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

(+)-(6S)-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.

(−)-(5S)-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.

(+)-(6S)-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.

(−)-(5S)-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.

(+)-(6S)-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.

(−)-(5S)-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

Kevin H. Bell and Philip S. Portoghese*,†

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455.
Received June 29, 1973

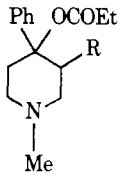
We recently have reported[2] on the relative stereochemistries of racemic diastereomers of **1** and have noted that, unlike the prodines **2**, the α isomer is considerably more potent than the β isomer. The corresponding allyl racemates also were found to possess a qualitatively similar stereostructure–activity 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.

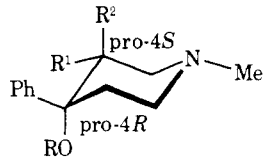


1, R = Pr
2, R = Me
3, R = $CH_2CH{=}CH_2$
4, R = Et

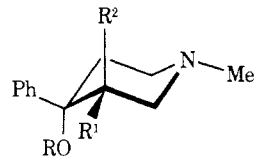
α series, *trans*-Ph:R
β series, *cis*-Ph:R

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	R¹	R²
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

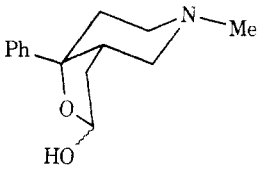
Enantiomers of **8** were readily obtained by Wolff–Kishner reduction of (−)- and (+)-**10** which were synthesized from (3R,4S)- and (3S,4R)-**5a** by a previously reported[3] procedure. Esterification of (3R,4S)-**8** afforded enantiomers of α-**4** having stereochemistries corresponding to **9**. 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†

Carl Kaiser,* Richard J. Warren, and Charles L. Zirkle

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101.
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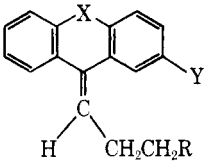
Among the geometrical isomers of aminopropylidene-substituted tricyclic derivatives with the general structure **1** potent neuroleptic activity has been associated with the *Z* (cis) geometry, *i.e.*, the configuration in which the side chain is oriented toward the substituted aromatic ring, in all 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 = N⟨⟩NMe

c, X = CH_2O; Y = 2—Cl; R = NMe_2

d, X = CH_2O; Y = 2—Cl; R = N⟨⟩$N(CH_2)_2OH$

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.