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Analogs of Phenothiazines. 3. Synthesis and Potential Antidepressant Activity of Some Phenothiazine Derivatives and Related Compounds Containing a Carbocyclic Basic Side Chain

CARL KAISER,* DAVID H. TEDESCHI, PHILIP J. FOWLER, ALEX M. PAVLOFF, BRUCE M. LESTER, AND CHARLES L. ZIRKLE

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania

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trans-2-(2-Chloro-10-phenothiazinyl)-*N*,*N*-dimethylcyclopropanemethylamine (**1**), a side chain modified analog of chlorpromazine, was prepared and found to have potent antidepressant activity in animals. Synthesis and pharmacological study of 34 analogs and derivatives of **1** are reported. Formation of rearranged products upon alkylation of several diphenylmethane derivatives with 2-bromo-*N*,*N*-dimethylcyclopropanecarboxamide and upon alkylation of phenothiazine with *trans*-2-dimethylaminomethylcyclohexyl tosylate is discussed.

As part of an investigation of the effect of alteration of chemical structure upon the neuropharmacological activity[1,2] of compounds related to chlorpromazine we prepared and studied a number of phenothiazine derivatives and related compounds containing a carbocyclic basic side chain. In animals, several of these side chain modified analogs of chlorpromazine produced potent pharmacological actions characteristic of the 6,7,6-tricyclic antidepressant agents. In the present paper we describe the synthesis of these compounds and some of their pharmacological properties.

Synthesis.—To prepare a series of phenothiazines and related compounds bearing a 2-aminomethylcyclopropyl substituent, as illustrated in Chart I, a phenothiazine or related tricyclic compound (ArH) was alkylated with ethyl 2-bromocyclopropanecarboxylate (method A) or the corresponding dimethylcarboxamide (method B). The bromo ester was prepared most conveniently from ethyl hydrogen 1,2-cyclopropanedicarboxylate[3] by a modified Hunsdiecker reaction;[4] it was readily converted into a dimethylcarboxamide. Both cis and trans bromo esters and amides, as well as mixtures of isomers, gave only one isomer of the alkylation products. The resulting 2-substituted cyclopropanecarboxylic esters and amides probably have a trans configuration,[5] as similar halogen displacement by *tert*-BuO^- proceeds through a cyclopropene to give the *trans*-*tert*-butoxy ester.[3,5] Furthermore, hydrolysis of an isomeric mixture of ethyl 2-(2-chloro-10-phenothiazinyl)-cyclopropanecarboxylates obtained from 2-chloro-10-vinylphenothiazine and ethyl diazoacetate (method C), a reaction in which the thermodynamically more stable trans isomer usually predominates,[6] gave mainly an acid identical with that obtained by method A.

As illustrated in Chart I cyclopropanecarboxylic acids obtained by methods A and C were converted into amides *via* mixed carboxylic–carbonic anhydrides. The amides were also obtained, usually in higher yields, by alkylation of ArH with 2-bromo-*N*,*N*-dimethylcyclopropanecarboxamide (method B). Reduction of the amides with LAH gave 2-substituted aminomethylcyclopropanes (Table I).

Some exceptions to the general utility of methods A and B were encountered in the reactions of certain analogs of phenothiazine. Although 5*H*-dibenz[*b*,*f*]-azepine was readily alkylated by the bromo ester, the resulting ester could not be used for the synthesis of **11** because loss of the 5-cyclopropyl substituent occurred upon alkaline hydrolysis. However, **11** was readily obtained by method B. Neither method A nor method B could be used to prepare **12**, the dihydro derivative of **11**, because all attempts to alkylate 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine failed. This compound was finally prepared by catalytic hydrogenation of **11**.

(1) M. P. Olmsted, P. N. Craig, J. J. Lafferty, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, **26**, 1901 (1961), paper 2 in this series.

(2) M. Gordon, P. N. Craig, and C. L. Zrikle, *Advan. Chem. Ser.*, **45**, 140 (1964).

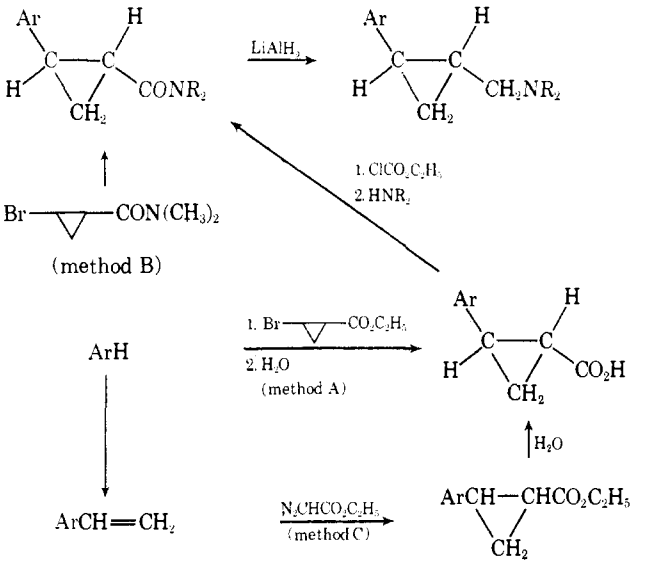
(3) K. Wiberg, R. K. Barnes, and J. Albin, *J. Amer. Chem. Soc.*, **79**, 4994 (1957).

(4) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

(5) This configurational assignment is further supported by the stereochemistry of the reaction of Na phenoxide and ethyl 2-bromocyclopropanecarboxylate, under the same conditions, Experimental Section, General Procedure a. Alkaline hydrolysis of the resulting ester gave *trans*-2-phenoxycyclopropanecarboxylic acid, mp 115–117°, in an overall yield of 65%. Ir spectra of this acid and the trans acid prepared according to literature directions [J. H. Looker and L. L. Braun, *J. Org. Chem.*, **23**, 930 (1958); J. Finkelstein, E. Chiang, and J. Lee, *J. Med. Chem.*, **8**, 432 (1965)] were identical and a mmp was not depressed.

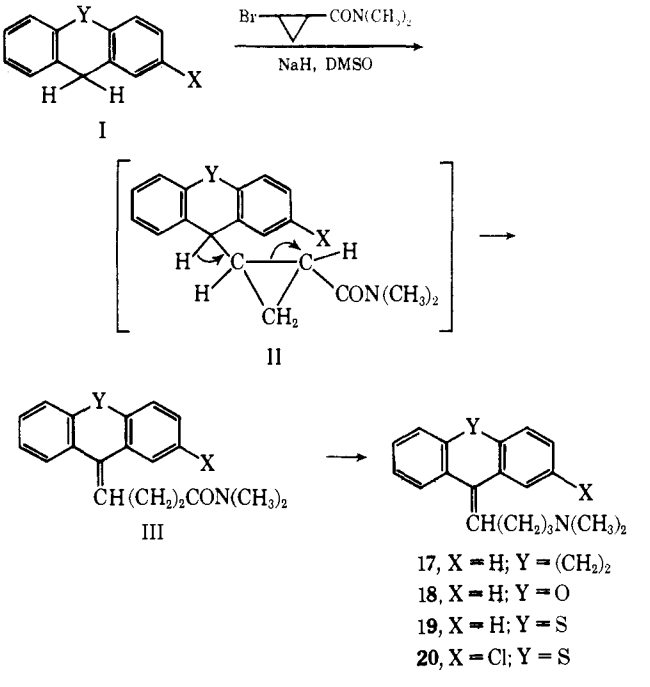
(6) For example, see (a) J. Farkăs, P. Kouřím, and F. Šorm, *Collect. Czech. Chem. Commun.*, **24**, 2460 (1959); (b) P. S. Skell and R. M. Etter, *Proc. Chem. Soc. London*, 443 (1961).

CHART I

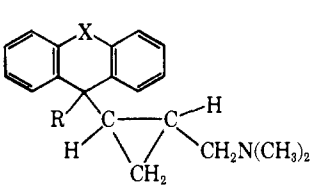


In an attempt to prepare similar cyclopropane derivatives of xanthene, thioxanthene, and dibenzo[*a*,*d*]-cycloheptane we studied the alkylation of these tricyclic compounds (I) with 2-bromo-*N*,*N*-dimethylcyclopropanecarboxamide using conditions identical with those used for N-alkylation of phenothiazines and related structures. In this case, alkylation was accompanied by opening of the cyclopropane ring. The products resulting after LAH reduction, as indicated in Chart II, were the 4-dimethylaminobutylidene derivatives **17–20**.

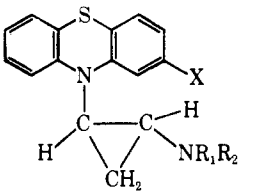
CHART II



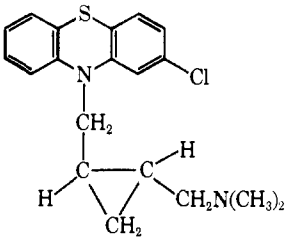
That this ring opening may involve abstraction of the benzylic proton from an intermediate cyclopropanecarboxamide (II) by the Na derivative of I followed by rearrangement of the resulting anion to III is suggested by the formation of a cyclopropane derivative **21**, and no ring-opened product, from a similar reaction of 9-methylthioxanthene which gives a cycloalkyl intermediate lacking a benzylic proton. Also, alkylation of dibenzo[*a*,*d*]cycloheptane [I, X = H; Y = $(CH_2)_2$] at a lower reaction temperature gave almost exclusively a cyclopropanecarboxamide which was converted into **22** upon reduction with LAH.



21, X = S; R = CH_3
22, X = $(CH_2)_2$; R = H



23, X = Cl; $R_1 = R_2 = CH_3$
24, X = Cl; $R_1 = R_2 = C_2H_5$
25, X = CF_3; R_1 = H; $R_2 = C_2H_5$



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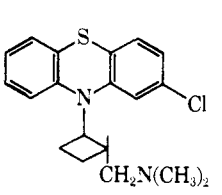
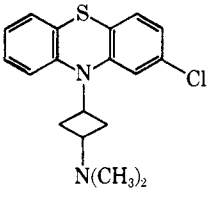
Lower homologs (**23–25**) of phenothiazines **1** and **3** were obtained from corresponding 2-(10-phenothiazinyl)cyclopropanecarboxylic acids by way of a modified Curtius reaction[7] and subsequent acylation, alkylation, and reduction, as described in the Experimental Section. A higher homolog (**26**) was prepared by alkylation of 2-chlorophenothiazine with *trans*-2-dimethylaminomethylcyclopropylmethyl tosylate.



27



28

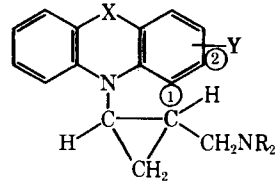
To prepare a 2-substituted cyclobutane derivative (**27**), 2-chlorophenothiazine was alkylated with either ethyl 1- or 2-bromocyclobutanecarboxylate (see ref 8 and 9, respectively) (apparently *via* a common ethyl 1-cyclobutenecarboxylate intermediate) to give the same, presumably trans, 2-substituted cyclobutanecarboxylic ester. Conversion of the ester into **27** was accomplished *via* the acid and dimethylamide. A 3-substituted congener (**28**) resulted upon alkylation of 2-chlorophenothiazine with a tosylate prepared from an isomeric mixture of 3-dimethylaminocyclobutanols.[10] Only one isomer was isolated from the resulting mixture; however, its stereochemistry was not established.

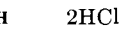
Preparation of several 2-(10-phenothiazinyl)cyclohexane derivatives related to **1** and **2** was undertaken according to patent[11] directions. Accordingly, phe-

(7) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).
(8) A. Campbell and H. N. Rydon, *J. Chem. Soc.*, 3002 (1953).
(9) R. Gelin, S. Gelin, and C. Boutin, *C. R. Acad. Sci.*, **260**, 6393 (1965).
(10) C. Beard and A. Burger, *Chem. Ber.*, **95**, 2535 (1962); M. Avram, C. D. Nenitzescu, and M. Maxim, *ibid.*, **90**, 1424 (1957).
(11) Nippon Shinyaku Co., Japanese Patent 5782 (1960); *Chem. Abstr.*, **55**, 6504 (1961).

TABLE I

trans-2-SUBSTITUTED AMINOMETHYLCYCLOPROPANES



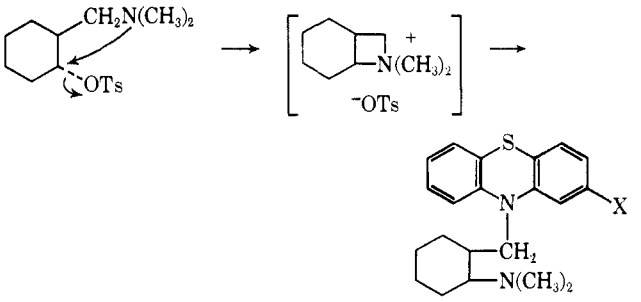
	X	Y	NR_2	Salt	Mp, °C	Recrystn solvent	Method[a]	Yield,[b] %	Formula[c]	Prevention of reserpine-induced ptosis[d] — Rats: Dose, mg/kg, po	Rats: Response, %	Mice: Dose, mg/kg, po	Mice: Response, %
1	S	2-Cl	NMe_2	HCl	238–239.5	$CHCl_3$–Et_2O	A, B[e]	28, 58	$C_{18}H_{20}Cl_2N_2S$	ED_{50} 7.6 (4.6–12.5)		ED_{50} 4.9 (3.1–7.6)	
2	S	H	NMe_2	HCl	233–234	EtOH–Et_2O	A	35	$C_{18}H_{21}ClN_2S$	ED_{50} 10.8 (5.5–21.1)		ED_{50} 6.8 (4.4–10.4)	
3	S	2-CF_3	NMe_2	HCl	254–255	EtOH–Et_2O	A	36	$C_{19}H_{20}ClF_3N_2S$	6.3	50	5	55
4	S	2-SCH_3	NMe_2	Maleate	197–199	H_2O	B	89	$C_{23}H_{26}N_2O_4S_2$	ED_{50} 8.4 (5.6–12.6)		ED_{50} 5.0 (2.9–8.6)	
5	S	1-Cl	NMe_2	HCl	227.5–229	EtOH–Et_2O	A	35	$C_{18}H_{20}Cl_2N_2S$	5	40	5	37
6	S	1-Cl	NHMe	HCl	253–254	EtOH–Et_2O	A	26	$C_{17}H_{18}Cl_2N_2S$	5	50		
7	S	2-Cl	NHMe	HCl	238–240	EtOH–Et_2O	A	24	$C_{17}H_{18}Cl_2N_2S$	5	67	5	80
8	S	2-Cl	NH_2	HCl	267–268	MeOH–Et_2O	A	30	$C_{16}H_{16}Cl_2N_2S$[f]	5	80	5	22
9	S	2-CF_3		2HCl	250–252 dec	MeOH–Et_2O	A	40	$C_{23}H_{28}F_3Cl_2N_3OS$	20	33	20	27
10	CH_2	H	NMe_2	HCl	230 dec	*i*-PrOH	B	66	$C_{19}H_{23}ClN_2$[i]	25	67	60	0
11	CH=CH	H	NMe_2	Maleate	200–201	EtOH	B	55	$C_{24}H_{26}N_2O_4$	ED_{50} 7.4 (4.5–12.1)			
12	$(CH_2)_2$	H	NMe_2	Maleate	149–151	EtOAc	*g*	64	$C_{24}H_{28}N_2O_4$	25	67		
13		H	NMe_2	HCl	204–205	EtOH–Et_2O	B	54	$C_{18}H_{23}ClN_2$	*h*			
14	O	H	NMe_2	HCl	256–258	EtOH–Et_2O	B	49	$C_{18}H_{21}ClN_2O$	100	50[h]		
15	O	2-Cl	NMe_2	HCl	235–237	EtOH–Et_2O	B	74	$C_{18}H_{20}Cl_2N_2O_3$[i]	ED_{50} ~33.0		25	67
16	S(O)	2-Cl	NMe_2	HCl	268.5–270 dec	EtOH–Et_2O	*k*	56	$C_{18}H_{20}Cl_2N_2OS$	5	40		
Imipramine hydrochloride										ED_{50} 8.6 (4.3–17.2)		ED_{50} 10.5 (6.2–17.8)	
Amitriptyline maleate										ED_{50} ~39.5		ED_{50} 15.5 (9.8–24.5)	

[a] Method A: prepd by alkylation of phenothiazine or related compounds with ethyl 2-bromocyclopropanecarboxylate followed by conversion into amine as described in the Experimental Section, procedures a, b, c, and d; method B: prepd by alkylation of phenothiazine or related compounds with 2-bromo-*N*,*N*-dimethylcyclopropanecarboxamide followed by LAH reduction, see Experimental Section, procedures a and d. [b] Overall yield from phenothiazine or related tricyclic compounds to salt of aminoalkylated derivatives. [c] All compounds were analyzed for C, H, N, and analytical values were within ±0.4% of calculated values unless noted otherwise. [d] See Pharmacology, Methods and Results. [e] Also prepd by method C, see Experimental Section. [f] *Anal.* ($C_{16}H_{16}Cl_2N_2S \cdot 0.75H_2O$): H_2O, 3.83. Found: H_2O, 3.74, 3.86. [g] Prepd by catalytic hydrogenation of 11, see Experimental Section. [h] At a dose of 200 mg/kg, po, in rats **13** produced decreased motor activity, hypotonia, mydriasis, piloerection, exophthalmia, bizarre behavior, and decreased body weight. [i] At a dose of 50 mg/kg, po in rats, **14** produced slight exophthalmia, hypothermia, anlagesia, and high body posture. [j] C, H anal. only. [k] Prepared by H_2O_2 oxidation of 1, see Experimental Section.

nothiazine and 2-chlorophenothiazine were treated with tosylates prepared from *cis*- and *trans*-2-dimethylaminomethylcyclohexanols.[12] Apparently, elimination[13] of tosylate occurred during attempted alkylation with the cis isomer which is stereochemically unsuited for formation of an azetidinium[13] intermediate. Phenothiazine was recovered and dimethylaminomethylcyclohexene was isolated. The *trans*-tosylate,[14] however, reacted readily with phenothiazine to give a rearranged product (**29**).

This rearrangement probably involves reaction of phenothiazine anion with the less substituted C atom of an azetidinium[13] intermediate as outlined in Chart III (perhaps in a concerted process). Rearrangements

CHART III



29, X = H; **30**, X = Cl

accompany similar alkylation with substituted β- and δ-haloalkylamines (see ref 15 and 16, respectively). This reaction course is also suggested by the cis geometry of the product which was established by the identity of **30**, obtained by this procedure, and a sample obtained by alkylation of 2-chlorophenothiazine with *cis*-2-chloromethylcyclohexyldimethylamine (IVa). The trans isomer (**31**) related to **30** was prepared similarly from the corresponding *trans*-haloamine (IVb).

For synthesis of IVa and IVb an AcOH solution of methyl *N*-methylanthranilate was hydrogenated in the presence of Pt to give mainly one of the two possible isomers of the saturated amino ester. When this ester was treated with base, epimerization occurred to yield an equilibrium mixture in which the isomeric ester predominated. The principal hydrogenation product is therefore assigned the cis (equatorial–axial) configuration to be anticipated from cis addition of H_2[17] and the equilibration product is assigned the thermodynamically more stable trans (equatorial–equatorial) configuration. Methyl *cis*- and *trans*-2-methylaminocyclohexanecarboxylates, thus obtained, were converted into IVa and IVb by treating the isomeric tertiary aminocarbinols resulting from LAH reduction of intermediate ethyl carbamate derivatives with $SOCl_2$.

(12) C. Mannich, *Arch. Pharm.*, **265**, 262 (1927); V. J. Traynelis and J. G. Dadura, *J. Org. Chem.*, **26**, 1813 (1961).

(13) For example, see (a) C. A. Grob and F. A. Jenny, *Tetrahedron Lett.*, **23**, 25 (1960); (b) C. A. Grob, *Gazz. Chim. Ital.*, **92**, 902 (1962).

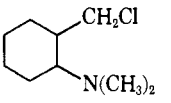
(14) A hydrochloride prepared from this isomer melted identically with reported tosylate hydrochloride.[11]

(15) P. Charpentier, *C. R. Acad. Sci.*, **225**, 306 (1947); R. C. Fuson and C. L. Zirkle, *J. Amer. Chem. Soc.*, **70**, 2760 (1948).

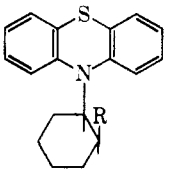
(16) M. S. Karasch and C. F. Fuchs, *J. Org. Chem.*, **9**, 359 (1944).

(17) Hydrogenation of similar disubstituted benzenes in AcOH with PtO_2 gives predominately cis products. For example, see: (a) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetsone, *J. Amer. Chem. Soc.*, **64**, 1985 (1942); (b) R. H. Baker and R. D. Schuetz, *ibid.*, **69**, 1250 (1947); (c) A. Skita, *Justus Liebigs Ann. Chem.*, **431**, 1 (1923); (d) K. von Auwers, *ibid.*, **420**, 84 (1920).

Finally, several *cis*-2-(10-phenothiazinyl)cyclohexane congeners of **1** were prepared from *trans*-2-(10-phenothiazinyl)cyclohexyl tosylate.[18] Tosylate displacement with Me_2NH gave **32**.[18] Similar displacement with CN^- followed by LAH reduction and methylation afforded **33** and **34**, respectively.



IVa, cis isomer
b, trans isomer



32, R = $N(CH_3)_2$
33, R = CH_2NH_2
34, R = $CH_2N(CH_3)_2$

Pharmacology. Methods and Results.—In preliminary screening of **1** in rats, imipramine-like rather than neuroleptic effects were noted. The principal overt actions observed upon oral administration of graded doses of 25–200 mg/kg were mydriasis and hypotonia. In mice the LD_{50} was 1440 mg/kg (po). The compound (50 mg/kg, po) produced blockade of conditioned avoidance response[19] in only 20% of rats and in mice the same dose suppressed electroshock-induced fighting behavior[20] in less than 30% of the pairs. It had only limited potency in several other tests in which most neuroleptic drugs are effective. In mice, mean prostration time following 100 mg/kg of hexobarbital[21] was increased a maximum of 49% following 100 mg/kg (po) of **1** and in rats the same dose was inactive in the pentylenetetrazole antagonist test.[22] Confinement motor activity[23] was neither increased nor decreased by 2-hr pretreatment of rats with 10–100 mg/kg (po) of **1**.

Like amitriptyline[24] and imipramine,[25] **1** (1 mg/kg, iv) potentiated norepinephrine pressor responses in pentobarbital-anesthetized dogs. It was also a potent antihistaminic as measured in guinea pigs by its ability to delay onset of prostration induced by a 12.5% histamine phosphate aerosol.[26] The oral dose of **1** producing a 250% increase (ED_{250}) in the delay of onset of prostration as compared to controls and its corresponding Feiller's limits was 11.7 (5.1–36.6) mg/kg. In this test, the ED_{250} for imipramine was 85.9 (56.9–133.8) mg/kg, and for amitriptyline 7.6 (5.0–11.6) mg/kg.

(18) J. R. Geigy A.-G., British Patent 947,002 (1964); *Chem. Abstr.*, **60**, 13254 (1964).

(19) L. Cook, E. Weidley, R. W. Morris, and P. A. Mattis, *J. Pharmacol. Exp. Ther.*, **113**, 11 (1955); L. Cook and E. Weidley, *Ann. N. Y. Acad. Sci.*, **66**, 740 (1957); D. H. Tedeschi, R. E. Tedeschi, L. Cook, P. A. Mattis, and E. J. Fellows, *Arch. Int. Pharmacodyn. Ther.*, **122**, 129 (1959).

(20) R. E. Tedeschi, D. H. Tedeschi, A. Mucha, L. Cook, P. A. Mattis, and E. J. Fellows, *J. Pharmacol. Exp. Ther.*, **125**, 28 (1959).

(21) D. W. Wylie, *Proc. Soc. Exp. Biol. Med.*, **98**, 716 (1958); R. E. Tedeschi, D. H. Tedeschi, and E. J. Fellows, *Can. Psychiat. Ass. J.*, **7**, *Suppl.*, 555 (1962).

(22) F. A. Baron, C. A. Vanderwerf, and D. H. Tedeschi, *J. Med. Chem.*, **10**, 276 (1967).

(23) D. H. Tedeschi, P. J. Fowler, W. H. Cromley, J. F. Pauls, R. Z. Eby, and E. J. Fellows, *J. Pharm. Sci.*, **53**, 1046 (1964).

(24) H. Besendorf, F. A. Steiner, and A. Hurlimann, *Schweiz. Med. Wochenschr.*, **92**, 244 (1962).

(25) R. Domenjoz and W. Theobold, *Arch. Int. Pharmacodyn. Ther.*, **120**, 450 (1959).

(26) (a) C. A. Leonard, T. Fujita, D. H. Tedeschi, C. L. Zirkle, and E. J. Fellows, *J. Pharmacol. Exp. Ther.*, **154**, 339 (1966); (b) B. N. Halpern, *Arch. Int. Pharmacodyn. Ther.*, **68**, 339 (1942).

As a primary measure of antidepressant activity,[25,27] **1** and its congeners were studied for their ability to prevent ptosis induced in rats and mice by 1 mg/kg (iv) of reserpine. In this test, 45 min after reserpine injection, animals treated at various time intervals prior to reserpine administration and controls are placed on a flat surface and following a 45-sec adjustment period are examined for ptosis. Significant ptosis in rats is defined as a 70% or greater closure of the palpebral fissure (50% in mice) which is uninterrupted for 15 or more seconds. Animals failing to exhibit ptosis either during the adjustment or test period are considered protected. The dose of drug at the time of peak effect which prevents ptosis in 50% of the animals (ED_{50}) and 95% fiducial limits were calculated by a log–probit method.[28] In cases where ED_{50}'s were not determined results are expressed in terms of maximum per cent prevention of ptosis in rats or mice treated with the dose indicated. The results of these studies are tabulated in Tables I and II.

In rats, **1** was approximately equipotent to imipramine and about 5 times more potent than amitriptyline, whereas in mice it had nearly twice the potency of imipramine and 3 times that of amitriptyline. Removing the 2-chloro substitutent (**2**), replacement by other groups such as trifluoromethyl (**3**) and methylmercapto (**4**), as well as relocating the 2-chloro substituent to the 1 position (**5**), had little or no influence upon potency in the reserpine-induced ptosis prevention test in either species. Secondary amines (**6**, **7**) retained a high degree of activity as did a primary amine (**8**). Replacing the Me_2N group of **3** with a 4-(2-hydroxyethyl)piperazinyl moiety (**9**) markedly diminished imipramine-like activity. In both rats and mice, oral doses of 25–200 mg/kg of **9** produced effects such as decreased motor activity, ptosis, catalepsy, and body postural changes, characteristic of neuroleptic drugs. Acridan (**10**), dibenzazepine (**11**), and dihydrodibenzazepine (**12**) congeners retained a high degree of imipramine-like activity; **11** was somewhat more potent than **1** in this test whereas **10** and **12** apparently were less effective, although ED_{50}'s were not determined. Diphenylamine (**13**) and 9-methylthioxanthene (**21**) congeners were not studied for ptosis prevention, but, in rats at 200 mg/kg (po), both compounds produced hypotonia and mydriasis. The dibenzocycloheptane (**22**) did not prevent reserpine-induced ptosis in rats treated with 25 mg/kg (po) but 50% prevention was observed in mice at this dose. Phenoxazines (**14**, **15**) related to **1** were considerably less potent than the parent. A 5-oxide derivative (**16**) of **1** retained ptosis-preventing potency; however, in rats this compound was considerably more toxic than other members of this series. An oral dose of 400 mg/kg of **16** produced convulsions and death.

Lower homologs (**23**–**25**) related to **1** and **3** retained significant activity but were considerably less potent than the parent (**1**), whereas imipramine-like activity was abolished in the higher homolog (**26**) in which the cyclopropyl substituent is separated from the phenothiazine by CH_2.

A 2-substituted cyclobutyl analog (**27**) exhibited antidepressant properties but it was less potent than **1**. The 3-substituted cyclobutane (**28**) and the various cyclohexane derivatives (**29**–**34**) were devoid of significant ptosis-preventing activity. Compounds **30** and **31** were also studied in the conditioned escape response test.[19] The cis isomer (**30**, 500 mg/kg, po) produced no specific blockade and the trans isomer (**31**, 400 mg/kg, po) blocked the conditioned response of only 20% of the animals.

Cyclopropane ring-opened congeners, **17**–**20**, lacked significant imipramine-like activity in rats; however, in a test for prevention of reserpine-induced ptosis in mice **20** was about 0.2 as potent as imipramine.

To investigate the possibility that the antidepressant actions of members of this series might arise from inhibition of monoamine oxidase, several of the compounds (**1**–**3**, **5**–**9**, **16**, **18**, and **19**) were examined for their ability to potentiate tryptamine-induced convulsions in rats.[29] None of these compounds (50 mg/kg, po) potentiated the tryptamine effect. Compound **1** also failed to inhibit MAO *in vitro* as measured by the method of Sjoerdsma, *et al.*[30]

Experimental Section[31]

Ethyl *trans*- and *cis*-2-Bromocyclopropanecarboxylates.[32]—A mixture of 100 g (0.633 mole) of ethyl hydrogen 1,2-cyclopropanedicarboxylate (prepd from diethyl *trans*-1,2-cyclopropanedicarboxylate[33] or a cis–trans mixture[34] as described by Wiberg[3]), 68.3 g (0.316 mole) of yellow HgO, and 950 ml of CCl_4 was stirred and refluxed for 2.5 hr under a H_2O separator; then a soln of 100.2 g (0.633 mole) of Br_2 in 100 ml of CCl_4 was added dropwise at 50–60° during 4 hr. After addn was completed, the mixt was stirred for 12 hr and then filtered and the filter cake was washed with CCl_4. The combined filtrates were washed (10% aq Na_2SO_3, aq $NaHCO_3$), dried ($MgSO_4$), and concd. Distn of the residue afforded 78.5 g (64%) of a colorless liquid, bp 38–46° (0.2 mm). Glpc, using a 1.83-m silicone rubber SE 30 column, 10% on Diatoport S, 80–100 mesh, at 130° showed two peaks with retention times of 2.3 (70–80%) and 2.9 (20–30%) min. The sample was distd using a Hyper-Cal high temperature distillation apparatus[35] with a 25 × 900 mm Podbelniak helipak column and an 80:1 reflux ratio. Ethyl *trans*-2-bromocyclopropanecarboxylate[36] (43.5 g) was collected as a first fraction: bp 71–73° (9 mm); $n^{25}D$ 1.4688, nmr peaks ($CDCl_3$) at δ 1.26 (t, 3, CH_3CH_2), 1.53 (m, 2, cyclopropyl-CH_2), 2.09 (m, 1, J_{sum} = 19 Hz, CHCO), 3.29 (m, 1, J_{sum} = 17 Hz, CHBr), and 4.19 (q, 2, CH_2O). After a 6.7-g intermediate fraction, bp 73–88° (9 mm), ethyl *cis*-2-

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(30) A. Sjoerdsma, T. E. Smith, T. D. Stevenson, and S. Udenfriend, *Proc. Soc. Exp. Biol. Med.*, **89**, 36 (1955).

(31) Melting points are corrected, boiling points are uncorrected. Nmr spectra were determined on a Varian Model A-60 spectrometer in the indicated solvents with absorption measured in ppm downfield from Me_4Si. Microanalyses were determined by Margaret Carroll and coworkers; spectral determinations were by Richard J. Warren and coworkers of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories.

(32) We are indebted to Drs. David Chan and Wilford Mendelson of Smith Kline and French Laboratories for improvements in this procedure.

(33) A. T. Blomquist and D. T. Longone, *J. Amer. Chem. Soc.*, **81**, 2012 (1959).

(34) G. Bonavent, M. Causse, M. Guitard, and R. Fraisse-Jullien, *Bull. Soc. Chim. Fr.*, 2462 (1964).

(35) Podbelniak Inc., Chicago, Ill.

(36) Stereochemical assignments are based upon the separation of the outermost nmr peaks (J_{sum}) for cyclopropyl CH, which would be expected to be greater for the cis isomer in which this proton interacts with 2 vicinal cis protons than for the trans isomer in which this proton interacts with only one vicinal cis proton. For example, see: J. Finkelstein, E. Chiang, and J. Lee, *J. Med. Chem.*, **8**, 432 (1965); J. D. Graham and M. T. Rogers, *J. Amer. Chem. Soc.*, **84**, 2249 (1962); H. M. Hutton and T. Schaeffer, *Can. J. Chem.*, **40**, 875 (1962); K. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **85**, 2788 (1963).

TABLE II
PREVENTION OF RESERPINE-INDUCED PTOSIS IN RATS

No.	Dose, mg/kg, po	Ptosis prevention, %
17	50	0[a]
18	50	0
19	[b]	
20	25	0[c]
21	[d]	
22	25	0[e]
23	50	40
24	50	40
25	50	40
26	100	0
27	50	60
28	15	0
29	10	0
30	100	0
31	100	25
32	10	0
33	[f]	
34	25	0

[a] In the test for prevention of reserpine-induced ptosis in mice, **17** had ED_{50} 47.0 (29.2–75.7) mg/kg. [b] Ataxia, bizarre behavior, increased curiosity, hypotonia, mydriasis, and analgesia were observed in rats receiving 50 mg/kg, po. [c] In mice, 50% potentiation of reserpine-induced ptosis was produced by 50 mg/kg, po. [d] Decreased motor activity, hypotonia, and mydriasis were observed in rats treated with 200 mg/kg, po. [e] In mice, 50% prevention of reserpine-induced ptosis was produced by 25 mg/kg, po. [f] Ataxia, hypotonia, and salivation were noted in rats receiving 100 mg/kg, po.

bromocyclopropanecarboxylate[36] (15.3 g) was collected; bp 88° (9 mm); $n^{25}D$ 1.4731; nmr peaks ($CDCl_3$) at δ 1.30 (t, 3, CH_3CH_2), 1.51 (m, 2, cyclopropyl-CH_2), 2.09 (m, 1, J_{sum} = 24 Hz, CHCO), 3.30 (m, 1, J_{sum} = 22 Hz, CHBr), and 4.25 (q, 2, CH_2O).

cis-**2-Bromocyclopropanecarboxylic Acid.**—Hydrolysis of ethyl *cis*-2-bromocyclopropanecarboxylate with excess H_2O–EtOH–KOH gave colorless crystals (90% yield), mp 69.5–71° after recrystn from cyclohexane. *Anal.* ($C_4H_5BrO_2$) C, H.

trans-**2-Bromocyclopropanecarboxylic Acid.**[3]—This was prepd from ethyl *trans*-2-bromocyclopropanecarboxylate in 90% yield as described for the cis isomer. Recrystn from H_2O gave colorless crystals, mp 65–67° (lit.[3] mp 66–67°). *Anal.* ($C_4H_5BrO_2$) C, H.

trans- **and** *cis*-**2-Bromo-***N*,*N*-**dimethylcyclopropanecarboxamide.**—A soln of 12.4 g (0.075 mole) of *trans*-2-bromocyclopropanecarboxylic acid and 15 g (0.125 mole) of $SOCl_2$ in Et_2O (50 ml) was allowed to stand at room temp for 6 hr and then concd at 40° (25 mm). The residual acid chloride was dild with Et_2O (100 ml) and satd at 0–10° with Me_2NH. After the mixt was dild (H_2O), the Et_2O soln was sepd, dried, and concd. Distn of the residue gave 11.7 g (81%) of a pale yellow liquid, bp 130–132° (25 mm). Glpc using a 46-cm silicone rubber SE 30, 2.5% on Gas Chrom Z column at 110° gave a single peak with a retention time of 4.5 min. *Anal.* ($C_6H_{10}BrNO$) H, calcd: C, 37.52. Found: C, 36.85.

cis-2-Bromo-*N*,*N*-dimethylcyclopropanecarboxamide, bp 135–143° (25 mm), glpc as described for trans isomer, one peak, retention time 5.7 min, was prepd (47% yield) in the same manner. Ir spectra of cis and trans isomers differed in the region between 7.9 and 8.4 μ and between 13.5 and 14.0 μ; the trans isomer had ir absorptions at 7.90 (m), 8.1 (s), 8.3 (m), and 13.55 (m) μ whereas the cis compd had absorptions at 7.95 (s), 8.02 (s), 8.4 (m), and 13.92 (s) μ.

A mixture of ethyl *cis*- and *trans*-2-bromocyclopropanecarboxylates (glpc, 79% trans and 21% cis) was hydrolyzed to a mixt of acids which was converted in the same manner into a mixt of *trans* and *cis*-2-bromo-*N*,*N*-dimethylcyclopropanecarboxamides: bp 121–129° (16 mm), glpc, 92% trans, 8% cis, in an overall yield of 62%.

General Procedures. (**a**) **Alkylation of Phenothiazines and Related Compounds.**—To a stirred suspension of 4.6 g (0.1 mole) of a 52% dispersion of NaH in mineral oil and 100 ml of DMSO, under N_2 at 25–30°, was slowly added 0.1 mole of phenothiazine or related compd in 150 ml of DMSO. The mixt was stirred and heated gradually to 70°. After H_2 evolution was completed (in all instances, no longer than 30 min was required), the mixt was cooled to 20° and a soln of 0.1 mole of the appropriate halide (generally, ethyl 2-bromocyclopropanecarboxylate or 2-bromo-*N*,*N*-dimethylcyclopropanecarboxamide, cis or trans isomers or mixtures) in 25 ml of DMSO was added slowly. The stirred mixt was heated at 90–100° for 1 hr, it was dild with 1 l. of ice-water, and extd (Et_2O). The exts were dried and concd to give crude product (amides, esters, or amines) containing mineral oil. Diluting the crude product with MeCN, extg the mixture with hexane, and concg the MeCN afforded the crude products free from mineral oil. Crude products were generally employed for further reaction without purification.

(**b**) **Hydrolysis of Ethyl** *trans*-**2-Substituted Cyclopropanecarboxylates.**—To a stirred soln of 0.1 mole of ester in 250 ml of EtOH was added slowly 0.15 mole of KOH in H_2O (50 ml). The mixt was refluxed for 2 hr, concd, and dild with H_2O. After extg (Et_2O), the H_2O soln was made acidic to ppt carboxylic acids (Table III) which were filtered and recrystd.

TABLE III
trans-2-(R-10-PHENOTHIAZINYL)CYCLOPROPANECARBOXYLIC ACIDS

R	Mp, °C	Recrystn solvent	Formula[a]
H	165–166	EtOAc–hexane	$C_{16}H_{13}NO_2S$
2-Cl	193–194	PhH–hexane	$C_{16}H_{12}ClNO_2S$
2-CF_3	182–184	PhH–hexane	$C_{17}H_{12}F_3NO_2S$
1-Cl	178–180	EtOAc–hexane	$C_{16}H_{12}ClNO_2S$

[a] All compds analyzed correctly for C, H, N.

(**c**) *trans*-**2-Substituted Cyclopropanecarboxamides from Carboxylic Acids.**—To 0.1 mole of carboxylic acid in 200 ml of Me_2CO was added 15.2 g (0.15 mole) of Et_3N. The soln was stirred and cooled to 0° and 16.2 g (0.15 mole) of ethyl chlorocarbonate was added dropwise. After the mixt was stirred at 0° for 30 min, an excess of the appropriate amine [50 ml of 40% aq $MeNH_2$ or Me_2NH, 50 ml of 28% aq NH_3, or 0.2 mole of 1-(2-hydroxyethyl)piperazine] was added slowly. The mixt was stirred at 25–30° for 2 hr, then dild with 1 l. of ice-water, and extd with CH_2Cl_2. The CH_2Cl_2 exts were dried and concd to give crude amides which were reduced to amines without purification.

(**d**) **Reduction of Carboxamides to Amines.**—To a stirred suspension of 0.1 mole of LAH in 350 ml of Et_2O was added slowly a soln of 0.5 mole of carboxamide in 100 ml of Et_2O (insol carboxamides were suspended in Et_2O or solids were added in portions). The mixt was stirred and refluxed for 2–8 hr (primary and secondary carboxamides were refluxed for 8 hr, tertiary amides for 2 hr), then 4 ml of 10% NaOH and 20 ml of H_2O were added dropwise *cautiously*. The mixt was filtered and the filtrate was extd with 0.5 *N* HCl. The acid exts were made alkaline with 10% NaOH and the pptd amines were extd (Et_2O). The exts were dried and concd to give crude products which were converted into the salts indicated in Table I. Additional compds prepd by LAH reduction of carboxamide derivatives resulting from alkylation of the appropriate tricyclic compd with 2-bromo-*N*,*N*-dimethylcyclopropanecarboxamide are listed in Table IV.

trans-**2-[5-(10,11-Dihydro-5***H*-**dibenz[***b*,*f*]**azepinyl)]-***N*,*N*-**dimethylcyclopropanemethylamine (12).**—A soln of 5.8 g (0.02 mole) of 11 in 150 ml of AcOH was brought to pH 2 with dry HCl, 0.6 g of PtO_2 was added, and the mixt was hydrogenated for 12 hr at 3.5 kg/cm². The mixt was filtered and the filtrate was concd *in vacuo*. The residue was dild (H_2O) and made alkaline with NaOH. The mixt was extd (Et_2O) and the exts were dried and concd. Maleic acid (2.5 g) was added to a soln of the residual oil in EtOH. Addition of Et_2O gave 3.2 g (40%) of **12** (Table I); uv λ_{max}^{EtOH} 244 mμ (ε 10,400).

trans-**2-(2-Chloro-10-phenothiazinyl)-***N*,*N*-**dimethylcyclopropanemethylamine 5-Oxide·HCl (16).**—A soln of 6.62 g (0.02 mole) of 1, 2.52 g (0.02 mole) of oxalic acid dihydrate, 80 ml of EtOH, and 20.8 ml of 3% H_2O_2 was refluxed for 24 hr. The soln was concd *in vacuo* and the residue was suspended in H_2O and

TABLE IV

Compd	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
17	154–155[b]	MeCN	72	$C_{21}H_{25}N \cdot C_6H_{13}NO_3S$[c]
18	208–210[d]	EtOH–Et_2O	23	$C_{19}H_{21}NO \cdot HCl$
19	184–186[e]	EtOH–Et_2O	21	$C_{19}H_{21}NS \cdot HCl$
20	174–176[f]	EtOH–Et_2O	14	$C_{19}H_{20}ClN \cdot C_6H_{13}NO_3S$[c]
21	170–172	EtOH–Et_2O	43	$C_{20}H_{23}NS \cdot C_6H_{13}NO_3S$[c]

[a] See footnote *a* in Table III. [b] Uv (EtOH) λ_{max} 238 mμ (ε 13,500). The base had an nmr peak ($CDCl_3$) at δ 5.87 (t, 1, J = 7 Hz, =$CHCH_2$). [c] Cyclohexylsulfamate. [d] The base had an nmr peak ($CDCl_3$) at δ 5.80 (t, 1, J = 7 Hz, =$CHCH_2$). [e] Nmr peak (D_2O) at δ 5.99 (m, 1, =$CHCH_2$). [f] The base had an nmr peak ($CDCl_3$) at δ 5.92 (t, 1, J = 7 Hz, =$CHCH_2$); uv (EtOH) λ_{max} 230, 270, 328 mμ (ε 32,800, 14,600, 2900).

made alkaline with NaOH. The mixt was extd (Et_2O) and the exts were dried and concd. Acidification of an EtOH soln of the residual oil with dry HCl and addition of Et_2O gave **16** (Table I).

trans-**2-[5-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptenyl)]-*N,N*-dimethylcyclopropanecarboxamide** was prepd by alkylation of 9.71 g (0.05 mole) of 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene[37] with 2-bromo-*N,N*-dimethylcyclopropanecarboxamide according to procedure a except that the bromoamide was added at 0–5° and the mixt was held at this temp for 30 min. The product was recrystd from EtOH–H_2O to give 5.0 g (33%) of colorless crystals: mp 132–137°; λ_{max}^{EtOH} 263, 266, 270, 273 mμ (ε 614, 612, 543, 478). *Anal.* ($C_{21}H_{23}NO$) C, H, N.

trans-**2-[5-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptenyl)]-*N,N*-dimethylcyclopropanemethylamine Maleate (22).**—Reduction of *trans*-2-[5-(10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptenyl)]-*N,N*-dimethylcyclopropanecarboxamide as described for procedure d gave 82% of **22** as colorless crystals, mp 118–120°, after recrystn from MeCN. *Anal.* ($C_{25}H_{29}NO_4$) C, H, N.

The free amine, liberated from maleate **22**, showed λ_{max}^{EtOH} 263, 266, 270, 273 mμ (ε 619, 617, 556, 510).

2-Chloro-10-vinylphenothiazine.—A MeOH suspension of methiodide, mp 230–231°, prepared from 2-chloro-10-(2-dimethylaminoethyl)phenothiazine[38] was stirred with an excess of Amberlite IRA-400-OH for 1 hr at 25°. The mixt was filtered, the filtrate was concd, and the residual oil was heated at 100° (25 mm) until gas evolution was completed. Recrystn of the residual solid from hexane gave 91% of colorless crystals, mp 78–80°. *Anal.* ($C_{14}H_{10}ClNS$) C, H, N.

2-(2-Chloro-10-phenothiazinyl)cyclopropanecarboxylic Acid (Method C).—To a stirred and refluxing suspension of 2 g of $CuSO_4$ in 100 ml of C_6H_6 was added dropwise a soln of 48 g (0.18 mole) of 2-chloro-10-vinylphenothiazine and 27.4 g (0.24 mole) of ethyl diazoacetate in 150 ml of C_6H_6. After addn was completed, the mixt was stirred and refluxed for 30 min and filtered, the filtrate was concd, and the residual oil was hydrolyzed by procedure b. The resulting crude acid mixt was extd (Et_2O) and the exts were dried and concd. When the residue was suspended in 200 ml of satd $NaHCO_3$ soln, a cryst salt pptd. An EtOH–H_2O soln of the salt was acidified with aq HCl to give 7.5 g (13%) of colorless crystals, mp 193–194°; mmp with *trans*-(2-chloro-10-phenothiazinyl)cyclopropanecarboxylic acid obtained by hydrolysis of the product of alkylation of 2-chlorophenothiazine with ethyl 2-bromocyclopropanecarboxylate was not depressed.

Acidification of the aq $NaHCO_3$ filtrate gave 1.2 g (2%) of colorless crystals, mp 173–175°, having a single spot (R_f 0.73) on Whatman No. 3MM paper with *n*-BuOH satd with aq NH_3. The trans acid had R_f 0.80 in this chromatographic system.

trans-**2-(2-Chloro-10-phenothiazinyl)-*N,N*-dimethylcyclopropylamine·HCl (23).**—*trans*-2-(2-Chloro-10-phenothiazinyl)-cyclopropanecarboxylic acid was converted into an isocyanate in nearly quant yield *via* a mixed carboxylic–carbonic anhydride according to the general directions of Weinstock.[7] The isocyanate (9.5 g, 0.03 mole) was stirred and refluxed with 60 ml of EtOH for 2 hr and the soln was concd to give 6.3 g of a carbamate, mp 168–171°, after recrystn from EtOAc–hexane. A stirred mixt of 6.3 g (0.017 mole) of the carbamate, 0.8 g (0.017 mole) of a 52% dispersion of NaH in mineral oil and 50 ml of DMSO was gradually heated to 70° for 5 min. The mixture was cooled to 25°, 5 ml of MeI was added, and it was heated to 60° for 30 min. After being diluted (H_2O), the mixt was extd (Et_2O) and the exts were dried and concd to give crude ethyl *trans*-2-(2-chloro-10-phenothiazinyl)-*N*-methylcyclopropanecarbamate which was reduced with LAH by procedure d. The hydrochloride **23** was obtained (5.2 g, overall yield, 49%), as colorless crystals, mp 214–215°, after recrystn from MeCN–Et_2O. *Anal.* ($C_{17}H_{18}Cl_2N_2S$) C, H, N.

trans-**2-(2-Chloro-10-phenothiazinyl)-*N,N*-diethylcyclopropylamine·HCl (24).**—*trans*-2-(2-Chloro-10-phenothiazinyl)cyclopropyl isocyanate (6.3 g, 0.02 mole), prepd as described for **23**,[7] in 50 ml of Et_2O was added dropwise to 50 ml of 3 *M* MeMgBr in Et_2O and the mixt was stirred and refluxed for 2 hr. The cooled reaction mixt was poured onto ice–aq HCl, the Et_2O layer was sepd, and the aq layer was extd with $CHCl_3$. Combined org exts were dried and concd to give crude *trans*-*N*-[2-(2-chloro-10-phenothiazinyl)cyclopropyl]acetamide. The crude amide was ethylated with EtI (NaH, DMSO) and the resulting tertiary amide was reduced with LAH in the same manner as described for **23**. The colorless crystalline hydrochloride **24**, 2.3 g (30% overall yield), melted at 183–185° after recrystn from EtOH–Et_2O. *Anal.* ($C_{19}H_{22}Cl_2N_2S$) C, H, N.

trans-*N*-**Ethyl-2-(2-trifluoromethyl-10-phenothiazinyl)cyclopropylamine·HCl (25).**—*trans*-2-(2-Trifluoromethyl-10-phenothiazinyl)cyclopropanecarboxylic acid (11.5 g, 0.03 mole) was converted into crude *trans*-*N*-[2-(2-trifluoromethyl-10-phenothiazinyl)cyclopropyl]acetamide by addn of excess MeMgBr to an intermediate isocyanate as described for **24**. Reduction of the amide with LAH as described under procedure d gave 8.2 g (71%) of colorless cryst hydrochloride **25**, mp 197–200° (from EtOH–Et_2O). *Anal.* ($C_{18}H_{18}ClF_3N_2S$) C, H, N.

trans-**2-Dimethylaminomethylcyclopropanemethanol.**—Ethyl hydrogen *trans*-1,2-cyclopropanedicarboxylate (47 g, 0.3 mole) was refluxed for 2 hr with $SOCl_2$ (42 g, 0.35 mole). The reaction mixt was distd and the colorless acid chloride, bp 113–120° (30 mm), was collected. Me_2NH was bubbled into a soln of the acid chloride (35.3 g, 0.2 mole) in 350 ml of Et_2O at 0° until the mixt was alkaline. After the mixt stood at 0° for 30 min, H_2O (50 ml) was added. The Et_2O soln was sepd, dried, and concd to give crude *trans*-2-carbethoxy-*N,N*-dimethylcyclopropanecarboxamide (37.0 g) which was reduced by procedure d. The amine (14.1 g, overall yield 37.5%) was a colorless liquid, bp 126–127° (38 mm). *Anal.* ($C_7H_{15}NO$) C, H, N.

trans-**2-(2-Chloro-10-phenothiazinylmethyl)-*N,N*-dimethylcyclopropanemethylamine·HCl (26).**—To a stirred soln of 6.5 g (0.05 mole) of *trans*-2-dimethylaminomethylcyclopropanemethanol in 30 ml of THF at 20° was added, in portions, 2.1 g (0.05 mole) of a 58% dispersion of NaH in mineral oil. The mixt was stirred and refluxed for 30 min, then cooled to 0°, and a soln of 9.5 g (0.05 mole) of *p*-TsCl in 20 ml of THF was added dropwise. After 10 min at 25°, the mixt was added dropwise to a suspension of 2.1 g (0.05 mole) of NaH in mineral oil and 11.7 g (0.05 mole) of 2-chlorophenothiazine in 50 ml of DMSO which had previously been stirred at 25° until H_2 evolution was completed. The mixt was heated at 100° for 1 hr, dild with ice-water, and extd (Et_2O). The Et_2O ext was extd with 5% aq AcOH. The acid exts were made basic with NaOH and the mixt was extd (Et_2O). After being dried, the Et_2O exts were concd and the residue was distd to give 11.4 g (66%) of a pale yellow liquid: bp 213–217° (0.6 mm); nmr peaks ($CDCl_3$) at δ 0.8 (m, 4), 2.5 (d, 2), 2.25 (s, 6), 3.75 (d, 2, J = 5 Hz), and 7.0 (m, 7). A hydrochloride **26** was prepd in MeCN–EtOAc, mp 184–186°. *Anal.* ($C_{19}H_{22}Cl_2N_2S$) C, H, N.

trans-**2-(2-Chloro-10-phenothiazinyl)-*N,N*-dimethylcyclobutanemethylamine Maleate (27).**—Alkylation of 2-chlorophenothiazine with either ethyl 1-bromocyclobutanecarboxylate[8] or ethyl 2-bromocyclobutanecarboxylate[9] by procedure a gave crude ethyl *trans*-2-(2-chloro-10-phenothiazinyl)cyclobutanecarboxylates having identical ir spectra. The crude esters were hydrolyzed to noncryst acids by procedure b. The acids were converted into amides by procedure c. Reduction of the amides by procedure d gave **27** maleate as colorless crystals, mp 144–145°, after recrystn (Me_2CO). The yield from ethyl 1-bromocyclobutanecarboxylate was 14.3%, and from 2-bromo ester, 62%. *Anal.* ($C_{23}H_{25}ClN_2O_4S$) C, H, N.

3-(2-Chloro-10-phenothiazinyl)-*N,N*-dimethylcyclobutylamine·HCl (28) was prepd by alkylation of 2-chlorophenothiazine (23.3 g, 0.1 mole) with a tosylate prepd from 11.7 g (0.1 mole) of an isomeric mixt of 3-dimethylaminocyclobu-

(37) W. Treibs and H. Klinkhammer, *Chem. Ber.*, **83**, 367 (1950).
(38) P. Charpentier, U. S. Patent 2,645,640 (1953).

tanols[10] in the same manner as described for **26**. The free amine (8.4 g, 25.6%) melted at 147–150° after recrystn (Me_2CO): tlc, silica gel G (0.1 *N* NaOH) and MeOH gave 2 major spots, R_f 0.57; 0.75. *Anal.* ($C_{18}H_{19}ClN_2S$) C, H, N.

A hydrochloride **28** prepd from the above amine weighed 3.2 g after two recrystns from EtOH–Et_2O, mp 263–265° dec; tlc as for base showed a single spot, R_f 0.75. *Anal.* ($C_{18}H_{20}Cl_2N_2S$): C, H, N.

A free base of mp 160–161°, obtained from **28**, showed nmr peaks ($CDCl_3$) at δ 2.1 [s, 6, $N(CH_3)_2$], 2.88 [m, 1, $HCN(CH_3)_2$] and 4.08 [m, 1, J = 7 Hz, $HC(CH_2)_2$].

***trans*-2-Dimethylaminomethylcyclohexyl Tosylate.**—A mixt of 11.7 g (0.07 mole) of *trans*-2-dimethylaminomethylcyclohexanol,[12] 14.9 g (0.08 mole) of *p*-TsCl, and 200 ml of $CHCl_3$ was stirred and refluxed for 1 hr and then concd. The residue crystd from EtOH–Et_2O to give 13.1 g (53%) of colorless crystals, mp 133–135°, lit.[13] mp 133–135°. A soln of hydrochloride in H_2O was saturated with K_2CO_3, and the mixt was extd with Et_2O. The dried Et_2O soln was concd to give the free amine which was employed for reaction without additional purification.

***cis*-2-Dimethylaminomethylcyclohexyl tosylate** was prepared from *cis*-2-dimethylaminomethylcyclohexanol[12] in the same manner as described for the trans isomer. As this hydrochloride did not crystallize it was converted into its free base and used for further reaction without purification.

Methyl *cis*-2-Methylaminocyclohexanecarboxylate.—A mixt of 49.3 g (0.3 mole) of methyl *N*-methylanthranilate, 6 g of PtO_2, and 240 ml of AcOH was hydrogenated at 3.5 kg/cm² for 4 hr at 25°. The mixt was filtered, the filtrate was concd, and the residue was dild with 10% aq HCl. A small amt of neutral material was removed by extn (Et_2O), then the acidic soln was made alkaline with NaOH. The mixt was extd (Et_2O) and the exts were dried and distd to give 41 g (80%) of colorless liquid, bp 107–111° (23 mm). A ***p*-nitrobenzamide** derivative melted at 127–128.5° after recrystn from EtOH–H_2O. *Anal.* ($C_{16}H_{20}N_2O_5$) C, H, N.

Methyl *trans*-2-Methylaminocyclohexanecarboxylate.—A soln of 10 g (0.058 mole) of methyl *cis*-2-methylaminocyclohexanecarboxylate and 0.3 g of NaOMe in 50 ml of MeOH was refluxed for 4 hr. The soln was evapd, dild with 5% aq HCl, and extd (Et_2O). After the H_2O soln was satd with K_2CO_3, the mixt was extd (Et_2O) and the exts were dried. Distn gave 6.6 g (66%) of a colorless liquid, bp 111–114° (25 mm). A ***p*-nitrobenzamide** melted at 99–100° after recrystn from hexane. *Anal.* ($C_{16}H_{20}N_2O_5$) C, H, N.

A mmp with methyl *cis*-*N*-(*p*-nitrobenzoyl)-*N*-methylcyclohexanecarboxylate was depressed.

***cis*-2-Dimethylaminocyclohexanemethanol.**—To a stirred mixt of 20 g (0.12 mole) of methyl *cis*-2-methylaminocyclohexanecarboxylate, 18.5 g of pyridine, and 25 ml of C_6H_6 at 0° was slowly added a soln of 14 g (0.13 mole) of ethyl chlorocarbonate in 25 ml of C_6H_6. After 2 hr at 25°, the mixt was extd with 10% aq HCl. The C_6H_6 was dried and distd to give 21.8 g (76%) of carbamate, bp 107–116° (1.3 mm); $n^{22}D$ 1.4654. Reduction of the carbamate with equimolar LAH in Et_2O in the usual manner gave 10.8 g (83%) of a colorless liquid, bp 87–92° (4 mm); $n^{23}D$ 1.4780. A **methiodide** was prepared in Me_2CO, mp 230.5–231.5° after recrystn (EtOH–Et_2O). *Anal.* ($C_{10}H_{22}INO$) C, H, N.

***trans*-2-Dimethylaminocyclohexanemethanol.**—Methyl *trans*-2-methylaminocyclohexanecarboxylate (57.8 g, 0.34 mole) was carboethoxylated in the same manner as described for the cis isomer to give 63.3 g (78%) of carbamate: bp 130–136° (1.3 mm); $n^{28}D$ 1.4637, which was reduced with LAH to give 35.0 g (86%) of colorless liquid, bp 90–99° (4 mm); $n^{26}D$ 1.4697. A **methiodide** melted at 202–203° after recrystn (EtOH–Et_2O). *Anal.* ($C_{10}H_{22}INO$) C, H.

***cis*-2-Chloromethyl-*N*,*N*-dimethylcyclohexylamine (IVa).**—A soln of 10.3 g (0.066 mole) of *cis*-2-dimethylaminocyclohexanemethanol in 40 ml of $CHCl_3$ and 40 ml of $SOCl_2$ was refluxed for 4 hr, and then concd *in vacuo*. The residual hydrochloride was dissolved in H_2O (50 ml), the soln was satd with K_2CO_3, and extd (C_6H_6). The C_6H_6 soln was dried and concd to give crude product which was employed for reaction without purification. For analysis, a picrate, mp 174.5–175.5° (from EtOH), was prepd. *Anal.* ($C_{15}H_{21}ClN_4O_7$) C, H, N.

***trans*-2-Chloromethyl-*N*,*N*-dimethylcyclohexylamine (IVb).**—This compd was prepd from *trans*-2-dimethylaminocyclohexanemethanol in 91% yield in the same manner as described for the cis isomer: bp 93–95° (12 mm); $n^{23}D$ 1.4763. A picrate melted at 150–153° after recrystn (EtOH). *Anal.* ($C_{15}H_{21}ClN_4O_7$) C, H, N.

***cis*-2-(2-Chloro-10-phenothiazinylmethyl)-*N*,*N*-dimethylcyclohexylamine·HCl (30).**—A stirred mixt of 7.21 g (0.031 mole) of 2-chlorophenothiazine, 0.81 g (0.035 mole) of $LiNH_2$, and 75 ml of xylene was refluxed for 1.5 hr, then 10.8 g (0.062 mole) of IVa in 50 ml of xylene was added during 15 min. After being stirred and refluxed for 12 hr, the mixt was cooled, 5 ml of EtOH was added, and the soln was extd with aq HCl. The acid exts were made alkaline with NaOH and the mixt was extd (Et_2O). After being dried, the Et_2O soln was distd and the fraction, 5.5 g (48%), bp 223–230° (0.5 mm), was collected. A hydrochloride **30** was prepared in EtOH, mp 250.5–252°. *Anal.* ($C_{21}H_{26}Cl_2N_2S$) C, H, N.

The same hydrochloride, mp 251–252°, was obtained in 60% yield by alkylation of 2-chlorophenothiazine with *trans*-2-dimethylaminomethylcyclohexyl tosylate according to procedure a. A mmp of the two samples was not depressed and their ir spectra were identical.

***trans*-2-(2-Chloro-10-phenothiazinylmethyl)-*N*,*N*-dimethylcyclohexylamine·HCl (31)** was prepd by alkylation of 24.9 g (0.106 mole) of 2-chlorophenothiazine with 10.6 g (0.106 mole) of IVb in the presence of 2.75 g (0.12 mole) of $LiNH_2$; yield 26.8 g (68%), bp 214–220° (0.3 mm). Hydrochloride **31** was obtained as colorless crystals, mp 259° dec, from MeOH–Et_2O. *Anal.* ($C_{21}H_{26}Cl_2N_2S$) C, H, N.

***cis*-2-(10-Phenothiazinylmethyl)-*N*,*N*-dimethylcyclohexylamine·HCl (29)** was prepd from 4.0 g (0.02 mole) of phenothiazine and 6.2 g (0.02 mole) of *trans*-2-dimethylaminomethylcyclohexyl tosylate according to procedure a; yield 4.0 g (53%) of colorless crystals (from EtOH–Et_2O); mp 258–259°. *Anal.* ($C_{21}H_{27}ClN_2S\cdot H_2O$) C, H, N, H_2O.

Attempted alkylation of phenothiazine with *cis*-2-dimethylaminocyclohexyl tosylate (0.028 mole) by procedure a gave 5.3 g (82%) of unchanged phenothiazine and 3.7 g of a colorless liquid, bp 52–54° (0.5 mm), which gave a **hydrochloride**, mp 207–209° after recrystn (*i*-PrOH–Et_2O). *Anal.* ($C_9H_{11}ClN\cdot 0.5H_2O$) C, H, N.

***cis*-2-(10-Phenothiazinyl)cyclohexanenitrile.**—A mixt of 21.0 g (0.05 mole) of *trans*-2-(10-phenothiazinyl)cyclohexyl tosylate[18] and 3.8 g (0.08 mole) of NaCN in 200 ml of DMSO was heated at 100° for 2 hr. The soln was dild with H_2O and extd with Et_2O. The exts were dried and concd to give 14.0 g (91%) of colorless crystals, mp 152–153°, after several recrystns (EtOAc–hexane). *Anal.* ($C_{19}H_{18}N_2S$) C, H, N.

***cis*-2-(10-Phenothiazinyl)cyclohexanemethylamine·HCl (33)** was prepd in 68% yield by LAH reduction of *cis*-2-(10-phenothiazinyl)cyclohexanenitrile: recrystd from EtOH–Et_2O, mp 184–187°, tlc homogeniety on silica gel G and MeOH–Me_2CO (95:5). *Anal.* ($C_{19}H_{23}ClN_2S\cdot 0.5H_2O$) C, H, N.

***cis*-2-(10-Phenothiazinyl)-*N*,*N*-dimethylcyclohexanemethylamine·HCl (34).**—A mixt of 12.8 g (0.04 mole) of free amine liberated from **33** and 100 ml of ethyl formate was refluxed for 20 hr. Concn of the soln gave 13.2 g of a formamide derivative, mp 169–172°, after recrystn (EtOAc). Methylation of the amide with excess MeI according to procedure a gave 10.7 g of an N-methylated formamide, mp 161–163° (from EtOH), which was reduced with equimolar LAH in Et_2O. The crude product in EtOH–Et_2O was treated with HCl to give 10.1 g (68%); mp 220–220° after recrystn (MeCN). *Anal.* ($C_{21}H_{27}ClN_2S$) C, H, N.

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