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10-Aminoacylphenothiazines

II. Aminobutyryl Derivatives

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The interesting pharmacological properties of 10-aminoacetyl- and 10-aminopropionyl-phenothiazines, described in a preceding paper [1] prompted us to extend our investigations to some aminobutyryl derivatives. α-Bromobutyrylphenothiazine and γ-bromobutyrylphenothiazine were prepared from phenothiazine and the haloacyl halides. The β-bromobutyryl and β-bromo-*iso*butyryl compounds were prepared from phenothiazine and the corresponding halogenated acid by the convenient method for obtaining acid amides described by Human and Mills [2]. α-Bromo*iso*butyryl bromide did not react with phenothiazine under the usual conditions. By treating the halogenated compounds with a number of secondary amines, the corresponding 10-aminobutyryl-phenothiazines were readily obtained.

The hydrochlorides of the compounds have been tested (S. Wiedling) for local anesthetic, antispasmodic and antihistaminic activities in the same way as the acetyl and propionyl compounds in the previous communication [1]. The results of the tests are summarised in Table 1.

Local anesthetic effect. All the compounds possessed a marked activity. They were, however, rather irritating to the rabbit eye.

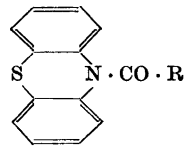
Antihistaminic effect. The most effective compound was slightly inferior to diphenhydramine but the majority had a substantially weaker effect. The most active compounds belonged to the γ-butyryl series.

Antispasmodic effect. Some of the compounds had outstanding spasmolytic properties. The β-butyryl and γ-butyryl derivatives had about the same activity and of these the diethylamino compounds were about as potent as atropine against spasms produced by acetylcholine. The marked difference in effect between the β-butyryl and the β-*iso*-butyryl derivatives is noteworthy. All the piperidino compounds were almost inactive.

Nicotinolytic effect. Some of the compounds have been tested against nicotine-induced tremors in rabbit. Their nicotinolytic activity was weaker

than that of the aminoacetyl and aminopropionyl derivatives, some of which have a very strong effect [3]. This shows that the nicotinolytic action has no relation to the antimuscarinic activity.

Table 1. Pharmacological properties of 10-aminobutyrylphenothiazines.



	R	Local anesthetic activity	Effect in reducing the spasm produced by		
			Acetyl-choline	$BaCl_2$	Histamine
V	$-CH(C_2H_5) \cdot N(CH_3)_2$	2	1.2		0.1
VI	$-CH(C_2H_5) \cdot N(C_2H_5)_2$	1	3	0.9	0.01
VII	$-CH(C_2H_5) \cdot NC_5H_{10}$	1	0.65		0.002
VIII	$-CH(C_2H_5) \cdot NC_4H_8$	5	1.9	2	0.01
IX	$-CH_2 \cdot CH(CH_3) \cdot N(CH_3)_2$		24	5	0.07
X	$-CH_2 \cdot CH(CH_3) \cdot N(C_2H_5)_2$	5	30	12	0.2
XI	$-CH_2 \cdot CH(CH_3) \cdot NC_4H_8$		10	1.1	0.1
XII	$-CH(CH_3) \cdot CH_2 \cdot N(CH_3)_2$		2.2		0.18
XIII	$-CH(CH_3) \cdot CH_2 \cdot NC_5H_{10}$		0.14		0.01
XIV	$-CH(CH_3) \cdot CH_2 \cdot NC_4H_8$		2		0.04
XV	$-(CH_2)_3 \cdot N(CH_3)_2$	2	13	7.5	0.8
XVI	$-(CH_2)_3 \cdot N(C_2H_5)_2$ *		30	2.9	0.6
XVII	$-(CH_2)_3 \cdot NC_5H_{10}$		0.1		0.01
XVIII	$-(CH_2)_3 \cdot NC_4H_8$	3.5	10	6	0.5
	Atropine sulphate		30		
	Papaverine-HCl			0.33	
	Xylocaine-HCl	1.0			
	Diphenhydramine-HCl		1.0	1.0	1.0

* The oxalate was used in the tests.

EXPERIMENTAL

Halogenobutyrylphenothiazines

10-(α-Bromobutyryl)-phenothiazine (I). α-Bromobutyryl bromide (35 g, 0.15 mole) was added to a solution of phenothiazine (19.9 g, 0.1 mole) in boiling toluene (100 ml). The mixture was refluxed for four hours, the solvent was evaporated and the residue (25 g, 72%) was recrystallised from ethanol; m.p. 120—121°. (Found: C 55.1; H 4.11; Br 22.7. $C_{16}H_{14}BrNOS$ (348.3) requires C 55.2; H 4.05; Br 22.9 %.)

10-(β-Bromobutyryl)-phenothiazine (II). β-Bromobutyric acid [4] (8.4 g, 0.05 mole) and pyridine (3.95 g, 0.05 mole) were dissolved in anhydrous ether (125 ml), thionyl chloride (5.95 g, 0.05 mole) in ether (10 ml) was cautiously added, and the mixture was set aside for three days at room temperature. Any excess of pyridine was precipitated as the hydrochloride by adding a small volume of ethereal hydrogen chloride, the reaction mixture was filtered and a solution of phenothiazine (6.6 g, 0.033 mole) in toluene (50 ml) was added. The ether was evaporated and the toluene solution kept at 85° for four hours. After cooling the resulting precipitate (9.4 g, 81%) was collected and recrystallised from benzene; m.p. 167—168°. (Found: C 54.6; H 3.89; Br 23.5. $C_{16}H_{14}BrNOS$ (348.3) requires C 55.2; H 4.05; Br 22.9%.)

10-(β-Bromoisobutyryl)-phenothiazine (III). This compound was prepared in the same way as II. β-Bromo*iso*butyric acid [5] (8.4 g) and phenothiazine (6.6 g) gave 9.6 g (83 %) of crude product, which after recrystallisation from ethanol melted at 110—111°. (Found: C 55.1; H 4.12; Br 22.7. $C_{16}H_{14}BrNOS$ (348.3) requires C 55.2; H 4.05; Br 22.9%).

10-(γ-Bromobutyryl)-phenothiazine (IV). Phenothiazine (5.3 g) and γ-bromobutyryl chloride [6] (7.5 g) were refluxed in toluene (60 ml) for three hours and the crude product (8.5 g, 91%) was recrystallised from ethanol; m.p. 88—90°. (Found: C 55.8; H 4.00; Br 23.2. $C_{16}H_{14}BrNOS$ (348.3) requires C 55.2; H 4.05; Br 22.9%).

Aminoacylphenothiazines

These compounds were prepared and isolated in essentially the same way as described in the previous communication in this series [1].

10-(α-Dimethylaminobutyryl)-phenothiazine (V). Dimethylamine (17 g) and 10-(α-bromobutyryl)-phenothiazine (I) (34.8 g) in benzene (100 ml) were heated in a sealed bottle at 85° overnight. The product (29.0 g, 93%) was recrystallised from methanol; m.p. 98—99°. (Found: C 69.5; H 6.32; N 9.17. $C_{18}H_{20}N_2OS$ (312.4) requires C 69.2; H 6.45; N 8.97%.)

10-(α-Diethylaminobutyryl)-phenothiazine (VI). Prepared similarly from diethylamine and I. Yield 77%. M.p. 64—66° (from ethanol). (Found: C 70.3; H 7.17; N 8.25. $C_{20}H_{24}N_2OS$ (340.5) requires C 70.5; H 7.10; N 8.23%.)

Hydrochloride. M.p. 202—203° (dec.), (from ethanol-ether 1 : 1). (Found: C 63.6; H 6.61; Cl 9.44. $C_{20}H_{24}N_2OS$. HCl (377.0) requires C 63.7; H 6.69; Cl 9.41%).

10-(α-Piperidinobutyryl)-phenothiazine (VII). Prepared from piperidine and I. Reflux five hours in toluene. Yield 83%. M.p. 86—88° (from methanol). (Found: C 71.1; H 7.15; N 7.84. $C_{21}H_{24}N_2OS$ (352.5) requires C 71.5; H 6.86; N 7.95%).

Hydrochloride. M.p. 214—216° (dec.), (from ethanol-ether 1 : 1). (Found: C 64.6; H 6.48; Cl 9.13. $C_{21}H_{24}N_2OS$. HCl (389.0) requires C 64.8; H 6.48; Cl 9.12%.)

10-(α-Pyrrolidinobutyryl)-phenothiazine hydrochloride (VIII). Prepared similarly from pyrrolidine and I. The oily base was directly converted to the hydrochloride. Yield 57%. M.p. 206—208° (dec.), (from acetone-ethanol 10 : 1). (Found: C 64.4; H 6.43; N 7.26. $C_{20}H_{22}N_2OS$. HCl (375.0) requires C 64.1; H 6.18; N 7.47%.)

10-(β-Dimethylaminobutyryl)-phenothiazine (IX). Prepared similarly from dimethylamine and II. Yield 87%. M.p. 94—95° (from ethanol). (Found: C 69.4; H 6.58; N 8.98. $C_{18}H_{20}N_2OS$ (312.4) requires C 69.2; H 6.45; N 8.97%.)

10-(β-Diethylaminobutyryl)-phenothiazine (X). Prepared similarly from diethylamine and II. Yield 21%. M.p. 62—63° (light petroleum). (Found: C 70.8; H 6.80. $C_{20}H_{24}N_2OS$ (340.5) requires C 70.5; H 7.10%.)

10-(β-Pyrrolidinobutyryl)-phenothiazine (XI). Prepared similarly from pyrrolidine and II in 74% yield. M.p. 119—120° (light petroleum). (Found: C 70.7; H 6.89; N 8.20. $C_{20}H_{22}N_2OS$ (338.5) requires C 71.0; H 6.57; N 8.28%).

10-(β-Dimethylaminoisobutyryl)-phenothiazine hydrochloride (XII). Prepared from dimethylamine and III. Yield 68%. The slightly soluble hydrochloride which separated when the reaction mixture was treated with hydrochloric acid melted at 251—252° (dec.) (from ethanol). (Found: C 62.0; H 6.22; N 7.79. $C_{18}H_{20}N_2OS$. HCl (348.9) requires C 62.0; H 6.07; N 8.03%).

10-(β-Piperidinoisobutyryl)-phenothiazine (XIII). Prepared in 71% yield from piperidine and III; m.p. 79—81° (light petroleum). (Found: C 71.2; H 6.94; N 8.02. $C_{21}H_{24}N_2OS$ (352.5) requires C 71.5; H 6.86; N 7.95%.)

10-(β-Pyrrolidinoisobutyryl)-phenothiazine hydrochloride (XIV). Prepared similarly from pyrrolidine and III. Yield 45%. The hydrochloride which separated when the reaction mixture was treated with hydrochloric acid melted at 231—233° (dec.). (From ethanol). (Found: C 63.8; H 6.46; N 7.24. $C_{20}H_{22}N_2OS$. HCl (375.0) requires C 64.1; H 6.18; N 7.47%.)

10-(γ-Dimethylaminobutyryl)-phenothiazine (XV). Prepared from dimethylamine and IV in 85% yield. M.p. 93—95° (from ethanol). (Found: C 68.9; H 6.29; N 8.99. $C_{18}H_{20}N_2OS$ (312.4) requires C 69.2; H 6.45; N 8.97%.)

10-(γ-Diethylaminobutyryl)-phenothiazine oxalate (XVI). Prepared similarly from diethylamine and IV; yield 58%. The oily base was converted to the oxalate; m.p. 151—153° (dec.), (from acetone). (Found: C 60.8; H 6.09; N 6.70. $C_{20}H_{24}N_2OS$. $(COOH)_2$ (430.5) requires C 61.4; H 6.09; N 6.51%.)

10-(γ-Piperidinobutyryl)-phenothiazine (XVII). Prepared similarly from piperidine and IV. Yield 22%. M.p. 78—80° (from light petroleum). (Found: C 71.8; H 7.03; N 7.93. $C_{21}H_{24}N_2OS$ (352.5) requires C 71.5; H 6.86; N 7.95%.)

10-(γ-Pyrrolidinobutyryl)-phenothiazine (XVIII). Prepared similarly from pyrrolidine and IV in 83% yield. M.p. 106—107° (light petroleum-ethanol 1 : 1). (Found: C 70.8; H 6.72; N 8.17. $C_{20}H_{22}N_2OS$ (338.5) requires C 71.0; H 6.57; N 8.28%.)

SUMMARY

The synthesis of fourteen 10-aminobutyryl derivatives of phenothiazine is described. Most of the compounds are powerful local anesthetics and some of them show outstanding spasmolytic properties.

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