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 spasmodolytic activity¹-³. 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 aminoesters containing the phenothiazine nucleus. A number of esters of phenothiazine-10-carboxylic acid were therefore synthesised and tested.

\[
\text{alkyl} \quad \text{alkyl}
\]

\[
\text{R} = -\text{CH}_2 \cdot \text{CH}_2 - \text{ or } -\text{CH(CH}_3) \cdot \text{CH}_2 -
\]

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 paper¹ 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-dietethylaminoethyl 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
inflection at 270 μ. The amides had also very similar spectra with maxima at 238 μ and 248 μ and a point of inflection at 290 μ.

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 spasmylytic 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.

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

<table>
<thead>
<tr>
<th>R</th>
<th>Salt tested</th>
<th>Effect * in reducing the spasm produced by</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>IV - O·CH₃·CH₄·N(CH₃)₂</td>
<td>HCl</td>
<td>5.5</td>
</tr>
<tr>
<td>V - O·CH₃·CH₄·N(C₂H₅)₂</td>
<td>HCl</td>
<td>13</td>
</tr>
<tr>
<td>VI - O·CH₃·CH₄·NC₆H₁₂O</td>
<td>H₂C₂O₄</td>
<td>0.15</td>
</tr>
<tr>
<td>VII - O·CH₃·CH₄·NC₂H₄</td>
<td>HCl</td>
<td>1.2</td>
</tr>
<tr>
<td>VIII - O·CH(CH₃)₂·CH₂·N(CH₃)₂</td>
<td>H₂C₂O₄</td>
<td>2.6</td>
</tr>
<tr>
<td>IX - O·CH(CH₃)₂·CH₂·NC₂H₆O</td>
<td>H₂C₂O₄</td>
<td>0.15</td>
</tr>
<tr>
<td>X - S·CH₃·CH₄·N(C₆H₅)₂</td>
<td>H₂C₂O₄</td>
<td>19</td>
</tr>
<tr>
<td>XI - O·CH₂·CH₂·N(CH₃)₂</td>
<td>Br⁻</td>
<td>3.3</td>
</tr>
<tr>
<td>XII - O·CH₃·CH₂·N(CH₃)₂C₆H₅</td>
<td>Br⁻</td>
<td>6</td>
</tr>
<tr>
<td>XIII - O·CH₂·CH₂·N(C₆H₅)₂CH₃</td>
<td>Br⁻</td>
<td>15</td>
</tr>
<tr>
<td>XIV - O·CH₂·CH₂·N(C₆H₅)₂</td>
<td>Br⁻</td>
<td>12</td>
</tr>
<tr>
<td>XVIII - NH·CH₃·CH₂·N(C₂H₅)₂</td>
<td>HCl</td>
<td>18</td>
</tr>
</tbody>
</table>

| Atropine sulphate | 30 |
| Diphenhydramine-HCl | 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. 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. Outstanding nicotinolytic properties were revealed by β-diethylaminooethyl phenothiazine-10-carboxylate (V) and, 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.

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Esters of phenothiazine-10-carboxylic acid

Phenothiazine-10-carboxyl chloride (I) used as starting material was obtained by the method of Paschke, * by heating phenothiazine with a small excess of phosphine 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. C₁₉H₁₈NO₂S (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 chlorhydrin (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 3.90; Cl 12.0; N 4.59. C₁₅H₁₄ClNO₂S (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 aminooxy 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. C₁₇H₁₅N₂O₄S · HCl (350.9) requires C 58.2; H 5.46; N 7.79 %.)

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. C₁₉H₁₈N₂O₂S · HCl (375.9) 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. C₁₅H₁₇N₂O₂S (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 ¹⁶. Yield, 34 %; m.p. 111—114° (dec.), from acetone. (Found: C 56.5; H 5.16; N 5.96. C₁₈H₁₆N₂O₄S · 2H₂C₂O₄ (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 ¹⁸ 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. C₁₉H₁₈N₂O₂S · 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 pyrrolidin-e (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-dimethylaminoisopropyl. Yield, 29 %; m.p. 181—182° (dec.) after recrystallisation from acetone. (Found: C 57.5; H 5.16; N 6.58. C₁₉H₁₈N₂O₂S · 2H₂C₂O₄ (418.5) requires C 57.4; H 5.30; N 6.70 %.)

β-Piperidinoisopropyl phenothiazine-10-carboxylate oxalate (IX). Prepared from I and β-piperidinoisopropanol ¹⁸. Yield, 68 %; m.p. 170—171° (dec.), from ethanol. (Found: C 59.6; H 5.81; N 5.98. C₁₉H₁₈N₂O₂S · 2H₂C₂O₄ (468.5) requires C 60.2; H 5.72; N 6.11 %.)

β-Diethylaminoisopropyl phenothiazine-10-thiocarboxylate oxalate (X). Prepared by the same method as the preceding esters from I and β-diethylaminothio mercaptan ¹⁸. Yield 56 %; m.p. 153—154° (dec.) after two recrystallisations from acetone. (Found: C 56.3; H 5.42; N 6.12. C₁₉H₁₈N₂O₂S · 2H₂C₂O₄ (448.5) requires C 56.2; H 5.39; N 6.25 %.)

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Quaternary derivatives

\(\beta\)-Dimethylaminomethyl phenothiazine-10-carboxylate methobromide (XI). \(\beta\)-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 methylobromide (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\(_{14}\)H\(_{13}\)BrN\(_2\)O\(_4\)S (409.4) requires C 52.8; H 5.17; N 6.84 %.)

The method 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\(_{14}\)H\(_{12}\)BrN\(_2\)O\(_4\)S (456.4) requires C 47.4; H 4.64; N 6.14 %.)

\(\beta\)-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 5.63; N 6.71. C\(_{14}\)H\(_{13}\)BrN\(_2\)O\(_4\)S (423.4) requires C 53.9; H 5.48; N 6.62 %.)

\(\beta\)-Diethylaminomethyl 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\(_{18}\)BrN\(_2\)O\(_4\)S (437.4) requires C 54.9; H 5.76; N 6.41 %.)

\(\beta\)-Diethylaminomethyl 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\(_{17}\)BrN\(_2\)O\(_4\)S (451.4) requires C 55.9; H 6.03; N 6.21 %.)

Amides of phenothiazine-10-carboxylic acid

N-(Phenothiazine-10-carboxyl)-diethylamine (XV). Phenothiazine-10-carboxyl chloride (L 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\(_{14}\)N\(_2\)OS (298.4) requires C 68.4; H 6.08; N 9.39 %.)

N-(Phenothiazine-10-carboxyl)-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\(_{19}\)H\(_{16}\)N\(_2\)OS (310.4) requires C 69.6; H 5.84; N 9.03 %.)

N-(Phenothiazine-10-carboxyl)-pyrididine (XVII). Prepared from I and pyrididine. Yield 68 %; m.p. 137—138°, from ethanol. (Found: C 70.8; H 5.75; N 9.52. C\(_{17}\)H\(_{14}\)N\(_2\)OS (296.4) requires C 68.9; H 5.44; N 9.45 %.)

N-(Phenothiazine-10-carboxyl)-N’,N’-diethylthelyenediamine hydrochloride (XVIII). A solution of I (5.0 g) and N,N-diethylthelyenediamine \(14^\circ\) (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 5.97; N 9.52. C\(_{19}\)H\(_{16}\)N\(_2\)OS · HCl + 2 CH\(_2\)OH (442.0) requires C 57.1; H 7.30; N 9.51 %.) On drying at 105° the weight was constant after a loss of 12.8 % (calc. for 2 CH\(_2\)OH: 14.5 %) and the m.p. was 184—186° (dec.). (Found: C 59.9; H 6.39; N 11.0. C\(_{19}\)H\(_{16}\)N\(_2\)OS · 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 spasmylytic and nicotinolytic activity.

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