markedly, as shown in comparing eq 13 with eq 10. This

$$\log L_{37}^{\text{blood}} = (-0.295 \pm 0.043) + (0.588 \pm 0.30) \log L_{37}^{\text{water}} + (0.411 \pm 0.020) \log L_{37}^{\text{oil}} \quad (13)$$

$$r = 0.9909,\ s = 0.178,\ n = 63$$

underlines the importance of considering data sets involving similar types of solutes in comparing properties of different biological media. It is highly likely that if solubilities of the aromatics in the other biological media were available and we had included these in the correlations, the absolute values of the oil coefficients would have changed from those in Table IV, but the differences from medium to medium would probably have been quite similar.

Concluding Comments. We underline the potential importance of the correlations described in this paper with the following explicit statement. Given the ability to calculate log L values through the double regression equation, eq 7, it follows that two relatively simple solubility measurements (that is, gas/liquid partition coefficients) of a given solute in water and oil should allow the estimation of solubilities of the solute in the various biological systems listed in Table III and should allow the estimation of the distribution of the solute between any pair of the various biological systems, with a precision of the same order as the average experimental error.

Acknowledgment. The work by R.W.T. was funded in part by the U.S. Public Health Service. M.J.K. and R.M.D. worked under Naval Surface Weapons Center Foundational Research Task IR-210. P.K.W. worked under Naval Medical Research and Development Command Work Unit MF58524.01D.003. The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large.

Registry No. 1, 7440-59-7; 2, 7440-01-9; 3, 7440-37-1; 4, 7439-90-9; 5, 7440-63-3; 6, 1333-74-0; 7, 7727-37-9; 8, 630-08-0; 9, 7782-44-7; 10, 10024-97-2; 11, 74-82-8; 12, 74-86-2; 13, 74-85-1; 14, 74-84-0; 15, 2551-62-4; 16, 124-38-9; 17, 75-19-4; 18, 115-10-6; 19, 60-29-7; 20, 67-64-1; 21, 75-45-6; 22, 67-66-3; 23, 79-01-6; 24, 109-93-3; 25, 75-15-0; 26, 406-90-6; 27, 76-38-0; 28, 124-72-1; 29, 26675-46-7; 30, 151-67-7; 31, 13838-16-9; 32, 679-84-5; 33, 593-53-3; 34, 353-36-6; 35, 460-13-9; 36, 420-26-8; 37, 75-03-6; 38, 78-93-3; 39, 107-87-9; 40, 96-22-0; 41, 591-78-6; 42, 108-10-1; 43, 110-43-0; 44, 71-43-2; 45, 108-88-3; 46, 100-41-4; 47, 95-47-6; 48, 108-38-3; 49, 106-42-3; 50, 103-65-1; 51, 98-82-8; 52, 100-42-5; 53, 71-43-2; 54, 108-90-7; 55, 95-50-1; 56, 541-73-1; 57, 75-09-2; 58, 56-23-5; 59, 75-34-3; 60, 107-06-2; 61, 71-55-6; 62, 79-00-5; 63, 630-20-6; 64, 79-34-5; 65, 156-59-2; 66, 156-60-5; 67, 127-18-4; 68, 540-54-5; 69, 78-87-5; 70, 109-69-3; 71, 543-59-9; H_2O, 7732-18-5.

Tetracyclic Pyridazines as Potential Psychopharmacological Agents

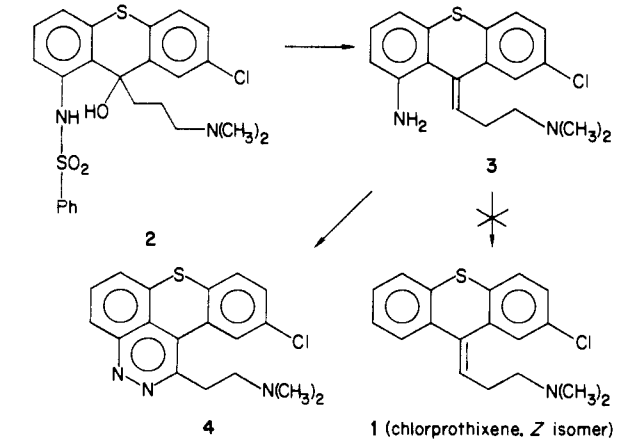
Bruce S. Ross and Robert A. Wiley*†

Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas 66045. *Received June 27, 1984*

Since the *Z* isomer of chlorprothixene (1) is far more active than its *E* counterpart, it was of interest to develop a stereoselective synthesis for this class of compounds. Insertion of a benzenesulfonamido group at the peri position of a chlorprothixene precursor did affect the stereochemistry of side-chain olefin formation, but after hydrolysis attempted removal of the resulting amine led to a Widman–Stoermer cyclization to afford the corresponding tetracyclic pyridazine-containing compound (4). Since this material displayed encouraging activity in neurotransmitter uptake inhibition studies, compounds in which the sulfur bridge was replaced with an ethano bridge similar to that found in imipramine (8) and with sulfur removed (7) were also prepared. These, together with the corresponding peri amino compounds (3, 5, and 6), were tested as neurotransmitter-uptake inhibitors. The two bridged arylamines 3 and 6 displayed potent and selective inhibition of norepinephrine uptake both when tested in vitro and after in vivo administration. The pyridazine-containing compounds exhibited reasonable activity in vitro, but the activity was lost when they were administered in vivo. None of the compounds displayed significant ability to interfere with spiroperidol binding.

Tricyclic psychopharmacological agents possess a wide variety of central and peripheral nervous system activities. In attempts to select for the desired activity, existing agents have been modified by substitution or have been stereochemically and conformationally defined. The antipsychotic chlorprothixene (1) is an early example of this. The *Z* isomer was originally separated by fractional crystallization and shown[1] to be the active component of the isomeric mixture. The original goal of this project was to develop a general stereoselective synthesis for thioxanthene-type antipsychotics such as chlorprothixene. In particular, a synthetic route (Scheme I) was proposed that utilized a peri-substituted benzenesulfonamido group on the alcohol precursor of chlorprothixene. It was hoped that steric interactions during dehydration of 2 would strongly favor the formation of the isomer analogous to (*Z*)-chlorprothixene and that the sulfonamido group could then be hydrolyzed to the aromatic amine 3 followed by diazotization and reduction to give (*Z*)-chlorprothixene. This

Scheme I



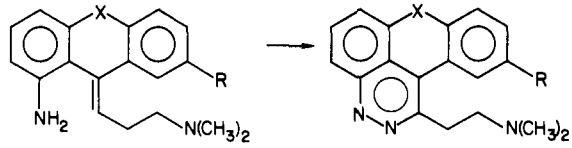
strategy eventually led to the desired *E* aromatic amine, but under the diazotization conditions, an initially unex-

†Present address: College of Pharmacy, The University of Iowa, Iowa City, IA 52242.

(1) Pelz, K.; Protiva, M. *Collect. Czech. Chem. Commun.* **1967**, *32*, 2161.

0022-2623/85/1828-0870$01.50/0

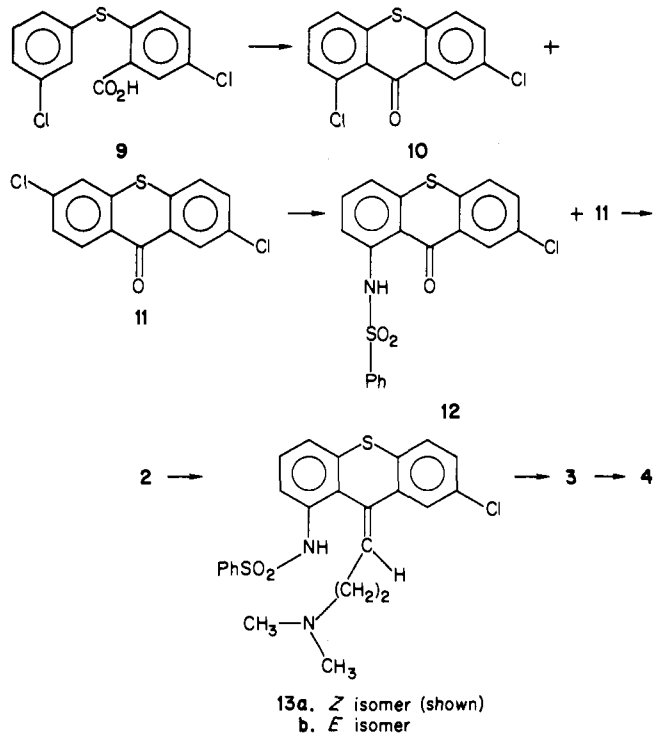
Scheme II



5. X=2H; R=Cl
6. X=C_2H_4; R=H

7. X=2H; R=Cl
8. X=C_2H_4; R=H

Scheme III



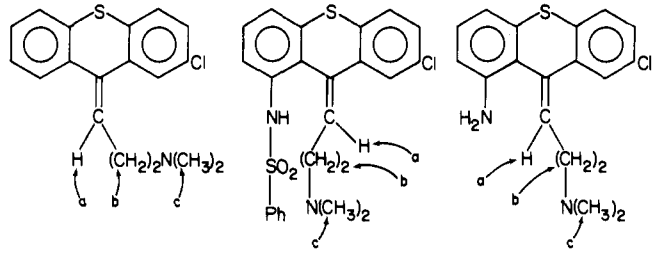
13a. Z isomer (shown)
b. E isomer

pected, fused pyridazine analogue of chlorprothixene formed. This structure (**4**) appeared unique in substitution and in the resulting geometry of the ring system.

Interest in the influence of the fused pyridazine moiety on biological activity prompted the synthesis of two more series of compounds (Scheme II). Compound **7** is an unbridged analogue of the first product and compound **8** is a fused pyridazine analogue of the antidepressant amitriptyline. These compounds and some of their intermediates have been tested as uptake inhibitors of neurotransmitters and as inhibitors of spiroperidol binding.

Chemistry. Synthesis of the chlorprothixene analogue **4** is shown in Scheme III. This was approached via the dichlorothioxanthone **10**, which was reported[2] to constitute the sole isomer found in cyclization of the phenylthiobenzoic acid **9**. In our hands, however, this cyclization afforded an equimolar mixture of the 1,7- and 2,6-isomers; these were not easily separated on a preparative scale. However, on reaction with benzenesulfonamide under alkaline conditions, only the chlorine at position 1, which is at an ortho-activated position, underwent reaction. This provided a convenient separation procedure. In principle, 2-[(4-chlorophenyl)thio]-6-chlorobenzoic acid could only cyclize to give the desired 1,7-dichloro isomer. However, the attempted synthesis of this from 2,6-dichlorobenzoic acid and 4-chlorothiophenolate led predominantly to the product of disubstitution. Addition of the γ-aminopropyl-Grignard reagent to the carbonyl group of **12** proceeded in satisfactory yield if 2.5 equiv were used, and the mixture was heated to solubilize the salt formed from the sulfonamide. Dehydration using HCl gas in benzene proceeded smoothly to afford a single isomer of the chlorprothixene analogue **13**. Dehydration using acetic acid gave a mixture of the two isomers of this material, which were separated chromatographically. Analysis of the NMR signals produced by the propylidene side-chain protons indicated (Table I) that those from one of the isomers strongly resembled similar signals from chlorprothixene. In the other isomer, the signals varied considerably from these positions, indicating interaction with the sulfonamido group. On this basis, the isomer obtained from the HCl dehydration was assigned the *Z* configuration (**13a**). Thus, influences other than the postulated steric repulsion must be operative during the dehydration.

Table I. NMR Data for Chlorprothixene and Analogues



compd	δ values H_a	H_b	H_c
chlorprothixene	5.88 (t, *J* = 7 Hz)	2.50 (m)	2.18 (s)
13a (*Z* isomer from HCl dehydration)	5.56 (dd)	2.26 (m)	2.56 (s)
13b (*E* isomer)	5.62 (t, *J* = 7.5 Hz)	2.49 (m)	2.33 (s)
3 (*E* isomer)	6.12 (t, *J* = 7 Hz)	2.44 (m)	2.19 (s)
17a (*Z* isomer, major product)	6.30 (t, *J* = 7 Hz)	2.04 (m)	2.29 (s)
17b (*E* isomer)	5.51 (m)	2.39 (m)	2.20 (s)
5 (*E* isomer)	6.25 (t, *J* = 7 Hz)	2.31 (m)	2.13 (s)
6 (*E* isomer)	5.97 (t, *J* = 7 Hz)	2.33 (m)	2.17 (s)

Cleavage of the sulfonamido group proved difficult but was finally accomplished with 25% HCl, which led to a single isomer of the amine product **3**, even when an isomer mixture of the starting material was used. The stereochemistry was inferred as *E* on the basis of NMR data (Table I). This assignment cannot be totally unambiguous because only one isomer was available, which crystallized in needles too small to allow X-ray analysis. However, it is strengthened by the close correlation between its side-chain NMR resonances (Table I) and those of chlorprothixene. Asscher et al.[3] have also observed in a series of polycyclic amitriptyline analogues that side-chain NMR signals were sensitive to stereochemistry. In their series, the spectrum for one isomer closely resembled that for amitriptyline itself, whereas those from the other isomer bore less similarity. Attempted removal of the amino moiety by diazotization and H_3PO_2 reduction gave a tetracyclic product, identified by spectral and elemental microanalysis as the fused pyridazine **4**. This is an example of the Widman–Stoermer synthesis[4] of cinnoline ring systems.

Initial efforts to prepare the phenylcinnoline **7** involved desulfurization of **4**, but this was unsuccessful. Attention was next directed to reaction between 2,3′-dichlorobenzophenone[5] and benzenesulfonamide, but this reaction

(2) Kannur, S. B.; Badiger, V. V.; Nargund, K. S. *J. Karnatak Univ.* **1964**, *9*, 52; *Chem. Abstr.* **1966**, *64*, 6616e.

(3) Asscher, Y.; Avnir, D.; Rotman, A.; Agranut, I. *J. Pharm. Sci.* **1982**, *71*, 122.

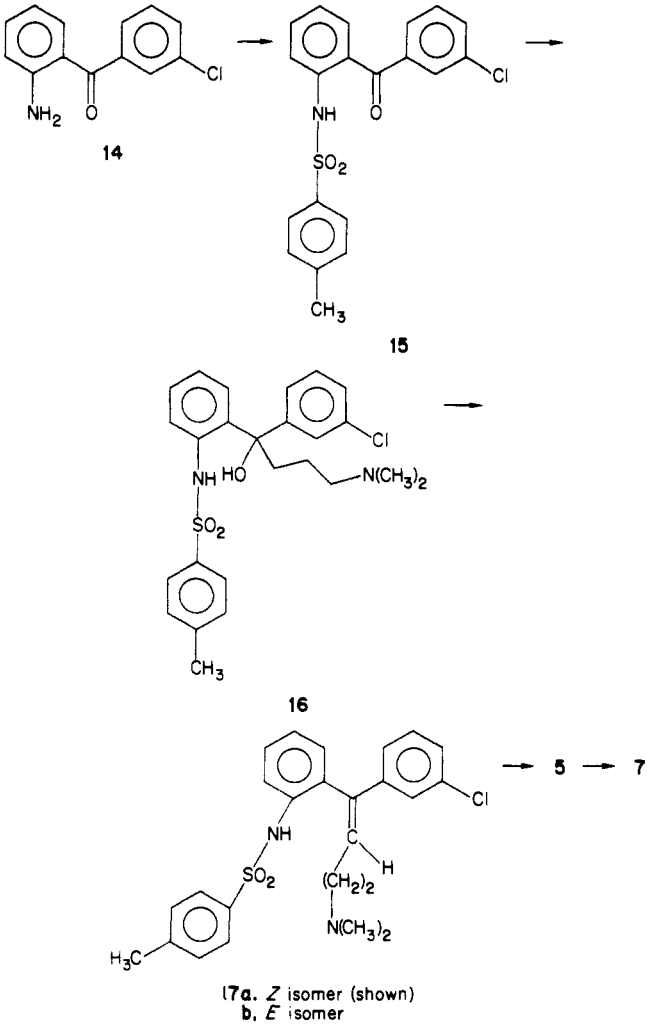
(4) Singerman, G. M. In "Heterocyclic Compounds"; Castle, R., Ed.; Wiley: New York, 1973; Vol. 27, p 19.

Table II. Neurotransmitter-Uptake Inhibition

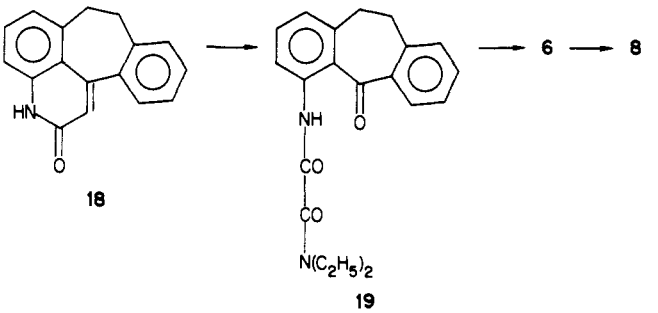
compd	ED_{50} "ex vivo", μmol/kg[a]		EC_{50} in vitro, μM[a]	
	NE[b]	5-HT[c]	NE	5-HT
3	16 (11–23)	>99 (35)	0.7 (0.2–10)	3.5 (2.0–6.4)
4	>117 (27%)	>117 (16%)	3.8 (2.3–7.0)	7.3 (3.2–25)
5	>102 (33%)	>102 (55)	>25 (37%)	0.5 (0.3–1.0)
7	>128 (49%)	>128 (42%)	3.5 (2.2–5.5)	4.2 (2.6–6.7)
6	15 (9.9–23)	55 (27–224)	2.2 (1.1–4.4)	1.6 (0.8–3.0)
8	>106 (13%)	>106 (11%)	6.6 (35–12)	27 (46%)
imipramine	63	126	1.3	0.3
desipramine	34	>132	0.07	12
amitriptyline	144	>144	5.4	2.9

[a] Results are expressed as ED_{50} or EC_{50}, with 95% confidence limits in parentheses. If 100% inhibition was not achieved, results are expressed as greater than the highest dose used, with the percent inhibition achieved at that dose in parentheses. [b] Norepinephrine. [c] Serotonin.

Scheme IV



Scheme V



did not occur, perhaps because the low-energy conformation of benzophenones decreases orbital overlap between carbonyl p orbitals and the ring π orbitals of the 2-chlorobenzene system, which could lead to less activation of the 2-chlorine. An attempted Grignard addition to 2-amino-3′-chlorobenzophenone led to 1,4-addition products only. However, reaction of this arylamine (**14**) with *p*-toluenesulfonyl chloride led to sulfonamide product **15**, which could undergo the Grignard addition to give **16** (Scheme IV). This product could be converted to the final product **7** essentially as described above. Both *Z* and *E* isomers of the sulfonamide compound **17** were obtained. On the basis of NMR data (Table I) it was possible to assign the minor isomer **17b** the *E* configuration analogous to chlorprothixene on the basis of the close correspondence of their side-chain NMR signals. Only one isomer of the amine **5** is available, so the structural assignment is slightly less secure, but the NMR data suggest, by analogy with those from **3** and **6**, that **5** has the *E* configuration. Unfortunately, this material also could only be made to crystallize in tiny needles that were unsuitable for X-ray analysis.

The amine corresponding to **3** was selected as the key compound in the synthesis of **8**. Preparation of this material[6] proceeded via the dibenzocycloheptapyridinone **18** (Scheme V). In our hands, reliable ozonolysis of this material required methylene chloride rather than acetic acid as the solvent and long reaction times. Since cleavage of the *N*-carboxyformyl group drastically reduced yields, we decided to introduce the side chain before cleaving the amide group. In order to carry out successfully the Grignard addition, it was necessary to convert the *N*-carboxyformyl group to the corresponding diethyloxamido group to afford **19**. The following addition, dehydration, hydrolysis, and cyclization were carried out as described in the Experimental Section.

Biology. To obtain a preliminary estimate of the biological activity that might be associated with this series of compounds, the ability of the phenothiazine-type substances (**3**, **4**, **13a**) to inhibit the uptake of norepinephrine, dopamine, and serotonin into rat cortical slices was measured[7] (data not shown). The results indicated reasonable activity for the series and encouraged further work.

The ability of all the arylamines and the compounds containing the fused pyridazine ring to inhibit uptake of norepinephrine and serotonin into mouse cortical slices was determined. These were used as indices of possible antidepressant-type activity. These experiments were done in two ways:[8] in vitro experiments were conducted by

(5) Haller, H. L.; et al. *J. Am. Chem. Soc.* **1945**, *67*, 1591.

(6) Galantay, E. U.S. Patent 3 458 578, 1969; *Chem. Abstr.* **1969**, *71*, 91166p.

(7) Ziance, R. J.; Rutledge, C. O. *J. Pharmacol. Exp. Ther.* **1972**, *180*, 118.

placing slices from normal mice in organ baths, adding the test drug, and comparing neurotransmitter uptake to that obtained in control slices. In "ex vivo" experiments the test drug was administered in vivo by intraperitoneal injection; after 1 h, slices were removed and their ability to take up neurotransmitters measured. The results are shown in Table II. Here it is seen that several of these compounds display interesting activity. The most interesting in vitro result is the marked selectivity displayed by the arylamine **5**. This compound is almost as potent as imipramine in inhibiting serotonin uptake but has little effect on norepinephrine. Significant in vitro inhibition of norepinephrine uptake does appear when there is no longer free rotation of both phenyl rings due to the addition of the pyridazine ring (**7**) or the bridge between the two aromatic rings. The activity of most of these compounds is markedly diminished when they are studied by using the "ex vivo" technique, probably because they either do not reach the brain or they are transformed to inactive metabolites. The two bridged arylamines **3** and **6**, while not as potent as uptake inhibitors of norepinephrine in vitro as desipramine, do display potent and selective ability to inhibit norepinephrine when studied by using the "ex vivo" technique. One possible explanation for these results is metabolic transformation of **3** and **6** to active secondary amine analogues. A similar enhancement in potency and selectivity for norepinephrine-uptake inhibition is seen in the conversion of imipramine to desipramine.

The ability of compounds **3–5**, **7**, **13a**, and **17a** to interfere with binding of spiroperidol to the dopamine receptor in rat striatal synaptosomes was also studied[9,10] (data not shown). Only the amine **3** showed a trace of activity in this test, which is primarily for antipsychotic activity, at 1–10 μM. All other compounds were inactive at 10 μM; the EC_{50} for chlorprothixene is 11 nM. This is perhaps not surprising for, although relatively few literature data are available,[11] antipsychotic activity is not normally associated with compounds bearing substituents in the 1-position.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses, when indicated only by the symbol of the element tested, were within ± 0.4% of the calculated values. Analyses were performed on a Hewlett-Packard CHN analyzer at the University of Kansas. Nuclear magnetic resonance spectra were recorded on a Varian FT-80 spectrophotometer with the values reported in terms of parts per million downfield from the internal standard, tetramethylsilane. Infrared spectra were recorded on a Beckman IR-33 or Perkin-Elmer 727 spectrophotometer. Mass spectra were recorded on a Varian CH-5 spectrometer.

2-[(3-Chlorophenyl)thio]-5-chlorobenzoic Acid (9). 3-Chlorobenenethiol (46.6 g, 0.322 mol), KOH pellets (30.8 g, 0.55 mol), and 500 mL of DMF were heated to reflux. The vapors were allowed to escape until the base dissolved. 2,5-Dichlorobenzoic acid (41.0 g, 0.215 mol) and copper bronze powder (0.10 g) were then added, and the solution was heated to reflux for 20 h.

The solvent was distilled until ca. 150 mL remained and the residue cooled and poured into 1.5 L of ether, affording a flocculent, white precipitate. This salt was collected, acidified with 10% HCl, and recrystallized from ethanol/water to give 48.6 g (76%) of the product: mp 167–168 °C.

An analytical sample was prepared by recrystallization from ethanol/water. White crystals: mp 169–170 °C (lit.[2] mp 179–180 °C). Anal. ($C_{13}H_8Cl_2O_2S$) C, H.

***N*-(Phenylsulfonyl)-1-amino-7-chloro-9*H*-thioxanthen-9-one (12).** A 50:50 mixture of 1,7- and 2,6-dichloro-9*H*-thioxanthen-9-one was prepared from **9** by the method of Nargund et al.[2] This mixture of thioxanthones (578 mg, 2.06 mmol), benzenesulfonamide (646 mg, 4.16 mmol), potassium acetate (323 mg, 3.12 mmol), and copper bronze powder (50 mg) in 10 mL of nitrobenzene was heated to reflux (205 °C) for 9 h. Ethanol (10 mL) was added, which gave a dark green precipitate. This was filtered, rinsed with ethanol, and recrystallized from HOAc/water, which left a mixture of the product and the unreacted 2,6-isomer. This was separated by vacuum sublimation [160 °C (0.05 mmHg) for 3 h] of the impurity, leaving 376 mg (70%) of analytically pure product. Larger scale purification can be done by suspending the product in 10% NaOH and toluene, filtering, triturating with hot toluene, and acidifying with dilute HCl. Bright yellow-green powder: mp 211–212 °C. MS, *m/e* 401 (M^+, base), 336, 260, 232, 205; NMR ($CDCl_3$) δ 10.00 (s, 1, NH), 8.85–7.00 (m, 11, arom); IR (KBr) 1610 cm^{-1} (C=O). Anal. ($C_{19}H_{12}NClO_3S_2$) C, H, N.

3-[*N*-(Phenylsulfonyl)-1-amino-7-chloro-9-hydroxy-9*H*-thioxanthen-9-yl]-*N*,*N*-dimethyl-1-propanamine (2). Magnesium turnings (0.60 g, 25 mmol) were crushed and put in a dry flask under nitrogen with 10 mL of anhydrous ether. Iodomethane (0.1 mL) was added to initiate the reaction, followed by the slow addition of 3-chloro-*N*,*N*-dimethyl-1-propanamine (2.42 g, 19.8 mmol) in 50 mL of ether to give an exothermic reaction. After 1 h, the starting ketone **12** (2.00 g, 4.96 mmol) was added all at once as a solid with 100 mL of dry toluene and formed the magnesium salt of the sulfonamide, which very slowly dissolved as the solution was heated to reflux for 10 h.

The solution was cooled and treated with 100 mL of 10% ammonium chloride solution, and the layers were separated. The aqueous layer was extracted with 100 mL of toluene, and the organic layers were combined, washed with 200 mL of water, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was dissolved in 150 mL of dry ether, filtered, and treated with HCl gas for 5 min. A white solid was filtered, rinsed with ether, and dried to give 1.60 g (65%) of the hydrochloride of the product.

An analytical sample of the free base was prepared by recrystallization of the free base from toluene. After the sample was allowed to stand for 3 days, large (2–3 mm on a side) colorless prisms formed: mp 174–175 °C. This material could also be recrystallized from ethanol, which gave fine, white needles: mp 159 °C sharp. Both samples were analytically pure and identical on TLC, NMR, IR, and MS. CI-(methane)-MS, *m/e* 488 (M^+), 471, 87 (base shown); NMR ($CDCl_3$) δ 7.86–7.06 (m, 11, arom), 2.52 (s, 3, $N(CH_3)_2$), 2.81–2.13 (m, 2, CH_2NMe_2), 1.56–0.88 (m, 4, $CH_2CH_2CH_2N$). Anal. ($C_{24}H_{25}N_2ClO_3S_2$) C, H. N.

(*E*)- and (*Z*)-3-[*N*-(Phenylsulfonyl)-1-amino-7-chloro-9*H*-thioxanthen-9-ylidene]-*N*,*N*-dimethyl-1-propanamine (13a and 13b). The starting alcohol **2** (90 mg, 0.20 mmol) was dissolved in 5 mL of benzene and treated with HCl gas for 15 min, forming a red oil. The flask was stoppered and allowed to stir overnight. The solvent was removed under reduced pressure to give a tan solid, which was dissolved in 2 mL of hot ethanol; this spontaneously crystallized. After cooling, the solid was filtered, washed with ether, and dried to afford 70 mg (81%) of the analytically pure hydrochloride salt of the product. A single isomer formed as determined by TLC, HPLC, and NMR; however, if the dehydration is carried out in AcOH (heated to reflux for 30 min), one-fourth of the product formed is the *E* isomer. Separation of the free bases was obtained on the medium-pressure LC using EtOAc/ethanol (4:1) on silica. An analytical sample of the *E* isomer hydrochloride salt was prepared by recrystallization from toluene and ethanol/EtOAc. The assignment of stereochemistry is based on assumptions described in the discussion section. Both isomers can form monohydrates of the salts. Recrystallization from tolueen removes the water from the *Z* isomer but not the other.

***Z* isomer:** fine, white cubes; mp 213.5–214.0 °C (monohydrate, mp ca. 170 °C, for a fluffy, white powder); CI-(methane)-MS, *m/e* 470 (M^+, base shown), 329, 284, 257; NMR ($CDCl_3$) of the base δ 7.28–7.05 (m, 11, arom), 6.51 (br s, 1, NH), 5.56 (dd, 1, =CH),

(8) Ross, S. B.; Ogren, S.-O.; Renyi, A. L. *Acta Pharmacol. Toxicol.* **1976**, *39*, 152.
(9) Leysen, J. E.; Gommeren, W.; Laduron, D. M. *Biochem. Pharmacol.* **1978**, *27*, 307.
(10) Hall, H.; Thor, L. *Life Sci.* **1979**, *24*, 2293.
(11) Kaiser, C.; Setler, P. E. It "Burger's Medicinal Chemistry", 4th ed.; Wolfe, M. E., Ed.; Wiley: New York, 1981; Part III, pp 851–1068.

2.62–2.00 (m, 4, CH_2CH_2), 2.56 (s, 6, N $(CH_3)_2$). Anal. ($C_{24}H_{23}N_2ClO_2S_2$·HCl) C, H, N.

***E* isomer**: fluffy, white powder; mp 207–209 °C; CI-(ammonia)-MS, *m/e* 470 (M^+, base shown), 257; NMR ($CDCl_3$) of the free base δ 7.60–6.98 (m, 11, arom), 5.62 (t, 1, =CH), 2.52–2.33 (m, 4, CH_2CH_2), 2.33 (s, 6, $N(CH_3)_2$). Anal. ($C_{24}H_{23}N_2ClO_2S_2$·HCl·H_2O) C, H, N.

(*E*)-3-(1-Amino-7-chloro-9*H*-thioxanthen-9-ylidene)-*N*,*N*-dimethyl-1-propanamine (3). The starting sulfonamide compound **13a** (1.15 g, 2.27 mmol) was added to 150 mL of 25% HCl in a flask under nitrogen. This formed a suspended white solid, which upon heating to 120 °C (oil bath T) very slowly dissolved and formed a bright red solution after 5 days.

The solution was then diluted with 500 mL of water, alkalinized with NaOH pellets, extracted with 3 × 250 mL of toluene, washed with 200 mL of water, and dried ($MgSO_4$) and the solvent removed under reduced pressure to afford a yellow oil (0.87 g). This was purified on a medium-pressure LC [silica; CH_2Cl_2/EtOAc/methanol (6:2:1)] to give 426 mg (62%) of a light yellow oil. Only one isomer could be detected by TLC, HPLC, and NMR. The assignment of stereochemistry is based on assumptions described in the Discussion section.

An analytical sample was prepared by making the dihydrochloride salt in toluene and recrystallizing twice from ethanol/EtOAc and drying in a 140 °C vacuum desiccator. Peach color powder: mp 228–230 °C; MS, *m/e* 330 (M^+), 270, 257, 237, 195, 58 (base); NMR ($CDCl_3$) of the free base δ 7.35 (d, 1, C8 H), 7.26–6.77 (m, 4, arom), 6.66 (dd, 1, C4 H), 6.30 (t, 1, =CH), 4.05 (br s, 2, NH_2), 2.60–2.30 (m, 4, CH_2CH_2), 2.16 (s, 6, $N(CH_3)_2$). Anal. ($C_{18}H_{19}N_2ClS$·2HCl) C, H. N.

10-Chloro-*N*,*N*-dimethyl[1]benzothiopyrano[4,3,2-*de*]cinnoline-1-ethanamine (4). The starting amine **3** (300 mg, 0.91 mmol) was suspended in 25 mL of 12% HCl. Sodium nitrite (66 mg, 0.96 mmol), in 1 mL of water, was added all at once. This immediately caused a deep blue solution to form. After 15 min, the solution was alkalinized with NaOH pellets, which formed a yellow precipitate. This was collected, rinsed with water, and dried to give 280 mg (90%) of the product.

An analytical sample was prepared by recrystallization in ethanol/water. Small, bright orange, rectangular plates: mp 151.5–152.0 °C; MS, *m/e* 341 (M^+), 313, 258, 219, 58 (base); NMR ($CDCl_3$) δ 8.06 (d, 1, C4 H), 7.92–7.26 (m, 5, arom), 3.56 (t, 2, CH_2CH_2N), 3.06 (t, 2, CH_2CH_2N), 2.33 (s, 6, $N(CH_3)_2$). Anal. ($C_{18}H_{16}N_3ClS$) C, H. N.

2-Amino-3′-chlorobenzophenone (14). Freshly crushed magnesium turnings (1.91 g, 78.5 mmol) were placed in a dry flask under nitrogen. 3-Bromochlorobenzene (15.0 g, 78.2 mmol) in 75 mL of anhydrous ether was added over 30 min and caused a vigorous reaction. After 30 more min, 2-aminobenzonitrile (4.41 g, 37.3 mmol) in 50 mL of dry toluene was added over 15 min. This immediately gave a deep yellow precipitate (amine anion), which after heating to reflux for 1 formed a pale yellow, milky emulsion. Most of the solvent was removed under reduced pressure and then the residue was treated with 50 mL of 25% sulfuric acid to hydrolyze the intermediate imine, which caused a vigorous reaction. After 1 h at 100 °C, the flask was cooled, diluted with 200 mL of water, alkalinized with NaOH pellets, extracted with 4 × 300 mL of ether, and dried ($MgSO_4$) and the volume of ether was distilled under reduced pressure to 250 mL. This solution was treated with HCl gas, which resulted in an orange-brown precipitate. This was suction filtered, rinsed with ether, and partitioned between 100 mL of CH_2Cl_2 and 25 mL of 10% NaOH. The aqueous layer was extracted with 2 × 100 mL of CH_2Cl_2. The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was dried to give 6.89 g (80%) of a yellow paste.

An analytically pure sample was prepared by using the medium-pressure LC (silica; hexane/EtOAc (5:1)). The oily residue solidified under vacuum after 3 days. Bright yellow solid: mp 74–76 °C (lit.[12] mp 78–80 °C).

2-[*N*-[(4-Methylphenyl)sulfonyl]amino]-3′-chlorobenzophenone (15). 2-Amino-3′-chlorobenzophenone (14; 6.89 g, 29.7 mmol) and 4-methylbenzenesulfonyl chloride (8.51 g, 44.6 mmol) were added to 100 mL of pyridine under nitrogen. The solution was heated to reflux for 1 h, and then most of the solvent was removed under reduced pressure. The residue was dissolved in 500 mL of ether and extracted with 5 × 200 mL of 5% NaOH (higher concentrations of base will not work as well). A red oil formed in the aqueous layer. This was acidified, extracted with 3 × 300 mL of ether, and dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was dried to give 7.61 g of product. TLC still showed product in the original ether layer. It was distilled under reduced pressure and the residue was put on the medium-pressure LC [silica; hexane/EtOAc (5:1)] to give 2.1 g of contaminated product. This was taken through an extraction sequence similar to the above and resulted in 490 mg of an analytically pure oil, which solidified under vacuum after 2 months. Total yield of the purified product was 71%. White solid: mp 93.0–93.5 °C; MS, *m/e* 385 (M^+), 230, 195, 111, 91 (base); NMR ($CDCl_3$) δ 9.81 (s, 1, NH), 7.76–6.99 (m, 12, arom), 2.25 (s, 3, CH_3); IR (KBr) 1650 cm^{-1} (C=O). Anal. ($C_{20}H_{16}NClO_3S$) C, H, N.

4-[2-[*N*-[(4-Methylphenyl)sulfonyl]amino]phenyl]-4-(3-chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-1-butanamine (16). Compound **16** was prepared in 74% yield from **15**, employing the same procedure used for the synthesis of **2**.

An analytical sample of the hydrochloride salt was prepared by dissolving the free base in toluene/ethanol (10:1), treating with HCl gas, heating until the solution was cloudy (ethanol escapes), cooling, filtering the precipitate, recrystallizing in the same way, and drying the purified material: a white, shiny, fluffy solid; mp 223.5–224.0 °C (free base is a white solid, mp 158.0–158.5 °C); MS, *m/e* 472 (M^+), 361, 317, 139, 58 (base); NMR ($CDCl_3$) of the free base δ 7.59–6.84 (m, 12, arom), 2.62–2.25 (m, 2, CH_2N), 2.25 (s, 3, Ar CH_3), 2.13 (s, 6, $N(CH_3)_2$), 2.13–1.25 (m, 4, $CH_2CH_2CH_2N$). Anal. ($C_{25}H_{30}N_2ClO_3S$·HCl) C, H, N.

(*E*)- and (*Z*)-4-[2-[[(4-Methylphenyl)sulfonyl]amino]phenyl]-4-(3-chlorophenyl)-*N*,*N*-dimethylbut-3-en-1-amine (17a and 17b). The starting alcohol **16** (300 mg, 0.608 mmol) was dissolved in 18 mL of HOAc and 3 mL of concentrated HCl. This was heated to reflux for 10 min, diluted with 100 mL of water, alkalinized with NH_4OH, extracted with 3 × 50 mL of ether, washed with 50 mL of water, and dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was dried to give 217 mg (78%) of a colorless oil. TLC and NMR suggested that both isomers had been formed. They were separated by preparative TLC [1 mm silica; hexane/EtOAc/ethanol (70:25:5)]. The *Z*/*E* ratio was ca. 3:1. The assignment of stereochemistry is based on assumptions described in the discussion section.

An analytical sample of the *Z* isomer was prepared by recrystallization from CH_2Cl_2/hexane/ether. Dense, white powder: mp 152–153 °C; MS, *m/e* 455, 454 (M^+), 298, 240, 204, 58 (base); NMR ($CDCl_3$) δ 7.88–6.69 (m, 12, arom), 6.30 (t, 1, =CH), 2.50–2.31 (m, 2, CH_2N), 2.29 (br s, 9, Ar CH_3, $N(CH_3)_2$), 2.04 (m, 2, CH_2CH_2N). Anal. ($C_{25}H_{28}N_2ClO_2S$) C, H. N.

(*E*)-4-(2-Aminophenyl)-4-(3-chlorophenyl)-*N*,*N*-dimethylbut-3-en-1-amine (5). Compound **5** was prepared in 85% yield from **16**, employing the same method used for the synthesis of **3**.

An analytical sample of the oxalate salt was prepared by recrystallization from EtOAc/ethanol. Cream colored flakes: mp 121–123 °C (small sample of white crystal, mp 125.5–6.0 °C); MS, *m/e* 300 (M^+), 240, 200, 130, 58 (base); NMR ($CDCl_3$) of free base δ 7.31–6.56 (m, 8, arom), 6.25 (t, 1, =CH), 3.44 (br s, 2, NH_2), 2.38–2.13 (m, 4, CH_2CH_2N), 2.13 (s, 6, $N(CH_3)_2$). Anal. ($C_{18}H_{21}N_2Cl$·$C_2H_2O_4$) C, H, N.

4-(3-Chlorophenyl)-*N*,*N*-dimethyl-3-cinnolineethanamine (7). Compound **7** was prepared in 89% yield from **5**, employing the same method used for the synthesis of **4**.

An analytical sample was prepared by two successive recrystallizations from CH_2Cl_2/hexane. Yellow needles: mp 116–117 °C (dihydrochloride, fine yellow needles, mp 205–207 °C); MS, *m/e* 311 (M^+), 283, 267, 189, 58 (base); NMR ($CDCl_3$) of the free base δ 8.55 (dd, 1, C8 H), 7.86–7.15 (m, 7, arom), 3.20 (br t, 2, CH_2CH_2N), 2.86 (br t, 2, CH_2CH_2N), 2.18 (s, 6, $N(CH_3)_2$). Anal. ($C_{18}H_{18}N_3Cl$) C, H, N.

2,3,7,8-Tetrahydrodibenzo[*f*][*jk*]cyclohepta[*c*]pyridin-2-one (18). Compound **18** was prepared as described[6] with the

(12) Chen, G.-S.; Gibson, M. S. *J. Chem. Soc., Perkin Trans.* **1975**, 1138.

following modifications. (1) The Reformatsky reagent was prepared by the method of Fieser and Johnson[13] with zinc granules and methyl bromoacetate. (2) The Friedel–Crafts cyclization was carried out in 175 mL of concentrated sulfuric acid at 80 °C for 15 min.

Under these conditions, the product 18 could be produced in 32% overall yield from 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one. An analytical sample was prepared by recrystallization from HOAc/methanol twice and drying in a 100 °C vacuum desiccator. Slightly pink, very fine needles: mp 278.5–279.0 °C (lit.[5] mp 279 °C).

4-(*N*,*N*-Diethyloxamido)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (19). A 500-mL male flask was equipped with a magnetic stirrer and a female bubbler. The starting pyridinone 18 (5.00 g, 20.2 mmol) was suspended in 400 mL of CH_2Cl_2. An O_3–O_2 gas mixture from a Welsbach ozone generator was bubbled through the solution, which caused a white solid to appear after 2 h. After flushing with nitrogen, 50 mL of 30% hydrogen peroxide (oxidative workup) and 50 mL of methanol (to increase solubility) were added, and the mixture was stirred for 10 min. The solution was washed with 2 × 100 mL of 5% HCl and the solvent removed under reduced pressure. The brown oil residue was dissolved in 300 mL of ether, extracted with 3 × 200 mL of 5% NaOH, acidified with HCl, extracted with 3 × 200 mL of CH_2Cl_2, and dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was dried to yield 3.24 g (48% crude) of a brown foam.

The intermediate carboxyformamido compound (2.84 g, 0.984 mmol) was suspended in 300 mL of toluene and heated to reflux. Thionyl chloride (2 mL) was added all at once, followed by an additional 1 mL after 5 min. The solution was heated to reflux for 20 min, allowing the excess thionyl chloride to escape. The solution was cooled to 25 °C and 15 mL of diethylamine was added slowly. After 2 h, the solution was washed with 3 × 100 mL of 5% NaOH, 2 × 150 mL of 5% HCl, and 200 mL of water and dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was dried to afford 2.0 g of a light yellow oil. The alkaline washings contained purified starting acid (recovered 0.94 g). The yield based on consumption of starting material is 89% (44% from tetracyclic starting material).

An analytical sample was prepared by crystallization from EtOAc/hexane (1:10). Straw colored bars (ca. 2 mm long): mp 114.5–115.5 °C; MS, *m/e* 350 (M^+), 250 (base), 100, 72; NMR ($CDCl_3$) δ 10.77 (br s, 1, NH), 8.28–8.09 (m, 2, C3 H, C5 H), 7.48–6.96 (m, 5, arom), 3.78, 3.47 (q, 4, $N(CH_2CH_3)_2$), 3.29–3.02 (m, 4, $ArCH_2CH_2Ar$), 1.28, 1.23 (t, 6, $N(CH_2CH_3)_2$); IR (solution in CCl_4) 3310 (NH), 1700 and 1640 (C=O) cm^{-1}). Anal. ($C_{21}H_{22}N_2O_3$) C, H. N.

(*E*)-3-(4-Amino-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-*N*,*N*-dimethyl-1-propanamine (6). The alcohol intermediate to compound 6 was prepared from 19 (2.60 g, 7.43 mmol) by employing the same method used in the synthesis of 2. This crude intermediate was heated under reflux with a mixture of 8 g of KOH pellets, 24 mL of methanol, and 6 mL of water. Water (40 mL) was then added and the mixture heated under reflux for 10 more min. The solution was worked up by extraction with 3 × 100 mL of toluene, reextracted with 3 × 100 mL of 5% HCl, alkalinized with NaOH, extracted with 2 × 150 mL of ether, washed with 200 mL of water, and dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was dried to give 1.56 g of a brown oil (72% crude). This was purified on medium-pressure LC [silica; CH_2Cl_2/methanol (3:1)] to give a 20% yield of the purified product. There appeared to be a single isomer produced as judged by TLC [silica gel; methylene chloride/methanol (3:1)] and NMR. The assignment of the stereochemistry is based on NMR spectral analysis (Table I).

An analytical sample was prepared by making the dihydrochloride in ether, removing the solvent under reduced pressure, recrystallizing from ethanol/EtOAc (3:10), and drying in a 100 °C vacuum desiccator. Off-white powder: mp 235–237 °C; MS, *m/e* 292 (small M^+), 218, 189, 58 (base); NMR ($CDCl_3$) of the free base δ 7.24–6.57 (m, 7, arom), 5.97 (t, 1, =CH), 3.42 (s, 2, NH_2), 3.33–2.55 (m, 4, $ArCH_2CH_2Ar$), 2.40–2.25 (m, 4, CH_2CH_2N), 2.17 (s, 6, $N(CH_3)_2$). Anal. ($C_{20}H_{24}N_2 \cdot 2HCl$) C, H, N.

7,8-Dichloro-*N*,*N*-dimethylbenzo[6,7]cyclohepta[1,2,3-*de*]cinnoline-1-ethanamine (8). Compound 8 was prepared in 93% yield from 6, employing the same method used for the synthesis of 4.

An analytical sample was prepared by making the dihydrochloride in ether and ethanol (ethanol needed to solubilize the free base), removing the solvent under reduced pressure, recrystallizing from ethanol/EtOAc, and drying in a 100 °C vacuum desiccator. Yellow crystals: mp 207.5–211 °C; MS, *m/e* 303 (small M^+), 275, 260, 245, 215, 58 (base); NMR ($CDCl_3$) of the free base δ 8.28 (br d, 1, C4 H), 7.63–6.88 (m, 6, arom), 3.31 (br s, 4, $ArCH_2CH_2Ar$), 3.00–2.63 (m, 4, CH_2CH_2N), 2.13 (s, 6, $N(CH_3)_2$). Anal. ($C_{20}H_{21}N_3 \cdot 2HCl$) C, H, N.

Biological Studies. White mice (18–22 g) were used in these studies; four animals were used per dose. Experiments labeled in vitro were done in untreated animals and those denoted as "ex vivo" 1 h after intraperitoneal injection of the test drug. Simultaneous uptake of [^{3}H]norepinephrine (NE) and 5-hydroxy-[^{14}C]tryptamine (5-HT) was measured in cerebral cortical and striatal slices as follows. The incubation mixture consisted of 60 mg of cortical slices, 20 mg of striatal slices, 0.2 nmol of [^{3}H]NE, 0.2 nmol of [^{14}C]-5-HT, the test compound in in vitro experiments, 0.48 μmol of pargyline, and 11 μmol of glucose in 2.0 mL of Krebs–Henseleit's buffer, pH 7.4. The incubation was performed for 5 min in an atmosphere of O_2 containing 6.5% CO_2. The tritium and ^{14}C activity in the dissolved (Soluene-350) slices was determined by using different channels for tritium and ^{14}C in a liquid-scintillation spectrometer. The active uptake was determined as that inhibited by 3×10^{-4} M cocaine. The potency of the test compound inhibiting the amine uptake was determined from log concentration inhibition curves by regression analysis and expressed as EC_{50} or ED_{50} with the 95% confidence intervals.

Acknowledgment. We are grateful to the National Institutes of Health (Training Grant GM-1341) for support and to Dr. Charles O. Rutledge and Karin Harryson of the University of Kansas and Maria Sallemark and Anna Renyi of Astra Laboratories for the biological results. We are particularly grateful to Dr. Thomas Högberg for many valuable discussions.

Registry No. 2, 96245-53-3; 2·HCl, 96245-55-5; 2 (*N*-(chloromagnesium) salt), 96245-54-4; 3, 96245-60-2; 3·2HCl, 96245-61-3; 4, 96245-62-4; 5, 96245-70-4; 5·oxalate, 96245-71-5; 6, 96245-77-1; 6·2HCl, 96245-78-2; 7, 96245-72-6; 7·2HCl, 96245-73-7; 8, 96245-79-3; 8·2HCl, 96258-22-9; 9, 5101-50-8; 9·K, 96245-51-1; 10, 5101-70-2; 11, 20092-85-7; 12, 96245-52-2; 13a, 96245-58-8; 13a·HCl, 96245-56-6; 13b, 96245-59-9; 13b·HCl, 96245-57-7; 14, 57479-65-9; 14 (imine bromomagnesium) salt), 96245-63-5; 14 (imine), 96245-64-6; 15, 96245-65-7; 16, 96245-66-8; 16·HCl, 96245-67-9; 17a, 96245-68-0; 17b, 96245-69-1; 18, 15920-42-0; 19, 96245-74-8; 19 (acid), 96245-75-9; 3-ClC_6H_4SH, 2037-31-2; 2,5-$Cl_2C_6H_3CO_2H$, 50-79-3; $PhSO_2NH_2$, 98-10-2; 3-BrC_6H_4Cl, 108-37-2; 2-$H_2NC_6H_4CN$, 1885-29-6; 4-$CH_3C_6H_4SO_2Cl$, 98-59-9; $HN(C_2H_5)_2$, 109-89-7; $Cl(CH_2)_3N(CH_3)_2$, 109-54-6; 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, 1210-35-1; 4-(*N*,*N*-diethyloxamido)-5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol, 96245-76-0.

(13) Fieser, L. F.; Johnson, W. S. *J. Am. Chem. Soc.* **1940**, *62*, 575.