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Aromatic Esters of Nonquaternary Carbon-4 Piperidinols as Analgesics[1]

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Aromatic carboxylic esters of 1-methyl-4-piperidinol were prepared and evaluated for analgesic activity. In addition, aralkyl, alkyl, and cycloalkyl carboxylates of the 4-piperidinol system and 3,4-dimethoxybenzoates of isomeric piperidinols (24–26) were synthesized. The 3,4-dimethoxybenzoate 23 was nearly twice as active as codeine in the mouse hot-plate assay. In monkeys, 23 showed no morphine-like physical dependence liability. *cis-* and *trans-*1,3-dimethyl-4-piperidinol esters 24 and 25 showed no binding to the opiate receptor in rat brain homogenates. The 3- and 4-monosubstituted and the 3,4-disubstituted benzoate esters were examined for qualitative structure–activity relationships with respect to parameters E_s^c and π. Various structural features of this series of compounds that may have an affinity for receptor binding sites are discussed.

Recent studies have shown that 1-methyl-4-piperidinol esters 1 and 2 and related structures possess analgesic activity and, in general, display no physical dependence liability of the morphine type in monkeys.[2,3] Furthermore, pyrrole ester 1 exhibits marginal affinity and piperonylate ester 2 virtually no affinity for the opiate receptor in rat brain homogenates.[3] Pethidine and alphaprodine, the well-known piperidine analgesics, have physical dependence and abuse liabilities. Structurally, 1 and 2 lack the

1
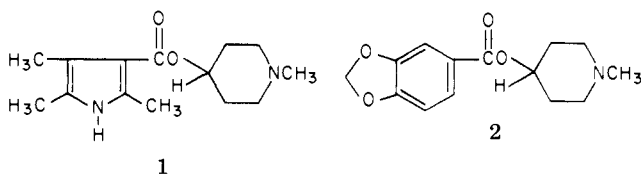
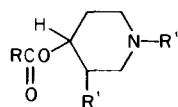quaternary phenyl substitution at C-4 of the piperidine ring that is present in pethidine and alphaprodine.

From earlier studies,[2,3] it became apparent that either a heterocyclic or an aromatic ring could be interchanged in the acyl part of these structures, 1 and 2, without any significant loss of activity. It was therefore of interest to extend the study of aromatic esters of the type similar to 2. In this series, substituent effects were examined, since π, E_s^c, and/or σ parameters may influence their receptor interaction, passage through the blood–brain barrier, and metabolism. Consequently, ortho-, meta-, and para-substituted benzoic esters of 1-methyl-4-piperidinol were studied extensively (Table I). In addition, aralkyl (27, 40–43), alkyl (44), and cycloalkyl (45) carboxylates of the 4-piperidinol system were synthesized in order to gain further insight into the aromatic ring involvement in receptor interactions. 3,4-Dimethoxybenzoates of *cis-* and *trans*-piperidinols (24–26) were prepared to determine if potency factors exist in stereoisomers of this type (Table

II). Selected compounds were assayed for binding affinity to the opiate receptor (Results and Discussion). The esters were synthesized by three procedures as outlined in the Experimental Section.

Results and Discussion

The compounds were assayed for analgesic activity by the mouse hot-plate[4] and Nilsen methods[5] (Table II). The unsubstituted benzoate ester of 1-methyl-4-piperidinol (3) had an ED_{50} of 9.6 in the mouse hot-plate assay. In general, alkyl substitutions of the aromatic ring had a detrimental effect on activity, with the exception of the 2-methyl- and 2,4,6-trimethyl-substituted esters (4, ED_{50} = 8.9, and 13, ED_{50} = 8.3, respectively). Ester 3 and the 2,6-dimethyl ester 9 were shown to have local anesthetic activity (see Table I for references). Compounds 33–38, containing electron-withdrawing halogen groups, were all less active than the parent benzoate 3. Compound 15 (ED_{50} = 16.6), having an electron-withdrawing hydroxyl group in the meta position, was one-half as potent as codeine. The methoxy-substituted benzoate esters of the nonstereospecific 1-methyl-4-piperidinol were the most active in this series. They displayed activity in the codeine range with the exception of the 2,6-dimethoxybenzoate 21, which exhibited low activity (ED_{50} = 73.8) in the mouse hot-plate assay. Interestingly, the 2-methoxy derivative 16 showed an ED_{50} of 10.6, whereas the bulkier 2-ethoxy (30), 2-phenoxy (31), and 2-phenethyl (32) compounds were only marginally active. The 3-methoxybenzoate 17 showed an ED_{50} of 6.1 in the hot-plate assay, whereas the 3,4-dimethoxybenzoate 23, the most active ester in this series, had an ED_{50} of 3.9 (hot-plate) (Chart I). It was nearly twice as active as codeine and 20% more active than pyrrole ester 1. The piperonylate ester 2, structurally related to 23, was shown to have an ED_{50} of 7.3,[3] whereas the 3,4-dimethyl (10) and 3,4-dichloro (37), analogues of

Table I. Nonquaternary Carbon-4 Piperidinol Esters

No.	R	R'	R''	Mp, °C	Formula	Recrystn solvent[a]	Yield, %	Analyses
3	C_6H_5	H	CH_3	223–225[c]	$C_{13}H_{17}NO_2 \cdot HCl$	C	65	C, H, N
4	2-$CH_3C_6H_4$	H	CH_3	215–215.5	$C_{14}H_{19}NO_2 \cdot HCl$	B	45	C, H, N
5	3-$CH_3C_6H_4$	H	CH_3	182–183	$C_{14}H_{19}NO_2 \cdot HCl$	B	28	C, H, N
6	4-$CH_3C_6H_4$	H	CH_3	217–218	$C_{14}H_{19}NO_2 \cdot HCl$	B	24	C, H, N
7	4-t-Bu-C_6H_4	H	CH_3	251–253	$C_{17}H_{25}NO_2 \cdot HCl$	B	31	C, H, N
8	2,5-$(CH_3)_2C_6H_3$	H	CH_3	183–184	$C_{15}H_{21}NO_2 \cdot HCl$	C	33	C, H, N
9	2,6-$(CH_3)_2C_6H_3$	H	CH_3	235–236[d]	$C_{15}H_{21}NO_2 \cdot HCl$	B	35	C, H, N
10	3,4-$(CH_3)_2C_6H_3$	H	CH_3	233–235	$C_{15}H_{21}NO_2 \cdot HCl$	B	35	C, H, N
11	3,5-$(CH_3)_2C_6H_3$	H	CH_3	219–220	$C_{15}H_{21}NO_2 \cdot HCl$	B	17	C, H, N
12	2,4,5-$(CH_3)_3C_6H_2$	H	CH_3	205.5–206.5	$C_{16}H_{23}NO_2 \cdot HCl$	C	36	C, H, N
13	2,4,6-$(CH_3)_3C_6H_2$	H	CH_3	228–231	$C_{16}H_{23}NO_2 \cdot HCl$	A	26	C, H, N
14	2,4,6-$(CH_3)_6C_6H_2$	H	$C_6H_5(CH_2)_2$	220–223	$C_{23}H_{29}NO_2 \cdot HCl$	A	9	C, H, N
15	3-HOC_6H_4	H	CH_3	221–222.5	$C_{13}H_{17}NO_3 \cdot HCl$	G	27	C, H, N
16	2-$CH_3OC_6H_4$	H	CH_3	183–184	$C_{14}H_{19}NO_3 \cdot HCl$	C	49	C, H, N
17	3-$CH_3OC_6H_4$	H	CH_3	173–174	$C_{14}H_{19}NO_3 \cdot HCl$	C	43	C, H, N
18	4-$CH_3OC_6H_4$	H	CH_3	226–227	$C_{14}H_{19}NO_3 \cdot HCl$	C	45	C, H, N
19	3-CH_3O-4-$CH_3C_6H_3$	H	CH_3	215–216	$C_{15}H_{21}NO_3 \cdot HCl$	C	23	C, H, N
20	2,3-$(CH_3O)_2C_6H_3$	H	CH_3	143–144	$C_{15}H_{21}NO_4 \cdot HCl$	C	31	C, H, N
21	2,6-$(CH_3O)_2C_6H_3$	H	CH_3	209–210	$C_{15}H_{21}NO_4 \cdot HCl$	C	50	C, H, N
22	3,5-$(CH_3O)_2C_6H_3$	H	CH_3	217–218.5	$C_{15}H_{21}NO_4 \cdot HCl$	C	46	C, H, N
23	3,4-$(CH_3O)_2C_6H_3$	H	CH_3	225–226	$C_{15}H_{21}NO_4 \cdot HCl$	C	66	C, H, N
24	3,4-$(CH_3O)_2C_6H_3$	CH_3 (cis)	CH_3	221–222	$C_{16}H_{23}NO_4 \cdot HCl$	C	37	C, H, N
25	3,4-$(CH_3O)_2C_6H_3$	CH_3 (trans)	CH_3	221.5–223.5	$C_{16}H_{23}NO_4 \cdot HCl$	C	70	C, H, N
26a	3,4-$(CH_3O)_2C_6H_3$	CO_2Et (cis)	CH_3	221–222	$C_{18}H_{25}NO_6 \cdot HCl$	C	17	H, N; C[b]
26b	3,4-$(CH_3O)_2C_6H_3$	CO_2Et (trans)	CH_3	195–195.5	$C_{18}H_{25}NO_6 \cdot C_4H_4O_4$	D	10	C, H, N
27	3,4-$(CH_3O)_2C_6H_2(CH_2)_2$	H	CH_3	167–168	$C_{17}H_{25}NO_4 \cdot HCl$	A	27	C, H, N
28	2,4,6-$(CH_3O)_3C_6H_2$	H	CH_3	197–199	$C_{16}H_{23}NO_5 \cdot HCl$	A	8	C, H, N
29	3,4,5-$(CH_3O)_3C_6H_2$	H	CH_3	229–232[e]	$C_{16}H_{23}NO_5 \cdot HCl$	C	37	C, H, N
30	2-$C_2H_5OC_6H_4$	H	CH_3	162–163	$C_{15}H_{21}NO_3 \cdot HCl$	H	68	C, H, N
31	2-$C_6H_5OC_6H_4$	H	CH_3	149.5–151	$C_{19}H_{21}NO_3 \cdot HCl$	B	32	C, H, N
32	2-$C_6H_5(CH_2)_2C_6H_4$	H	CH_3	206–209	$C_{21}H_{25}NO_2 \cdot HCl$	B	31	C, H, N
33	2-FC_6H_4	H	CH_3	202–202.5	$C_{13}H_{16}FNO_2 \cdot HCl$	B	38	C, H, N
34	3-FC_6H_4	H	CH_3	234–235	$C_{13}H_{16}FNO_2 \cdot HCl$	B	67	C, H, N
35	4-FC_6H_4	H	CH_3	227–228	$C_{13}H_{16}FNO_2 \cdot HCl$	B	38	C, H, N
36	3-F-4-$CH_3C_6H_3$	H	CH_3	202–203	$C_{14}H_{18}FNO_2 \cdot HCl$	C	43	C, H, N
37	3,4-$Cl_2C_6H_3$	H	CH_3	235–236	$C_{13}H_{15}Cl_2NO_2 \cdot HCl$	C	55	C, H, N
38	2,3,5-$I_3C_6H_2$	H	CH_3	193–205	$C_{13}H_{14}I_3NO_2 \cdot HCl$	G	28	C, H, N
39	9-Fluorenyl	H	CH_3	211.5–213[f]	$C_{20}H_{21}NO_2 \cdot HCl \cdot H_2O$	C	22	C, H, N
40	$C_6H_5CH_2$	H	CH_3	182.5–184	$C_{14}H_{19}NO_2 \cdot HCl$	C	23	C, H, N
41	$C_6H_5CH(CH_3)$	H	CH_3	196–197	$C_{15}H_{21}NO_2 \cdot HCl$	C	42	C, H, N
42	$C_6H_5CH{=}CH$	H	CH_3	230–232	$C_{15}H_{19}NO_2 \cdot HCl$	C	71	C, H, N
43	3-$C_6H_5(CH_2)_3$	H	CH_3	132–133	$C_{16}H_{23}NO_2 \cdot HCl$	C	30	C, H, N
44	C_2H_5	H	CH_3	153–154	$C_9H_{17}NO_2 \cdot HCl$	A	80	C, H, N
45	1-Adamantyl	H	CH_3	218–219	$C_{17}H_{27}NO_2 \cdot HCl \cdot 0.25H_2O$	A	46	C, H, N

[a] A = acetone, B = acetone–ethanol, C = acetone–methanol, D = acetone–ether, E = methanol–ether, F = methanol, G = ethanol, H = acetone–methanol–ether. [b] C: calcd, 55.74; found, 55.30. [c] Lit.[27] mp 219–220 °C. [d] Lit.[28] mp 233–233.5 °C. [e] Lit.[29] mp 234–235 °C. [f] Lit.[30] mp 220 °C.

Table II. Analgesic Activity[a]

Compd	ED$_{50}$, mg/kg sc[b]	
	Hot-plate	Nilsen
1	4.9 (3.6-6.5)	7.1 (5.3-9.4)
2	7.3 (4.7-11.4)	
3	9.6 (6.7-14.0)	
4	8.9 (5.6-14.3)	
5	Inactive	
6	18.2 (11.8-28.1)	
7	23.3 (16.9-32.2)	
8	12.5 (8.5-18.3)	
9	15.2 (8.3-27.8)	
10	Marginally act. at 20	
11	24.4 (11.5-51.4)	
12	20.0 (13.7-29.3)	
13	8.3 (6.3-11.0)	46.0 (35.8-59.2)
14	37.0 (16.6-82.5)	
15	16.6 (11.1-24.8)	
16	10.6 (8.0-14.1)	
17[c]	6.1 (3.8-9.9)	
18	10.5 (7.9-14.1)	
19	11.9 (8.2-17.3)	
20	8.9 (5.4-14.8)	19.6 (13.6-28.3)
21	73.8 (60.2-90.4)	
22	9.3 (6.7-12.8)	
23[c]	3.9 (2.6-5.8)	13.1 (9.6-17.7)
24	Marginally act. at 20	
25	8.3 (6.3-11.0)	
26a[d]	4.0 (2.4-6.7)	Marginally act. at 20
26b	11.8 (7.7-17.9)	
27	30.7 (20.4-46.3)	32.0 (19.7-51.9)
28	11.6 (7.9-16.9)	
29	15.4 (11.8-20.0)	
30	Marginally act. at 20	
31	Marginally act. at 20	
32	Marginally act. at 50	
33	10.6 (6.6-17.0)	
34	15.1 (8.2-27.8)	
35	11.5 (8.5-15.6)	
36	13.9 (9.7-20.0)	
37	27.1 (16.3-45.1)	
38	Inactive	
39	Inactive	
40	Inactive	
41	25.4 (15.8-40.8)	
42	16.2 (11.0-23.7)	
43	Inactive	
44	20.2 (8.4-18.4)	
45	15.9 (10.5-24.3)	
Codeine	7.5 (6.7-8.3)	4.5 (2.7-7.6)
Morphine	1.2 (0.9-1.3)	0.8 (0.6-1.2)

[a] Tested subcutaneously as water-soluble salts as indicated in Table I. [b] Numbers in parentheses are the 95% confidence limits obtained by probit analysis. [c] No toxicity noted at the doses tested, except at 54.5 mg/kg for 23; refer to Discussion. [d] Toxicity noted at 20 mg/kg.

Chart I[a]

4, R = CH$_3$
16, R = OCH$_3$
30, R = OC$_2$H$_5$
31, R = C$_6$H$_5$O-
32, R = C$_6$H$_5$CH$_2$CH$_2$-

10, R = CH$_3$; R' = CH$_3$
15, R = OH; R' = H
17, R = OCH$_3$; R' = H
23, R = OCH$_3$; R' = OCH$_3$
37, R = Cl; R' = Cl

24, R = CH$_3$
26a, R = CO$_2$C$_2$H$_5$

25, R = CH$_3$
26b, R = CO$_2$C$_2$H$_5$

23, R, R' = OCH$_3$; n = 0
27, R, R' = OCH$_3$; n = 2
3, R, R' = H; n = 0
40, R, R' = H; n = 1
43, R, R' = H; n = 3

41, R = C$_6$H$_5$CH(CH$_3$)-
42, R = C$_6$H$_5$CH=CH-

[a] These compounds were obtained as salts as indicated in Table I.

benzoates (series 1-3, respectively) were correlated with these parameters. As shown in Table III for these three series, there was a fairly consistent trend, but not entirely, in displaying $+E_s^c-\pi$ effects [i.e., increasing activity (log $1/C$) with increasing Taft steric values ($+E_s^c$) and decreasing lipophilic values ($-\pi$)]. Two exceptions, 3-methoxy (17) and 3-hydroxy (15), correlated poorly with the other analogues of series 1 with regard to both parameters. The $-\pi$ effect in series 1-3 may be due to the fact that highly lipophilic molecules tend to be localized by the first protein or lipid they come in contact with, and thus they are unable to cross the blood-brain barrier[7] that is necessary to provide the analgesic response. The $+E_s^c$ effect may also reflect the ease of transport of these molecules. The influence of certain substituents (i.e., methoxy groups of 23) at the receptor level, where steric and lipophilic factors would also be of importance, is discussed later. Relevant activity correlations with the Hammett electronic parameter (σ) did not exist for these esters.

Potency differences were noted in the *cis-* and *trans-*1,3-dimethyl-4-piperidinol 3,4-diethoxybenzoates (24, marginally active at 20, and 25, ED$_{50}$ = 8.3, respectively) and in the *cis-* and *trans-*1-methyl-3-carboethoxy-4-piperidinol 3,4-dimethoxybenzoates (26a, ED$_{50}$ = 4.0, and 26b, ED$_{50}$ = 11.8, respectively). Large potency factors have been noted in the diastereomeric pairs of the prodine, [10-12] promedol,[13] and pethidine[14] series.

The 3,4-dimethoxybenzoate 23 showed no morphine-like physical dependence liability in monkeys.[15] In single-dose suppression studies, it caused no apparent effects at 2.0 and 4.0 mg/kg. In nonwithdrawn monkeys, it produced slight nausea at 4.0 mg/kg and nausea and piloerection at 8.0 mg/kg but no precipitation of abstinence signs. At a higher dose (16.0 mg/kg), one monkey convulsed 5 min after injection of the drug; in another test, retching and vomiting and preconvulsive appearance were observed, but it was not a typical morphine withdrawl syndrome. Pyrrole

23, exhibited marginal activity and an ED$_{50}$ of 27.1, respectively. In the Nilsen assay, 23 was one-third as active as codeine. Morphine and related drugs are nearly equipotent in these two assay systems.[5] Ester 17 displayed no toxicity in mice at 1.56-25 mg/kg (hot-plate assay) and compound 23 exhibited no toxicity in the hot-plate or Nilsen assays (1.25-20 mg/kg and 5-40 mg/kg, respectively). At a higher dose (23, 54.5 mg/kg), toxicity developed.

During the course of this work, structure-activity correlations of the substituted benzoate esters with regard to physicochemical parameters of the Hansch method[6,7] became apparent. Using the qualitative procedure described by Topliss and Martin, [8,9] without applying regression analysis, correlations were made with substituent constants E_s^c and π (Table III). The analgesic activity of the 3- and 4-monosubstituted and the 3,4-disubstituted

Table III. Physicochemical Parameters

Series	Compd	Aromatic ring substitution	Log $1/C^a$	E_s^c	π
1	**5**	3-CH$_3$	Inact.	0.00	+ 0.51
	34	3-F	1.26	+ 0.78	+ 0.15
	3	3-H	1.43	+ 1.24	0.00
	17	3-OCH$_3$	1.68	+ 0.69	+ 0.12
2	**7**	4-t-Bu	1.13	− 0.15	+ 1.68
	6	4-CH$_3$	1.17	0.00	+ 0.60
	35	4-F	1.38	+ 0.78	+ 0.15
	18	4-OCH$_3$	1.38	+ 0.69	− 0.04
	3	4-H	1.43	+ 1.24	0.00
3	**10**	3,4-(CH$_3$)$_2$	Marginally act.	0.00	+ 1.11
	37	3,4-Cl$_2$	1.08	+ 0.54	+ 1.46
	36	3-F,4-CH$_3$	1.32	+ 0.78	+ 0.75
	19	3-OCH$_3$,4-CH$_3$	1.40	+ 0.69	+ 0.72
	3	3,4-H$_2$	1.43	+ 1.24	0.00
	23	3,4-(OCH$_3$)$_2$	1.91	+ 1.38	+ 0.08

^{a} $C = ED_{50}$ in mmol/kg.

ester **1** and piperonylate **2** also showed no morphine-like physical dependence liabilities.[2,3] In this context, as stated earlier, it should be noted that pethidine and alphaprodine analgesics have morphine-like side effects, including physical dependence and abuse liabilities.[16,17]

cis- and *trans*-1,3-dimethyl-4-piperidinol esters **24** and **25** showed no in vitro binding to the opiate receptor in rat brain homogenates, where $K > 100\,000$ (nanomolar amount concentration of drug required to reduce [^{3}H]dihydromorphine binding to rat brain homogenates by 50%).[18] Heterocyclic esters of the nonquaternary 1-methyl-4-piperidinol also failed to show significant affinity for this receptor, with the exception of pyrrolecarboxylate **1**, which showed marginal binding.[3] As discussed previously,[3] different receptor sites may have an affinity for these nonopiate-like compounds, or a completely different receptor or family of receptors may be involved.[19,20] It was previously postulated that the heterocyclic or aromatic ring of these compounds could undergo van der Waals type of bonding to a receptor site via their aromatic electrons.[3] In the case of the most active derivative in this study (**23**), the 3,4-dimethoxy groups could conceivably bind to an accessory site via hydrogen bonding interactions, or they may exist in a lipophilic pocket[6] adjacent to the aromatic receptor site. The carbonyl oxygen and the protonated nitrogen may also have an affinity for binding sites on the receptor. These functions, present in pethidine and prodine,[21,22] and the protonated nitrogen, present in levorphanol,[23] have been postulated as structural features involved in opiate receptor binding. If binding occurs at the aromatic ring, as well as with the nitrogen and carbonyl functions in this series, then separation of the aromatic ring and the carbonyl by methylene group(s) could conceivably result in a lowering of analgesic potency in comparison with the parent benzoate. To assess this, aralkyl esters **27** and **40–43** were prepared. Compounds **40**, **41**, and **43**, in which the benzene ring is removed from the carbonyl group by 1–3 methylenes, were marginally active or inactive, whereas the parent benzoate **3** had an ED$_{50}$ of 9.6. Cinnamate ester **42** (ED$_{50}$ = 16.2) retains some activity, possibly because the benzene ring is conjugated with the double bond. The 3,4-dimethoxyphenylpropionate **27**, with two carbons separating the aromatic and carbonyl functions, showed an ED$_{50}$ of 30.7, whereas the parent dimethoxybenzoate **23** had an ED$_{50}$ of 3.9 (hot-plate assay). The increased bulkiness of the aralkyl groups may also tend to partially remove the carbonyl and the protonated nitrogen from their respective receptor sites and thus decrease their bonding forces. Since the propionate ester **44**[3] and adamantoyl ester **45**[3] retain some

activity and some of the aromatic esters are inactive, other factors such as metabolic disposition and ability to cross the blood–brain barrier[24-26] [where both lipophilic (π) and steric effects (E_s^c) discussed earlier could be involved] apparently play important roles in the activity of these esters.

Additional work on the structure–activity relationships of these esters, including further CNS evaluation of **23**, and the preparation of radioactive substrates for receptor assays is in progress.

Experimental Section

Melting points were taken on a Kofler hot stage and are corrected. Analytical results obtained were within ±0.4% of theoretical values. Infrared spectra (in chloroform, unless otherwise noted) were obtained on a Perkin-Elmer spectrometer Model 237 B. Varian Model A-60A was used for the NMR. Optical rotations were obtained on a Perkin-Elmer polarimeter, Model 141.

cis-1,3-Dimethyl-4-piperidinol. A mixture of 7.431 g (0.058 mol) of 1,3-dimethyl-4-piperidone and 400 mg of PtO in 50 mL of MeOH was hydrogenated at atmospheric pressure for 3.75 h, at which time the calculated amount of hydrogen was taken up. The catalyst was removed by filtration and the solvent removed in vacuo. Spinning band distillation of the crude oil gave 4.0 g (53%) of *cis*-1,3-dimethyl-4-piperidinol in the forerun: bp 89–90.5 °C (10.5 mm); IR 984 cm^{-1} [lit.[32] bp 87–88 °C (10 mm); IR 988 cm^{-1}].

trans-1,3-Dimethyl-4-piperidinol. A solution of 1.0 g (0.027 mol) of sodium borohydride in 10 mL of H$_2$O containing 2 drops of 5.0 N NaOH was cooled in an ice bath and magnetically stirred. To this solution was added 7.0 g (0.055 mol) of 1,3-dimethyl-4-piperidone in 25 mL of cold H$_2$O dropwise over a period of 30 min. The solution (pH 10.6) was then stirred an additional 4 h in the cold. The solution was acidified with cold 5% HCl to pH 1.7 and then basified with potassium carbonate to pH 10.1. The mixture was saturated with NaCl and extracted three times with 150-mL portions of Et$_2$O. The ethereal extracts were dried over magnesium sulfate and Drierite and evaporated. The colorless oil was distilled using a micro-spinning-band apparatus. The forerun, bp 81–90 °C (10 mm), contained a mixture of cis and trans isomers. *trans*-1,3-Dimethyl-4-piperidinol was obtained as a colorles oil: bp 91–91.5 °C (10 mm); yield 2.8 g (39%); IR 974 cm^{-1} [lit.[32] bp 90–91 °C (10 mm); IR 974 cm^{-1}].

3,4-Dimethoxybenzoate of *cis*-1,3-Dimethyl-4-piperidinol (24). A mixture of 1.202 g (6.6 mmol) of 3,4-dimethoxybenzoic acid and 16 mL of thionyl chloride was refluxed for 30 min. The excess thionyl chloride was removed under reduced pressure and the crude acid chloride was mixed with dry benzene and evaporated. To the acid chloride was added 517 mg (4.0 mmol) of *cis*-1,3-dimethyl-4-piperidinol in 16 mL of dry pyridine (over 4A molecular sieves). The mixture was refluxed for 5 h. The pyridine was removed in vacuo, the residue mixed with CH$_2$Cl$_2$, and the solvent evaporated. The reaction mixture was chromatographed

on 40 g of silica gel, 70–230 mesh ASTM. Elution with 4–8% MeOH in CH_2Cl_2 gave the desired ester plus impurities (by TLC). A second chromatography (silica gel, elution with 6–10% MeOH in CH_2Cl_2) and recrystallization from MeOH–acetone gave 488 mg (37%) of colorless solid (24·HCl salt): mp 221–222 °C; $[\alpha]^{21}_D$ +0.6 ($CHCl_3$); IR 970, 955, and 937 cm^{-1}; $NMR^{32,33}$ ($CDCl_3$) δ 5.25 (m, C-4 piperidine H); TLC R_f 0.30 (Analtech silica gel GF; $CHCl_3$–MeOH, 9:1). For analysis, see Table I.

3,4-Dimethoxybenzoate of *trans*-1,3-Dimethyl-4-piperidinol (25). This compound was prepared in a manner similar to that described above for the cis isomer. From 1.202 g (6.6 mmol) of 3,4-dimethoxybenzoic acid, 16 mL of thionyl chloride, and 517 mg (4.0 mmol) of *trans*-1,3-dimethyl-4-piperidinol there was obtained the crude ester, which after chromatographing on 40 g of silica gel (elution with 8–12% MeOH in CH_2Cl_2) and crystallization from acetone–MeOH gave 919 mg (70%) of a beige solid. Additional recrystallization from acetone–MeOH gave the analytical sample (25·HCl salt): mp 221.5–223.5 °C; $[\alpha]^{21}_D$ –0.6 ($CHCl_3$); IR 982 cm^{-1}; NMR ($CDCl_3$) δ 4.80 (m, C-4 piperidine H); TLC R_f 0.45 (Analtech silica gel GF; $CHCl_3$–MeOH, 9:1). For analysis, see Table I.

1-Methyl-3-carboethoxy-4-piperidone. This compound was prepared in a manner similar to that described by McElvain.[31] To a solution of 47.5 g (0.7 mol) of methylamine hydrochloride and 256.5 g (1.4 mol) of ethyl 3-bromopropionate in 760 mL of 95% EtOH was added 450 g of silver oxide over a period of 1 h. Spinning band distillation of the crude pale yellow oil gave 13.3 g (94%) of the desired piperidone as a colorless oil, bp 88.5 °C (2 mm) [lit.[31] 114–116 °C (4 mm)].

3,4-Dimethoxybenzoate of *cis*-1-Methyl-3-carboethoxy-4-piperidinol (26a). Hydrogenation of 5.705 g (0.031 mol) of 1-methyl-3-carboethoxy-4-piperidone with 225 mg of PtO in a manner described above gave 3.5 g of a mixture of piperidinols (7:3, cis–trans), bp 82–83 °C (2 mm), that could not be separated by further spinning band distillation. The piperidinol mixture (predominantly cis, 562 mg, 3.0 mmol) was esterified in the usual manner with the acid chloride obtained from 902 mg (4.95 mmol) of 3,4-dimethoxybenzoic acid. After two chromatographic separations of the crude reaction mixture (silica gel, elution with 6–8% MeOH in CH_2Cl_2) and crystallization from acetone–MeOH, there was obtained 193 mg (17%) of the pure cis ester (26a·HCl salt): mp 221–222 °C; $[\alpha]^{21}_D$ +0.2 ($CHCl_3$); IR 985, 953 cm^{-1}; NMR ($CDCl_3$) δ 5.70 (m, C-4 piperidine H); TLC R_f 0.54 (Analtech silica gel GF; $CHCl_3$–MeOH, 9:1). For analysis, see Table I.

3,4-Dimethoxybenzoate of *trans*-1-Methyl-3-carboethoxy-4-piperidinol (26b). Reduction of 1-methyl-3-carboethoxy-4-piperidone (6.4 g, 0.035 mol) with 680 mg of sodium borohydride in a manner described above gave 2.1 g of a mixture of piperidinols (6:4, trans–cis), bp 60–72.5 °C (1.0 mm), that could not be separated by further spinning band distillation. The piperidinol mixture (predominantly trans, 749 mg, 4.0 mmol) was esterified with the acid chloride obtained from 1.202 g (6.6 mmol) of 3,4-dimethoxybenzoic acid. After two chromatographic separations of the crude reaction mixture (silica gel, elution with 2–8% MeOH in CH_2Cl_2) there was obtained 152 mg (10%) of 26b·HCl salt that was homogeneous by TLC: IR 976, 943, and 917 cm^{-1}; NMR ($CDCl_3$) δ 5.30 (m, C-4 piperidine H); TLC R_f 0.70 (silica gel GF; $CHCl_3$–MeOH, 9:1). Attempts to crystallize the 26b·HCl salt were unsuccessful and, hence, it was converted to the free base, dissolved in ether, and converted to the maleate salt by slow addition of a dilute solution of maleic acid in ether. Recrystallization from acetone–ether gave 26b maleate: mp 195–195.5 °C; $[\alpha]^{21}_D$ –0.3 ($CHCl_3$). For analysis, see Table I.

Piperidinol Esters. The remaining esters were prepared using the general procedure outlined below, except for compounds 15, 27, and 40–44 which are described after the general procedure.

A solution of 11.25 mmol of the carboxylic acid in 20–30 mL of thionyl chloride was refluxed for 30 min. The excess thionyl chloride was then removed in vacuo and the residue was mixed with dry benzene (over 3A molecular sieves) and evaporated. No attempt was made to isolate and purify the acid chloride. To the crude acid chloride was added 6.75 mmol of the appropriate 4-piperidinol in 32 mL of dry pyridine and the mixture refluxed for 3–4 h. The pyridine was removed in vacuo and the residue mixed and evaporated two times with CH_2Cl_2. The crude reaction mixture was chromatographed on 70 g of silica gel (elution with

increasing percentages of MeOH in CH_2Cl_2), unless otherwise stated. The compounds were eluted from the column at the percentages of MeOH indicated: 32, 1%; 14, 2–4%; 21, 30, 4–8%; 8, 38, 4–12%; 31, 5%; 45, 5–12%; 3, 12, 13, 16–20, 22, 36, 6–8%; 39, 7–10%; 28, 8–10%. Homogeneous fractions, as indicated by TLC ($CHCl_3$–MeOH, 9:1; silica gel GF) and appropriate ester bands in the infrared [representative examples: IR 15, 1706 cm^{-1} (Nujol); 23, 1709 cm^{-1}; 27, 1730 cm^{-1}; 42, 1707 cm^{-1}; 44, 1736 cm^{-1}], were combined, evaporated, and recrystallized from the designated solvent (Table I) to yield the ester as the HCl salt. Esters 4–7, 9–11, 23, 29, 33–35, and 37 crystallized from the reaction mixture directly or by addition of a small amount of benzene to the reaction mixture and were recrystallized as designated in Table I.

Compounds 27 and 40–44 were prepared in a manner similar to that described above except that 25 mL of dry benzene was more satisfactory that pyridine. Compounds 42–44 precipitated directly from the reaction mixture and were removed by suction filtration and recrystallized. Esters 27, 40, and 41 were chromatographed as described above (elutions: 27, 6% MeOH; 40, 6–8% MeOH; and 41, 4–8% MeOH).

Ester 15 was prepared by heating 6.9 g (0.05 mol) of 3-hydroxybenzoic acid and 7.0 g (0.06 mol) of 1-methyl-4-piperidinol in a 35-mL conical flask (oil bath, 150–160 °C) until the mixture liquefied. Anhydrous HCl gas was bubbled through the hot solution for 1.5 h. Heating was continued for an additional 16 h; the mixture was cooled and the brown gummy residue dissolved in 100 mL of hot absolute EtOH. On cooling, 5.26 g of 15 was obtained as tan-colored crystals. A second recrystallization from EtOH gave 3.7 g of analytically pure 15 (Table I).

References and Notes

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Nonsteroidal Antiinflammatory Agents. 2. Derivatives/Analogues of Dibenz[b,e]oxepin-3-acetic Acid

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6,11-Dihydro-11-oxodibenz[b,e]oxepins and some related compounds have been synthesized and evaluated for antiinflammatory effect according to the carrageenan paw edema method in rats. The structure–activity relationships have been discussed among acetic acid, carboxylic acid, alcohol, and tetrazole derivatives of dibenzoxepins and acetic acid derivatives of thienobenzoxepins and of the corresponding thiepins. The 3-isopropyl alcohol **9** and 11-deoxo-3-propionic acid (**49**) were more active than indomethacin but not as active as the title compound (i.e., **43**). Carboxylic acids, tetrazoles, esters, amides, and ketones were less active than the corresponding acetic acids. Three compounds (**31**, **33**, and **34**) were evaluated for ulcerogenicity and lethality but none surpassed 6,11-dihydro-11-oxodibenz[b,e]oxepin-3-acetic acid (**41**) in therapeutic ratio.

Some compounds (**40–43**) in the series of 6,11-dihydro-11-oxodibenz[b,e]oxepinacetic acids were already reported[1] to have favorable properties as antiinflammatory agents in comparison with indomethacin, phenylbutazone, and ketoprofen. Aultz et al.[2] have recently reported on the chemical and pharmacological studies of dibenzoxepin-2-acetic acids and their thieno and furano analogues independently of our work. In the present paper, we describe the structure–activity relationships of the following compounds which were synthesized in this institute: (1) 6,11-dihydro-11-oxodibenz[b,e]oxepinacetic acid derivatives (esters, amides, and deoxo compounds), (2) dibenzoxepins with alcohol, carboxylic acid, or tetrazole moiety in the "A" ring, (3) dibenzoxepins with the acetic acid moiety in the "C" ring (Figure 1), and (4) thienobenzoxepins and the corresponding thiepins.

Chemistry. The synthetic routes chosen for the preparation of alcohol, tetrazole, tetrazolylmethyl, butenone, and butanone derivatives (IV, VII, VIII, and **29**) of dibenz[b,e]oxepin are illustrated in Scheme I. The cyano compounds I, prepared by condensation of 2-cyanobenzyl halide with 3- or 4-hydroxyphenylalkanols, were hydrolyzed with 5 N NaOH to the corresponding carboxylic acids. After acetylation of the alcohol moiety to protect it against phosphorylation, cyclization of the acetoxy compounds II using PPE afforded the dibenz[b,e]oxepins III, which were deblocked by successive treatment with NaOH in MeOH to provide the free alcohols IV. However, an attempt to cyclize the *p*-acetoxymethyl compound II was unsuccessful and only gave an unknown compound containing phosphorus. Consequently, the synthesis of the 2-acetoxymethyldibenz[b,e]oxepin (**2**) was accomplished by brominating the 2-methyl compound and treating the resulting 2-bromomethyl compound **1** with AcONa in AcOH.

The chloromethyl compounds were prepared from the corresponding alcohols IV ($n = 0$) with $SOCl_2$ and con-

verted to the cyanomethyl compounds VI ($m = 1$) by reaction with NaCN. Oxidation of IV ($n = 0$) with CrO_3 afforded the carboxylic acids V, which were converted to the corresponding cyano compounds VI ($m = 0$) by successive treatment with $SOCl_2$, 28% NH_4OH, and tosyl chloride–pyridine–DMF via the carboxamides. Treatment of VI ($m = 0, 1$) with NaN_3 gave the corresponding tetrazole derivatives VII. On the other hand, MnO_2 oxidation of IV ($n = 0$) provided the aldehydes which were condensed with an appropriate methyl ketone to yield VIII. The 3-butenone compound VIII (R = Me) was hydrogenated to **29**, using Pd/C as a catalyst.

Reaction of the dibenz[b,e]oxepin-2- and -3-acetic acids with diethylaminoethyl chloride gave the corresponding esters, while the other esters and amides shown in Table I were prepared from the oxepinacetic acids by treatment with $SOCl_2$ and then with alcohols, amines, or a phenol.

The phenoxymethylbenzoic acid **65**, prepared from 5-hydroxymethylphthalide with sodium phenolate, was treated with $SOCl_2$ and then cyclized to the dibenz[b,e]oxepin **37** in the presence of $AlCl_3$. Cyanation of **37** with NaCN followed by acid hydrolysis yielded **39**.

Some dibenz[b,e]oxepinone derivatives were reduced as indicated in Scheme II. Reaction of the 2-acetic acids IXm with Zn in AcOH smoothly produced the 11-methylene compounds **45** and **46**, whereas that of 3-acetic acids IXn gave many kinds of products, and heating of IXn with Zn–amalgam in HCl–toluene afforded the corresponding 11-methylene compounds **48** and **49**. Further, reduction of IXm with $NaBH_4$ and treatment of IXn with Zn in NaOH gave the corresponding 11-hydroxy compounds **44** and **47**, respectively. Various dibenz[b,e]oxepin derivatives obtained above and their intermediates are listed in Tables I–IV.

Acetic acid derivatives of thienobenzoxepins and the corresponding thiepins were synthesized by the procedure described in series 3.[3]