°C. NMR (DMSO-d_6) 1.55 (s, 6 H, 2 CH_3), 4.42 (s, 2 H, CH_2), 6.71–7.22 (q, 4 H, aromatics), 7.32 (s, 5 H, aromatics), 7.69 (s, 1 H, NH), 4.70 (s, 1 H, COOH). Anal. ($C_{15}H_{12}Cl_2N_2O_4$) C, H, N.

Compounds 16a–c. Bezafibrate (**16c**), its 3,5-dichloro analogue (**16a**), and its α-carboxylic derivative (**16b**) were prepared by using methods described in the literature.[3]

Oxygen-Dissociation Curves. For determination of the effects of various compounds on the affinity of hemoglobin for oxygen in intact red cells, 30-μL aliquots of freshly drawn, heparinized, normal whole blood were added to 5 mL of the test compounds and diluted to the desired concentrations in 0.1 M HEPES buffer (pH 7.4). The final concentration of hemoglobin in these red-cell suspensions was 12.5 ± 0.5 μM as measured spectrophotometrically.[5] The mixtures were equilibrated for 30 min at 37 °C before being placed in the instrument chamber for oxygenation. A new method was devised for preparation of membrane-free hemoglobin: erythrocytes were washed five times in 20 volumes of 0.15 M NaCl solution, and the packed cells free of leukocytes, platelets, and serum proteins were diluted with 5 volumes of distilled water. The hemolysates were then passed sequentially through a double layer of Whatman filter paper #1 and a single layer of Whatman #5, followed by filtration through 1.2, 0.8, 0.45, and 0.22 μm-pore size Millipore filters all placed in a Swinex-47 Millipore filter holder. For the study of the effects of various compounds on hemoglobin in solution, the test compounds were first dissolved in 5-mL aliquots of 0.1 M HEPES buffer (pH 7.4), hemoglobin was added at a final concentration of 12.5 ± 0.5 μM, and then oxygen-dissociation curves were determined after 30-min incubation at 37 °C. In both the intact red-cell suspensions and membrane-free hemoglobin solutions, the molar ratio of hemoglobin to the test compound was 80 ± 3:1, when the test compound was at 1 mM.

Acknowledgment. We wish to thank Professor Max F. Perutz for reviewing the manuscript and Barbara Barrett-Clayton for outstanding secretarial assistance.

Registry No. **2**, 117011-70-8; **3**, 79925-16-9; **4**, 121809-54-9; **5**, 7159-95-7; **6**, 121809-55-0; **7**, 121809-56-1; **8a**, 121809-57-2; **8b1**, 121809-65-2; **8b2**, 121809-66-3; **8b3**, 121809-67-4; **8c1**, 121809-68-5; **8c2**, 121809-69-6; **8c3**, 121809-70-9; **8d**, 121809-71-0; **8e1**, 121809-72-1; **8e2**, 121809-73-2; **8f1**, 121809-74-3; **8f2**, 121809-75-4; **8f3**, 121809-76-5; **8g1**, 121809-77-6; **8g2**, 121809-78-7; **8g3**, 121809-79-8; **8g4**, 117011-50-4; **8g5**, 121809-80-1; **8h1**, 121809-81-2; **8h2**, 121809-82-3; **8i**, 121809-83-4; **8j**, 121809-84-5; **8k**, 121809-85-6; **8l1**, 121809-86-7; **8l2**, 121809-87-8; **8m**, 121809-88-9; **8n**, 121809-89-0; **8o**, 121809-94-7; **8p**, 121809-90-3; **9**, 1222-74-8; **10a**, 121809-58-3; **10b**, 121809-91-4; **11**, 121809-59-4; **12**, 121809-60-7; **13**, 121809-61-8; **14**, 121809-62-9; **15**, 121809-63-0; **16a**, 121809-64-1; **16b**, 121809-93-6; **16c**, 41859-67-0; *p*-cyanophenol, 767-00-0; *p*-aminophenol, 123-30-8; 3,4,5-trichloroaniline, 634-91-3; 3,4,5-trichlorophenyl isocyanate, 35753-93-6; *p*-aminobenzaldehyde, 556-18-3; *p*-formalphenyl isocyanate, 111616-43-4; 3,4,5-trimethoxyphenylisocyanate, 1016-19-9; *p*-phenylphenol, 92-69-3; *p*-chlorobenzoyl chloride, 122-01-0; 3,5-dichlorobenzoyl chloride, 2905-62-6; *p*-chlorohippuryl chloride, 121809-92-5; *S*-methyl(4-chlorophenyl)isothiourea, 39536-21-5; (4-aminophenoxy)acetic acid, 2298-36-4; 3,4-dichlorophenyl isocyanate, 102-36-3; 3,5-dichlorophenylisocyanate, 34893-92-0.

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The Xanthene-9-spiro-4′-piperidine Nucleus as a Probe for Opiate Activity

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A series of novel 1′-methylxanthene-9-spiro-4′-piperidines has been prepared in the search for opiate analgesics with improved pharmacological properties. It has been found that introduction of a hydroxyl group into the 4-position of the xanthenespiropiperidine nucleus produces a potent μ-opiate agonist. The structure–activity relationship of the series has been explored by use of isosteric replacements of the phenolic hydroxyl group. Moreover, the effect of altering the conformation of the piperidine ring has been studied. It was interesting to note that, in compounds lacking the phenolic hydroxyl group, opiate activity could be produced by introduction of the (phenylamino)ethyl group instead of methyl at the 1′-position.

It has long been the objective of medicinal chemists to prepare analgesics with the efficacy of morphine (1; see Chart I) as pain killers while lacking the serious and use-limiting side effects of nausea, respiratory depression, and addictive liability.[1,2] A wide variety of compounds related to the natural opiates or of completely novel structure have been investigated, and interesting hypothetical models of the receptor have been advanced in an attempt to explain the structure–activity data.[3–7] The discovery of different types of opiate receptor[8,9] has shown why in the past it was so difficult to construct a single model that would satisfactorily explain all the results. Our knowledge of the existence of μ, δ, and κ receptor subtypes of opiate receptors allows a reevaluation of earlier hypotheses of structure activity. This is particularly relevant in the role of the phenolic hydroxyl group in contributing to μ-opiate properties in compounds related to morphine.[10,11]

In the search for novel compounds with opiate properties, we have studied the xanthenespiropiperidine as a nucleus. Substitution in the aromatic rings produces compounds with a variety of pharmacological properties.[12,13] In this paper we describe the synthesis of sub-

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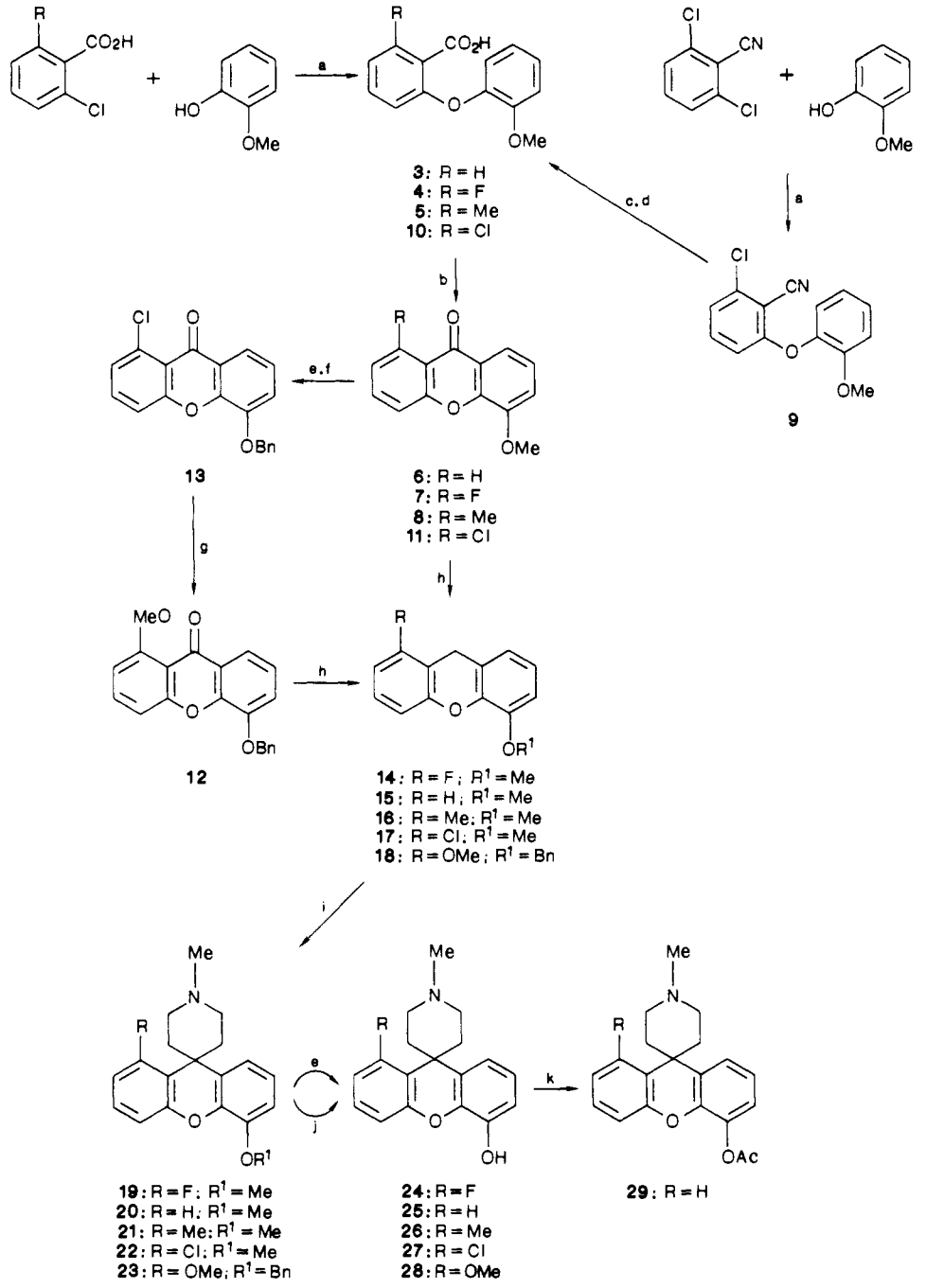
0022-2623/89/1832-2357$01.50/0

Scheme I[a]



[a] (a) NaOMe–Cu; (b) PPA; (c) NaOH; (d) $AmNO_2$–HCl; (e) 45% HBr–HOAc; (f) $PhCH_2Br$; (g) NaOMe–DMF; (h) B_2H_6; (i) MeN-$(CH_2CH_2Cl)_2$–$NaCH_2SOMe$; (j) H_2–5% Pd/C; (k) Ac_2O–Py.

stituted xanthenespiropiperidines and their opiate properties and discuss the structural requirements for μ-opiate receptor activity.

Chemistry

Synthetic routes to xanthenespiropiperidines varied according to the substitution pattern required. Spiroalkylation of xanthenes with *N*-methyl-2,2′-dichlorodiethylamine was particularly useful when a methyl substituent was required on the nitrogen atom. The parent compound **2** was prepared in one step from xanthene by this method. Suitably substituted xanthenes were synthesized by Ullman condensation of *o*-halobenzoic acids with a variety of phenols (Scheme I). The *o*-arylbenzoic acids **3**, **4**, and **5** were cyclized with polyphosphoric acid to the xanthones **6**, **7**, and **8**. 2,6-Dichlorobenzonitrile was converted, via the intermediates **9** and **10**, to 1-chloro-5-methoxyxanthone (**11**), which served as an intermediate for the synthesis of the xanthone **12**.

This procedure went through compound **13** making use of nucleophilic displacement of the active chloro substituent by methoxide. The xanthones **6**, **7**, **8**, **11**, and **12** were reduced with diborane to the xanthenes **14**, **15**, **16**, **17**, and **18**, which were converted by alkylation to the spiropiperidines **19**, **20**, **21**, **22**, and **23**. These ethers were deprotected according to standard literature procedures, giving the target phenolic spiropiperidines **24**, **25**, **26**, **27**, and **28**, and compound **25** was converted to the acetate **29** with acetic anhydride.

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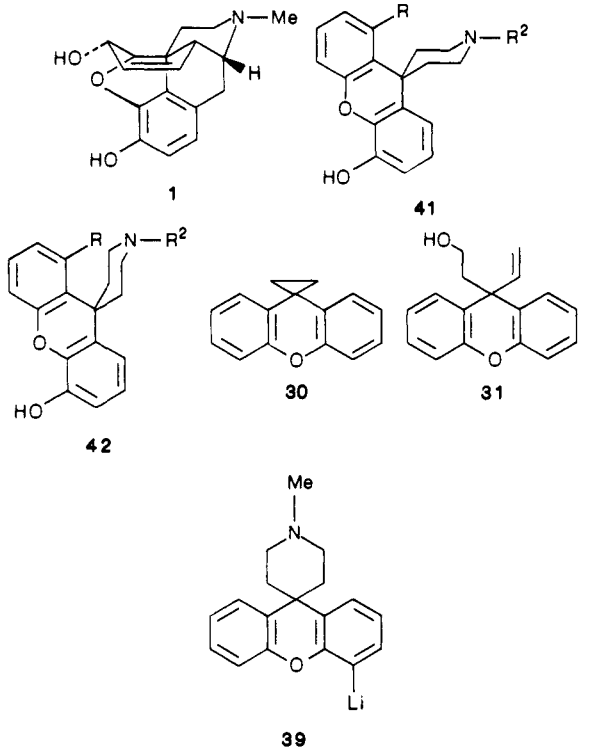
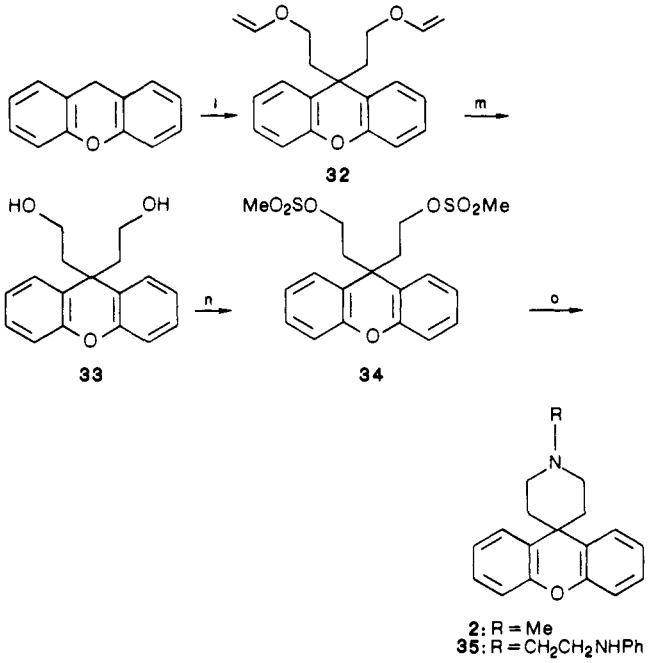
Chart I



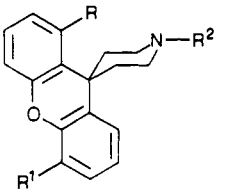
Scheme II[a]



[a] (l) $ClCH_2CH_2OCH{=}CH_2$-$NaCH_2SOMe$; (m) H^+; (n) $MeSO_2Cl$-Py; (o) RNH_2.

Xanthenes could also be dialkylated with 2-chloroethyl vinyl ether. When this alkylation was conducted at room temperature or above, the unusual products **30** and **31** were formed.[14] However, at 0 °C, the dialkylated product **32** (see Scheme II) was obtained in good yield and was converted, via the diol **33**, to the dimesylate **34**. The dimesylate reacted with a variety of primary amines to give spiropiperidines. This method was particularly useful for the synthesis of compound **35** and of potential opiate antagonists and partial agonists.[12]

Table I. Relative Potency of Xanthenespiropiperidines in the Electrically Stimulated Guinea Pig Ileum Test



no.	R	R^1	R^2	rel potency[a] (normorphine = 1)
2	H	H	Me	
25	H	OH	Me	0.175 ± 0.06
29	H	OAc	Me	1.0 ± 0.2
36	H	NH_2	Me	0.055 ± 0.017
40	H	NHAc	Me	0.008 ± 0.005
37	H	SH	Me	0.001 ± 0.001
38	H	CH_2OH	Me	0.004 ± 0.002
24	F	OH	Me	0.16 ± 0.003
27	Cl	OH	Me	0.031 ± 0.02
26	Me	OH	Me	0.237 ± 0.16
28	OMe	OH	Me	0.094 ± 0.03
35	H	H	CH_2CH_2NHPh	3.5 ± 1.2
methadone				0.91 ± 0.18

[a] All results are expressed relative to the standard, normorphine the mean IC_{50} of normorphine was 31.3 ± 3.9 nM.

Isosteric replacements of the phenolic hydroxyl group to give compounds **36–38** were achieved (see Scheme III) by quenching the anion **39**, generated from **2** by using *tert*-butyllithium, with hydroxylamine *O*-methyl ether, sulfur, and formaldehyde, respectively.[15] The amide **40** was derived from the amine **36** by acylation with acetic anhydride. Compound **25** could also be prepared in low yield according to this anion route, using *tert*-butyl perbenzoate followed by acid treatment to remove the *tert*-butyl group.

Biology

The field-stimulated guinea pig ileum preparation was set up as described in the literature.[16] Cumulative dose–response curves were produced for both normorphine and the test compounds. IC_{50} values (concentrations to produce 50% inhibition of the electrically evoked twitch) were calculated by linear regression. All potencies were expressed relative to normorphine which was assayed on the same tissues.

In vivo activity was measured by using the acetic acid induced writhing model in mice.[17] Groups of twelve mice were dosed subcutaneously with test compound or saline. Thirty minutes later the mice received an intraperitoneal injection of 0.4 mL of 0.4% acetic acid. The number of abdominal constriction responses occurring in the subsequent 15 min were counted. The ED_{50} dose was defined as that required to reduce the number of responses to 50% of the control level.

Results and Discussion

The parent xanthenespiropiperidine structure **2** was a depressant of the central nervous system but had no opiate properties (see Table I). Introduction of a phenolic hydroxyl group produced a dramatic change in biological properties. For example, compound **25** with obvious structural similarities to morphine (**1**) had one-fifth the

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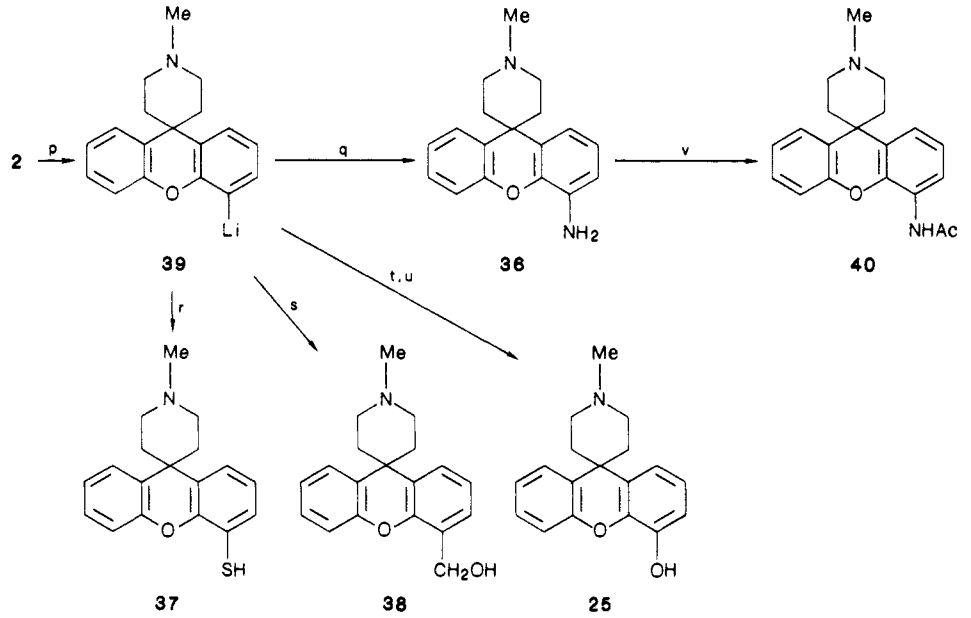
Scheme III[a]



[a] (p) t-BuLi; (q) NH_2OMe; (r) S; (s) HCHO; (t) $PhCO_2O$-t-Bu; (u) 3 N HCl; (v) Ac_2O-Py.

potency of normorphine at inhibiting the electrically evoked contraction of the guinea pig ileum. Naloxone antagonism studies revealed an equilibrium dissociation constant (K_e) of 1.3 nM, which indicated that, like morphine, the action of this compound was mediated via the opioid μ-receptor.[18] The acetate **29** was equipotent with normorphine in this tissue.

A few examples of isosteric replacement of the phenolic hydroxyl group have been reported in the benzomorphan series.[19-21] This was a particularly easy topic to study in xanthenespiropiperidines as the compounds with $-NH_2$ (**36**), $-NHCOCH_3$ (**40**), -SH (**37**), and $-CH_2OH$ (**38**) substituents could all be made from the common intermediate **39**. None of these replacements produced improvements in activity.

A unique feature of the structure of morphine (**1**) is a phenyl group held rigidly axial to a piperidine ring. In xanthenespiropiperidines, e.g., **25**, the piperidine ring is flexible and can flip between two chair conformations, **41** and **42**, only one of which, **41**, represents the conformation found in the opiate alkaloids. Clearly, substitution at the 1-position would force the ring over to a more "morphine-like" conformation. However, in 1-substituted 5-hydroxyxanthenespiropiperidines where the 1-H was replaced by F, Cl, CH_3, and OCH_3 (**24**, **27**, **26**, and **28**, respectively), no dramatic increase in opiate activity was observed.

The role of the phenolic hydroxyl group in opiates is still puzzling.[10,11] In rigid structures closely related to morphine (**1**), e.g., benzomorphans and morphinans, the hydroxyl group seems to be required for high μ-receptor activity. In more flexible structures, it is required in some, e.g., profadol[22] and the enkephalins,[23] but not in others like etonitazine[24] and the fentanyl group.[25] Although the phenolic hydroxyl group seemed to be essential for opiate activity in xanthenespiropiperidines with a methyl substituent on the nitrogen atom, it was interesting that potent opiate properties appeared in compound **35** with an extended lipophilic side chain. Such side chains dramatically raise opiate potency in some meperidine derivatives, and it has been argued by Snyder et al.[6] that occupancy of two key lipophilic sites stabilizes the agonist conformation of the receptor.

Although this paper is primarily concerned with examination of the structural requirements of xanthenespiropiperidine analogues for opioid μ-receptor activity, this class of compounds also showed analgesic activity in vivo.[12] For example, compound **25** had an ED_{50} of 1.3 (1.0–1.7) mg/kg when dosed subcutaneously in the acetic acid writhing test in mice. The acetate **29** was twice as active as **25**. In the same test, methadone and morphine had ED_{50}'s of 0.27 (0.12–0.58) and 0.41 (0.28–0.62) mg/kg, respectively.

Conclusion

The xanthenespiropiperidine framework (cf. Table I) represents a new simple opioid structure. Good μ-receptor activity was found in "morphine-like" phenolic spiropiperidines (e.g., **25**), but the most potent activity in the series was achieved with compound **35** which is structurally less like morphine (**1**). It would be interesting to explore other tricyclic systems as well as substitution in the piperidine ring and to examine interactions with the μ- and other opiate receptors.

Experimental Section

Melting points were determined on a Kofler block apparatus and are uncorrected. NMR were recorded with Bruker 200- and 400-MHz spectrometers. All compounds gave NMR and IR spectra consistent with their structure. For example, compound **2** had ^1H NMR ($CDCl_3$, 400 MHz) δ 2.32 (t, 4 H, CH_2), 2.38 (s, 3 H, N-CH_3), 2.65 (t, 4 H, N-CH_2), 6.82 → 7.5 (7, H, aromatic

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protons all of which were separately identifiable on expansion).

Compounds **2**, **25**, **29**, **24**, **27**, **26**, and **28** were prepared by using similar chemistry. Only the synthetic procedure for **24** is described in detail, and the physical properties of novel structurally related compounds are tabulated. Any deviations from normal procedures are also described.

Preparation of 1-Fluoro-5-hydroxy-1'-methylxanthene-9-spiro-4'-piperidine (24). 2-Fluoro-6-(2-methoxyphenoxy)benzoic Acid (4). A mixture of 2-chloro-6-fluorobenzoic acid (30.0 g, 0.17 mol), 2-methoxyphenol (24.8 g, 0.2 mol), and copper bronze (1.0 g) was added to a solution of sodium methoxide in MeOH prepared from sodium (8.5 g, 0.37 mol) and MeOH (150 mL). The excess MeOH was then evaporated and 1,2-dichlorobenzene (150 mL) added to the residue. The mixture was stirred and heated under reflux for 2 h. After cooling, the mixture was filtered and the product was extracted with saturated $NaHCO_3$ solution. The $NaHCO_3$ extract was acidified with 3 N HCl, and the solid that separated was filtered, washed with water, and dried. The solid was crystallized from toluene/petroleum ether to give 23.0 g (51% yield) of pure acid, mp 147–150 °C. Anal. ($C_{14}H_{11}FO_4$) C, H.

2-Methyl-6-(2-methoxyphenoxy)benzoic acid (**5**) was also made by the above route; mp 144–145 °C. Anal. ($C_{15}H_{14}O_4$) C, H.

1-Fluoro-5-methoxyxanthone (7). A mixture of 2-fluoro-6-(2-methoxyphenoxy)benzoic acid (4; 22.0 g, 0.08 mol) and polyphosphoric acid (110 g) was heated on a steam bath for 2 h. The mixture was then poured into dilute ammonium hydroxide solution, and the precipitate that separated was filtered off and dried. Recrystallization of the solid from i-PrOH gave 14.6 g (71% yield) of the xanthone (**7**), mp 219–220 °C. Anal. ($C_{14}H_9FO_3$) C, H.

Also made by the above method were the following: 1-methyl-5-methoxyxanthone (**8**) [mp 180–181 °C; MS *m/e* 240 (M^+)] and 1-chloro-5-methoxyxanthone (**11**) (mp 220–221 °C). Anal. ($C_{14}H_9ClO_3$) C, H.

1-Fluoro-5-methoxyxanthene (14). Borane–THF complex (40 mL of a 1.0 M solution in THF) was added to a stirred mixture of 1-fluoro-5-methoxyxanthone (**7**; 13.0 g, 0.053 mol) and THF (150 mL) in an argon atmosphere at room temperature. After the addition, the mixture was heated under reflux for 3 h. The mixture was then cooled and poured slowly into ice–water. The solid that separated was filtered off and crystallized from MeOH to give 10.5 g (85% yield) of the xanthene (**14**), mp 105–107 °C. Anal. ($C_{14}H_{11}FO_2$) C, H.

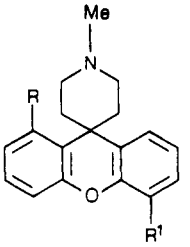
Also made by the above method were the following: 1-methyl-5-methoxyxanthene (**16**) [mp 97–98 °C; anal. ($C_{15}H_{14}O_2$) C, H]; 1-chloro-5-methoxyxanthene (**17**) [mp 144–145 °C; MS *m/e* 246 (M^+)]; and 1-methoxy-5-(benzyloxy)xanthene (**18**) [mp 102 °C; MS *m/e* 318 (M^+)].

1-Fluoro-5-methoxy-1'-methylxanthene-9-spiro-4'-piperidine (19). NaH (80%, 4.5 g, 0.15 mol) was added to dry DMSO (120 mL), and the mixture was stirred under nitrogen at 65 °C until evolution of hydrogen had ceased. The resulting solution was cooled and then added dropwise to a stirred mixture of 1-fluoro-5-methoxyxanthene (**14**; 6.6 g, 0.029 mol), *N*-methylbis(2-chloroethyl)amine hydrochloride (7.2 g, 0.037 mol), THF (120 mL), and DMSO (120 mL) cooled in an ice bath. After the addition, the mixture was allowed to reach room temperature, stirred for 30 min, and then poured into water, and the product was extracted with EtOAc. The EtOAc extract was washed with water, dried ($MgSO_4$), and evaporated to give a gummy residue (8.7 g). This residue was chromatographed on basic alumina (Woelm grade III) eluting with $CHCl_3$/petroleum ether. The required fractions eluted with 25% $CHCl_3$/petroleum ether were combined and evaporated to give a gum which was dissolved in dry ether. Addition of ethereal HCl precipitated the hydrochloride salt which was crystallized from EtOH/ether, to give 5.6 g (55.9% yield), mp 195–200 °C. Anal. ($C_{19}H_{20}FNO_2 \cdot HCl \cdot 0.25H_2O$) C, H, N.

The compounds in Table II were also made by the above method.

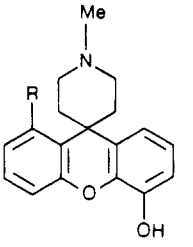
1-Fluoro-5-hydroxy-1'-methylxanthene-9-spiro-4'-piperidine (24). A mixture of 1-fluoro-5-methoxy-1'-methylxanthene-9-spiro-4'-piperidine hydrochloride salt (**19**; 1.5 g, 0.0043 mol) and 48% aqueous HBr (50 mL) was heated under reflux for 1.5 h. The solution was then cooled and added slowly to saturated $NaHCO_3$ solution, and the product was extracted with EtOAc. The EtOAc extract was washed with water, dried ($MgSO_4$), and evaporated to give a gummy residue. The residue was dissolved in i-PrOH and ethereal HCl added. The mixture was evaporated to dryness, and the hydrochloride salt was crystallized from i-PrOH/ether to give 1.1 g (76% yield), mp >300 °C. Anal. ($C_{18}H_{18}FNO_2 \cdot HCl$) C, H, N.

Table II



no.	R	R^1	mp, °C	anal. C, H, N
2	H	H	220–222	$C_{18}H_{19}NO \cdot HCl$
20	H	OMe	234–236	$C_{19}H_{21}NO_2 \cdot HCl \cdot 0.5H_2O$
21	Me	OMe	233–235	$C_{20}H_{23}NO_2 \cdot HCl \cdot 0.5H_2O$
22	Cl	OMe	126–130	$C_{19}H_{20}ClNO_2 \cdot HCl \cdot 2H_2O$
23	OMe	OBn	115–117	$C_{26}H_{27}NO_3 \cdot HCl \cdot 1.5H_2O$

Table III



no.	R	mp, °C	anal. C, H, N
25	H	171–173	$C_{18}H_{19}NO_2$
26	Me	298–300 dec	$C_{19}H_{21}NO_2 \cdot HCl \cdot 0.5H_2O$
27	Cl	297–300 dec	$C_{18}H_{18}ClNO_2 \cdot HCl \cdot 0.5H_2O$

The compounds in Table III were also made by the above method.

Preparation of 4-Acetoxy-1'-methylxanthene-9-spiro-4'-piperidine (29). Excess acetic anhydride was added to 4-hydroxy-1'-methylxanthene-9-spiro-4'-piperidine hydrochloride (**25**; 0.3 g, 0.009 mol) in dry pyridine (10 mL) and the mixture left at room temperature overnight. The solvents were evaporated and the residue in $CHCl_3$ treated with ethereal HCl. The hydrochloride of **29** was recrystallized from i-PrOH/ether: yield 0.25 g (73%); mp 216–220 °C; MS *m/e* 323 (M^+).

5-Hydroxy-1-methoxy-1'-methylxanthene-9-spiro-4'-piperidine Hydrochloride (28). A solution of 5-(benzyloxy)-1-methoxy-1'-methylxanthene-9-spiro-4'-piperdine hydrochloride (**23**; 0.075 g, 0.17 mmol) in MeOH (10 mL) containing 5% Pd/C (0.01 g) was shaken in an atmosphere of hydrogen for 2 h at room temperature. The catalyst was then filtered and the MeOH evaporated to small volume (1 mL), and ether was added. The product crystallized to give **28**: yield 0.03 g (50%); mp 274–275 °C dec. Anal. ($C_{19}H_{21}NO_3 \cdot HCl \cdot 0.25H_2O$) C, H, N.

2-Chloro-6-(2-methoxyphenoxy)benzoic Acid (10). 3-Chloro-2-cyano-2'-methoxydiphenyl Ether (9). A solution of 2-methoxyphenol (7.44 g, 0.06 mol) in DMSO (30 mL) was added to a stirred suspension of NaH (80%, 1.8 g, 0.06 mol) at room temperature. When evolution of hydrogen had ceased, a solution of 2,6-dichlorobenzonitrile (9.5 g, 0.055 mol) in DMSO (150 mL) was added, and the mixture was then stirred and heated on a steam bath for 16 h. The mixture was then cooled and poured into water (1.5 L) and the product extracted with EtOAc. The EtOAc extract was washed with 3 N NaOH solution and water and dried ($MgSO_4$). EtOAc was evaporated to give a solid which was crystallized from EtOH to give **9**: yield 10.1 g (62%); mp 86–87 °C. Anal. ($C_{14}H_{10}ClNO_2$) C, H, N.

A mixture of 3-chloro-2-cyano-2′-methoxydiphenyl ether (**9**; 10.0 g, 0.039 mol) in EtOH (100 mL) and NaOH (40.0 g) in water (100 mL) was stirred and refluxed for 20 h. The mixture was then cooled and diluted with water, and the product was extracted with EtOAc. The EtOAc extract was washed with water and dried ($MgSO_4$). The EtOAc was evaporated and the product was crystallized from EtOAc/petroleum ether to give 7.9 g (73% yield) of 2-chloro-6-(2-methoxyphenoxy)benzamide, mp 132 °C. Anal. ($C_{14}H_{12}ClNO_3$) C, H, N.

A mixture of the above amide (1.0 g, 0.0036 mol), saturated ethereal HCl (5 mL), and amyl nitrite (1.0 g, 0.008 mol) in dioxane (30 mL) was stirred at room temperature for 16 h. The mixture was then evaporated to dryness and the residue dissolved in ether, and the product was extracted with saturated $NaHCO_3$ solution. The extract was washed with ether and then acidified with 3 N HCl solution. The solid that separated was filtered and crystallized from EtOAc/petroleum ether to give 2-chloro-6-(2-methoxyphenoxy)benzoic acid (**10**): yield 0.38 g (38%); mp 155–157 °C; MS *m/e* 278 (M^+).

5-(Benzyloxy)-1-methoxyxanthone (12). A mixture of 1-chloro-5-methoxyxanthone (**17**; 6.5 g, 0.025 mol) and CH_2Cl_2 (250 mL) was cooled to −20 °C, and boron tribromide (8 mL, 0.085 mol) in CH_2Cl_2 (20 mL) was added dropwise with stirring. The mixture was then allowed to reach room temperature and stirred for 3 h. The mixture was poured into ice–water, and the solid that separated was filtered and slurried with MeOH to give 1-chloro-5-hydroxyxanthone, 3.3 g. Without further purification, this product (3.2 g, 0.013 mol) was dissolved in DMF (100 mL) and cooled in ice. NaH (80%, 0.4 g, 0.013 mol) was added, followed by benzyl bromide (2.6 g, 0.015 mol). The mixture was stirred at room temperature for 3 h and then poured into water, and the product was extracted with EtOAc. The EtOAc extract was washed with water, dried ($MgSO_4$), and evaporated to give a crude solid which was chromatographed on silica gel, eluting with 50% $CHCl_3$/petroleum ether followed by $CHCl_3$. 1-Chloro-5-(benzyloxy)xanthone (**13**) was crystallized from MeOH/$CHCl_3$ to give 3.0 g (37% overall yield): mp 160–161 °C; MS *m/e* 336 (M^+).

A mixture of the above xanthone (**13**; 2.5 g, 0.007 mol) and NaOMe—prepared from NaH (80%, 1.5 g, 0.05 mol) and MeOH (20 mL) in DMF (100 mL)—was stirred and heated at 90 °C for 2.5 h. The mixture was then cooled and poured into water. The solid that separated was purified by chromatography on silica gel, eluting with $CHCl_3$ to give 5-(benzyloxy)-1-methoxyxanthone (**12**): yield 1.4 g (60%); mp 180 °C (lit.[26] 196–198 °C); MS *m/e* 332 (M^+).

1′-Methyl-4-aminoxanthene-9-spiro-4′-piperidine (36). To a solution of 1′-methylxanthene-9-spiro-4′-piperidine (**2**; 1.3 g, 0.005 mol) in hexane (25 mL) under argon was added a solution of *tert*-butyllithium in pentane (1.6 M, 3.5 mL, 0.006 mol) dropwise with stirring at room temperature. After the mixture was stirred for 1 h at room temperature, a solution of hydroxylamine methyl ether (0.4 g, 0.009 mol) in hexane (5 mL) was added dropwise. The mixture was stirred for 1 h at room temperature, and water was then added. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to give an oil which solidified on standing. The solid was crystallized from hexane to give compound **36**: yield 0.1 g (7%); mp 173–174 °C. Anal. ($C_{18}H_{20}N_2O$) C, H, N.

1′-Methyl-4-acetamidoxanthene-9-spiro-4′-piperidine (40). Acetic anhydride (0.5 mL, 0.005 mol) was added to a solution of **4** (0.06 g, 0.0002 mol) in ether at room temperature. The mixture was stirred for 0.5 h at room temperature. A saturated solution of Na_2CO_3 was then added and the organic layer separated, washed with water, dried ($MgSO_4$), and evaporated. The residue was crystallized from hexane to give compound **40**: yield 0.023 g (33%); mp 176–178 °C. Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.

The preparations of 1′-methyl-4-mercaptoxanthene-9-spiro-4′-piperidine (**37**) and 1′-methyl-4-(hydroxymethyl)xanthene-9-spiro-4′-piperidine (**38**) were carried out in essentially the same manner as that described for 1′-methyl-4-aminoxanthene-9-spiro-4′-piperidine (**40**) but by using sulfur and paraformaldehyde, respectively, to react with the anion formed with *tert*-butyllithium. Compound **37** had mp 190–192 °C [anal. [$C_{18}H_{19}NOS\cdot(CO_2H)_2\cdot 0.25H_2O$] C, H, N], and compound **38** had mp 167–169 °C [anal. ($C_{19}H_{21}NO_2\cdot 0.25H_2O$) C, H, N].

1′-[2-(Phenylamino)ethyl]xanthene-9-spiro-4′-piperidine (35). 9,9-Bis[2-[(methylsulfonyl)oxy]ethyl]xanthene (34). NaH (60%, 24 g, 0.6 mol) was washed with sodium-dried petroleum ether under an atmosphere of nitrogen. DMSO (300 mL) was then added and the mixture heated at 65 °C until evolution of hydrogen ceased (1 h). The mixture was cooled to room temperature, and xanthene (36.4 g, 0.2 mol) in DMSO (300 mL) was added dropwise during 20 min to give a blood red solution which was cooled in an ice–water bath. To the cooled solution was added dropwise 2-chloroethyl vinyl ether (42.6 g, 0.31 mol) during 30 min and the mixture stirred for a further 30 min. The mixture was poured into water and the product extracted with ether (5 times). The ether extract was washed with water, dried ($MgSO_4$), and evaporated to give a crude product which was heated with HCl (15 mL) and water (400 mL) on a steam bath with stirring for 5 h. The mixture was cooled, and the product was extracted with ether (3 times). The combined ether extracts were washed with water, dried ($MgSO_4$), and evaporated to give a solid which was crystallized from $CHCl_3$/petroleum ether to give 9,9-bis(2-hydroxyethyl)xanthene (**33**): yield 29 g (51%); mp 144–145 °C. Anal. ($C_{17}H_{18}O_3$) C, H.

A solution of 9,9-bis(2-hydroxyethyl)xanthene (**33**; 27 g, 0.1 mol) in pyridine (200 mL) was cooled in an ice bath, and methanesulfonyl chloride (18 mL, 0.24 mol) was added dropwise with stirring. After the addition was complete, the mixture was stirred at 0–5 °C for 1 h and then allowed to reach room temperature and left overnight. The mixture was then poured onto 3 N HCl/ice. The crystalline solid that separated was filtered off and recrystallized from acetone/petroleum ether to give 9,9-bis[2-[(methylsulfonyl)oxy]ethyl]xanthene (**34**): yield 35.2 g (84%); mp 121–122 °C. Anal. ($C_{19}H_{22}O_7S_2$) C, H.

A solution of 9,9-bis[2-[(methylsulfonyl)oxy]ethyl]xanthene (**34**; 1.27 g, 0.003 mol) and 2-(phenylamino)ethylamine (1.625 g, 0.012 mol) in absolute alcohol (50 mL) was refluxed for 20 h. The mixture was then evaporated to dryness, and the residue was basified with 3 N NaOH and the product extracted with EtOAc. The EtOAc extract was washed with water, dried ($MgSO_4$), and evaporated to give a gum which was chromatographed on alumina (Woelm grade III basic), eluting with 20% $CHCl_3$/petroleum ether. The solid eluted was dissolved in EtOH and ethereal HCl was added to precipitate the dihydrochloride salt which was crystallized from EtOH/ether to give **35**: yield 1 g (88%); mp 236–238 °C dec. Anal. ($C_{25}H_{26}N_2O\cdot 2HCl$) C, H, N.

Acknowledgment. We thank Dr. M. J. Turnbull and Dr. W. R. Buckett for their pharmacological guidance.

Registry No. **2**, 65142-97-4; **2**·HCl, 57315-93-2; **3**, 21905-73-7; **4**, 57317-67-6; **5**, 121618-89-1; **6**, 6702-58-5; **7**, 57317-73-4; **24**, 121619-06-5; **9**, 92161-49-4; **10**, 121618-91-5; **11**, 121618-92-6; **12**, 37570-59-5; **13**, 121618-93-7; **14**, 57317-80-3; **15**, 38731-90-7; **16**, 121618-94-8; **17**, 121618-95-9; **18**, 121618-96-0; **19**, 57317-25-6; **20**, 57316-00-4; **21**, 121618-97-1; **22**, 121618-98-2; **23**, 121618-99-3; **38**, 57316-77-5; **24**·HCl, 57317-47-2; **25**, 57316-01-5; **25**·HCl, 121619-00-9; **26**, 121619-07-6; **26**·HCl, 121619-01-0; **27**, 121619-08-7; **27**·HCl, 121619-02-1; **28**, 121619-09-8; **28**·HCl, 121619-03-2; **29**, 65142-96-3; **29**·HCl, 57316-02-6; **32**, 57315-95-4; **33**, 57315-99-8; **34**, 57315-97-6; **35**, 121619-12-3; **35**·HCl, 121619-04-3; **36**, 57316-74-2; **37**, 57316-75-3; **37** oxalate, 121619-05-4; **38**, 57316-77-5; **40**, 57316-78-6; $MeN(CH_2CH_2Cl)_2$·HCl, 55-86-7; 2-methoxyphenol, 90-05-1; 2-chloro-6-fluorobenzoic acid, 434-75-3; 2-chloro-6-methylbenzoic acid, 21327-86-6; 2,6-dichlorobenzonitrile, 1194-65-6; 2-chloro-6-(2-methoxyphenoxy)benzamide, 121619-10-1; 2-chloroethyl vinyl ether, 110-75-8; xanthene, 92-83-1; 1-chloro-5-hydroxyxanthone, 121619-11-2; 2-(phenylamino)ethylamine, 1664-40-0.

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