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10-Aminoacylphenothiazines

III. Quaternary salts

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Quaternization of pharmacologically active tertiary amines usually leads to compounds which differ from the parent amines in their pharmacological properties. In general, quaternization enhances the neurotropic antispasmodic effect while the musculotropic effect decreases[1]; the antihistamine activity may remain unchanged but is generally diminished[2]; the local anesthetic effect is almost completely destroyed[3]. Numerous exceptions from these generalisations are of course known.

The 10-aminoacylphenothiazines described in the previous papers in this series[4,5] have an unusually great range of action, as most of them possessing antihistaminic, antispasmodic, local anesthetic, and nicotinolytic action to a varying extent. It was considered by the present author therefore, that quaternization of these tertiary amines would afford an excellent opportunity of studying the general effect of this procedure on different pharmacological properties.

Most of the quaternary salts were prepared by the alkylation of a 10-dialkylaminoacylphenothiazine with a methyl or ethyl halide. The aminoacetyl and β-aminopropionyl derivatives were most reactive; α-Diethylaminopropionyl-, and β- and γ-diethylaminobutyrylphenothiazine could not be quaternized. When for instance the α-diethylaminopropionyl compound was heated with ethyl bromide, the hydrobromide of the tertiary amine starting material was formed.

A few quaternary salts were prepared from a halogenoacylphenothiazine and a tertiary amine. Only halogenoacetylphenothiazines reacted smoothly with amines in this way. When other halogenoacyl derivatives were treated with a tertiary amine, hydrogen halide was usually split off from the halogenoacyl group, and the hydrohalide of the amine was obtained as the only product. Pyridine, however, yielded quaternary pyridinium salts.

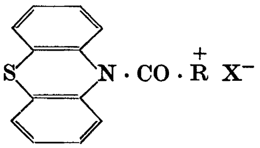
Most of the salts and especially the iodides were slightly soluble in water (usually < 1 %). Their aqueous solutions were rather unstable and became opalescent in a couple of days. In weakly alkaline solutions the salts were decomposed instantaneously into phenothiazine and the corresponding betaine.

The quaternary salts have been tested for local anesthetic, antispasmodic and antihistaminic activity by the same technique as the tertiary amines in the previous communications in this series *, and also for nicotinolytic and ganglion-blocking effect.

Local anesthetic effect. All compounds tested were inactive on rabbit *cornea.* Thus the quaternization had destroyed the strong effect of the parent amines.

Antispasmodic effect. The results of the tests on isolated guinea pig *ileum* for cholinolytic activity are shown in Table 1. The quaternary salts with one exception (compound XII) were more active than the parent tertiary amines. No consistent relationship between cholinolytic activity and chemical structure could be discerned.

Table 1. Cholinolytic and antihistaminic properties of quaternary salts of 10-aminoacyl-phenothiazines.



	R	X	Effect * in reducing the spasm produced by	
			Acetyl-choline	Histamine
I	$-CH_2 \cdot N(CH_3)_3$	Br	2.7	0.02
III	$-CH_2 \cdot N(CH_3)_2C_2H_5$	I	13	
IV	$-CH_2 \cdot N(C_2H_5)_2CH_3$	I	19	
V	$-CH_2 \cdot N(C_2H_5)_3$	Cl	36	0.03
VII	$-CH_2 \cdot NC_5H_5$ **	Cl	28	0.04
VIII	$-CH(CH_3) . N(CH_3)_3$	I	16	
IX	$-CH(CH_3) . NC_5H_5$ **	I	2.7	0.025
X	$-CH_2 \cdot CH_2 \cdot N(CH_3)_3$	Br	14	0.1
XII	$-CH_2 \cdot CH_2 \cdot N(CH_3)_2C_2H_5$	Br	4	0.02
XIV	$-CH_2 . CH_2 \cdot N(C_2H_5)_2CH_3$	Br	12	0.04
XVI	$-CH_2 . CH_2 \cdot NC_5H_5$ **	Cl	37	
XVII	$-CH_2 \cdot CH(CH_3) . N(CH_3)_3$	Br	36	0.1
XVIII	$-CH_2 \cdot CH(CH_3) \cdot N(CH_3)_2C_2H_5$	Br	28	0.3
XIX	$-CH(CH_3) \cdot CH_2 \cdot N(CH_3)_3$	Br	3.5	
XX	$-(CH_2)_3 \cdot N(CH_3)_3$	I	22	0.07
	Atropine sulphate		30	
	Diphenhydramine-HCl		1.0	1.0

* The activity figures refer to the cationic part of the salts.
** Pyridinium.

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* Acknowledgement is made to Dr. S. Wiedling of Astra's Biological Department for performing these tests. Details will be published elsewhere.

The quaternary salts have also been tested for musculotropic spasmolytic activity on spasm of guinea pig small intestine caused by barium chloride. The results were, however, rather confusing. This may be due to the recent finding, that barium ions do not produce a purely musculotropic spasm on guinea pig small intestine [6,7], but also stimulate the ganglion cells, thereby causing the release of the peripheric mediator at the nerve endings. Thus the spasm produced by barium is of "mixed" nature and can be abolished or reduced not only by musculotropic antispasmodics but also by anticholinergic or ganglion-blocking agents. It is evident, that a test may easily give confusing results especially with compounds having a broad range of action. Edlund and Lohi [7] found, however, that if rat *ileum* was used for the tests, the contractions caused by barium were unaffected by anticholinergic and ganglion-blocking drugs and are apparently of purely musculotropic origin. The quaternary salts described in this paper have been tested by this method together with the parent amines. The results will be published elsewhere [8], but it may be mentioned, that quaternization strongly decreases the high activity of the tertiary amines.

Antihistaminic effect. The results from the tests are shown in Table 1. Quaternization usually lowered the activity, but the two quaternary β-butyryl derivatives were more active than the parent amines.

Nicotinolytic effect. Some of the compounds have been tested for their ability to inhibit nicotine-induced tremors in rabbits *. It was found, that quaternization destroyed the nicotinolytic effect of the tertiary amines [9].

Ganglion-blocking effect. The salts showed in general a very strong ganglion-blocking activity when tested on the peristaltic reflex. The results will be published elsewhere [10].

EXPERIMENTAL

Halogenoacylphenothiazines

In addition to the halogenoacylphenothiazines previously reported [4,5] the following compounds of this class were prepared.

10-Bromoacetylphenothiazine. A solution of phenothiazine (10 g, 0.05 mole), and bromoacetyl bromide [11] (15.2 g, 0.075 mole) in benzene (50 ml) was refluxed for two hours. On cooling, the reaction product separated (8.5 g, 53 %) and was recrystallised twice from ethanol — light petroleum (1 : 1); m.p. 121—122°. (Found: C 52.5; H 3.26; Br 25.1. $C_{14}H_{10}BrNOS$ (320.2) requires C 52.5; H 3.15; Br 25.0 %.)

10-Iodoacetylphenothiazine. A mixture of 10-chloroacetylphenothiazine (5.5 g, 0.02 mole), potassium iodide (6.6 g, 0.04 mole), and acetone (50 ml) was refluxed for two hours. After filtration, the solvent was evaporated, and the crude product (5.6 g, 76 %) was recrystallised from ethanol yielding yellow crystals melting at 129—131°. (Found: C 45.6; H 2.84; I 34.6. $C_{14}H_{10}INOS$ (367.2) requires C 45.8; H 2.75; I 34.6 %.)

10-(β-Bromopropionyl)-phenothiazine. This compound was prepared in 82 % yield from β-bromopropionyl chloride ** and phenothiazine as described for the corresponding chloro compound; m.p. 144—145° (from ethanol). (Found: C 54.5; H 3.62; Br 24.0. $C_{15}H_{12}BrNOS$ (334.2) requires C 53.9; H 3.62; Br 23.9 %.)

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* Acknowledgement is made to Dr. T. Edlund, Uppsala, for performing these tests.

** β-Bromopropionyl chloride was prepared according to Rajagopalan [12]. The boiling point of the product was 65—67°/25 mm in agreement with the b.p. recorded by Hamilton and Simpson [13] but at variance with the value reported by Rajagopalan (115—117°/30 mm).

10-(γ-Chlorobutyryl)-phenothiazine. Prepared in 86 % yield by refluxing γ-chlorobutyryl chloride [14] and phenothiazine in toluene for six hours; m.p. 95—96° (from methanol). (Found: C 63.1; H 4.49; Cl 12.1. $C_{16}H_{14}ClNOS$ (303.8) requires C 63.3; H 4.64; Cl 11.7 %.)

Quaternary salts

The quaternary salts were prepared in essentially the same way. The appropriate dimethylamino- or diethylaminoacylphenothiazine was dissolved in acetone or nitrobenzene and an excess of the methyl or ethyl halide was added. In most cases the quaternary salt began to crystallise immediately. The mixture was allowed to stand over night at room temperature, and the product was collected, washed with acetone, and dried. In a few cases it was necessary to heat the reactants. The salts usually separated in a quite pure state. Most of them were recrystallised, but this procedure was omitted with some compounds, as the melting points and analyses seemed to indicate that they tended to decompose. A few of the quaternary salts were prepared by the reaction of haloacylphenothiazines with tertiary amines.

10-(Dimethylaminoacetyl)-phenothiazine methobromide (I). 10-(Dimethylaminoacetyl)-phenothiazine (2.0 g) was dissolved in acetone (20 ml), and a solution of methyl bromide (10 ml) in acetone (10 ml) was added. The salt began to separate instantly, and was collected next day and washed with acetone. The methobromide (2.65 g, 99 %) melted at 236—237° (dec.). (Found: C 53.5; H 5.33; Br 21.0. $C_{17}H_{19}BrN_2OS$ (379.3) requires C 53.8; H 5.05; Br 21.1 %.) The *methiodide* (II) was prepared similarly in 98 % yield; m.p. 234—235° (dec., from methanol). (Found: C 48.0; H 4.54. $C_{17}H_{19}IN_2OS$ (426.3) requires C 47.9; H 4.49 %.)

10-(Dimethylaminoacetyl)-phenothiazine ethiodide (III). The reactants were dissolved in nitrobenzene and heated on the water bath for 1.5 hours. Yield 91 %; m.p. 216—218° (dec.) after recrystallisation from methanol. (Found: C 49.2; H 4.74. $C_{18}H_{21}IN_2OS$ (440.4) requires C 49.1; H 4.81 %.)

10-(Diethylaminoacetyl)-phenothiazine methiodide (IV). The phenothiazine base was heated with methyl iodide in nitrobenzene at 100° for 24 hours. The salt separated on standing at room temperature for two months. Yield 24 %; m.p. 198—200° (dec., from methanol). (Found: C 50.1; H 5.11. $C_{19}H_{23}IN_2OS$ (454.4) requires C 50.2; H 5.10 %.)

10-(Diethylaminoacetyl)-phenothiazine ethochloride (V). 10-Chloroacetylphenothiazine (2.8 g, 0.01 mole) and triethylamine (5.0 g, 0.05 mole) were dissolved in nitrobenzene (25 ml) and heated at 100° for 5 hours. After cooling, the crystalline precipitate (2.3 g) was collected; m.p. 185—186° (dec.). Recrystallisation from acetone or ethanol-ether (1 : 1) did not change the m.p. Analysis indicated, that the reaction product was an *addition compound* containing approximately one mole of the expected quaternary salt and one mole of triethylamine hydrochloride, the latter obviously formed as a by-product. (Found: C 60.0; H 8.04; Cl 13.3; N 8.32. $C_{20}H_{25}ClN_2OS + (C_2H_5)_3N \cdot HCl$ (514.6) requires C 60.7; H 8.03; Cl 13.8; N 8.17 %.)

The above product (2.0 g) was heated in a sublimation apparatus at 0.01 mm at 100° for 12 hours. A part of the product sublimed; m.p. 253—254° undepressed on admixture with an authentic specimen of triethylamine hydrochloride. The residue (1.50 g, calc. 1.46 g) had m.p. 194—195° (dec.). Recrystallisation from ethanol-ether did not change the m.p. (Found: C 63.0; H 6.56; Cl 9.13; N 7.30. $C_{20}H_{25}ClN_2OS$ (376.9) requires C 63.7; H 6.69; Cl 9.41; N 7.43 %.)

The corresponding *ethiodide* (VI) was prepared in 77 % yield by heating the tertiary amine with ethyl iodide in nitrobenzene at 100° over night; m.p. 198—199° (dec., from methanol). (Found: C 50.8; H 5.26; N 6.19. $C_{20}H_{25}IN_2OS$ (468.4) requires C 51.3; H 5.38; N 5.98 %.)

10-(Pyridiniumacetyl)-phenothiazine chloride (VII). 10-Chloroacetylphenothiazine (2.8 g) was heated in pyridine (25 ml) on the water bath for one hour. The quaternary salt crystallised on cooling (3.4 g, 96 %); m.p. 252—253° (dec., from ethanol). (Found: C 63.9; H 4.24; Cl 9.23. $C_{19}H_{15}ClN_2OS$ (354.9) requires C 64.3; H 4.26; Cl 9.99 %.)

10-(a-Dimethylaminopropionyl)-phenothiazine methiodide (VIII). Prepared in 64 % yield in the same way as the corresponding acetyl derivative; m.p. 230—231° (dec., from methanol). (Found: C 48.8; H 4.77; N 6.30. $C_{18}H_{21}IN_2OS$ (440.4) requires C 49.1; H 4.81; N 6.36 %.)

10-(α-Pyridiniumpropionyl)-phenothiazine iodide (IX). 10-(α-Bromopropionyl)-phenothiazine (10.0 g) was heated in pyridine (75 ml) on the water bath for two hours. The resulting *bromo salt* (11.6 g, 84 %) melted at 218—220° (dec.) but analysis indicated that it was not quite pure. Addition of a saturated potassium iodide solution to the aqueous solution of the bromide yielded a faint yellow iodide; m.p. 218—219° (dec., from ethanol). (Found: C 51.8; H 3.78; N 5.98. $C_{20}H_{17}IN_2OS$ (460.3) requires C 52.2; H 3.72; N 6.09 %.)

10-(β-Dimethylaminopropionyl)-phenothiazine methobromide (X). The tertiary base was alkylated with methyl bromide in acetone at room temperature. Yield 88 %; m.p. 234—235°. (Found: C 54.8; H 5.34; Br 20.4. $C_{18}H_{21}BrN_2OS$ (393.4) requires C 55.0; H 5.38; Br 20.3 %.)

The *methiodide* (XI) was prepared similarly in 99 % yield; m.p. 198—200°. (Found: C 49.0; H 4.86. $C_{18}H_{21}IN_2OS$ (440.4) requires C 49.1; H 4.81 %.)

10-(β-Dimethylaminopropionyl)-phenothiazine ethobromide (XII). Prepared in the same manner as X in 84 % yield; m.p. 209—210°. (Found: C 56.2; H 5.42; Br 19.7. $C_{19}H_{23}BrN_2OS$ (407.4) requires C 56.0; H 5.69; Br 19.6 %.)

The *ethiodide* (XIII) was obtained similarly in 89 % yield; m.p. 167—168° (from methanol). (Found: C 50.0; H 5.00; N 6.33. $C_{19}H_{23}IN_2OS$ (454.4) requires C 50.2; H 5.10; N 6.17 %.)

10-(β-Diethylaminopropionyl)-phenothiazine methobromide (XIV). Prepared by the same method in 86 % yield; m.p. 202—203°. (Found: C 56.8; H 6.18. $C_{20}H_{25}BrN_2OS$ (421.4) requires C 57.0; H 5.98 %.)

The *methiodide* (XV) was obtained similarly in 96 % yield; m.p. 183—184° (from methanol). (Found: C 50.8; H 5.19; N 5.98. $C_{20}H_{25}IN_2OS$ (468.4) requires C 51.3; H 5.38; N 5.98 %.)

10-(β-Pyridiniumpropionyl)-phenothiazine chloride (XVI). Prepared in 60 % yield by heating 10-(β-chloropropionyl)-phenothiazine with pyridine on the water bath for 3 hours; m.p. 216—217° (dec., from ethanol-light petroleum 1 : 1). (Found: C 64.4; H 4.70; N 7.94. $C_{20}H_{17}ClN_2OS$ (368.9) requires C 65.1; H 4.65; N 7.60 %.)

10-(β-Dimethylaminobutyryl)-phenothiazine methobromide (XVII). The tertiary base was alkylated with methyl bromide in acetone at room temperature. Yield 88 %; m.p. 226—228° (dec.). (Found: C 55.8; H 5.73; Br 19.7. $C_{19}H_{23}BrN_2OS$ (407.4) requires C 56.0; H 5.69; Br 19.6 %.)

10-(β-Dimethylaminobutyryl)-phenothiazine ethobromide (XVIII). Prepared similarly to XVII in 73 % yield; m.p. 205—206° (dec.). (Found: C 56.7; H 6.10; Br 19.1. $C_{20}H_{25}BrN_2OS$ (421.4) requires C 57.0; H 5.98; Br 19.0 %.)

10-(β-Dimethylaminoisobutyryl)-phenothiazine methobromide (XIX). Prepared in the same way as XVII in 95 % yield; m.p. 243—246° (dec., from ethanol). (Found: C 56.0; 5.71; Br 20.0. $C_{19}H_{23}BrN_2OS$ (407.4) requires C 56.0; H 5.69; Br 19.6 %.)

10-(γ-Dimethylaminobutyryl)-phenothiazine methiodide (XX). Prepared similarly to XVII in 47 % yield; m.p. 185—187°. (Found: C 50.6; H 5.35. $C_{19}H_{23}IN_2OS$ (454.4) requires C 50.2; H 5.10 %.)

SUMMARY

A series of quaternary salts of 10-aminoacylphenothiazines has been prepared and tested for pharmacological activity. Most of the new compounds are powerful cholinolytic and ganglion-blocking agents.

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