SYNTHESIS AND COMPARISON OF ACTIVITY OF 2- AND 3-DIMETHYLSULFAMIDOPHENOTHIAZINE DERIVATIVES*

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Some highly potent medicinal agents (i.e., Majeptil, dimethothiazine, and pipothiazine) are found among the derivatives of 2-dimethylsulfamidophenothiazine (I). On the other hand, the activities of 3-dimethylsulfamidophenothiazine (II) derivatives have been little investigated, and literature reports are scarce. Although it has been well established that the pharmacological activity of phenothiazine derivatives varies markedly with the substitution pattern on the phenothiazine ring system, only a single work has been devoted to the investigation of this problem [1].

In order to establish the correlation between the pharmacological activity and the sulfamido group position on the phenothiazine nucleus, we have undertaken the synthesis of five pairs of derivatives of compounds I and II. Specifically, the following variations of the aminoalkyl and aminoacyl substituents on nitrogen atom were investigated: two pairs of alkyl derivatives with methylpiperazinyl and piperidinyl residues and three pairs of acyl derivatives containing dimethylamino, morpholino, and methylpiperazino groups.

Synthesis of compound II was accomplished by cyclization and Smiles' rearrangement of suitably substituted diphenylsulfide. This method is applicable for the preparation of numerous substituted phenothiazines, most often those with the halogen or nitro group substitution pattern [2-4].

The preparation of compound II and its derivatives is described by the following scheme: the 2-amino-2'-nitro-4'-dimethylsulfamidodiphenylsulfide (III) was prepared by a method described earlier [5] and acylated with either acetyl chloride or formic acid. The resulting acetyl (formyl, respectively) derivative IV was converted to N-acyl-3-dimethylsulfamidophenothiazine by treatment with sodium hydroxide in anhydrous acetone and without further purification hydrolyzed to give compound II. The hydrolysis was accomplished using sodium hydroxide in aqueous ethanol.

*Synthesis in the phenothiazine series. Communication XXXVIII.

TABLE 1. 10-Aminopropionyl Derivatives of 2- and 3-Dimethylsulfamidophenothiazine (hydrochlorides and dihydrochlorides)

Compound	mp, °C	Found, %			Empirical formula	Calc., %		
		Cl	N	S		Cl	N	S
IX	198—200	7,31	9,03	13,50	$C_{21}H_{25}N_3O_4S_2 \cdot HCl$	7,33	8,68	13,24
X	211—2	12,99	10,27	11,69	$C_{22}H_{28}N_4O_3S_2 \cdot 2HCl$	13,29	10,49	12,01
XIII	—	7,48	8,88	13,37	$C_{21}H_{27}N_3O_3S_2 \cdot HCl$	7,55	8,94	13,64
XIV	152—4	7,05	8,98	13,28	$C_{21}H_{25}N_3O_4S_2 \cdot HCl$	7,33	8,68	13,24
XV	214—4,5	13,13	10,41	11,69	$C_{22}H_{22}N_4O_3S_2 \cdot 2HCl$	13,29	10,49	12,01

Note: All compounds melted with decomposition; compound XIII does not have a characteristic melting point. Compound IX was crystallized from ethanol–ethyl acetate; X from n-butanol; XIV from acetone–ethyl acetate; XV from isopropanol.

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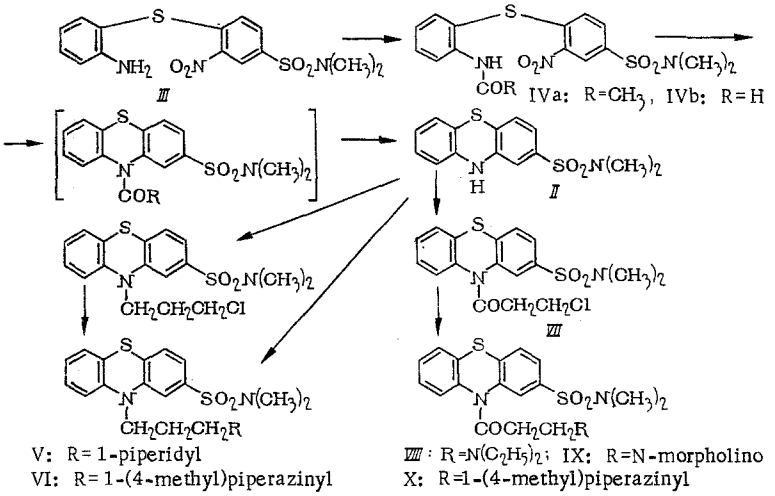
The 10-(3-chloropropyl)-3-dimethylsulfamidophenothiazine was obtained from compound II by treatment with 1-chloro-3-bromopropane in liquid ammonia and sodium amide solution and further reacted with piperidine to yield 10-[3-(1-piperidyl)propyl]-3-dimethylsulfamidophenothiazine V. The sodium amide was prepared in a manner reported previously [6]. The N-methylpiperazinopropyl derivative VI was prepared by refluxing the toluene solution of II with 1-methyl-4-(3-chloropropyl)piperazine in the presence of sodium hydroxide. The reaction of compound II with β-chloropropionyl chloride gave 10-(β-chloropropionyl)-3-dimethylsulfamidophenothiazine VII which was converted into corresponding aminocyl derivatives of II (VIII-X, see Table 1) by reactions with selected secondary amines.



III

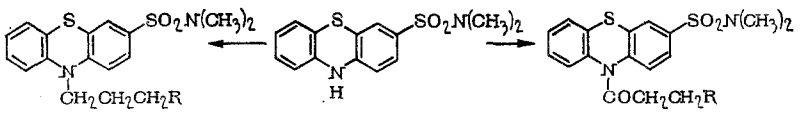
IVa: R=CH_3, IVb: R=H

II

V: R=1-piperidyl
VI: R=1-(4-methyl)piperazinyl

VII: R=$N(C_2H_5)_2$; IX: R=N-morpholino
X: R=1-(4-methyl)piperazinyl

The corresponding aminopropyl and aminopropionyl derivatives of I were synthesized in an analogous manner for comparison of pharmacological activity (compounds XI-XV, see Table 1). Compound XII has been reported earlier [5].



XI: R=1-piperidyl
XII: R=1-(4-methyl)piperazinyl

I

XIII: R=$N(C_2H_5)_2$
XIV: R=N-morpholino
XV: R=1-(4-methyl)piperazinyl

The pharmacological activity of 10-acyl derivatives was evaluated on the basis of the following criteria: potentiation of the effects of phenamine [7] and barbiturates; surpression of orientation capability in the rod climbing test; impairment of coordination by the method of [8]; and abolition of trifluazine-induced catalepsy. The 10-alkyl derivatives I and II were, in addition to the previous tests, tested for induction of catalepsy and surpression of phenamine-induced sterotypic movements.

The aqueous solutions of the compounds tested were administered intraperitoneally to mice, average weight 18-22 g.

A method previously reported [9] for numerical determination of ED_{50} at statistical confidence factor $P = 0.05$ was utilized.

It was found that in the series of 10-aminoalkyl-substituted derivatives of I and II, all compounds possessed antagonist activity to phenamine, potentiated hexobarbital- and meprobamate-induced sleep, induced catalepsy, and impaired orientation reflexes. Impairment of coordinated motion and ataxia were observed in high doses (Table 2).

The transition from aminoalkyl to aminoacyl phenothiazine analogs resulted in qualitative changes in the pharmacological activity profile. The 10-aminoacyl analogs of I and II possessed the following characteristic activities: potentiation of phenamine-induced sterotypic movements in mice and reversal of catalepsy induced by narcoleptics (trifluazine); potentiation of barbiturate depression and, in higher doses, impairment of orientation and coordination (Table 2). The spectra of activities of 10-aminoacyl analogs of I and II are similar to the earlier investigated 10-aminoalkyl phenothiazines with either 2-chloro or 2-trifluoromethyl substitution (chlorazicin and fluorazicin) and mimic tricyclic antidepressants of imipramine and amitriptyline type.

TABLE 2. Comparison of the Activity of 2- and 3-Dimethylsulfamidophenothiazine Derivatives

Compound	Ability to either reverse or potentiate phenamine-induced movements	Impairment of orientation	Impairment of coordination	Potentiation of hexobarbital-induced sleep	Potentiation of meprobamate-induced sleep	Ability to either reverse or induce catalepsy
	ED_{50} μmole/kg					
XI	0,17* (0,08—0,31)	17,22 (9,3—31,86)	100,75 (80,6—125,93)	5,33 (4,01—7,06)	8,61 (5,3—13,95)	17,22‡ (9,3—31,86)
V	~86,1*	122,28 (65,74—227,45)	301,41 (243,05—373,75)	130,89 (68,17—24,29)	279,02 (235,44—330,52)	>258,35‡
XII	—	0,6 (0,47—0,71)	5,8 (34,7—9,33)	0,97 (0,65—1,47)	0,91 (0,65—1,25)	0,52‡ (0,39—0,65)
VI	—	41,25 (24,97—67,97)	>76	43,43 (28,88—65,14)	17,8 (14,11—26,62)	10,85‡ (10,42—11,07)
XIII	12,76† (9,57—16,8)	361,54 (274,35—472,13)	319,01 (229,68—446,61)	136,11 (78,69—233,94)	—	—
VIII	16,61† (10,71—25,76)	465,34 (398,37—544,45)	407,17 (267,87—618,6)	382,25 (289,51—504,57)	—	—
XV	38,42† (24,46—60,31)	—	—	49,67 (19,86—124,17)	8,61 (5,99—14,43)	86,1** —16,6%
X	38,42† (24,46—60,31)	—	—	64,66 (41,79—100,28)	8,61 (5,99—14,43)	86,1** —16,6%
XIV	35,12† (14,09—87,8)	~500	~206,6	82,64	126,07 (90,66—175,18)	—
IX	30,99† (12,39—77,5	~500	371,9 (308,9—446)	~50	~20,5	—

*Ability to reverse phenamine-induced sterotypic movements.

†Ability to potentiate phenamine-induced sterotypic movements.

‡Ability to induce catalepsy.

**Ability to reverse catalepsy.

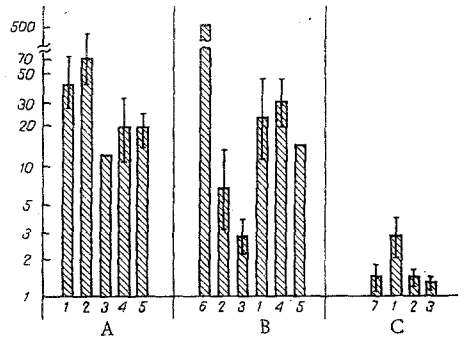


Fig. 1. Comparison of the activities of 2- and 3-sulfamidophenothiazine derivatives (the activity of 3-substituted derivatives was arbitrarily set as 1). Abscissa: 1) potentiation of hexobarbital-induced sleep; 2) impairment of orientation; 3) impairment of coordination; 4) potentiation of meprobamate-induced sleep; 5) ability to induce catalepsy; 6) reversal of phenamine-induced stereotypic movements; 7) potentiation of phenamine-induced stereotypic movements. The standard error of the corresponding activity was determined at statistical confidence factor $P = 0.05$ according to the method reported in [9]. Ordinate: activity values plotted on a logarithmic scale for 10-methylpiperazinyl derivatives (A); 10-piperidinopropionyl derivatives (B); 10-dimethylaminopropionyl derivatives (C).

The shift of the dimethylsulfamido group from position 2 to position 3 (the substitution pattern on the nitrogen atom being unaltered) did not result in qualitative improvement of the pharmacological activity spectrum but led to a substantial decrease of activity in the existing activity range. Thus, in the series of dimethylaminopropionyl derivatives the shift from position 3 to position 2 significantly increased the potentiation of phenamine-induced stereotypic movements and hexobarbital-induced sleep together with impairment of orientation and coordination (see Table 2 and Fig. 1). Similarly, increase of activity was observed in morpholinpropionyl and methylpipirazinopropionyl derivatives of I and II when the dimethylsulfamido group was shifted from position 3 to position 2.

The differences in activity were even more pronounced in the series of alkyl derivatives of I and II than in the acyl derivative series. Thus, the shift of the dimethylsulfamido group from position 3 to position 2 of the piperidyl and methylpiperazinyl derivatives of I and II resulted in a statistically significant increase of activity by all the criteria used: potentiation of hexobarbital- and meprobamate-induced sleep was 25-42 and 27 times, respectively; the reversal of phenamine effects, 500 times, impairment of orientation, 50 times; induction of catalepsy, 22 times.

These data lead us to the conclusion that in both the 10-aminoalkyl and 10-aminoacyl series the compounds with the dimethylsulfamido group in position 2 have significantly greater activities than the corresponding 3-substituted derivatives. The activity differences are more pronounced in the N-alkylamino derivative series but follow the same pattern established for corresponding aminoacyl derivatives of phenothiazine.

EXPERIMENTAL

2-Acetamido-2'-nitro-4'-dimethylsulfamidodiphenylsulfide (IVa). A 15-g solution of III in 10 ml of chloroform was refluxed 3 h with 3.5 ml of acetyl chloride and then cooled. The precipitate was filtered off and washed with benzene, giving 12.2 g of compound IVa. The filtrate was evaporated and from the residue we isolated an additional 2.6 g of IVa. Total yield 88%; mp 183-184° (from ethanol). Found: N 10.49; S 16.31. $C_{16}H_{17}N_3O_5S_2$. Calculated: N 10.49; S 16.20.

2-Formamido-2'-nitro-4'-dimethylsulfamidodiphenylsulfide (IVb). A 10-g mixture of III and 100 ml of 80% formic acid was refluxed for 10 h, cooled, and poured on ice. The precipitate was separated and washed with water. Yield 9.7 g of IVb, mp 166-167° (decomp.; from ethanol). Found: N 10.95; S 16.93. $C_{15}H_{15}N_3O_5S_2$. Calculated: N 11.02; S 16.80.

3-Dimethylsulfamidophenothiazine (II). A solution of 0.4 g of sodium hydroxide in 10 ml of absolute ethanol was added to a solution of 4.0 g of IVa in 50 ml of anhydrous acetone and the mixture refluxed 1 h. Then a solution of 0.4 g of sodium hydroxide in 10 ml of 50% of aqueous ethanol was added and refluxing continued for an additional 2 h. The reaction mixture was evaporated to half of the original volume and cooled. The light-tan crystals were separated and recrystallized from acetone. Yield 2.25 g (75%) of II; mp 203-204° (from acetone). Compound II was obtained from IVb in the same manner in 70% yield. Found: N 9.13; S 20.99. $C_{14}H_{14}N_2O_2S_2$. Calculated: N 9.15; S 20.91.

10-[3-(1-Piperidyl)propyl]-3-dimethylsulfamidophenothiazine Tartrate (V). A fine suspension of sodium amide in liquid ammonia was prepared from 0.5 g of sodium and 0.01 g of ferric nitrate according to the method reported previously [6]; then 6.04 g of II was added during 15-20 min while stirring. The stirring was continued an additional 2.5 h, 4.7 g of 1-chloro-3-bromopropane was added dropwise, and the re-

action mixture stirred 2 h. Then 10 ml of anhydrous toluene was added and the ammonia allowed to evaporate overnight at room temperature. After the addition of a further 10 ml of toluene the mixture was carefully heated, then refluxed 1 h and cooled. The precipitate was filtered off and the filtrate evaporated in vacuo, giving 4.0 g (53%) of 10-(3-chloropropyl)-3-dimethylsulfamidophenothiazine as a viscous oil which was heated without purification for 15 h at 100° with 2.5 ml of piperidine. The reaction mixture was worked up with 5% hydrochloric acid and water, and the acidic solution heated with charcoal and filtered. The gummy product was precipitated by addition of alkali to the filtrate, dissolved in benzene, and the solution dried with magnesium sulfate. Then a solution of tartaric acid in ether was added and 1.4 g of the tartrate V was isolated. The compound lacks characteristic melting point. Found: N 6.95; S 10.93. $C_{22}H_{29}N_3O_2S_2 \cdot C_4H_6O_6$. Calculated: N 7.25; S 11.04.

10-[3-(1-Piperidinyl)propyl]-2-dimethylsulfamidophenothiazine Tartrate (XI). The compound was prepared in a manner analogous to that for V. A characteristic melting point is lacking. Found: N 7.51; S 11.09. $C_{22}H_{29}N_3O_2S_2 \cdot C_4H_6O_6$. Calculated: N 7.23; S 11.04.

10-[3-(4-Methylpiperazino-1-)propyl]-3-dimethylsulfamidophenothiazine Dihydrochloride (VI). A mixture of 3.9 g of II, 4.0 g of powdered sodium hydroxide, and 50 ml of anhydrous toluene was refluxed 1 h, then 5.0 g of 1-methyl-4-(3-chloropropyl)piperazine dihydrochloride was added in small portions and the mixture refluxed 10 h while stirring. Water (30 ml) was added after cooling and the toluene layer washed with water and extracted with 8% hydrochloric acid. The acidic extract was heated with charcoal and filtered. The filtrate was made basic with sodium hydroxide and the liquid decanted. The gummy residue was washed with water, redissolved in toluene, and dried over magnesium sulfate. The dihydrochloride of VI was precipitated out by addition of ethanolic HCl in 65% (4.3 g) yield. Mp 240-241° (decomp., from dimethylformamide). Found: Cl 13.27; N 11.21; S 12.12. $C_{22}H_{30}N_4O_2S_2 \cdot 2HCl$. Calculated: Cl 13.65; N 10.78; S 12.35.

10-(β-Chloropropionyl)-3-dimethylsulfamidophenothiazine (VII). A solution of 3.0 g of II and 1.5 g of β-chloropropionyl chloride in 20 ml of anhydrous toluene was refluxed 30 h and cooled. The solid was filtered and washed with toluene. Yield 3.2 g of VII (82%), mp 143-146° (from toluene). Found: Cl 9.28; S 16.24. $C_{17}H_{17}ClN_2O_3S_2$. Calculated: Cl 8.95; S 16.13.

10-(β-Chloropropionyl)-2-dimethylsulfamidophenothiazine. The compound was obtained in a manner analogous to VII and crystallized from toluene. Yield 95%, mp 195-196° (from toluene). Found: Cl 9.35; S 16.38. $C_{17}H_{17}ClN_2O_3S_2$. Calculated: Cl 8.95; S 16.13.

10-(β-Diethylaminopropionyl)-3-dimethylsulfamidophenothiazine Tartrate (VIII). A solution of 5 g of VII and 3 g of diethylamine in 30 ml of anhydrous toluene was refluxed 3 h, cooled, the precipitate separated, and the filtrate extracted with 7% hydrochloric acid. The acidic extract was decolorized with charcoal, filtered, and the product precipitated by addition of alkali. The gummy precipitate was washed with water and extracted with ether. The extract was dried over magnesium sulfate and the tartrate VIII was precipitated by addition of tartaric acid in ether. The purification was accomplished by conversion of the salt into the free base and repeated precipitation with tartaric acid. The product does not have a characteristic melting point. Found: N 7.27; S 10.16. $C_{21}H_{27}N_3OS_2 \cdot C_4H_6O_6 \cdot H_2O$. Calculated: N 6.98; S 10.65.

The rest of the aminopropionyl derivatives of I and II listed in Table 1 were prepared in the same manner.

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