similarity make this unlikely.

These findings support the conclusions of Cragoe et al.[7] and Woltersdorf et al.[8] that alkylation of renal tissue may not be a major mechanism by which EA and EA-related compounds induce a diuretic response. If renal tissue alkylation is not an essential event in the observed diuresis induced by EA and EA-related compounds, then it seems quite logical to disregard functional groups with alkylating properties when designing new diuretic agents. The main reason for this consideration is that most alkylating agents react with the array of nucleophiles in vivo in a very indiscriminate manner, and the result is usually a marked degree of toxicity. Recent work in our laboratory supports this contention in that certain specifically designed alkylating agents possess tremendous nephrotoxic potential (to be published).

Acknowledgment. The authors are indebted to Sandra A. Smith, Tom Mehalas, Julie Aufderheide, Joan Tarloff, and Larry Collins for their excellent technical assistance, and to the Pharmaceutical Manufacturers Association Foundation, Inc., Washington, D.C. 20005, for awarding a Faculty Development Award in Basic Pharmacology to D.A.K. during the period of this research. In addition, the authors thank Dr. E. J. Cragoe, Jr., of Merck Sharp & Dohme Research Laboratories, West Point, Pa., for a generous supply of ethacrynic acid.

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Synthesis and Analgesic Activity of Some Spiro[dibenz[*b,f*]oxepin-10,4′-piperidine] Derivatives

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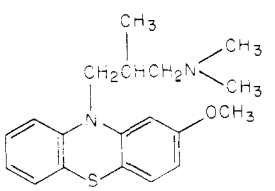
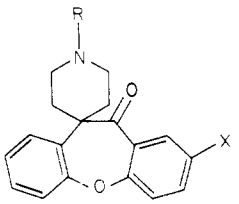
A series of 10,11-dihydro-11-oxospiro[dibenz[*b,f*]oxepin-10,4′-piperidine] derivatives (II) was synthesized and evaluated for analgesic activity in the phenylquinone writhing assay (PQW) and the tail-flick test in mice. Preliminary structure–activity correlations indicate that optimum activity is associated with a short-chain ($R \leq C_2$) N substituent and a nuclear fluorine function, as exemplified by **9b**. This compound, when administered orally, was equipotent to morphine in protecting against mouse writhing. The observation that the PQW activity of **9b** remained relatively unchanged after naloxone challenge seems to favor a nonnarcotic profile.

Although significant analgesic activity has been reported for a number of psychotropic agents with linear, tricyclic structures,[1-3] compounds of this type, in general, have rarely been investigated clinically as analgetics because of their diverse pharmacological actions. One notable exception to this is methotrimeprazine (I), a phenothiazine-like neuroleptic which is also active as a nonnarcotic analgesic agent.[4,5] When administered subcutaneously in man, methotrimeprazine is almost equipotent to morphine in controlling postoperative pain; extensive clinical use for this drug, however, has so far been precluded by its lack of oral efficacy and a high incidence of untoward side effects associated with oral use. As part of a program designed to search for new classes of analgesics based on the tricyclics, we have synthesized and evaluated pharmacologically a series of oxospiro[dibenz[*b,f*]oxepin-10,4′-piperidine] derivatives (II), and results from the preliminary studies are reported in this paper. The synthesis of these semirigid tetracycles appeared attractive to us because it is frequently suggested that the lack of specificity in biological activity can be linked to a high degree of conformational flexibility of the drug molecule;[6] thus, by locking the aminoalkyl side chain into a well-



I



II, X = H, F, or Cl;
R = H, alkyl, cycloalkyl, or aralkyl

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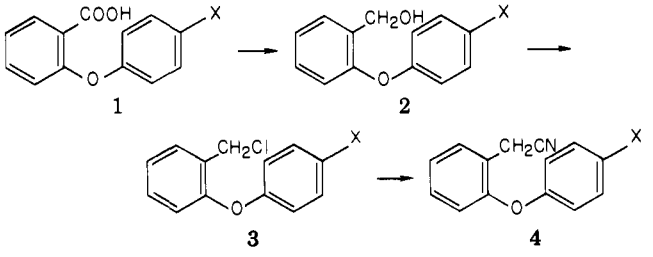
Scheme I



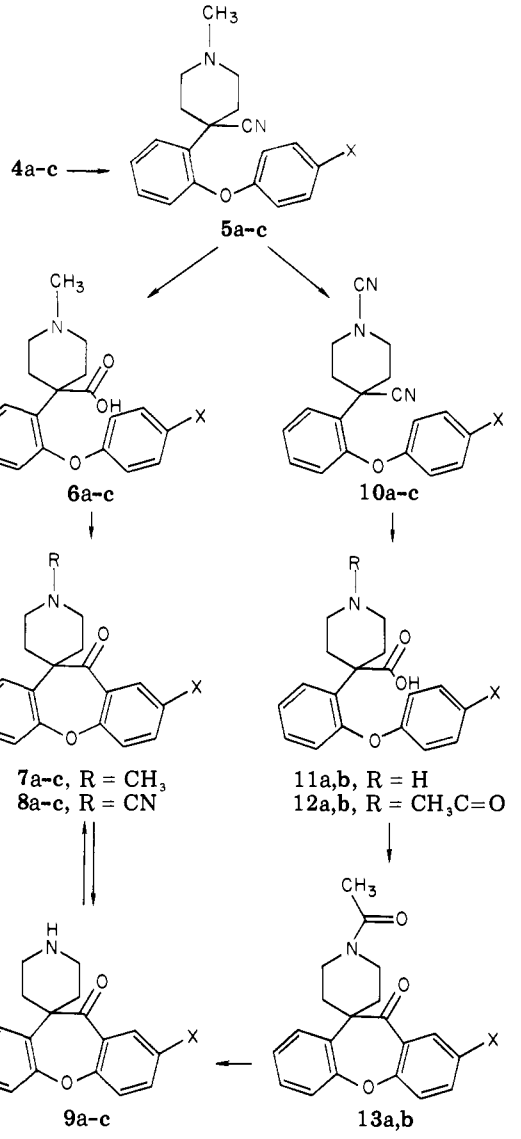
a, X = H; b, X = F; c, X = Cl

defined position, such as in II, the multitude of conformational possibilities would be greatly lessened, and, hopefully, a better separation of the undesired CNS effects from the analgesic activity would then be obtained. Furthermore, the oxospiro[dibenz[*b,f*]oxepin-10,4'-piperidine] derivatives (II) incorporate many structural features considered important for analgesic activity: an aromatic nucleus attached at C_4 of a piperidine ring, which in turn is connected to a carbonyl function at the same carbon; combinations such as these are found to be recurrent in many classes of analgesic agents as exemplified by meperidine and ketobemidone.

Chemistry. The key intermediates **4a–c** were synthesized according to Scheme I from the appropriately substituted phenoxybenzoic acids **1a–c**. Thus, reduction of **1a–c** with Vitride® (method A) to the corresponding alcohols **2a–c**[7] proceeded in high yields, and the subsequent reaction of **2a–c** with thionyl chloride (method B) gave chlorides **3a–c**, which were converted quantitatively to the nitriles **4a–c** with sodium cyanide in Me_2SO (method C). With the exception of **2b**, **3b**, and **4b** of the fluoro-substituted series, all other precursors described in Scheme I have been prepared previously by a comparable route.[8]

The main synthetic pathway, including construction of the piperidine ring and cyclization to the tetracyclic system, is outlined in Scheme II. Phenylacetonitriles **4a–c** underwent a facile bisalkylation with 2,2'-dichloro-*N*-methyldiethylamine in the presence of sodium hydride (method D) to give the cyanopiperidines **5a–c** in up to 90% yield. Acid hydrolysis of **5a–c** with 48% hydrobromic acid (method E) led to good yields of **6a–c**, isolable either as the free amino acids or as hydrobromides. Cyclodehydration of **6a–c** to **7a–c** with polyphosphoric acid (method F) proceeded with varying degrees of ease (H > F > Cl), correlating well with the order of deactivation among nuclear halogen substituents.[9] Compounds **7a–c** were demethylated with cyanogen bromide (method G),[10] and the resultant crystalline cyanamides **8a–c** were converted to the secondary amines **9a–c** with dilute hydrochloric acid (method H). In general, direct alkylation of **9a–c** with alkyl halides (method I) went smoothly to afford the various target compounds **15a,c–20a,c** and **21c–23c** as described in Table III; methylation of **9a–c**, however, could only be carried out under the conditions of Eschweiler–Clarke with formic acid and formaldehyde (method J). An alternative approach to the tetracyclic target system was also devised: the cyanopiperidines **5a–c** were first demethylated to **10a–c**, and hydrolysis of **10a,b** by method E gave **11a,b**, which were converted to the *N*-acetyl derivatives **12a,b** with acetic anhydride in pyridine (method K). Cyclization of **12a,b** via an intramolecular Friedel–Craft reaction (method L) occured readily to afford tetracycles **13a,b** and the subsequent cleavage of the amide group was effected quantitatively with dilute hydrochloric acid (method M). The latter approach,

Scheme II



a, X = H; b, X = F; c, X = Cl

despite being more tedious, offered some advantages in large-scale preparations of target compounds bearing N substituents other than the methyl radical.

Preliminary attempts to effect hydrogenolysis of the carbonyl function in **7a** were unsuccessful. Compound **7a** failed to form dithiane derivatives (to be desulfurized by Raney nickel) due to steric hindrance, and catalytic hydrogenation, carried out under a variety of conditions, afforded only complex mixtures of products as a result of skeletal rearrangements.

Pharmacology and Discussion of Results. Analgesic activity of the oxospiro[dibenz[*b,f*]oxepin-10,4'-piperidine] derivatives (II) was determined by measuring the inhibition of phenyl-*p*-benzoquinone induced writhing (PQW) and the delay in response to noxious heat stimuli in mice (D'Amour–Smith tail-flick method). The PQW test is used to detect both weak and strong analgesics, while the tail-flick test is sensitive to the strong, opiate-like analgesics. As shown by the results summarized in Table III, potent antinociceptive activity was displayed by several compounds of the series.

The most active analogues in the PQW screen were those bearing short-chain N substituents ($H \leq R \leq C_2$), as exemplified by **7a–c**, **9a–c**, and, to a lesser degree, **14a** and **17a,c**. A prominent feature of compounds in the **7** and **9**

series was the significant activity shown after oral administration. When given per os, compounds **7b** and **9b** were equipotent to morphine and ten times more active than propoxyphene, whereas by subcutaneous administration they were three to six times less potent than the former, yet twice as active as the latter. The ED_{50} po/ED_{50} sc ratio is approximately 1 for **7b** and **9b** and 1.5, 2.0, and 4.5 for **7c**, **9c**, and **9a**, respectively. These values appear to be more favorable than the ratio 6.3 found for propoxyphene, which is clinically used by oral administration. In general, compounds with larger N substituents ($R > C_2$) exhibited diminished activity in the PQW screen except for **18a**, a butyrophenone derivative ($ED_{50} < 5$ mg/kg) which quite possibly possesses a CNS depressant component.[11,12] Further consideration of SAR shows that activitiy in this test decreases within a subseries when the nuclear fluorine is replaced by hydrogen or chlorine.

Inspection of Table III also reveals that the tail-flick activity of the spiro[dibenz[*b,f*]oxepin-10,4′-piperidine] derivatives (II) generally ranged from inactive to weak or moderately active when compared with morphine. The clinical usefulness of compounds exhibiting activity comparable to morphine in the PQW, yet only marginally active in the tail-flick assay, has been clearly demonstrated for several of the narcotic-antagonist analgesics of the benzomorphan class.[13,14] In this regard, the profile of analgetic activity displayed by compounds II in the present study appears to be a favorable one.

It has been well established that not all compounds exhibiting potent antinociceptive activity in the PQW assay are analgetic agents of potential clinical use. In order to eliminate false leads, the rotorod test has been used[15,16] to measure the separation between doses required to produce antinociception and those required to produce discoordination, i.e., falling from the rotating rod. Using this approach, the ratio of ED_{50} rotorod/ED_{50} PQW for compound **9b** (the most active analogue in this series) was determined to be 17.6, suggesting that the antinociceptive activity observed in the PQW screen may, in fact, be reflective of an analgesic effect.

In summary, the spiro[dibenz[*b,f*]oxepin-10,4′-piperidine] derivatives (II) represent a novel class of potential analgetic agents, some with marked oral potency and an interesting (possibly nonnarcotic) profile.[17] In-depth studies on a few selected congeners from this series are currently in progress.

Experimental Section

The structure of all compounds are supported by their IR (Perkin-Elmer 457) and ^1H NMR (JEOLCO C60HL) (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 analysis were indicated only 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-Fluorophenoxy)benzyl Alcohol (2b). Method A. To a solution of 2-(4-fluorophenoxy)benozic acid[19] (15 g, 64.5 mmol) in 150 mL of anhydrous benzene was added dropwise 36 mL of 70% sodium dihydrobis(2-methoxyethanolate-*O,O′*)aluminate (Vitride®) in benzene over a period of 1 h. The solution was stirred at room temperature for 0.5 h and allowed to stand overnight. The cooled mixture was decomposed with 100 mL of 10% sodium hydroxide and extracted three times with benzene. The combined benzene solution, after washing and drying ($MgSO_4$), was concentrated to a yellowish oil which, upon distillation under vacuum, gave 15.0 g (98%) of **2b** as a colorless liquid: bp 119–122 °C (0.1 mmHg). Anal. ($C_{13}H_{14}O_2$) C, H, F.

2-(4-Chlorophenoxy)benzyl alcohol (2c) was prepared from **1c**[8] in 97% yield by method A: bp 145–148 °C (0.8 mmHg), lit.[8] 152 °C (1.1 mmHg).

2-(4-Fluorophenoxy)benzyl Chloride (3b). Method B. To 13.0 g (60 mmol) of **2b** in 80 mL of anhydrous benzene at 25 °C was added 8.50 g (71.5 mmol) of thionyl chloride over 5 min. The clear solution was stirred at room temperature for 16 h and poured onto 350 g of crushed ice containing 40 mL of saturated sodium bicarbonate. The benzene solution was washed with water, dried ($MgSO_4$), and concentrated to an oily residue. Distillation of the crude chloride in vacuo afforded 12.7 g (89%) of **3b** as a colorless liquid: bp 106–109 °C (0.16 mmHg). Anal. ($C_{13}H_{10}ClFO$) C, H, F.

2-Phenoxybenzyl chloride (3a) was prepared from **2a** in 85% yield by method B as a clear oil: bp 152–155 °C (12 mmHg), lit.[8] 170–172 °C (16 mmHg).

2-(4-Chlorophenoxy)benzyl chloride (3c) was prepared from **2c** in 89% yield by method B as a yellowish, viscous oil: bp 135–138 °C (0.2 mmHg), lit.[8] 140 °C (0.8 mmHg).

2-(4-Fluorophenoxy)phenylacetonitrile (4b). Method C. To 2.88 g of sodium cyanide in 120 mL of sieve-dried Me_2SO was added 12.0 g (50.7 mmol) of **3b** at room temperature over 30 min. The solution was stirred for 15 h and was poured onto 200 g of crushed ice. The mixture was extracted with ether, and the combined ether solution was washed, dried ($MgSO_4$), and concentrated under reduced pressure to a clear oil. Distillation of the crude product in vacuo afforded 13.8 g (89%) of **4b**, which solidified on cooling: mp 36–38 °C. Anal. ($C_{14}H_{10}FNO$) C, H, N.

2-Phenoxyphenylacetonitrile (4a) was obtained from **3a** in 89% yield by method C as a mobile oil: bp 150–154 °C (0.8 mmHg), lit.[8] 161 °C (3 mmHg).

2-(4-Chlorophenoxy)phenylacetonitrile (4c) was prepared from **3c** in 91% yield by method C: MS *m/e* 243 (M^+). This product was homogeneous by TLC (silica gel–CH_2Cl_2) and was used without further purification.

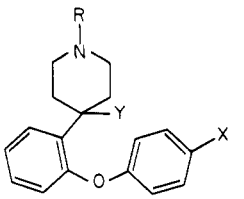
4-Cyano-1-methyl-4-(2-phenoxyphenyl)piperidine Hydrochloride (5a). Method D. To a solution of **4a** (4.4 g, 22 mmol) in 50 mL of anhydrous DMF[20] was added 2.94 g of NaH (99%) in small portions. Evolution of gas was immediate and the mixture turned reddish brown. After stirring the mixture at room temperature for 30 min, a solution of 3.95 g (20 mmol) of 2,2′-dichloro-*N*-methyldiethylamine hydrochloride (Aldrich) in 50 mL of DMF was added dropwise, and the mixture was stirred at 80 °C under N_2 for 16 h. Ice (100 g) was added and the mixture was extracted with ether. The combined ether solution was washed, dried (K_2CO_3), and concentrated to a brown oil. The crude product was purified by passing through a short column of alumina packed in ether: elution with ether afforded a clear oil which was converted to a crystalline hydrochloride with ethereal HCl. The solid was recrystallized from acetone–ether to give 5.9 g (90%) of **5a**. Properties of **5a**, and of **5b,c** prepared in a similar manner, are included in Table I.

1-Methyl-4-(2-phenoxyphenyl)piperidine-4-carboxylic Acid (6a). Method E. The free base from 2.3 g (7 mmol) of **5a** in 25 mL of 48% hydrobromic acid was stirred at reflux for 16 h. The excess acid was removed under reduced pressure and the glassy residue was dissolved in 50 mL of aqueous ethanol (1:1, v/v). The solution was applied on a column of cation-exchange resin (50 g of Bio-Rad AG-DOW-X8; polysulfonic acid) packed in water. The column was washed exhaustively with water until the effluent was neutral, and the amino acid was removed from the column with 1 N NH_4OH. Concentration of the ammoniacal solution led to a 1.8 g (83%) of **6a** which was analytically pure after drying under vacuum at 150 °C. Properties of **6a**, and of **6b,c** prepared in a similar manner, are included in Table I.

Alternatively, compounds **6a–c** could be isolated in a less pure form by adjusting the pH of the hydrolysates to 8 with dilute NH_4OH; the precipitated amino acids were washed with water and recrystallized from aqueous ethanol.

10,11-Dihydro-1′-methyl-11-oxospiro[dibenz[*b,f*]oxepin-10,4′-piperidine] Hydrobromide (7a). Method F. To 10.2 g of **6a** (32.8 mmol) was added 75 mL of polyphosphoric acid with good stirring. The mixture was stirred at 90–95 °C for 1 h, cooled, and diluted with 300 g of crushed ice. Basification with 58% NH_4OH liberated an oil, which was extracted into ether. The

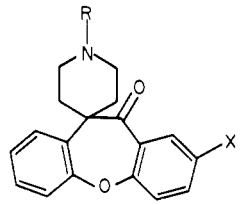
Table I. 4-(Aryloxy)piperidine Derivatives[a]



no.	R	X	Y	start. material	meth	mp, °C	yield,[b] %	recrystn[c] solv	formula	anal.
5a	CH_3	H	CN	4a	D	242-244	90	A-E	$C_{19}H_{20}N_2O\cdot HCl$	C, H, Cl, N
5b	CH_3	F	CN	4b	D	104-107	81	C	$C_{19}H_{19}FN_2O$	C, H, F, N
5c	CH_3	Cl	CN	4c	D	99-100.5	46	B-H	$C_{19}H_{19}ClN_2O$	C, H, Cl, N
6a[e]	CH_3	H	COOH	5a	E	257-259	83	D-F	$C_{19}H_{21}NO_3$	C, H, N
6b[e]	CH_3	F	COOH	5b	E	284-286	37	D-F	$C_{19}H_{20}FNO_3$	C, H, F, N
6c[e]	CH_3	Cl	COOH	5c	E	~320	51	D-F	$C_{19}H_{20}ClNO_3$	C, H, Cl, N
10a	CN	H	CN	5a	G	100-101	73	A	$C_{19}H_{17}N_3O$	C, H, N
10b	CN	F	CN	5b	G	108-110	80	B-H	$C_{19}H_{16}FN_3O$	C, H, N
10c	CN	Cl	CN	5c	G	135-136	90	A	$C_{19}H_{16}ClN_3O$	C, H, Cl, N
11a	H	H	COOH	10a	E	247-249	90	A-E-G	$C_{18}H_{19}NO_3\cdot HBr$	C, H, Br, N
11b	H	F	COOH	10b	E	*d*	75	E-G	$C_{18}H_{18}FNO_3\cdot HBr$	C, H, N
12a	CH_3CO	H	COOH	11a	K	195-197	76	A	$C_{20}H_{21}NO_4$	C, H, N
12b	CH_3CO	F	COOH	12b	K	197-194	64	A-E	$C_{20}H_{20}FNO_4$	C, H, N

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the structures. [b] Isolated yield; no efforts were made to optimize these yields. [c] A = acetone; B = benzene; C = cyclohexane; D = water; E = ethyl ether; F = ethanol; G = methanol; H = hexane; I = pentane. [d] Decomposed gradually after 180 °C; no sharp melting range was observed. [e] Also purified by ion-exchange chromatography over Bio-Rad AG-DOW-X8, 1 N NH_4OH as eluant.

Table II. 10,11-Dihydro-11-oxospiro[dibenz[*b,f*]oxepin-10,4'-piperidine] Derviatives[a]

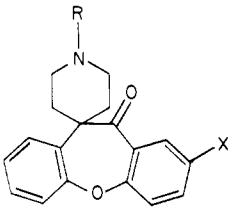


no.	R	X	start. material	meth	mp, °C	yield,[b] %	recrystn[c] solv	formula	anal.
7a	CH_3	H	6a	F	>320	71	E-G	$C_{19}H_{19}NO_2\cdot HBr$	C, H, Br, N
7b	CH_3	F	6b	F	295-296.5	73	E-G	$C_{19}H_{18}FNO_2\cdot HBr$	C, H, F, N
7c	CH_3	Cl	6c	F	304-306	78	E-G	$C_{19}H_{18}ClNO_2\cdot HBr$	C, H, Br, N
8a	CN	H	7a	G	98.5-100	85	E-I	$C_{19}H_{16}N_2O_2$	C, H, N
8b	CN	F	7b	G	105-106	68	A-I	$C_{19}H_{15}FN_2O_2$	C, H, F, N
8c	CN	Cl	7c	G	141.5-143	72	A	$C_{19}H_{15}ClN_2O_2$	C, H, N
9a	H	H	8a	H	280-282	78	A-E-G	$C_{18}H_{17}NO_2\cdot HBr$	C, H, Br, N
9b	H	F	8b	H	297-299	90	A-E-G	$C_{18}H_{16}FNO_2\cdot HCl$	C, H, F, N
9c	H	Cl	8c	H	223-225	48	A	$C_{18}H_{16}ClNO_2\cdot HBr$	C, H, N
13a	$CH_3C(=O)$	H	12a	L	171-172	82	B-H	$C_{20}H_{19}NO_3$	C, H, N
13b	$CH_3C(=O)$	F	12b	L	143-145	34	B-H	$C_{20}H_{18}FNO_3$	C, H, N
14a	CH_2-c-C_3H_5	H	9a	N	258-259	60	E-G	$C_{22}H_{23}NO_2\cdot HBr$	C, H, Br, N
14c	CH_2-c-C_3H_5	Cl	9c	N	302-305	63	A-E-G	$C_{22}H_{22}ClNO_2\cdot HBr$	C, H, N
15a	$(CH_2)_2C_6H_5$	H	9a	N	>320	62	A-E	$C_{26}H_{25}NO_2\cdot HBr$	H, Br, N, C[d,e]
15c	$(CH_2)_2C_6H_5$	Cl	9c	N	136.8-138	51	A	$C_{26}H_{24}ClNO_2$	C, H, Cl, N
16a	$CH_2C{\equiv}CH$	H	9a	N	241-242	58	A-E-G	$C_{21}H_{19}NO_2\cdot HBr$	C, H, Br, N
16c	$CH_2C{\equiv}CH$	Cl	9c	N	148-150	35	B	$C_{21}H_{18}ClNO_2$	C, H, Cl, N
17a	$(CH_2)_2OH$	H	9a	N	263-266	70	A-E-G	$C_{20}H_{21}NO_3\cdot HBr$	C, H, Br, N
17c	$(CH_2)_2OH$	Cl	9c	N	240.5-242	41	A-E-G	$C_{20}H_{20}ClNO_3\cdot HBr$	C, H, N
18a	$(CH_2)_3C(=O)$-C_6H_4-4-F	H	9a	N	260-262	83	E-G	$C_{28}H_{26}FNO_3\cdot HBr$	C, H, Br, N
18c	$(CH_2)_3C(=O)$-C_6H_4-4-F	Cl	9c	N	220-221	38	A-E	$C_{28}H_{25}ClFNO_3\cdot HBr$	C, H, N
19a	$(CH_2)_3OC_6H_5$	H	9a	N	213-215	57	E-G	$C_{27}H_{27}NO_3\cdot HBr$	C, H, N
19c	$(CH_2)_3OC_6H_5$	Cl	9c	N	105-106	74	A	$C_{27}H_{26}ClNO_3$	C, H, Cl, N
20c	$CH_2C=C(CH_3)_2$	Cl	9c	N	267-268	55	A-E-G	$C_{23}H_{24}ClNO_2\cdot HBr$	C, H, N
21c	$CH_2CH=CH_2$	Cl	9c	N	293-295	61	G	$C_{21}H_{20}ClNO_2\cdot HBr$	C, H, N
22c	C_2H_5	Cl	9c	N	302-304	63	G	$C_{20}H_{20}ClNO_2\cdot HBr$	C, H, N
23c	*n*-C_3H_7	Cl	9c	N	315-316	77	A-E-G	$C_{21}H_{22}ClNO_2\cdot HBr$	C, H, N

[a-c] See corresponding footnotes to Table I. [d] Anal. Calcd: C, 67.20. Found: C, 66.69. [e] Mass spectrum *m/e* 383 (molecular ion of the free base).

combine ether solution, after washing and drying (K_2CO_3), was a heavy oil. The crude product was purified by column chromatography over silica packed in CH_2Cl_2: elution with a mixture of CH_3OH–CH_2Cl_2 (1:10) afforded a colorless oil, which was

Table III. Pharmacology of 10,11-Dihydro-11-oxospiro[dibenz[*b*,*f*]oxepin-10,4′-piperidine] Derivatives



compd[a]	R	X	analgesic act.:[b] ED_{50}, mg/kg phenylquinone writhing	tail flick
7a	CH_3	H	5.2 (3.3-13.2)	13% at 25 mg/kg
7b	CH_3	F	1.9 (1.6-2.3), 2.0 (1.9-2.1)[e]	30% at 25 mg/kg
7c	CH_3	Cl	3.5 (3.2-3.9), 5.2 (4.3-6.0)[e]	13.2 (11.0-27.0)
9a	H	H	1.7 (1.6-1.8), 7.5 (7.0-8.0)[e]	60% at 25 mg/kg
9b	H	F	1.6 (1.5-1.7), 2.2 (2.1-2.3)[e]	75% at 25 mg/kg, 51.4 (48-55.6)[e]
9c	H	Cl	3.7 (3.2-4.2), 7.7 (7.0-8.4)[e]	12.0 (11.0-27.5)
14a	CH_2-c-C_3H_5	H	6.0 (5.6-6.4), 59% at 25 mg/kg[e]	*c*
14c	CH_2-c-C_3H_5	Cl	31% at 25 mg/kg	0% at 25 mg/kg
15a	$(CH_2)_2C_6H_5$	H	21.0 (18.9-24.1)	40% at 25 mg/kg
15c	$(CH_2)_2C_6H_5$	Cl	30% at 25 mg/kg	0% at 25 mg/kg
16a	$CH_2C{\equiv}CH$	H	57% at 25 mg/kg	20% at 25 mg/kg
16c	$CH_2C{\equiv}CH$	Cl	32% at 25 mg/kg	10% at 25 mg/kg
17a	$(CH_2)_2OH$	H	2.8 (2.5-3.1)	40% at 25 mg/kg
17c	$(CH_2)_2OH$	Cl	7.0 (5.3-8.3)	30% at 25 mg/kg
18a	$(CH_2)_3C(=O)C_6H_4$-4-F	H	67% at 5 mg/kg[e]	60% at 25 mg/kg
18c	$(CH_2)_3C(=O)C_6H_4$-4-F	Cl	49% at 25 mg/kg	20% at 25 mg/kg
19a	$(CH_2)_3OC_6H_5$	H	55% at 25 mg/kg	20% at 25 mg/kg
19c	$(CH_2)_3OC_6H_5$	Cl	54% at 25 mg/kg	0% at 25 mg/kg
20c	$CH_2CH{=}C(CH_3)_2$	Cl	42% at 25 mg/kg	*d*
21c	$CH_2CH{=}CH_2$	Cl	37% at 25 mg/kg	10% at 25 mg/kg
22c	C_2H_5	Cl	67% at 25 mg/kg	0% at 25 mg/kg
23c	*n*-C_3H_7	Cl	22% at 25 mg/kg	10% at 25 mg/kg
pentazocine			2.4 (2.1-2.9)	14.6 (7.4-24.4)
morphine[f]			0.36 (0.33-0.40), 1.9 (1.7-2.1)[e]	3.8 (1.7-9.5)
propoxyphene			3.9 (3.5-4.3), 24.6 (22.5-27.0)[e]	

[a] The vehicle control used in all three biological tests consists of distilled water and a few drops of Tween 80. [b] Determined by subcutaneous administration unless otherwise specified. [c] Not determined. [d] CNS effects required a lower initial screening dose in this test. [e] Determined by oral administration. [f] Morphine sulfate was used.

converted to 8.4 g (71%) of a crystalline hydrobromide (**7a**) with ethereal HBr. Properties of **7a**, and of **7b,c** prepared in a similar manner, are included in Table II.

Alternatively, compounds **7a–c** could be prepared from **9a–c**, respectively, by method J.

1′-Cyano-10,11-dihydro-11-oxospiro[dibenz[*b*,*f*]oxepin-10,4′-piperidine] (8a). Method G. The free base from 8.3 g (23 mmol) of **7a** was dissolved in 22 mL of CH_2Cl_2 and added, over 15–30 min, to a well-stirred mixture of 2.74 g of cyanogen bromide and 14 g of potassium carbonate in 36 mL of anhydrous CH_2Cl_2. The mixture was refluxed for 2 h, cooled to room temperature, and filtered. Removal of the solvent under reduced pressure left a glassy residue, which was heated with 50 mL of boiling methanol to decompose the unreacted cyanogen bromide. The solution was again concentrated to dryness; trituration of the oily residue with acetone–pentane deposited 5.7 g of 8a. Properties of **8a**, and of **8b,c** prepared in a similar manner, are included in Table II.

10,11-Dihydro-11-oxospiro[dibenz[*b*,*f*]oxepin-10,4′-piperidine] Hydrobromide (9a). Method H. A mixture of 8a (3.03 g, 10 mmol) in 38 mL of 3 N HCl was stirred at reflux for 16 h. The almost clear solution was diluted with ice and extracted with ether to remove neutral materials. Basification with 58% NH_4OH liberated an oil, which was extracted into ether, washed, and dried (K_2CO_3). The crude amine was converted to its hydrobromide with etheral HBr, and recrystallization from methanol–acetone–ether gave 2.81 g of **9a**. Properties of **9a**, and of **9b,c** prepared in a similar manner, are included in Table II.

Alternatively, compounds **9a,b** could be prepared from **13a,b** by method M.

Conversion of 9a to 7a by Methylation. Method J. The free base from 1.24 g (4 mmol) of **9a** in 8 mL of formic acid was refluxed for 2 h before 7.2 mL of formalin (38% HCHO in water) was added. Stirring and refluxing were continued for 16 h. The excess reagents were removed under reduced pressure, and the residue was triturated with water and basified with dilute NaOH. The liberated oil was extracted into ether, washed, and dried (K_2CO_3). Treatment of the residual oil with ethereal HBr afforded 2.0 g (57%) of **7a**, which was identical with an authentic sample obtained by method F. Compounds **9b,c** could be converted, respectively, to **7b,c** by method J in comparable yields.

1,4-Dicyano-4-(2-phenoxyphenyl)piperidine (10a). To a stirred mixture of 1.5 g of cyanogen bromide and 6.0 g of K_2CO_3 in 30 mL of CH_2Cl_2 was added 2.6 g (9 mmol) of the free base from **5a** in 22 mL of CH_2Cl_2 according to method G. After stirring at reflux for 2 h, the mixture was filtered and the filtrate was concentrated to a solid residue. Recrystallization from acetone–hexane gave 2.0 g (73%) of **10a** as rhombic crystals. Properties of **10a**, and of **10b,c** prepared in a similar manner, are included in Table I.

4-(2-Phenoxyphenyl)piperidine-4-carboxylic Acid Hydrobromide (11a). A mixture of **10a** (8.0 g, 26.4 mmol) in 120 mL of 48% hydrobromic acid was stirred at reflux for 16 h according to method E. The excess acid was removed under reduced pressure, and the glassy residue was dissolved in 100 mL of water. Crystals began to deposit after standing at 0 °C and, after 24 h, were removed by filtration. Recrystallization from methanol–acetone–ether gave 9.0 g (90%) of **11a**, which was dried in vacuo at 150 °C to be free of solvated water. Properties of **11a**, and of **11b** prepared in a similar manner, are included in Table I.

1-Acetyl-4-(2-phenoxyphenyl)piperidine-4-carboxylic Acid (12a). Method K. A mixture of **11a** (8.0 g, 21 mmol) and 10 mL of acetic anhydride in 50 mL of anhydrous pyridine was stirred at reflux for 4 h. The clear solution was concentrated under vacuum to a residue, which was triturated with 100 mL of 1 N HCl. The insoluble oil was extracted with $CHCl_3$, washed with 1 N HCl, and dried ($MgSO_4$). Removal of solvent left a solid residue, which was recrystallized from acetone to give 5.3 g (76%) of **12a** in small prisms. Properties of **12a**, and of **12b** prepared

in a similar manner, are included in Table I.

1'-Acetyl-10,11-dihydro-11-oxospiro[dibenz[*b,f*]oxepin-10,4'-piperidine] (13a). Method L. A mixture of 3.4 g (10 mmol) of **12a** and 5 mL of freshly distilled thionyl chloride was warmed on a steam bath for 5 min until a clear solution was formed. The excess reagent was removed at 50 °C under reduced pressure, and the resulting solid was dissolved in 100 mL of 1,2-dichloroethane and added slowly to 1.9 g (40% excess) of aluminum chloride. Stirring was maintained at reflux for 2 h, during which the color of the reaction mixture changed from greenish to light tan. Ice (50 g) was added; the mixture was extracted three times with $CHCl_3$, and the combined organic solution was washed with dilute NaOH and water and dried ($MgSO_4$). Removal of ether in vacuo left a solid residue, which was recrystallized from benzene–hexane to give 2.62 g (82%) of **13a** as colorless prisms. Properties of **13a**, and **13b** prepared in a similar manner, are included in Table II.

Conversion of 13a to 9a by Acid Hydrolysis. Method M. A mixture of **13a** (2.0 g, 6.2 mmol) in 15 mL of 3 N HCl was stirred at reflux under N_2 for 3 h. The clear solution was diluted with 100 mL of water and extracted with ethyl acetate to remove any unreacted amide. Basification of the acidic solution with NH_4OH liberated an oil, which was extracted with ether, washed, and dried (K_2CO_3). Removal of ether under vacuum left a clear oil, which was converted to 2.1 g (93%) of **9a**, identical with an authentic sample prepared by method H. Similarly, **13b** was converted to **9b** in comparable yield.

1'-(Cyclopropylmethyl)-10,11-dihydro-11-oxospiro[dibenz[*b,f*]oxepin-10,4'-piperidine] Hydrobromide (14a). Method I. A mixture of the free base from 2.55 g (7.1 mmol) of **9a**, 740 mg of chloromethylcyclopropane, 1.8 g of $NaHCO_3$, and 1.8 g of KI in 15 mL of DMF was stirred under N_2 at 70–80 °C for 16 h. The cooled suspension was diluted with water and extracted with ether. The combined ether extract was washed, dried (K_2CO_3), and concentrated to an oily residue. Column chromatography of the crude product over alumina (ether as eluant), followed by treatment with ethereal HBr, afforded a crystalline hydrobromide, which was recrystallized from methanol–ether to give 1.7 g (60%) of **14a**. Properties of **14a**, and of **14c**, **15a,c–17a,c**, **19a,c**, and **20c–23c** prepared in similar manners, are included in Table II.

1'-[3-(*p*-Fluorobenzoyl)propyl]-10,11-dihydro-11-oxospiro[dibenz[*b,f*]oxepin-10,4'-piperidine] (18a). The free base from 1.7 g (4.6 mmol) of **9a** was alkylated with 1.4 g of γ-chloro-*p*-fluorobutyrophenone ethylene ketal, 1.0 g of $NaHCO_3$, 1.0 g of KI, and 15 mL of DMF according to method I. The crude tertiary amine, after workup, was stirred with 16 mL of 95% ethanol and 16 mL of 3 N HCl at room temperature for 16 h to effect complete hydrolysis of the ketal ring. The acidic solution was basified with 40% NaOH and the liberated amino ketone was extracted into ether, dried, and concentrated. The crude product was purified by passing through an alumina column packed in ether; elution with ether afforded a clear oil, which was converted to 2.0 g (83%) of **18a** as colorless prisms. Properties of **18a**, and of **18b** prepared in a similar manner, are included in Table II.

Phenylquinone-Induced Writhing in Mice (PQW). The procedure employed was a modification of the method of Siegmund et al.[21] Groups of five male CD-1 Charles River mice weighing 18–24 g were administered the test drug (sc or po) 15, 30, 60, and 90 min prior to the injection of a phenyl-*p*-benzoquinone (Eastman) solution (0.125% in a 5% aqueous ethanol solution) at the initial screening dose of 25 mg/kg. Control mice were treated with an equal volume of vehicle. After phenylquinone injection the mice were placed individually in 1000-mL beakers, and 5-min later the number of writhes was recorded for a 10-min period. The peak time of test drug activity was thereby determined. A dose–response study was performed in a similar manner, except that ten animals were used at the peak time of activity. Animals were dosed and tested in a randomized manner using four drug doses and one control group. Drug activity is expressed as the percent inhibition of the number of writhes, and an estimated ED_{50} is calculated by a computer linear-regression analysis.

Modified D'Amour–Smith Analgesia (Tail-Flick) in Mice. The procedure used was a modification of the test developed by D'Amour and Smith.[22] Groups of ten male Charles River (CD-1) mice were individually placed in a restraining Plexiglas compartment and subsequently a noxious stimulus was produced by an intense light beam. The subjects quickly responded by flicking their tails. This reaction time, the intervals between stimulus onset and response, was measured and recorded. Prior to drug administration, two control readings of reaction time were taken. Subjects were discarded if their reaction times varied by more than 1 s or if their inclusion would cause the spread of reaction times to exceed 3 s. For both sets of control readings, a cutoff (co) time was thus determined. Test compounds were administered subcutaneously, and control mice received an equal volume (10 mL/kg) of vehicle. For a time response, the animals were tested 15, 30, 45, and 60 min after dosing. Animals which responded after the determined co value were called positive, indicative of analgesia. For a dose range, the animals were tested at the peak time with a minimum of three doses in addition to vehicle control. Percent analgesia was calculated for each dose, and estimated ED_{50} values were determined using a linear-regression analysis.

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