SYNTHESIS IN THE PHENOTHIAZINE SERIES

XX. 2-Alkylaminoacylamino- and 2-Alkylaminoalkylamino-Substituted Phenothiazine and 10-Methylphenothiazine

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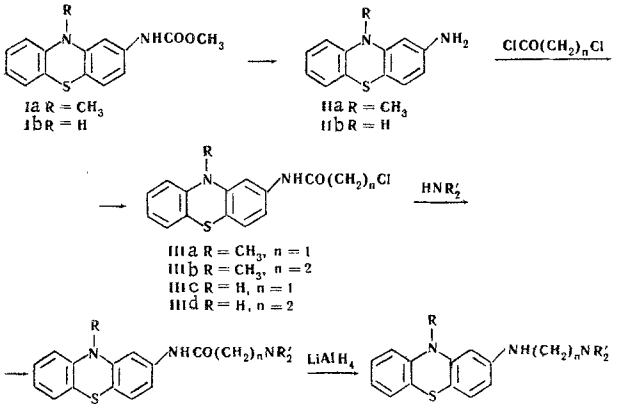
Some 2-dialkylaminoacylamino- and 2-dialkylaminoalkylamino-substituted phenothiazines and 10-methylphenothiazine are synthesized.

According to published results [1] 10-methyl-3-(dialkylaminoacyl)-amido- and 10-methyl-3-(dialkyl aminoalkyl) aminophenothiazines give rise to motor stimulation and tremor. It was of interest to determine how change in position of an amino group affects pharmacological action. For that purpose we synthesized some 2-dialkylaminoacylamido- and 2-dialkylaminoalkylamino-substituted phenothiazines, and 10-methylphenothiazine.

Sulfuration of the methyl ester of diphenylamino-3-carbamic acid [2,3] gives the methyl ester of phenothiazine-3-carbamic acid, and methylation of the latter with methyl iodides provides a synthesis of the methyl ester of 10-methylphenothiazine-2-carbamic acid (Ia). Alkaline hydrolysis of Ia converts it to 10-methyl-2-aminophenothiazine (IIa), and correspondingly the methyl ester of phenothiazine-2-carbamic acid (Ib) is hydrolyzed to 2-aminophenothiazine (IIb) [4]. The resultant amines, under the conditions of the Schotten-Baumann reaction, give on treatment with chloracetyl chloride and β-chloropropionyl chloride, 10-methyl-2-(ω-chloroacylamido)- and 2-(ω-chloroacylamido) phenothiazine (IIIa–e). By treatment with secondary amines in aromatic hydrocarbons the chloroacylphenothiazines obtained are converted into 10-methyl-2-(ω-aminoacylamido)- and 2-(ω-aminoacylamido) phenothiazines (IVa-g) some of which are reduced by lithium aluminum hydride to the corresponding 2-(ω-alkylaminoalkylamino)-substituted phenothiazine and 10-methylphenothiazine (Va–c).

Pharmacological testing was carried out under the supervision of Yu. I. Vikhlyaev. The action of our synthesized 10-methyl-2-(ω-dialkylaminoacyl) amido- and 10-methyl-2-(ω-dialkylaminoalkyl) aminophenothiazine resembles that of 10-methyl-3-(dialkylaminoacyl) amido- and 10-methyl-3-(dialkylaminoalkyl) aminophenothiazines. Obviously, a change in position of the substituted amino group of 10-methylphenothiazine (position 2 or 3), does not substantially change the pharmacological properties. 2-(ω-Dialkylaminoacyl) amido- and 2-(ω-dialkylaminoalkyl) aminophenothiazines and 10-methylphenothiazines differ from the previously synthesized [5,6] in that instead of exhibiting a sedative action, they cause motor stimulation and tremor, like the above-mentioned 10-methylphenothiazine derivatives with a substituted amino group at position 3.



IVa P = R' = CH_3, n = 1
IVb R = CH_3, R' = C_2H_5, n = 1
IVc R = R' = CH_3, n = 2
IVd R = CH_3, R' = C_2H_5, n = 2
IVe R = H, R' = C_2H_5, n = 1
IVf R = H, R' = C_2H_5, n = 2
IVg R = H, NR'$_2$ = $NC_4H_8N-CH_3$, n = 2

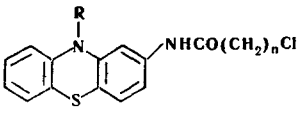
Va R = R' = CH_3, n = 2
Vb R = R' = CH_3, n = 3
Vc R = H, R' = C_2H_5, n = 3

EXPERIMENTAL

Methyl 10-methylphenothiazine-2-carbamate (Ia). 4 g (0.015 mole) methyl phenothiazine-2-carbamate and 4 ml MeI in 30 ml MeOH were heated together for 12 hr in a steel flask, in a boiling water-bath. The precipitate formed on cooling was filtered off, yield 2.6 g (62.8%) substance mp 139–140°, after recrystallizing from EtOH it had mp 148–149° [4].

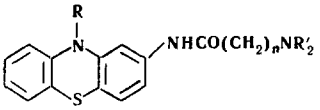
10-Methyl-2-aminophenothiazine (IIa). 3 g (0.01 mole) methyl 10-methylphenothiazine-2-carbamate was refluxed for 8 hr with 60 ml 25% KOH, and after cooling the products were extracted with ether. After drying over $MgSO_4$, and ether solution of HCl was added, to give the amine hydrochloride, yield 1.5 g (53.5%). Pale blue crystalline compound, melts with decomposition about 235°, readily soluble in MeOH and EtOH, insoluble in EtOAc, and benzene. Treatment of the hydrochloride with alkali gives the base, crystallized ex aqueous EtOH, mp 160°. The literature give [7] mp 160°. Found: C 68,61; 68.42; H 5.37; 5.43; N 12.31; 12.13; S 14.10; 14.03%. Calculated for $C_{13}H_{12}N_2S$: C 68.38; H 5.30; N 12.27; S 14.05%. The hydrochloride prepared from the pure base gave: found: Cl 13.40; 13.51; N 10.48; 10.78; S 12.32; 12.17%. Calculated for $C_{13}H_{12}N_2S \cdot HCl$: Cl 13.39; N 10.58; S 12.11%.

Table 1

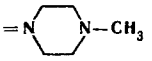


Compound	R	n	Mp, °C (solvent)	Formula	Element	Found, %	Calculated, %	Yield, %
IIIb	CH_3	2	144—145 (toluene)	$C_{16}H_{15}ClN_2OS$	Cl S	11.04; 10.88 9.88; 9.93	11.12 10.06	60
IIIc	H	1	180 (aqueous EtOH)	$C_{14}H_{11}ClN_2OS$	Cl S	12.09 11.07; 11.10	12.19 11.02	72
IIId	H	2	219 (EtOH, dichloroethane)	$C_{15}H_{13}ClN_2OS$	S	10.29; 10.17	10.52	64

Table 2



Compound	R	R′	n	Derivative	Mp, °C (solvent)	Formula	Element	Found, %	Calculated, %	Yield, %
IVc	CH_3	CH_3	2	Base	118,5—120 (benzene)	$C_{18}H_{21}N_3OS$	N S	12.67; 12.73 9.70; 9.62	12.83 9.79	84
				Hydrochloride	221—226 (EtOH)	$C_{18}H_{21}N_3OS \cdot HCl$	Cl N S	9.63; 9.68 11.32; 11.52 8.77; 8.72	9.74 11.54 8.81	
IVd	CH_3	C_2H_5	2	Hydrochloride	160 (dry EtOH)	$C_{20}H_{25}N_3OS \cdot HCl$	Cl N S	8.90; 8.91 10.43; 10.58 7.93; 8.09	8.77 10.40 7.94	41
IVe	H	C_2H_5	1	Hydrochloride	259 (EtOH)	$C_{18}H_{21}N_3OS \cdot HCl$	Cl S	9.79; 9.85 8.95; 8.85	9.74 8.81	
				Base	131—132 (aqueous EtOH)	$C_{18}H_{21}N_3OS$	N S	12.81; 12.82 9.75; 9.60	12.83 9.79	75,5
IVf	H	C_2H_5	2	Hydrochloride	150—151 (aqueous EtOH)					
				Hydrochloride	215—216 (water)	$C_{19}H_{23}N_3OS \cdot HCl$	Cl S	9.27; 9.28 8.25; 8.26	9.38 8.48	80
IVg	H	*	2	Base	151—152 (CCl_4)					
				Hydrochloride	242 (decomp, EtOH)	$C_{20}H_{24}N_4OS \cdot 2HCl$	Cl S	15.96; 15.86 6.91; 6.90	16.03 7.26	49

* $NR_2 =$ 

10-Methyl-2-chloroacetylaminophenothiazine (IIIa). A mixture of 2.64 g (0.01 mole) 10-methyl-2-aminophenothiazine, 1.7 g (0.2 mole) $NaHCO_3$, 10 ml dichloroethane, 5 g water, and 5 g ice was stirred and cooled with ice, then a solution of 1.2 g chloroacetyl chloride in 10 ml dry dichloroethane added over a period of 2 hr. After the chloroacetyl chloride had been added, the reaction mixture was stirred for 1 hr more. 1.3 g (42.6%) of a grayish crystalline substance was isolated, mp 144°. After recrystallizing from aqueous MeOH it had mp 158°. The compound was readily soluble in dioxane and dichloroethane. Found: Cl 11.98; 11.84; S 10.78; 10.75%. Calculated for $C_{15}H_{13}ClN_2OS$: Cl 11.63; S 10.52%.

IIIb–d were prepared similarly (see Table 1).

10-Methyl-2-(dimethylaminoacetyl) amidophenothiazine (IVa). 20 ml 20% solution of Me_2NH in benzene was added to 5 g (0.016 mole) 10-methyl-2-chloroacetylamidophenothiazine. The reaction was run in a sealed tube at room temperature. Next day the $Me_2NH \cdot HCl$ which separated was filtered off, and the benzene distilled off from the filtrate. 5 g oily residue was obtained, which was dissolved in ether, and the hydrochloride obtained by treatment with an ether solution of HCl gas mp 220–222°, yield 4.24 g (73.7%). Recrystallized from dry EtOH it was a bluish compound, mp 226–227°. Found: N 12.02; 11.82; S 9.43; 9.33%. Calculated for $C_{17}H_{19}N_3OS \cdot HCl$: N 12.00; S 9.17%. IVc was prepared similarly (see Table 2).

10-Methyl-2-(diethylaminoacetyl)amidophenothiazine (IVb). 0.68 g (2.2 mole) 10-methyl-2-chloroacetylamidophenothiazine, 1 g (13.7 mmole) Et_2NH, and 5 ml benzene were refluxed together for 10 hr, the $Et_2NH \cdot HCl$ removed, and the benzene distilled off; the honey-like residue crystallized on prolonged trituration with ether, yield 0.68 g (89%), mp 60–62°, hydrochloride mp 229° (ex dry EtOH). Found: Cl 9.81; 9.76; S 8.48; 8.44%. Calculated for $C_{19}H_{23}N_3OS \cdot HCl$: Cl 9.38; S 8.48%. IVd-g were prepared similarly (see Table 2).

10-Methyl-2-[(2'-dimethylamino)ethylamino]phenothiazine (Va). A 3-necked flask was fitted with stirrer, reflux condenser, and dropping funnel, and protected with a $CaCl_2$ tube. Into the flask was introduced 0.54 g (0.015 mole) $LiAlH_4$ in 11 ml dry ether, which was stirred, and 3 g (0.009 mole) 10-methyl-2-dimethylaminoacetylamidophenothiazine in 300 ml dry ether added over a period of 1 hr 30 min. Then the mixture was stirred and refluxed for 16 hr. Excess $LiAlH_4$ was destroyed with moist ether, then with water. The mixture was filtered, the ether layer separated off, dried over $MgSO_4$, and worked up to give 2.2 g (78%) impure yellow base. It was converted to the dihydrochloride mp 192–193° (ex dry EtOH). Found: N 11.40; 11.59; S 8.99; 8.80%. Calculated for $C_{17}H_{21}N_3S \cdot 2HCl$: N 11.28; S 8.61%.

10-Methyl-2-[(3'-dimethylamino)propylamino] phenothiazine. (Vb). This was prepared similarly, from 2.5 g (0.007 mole) 10-methyl-2-(β-dimethylpropionylamido)phenothiazine (IVc), yield of dihydrochloride 2 g (77%), colorless substance, turning red in air, mp 184–185° (ex dry EtOH), soluble in water and EtOH, slightly soluble in EtOAc. Found: N 10.71; 10.87; S 8.64; 8.68%. Calculated for $C_{18}H_{23}N_3S \cdot 2HCl$: N 10.87; S 8.30%.

2-[(3'Diethylamino)propylamino] phenothiazine. Prepared similarly from 1.71 g (0.005 mole 2-(3-diethylaminopropionylamido)phenothiazine. Yield of hydrochloride 0.61 g (38.5%), mp 275° (ex dry iso-PrOH). Found: Cl 9.80; 9.69; S 8.95%. Calculated for $C_{19}H_{25}N_3S \cdot HCl$: Cl 9.74; S 8.81%.

REFERENCES

1. Yu. I. Vikhlyaev, Materials of the IX All-Union Pharmacological Conference [in Russian], Sverdlovsk, 52, 1961.

2. S. V. Zhuravlev and V. A. Skorodumov, ZhOKh, 31, 3131, 1961.

3. S. V. Zhuravlev and A. E. Gritsenko, ZhOKh, 33, 597, 1963.

4. A. N. Gritsenko and S. V. Zhuravlev, ZhOKh, 33, 3697, 1963.

5. S. V. Zhuravlev and A. N. Gritsenko, ZhOKh, 26, 3385, 1956.

6. A. N. Gritsenko and S. V. Zhuravlev, ZhOKh, 30, 2640, 1960.

7. G. Cauquil, A. Casadevall, and E. Casadevall, Bull. soc. chim. France, 608, 1962.

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