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Synthesis and Biological Activity of Some 5-Substituted 2,4-Diamino-6-alkylpyrimidines. 3†

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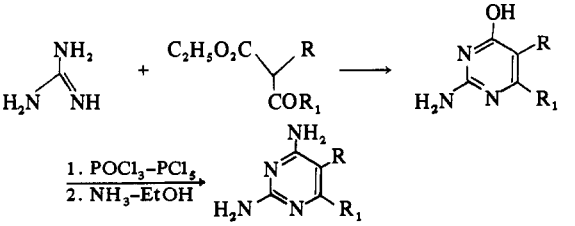
2,4-Diamino-6-methylpyrimidines having saturated straight-chain alkyl groups (C_3, C_5–C_8, C_{10}) in the 5 position were less potent growth inhibitors (ID_{50} 1.1 to 53 μM) of mouse mammary adenocarcinoma cells (TA3) *in vitro* than 2,4-diamino-5-(1-adamantyl)-6-methylpyrimidine (DAMP) (**15a**) (ID_{50} 6.0 nM). The ID_{50} values for another series of 2,4-diamino-6-methylpyrimidines having increasingly bulky 5 substituents decreased in the order 1-hexyl (**10a**) (2.5 μM), cyclohexyl (**14**) (0.40 μM), and 1-adamantyl (15a) (6.0 nM). The effects of two additional variables on the biological activity were investigated. 2,4-Diamino-5-(1-hexyl)-6-ethylpyrimidine (**16**) was 7 times more effective as an inhibitor than the corresponding 6-methyl analog (10a). The ethanesulfonic acid (ESA) salts of two diaminopyrimidines were 3 and 5 times more potent as growth inhibitors than the corresponding free bases. The best inhibitor of the entire study was 2,4-diamino-5-(1-adamantyl)-6-ethylpyrimidine ESA salt (**17**) with an ID_{50} of 0.25 nM which was about 30 times as active as methotrexate (ID_{50} 8.0 nM) when tested under the same conditions.

2,4-Diamino-5-(1-adamantyl)-6-methylpyrimidine[2] (DAMP) (**15a**) has been found to be a potent growth inhibitor of mouse mammary adenocarcinoma cells (TA3) *in vitro* and was subsequently shown to be a potent inhibitor of mammalian dihydrofolate reductase.[3]

It has been demonstrated by Baker, *et al.*,[4] that lipophilic substituents in position 5 of 2,4-diaminopyrimidines increase binding of these compounds to pigeon liver dihydrofolate reductase due to hydrophobic interactions. Since Nemethy and Scheraga[5] have shown that alkyl chains are coiled in aqueous systems, one would expect these groups to resemble the rigid adamantyl structure in such an environment. It was of interest, therefore, to prepare and test the biological activity of primidines with long alkyl chains at C-5.

Syntheses. The diaminopyrimidines were prepared by the standard route of condensation of guanidine with an appropriately substituted β-keto ester to form the 2-amino-4-hydroxy-5-substituted-6-alkylpyrimidines (Scheme I). The

Scheme I

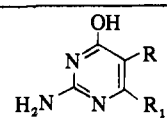


physical constants for the 4-hydroxypyrimidines are given in Table I.

Baker, *et al.*,[4a] have previously reported preparation of 2 and 4 (Table I) by the same method used here. Another group[6] had described preparation of these pyrimidines by direct condensation of equal molar quantities of guanidine

†Presented in part before the joint ASPET–DMC meeting, University of Vermont, Burlington, Aug 24, 1971.[1] The synthetic work was supported in part by Grant CA-02906 and biological testing by CA-11047 from the National Cancer Institute of the U. S. Public Health Service.

Table I. 2-Amino-4-hydroxypyrimidines[a]



No.	R	R_1	Formula	Mp,[b] °C	R_f[c]	Uv max, mμ[d]	% yield
1	c-C_6H_{11}	CH_3	$C_{11}H_{17}N_3O$	315-317[e]		230, 292	39
2	C_6H_{13}	CH_3	$C_{11}H_{19}N_3O$	250-253[f]	0.74	230, 278[g]	22
3	C_7H_{15}	CH_3	$C_{12}H_{21}N_3O$	238-241		232, 279[g]	42
4	C_8H_{17}	CH_3	$C_{13}H_{23}N_3O$	221-224[h]	0.74	232, 277.5[g]	46
5	$C_{10}H_{21}$	CH_3	$C_{15}H_{27}N_3O$	195-196	0.61	228, 290	60
6	C_6H_{13}	C_2H_5	$C_{12}H_{21}N_3O$	184-188	0.70	227, 292	30
7	$C_{10}H_{15}$[i]	C_2H_5	$C_{16}H_{23}N_3O$	315-316	0.62	227, 292	41

[a]All compounds were prepared by procedure A of the Experimental Section and were analyzed for C, H, and N; all analyses were within ±0.4%. Spectral data were consistent with assigned structures. [b]Recrystd from 95% EtOH unless otherwise stated. [c]Silica gel on aluminum with MeOH as eluent. [d]In abs EtOH unless stated otherwise. [e]Recrystd EtOH-H_2O (1:1). [f]Ref 4a, mp 253-255°; ref 6, mp 214-217°. [g]0.5 *N* NaOH. [h]Ref 4a, mp 222-223°; ref 6, mp 178-180°. [i]1-Adamantyl.

pionylacetate in the presence of BF_3.

Ethanesulfonic acid (ESA) salts of several of the diaminopyrimidines have been prepared according to procedures described in the Experimental Section in order to improve the solubilities of these compounds and to study the effect of this conversion on the biological activity.

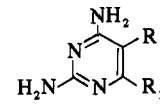
Biological Data. The diaminopyrimidines were tested as growth inhibitors of mouse mammary adenocarcinoma cells (TA3) *in vitro* using the procedure described earlier.[2] The results are summarized in the last column of Table II.

Discussion

From examination of the data presented in Table II, it can be seen that DAMP (**15a**) is at least 100 times more effective a growth inhibitor of the TA3 cells than the 2,4-diamino-6-methylpyrimidines having the saturated 5-alkyl substituents C_3 (**8**), C_5 (**9**), C_6 (**10a**), C_7 (**11**), C_8 (**12a**), and C_{10} (**13**).

The cyclohexyl moiety of pyrimidine **14** represents a structure which is intermediate between the saturated

Table II. Physical Properties of 2,4-Diaminopyrimidines Used as Growth Inhibitors of TA3 Cells *in Vitro*



No.	Experimental procedure	R	R_1	Formula[a]	Mp, °C	Recrystn solvent[b]	R_f[c]	Uv max, mμ[d]	% yield[e]	ID_{50},[f] μM
8	B	C_3H_7	CH_3	$C_8H_{14}N_4$[g]	195-197	AB		234, 287.5	61	53
9	B	C_5H_{11}	CH_3	$C_{10}H_{18}N_4$[h]	143-144		0.50	233, 287.5	79	3.0
10a		C_6H_{13}	CH_3	$C_{11}H_{20}N_4$[i]	123-125	None	0.30	233, 288	13	2.5
10b	C	C_6H_{13}	CH_3	$C_{13}H_{26}O_3N_4S$[j]	200-202	None		283	26	0.90
11	B	C_7H_{15}	CH_3	$C_{12}H_{22}N_4$	113-115	EtOH	0.45	233, 287.5	19	1.6
12a	B	C_8H_{17}	CH_3	$C_{13}H_{24}N_4$	119-122	N	0.50	233, 287.5	22	2.3
12b	D	C_8H_{17}	CH_3	$C_{15}H_{30}O_3N_4S$[j]	218-220	None		277	20	1.9
13	B	$C_{10}H_{21}$	CH_3	$C_{15}H_{28}N_4$	136-138	N	0.39	232, 286	20	1.1
14	B	c-C_6H_{11}	CH_3	$C_{11}H_{18}N_4$	258-262	EtOH		230, 293	42	0.40
15a[k]		$C_{10}H_{15}$[l]	CH_3	$C_{15}H_{22}N_4$	274-275	EtOH	0.40	228, 291	18	0.006
15b	D	$C_{10}H_{15}$[l]	CH_3	$C_{17}H_{28}O_3N_4S$[j]	240-241	*i*-PrOH		282	18	0.0011
16	B	C_6H_{13}	C_2H_5	$C_{12}H_{22}N_4$	146-148	AB	0.40	230, 287	40	0.34
17	C	$C_{10}H_{15}$[l]	C_2H_5	$C_{18}H_{30}O_3N_4S$[j]	213-215	PrOH		284	8	0.00025
18		Methotrexate								0.008

[a]Compounds were analyzed for C, H, and N except 10b and 12b which were analyzed for C and H; all ethane sulfonic acid salts were also analyzed for S. All analyses were within ±0.4% of the calculated values. Ir spectra were consistent for the assigned structures. [b]AB, dissolved in HAc-H_2O (1:1) and precipitated by addition of 0.1 *N* NaOH; N, dissolved in EtOH, precipitated by addition of 0.1 *N* NaOH. [c]Silica gel on aluminum eluted with MeOH. [d]Abs EtOH. [e]From crude 4-Cl·HCl. [f]Footnote ‡. [g]Used in previous screening studies (see ref 7) but preparation and physical properties not reported. [h]B. R. Baker, *et al.*[4a] [i]Free base isolated, analyzed, and used for biological testing after neutralization of the ESA salt by concd NH_4OH. [j]Ethane sulfonic acid salt. [k]Ref 2. [l]1-Adamantyl.

carbonate and ethyl alkylacetoacetate, neat, heated to 140-160° in an oil bath for 17 hr. However, no yields or spectral data were given and melting points of 214-217° and 178-180° were observed for **2** and **4**, respectively. In contrast, Baker, *et al.*,[4a] report melting points of 253-255° for **2** and 222-223° for **4**. Our melting points are in agreement with those of Baker, *et al.*

The 4-hydroxypyrimidines were converted to the crude 4-chloropyrimidines by $POCl_3$-PCl_5 and aminated without further purification with NH_3 in EtOH to form the corresponding diaminopyrimidines. Preparation of the crude chloropyrimidines is described in the Experimental Section as well as the synthesis of the diaminopyrimidines. Pertinent data for the diaminopyrimidines are summarized in Table II.

The β-keto esters needed for synthesis of the pyrimidines with straight hydrocarbon chains were prepared by condensation of ethyl acetoacetate with the appropriate alkyl halide. Ethyl α-(1-adamantyl)-β-oxovalerate (**19**) was prepared by condensation of 1-adamantanol with ethyl propionylacetate in the presence of BF_3.

Ethanesulfonic acid (ESA) salts of several of the diaminopyrimidines have been prepared according to procedures described in the Experimental Section in order to improve the solubilities of these compounds and to study the effect of this conversion on the biological activity.

Biological Data. The diaminopyrimidines were tested as growth inhibitors of mouse mammary adenocarcinoma cells (TA3) *in vitro* using the procedure described earlier.[2] The results are summarized in the last column of Table II.

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From examination of the data presented in Table II, it can be seen that DAMP (**15a**) is at least 100 times more effective a growth inhibitor of the TA3 cells than the 2,4-diamino-6-methylpyrimidines having the saturated 5-alkyl substituents C_3 (**8**), C_5 (**9**), C_6 (**10a**), C_7 (**11**), C_8 (**12a**), and C_{10} (**13**).

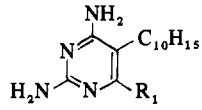
The cyclohexyl moiety of pyrimidine **14** represents a structure which is intermediate between the saturated straight-chain hydrocarbon and the symmetrical three-ring adamantane substituent. The ID_{50}‡ values of the 2,4-diamino-6-methylpyrimidines with 1-hexyl (**10a**), cyclohexyl (**14**), and 1-adamantyl (**15a**) in the 5 position reflect this relationship by decreasing in the same order: 2.5, 0.40, 0.006 μ*M*, respectively.

To study the effects of alteration of the 6 substituent, an ethyl group was introduced into the diaminopyrimidine system in place of the methyl. It was found that 2,4-diamino-5-(1-hexyl)-6-ethylpyrimidine (**16**) displayed 7 times the biological activity of the analogous 6-methylpyrimidine (**10a**).

All of the pyrimidines were quite difficult to dissolve under conditions necessary for biological testing. The solubility was increased by conversion of some of these compounds (**10a**, **12a**, **15a**) to their ESA salts (**10b**, **12b**, **15b**). The hexyl ESA salt (**10b**) appeared to be 3 times more ac-

‡ID_{50} is defined as the concentration of material required to inhibit growth of the cells by 50%.

Table III. Effect of 6 Substituent and ESA Salt Formation on the Growth Inhibitory Potency of 2,4-Diamino-5-(1-adamantyl)pyrimidines on TA3 Cells *in Vitro*



	ID_{50}, n*M*	
R_1	Free base	Ethanesulfonic acid salt
H[a]	330	
CH_3[a]	6.0	1.1
C_2H_5		0.25
Methotrexate	8.0	

[a] Ref 2.

tive than the free base (**10a**), the adamantyl ESA salt (**15b**) 5 times more active than its free base (**15a**), while the octyl ESA salt (**12b**) was about as active as the free base (**12a**). The increases in the inhibitory potency of the ESA salts, as compared with the free bases, are most likely due to the poor solubility of the free bases. Thus, the actual amount of the free bases in solution are probably less than the total amount in the medium resulting in overly high ID_{50} values for the bases.

Since the activity of the hexylpyrimidine (**10a**) was improved by conversion to the ESA salt and by substitution of 6-ethyl for 6-methyl, 2,4-diamino-5-(1-adamantyl)-6-ethylpyrimidine (DAEP) ESA salt (**17**) was prepared and tested. The data in Table III summarize the effects of the 6 substituent and ESA salt formation on the biological activity of the adamantylpyrimidines. It can be seen that the 6 substituent effects the activity in the order $C_2H_5 > CH_3 \gg H$. DAEP ESA salt (**17**) (ID_{50} 0.25 n*M*) was 4 times more active than the DAMP analog (**15b**) and 30 times more active than methotrexate (**18**) (ID_{50} 8.0 n*M*) in inhibiting the growth of the TA3 cells in culture. This pyrimidine has subsequently been found to be a stochiometric inhibitor of dihydrofolate reductase from S-180 cells.§

Several of the compounds reported here are currently undergoing animal testing in our facilities; results will be presented in a separate paper. Further investigations are in progress to evaluate the effects of other substituents and also elucidate the mode of action of these compounds.

Experimental Section

All tlc work was performed on Brinkman F-254 silica gel plates on aluminum. All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Uv spectra were recorded on a Cary 14 spectrophotometer. Elemental analyses were detd by G. I. Robertson, Jr., Florham Park, N. J. No attempts were made to optimize the yields of the reactions below. The column used for vpc was 4 ft, 15% SGR on Chromosorb W treated with HMDS. Prepn and use of the mouse mammary adenocarcinoma cells (TA3) for *in vitro* testing has been described in detail in paper 2[2] of this series.

Ethyl α-(1-adamantyl)-β-oxovalerate (**19**) was prepd following the procedure described elsewhere[8] for the prepn of ethyl aceto(1-adamantyl)acetate by passing BF_3 over the mixt of 1-adamantanol (5.0 g, 32.9 mmoles) and ethyl propionylacetate (5.0 g, 34.7 mmoles) in 100 ml of pentane. Work-up gave 3.5 g of 90% pure material (vpc) (34%) which was used without further purification to prep 2-amino-4-hydroxy-5-(1-adamantyl)-6-ethylpyrimidine. The analytical sample was trapped from vpc. Ir spectra are very similar to ethyl aceto(1-adamantyl)acetate. *Anal.* ($C_{17}H_{26}O_3$) C, H.

(Procedure A) 2-Amino-4-hydroxy-5-(1-octyl)-6-methylpyrimidine (5). Ethyl aceto(1-octyl)acetate was prepd by the usual method of alkylation of the Na salt of ethyl acetoacetate (generated *in situ*) with 1-octyl iodide in abs EtOH. Et_2O extn of an aqueous mixt of the product of the reaction gave, upon evapn >80% pure material (vpc) which was used without further purification in the next step.

A soln of NaOEt (4.18 g of Na, 0.18 g-atom in 170 ml of abs EtOH) was cooled in an ice bath and guanidine·HCl (8.65 g, 91 mmoles) was added. After stirring for 10 min, ethyl aceto(1-octyl)-acetate (22 g, 91 mmoles) was added and the reaction mixt refluxed for 3 hr. The vol was then reduced under vacuum to 80 ml, and the reaction mixt was poured with stirring into 11. of H_2O. After neutralization with aqueous HCl to pH 6.5, the solid product was collected, washed with H_2O, Me_2CO, and Et_2O and recrystd from 95% EtOH to give 10.0 g, mp 221–224°. See data in Table I.

General Preparation of 4-Chloropyrimidine·HCl (Reaction Conditions and Initial Work-Up). The 4-hydroxypyrimidine was mixed with $POCl_3$ and PCl_5 (1:5:1) and refluxed 1 hr past the time that soln occurred. After cooling, the reaction mixt was slowly poured onto ice (300 parts) with vigorous stirring to give an oil which gradually solidified on standing. Analytical data were not obtained for any of the crude chloro compds listed here. Identification is based on the successful conversion to the diamino compd, and evidence presented in paper 2[2] of this series. The work-up is completed for each compd following the procedures listed below.

2-Amino-4-chloro-5-(1-propyl)-6-methylpyrimidine·HCl (20). The solid from initial work-up was collected, washed with H_2O, and dried in a desiccator, 5.0 g of the 4-hydroxypyrimidine gave 950 mg of product (14%).

2-Amino-4-chloro-5-(1-pentyl)-6-methylpyrimidine·HCl (21). The gummy solid from initial work-up was extd from the aqueous mixt with Et_2O. The Et_2O exts were washed, in turn, with H_2O and dried ($MgSO_4$). After filtration, the Et_2O soln was reduced in vol and the desired product was pptd by addtn of petr ether, 1.29 g of product, mp 135–140°, from 2.0 g of the 4-hydroxypyrimidine (50%).

2-Amino-4-chloro-5-(1-hexyl)-6-methylpyrimidine·HCl (22). The aqueous mixt from the initial work-up was extd with $CHCl_3$–Et_2O (1:1). A white solid was collected from the organic phase, 1.45 g of product from 2.0 g of starting material (58%).

2-Amino-4-chloro-5-(1-cyclohexyl)-6-methylpyrimidine·HCl (23). This compd was prepd following the procedure for **20**, 1.75 g, mp 220–230° from 1.35 g of starting material (100%).

4-Amino-4-chloro-5-(1-heptyl)-6-methylpyrimidine·HCl (24). The aqueous mixt from the initial work-up was extd with Et_2O–$CHCl_3$ (1:1), upon drying ($MgSO_4$) and evapn of the solvent, a quantitative yield of product was obtained.

2-Amino-4-chloro-5-(1-octyl)-6-methylpyrimidine (25). The aqueous mixt from the initial work-up was extd with Et_2O. The Et_2O layer was washed with satd $NaHCO_3$ and with H_2O. The white product was collected (1.1 g, 50% from 2.0 g of 4-hydroxypyrimidine).

2-Amino-4-chloro-5-(1-decyl)-6-methylpyrimidine·HCl (26). The aqueous mixt from initial work-up was extd with Et_2O, washed with H_2O, and dried ($MgSO_4$). Evapn of the ether gave a gummy solid which was used without further purification, 0.5 g of 4-hydroxypyrimidine gave 0.56 g of product (93%).

2-Amino-4-chloro-5-(1-hexyl)-6-ethylpyrimidine·HCl (27). The aqueous mixt was extd with Et_2O and the Et_2O layer was washed with H_2O and dried ($MgSO_4$). The Et_2O was evapd to the satn point and cooled to below 0°; the resulting solid was collected and washed with cold Et_2O: 2.35 g from 5.0 g of 4-hydroxypyrimidine (38%).

(Procedure B) 2,4-Diamino-5-(1-adamantyl)-6-ethylpyrimidine (12a). The 4-chloropyrimidine·HCl (2.0 g, 6.85 mmoles) (**25**) was mixed with abs EtOH and satd with NH_3 at 0°. The reaction mixt was heated in a bomb at 170° for 24 hr and then cooled. After evapn of the solvent, the residue was dissolved in aqueous AcOH (1:1), treated with charcoal, and filtered. The pH was adjusted to 12 by slow addn of 10 *N* NaOH; the solid (410 mg) which formed was collected and dissolved in EtOH. The product was pptd by addn of of 0.1 *N* NaOH, mp 119–122°.

(Procedure C) 2,4-Diamino-5-(1-adamantyl)-6-ethylpyrimidine ESA Salt (17). 2-Amino-4-chloro-5-(1-adamantyl)-6-ethylpyrimidine·HCl was prepd in the usual manner from the 4-hydroxypyrimidine and $POCl_3$–PCl_5. The reaction mixt was poured onto ice, and the solid 4-chloropyrimidine collected by filtration (1.22 g, 3.73 mmoles) and heated at 150° for 6 hr in a bomb contg 40 ml of EtOH satd with NH_3 at 0°. The bomb was allowed to cool and stand for 12 hr at room temp before opening. The solvent was evapd, and the residue dissolved in abs EtOH, treated with charcoal, and filtered. The filtrate was added to Et_2O, the resulting solid collected (0.71 g), then stirred for 1 hr in 3 *N* NaOH, again collected, and washed with H_2O until washings were neutral (0.33 g). The solid was redissolved in abs EtOH (15 ml) and mixed with $C_2H_5SO_3H$

§Personal communication, Dr. Y. K. Ho of this department.

(0.133 g, 10 mmoles). The soln was allowed to stand 12 hr and then poured into Et_2O. The solid was collected and washed with Et_2O (230 mg, mp 188–193°), recrystd from *n*-PrOH, mp 213–215° (80 mg); uv (abs EtOH) max 214, 284, min 263 mμ.

(Procedure D) 2,4-Diamino-5-(1-adamantyl)-6-methylpyrimidine ESA Salt (15b). DAMP (15a) (320 mg, 1.23 mmoles) was dissolved in abs EtOH (110 ml), $C_2H_5SO_3H$ (0.137 g, 1.24 mmoles) was added to this soln, the reaction mixt stirred at room temp for 0.5 hr, and the vol reduced to about 20 ml under vacuum, poured into Et_2O, and refrigerated for 4 hr. After collection and washing with Et_2O, the solid product (360 mg) was recrystd, PrOH (28 ml).

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Analogs of Phenothiazines. 4. Effect of Structure upon Neuropharmacological Activity of Some Chlorpromazine Analogs of the Diphenylmethane Type

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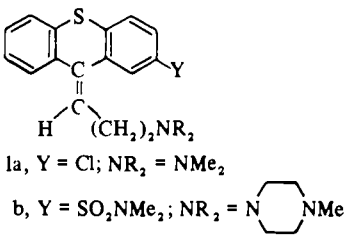
The synthesis of a series of chlorpromazine analogs of the diphenylmethane type, *i.e.*, aminoalkyl and aminoalkylidene derivatives of diphenylmethane, xanthene, thioxanthene, and dibenzocycloheptane, is described. These compounds, prepared as analogs of the tricyclic psychotropic agents, were investigated in several pharmacological tests for psychotropic activity. One of the geometric isomers (presumably, the cis isomer) of *N,N*-dimethyl-2-trifluoromethylthioxanthen-$\Delta^{9,\gamma}$-propylamine (**25**) and the related xanthene **38** were more potent than chlorpromazine in several animal tests in which many neuroleptic agents are active. Aminoalkyl derivatives **58** and **65**, the side-chain-reduced congeners of these olefins, were nearly equipotent with chlorpromazine in various pharmacological tests for neuroleptic activity. Some of the intermediate carbinols (V), congeners of the antiemetic agent, diphenidol, were examined for their ability to inhibit apomorphine-induced emesis in dogs. Two of these compounds, *p*-Cl (**14**) and *p*-CF_3 (**19**) congeners of diphenidol, were more potent than the parent. Structure-activity relationships of these series of compounds are discussed.

Of the many tricyclic analogs of the antipsychotic (neuroleptic) phenothiazines studied since the discovery of chlorpromazine [1-4] the thioxanthene derivative chlorprothixene (Ia) was the first reported to have potent chlorpromazine-like activity.[5] Research in several laboratories has produced other thioxanthenes of type I which are clinically effective neuroleptic agents. Two drugs of this class, Ia and thiothixene (Ib),[6,7] are currently marketed in the United States.

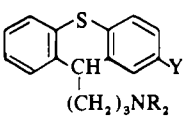
Although structure-activity studies suggest that the pharmacological activity of thioxanthenes and phenothiazines generally varies with structure in a similar way, the published data,[5,8-11] many of which have been obtained only in mice by procedures which do not reliably predict neuroleptic potency,[12,13] are difficult to interpret. Less information is available on the activity of the saturated thioxanthenes II which apparently have not been studied as much as the type I compounds. It was concluded from an early study of a few saturated derivatives in our laboratories and elsewhere[8] that they were considerably less potent than the unsaturated thioxanthenes. Even scantier data on the pharmacological activity of xanthene,[14,15] dibenzocycloheptene,[16-18] dihydroanthracene analogs of I and II, and of the "ring-opened" analogs, the diphenylmethane[14,19,20] derivatives, III and IV, have been published.

As part of an extensive study of structure-activity relationships in the phenothiazine series[21] we have investigated many diphenylamine and diphenylmethane derivatives, in-



Ia, Y = Cl; NR_2 = NMe_2

b, Y = SO_2NMe_2; NR_2 = N NMe



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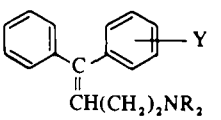

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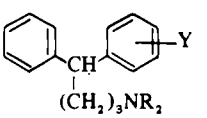

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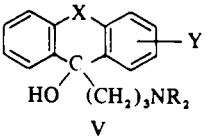
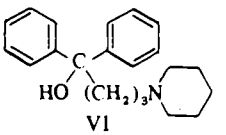
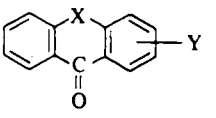


V

X = S, O, ——

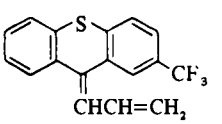


VI



VII

X = S, O, ----



VIII