SYNTHESES IN THE PHENOTHIAZINE SERIES

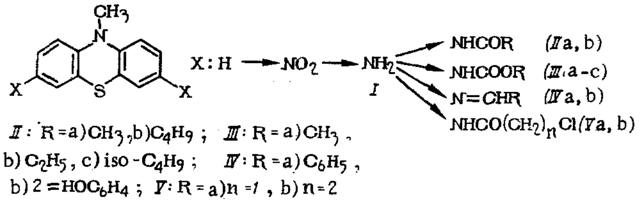
XLI. 3,4-DIAMINO-10-METHYLPHENOTHIAZINE

G. A. Khutornenko, N. S. Panshina,
and S. V. Zhuravlev

UDC 615.31:547.869.2

It has been established by previous investigations [1] on 3-amino-10-methylphenothiazine that 3-(dialkylaminoalkylamino)-10-methylphenothiazine shows a high biological activity under experimental conditions and causes motor stimulation and tremors in animals.

With the intention of studying the relationship between the biological activity and the number of analogous substituents in the phenothiazine nucleus we have synthesized 3,7-diamino-10-methylphenothiazine and several of its derivatives.



II: R = a) CH_3, b) C_4H_9; III: R = a) CH_3, b) C_2H_5, c) iso-C_4H_9; IV: R = a) C_6H_5, b) 2 = HOC_6H_4; V: R = a) n = 1, b) n = 2

Catalytic hydrogenation of 3,7-dinitro-10-methylphenothiazine-5-oxide [2] over a nickel catalyst in acetic acid or methanol gave I which was characterized both in the form of the free base and as the hydrochloride. In contrast to 3,7-diaminophenothiazine and 3,7-diamino-10-acetylphenothiazine-5-oxide [3], the diamine I is more stable to the action of atmospheric oxygen and may be stored as the base.

Reaction of I with acetic anhydride in pyridine gave IIa which was identical to the previously known product [2]. Reaction of I with chlorocarbonate, with butyric acid chloranhydride, and with aromatic aldehydes gave esters of 10-methylphenothiazinedicarbamic-3,7 acid (IIIa-c), 10-methyl-3,7-butyrylamidophenothiazine (IIb), and Schiff bases (IVa and b) respectively. The action of chloroacetyl chloride and β-chloroprppionyl chloride on I gave 10-methyl-3,7-(φ-chloroacylamido)-phenothiazine (IVa and b).

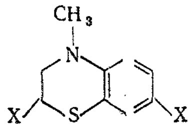
Pharmacological investigation of the diesters of 10-methylphenothiazinedicarbamic-3,7 acid (III, IV, V) has established that they have a weak sedative influence which was shown by tests of potentiation of hexenal sleep and disruption of orientation reactions. These compounds are of interest because of the fact that the sedative effect is supplemented by an antispasmodic effect with respect to the anticorazol test. The most effective in both sedative and antispasmodic effect is the diester V. No myorelaxant properties are observed in these compounds. They have a greater overall depressant activity than the known preparations with similar type of action.

EXPERIMENTAL METHOD

3,7-Diamino-10-methylphenothiazine (I). Hydrogenation is carried out on 14 g of 3,7-dinitro-10-methylphenothiazine-5-oxide in 290 ml glacial acetic acid in the presence of 18 g of nickel catalyst at room temperature for 4 h until the starting material is dissolved. After removal of the catalyst a dilute solution of caustic soda is added to the filtrate to bring the pH to 9.0 and the precipitate thrown down filtered off, washed with water, and dried in a desiccator. A yield of 8.5 g (80%) of material is obtained which is crystallized from methanol. The bluish-gray crystals with mp 172-174° (from dichloroethane) are soluble in alcohol and acetone. Found, %: N 17.11; S 13.25. Calculated for $C_{13}H_{13}N_3S$, %: N 17.28; S 13.14.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 2, pp. 43-45, February, 1976. Original article submitted December 8, 1974.

TABLE 1. Derivatives of 3,7-Diamino-10-Methylphenothiazine



Compound	X	Yield (%)	mp (in deg)*	Found (%)		Empirical formula	Calculated (%)	
				N	S		N	S
IIb	$NHCOC_4H_7$	47	277—9	11,20	8,38	$C_{21}H_{25}N_3O_2S$	10,96	8,36
IIIb	$NHCOOC_2H_5$	76	225—7	10,68	8,45	$C_{19}H_{21}N_3O_4S$	10,82	8,25
IIIc	$NHCOOC_4H_9$	80	197—8	9,48	7,38	$C_{23}H_{29}N_3O_4S$	9,48	7,19
IVb	$N{=}CHC_6H_4OH{=}2$	70	237—8	9,45	7,09	$C_{27}H_{21}N_3O_2S$	9,30	7,10
Vb	$NHCO(CH_2)_2Cl$	60	242—3	—	7,58	$C_{19}H_{19}Cl_2N_3O_2S$	—	7,55

*IIb is crystallized from alcohol, IIIb and c from dioxane, IVb from toluene, and Vb from methanol.

Note. Found for Vb, %: Cl 16.48; calculated, %: Cl 16.71.

The hydrochloride I was obtained in the form of white crystals with a bluish tinge which, on heating above 220°, did not melt but darkened. Found, %: Cl 22.49; N 13.01; S 10.21. Calculated for $C_{13}H_{15}Cl_2N_3S$, %: Cl 22.42; N 13.28; S 10.10.

3,7-Diacetylamido-10-methylphenothiazine (IIa). 8 ml of pyridine and 6 ml of acetic anhydride were added to 1.21 g of I, the mixture heated to boiling, and left for 12 h at room temperature. The reaction mixture was poured out into 50 ml of cold water and the precipitate formed separated. 0.9 g (55%) of material is obtained with a mp of 263-265° (from methanol); according to the literature data [3] the mp is 265°.

Dimethyl Ester of 10-Methylphenothiazinedicarbamic-3,7 Acid (IIIa). A solution of 2.43 g of I in 100 ml of methanol is cooled to 5-7° and 1.4 g of methylchlorocarbonate added dropwise with stirring over a period of 30 min. Another 1.4 g of methylchlorocarbonate and a solution of 1.86 g sodium carbonate in 6 ml of water were then added simultaneously and stirred for 30 min under the same conditions. After addition to the reaction mixture of 100 ml of water the precipitate was filtered off. 3.05 g (85%) of material with mp 253-254° (from dioxane) was obtained. Found, %: C 56.92; H 4.82; N 11.77; S 8.87. Calculated for $C_{17}H_{17}N_3O_4S$, %: C 56.81; H 4.76; N 11.77; S 8.92. Compounds IIb and IIIb and c are obtained similarly (see Table 1).

3,7-Benzylideneamino-10-methylphenothiazine (IVa). To a solution of 1.2 g of I in 25 ml of glacial acetic acid 1.8 ml of benzaldehyde was added, the mixture was stirred well and left overnight. Addition of water precipitates 1.6 g (75%) of material. The yellow crystals with mp 224-226° (from toluene) are readily soluble in dichloroethane and, to a lesser extent, in alcohol. Found, %: N 9.85; S 7.81. Calculated for $C_{37}H_{21}N_3S$, %: N 10.01; S 7.64. Compound IVb was obtained similarly (see Table 1).

3,7-Chloroacetylamido-10-methylphenothiazine (Va). A solution of 5.65 g chloroacetylchloride in 20 ml dichloroethane was added to a mixture of 4.86 g of I, 4.65 g of sodium bicarbonate, 40 ml of dichloroethane, 13 ml of water, and 13 g of ice at 0-5° and stirring continued for 2 h. On cooling, the reaction mixture was stirred for a further 30 min. The precipitate was filtered off, washed with water, dried in dioxane. 5 g (63%) of a light-gray material was obtained with a mp of 239-241° and solubility in alcohol and acetic acid. Found, %: N 10.37; S 8.31. Calculated for $C_{17}H_{15}Cl_2N_3O_2S$, %: N 10.60; S 8.09.

Compound Vb was obtained similarly (see Table 1).

LITERATURE CITED

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3. G. A. Khutornenko, N. S. Panshina, and S. V. Zhuravlev, Khimiya Geterotsikl. Soedin., No. 3, 325-327 (1972).