Esters of 4-[3-[2-(Trifluoromethyl)phenothiazin-10-yl]propyl]-1-piperazineethanol and Related Compounds as Long-Acting Antipsychotic Agents. Synthesis of the 1-Adamantoate, the First Crystalline Base. 4

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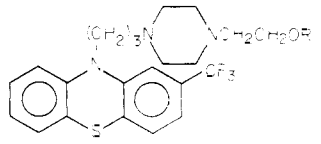
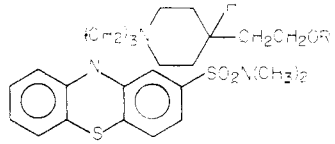
A number of new esters of fluphenazine are described; among these was the 1-adamantoate, **1h**, the first highly crystalline ester of that drug. The 1-adamantoate of pipotiazine, **2b**, typically, was an oil. Following a single subcutaneous or intramuscular injection of 25 mg/kg of either **1h** or **2b**, dissolved in sesame oil, each ester was found to be a potent and long-acting inhibitor of conditioned avoidance behavior in the rat.

The past decade has witnessed an accelerating clinical acceptance of the prototype long-acting antipsychotic agents, fluphenazine enanthate (**1b**) and decanoate (**1c**)[1,2] and this phenomenon has stimulated a search for similar agents in a number of other laboratories.[3] In clinical practice, these esters are administered via subcutaneous or intramuscular injections as a sterile solution of 25 mg of the base in 1 ml of sesame oil. The depot that is formed slowly releases the ester to the surrounding biophase at a rate that evokes a therapeutic response in chronic schizophrenia for a period of from 1 to 6 weeks.



1a, R = H (fluphenazine)
b, R = n-$C_6H_{13}CO$
c, R = n-$C_9H_{19}CO$
d, R = n-$C_5H_{11}CO$
e, R = $(CH_3)_2CH(CH_2)_2CO$
f, R = n-$C_{11}H_{23}CO$



2a, R = H (pipotiazine)
b, R = 
1g, R = n-$C_{13}H_{27}CO$
h, R = 

Although selected salts of these esters are crystalline, the bases have been isolated only as viscous oils that cannot be purified by any conventional technique, including chromatography or molecular distillation. As a consequence, a suitable crystalline salt is first prepared, purified by recrystallization, and then treated under mild conditions with aqueous alkali, and the base is recovered by extraction with a solvent like benzene.

This note has a twofold purpose: (a) to report the synthesis and duration of activity in the laboratory of several additional related esters, **1d–g**, not previously described,[1] each of which, as the base, was isolated as an oil and (b) to describe the synthesis of the first crystalline base of an ester of fluphenazine, the 1-adamantoate, **1h**.[4] Although highly crystalline,[5] **1h** was readily soluble in sesame oil and, following a single intramuscular injection of 25 mg/kg, dissolved in sesame oil, demonstrating a duration of activity in excess of 30 days. The 1-adamantoate of pipotiazine (**2b**), typically, was isolated as an oil which could not be induced to crystallize; again, however, following the intramuscular injection of the compound, at a dose of 25 mg/kg, dissolved in sesame oil, a duration of activity in excess of 30 days was observed. The CNS activity reported here, in particular with **1h** and **2b**, is of considerable significance in view of the decrease or, indeed, the complete absence of that type of activity reported with other 1-adamantoyl and related derivatives of other psychotropic agents containing a carbinol functionality.[6,7]

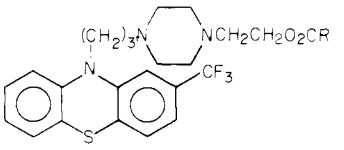
The esters, **1d–g**, were prepared from molar equivalents of **1a** and the appropriate acyl chloride in benzene solution;[1] in the preparation of **1h** and **2b**, an equivalent amount of triethylamine was added, in addition, to the reaction mixture.

Experimental Section

All compounds were homogeneous by paper chromatography or by TLC. The melting points were taken in an electrically heated oil bath and are uncorrected. The ^1H NMR and IR spectra and the microanalyses were obtained from the Analytical Department of this Institute; analyses for the indicated elements were obtained on all products and were within ±0.3% of theory.

The duration and potency of these compounds were determined in the CNS Section, Department of Pharmacology, of this Institute employing the pole jump procedure[8] or the one-way avoidance or shelf-jump procedure.[9] In the former, the apparatus consisted of a wood box containing a stainless steel grid floor that was provided with electrical contacts for shocking the rats and a centrally located, vertical wooden pole for escape. The stimulus supplied to the grid through an inductorium was approximately 0.1 mA of 60-cycle ac at 40 V. The conditioning stimulus was the sound from a buzzer attached directly to the test chamber. Female albino rats, in a weight range of 175–295 g, were trained by an electrical shock lasting 30 s to escape by climbing the pole (unconditioned response). Subsequently, the same rats were trained to escape only at the sound of a buzzer maintained for 12 s (conditioned response). Over 90% of the rats learned the required response after 3 or 4 daily trials on 5 consecutive days and were used in the tests. The trained animals retained the conditioned response without reinforcement for at least 6 weeks. If the test compound was administered and was effective, the trained (conditioned) rats did not respond to the buzzer even after 12 s and made no attempt to escape. A second response, "latency", involved the time required for the rats which did not escape following dosage to escape after being shocked. The latter data could be used to compare a series of compounds for their "sedating" side effect, and this laboratory observation was found to correlate well with the degree of sedation observed in humans. Following administration of the ester dissolved in sesame oil as a single subcutaneous or intramuscular dose of 25 mg/kg to ten trained rats, each rat was challenged three times successively each day, until the conditioned response, initially less than 10%, was increased to 50%, i.e., half of the rats climbed the pole at the sound of the buzzer. For **1b**, this occurred at 12–16 days while with **1c**, this was observed after 28–32 days. These two compounds have now been used therapeutically in chronic schizophrenia in hundreds of thousands of patients[10] and these studies in humans have demonstrated that a single dose of 25 mg of **1b** produces a therapeutic response in that disease state for about 14 days, while a single dose of 25 mg of **1c** produces a similar therapeutic

Table I. Esters of Fluphenazine



Compd no.	R	Salt: Formula	Mp, °C	Recrystn solvent	Yield, %[a]	Base: Formula	Yield, %[b]	Duration of act., days[c]
1d	n-C_5H_{11}	$C_{28}H_{36}F_3N_3O_2S \cdot 2HCl$	175-177	MeCN	45	$C_{28}H_{36}F_3N_3O_2S$	78	8-10
1e	$(CH_3)_2CH(CH_2)_2$	$C_{28}H_{36}F_3N_3O_2S \cdot 2HCl$	171-172	2-PrOH	93	$C_{28}H_{36}F_3N_3O_2S$	91	8-10
1f	n-$C_{11}H_{23}$	$C_{34}H_{48}F_3N_3O_2S \cdot 2HCl$	111-113	Me_2CO-Et_2O	95	$C_{34}H_{48}F_3N_3O_2S$	92	28-32
		$C_{34}H_{48}F_3N_3O_2S \cdot (CO_2H)_2$	221-222	EtOH	95			
1g	n-$C_{13}H_{27}$	$C_{36}H_{52}F_3N_3O_2S \cdot 2HCl$	116-119	Me_2CO-Et_2O	95	$C_{36}H_{52}F_3N_3O_2S$	96	28-32

[a] Yield based on recrystallized salt. [b] Recovery of base from recrystallized salt. [c] The dosage, subcutaneously or intramuscularly, was standardized at ~32 mg/kg of the base in ~5% solution in sesame oil; with this regimen, fluphenazine enanthate had a duration of activity of 12-14 days while fluphenazine decanoate had a duration of 28-32 days.

response for about 28 days. In this fashion, these data in humans have been extrapolated to consider a 50% inhibition of the conditioned avoidance as the cutoff point in the rat, at a dose of 25 mg/kg.

The Tenen procedure employed a Plexiglas box inside of which was a sliding wall programmed to recede simultaneously with the onset of an auditory stimulus and to reveal an escape platform to the rat who was below on a grid floor. The wall traveled at a rate fast enough to permit an avoidance response to be made in about 1 s and yet slow enough to provide a gentle return of the rat from the shelf to the grid floor below for a repeat trial. Photoelectric cells were so designed as not to be disrupted by the movement of the sliding wall when it traveled at the normal rate; the escape of the rat from the grid by jumping to the shelf disrupted the circuit, and the phenomenon was recorded. Again, ten rats were used for each compound, and the evaluation proceeded as described above for the pole jump procedure.

The preparation of **1h** and **2b** is given in detail. Pertinent data for **1d-g** are summarized in Table I; the procedure employed to prepare those compounds has been described.[1]

4-[3-[2-(Trifluoromethyl)phenothiazin-10-yl]propyl]-1-piperazineethanol Ester with 1-Adamantanecarboxylic Acid (1h). To a stirred solution of 9.10 g (0.021 mol) of **1a** (obtained by molecular distillation) and 5.00 g (0.025 mol) of 1-adamantanecarbonyl chloride in 200 ml of anhydrous C_6H_6 was added 2.53 g (0.025 mol) of triethylamine and the mixture stirred and heated under reflux for 18 h in a nitrogen atmosphere and under anhydrous conditions. The cooled mixture was filtered from $(Et)_3N \cdot HCl$ (3.25 g, 0.023 mol), and the filtrate concentrated in vacuo to give 17.0 g of an oil. The oil was dissolved in 225 ml of boiling hexane and filtered (Hyflo), and the filtrate was allowed to cool spontaneously and then refrigerated at 0 °C to give 10.04 g (80% yield) of **1h**: mp 96-98 °C [Anal. ($C_{33}H_{40}F_3N_3O_2S$) C, H, N; N.E. ($HClO_4$)]; IR ($CDCl_3$) no absorption in the 3300-3600-cm^{-1} region, 1720 cm^{-1} (ester CO); ^1H NMR ($CDCl_3$) δ 4.16 (t, J = 2 Hz, 2 H, CH_2OCO), 3.93 (t, J = 3 Hz, 2 H, CH_2 at position 10 of the phenothiazine ring), the 7 Ar-H and 29 aliphatic-H were seen as multiplets at 6.80-7.30 and 1.60-2.70, respectively.

To a boiling solution of 0.55 g (0.0092 mol) of **1h** in 5.0 ml of MeCN was added dropwise 2.0 ml of 4 N 2-PrOH·HCl. The clear solution was allowed to cool spontaneously, and the solid that separated was filtered and recrystallized from 10 ml of MeCN to give 0.55 g (94% yield) of **1h**·2HCl: mp 244-245 °C dec [Anal. ($C_{33}H_{40}F_3N_3O_2S \cdot 2HCl$) C, H, N, Cl; N.E. ($HClO_4$)].

2-[1-[3-[2-(Dimethylamino)sulfonyl-10-phenothiazinyl]-propyl]-4-piperidinyl]ethanol Ester with 1-Adamantanecarboxylic Acid (2b). To a stirred solution of 9.92 g (0.021 mol) of **2a** (Rhone-Poulenc, 19366 R.P., Lot TY1915) in 225 ml of anhydrous C_6H_6 was added 5.00 g (0.025 mol) of 1-adamantanecarbonyl chloride, followed by 2.53 g (0.025 mol) of Et_3N, dropwise. Following this, the reaction conditions and work-up described for **1h** were followed. The crude base (15.45 g) could not be induced to crystallize nor could a crystalline maleic acid salt be prepared. The base (15.00 g) dissolved in 100 ml of boiling Me_2CO was treated with a solution of 4.75 g (0.044 mol) of $(CO_2H)_2 \cdot H_2O$ in 50 ml of Me_2CO. Prolonged cooling gave 13.78 g of **2b**·$(CO_2H)_2$, mp 155-156 °C dec. This, recrystallized from 270 ml of MeCN, gave 13.15 g (86% yield) of pure **2b**·$(CO_2H)_2$: mp unchanged at 155-156 °C dec [Anal. ($C_{35}H_{47}N_3O_4S_2 \cdot C_2H_2O_4$) C, H, N, S].

To 11.85 g (0.016 mol) of pure **2b**·$(CO_2H)_2$, suspended in 100 ml of water, was added 200 ml of Et_2O and 8.0 g of powdered $NaHCO_3$. One hour of vigorous agitation was required to form a clear two-phase system. The Et_2O layer was separated, washed with saturated aqueous NaCl, dried, and concentrated from a bath at 60-65 °C to give 10.07 g (96% recovery) of **2b**, as a viscous oil [Anal. ($C_{35}H_{47}N_3O_4S_2$) (C, H, N, S]: IR ($CDCl_3$) no absorption below 3000 cm^{-1}, 1705 cm^{-1} (ester CO); ^1H NMR ($CDCl_3$) δ 3.78-4.18 (m, 4 H, CH_2OCO plus CH_2 at position 10 of the phenothiazine ring), the 7 Ar-H and 36 aliphatic-H were seen as multiplets at 6.82-7.23 and 1.00-3.00, respectively.

References and Notes

(1) For paper 3, see H. L. Yale, A. I. Cohen, and F. Sowinski, *J. Med. Chem.*, **6**, 347 (1963).

(2) A decade of clinical use of the two esters has been reviewed by F. J. Ayd, *Am. J. Psychiat.*, **132**, 491 (1975), and by J. E. Groves and M. R. Mandel, *Arch. Gen. Psychiat.*, **32**, 893 (1975).

(3) Among the products currently undergoing clinical investigation are Schering's perphenazine enanthate and decanoate, Rhone-Poulenc's pipotiazine undecylenate and palmitate, and Lundbeck's flupenthixol decanoate. In addition, Protiva and his group at the Research Institute for Pharmacy and Biochemistry in Prague have reported on the synthesis and activities of several long-chain esters of their tricycle [cf. J. O. Jilek, K. Sindelar, A. Dlabac, E. Kazdova, J. Pomykacek, Z. Sedivy, and M. Protiva, *Collect. Czech. Chem. Commun.*, **38**, 1190 (1973), for the work of Protiva's group, as well as references to clinical studies with the above products].

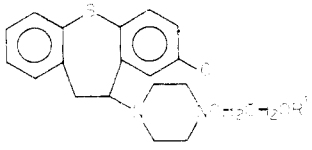
(4) From a practical point of view, a crystalline base would be a most attractive substitute for either **1b** or **1c**. Numerous problems develop in a manufacturing plant in the handling of sticky, extremely viscous oils. For example, they strongly retain the solvent used in their isolation; subdividing, weighing, transfer, and solution in sesame oil are time-consuming and frequently lead to waste of these very expensive compounds. Another peculiar characteristic of these oils is their large coefficient of expansion at low temperature. Thus, before this property was recognized, large glass containers of bulk material, shipped air freight, in the unheated holds of aircraft, were found cracked and leaking on arrival.

(5) The crystals of **1h** obtained from hexane belong to the triclinic space group $P\bar{1}$, with two molecules in the unit cell, related by a center of symmetry. The cell constants are a = 11.398 Å, b = 8.799 Å, c = 16.859 Å, α = 98.27°, β =

112.76°, and $\gamma = 99.66°$ (these are unpublished data obtained by Mrs. Barbara Toeplitz of this Institute).

(6) The two procedures employed for the evaluation of these compounds are described in the Experimental Section.

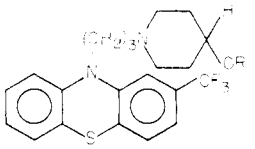
(7) J. O. Jilek, A. Dlabac, and M. Protiva, at the Conference on the Chemistry of Psychotropic Agents held at Usti nad Labem, May 13–17, 1974, reported that the 1-adamantanoate, **4**, of the highly potent neuroleptic, **3**, was totally devoid of activity when evaluated against apomorphine-induced emesis in the dog or catalepsy in the rat. These tests are widely employed in other laboratories, especially in Europe, to evaluate long-acting neuroleptics [see, for example, L. Joulou, G. Bourat, R. Ducrot, J. Fournel, and C. Garret, *Acta Psychiat. Scand., Suppl.*, **241**, 9 (1973)], and data from these tests compare well with data obtained on inhibition of conditioned avoidance behavior. Thus, the lack of activity with 4 reinforces the concept that the efficacy of 1**h** and **2b** is unique. Although R. T. Rapara, R. J. Kraay, and K. Gerzon, *J. Med. Chem.*, **8**, 580 (1965), have shown that the highly symmetrical cage-like adamantane molecule confers lipophilic character, steric hindrance, and, in its esters, a unique stability toward hydrolysis, these attributes, in toto, do not necessarily lead to an active compound.



3, R^1 = H

4, R^1 =

Another example to demonstrate that long-chain fatty acid esters of an active antipsychotic agent may not lead to an active, long-acting ester, and may, in fact, lead to an inactive compound, has been observed with **5**. In the conditioned avoidance procedure, **5** [French Patent 1 305 353; *Chem. Abstr.*, **58**, 9092 (1963)] was found to have 0.5–1.0 times the potency of 1**a**, the most potent phenothiazine available, on a milligram basis, in medicine. When, however, **5** was converted to the laurate and myristate esters, **6** and **7**, respectively, both compounds were inactive in the conditioned avoidance procedure. Note that 1**f** and 1**g** (Table I), the laurate and myristate of 1**a**, were both potent and long-acting derivatives.



5, R = H
6, R = n-$C_{11}H_{23}CO$
7, R = n-$C_{13}H_{27}CO$

It is also worth noting that very recently, B. T. Ho, L. F. Englert, and M. L. McKenna, *J. Med. Chem.*, **19**, 850 (1976), have reported that the 1-adamantylcarbamate of 1**a** was less effective than was 1a in several laboratory tests designed to uncover amphetamine antagonism.

(8) J. J. Piala, J. P. High, G. L. Hassert, Jr., J. C, Burke, and B. N. Craver, *J. Pharmacol. Exp. Ther.*, **127**, 55 (1959).

(9) S. S. Tenen, *Psych. Sci.*, **6**, 407 (1966).

(10) S. R. Hirsch, R. Gaind, P. D. Rohde, B. C. Stevens, and J. K. Wing, *Br. Med. J.*, 633 (1973).

Substituent Constants for Correlation Analysis

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Constants for π and σ have been measured for a miscellaneous group of aromatic substituents of interest to medicinal chemists. Swain and Lupton's $\mathcal{F}$ and $\mathcal{R}$ values have been calculated from the σ constants. Values for molar refractivity are also given for each of the substituents.

The use of substituent constants in the field of physical organic chemistry has had an enormous impact on the study of organic reaction mechanisms.[1-3] The use of such constants has enabled us to delineate the role of substituents on organic and biochemical processes in terms of polar, resonance, steric,[4] hydrophobic,[5] and polarizability[6] vectors. There is a dichotomy between the fields of physical organic chemistry and biomedicinal chemistry in that interest in the former field centers on more and more precise definitions of electronic[7] and steric[8] constants in order to enable one to formulate sharper relationships in relatively well-defined homogeneous organic reactions. On the other hand, biomedicinal chemists need a great variety of substituent constants on a range and type of substituent far beyond the current interests of physical organic chemists. Moreover, the noise in the dependent variables with which the biomedicinal chemist is forced to work is so large that the quality of the substituent constants is not as critical as is the need for having the largest possible number of substituents parameterized. For this reason we have been collecting Hammett–Taft constants as well as hydrophobic constants[6] from whatever source available. Table I contains constants on a miscellaneous set of substituents with which we became involved in correlation analysis and is an extension of our earlier compilation.[6] All of the π constants were determined in our laboratory from the benzene solute system, i.e., by partitioning X-C_6H_5 between octanol and water. Some of the σ constants were determined in our laboratory; others, as indicated, have been taken from the literature.

Experimental Section

A number of the compounds used in determining π and σ have not been previously reported. Their preparation and properties are considered below. The purity of all compounds was checked by thin-layer chromatography as well as elemental analysis. The carbon–hydrogen analyses all agreed with the theoretical analyses within 0.4. The analyses were made by C. F. Geiger of Ontario, Calif.

The hydrazone derivatives of benzoic acid were all prepared by reaction of the appropriate hydrazine with 3- or 4-carboxybenzaldehyde.

3-Carboxybenzaldehyde carbazone was purified by precipitation from alkaline solution and extraction with hot absolute ethanol: mp 230–231 °C.

4-Carboxybenzaldehyde carbazone was purified as in the 3 isomer: mp 284 °C.

3-Carboxybenzaldehyde thiosemicarbazone was recrystallized from methanol: mp 284 °C.