$\times 10^{-3}$ sec^{-1} ($t_{1/2}$ = 4.3 min).

(+)-(6*S*)-**Methadone** (1, **Figure** 1): CD (*c* 0.1, hexane) $[\theta]_{330}$ −310, $[\theta]_{320}$ −2970, $[\theta]_{310}$ −7180, $[\theta]_{300}$ −10,520, $[\theta]_{294}$ −11,080, $[\theta]_{290}$ −10,077, $[\theta]_{280}$ −7920, $[\theta]_{271}$ −1350, $[\theta]_{269}$ −1390, $[\theta]_{267}$ 0, $[\theta]_{264}$ 1040, $[\theta]_{262}$ 940; CD (*c* 0.1, $CHCl_3$) $[\theta]_{330}$ 120, $[\theta]_{323}$ 300, $[\theta]_{320}$ 190, $[\theta]_{318}$ 0, $[\theta]_{310}$ −1980, $[\theta]_{300}$ −5320, $[\theta]_{289}$ −6980, $[\theta]_{280}$ −5820, $[\theta]_{272}$ −1240, $[\theta]_{270}$ −1420, $[\theta]_{267}$ 0; CD (*c* 0.1, CH_3OH) $[\theta]_{330}$ 230, $[\theta]_{320}$ 2320, $[\theta]_{310}$ 4490, $[\theta]_{307}$ 4870, $[\theta]_{300}$ 4100, $[\theta]_{290}$ 1860, $[\theta]_{280}$ 0, $[\theta]_{277}$ −230, $[\theta]_{272}$ +1080, $[\theta]_{268}$ 740, $[\theta]_{265}$ 1480, $[\theta]_{260}$ 1110; CD (*c* 0.1, CH_3CN) $[\theta]_{330}$ 0, $[\theta]_{320}$ −1240, $[\theta]_{310}$ −5570, $[\theta]_{300}$ −10,090, $[\theta]_{292}$ −11,460, $[\theta]_{290}$ −11,370, $[\theta]_{280}$ −8940, $[\theta]_{271}$ −1485, $[\theta]_{269}$ −1700, $[\theta]_{267}$ 0.

(−)-(5*S*)-**Isomethadone** (2, **Figure** 2): CD (*c* 0.1, hexane) $[\theta]_{340}$ −120, $[\theta]_{330}$ −140, $[\theta]_{320}$ −5250, $[\theta]_{310}$ −8160, $[\theta]_{307}$ −8320, $[\theta]_{300}$ −7950, $[\theta]_{290}$ −5570, $[\theta]_{280}$ −2970, $[\theta]_{275}$ −2220, $[\theta]_{274}$ −2290, $[\theta]_{269}$ −1490, $[\theta]_{266}$ −1560, $[\theta]_{263}$ −500, $[\theta]_{262}$ −580, $[\theta]_{260}$ −460; CD (*c* 0.1, $CHCl_3$) $[\theta]_{330}$ −920, $[\theta]_{320}$ −4330, $[\theta]_{310}$ −6810, $[\theta]_{307}$ −7010, $[\theta]_{300}$ −6510, $[\theta]_{290}$ −4430, $[\theta]_{280}$ −2050, $[\theta]_{277}$ −1610, $[\theta]_{274}$ −1760, $[\theta]_{270}$ −1130, $[\theta]_{268}$ −1470, $[\theta]_{264}$ −670, $[\theta]_{260}$ −1110; CD (*c* 0.1, CH_3OH) $[\theta]_{330}$ −870, $[\theta]_{320}$ −4550, $[\theta]_{310}$ −7980, $[\theta]_{275}$ −2350, $[\theta]_{274}$ −2350, $[\theta]_{269}$ −1520, $[\theta]_{267}$ −1630, $[\theta]_{263}$ −870, $[\theta]_{260}$ −930.

(+)-(6*S*)-**Methadone Methyl Iodide** (1·CH_3I, **Figure** 3): CD (*c* 0.1, $CHCl_3$) $[\theta]_{330}$ 300, $[\theta]_{320}$ 8700, $[\theta]_{310}$ 24,600, $[\theta]_{302}$ 33,600, $[\theta]_{299}$ 32,600, $[\theta]_{295}$ 32,700, $[\theta]_{290}$ 28,100, $[\theta]_{280}$ 17,000, $[\theta]_{275}$ 13,300, $[\theta]_{273}$ 12,900, $[\theta]_{270}$ 9000; CD (*c* 0.1, CH_3OH) $[\theta]_{330}$ 400, $[\theta]_{320}$ 8900, $[\theta]_{310}$ 22,100, $[\theta]_{303}$ 34,700, $[\theta]_{299}$ 29,700, $[\theta]_{295}$ 34,800, $[\theta]_{290}$ 25,900, $[\theta]_{280}$ 16,200, $[\theta]_{274}$ 11,300, $[\theta]_{272}$ 10,800, $[\theta]_{270}$ 8800, $[\theta]_{267}$ 6900, $[\theta]_{266}$ 6800, $[\theta]_{260}$ 2800, $[\theta]_{250}$ 0.

(−)-(5*S*)-**Isomethadone Methyl Iodide** (2·CH_3I, **Figure** 3): CD (*c* 0.1, $CHCl_3$) $[\theta]_{330}$ −1000, $[83]_{320}$ −15,600, $[\theta]_{310}$ −35,800, $[\theta]_{303}$ −45,300, $[\theta]_{295}$ −43,000, $[\theta]_{290}$ −36,300, $[\theta]_{280}$ −21,300, $[\theta]_{275}$ −17,200; CD (*c* 0.1, CH_3OH) $[\theta]_{330}$ −1100, $[\theta]_{320}$ −14,400, $[\theta]_{310}$ −32,100, $[\theta]_{303}$ −38,800, $[\theta]_{300}$ −38,500, $[\theta]_{297}$ −38,300, $[\theta]_{290}$ −31,400, $[\theta]_{280}$ −18,200, $[\theta]_{274}$ −13,500, $[\theta]_{267}$ −8500, $[\theta]_{261}$ −4100, $[\theta]_{255}$ −2300.

(+)-(6*S*)-**Methadone Hydrochloride** (1·**HCl**, **Figure** 4): CD (*c* 0.025, $CHCl_3$) $[\theta]_{330}$ 0, $[\theta]_{320}$ 5900, $[\theta]_{310}$ 17,300, $[\theta]_{302}$ 24,000, $[\theta]_{298}$ 23,400, $[\theta]_{295}$ 23,700, $[\theta]_{290}$ 20,400, $[\theta]_{280}$ 11,700, $[\theta]_{275}$ 9100, $[\theta]_{274}$ 8900, $[\theta]_{270}$ 6600, $[\theta]_{268}$ 5700, $[\theta]_{267}$ 5500, $[\theta]_{262}$ 2500, $[\theta]_{260}$ 2300, $[\theta]_{255}$ 600, $[\theta]_{254}$ 600, $[\theta]_{252}$ 0; CD (*c* 0.1, CH_3OH) $[\theta]_{330}$ 200, $[\theta]_{320}$ 6800, $[\theta]_{310}$ 25,800, $[\theta]_{300}$ 40,800, $[\theta]_{295}$ 42,100, $[\theta]_{290}$ 39,400, $[\theta]_{280}$ 26,200, $[\theta]_{273}$ 17,800, $[\theta]_{272}$ 17,600, $[\theta]_{270}$ 16,300, $[\theta]_{267}$ 11,700, $[\theta]_{265}$ 11,500, $[\theta]_{260}$ 6100, $[\theta]_{258}$ 5500, $[\theta]_{255}$ 3000, $[\theta]_{253}$ 2400, $[\theta]_{247}$ 0.

(−)-(5*S*)-**Isomethadone Hydrochloride** (2·**HCl**, **Figure** 4): CD (*c* 0.025, $CHCl_3$) $[\theta]_{330}$ −1500, $[\theta]_{320}$ −16,600, $[\theta]_{310}$ −36,800, $[\theta]_{303}$ −45,800, $[\theta]_{300}$ −45,400, $[\theta]_{295}$ −43,200, $[\theta]_{290}$ −36,400, $[\theta]_{280}$ −20,900, $[\theta]_{276}$ −17,300, $[\theta]_{274}$ −15,900, $[\theta]_{270}$ −11,200, $[\theta]_{267}$ −10,500, $[\theta]_{263}$ −5700, $[\theta]_{260}$ −4600, $[\theta]_{257}$ −2800, $[\theta]_{255}$ −2800, $[\theta]_{250}$ −1000; CD (*c* 0.025, CH_3OH) $[\theta]_{330}$ −1200, $[\theta]_{320}$ −10,800, $[\theta]_{310}$ 24,900, $[\theta]_{303}$ −32,000, $[\theta]_{300}$ −32,100, $[\theta]_{297}$ −32,000, $[\theta]_{290}$ −27,100, $[\theta]_{280}$ −16,300, $[\theta]_{275}$ −12,200, $[\theta]_{273}$ −11,500, $[\theta]_{270}$ −8900, $[\theta]_{267}$ −7700, $[\theta]_{263}$ −4800, $[\theta]_{260}$ −3900, $[\theta]_{258}$ −2600, $[\theta]_{253}$ −1500, $[\theta]_{250}$ −1000.

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Notes

Stereochemical Studies on Medicinal Agents. 17.[1] Synthesis, Absolute Configuration, and Analgetic Potency of Enantiomeric Diastereomers of 3-Ethyl and 3-Propyl Derivatives of 1-Methyl-4-phenyl-4-propionoxypiperidine

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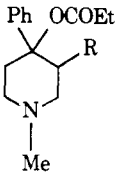
We recently have reported[2] on the relative stereochemistries of racemic diastereomers of **1** and have noted that, unlike the prodines **2**, the α isomer is considerably more potent than the β isomer. The corresponding allyl racemates also were found to possess a qualitatively similar stereostructure–activity relationship; however, on a quantitative basis (±)-α-**3** is 15 times more potent than morphine and 24 times that of (±)-α-**1**. A subsequent report[3] on the optical isomers of **3** revealed that α-**3** possesses high enantiomeric stereoselectivity [potency ratio, (3*R*,4*S*)/(3*S*,4*R*) = 260], while the much less active β-**3** exhibits an enantiomeric potency ratio of unity. This is in marked contrast to the stereochemical behavior of α-**2**[4] where potency and enantiomeric stereoselectivity are one order of magnitude lower [(3*R*,4*S*)/(3*S*,4*R*) = 25] than α-*3*. Moreover, β-**2**[4] also shows a striking difference (when compared to β-**3**) in that it possesses moderate enantio-

† This paper is dedicated to Professor Burger in recognition of his many accomplishments in the field of medicinal chemistry.

meric stereoselectivity [(3S,4S)/(3R,4R) = 13].

While the stereostructure–activity relationship that has emerged from these studies is consistent with the idea that the analgetic receptor is capable of distinguishing between the pro-4R and pro-4S enantiotopic edges[4,5] of the piperidine ring in potent narcotic analgetics, we were unable to account for the very high enantiomeric potency ratio for α-3. In this regard one or two structural features of the 3-allyl group might be responsible for this high ratio; these are the allylic double bond or the presence of a three-carbon chain. Additionally, we were interested in learning which of these features are also responsible for the absence of enantiomeric stereoselectivity in β-3.

In order to ascertain which of these structural features plays a dominant role in the stereoselectivity of 3 at analgetic receptors, we decided to prepare optical antipodes of 1 and 4 and examine their enantiomeric potency ratios.

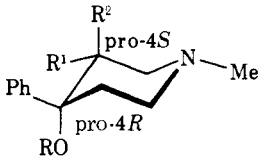


1, R = Pr
2, R = Me
3, R = $CH_2CH{=}CH_2$
4, R = Et

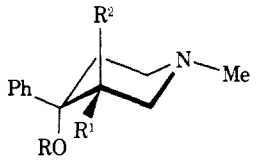
α series, *trans*-Ph:R
β series, *cis*-Ph:R

Chemistry. Since we had previously[3] prepared **5a** and **5b** and determined their absolute stereochemistries, we utilized these compounds for the preparation of optically active 1 and 4. The chief advantage of this procedure was that all of the optically active products would be of known absolute configuration.

Catalytic hydrogenation of the four optically active allyl compounds **5a,b** afforded the corresponding propyl isomers **6a,b**. The desired esters 1 [(3R,4S)-**7a**, (3S,4R)-**7a**, (3S,4S)-**7b**, (3R,4R)-**7b**] were obtained by treatment of the optically pure alcohols **6a,b** with propionyl chloride.



4S series



4R series

	R	R^1	R^2
5a	H	$CH_2CH{=}CH_2$	H
b	H	H	$CH_2CH{=}CH_2$
6a	H	Pr	H
b	H	H	Pr
7a	EtCO	Pr	H
b	EtCO	H	Pr
8	H	Et	H
9	EtCO	Et	H

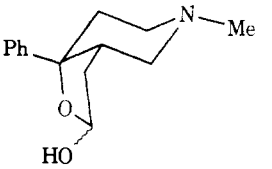
Enantiomers of 8 were readily obtained by Wolff–Kishner reduction of (−)- and (+)-**10** which were synthesized from (3R,4S)- and (3S,4R)-**5a** by a previously reported[3] procedure. Esterification of (3R,4S)-**8** afforded enantiomers of α-4 having stereochemistries corresponding to **9**. Unfortunately, we were unsuccessful in preparing the β isomers of the 3-ethyl analog because no defined product was obtained when **5b** was subjected to oxidation with OsO_4–$NaIO_4$ as described[3] for **5a**.

Stereostructure–Activity Relationship. The analgetic potencies of the optical isomers were determined by the hot-plate procedure[6] and are shown in Table I. It can be noted that the more potent antipodes in the α series [(−)-**7a**, (−)-**9**] contain a 4S chiral center. Moreover, the potencies of these isomers are statistically indistinguishable from one another and from (3R,4S)-α-2.[4] This, together with the fact that all of the enantiomeric potency ratios for α-2, **7a**, and **9** are of similar magnitude [(3R,4S)/(3S,4R) ~ 25], suggests very similar or identical modes of interaction of these compounds with analgetic receptors.‡ It thus appears that the tenfold increase in the enantiomeric potency ratio reported for α-**3** can be attributed exclusively to the presence of the allylic double bond. Moreover, it can be noted that the data presented in this study are consistent with the hypothesis[4,5] that an equatorial 3-alkyl group located on the pro-4R edge of the piperidine ring interferes with drug receptor association.

Table I. Analgetic Potencies of Enantiomeric Diastereomers of 3-Ethyl and 3-Propyl Derivatives of 1-Methyl-4-phenyl-4-propionoxypiperidine

Compd[a]	Configuration	ED_{50}, mg/kg[b]
(−)-**7a** [(−)-α-**1**]	3R,4S	1.0 (0.78–1.26)[c]
(+)-**7a** [(+)-α-**1**]	3S,4R	25.2 (19.5–32.6)
(+)-**7b** [(+)-β-**1**]	3S,4S	Inactive at 100
(−)-**7b** [(−)-β-**1**]	3R,4R	11.4 (8.9–14.8)
(−)-**9** [(−)-α-**4**]	3R,4S	0.9 (0.74–1.09)
(+)-**9** [(+)-α-**4**]	3S,4R	25[d]
Morphine[e]		1.2

[a] Tested as the HCl salts. [b] Tested sc in mice by the hot-plate procedure.[6] [c] Confidence interval (95%). [d] Due to insufficient compound only two dose levels were tested. At 50 mg/kg six of ten mice gave a response and at 20 mg/kg only two out of ten were affected. [e] A. E. Jacobson and E. L. May, *J. Med. Chem.*, 8, 563 (1965).



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From a qualitative point of view, the β-propyl compound **7b** behaves in a fashion that is similar to the β-allyl isomer β-**3** in that both (+) and (−) enantiomers possess low potencies relative to one of the enantiomers in the α series. This therefore is consistent with the proposal[2,3] that a hydrophobic pocket on the receptor is capable of accommodating an axial 3-alkyl substituent (situated on the pro-4S edge of the piperidine ring) of less than three carbons. The fact that the α and β racemates of 4 have nearly equal potencies[8] suggests that the hydrophobic pocket can fully accommodate an axial 3-ethyl group. An axial propyl or allyl group cannot fit this pocket and consequently the affinity of the molecule is greatly reduced. When the 3-alkyl group is located on the pro-4R enantiotopic edge of the piperidine ring, it will also hinder drug-receptor association for reasons described previously,[3]

‡ The enantiomeric potency ratios most likely reflect events at the receptor, as it has been demonstrated[7] that closely related enantiomeric diastereomers of prodine (2) achieve nearly identical brain levels after sc administration.

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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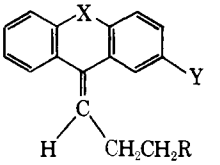
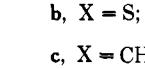
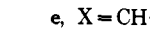
Among the geometrical isomers of aminopropylidene-substituted tricyclic derivatives with the general structure **1** potent neuroleptic activity has been associated with the *Z* (cis) geometry, *i.e.*, the configuration in which the side chain is oriented toward the substituted aromatic ring, in all 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.