thereby leading to low enantiomeric stereoselectivity and low potency.

Experimental Section

Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Where analyses are indicated only by symbols of the elements, they are within ±0.4% of the theoretical values. Ir spectra were obtained with Perkin-Elmer 237B and Beckmann IR9 instruments on $CHCl_3$ solutions in 0.1-mm cells. Nmr spectra were measured with a Varian A-60D spectrometer at ambient temperature on approximately 10% solutions in $CDCl_3$ (Me_4Si). All spectra were consistent with the proposed structures. Melting points were determined with a Mel-Temp apparatus and are corrected. Optical rotations were measured with a Perkin-Elmer 141 photoelectric polarimeter on 1% solutions in MeOH at 22°.

(+)-(3*S*,4*R*)- and (−)-(3*R*,4*S*)-1-Methyl-4-phenyl-3-propyl-4-piperidinol (6a). The allyl enantiomers **5a** were hydrogenated as described previously for the racemate.[2] (+)-(3*S*,4*R*)-**5a** yielded (+)-(3*S*,4*R*)-**6a** (86%): mp 127–128° (hexane); $[\alpha]_D$ +25.1°. (−)-(3*R*,4*S*)-**5a** yielded (−)-(3*R*,4*S*)-**6a** (93%): mp 128–128.5° (hexane); $[\alpha]_D$ −25.8°. *Anal.* [$C_{15}H_{23}NO$, (+) and (−)] C, H, N.

(−)-(3*R*,4*R*)- and (+)-(3*S*,4*S*)-1-Methyl-4-phenyl-3-propyl-4-piperidinol (6b). The allyl enantiomers **5b** were hydrogenated as described previously for the racemate.[2] (−)-(3*R*,4*R*)-**5b** yielded (3*R*,4*R*)-**6b**, $[\alpha]_D$ −69.9°, and (+)-(3*S*,4*S*)-**5b** yielded (3*S*,4*S*)-**6b**, $[\alpha]_D$ +70.6°, as colorless oils whose ir spectra were identical with that of the racemate. *Anal.* [$C_{15}H_{23}NO$, (+) and (−)] C, H, N.

(+)-(3*S*,4*R*)- and (−)-(3*R*,4*S*)-1-Methyl-4-phenyl-4-propionoxy-3-propylpiperidine Hydrochloride (7a·HCl). Reaction of (+)- and (−)-**6a** with propionyl chloride as described previously[2] for the racemate afforded (3*S*,4*R*)-**7a**·HCl, $[\alpha]_D$ +1.8°, and (3*R*,4*R*)-**7a**·HCl, $[\alpha]_D$ −1.7°, respectively. Both salts are very hygroscopic and were purified by sublimation [160° (0.1 mm)]. Both enantiomers softened at ~60° and had melting points of 75–80°. *Anal.* [$C_{18}H_{28}NClO_2$, (+) and (−)] C, H, N.

(−)-(3*R*,4*R*)- and (+)-(3*S*,4*S*)-1-Methyl-4-phenyl-4-propionoxy-3-propylpiperidine Hydrochloride (7b·HCl). Esterification of (−)-**6b** as described above afforded (3R,4R)-**7b**·HCl: $[\alpha]_D$ −22.2°; mp 151–152° (recrystallized from EtOAc). The same procedure with (+)-**6b** gave (3*S*,4*S*)-**7b**·HCl: $[\alpha]_D$ +21.8°; mp 151–152° (recrystallized from EtOAc). *Anal.* [$C_{18}H_{28}NClO_2$, (+) and (−)] C, H, N.

Conversion of 4-Hydroxy-1-methyl-4-phenyl-3-piperidinylacetaldehyde Hemiacetal (10) to *r*-3-Ethyl-1-methyl-4-phenyl-*c*-4-piperidinol (8). A mixture of (±)-**10**[3] (0.466 g, 0.002 mol), 95% $N_2H_4 \cdot H_2O$ (0.2 ml, 0.006 mol), and diethylene glycol (3 ml) was warmed on a steam bath for 20 min. Solid KOH (0.34 g, 0.006 mol) was added and the mixture was heated at 215° for 30 min. The cooled solution was diluted with H_2O (10 ml) and chilled, and the product [(±)-**8**], 0.343 g (79%), was collected and recrystallized (hexane): mp 100–100.5° (lit.[8] mp 96–97°). Similarly, (−)-(3*S*,4*R*)-**10** gave (3*S*,4*R*)-**8** (78%): $[\alpha]_D$ +1.7°; mp 119–119.5° (hexane). (+)-(3*R*,4*S*)-**10** afforded (3*R*,4*S*)-**8** (78%): $[\alpha]_D$ −1.6°; mp 120–120.5° (hexane). *Anal.* [$C_{14}H_{21}NO$, (±), (+), and (−)] C, H, N.

***r*-3-Ethyl-1-methyl-4-phenyl-*c*-4-propionoxypiperidine Hydrochloride (9).** Compound **8** was treated with propionyl chloride in the usual manner. Accordingly, (+)-(3*S*,4*R*)-**8** was converted to (3*S*,4*R*)-**9**·HCl, $[\alpha]_D$ −14.0°, and (−)-(3*R*,4*S*)-**8** gave rise to (3*R*,4*S*)-**9**·HCl, $[\alpha]_D$ +13.8°. Both enantiomers were extremely hygroscopic and purified by sublimation at 160° (0.1 mm). No sharp melting point was observed on melting. In contrast, (±)-**9** was nicely crystalline: mp 226–227° (acetone) (lit.[8] mp 229–230°); nmr δ 7.28 (m, 5, Ar H, $W_{1/2}$ = 6 Hz), 2.88 (d, 3, $W_{1/2}$ = 5 Hz, $^+NHCH_3$), 2.56 (q, 2, $W_{1/2}$ = 7 Hz, $COCH_2CH_3$), 1.22 (5, CH_3CH_2CO and $-CH_2CH_3$), 0.68 (t, 3, $W_{1/2}$ = 7 Hz, CH_2CH_3). *Anal.* [$C_{17}H_{26}NO_2Cl$, (±), (+), and (−)] C, H, N.

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Analogs of Phenothiazines. 6. Stereochemical Assignment of Isomeric Aminoalkylidene Derivatives of Xanthenes and Thioxanthenes with Neuropharmacological Activity†

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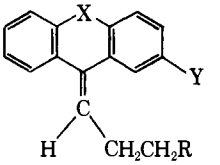
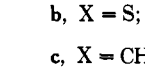
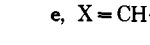
Among the geometrical isomers of aminopropylidene-substituted tricyclic derivatives with the general structure **1** potent neuroleptic activity has been associated with the *Z* (cis) geometry, *i.e.*, the configuration in which the side chain is oriented toward the substituted aromatic ring, in all cases where configuration has been established.[1] X-Ray crystallography established the *Z* configuration for the clinically effective antipsychotic thioxanthenes, chlorprothixene (**1a**)[2] and thiothixene (**1b**).[3] Infrared spectroscopy demonstrated the same configuration for the more potent neuroleptic in similar pairs of isomeric aminoalkylidene-substituted thioxanthenes.[4] Other spectroscopic techniques (uv and nmr) were employed to establish that in a series of 11-(3-aminopropylidene)dibenz[*b*,*e*]oxepins the isomer with greatest potency in a rat conditioned disruption test was the one (**1c**) in which the side chain is oriented toward both the ring heteroatom and the 2 substituent.[5] Another cis-aminoalkylated dibenz[*b*,*e*]oxepin, pinoxepin (**1d**), is a clinically effective antipsychotic agent,[6] with potency similar to that of the related phenothiazine, perphenazine, in a rat conditioned avoidance test.[5] Likewise the *Z* isomer of the dibenzocycloheptatriene **1e** (configuration established by X-ray analysis[7]) was much more effective than the *E* form in a conditioned avoidance test.[8]



1a, X = S; Y = Cl; R = NMe_2

b, X = S; Y = SO_2NMe_2; R = 

c, X = CH_2O; Y = 2—Cl; R = NMe_2

d, X = CH_2O; Y = 2—Cl; R = 

e, X = CH=CH; Y = Cl; R = NMe_2

Studies in our laboratory also revealed a striking difference in the neuropharmacological properties of the geometrical isomers of several aminopropylidene derivatives of ring-substituted xanthenes and thioxanthenes.[9] In view of the numerous examples of greater activity of *Z* isomers as compared to their *E* counterparts, the more potent member of each pair was presumed to have the *Z* orientation, but the stereochemistry was not established chemically. The recent development of paramagnetic complexes

†This note is dedicated to Alfred Burger, our long-time friend, a source of encouragement and advice, and a respected consultant.

Table I. Nmr Data for Isomeric Aminoalkylidene Derivatives of Xanthenes and Thioxanthenes

No.	X	Y	R	A	Sample concn, M^a	$\Delta\delta H_a$, ppm[b]	Stereochemical assignment
1a[c]	S	Cl	H	NMe_2	0.32	0.57	*Z*
2[d]	S	Cl	H	NMe_2	0.32	*e*	*E*
3[f]	S	CF_3	H	NMe_2	0.28	0.45	*Z*
4[g]	S	CF_3	H	NMe_2	0.28	*e*	*E*
5[f]	S	CF_3	H	$N(CH_2)_4$	0.28	0.38	*Z*
6[g]	S	CF_3	H	$N(CH_2)_4$	0.36	*e*	*E*
7[f]	O	Cl	H	NMe_2	0.30	0.40	*Z*
8[g]	O	Cl	H	NMe_2	0.30	*e*	*E*
9[f]	O	CF_3	H	NMe_2	0.20	0.26	*Z*
10[g]	O	CF_3	H	NMe_2	0.34	*e*	*E*
11[f]	O	CF_3	Me	NMe_2	0.36	0.42	*Z*
12[g]	O	CF_3	Me	NMe_2	0.36	*e*	*E*

[a] Concentration of sample in $CDCl_3$ solution (mol/l.). See Experimental Section. [b] Downfield shift of H_a signal observed upon addition of tris(dipivalomethanato)europium measured as described in the Experimental Section. [c] Chlorprothixene. See ref 2. [d] The "cis" isomer, ref 12. See ref 2 for correction in stereochemical assignment. [e] No shift in H_a was detected under the conditions described in the Experimental Section. [f] Isomer A, ref 9. [g] Isomer B, ref 9.

of trivalent rare earth metals which can coordinate with electronegative substituents, such as an amino group, to induce large changes of chemical shifts of closely proximate protons in the nmr spectrum now provides a convenient method for establishing the configuration of these isomers.[10] In the *Z* isomers the C-1 proton (H_a, Table I) of the tricyclic system is in the field of the amino group coordinated with the paramagnetic complex. Consequently, the H_a signal, normally in the overall aromatic multiplet, is shifted downfield and can be distinguished from the other aromatic protons. In the *E* isomers the H_a proton, outside the field of the coordinated shift reagent, is not significantly influenced. Thus, induction of a shift of the H_a signal (Table I) enables assignment of the *Z* stereochemistry to aminopropylidene derivatives of ring-substituted tricyclics. In fact, this method has been used to establish the stereochemical configuration of several 3-substituted *N,N*-dimethyl-5*H*-dibenzo[*a,d*]cycloheptene-$\Delta^{5,\gamma}$-propylamines, using tris(dipivalomethanato)europium as the shift reagent.[11] As tabulated in Table I this method was employed to assign configurations to our series of isomeric aminopropylidene derivatives of ring-substituted xanthenes and thioxanthenes. Chlorprothixene (1a) and its isomer **2**[12] were included for comparative purposes.

In all instances neuropharmacological activity predominated in the *Z* isomers as anticipated. Thus the *Z* isomer **3** is strikingly more potent than the *E* form **4** in dose range, conditioned avoidance, and ptosis production tests in rats, a rage test in mice, and an antiapomorphine test in dogs.[9] Similarly, the *Z* isomer **5** caused slightly decreased motor activity, hypothermia, and slight ptosis at 6.8 mg/kg po in the rat dose range procedure carried out as described previously.[9] At 25 mg/kg po, these effects were marked. Moderate hypotonia, catalepsy, and a characteristic hind limb spread were also observed. Conversely, in the same test the *E* isomer **6** (25 mg/kg po) was only weakly effective. Slight ptosis and moderately decreased motor activity were observed in only one of the three rats examined. The *Z* isomers of 2-chloro- and 2-trifluoromethyl-*N,N*-dimethylxanthene-$\Delta^{9,\gamma}$-propylamines (**7** and **9**, respectively) were markedly more potent neuroleptics than their *E* counterparts, **8** and **10**.[9] Neither of the branched chain xanthenes (**11** or **12**) showed very potent neuropharmacological activity; however, the isomer **11**, which caused a moderate decrease in motor activity, hypotonia, distended testes, and ptosis at 271 mg/kg po, in the rat dose range test,[9] was more potent than the *E* isomer **12** which produced only a slight decrease in motor activity, salivation, and mydriasis under similar conditions.

Experimental Section

Nmr Determinations. Solutions were prepared by adding approximately 50 mg (concentrations are listed in Table I) of the test compound to 0.5 ml of $CDCl_3$. Nmr spectra were obtained at ambient temperature using a Jeol C6OH spectrometer. After addition of approximately one-third of the sample weight of tris(dipivalomethanato)europium (15 mg in most cases) the spectra were again determined. The downfield shift ($\Delta\delta H_a$, Table I) was determined as the difference of the H_a signal in the presence and absence of the shift reagent. In the case of CF_3-substituted derivatives, the H_a signals, even in the absence of the shift reagent, appeared as a distinct singlet at about 7.9 ppm. For Cl-substituted derivatives original location of H_a was taken as the farthest downfield peak in the aromatic multiplet. All shifts were measured relative to Me_4Si as the internal standard. As magnitude of induced chemical shift is related to the ratio of paramagnetic reagent and test compound, the above conditions employing a constant ratio of compound to shift reagent, *i.e.*, one which causes about a 0.5-ppm shift of the H_a signal of the *Z* isomers, were selected.

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Phenylmorphan Agonists-Antagonists

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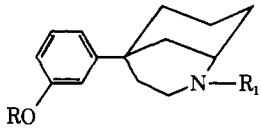
In 1953[1] Clark, *et al.*, reported that substitution of allyl, methallyl, *n*-propyl, or isobutyl for methyl in morphine-type structures containing a free phenolic group at C-3 "invariably produced compounds capable of counteracting the analgesic effect of morphine." Since that time, similar modifications of oxymorphone,[2,§] like morphine a pentacyclic molecule, 3-hydroxy-*N*-methylmorphinan (tetracyclic),[3] 2′-hydroxy-6,7-benzomorphans (tricyclic),[4] and several hexacyclic structures (etheno- and ethanooripavines)[5] have given stronger narcotic antagonists, propyl, allyl, and cyclopropylmethyl being the most effective nitrogen substituents. In an extension of research to bicyclic structures, (±)- and (+)-5-*m*-hydroxyphenyl-2-methylmorphans (**1** and **8**)[6] have been converted to 2-propyl, allyl, and cyclopropylmethyl congeners (**5**-**7** and **12**-**14**).



(±) series	(+) series
1, R = H; R_1 = Me	**8**, R = H; R_1 = Me
2, R = R_1 = Me	**9**, R = R_1 = Me
3, R = Me; R_1 = H	**10**, R = Me; R_1 = H
4, R = R_1 = H	**11**, R = R_1 = H
5, R = H; R_1 = Pr	**12**, R = H; R_1 = Pr
6, R = H; R_1 = $CH_2CH{=}CH_2$	**13**, R = H; R_1 = $CH_2CH{=}CH_2$
7, R = H; R_1 = CH_2—◁	**14**, R = H; R_1 = CH_2—◁

The phenylmorphans contain the phenolic hydroxyl in the same relative position (meta to the quaternary carbon linkage) as the above-mentioned more compact, rigid molecules. And (+) isomer **8** is some three times more potent than morphine with high physical dependence capacity (PDC) in monkeys; the racemate, morphine-like in analgesic potency, has intermediate PDC, but the (−) isomer, also as potent as morphine for analgesia, is a nalorphine-like antagonist in morphine-dependent monkeys.[6b] It was, therefore, of interest to compare the (+) and the (±) series.

Chemistry. The allyl and propyl substituents were introduced by direct alkylation of **4** and **11** using allyl bromide and propyl iodide, respectively.[3b,4b] Acylation of **4** and **11** with cyclopropylcarbonyl chloride and subsequent reduction with $LiAlH_4$ gave **7** and **14**.

Phenols **4** and **11** were prepared from methyl ethers **3** and **10** (boiling 48% HBr), in turn prepared by von Braun N-demethylation[7] of **2** and **9**. Compound **9** was produced by diazomethane methylation of **8**.[6]

Pharmacology. As seen in Table I and as reported before,[6] *N*-methyl racemate **1** is a morphine-like analgesic in mice with intermediate capacity to suppress morphine abstinence in monkeys, and the (+) isomer **8** is three times more potent in both respects. The (−) isomer, on the other hand, comparable to morphine as an analgesic, is weakly nalorphine-like in morphine-dependent monkeys.[6,8]

N-Propyl compound **5** is about half as strong as pentazocine as an analgesic and 0.01 as strong as nalorphine as an antagonist with a greater duration of action; the (+) isomer **12** is comparable to **5** as an antagonist with more than twice the agonistic potency. Cyclopropylmethyl derivatives **7** and **14** are similar in effect to the *N*-propyl relatives with, surprisingly,‡ a shorter duration of action and, as expected, higher analgesic activity in the Nilsen than in the hot-plate test. These four compounds appear similar to pentazocine, with steeper dose-response curves, perhaps longer duration of antagonistic effect, and fewer side actions. Allyl compounds **6** and **13**, again pentazocine-like for analgesia, were essentially inactive as antagonists but like **5**, **12**, **7**, and **14** would not substitute for morphine. It seems worthy of note that despite the marked differences in pharmacology between *N*-methyl compound **8** and the (−) isomer,[6] the (±)- and (+)-N-substituted compounds, [**5** *vs.* **12**, **6** *vs.* **13**, **7** *vs.* **14**] differ little in substitution behavior in morphine-dependent monkeys. For analgesia, however, the (+) isomers were consistently two to three times more potent than corresponding racemates in the Nilsen test. With the hot plate, only propyl compound **12** was (three times) stronger than its racemic relative.

Thus, it is apparent that *potent* antagonists cannot necessarily be fashioned from corresponding *potent* analgesics with simply a *m*-phenolic group attached to a quaternary carbon. Other structural requisites may be a phenethylamine fragment[4b] and/or an additional fused ring to hold the *m*-phenolic ring in a fixed axial position.[4b] The phenylmorphans, like pethidine, have a nonrigid equatorial phenyl group.

Experimental Section

Melting points were taken in a Hershberg apparatus (total-immersion thermometers). Infrared and mass spectral data are compatible with the structures shown. Elemental analyses, as indicated by C, H, N, and Br, were within ±0.4% of theory. Rotations were made at a concentration of 1 g/100 ml of H_2O in a Perkin-Elmer 141 polarimeter.

(+)-5-*m*-Methoxyphenyl-2-methylmorphan (9) Hydrobromide. MeOH (50 ml), 3 g of **8**,[6b] and 200 ml of ethereal CH_2N_2 (from 20 g of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine) were left for 24 hr and evaporated to dryness. The residue (in ether) was washed with 5% NaOH and then H_2O. Drying ($MgSO_4$) and distillation [bp 130° (0.2 mm)] gave 2.8 g (88%) of **9**. The HBr salt (from Me_2CO–EtOH, 9:1) melted at 199–201°. *Anal.* ($C_{16}H_{24}BrNO$) C, H, N.

(+)-5-*m*-Methoxyphenylmorphan (10) Hydrobromide. This compound, mp 154–155° (from Me_2CO–Et_2O), was obtained (43% yield) in the von Braun reaction on **9** as described before[7] (recovery of **9**, 19%). *Anal.* ($C_{15}H_{22}BrNO$) C, H, N.

(±)-5-*m*-Hydroxyphenylmorphan (4). Compound **3**·HBr[7] (2.7 g) and 15 ml of 48% HBr were refluxed together for 45 min and evaporated to dryness *in vacuo*. The crystalline residue in H_2O was made basic with 12 *M* NH_4OH to give 1.8 g (93%) of **4**, mp 216–223°. Sublimation [160–180° (0.01 mm)] and recrystallization from Me_2CO gave pure **4**, mp 232–234° dec. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

Von Braun demethylation of the OAc derivative of **3** gave a 26% yield of **4** and a 19% recovery of **3**.

(+)-5-*m*-Hydroxyphenylmorphan (11). As described for **4**, compound **11** was obtained from **10** in 83% yield, mp 233–234° dec. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

(±)-5-*m*-Hydroxyphenyl-2-propylmorphan (5) Hydrobromide. Propyl iodide (0.5 g), 0.6 g of **4**, 0.8 g of K_2CO_3, and 17 ml of

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‡ Formerly Visiting Associate from Tanabe Seiyaku Co., Ltd., Tokyo.
§ H. Blumberg, personal communication.

‡ Cyclazocine,[4b] naltrexone,§ and similar *N*-cyclopropylmethyl compounds are noted for their long duration of action.