoxyphenyl)-2-methyl-8-oxo-2-azabicyclo[3.2.1]octane Methobromide (5). A well-stirred solution of **3** (1.7 g, 4 mmol) in 10 mL of water was treated dropwise with concentrated ammonia while the temperature was kept below 0 °C. After the solution was stirred cold for 2 h, the crystalline precipitate was filtered and air-dried. Recrystallization from boiling ethanol (95%) afforded 1.1 g (80%) of shiny platelets, mp 255–258 °C dec. Anal. ($C_{16}H_{22}BrNO_2$) C, H, Br, N.

1-Bromo-5-(4-methoxyphenyl)-2-methyl-8-oxo-2-azabicyclo[3.2.1]octane Methobromide (6). A suspension of 1.0 g (2 mmol) of **4** in 10 mL of water was stirred vigorously at 5 °C while 1 mL of concentrated ammonia was added dropwise. The lumpy hydrobromide salt soon began to disintegrate and a finely crystalline product began to form. The mixture was stirred for an additional 2 h before the solid was filtered and air-dried. The crude product was recrystallized from 95% ethanol to give 0.61 g (75%) of shiny prisms, mp 192–194 °C dec. Anal. ($C_{16}H_{21}Br_2NO_2$) C, H, Br, N.

5-(4-Methoxyphenyl)-2-methyl-8-oxo-2-azabicyclo[3.2.1]octane (7). Dry distillation of **5** (6.5 g, 19 mmol) at 260 °C at 0.3 mmHg in the presence of sand afforded 3.5 g (74%) of heavy oil, which solidified upon standing. Recrystallization of the crude amine from acetone–hexane (1:10, v/v) afforded rhombic crystals, mp 96–97 °C. Anal. ($C_{15}H_{19}NO_2$) C, H, N.

5-(4-Methoxyphenyl)-2-methyl-2-azabicyclo[3.2.1]octane Hydrobromide (8). A solution of **7** (3.0 g, 12 mmol), 4 mL of 95% hydrazine hydrate, and 3.0 g of 85% potassium hydroxide pellets in 24 mL of triethylene glycol was stirred at 170 °C for 4 h. The reaction temperature was raised gradually to 190 °C during 60 min and was subsequently kept there for 1 h as water was slowly distilled off. The cooled reaction mixture was poured onto ice and extracted three times with ether. The ether solution, after washing (4 × 150 mL of water) and drying (K_2CO_3), was treated with a large excess of ethereal HBr to give a crystalline hydrobromide. Recrystallization of the crude salt from methanol–ether gave 2.8 g (78%) of microscopic granules. Properties of **8** are included in Table I.

2-Cyano-5-(4-methoxyphenyl)-2-azabicyclo[3.2.1]octane (9). To a well-stirred solution of 5.1 g of cyanogen bromide in 35 mL of $CHCl_3$ was added dropwise a solution of **8** (10.0 g of the free base, 42 mmol) in 80 mL of $CHCl_3$ during 2 h. Workup according to the previously described procedure[1] afforded 9.5 g (93%) of colorless crystals, mp 110–112 °C. An analytical sample was recrystallized from acetone–hexane. Anal. ($C_{15}H_{18}N_2O$) C, H, N.

5-(4-Methoxyphenyl)-2-azabicyclo[3.2.1]octane Hydrobromide (10). A suspension of **9** (17.0 g, 70 mmol) in 250 mL of 2 N HCl was stirred at reflux for 18 h. The clear solution was cooled and basified with 40% NaOH, and the liberated amine was extracted into ether. After drying (K_2CO_3) and concentration in vacuo, the crude oil was distilled at 135–138 °C (0.3 mmHg)

to give 13 g (86%) of a colorless liquid, which solidifed upon cooling, mp 31–33 °C. Its hydrobromide salt (10) was prepared in ether and recrystallized from methanol–acetone–ether. Properties of 10 are included in Table I.

5-(4-Methoxyphenyl)-2-*n*-propyl-2-azabicyclo[3.2.1]octane Hydrobromide (11). Method A. A mixture of 10 (1.5 g of the free base, 6.9 mmol), 1.4 g of *n*-propyl iodide (15% excess), and 1.2 g of sodium bicarbonate in 20 mL of DMF was stirred at 80 °C for 16 h. Workup according to the previously described procedure[1] afforded a clear oil, which was converted to 1.8 g of 11 with ethereal HBr. Properties of 11, and 13 prepared in a similar manner, are included in Table I.

5-(4-Hydroxyphenyl)-2-azabicyclo[3.2.1]octane Hydrobromide (15). Method B. A mixture of 10 (2.7 g, 9.2 mmol) in 20 mL of 48% hydrobromic acid was stirred at 120 °C for 30 min. The excess acid was removed in vacuo, and the solid residue was recrystallized from ethanol–ether to give 2.3 g of 15 as rhombic crystals. Properties of 15, and of 16–19 prepared in a similar manner, are included in Table I.

5-(4-Methoxyphenyl)-2-phenethyl-2-azabicyclo[3.2.1]octane Hydrobromide (12). Method C. A mixture of 1.9 g (8.7 mmol) of the free base from 10 and 1.7 g of sodium bicarbonate in 40 mL of $CHCl_3$ was treated dropwise with 2.1 g of phenylacetyl chloride during 10 min. After stirring at room temperature for 4 h, the mixture was poured onto 100 g of ice–water, and the $CHCl_3$ solution was washed consecutively with dilute HCl, aqueous $NaHCO_3$, and water. After drying over $MgSO_4$ and removal of solvent, the crude amide (homogeneous by TLC) was reduced with 1.1 g of lithium aluminum hydride in 70 mL of THF for 3 h. Workup in the usual manner led to a pale yellowish oil, which was converted to a crystalline hydrobromide with ethereal HBr. Recrystallization of the crude salt from methanol–acetone–ether gave 1.8 g of 12. Properties of 12 are included in Table I.

2-(Cyclopropylcarbonyl)-5-(4-hydroxyphenyl)-2-azabicyclo[3.2.1]octane Cyclopropanecarboxylate (14). Method D. To a stirred suspension of 2.0 g (6.9 mmol) of 15 and 5.0 g of triethylamine in 30 mL of $CHCl_3$ was added dropwise 2.35 g of cyclopropylcarbonyl chloride (Aldrich Chemical Co.) in 2 mL of $CHCl_3$. The mixture was stirred at room temperature overnight and concentrated in vacuo to a semicrystalline residue. Trituration with $CHCl_3$, followed by washing and drying ($MgSO_4$), afforded 2.0 g of 14. Properties of 14 are included in Table I.

2-(Cyclopropylmethyl)-5-(4-hydroxyphenyl)-2-azabicyclo[3.2.1]octane Hydrobromide (20). Method E. A solution of 1.9 g (5.6 mmol) of 14 in 20 mL of THF was added dropwise to a refluxing mixture of 0.6 g of lithium aluminum hydride in 30 mL of THF. The mixture was heated under reflux for 3 h and decomposed with water. Workup in the usual manner led to a phenolic amine, which was converted to 1.6 g of a crystalline hydrobromide (20) in ether. Properties of 20 are included in Table I.

[^{3}H]Naloxone Binding. Binding assays were conducted employing modifications of the method described by Pert and Snyder.[6] Male Wistar rats weighing 100–150 g were sacrificed by cervical dislocation and their brains rapidly removed. Brain minus cerebellum was homogenized in 20 volumes of cold 50 mM Tris-HCl, pH 7.4, using a Tekmar homogenizer (30 s at a medium setting of 40–50) and then centrifuged for 10 min at 40000*g*. The pellet was washed twice and the supernatant discarded. The final pellet was then dispersed (Tekmar homogenizer, 5 s at medium speed) in 50 volumes of the 50 mM Tris-HCl buffer. For binding assays, 500 μL of tissue suspension was added to all tubes. For the determination of total binding, each tube contained in final concentration dextrophan (0.1 μM), Tris-HCl, pH 7.4 at 37 °C (50 mM), and [^{3}H]naloxone (5 nM). Nonspecific binding tubes contained levorphanol (0.1 nM), Tris-HCl, pH 7.4 at 37 °C (50 mM), and [^{3}H]naloxone (5 nM). Test drugs were run as follows: Tris-HCl, pH 7.4 at 37 °C (50 mM), [^{3}H]naloxone (5 nM), and varying concentrations of test drug. All incubation mixtures were in a final volume of 1.0 mL. All tubes were incubated for 30 min at 37 °C and the reaction was terminated by filtration through Whatman GF/B filters under vacuum. The filters were washed three times with 5 mL of chilled 50 mM Tris-HCl buffer, pH 7.4, and then transferred to scintillation vials. Ten milliliters of scintillation fluid (3a70B counting cocktail, Research Products, Inc.) was added and radioactivity determined with a Beckman LS-355 liquid scintillation system.

The stereospecific binding of [^{3}H]naloxone was determined by the difference between the total radioactivity bound in the presence of 0.1 μM dextrorphan minus the radioactivity bound in the presence of 0.1 μM levorphanol. The data were converted to percent [^{3}H]naloxone displaced by test drug, and IC_{50} values were obtained using computer-derived Litchfield–Wilcoxin log-probit analyses.

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(7) Compound 20 evoked a 10% antagonistic response when administered sc at 50 mg/kg; see ref 1 for experimental details.

Antiinflammatory Effects of Some Copper Complexes

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Copper complexes of a range of ligands have been prepared and evaluated for antiinflammatory activity and irritancy after oral, subcutaneous, and local administration in rats and guinea pigs. The antiinflammatory activities were found to depend on the species used and the route of administration. When nonantiinflammatory ligands were used, the response was generally dose dependent. With D-penicillamine and when the ligands were themselves antiinflammatory in animal models of inflammation—as was the case with flufenamic acid, levamisole, aspirin, L-histidine, and 2-amino-2-thiazoline—differences in antiinflammatory activity were observed between the copper complexes and the free ligands. In some cases, the copper complexes were the more effective. There was a weak correlation between local (subplantar) irritation and the dose of copper but, for four compounds studied in more detail, the response in the local subplantar test and degree of antiinflammatory activity were not related, suggesting that the action of copper is not solely by a counterirritant mechanism. No obvious differences between the activities of copper(I) and copper(II) compounds were observed, suggesting that a common metabolite may be involved in the antiinflammatory action of copper.

Sorenson[2] has observed that copper complexes of nonantiinflammatory ligands administered subcutaneously to the rat produce an antiinflammatory effect in several animal models of inflammation and that copper complexes

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