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Basically Substituted Derivatives of Phenothiazine-10-carboxylic Acid

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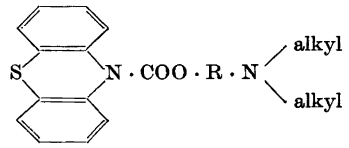
Previous work on 10-aminoacylphenothiazines has shown that several members of this class possess strong spasmolytic activity [1–3]. However, most synthetic antispasmodic agents hitherto known are in their chemical structure carboxylic acid esters of aminoalcohols, and it was therefore considered to be of interest to study the pharmacological properties of some amino-esters containing the phenothiazine nucleus. A number of esters of phenothiazine-10-carboxylic acid were therefore synthesised and tested.



R = $-CH_2 \cdot CH_2-$ or $-CH(CH_3) \cdot CH_2-$

The new esters were smoothly obtained by the reaction of phenothiazine-10-carbonyl chloride with the appropriate aminoalcohol, or by the reaction of the acid chloride with a halohydrin to form a halogenoalkylester, which was then treated with a secondary amine. Attempts to obtain aminoesters by transesterification of methyl phenothiazine-10-carboxylate were unsuccessful.

In addition to the amino esters one thiolester and some amides of phenothiazine-10-carboxylic acid were prepared, and some of the aminoesters were converted into quaternary salts by means of alkyl halogenides.

Absorption spectra. In a previous paper [1] the ultra-violet absorption spectra of some 10-alkyl and 10-acyl derivatives of phenothiazine were measured. As a comparison the absorption of two esters (methyl and β-diethylamino-ethyl phenothiazine-10-carboxylate) and two amides [N-(phenothiazine-10-carbonyl)-piperidine and -pyrrolidine] were determined. The measurements were made with a Beckman Model DU spectrophotometer using ethanol as solvent. The two types of spectra are shown in Fig. 1. The esters, which had almost identical spectra, had maxima at 231 mμ and 256 mμ and a point of

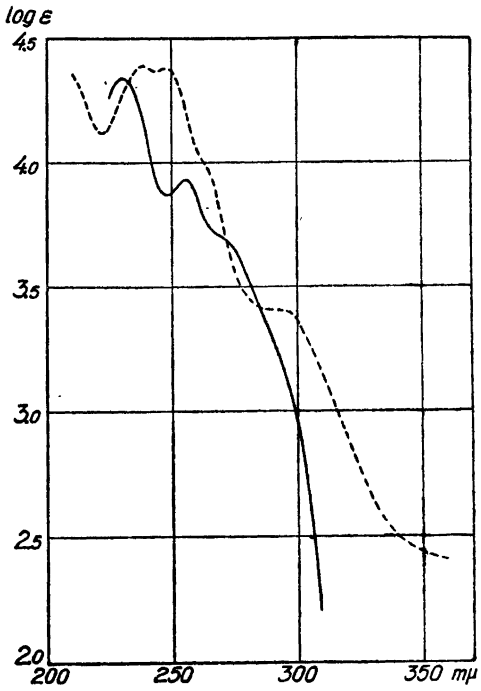


Fig. 1. The absorption spectra of β-diethylaminoethyl phenothiazine-10-carboxylate (————) and N-(phenothiazine-10-carbonyl)-piperidine (— — — —) in abs. ethanol (concentrations ca. 3 × 10⁻⁵ M).

inflection at 270 mμ. The amides had also very similar spectra with maxima at 238 mμ and 248 mμ and a point of inflection at 290 mμ.

PHARMACOLOGY

The new compounds have been tested for local anesthetic, antispasmodic, antihistaminic, nicotinolytic, and ganglionic blocking activity *.

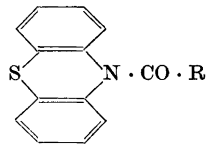
Local anesthetic effect. The tertiary amines were strong anesthetics (1—6 times the activity of Xylocaine, when tested on the rabbit *cornea*). They were, however, rather irritating and had a longer time of onset. The quaternary salts were inactive.

Antispasmodic effect. The results of the tests for cholinolytic activity on isolated guinea pig intestine are shown in Table 1. Several compounds possess considerable cholinolytic activity. Quaternization of the tertiary amines seems to have little influence on the activity.

The new compounds have also been tested for musculotropic spasmolytic activity on spasm of rat *ileum* caused by barium chloride. The results will be

* Acknowledgement is made to Dr. S. Wiedling of Astra's Biological Department for performing the tests for local anesthetic, cholinolytic and antihistaminic effect.

Table 1. Cholinolytic and antihistaminic properties of derivatives of phenothiazine-10-carboxylic acid.



	R	Salt tested	Effect * in reducing the spasm produced by	
			Acetyl-choline	Histamine
IV	$-O \cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$	HCl	5.5	0.4
V	$-O \cdot CH_2 \cdot CH_2 \cdot N(C_2H_5)_2$	HCl	13	0.13
VI	$-O \cdot CH_2 \cdot CH_2 \cdot NC_4H_8O$	$H_2C_2O_4$	0.15	
VII	$-O \cdot CH_2 \cdot CH_2 \cdot NC_4H_8$	HCl	1.2	0.2
VIII	$-O \cdot CH(CH_3) \cdot CH_2 \cdot N(CH_3)_2$	$H_2C_2O_4$	2.6	0.02
IX	$-O \cdot CH(CH_3) \cdot CH_2 \cdot NC_5H_{10}$	$H_2C_2O_4$	0.15	
X	$-S \cdot CH_2 \cdot CH_2 \cdot N(C_2H_5)_2$	$H_2C_2O_4$	19	0.04
XI	$-O \cdot CH_2 \cdot CH_2 \cdot \overset{+}{N}(CH_3)_3$	Br^-	3.3	0.2
XII	$-O \cdot CH_2 \cdot CH_2 \cdot \overset{+}{N}(CH_3)_2C_2H_5$	Br^-	6	
XIII	$-O \cdot CH_2 \cdot CH_2 \cdot \overset{+}{N}(C_2H_5)_2CH_3$	Br^-	15	0.12
XIV	$-O \cdot CH_2 \cdot CH_2 \cdot \overset{+}{N}(C_2H_5)_3$	Br^-	12	0.07
XVIII	$-NH \cdot CH_2 \cdot CH_2 \cdot N(C_2H_5)_2$	HCl	18	0.1
	Atropine sulphate		30	
	Diphenhydramine-HCl		1	1

* The activity figures refer to the base. The activities of the quaternary salts refer to the cationic part of the molecule.

published and discussed elsewhere [4]. Great activity was shown by β-diethylaminoethyl phenothiazine-10-carboxylate (V) especially. The quaternary compounds were less active than the parent tertiary amines.

Antihistaminic effect. The results are shown in Table 1. None of the compounds were as active as diphenhydramine. Quaternization seems to lower the activity a little.

Nicotinolytic effect. Some of the compounds have been tested by the method of Bovet and Longo [5]. Outstanding nicotinolytic properties were revealed by β-diethylaminoethyl phenothiazine-10-carboxylate (V) [6,7], which seems to be one of the most active nicotinolytic agents known at present. One of the quaternary compounds (XIII) was tested but was ineffective.

Ganglionic blocking effect. The quaternary salts (XI—XIV) showed a strong ganglionic blocking activity when tested on the peristaltic reflex. The results will be published elsewhere [8].

EXPERIMENTAL

Esters of phenothiazine-10-carboxylic acid

Phenothiazine-10-carbonyl chloride (I) used as starting material was obtained by the method of Paschkowezky [9] by heating phenothiazine with a small excess of phosgene in toluene in a sealed vessel at 95—100°, for two hours. Yield 85—90 %; m.p. 172—173°.

Methyl phenothiazine-10-carboxylate (II). A solution of phenothiazine (10.0 g) and methyl chloroformate (6.0 g) in toluene (15 ml), was heated in a sealed vessel at 100° for 20 hours, and then at 120° for a further 4 hours. After cooling, the dark mixture was filtered giving 6.5 g (51 %) of the crude crystalline ester. Two recrystallisations from methanol afforded colourless crystals, m.p. 118—120°. (Found: C 65.5; H 4.45; N 5.62. $C_{14}H_{11}NO_2S$ (257.3) requires C 65.3; H 4.31; N 5.45 %.)

β-Chloroethyl phenothiazine-10-carboxylate (III). A mixture of I (2.6 g) and ethylene chlorohydrin (10 ml), was refluxed until hydrogen chloride was no longer evolved (12 hours). On cooling, white crystals separated (2.0 g, 65 %); m.p. 146—148° after two recrystallisations from acetone. (Found: C 59.2; H 3.80; Cl 12.0; N 4.59. $C_{15}H_{12}ClNO_2S$ (305.8) requires C 58.9; H 3.96; Cl 11.6; N 4.58 %.)

β-Dimethylaminoethyl phenothiazine-10-carboxylate hydrochloride (IV). A solution of I (2.6 g, 0.01 mole) and β-dimethylaminoethanol (2.2 g, 0.025 mole) in toluene (10 ml) was refluxed for two hours. After cooling the resultant β-dimethylaminoethanol hydrochloride was removed by filtration. The toluene solution was washed with water and dried over calcium chloride, and the aminoester isolated by the addition of ethereal hydrogen chloride. The crude product (2.9 g, 83 %) was recrystallised from ethanol; m.p. 212—213° (dec.). (Found: C 57.8; H 5.48; N 7.99. $C_{17}H_{18}N_2O_2S \cdot HCl$ (350.9) requires C 58.2; H 5.46; N 7.99 %.)

β-Diethylaminoethyl phenothiazine-10-carboxylate (V). The *hydrochloride* of this compound was prepared by the method used for IV. Yield 95 %; m.p. 163—164° after recrystallisation from ethanol-light petroleum (2 : 1). (Found: C 59.8; H 6.25; N 7.20. $C_{19}H_{22}N_2O_2S \cdot HCl$ (378.9) requires C 60.2; H 6.12; N 7.40 %.) From the hydrochloride the free base was obtained in solid form; m.p. 54—56° (from ethanol). (Found: C 66.7; H 6.59; N 8.15. $C_{19}H_{22}N_2O_2S$ (342.5) requires C 66.6; H 6.47; N 8.18 %.)

β-Morpholinoethyl phenothiazine-10-carboxylate oxalate (VI). Prepared from I and β-morpholinoethanol [10]. Yield, 34 %; m.p. 111—114° (dec.), from acetone. (Found: C 56.5; H 5.16; N 5.96. $C_{19}H_{20}N_2O_3S \cdot H_2C_2O_4$ (446.5) requires C 56.5; H 4.97; N 6.28 %.)

β-Pyrrolidinoethyl phenothiazine-10-carboxylate hydrochloride (VII).

Method A. I and β-pyrrolidinoethanol [11] afforded VII by the usual method. Yield, 82 %; m.p. 215—217° (dec.) after recrystallisation from ethanol. (Found: C 60.8; H 6.00; N 7.35. $C_{19}H_{20}N_2O_2S \cdot HCl$ (376.9) requires C 60.5; H 5.62; N 7.43 %.)

Method B. A solution of β-chloroethyl phenothiazine-10-carboxylate (1.8 g) and pyrrolidine (1.05 g) in toluene (10 ml), was refluxed for two hours. The reaction mixture was filtered, washed with water and dried over calcium chloride. Addition of ethereal hydrogen chloride gave the hydrochloride of the β-pyrrolidinoethyl ester. Yield, 0.60 g, 27 %; m.p. 214—216° (dec.), from ethanol, undepressed on admixture with the product prepared by method A above.

β-Dimethylaminoisopropyl phenothiazine-10-carboxylate oxalate (VIII). Obtained from I and β-dimethylamino*iso*propanol. Yield, 29 %; m.p. 181—182° (dec.) after recrystallisation from acetone. (Found: C 57.5; H 5.16; N 6.58. $C_{18}H_{20}N_2O_2S \cdot H_2C_2O_4$ (418.5) requires C 57.4; H 5.30; N 6.70 %.)

β-Piperidinoisopropyl phenothiazine-10-carboxylate oxalate (IX). Prepared from I and β-piperidino*iso*propanol [12]. Yield, 68 %; m.p. 170—171° (dec.), from ethanol. (Found: C 59.6; H 5.81; N 5.88. $C_{21}H_{24}N_2O_2S \cdot H_2C_2O_4$ (458.5) requires C 60.2; H 5.72; N 6.11 %.)

β-Diethylaminoethyl phenothiazine-10-thiocarboxylate oxalate (X). Prepared by the same method as the preceding esters from I and β-diethylaminoethyl mercaptan [13]. Yield 56 %; m.p. 158—160° (dec.) after two recrystallisations from acetone. (Found: C 56.3; H 5.42; N 6.12. $C_{19}H_{22}N_2OS_2 \cdot H_2C_2O_4$ (448.5) requires C 56.2; H 5.39; N 6.25 %.)

Quaternary derivatives

β-Dimethylaminoethyl phenothiazine-10-carboxylate methobromide (XI). β-Dimethylaminoethyl phenothiazine-10-carboxylate hydrochloride (0.63 g) was dissolved in water and the solution was made alkaline. The oily base was extracted with ether and the extract was dried and evaporated. The residue was dissolved in acetone (5 ml) and methyl bromide (2 ml) added. The quaternary salt began to crystallise immediately. The mixture was allowed to stand over night at room temperature, and the product was collected and washed with acetone. Yield, 0.63 g, 78 %; m.p. 248—249° (dec.) after recrystallisation from acetone-ethanol (1 : 1). (Found: C 53.1; H 5.20; N 6.75. $C_{18}H_{21}BrN_2O_2S$ (409.4) requires C 52.8; H 5.17; N 6.84 %.)

The *methiodide* was prepared similarly in 71 % yield; m.p. 235—236° (dec.), from acetone-ethanol. (Found: C 46.9; H 4.74; N 6.27. $C_{18}H_{21}IN_2O_2S$ (456.4) requires C 47.4; H 4.64; N 6.14 %.)

β-Dimethylaminoethyl phenothiazine-10-carboxylate ethobromide (XII). Prepared in the same manner as XI in 78 % yield; m.p. 233—234° (dec.) after recrystallisation from methanol. (Found: C 53.2; H 5.53; N 6.71. $C_{19}H_{23}BrN_2O_2S$ (423.4) requires C 53.9; H 5.48; N 6.62 %.)

β-Diethylaminoethyl phenothiazine-10-carboxylate methobromide (XIII). Obtained in 68 % yield; m.p. 220—221° (dec.), from acetone-ethanol. (Found: C 55.7; H 5.87; N 6.43. $C_{20}H_{25}BrN_2O_2S$ (437.4) requires C 54.9; H 5.76; N 6.41 %.)

β-Diethylaminoethyl phenothiazine-10-carboxylate ethobromide (XIV). The reactants were kept at 40° for 48 hours. Yield 55 %; m.p. 213—215° (dec.), from acetone-ethanol. (Found: C 55.4; H 5.74; N 6.35. $C_{21}H_{27}BrN_2O_2S$ (451.4) requires C 55.9; H 6.03; N 6.21 %.)

Amides of phenothiazine-10-carboxylic acid

N-(Phenothiazine-10-carbonyl)-diethylamine (XV). Phenothiazine-10-carbonyl chloride (I, 2.6 g) was refluxed with diethylamine (2.2 g) in toluene (10 ml) for two hours. The mixture was filtered in order to remove diethylamine hydrochloride, washed with water and evaporated to dryness *in vacuo*. The residue (2.9 g, 97 %) was recrystallised from ethanol; m.p. 91—93°. (Found: C 68.3; H 6.00; N 9.43. $C_{17}H_{18}N_2OS$ (298.4) requires C 68.4; H 6.08; N 9.39 %.)

N-(Phenothiazine-10-carbonyl)-piperidine (XVI). Obtained by the method for XV above, from I and piperidine. Yield, 73 %; m.p. 118—120°, from ethanol. (Found: C 69.2; H 5.61; N 9.33. $C_{18}H_{18}N_2OS$ (310.4) requires C 69.6; H 5.84; N 9.03 %.)

N-(Phenothiazine-10-carbonyl)-pyrrolidine (XVII). Prepared from I and pyrrolidine. Yield 68 %; m.p. 137—139°, from ethanol. (Found: C 68.8; H 5.75; N 9.52. $C_{17}H_{16}N_2OS$ (296.4) requires C 68.9; H 5.44; N 9.45 %.)

N-(Phenothiazine-10-carbonyl)-N',N'-diethylethylenediamine hydrochloride (XVIII). A solution of I (5.0 g) and N,N-diethylethylenediamine [14] (5.5 g) in toluene (10 ml) was refluxed for two hours. After cooling the clear solution was washed with water. On extraction of the solution with 2 *N* hydrochloric acid the reaction product separated as the hydrochloride (7.0 g, 98 %); m.p. 180—181° (dec.). Recrystallisation of this product from methanol yielded crystals of m.p. 142—144°, apparently containing two moles of methanol of crystallisation. (Found: C 57.5; H 6.97; N 9.52. $C_{19}H_{23}N_3OS \cdot HCl + 2\ CH_3OH$ (442.0) requires C 57.1; H 7.30; N 9.51 %.) On drying at 105° the weight was constant after a loss of 13.8 % (calc. for 2 CH_3OH: 14.5 %) and the m.p. was 184—186° (dec.). (Found: C 59.9; H 6.39; N 11.0. $C_{19}H_{23}N_3OS \cdot HCl$ (377.9) requires C 60.4; H 6.40; N 11.1 %.)

SUMMARY

A series of basically substituted derivatives of phenothiazine-10-carboxylic acid has been prepared. Some of the compounds possess strong spasmolytic and nicotinolytic activity.

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