ACTA CHEMICA SCANDINAVICA 3 (1949) 247—255

Antihistamine Agents

IV. Piperidino- and Morpholinoalkyl Derivatives of Phenothiazine

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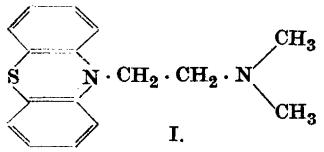
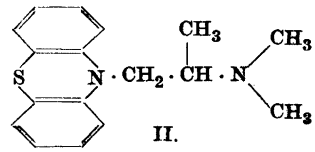
Dimethylaminoalkyl derivatives of phenothiazine were reported by Halpern and Ducrot [1] to possess excellent antihistaminic activity. Thus 10-(β-dimethylaminoethyl)-phenothiazine (I) was found to protect guinea pigs against 400 lethal doses of histamine and 10-(β-dimethylaminopropyl)-phenothiazine (II) protected against 1500 lethal doses, whereas Neo-Antergan, the most potent antihistamine agent known before, protected against only 80 lethal doses under similar conditions. Recently the synthesis of a series of 10-[β-(N-pyrrolidyl)-alkyl]-phenothiazines has been described [2]. One of these compounds, 10-[β-(N-pyrrolidyl)-ethyl]-phenothiazine (III), exerted a very strong antihistaminic activity [3].



I.



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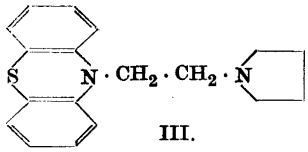
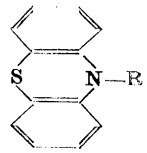


III.

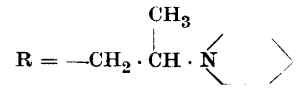
In connection with earlier works on synthetic antihistamine agents in this laboratory some piperidino- and morpholinoalkyl derivatives of phenothiazine have been prepared. These compounds (IV—VII) were obtained by condensing the hydrochlorides of β-(N-piperidino)-ethyl chloride, β-(N-morpholino)-ethyl chloride, α-(N-piperidino)-β-chloropropane and α-(N-morpholino)-β-

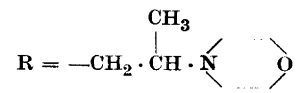
chloropropane with phenothiazine in the presence of sodium amide. In order to liberate the aminoalkyl chloride from its hydrochloride two equivalents of the condensing agent was used.



IV. R = $-CH_2 \cdot CH_2 \cdot N$ 

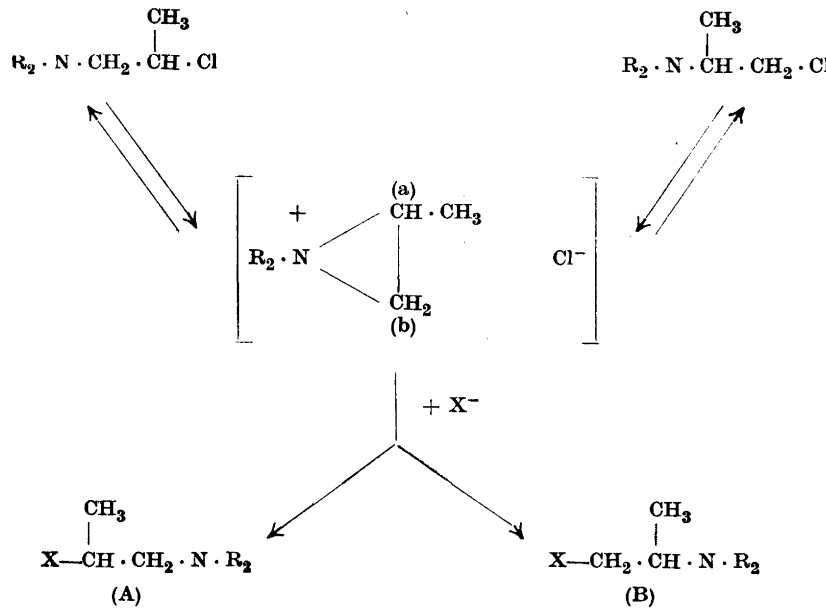
V. R = $-CH_2 \cdot CH_2 \cdot N$ 

VI. R = $-CH_2 \cdot CH(CH_3) \cdot N$ 

VII. R = $-CH_2 \cdot CH(CH_3) \cdot N$ 

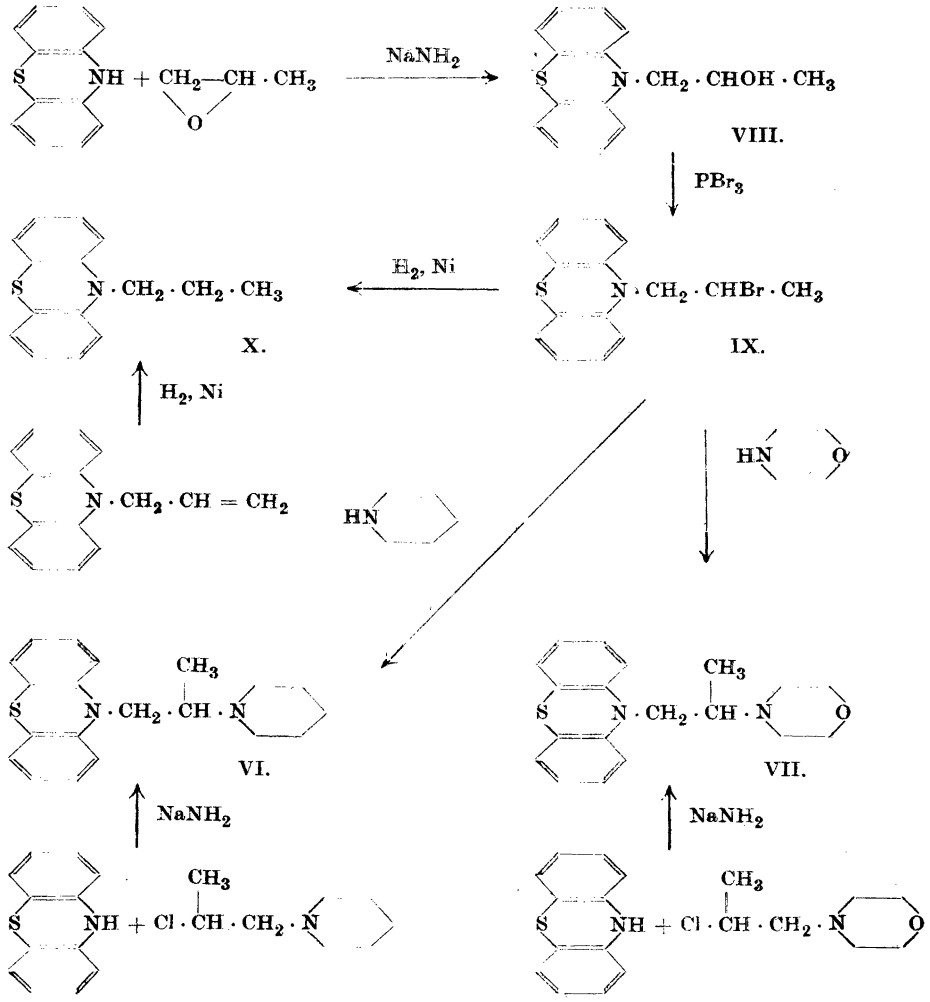
Pharmacological data concerning these compounds will be published elsewhere.

It is known that in the use of α-alkylamino-β-chloropropanes as alkylating agents a rearrangement takes place, the reaction product being a mixture of the expected product (A) and the rearranged one (B) [4–6]. The same result is obtained in alkylations with the isomeric α-chloro-β-alkylaminopropanes [7, 8].



It has been proposed [4, 5, 9] and shown [10] that under the influence of alkaline condensing agents the alkylaminochloropropanes give rise to a cyclic imonium ion, which then reacts with an anion X^- to yield two isomeric compounds (A and B), depending on whether the reagent X^- attacks the ethylene imonium ion at (a) or (b). Since the position (b) is least substituted, it is probable that it will be the favored point of attack, the main product thus having the structure (B).

In the reaction between phenothiazine and alkylaminochloropropanes, however, only one product seems to have been isolated. Charpentier [8] showed that α-dimethylamino-β-chloropropane and α-chloro-β-dimethylaminopropane



yielded the same compound and he was able to prove, that it had the structure represented by (B) above. The American investigators [2] found only one isomer too in the reaction between phenothiazine and α-(N-pyrrolidyl)-β-chloropropane. They gave it the structure (B) without proof.

In the present investigation only one reaction product could be isolated in the reaction between phenothiazine and α-(N-piperidino)-β-chloropropane or α-(N-morpholino)-β-chloropropane. It could be shown that rearrangements had occurred in both reactions and that the compounds obtained possessed the structure VI and VII, respectively. This was performed by preparing these two compounds in a quite different way. Phenothiazine reacted smoothly with propylene oxide in the presence of sodium amide, giving 10-(β-hydroxypropyl)-phenothiazine (VIII). On treating this compound with phosphorus tribromide 10-(β-bromopropyl)-phenothiazine (IX) was formed. The structure of VIII and IX was established by hydrogenation of IX, which yielded a compound identical with 10-propylphenothiazine (X) prepared from 10-allylphenothiazine. On treating 10-(β-bromopropyl)-phenothiazine with piperidine and morpholine, respectively, two compounds were obtained (VI and VII), which must be 10-[β-(N-piperidino)-propyl]- and 10-[β-(N-morpholino)-propyl]-phenothiazine.

These two amines proved to be completely identical with the products obtained on treating phenothiazine with α-(N-piperidino)-β-chloropropane and α-(N-morpholino)-β-chloropropane.

EXPERIMENTAL

10-[β-(N-Piperidino)-ethyl]-phenothiazine

To a mechanically stirred suspension of sodium amide in toluene (100 ml), prepared from sodium (4.6 g) and liquid ammonia according to Vaughn, Vogt, and Nieuwland [11], was added phenothiazine (19.9 g) in toluene (50 ml). The mixture was refluxed for two hours, and β-(N-piperidino)-ethyl chloride hydrochloride [12] (18.4 g) was added. After stirring for fifteen hours at the refluxing temperature the mixture was cooled and the inorganic salts filtered off. To the toluene solution was added a saturated solution of oxalic acid in ether, until no more precipitate was formed. The crude, crystalline oxalate (32.2 g) was crystallised twice from 50 % ethanol. M. p. 198—199° with decomposition.

$C_{19}H_{22}N_2S \cdot (COOH)_2$ (400.5)	Calc.	C 63.0	H 6.0
	Found	» 63.5	» 6.1

The base was obtained by suspending the oxalate in water and adding N sodium hydroxide. This yielded an oil, which was extracted with ether. The ether was dried over calcium chloride and distilled off. The residue distilled at 0.25 mm at 240° in the

bath giving a colourless oil, which crystallised in a couple of days. M. p. 39—40°. After recrystallisation from light petroleum the base melted at 43—44°.

$C_{19}H_{22}N_2S$ (310.5)	Calc.	C 73.5	H	7.1	N	9.0
	Found	» 73.4	»	7.05	»	9.0

The hydrochloride was prepared by adding a solution of hydrogen chloride in ether to an ether solution of the base. M. p. 165—166° after recrystallisation twice from acetone.

$C_{19}H_{22}N_2S \cdot HCl$ (346.9)	Calc.	C 65.8	H	6.7	Cl	10.2
	Found	» 65.2	»	6.7	»	10.2

10-[β-(N-Morpholino)-ethyl]-phenothiazine

This compound was prepared from phenothiazine (26.8 g) and β-(N-morpholino)-ethyl chloride hydrochloride [13] (24.8 g) in the same way as described above. The compound was isolated from the filtered reaction mixture by adding oxalic acid in ether. The oxalate (27.5 g) was recrystallised twice from acetone. M. p. 194—195° with decomposition.

$C_{18}H_{20}N_2OS \cdot (COOH)_2$ (402.5)	Calc.	C 59.7	H	5.5
	Found	» 59.8	»	5.4

The base obtained from the oxalate distilled at a bath temperature of 225° at 0.25 mm. It soon hardened into white crystals with the m. p. 70—71°. Crystallisation from light petrol raised the m. p. to 74—74.5°. This compound has also been prepared by Gilman and Shirley [14] by treating 10-(β-chloroethyl)-phenothiazine with morpholine. They obtained the m. p. 74.5—75.5°.

$C_{18}H_{20}N_2OS$ (312.4)	Calc.	C 69.2	H	6.45	N	9.0
	Found	» 69.2	»	6.4	»	9.0

The hydrochloride could be prepared in the usual manner. It was however very hygroscopic and was difficult to obtain in a pure state.

10-(β-Hydroxypropyl)-phenothiazine

To a stirred suspension of sodium amide in toluene (150 ml), prepared from sodium (6.9 g), phenothiazine (60 g) was added. The mixture was refluxed for ten hours. After cooling to 60° propylene oxide (26.1 g) dissolved in toluene (150 ml) was added in portions. The mixture was then refluxed for further two hours, cooled to room temperature, filtered, and washed twice with water (50 ml). The solvent was then evaporated and the residue was distilled in vacuum. B. p. 192—196°/0.3—0.5 mm. The distillate (53.4 g) consisted of a colourless almost glassy mass.

$C_{15}H_{15}NOS$ (257.3)	Calc.	C 70.0	H	5.9
	Found	» 70.0	»	5.9

10-(β-Bromopropyl)-phenothiazine

A mixture of 10-(β-hydroxypropyl)-phenothiazine (10 g), phosphorus tribromide (20 g), and chloroform (20 ml) was refluxed for one hour. After cooling the solution was shaken with sodium bisulfite solution, dried over calcium chloride and evaporated to dryness. The crystalline residue (12.2 g) was recrystallised twice from ethanol. M. p. 125—126°.

$C_{15}H_{14}BrNS$ (320.3)	Calc.	Br 25.0	N 4.4
	Found	» 25.4	» 4.3

10-Propylphenothiazine

A. 10-Allylphenothiazine [14] (5.0 g), dissolved in ethanol (50 ml), was hydrogenated at room temperature and normal pressure with Raney nickel as a catalyst. The calculated amount of hydrogen was added in twenty minutes. The solution was filtered and the solvent evaporated. The oily residue distilled at 162—165°/0.02 mm, yielding an almost colourless oil (4.1 g), which solidified in two weeks. Recrystallisation from ethanol yielded white crystals melting at 49.5—50°.

$C_{15}H_{15}NS$ (241.3)	Calc.	C 74.6	H 6.3
	Found	» 74.6	» 6.3

B. 10-(β-Bromopropyl)-phenothiazine (1.1 g) and potassium hydroxide (0.2 g) were dissolved in ethanol (50 ml) and shaken with hydrogen at ordinary temperature and pressure in presence of Raney nickel. After twenty minutes the calculated amount of hydrogen was consumed. The solution was filtered and concentrated in vacuum to about 5 ml. On cooling, white needles (0.6 g) melting at 49.5—50° separated. A mixed melting point with the 10-propylphenothiazine prepared from 10-allylphenothiazine showed no depression.

10-[β-(N-Piperidino)-propyl]-phenothiazine

A. In a manner identical with that described above phenothiazine (24.5 g), α-(N-piperidino)-β-chloropropane hydrochloride [15], and two equivalents of sodium amide in toluene (100 ml) were refluxed for fourteen hours. The reaction mixture was filtered and extracted with 2.5 N hydrochloric acid (100 ml). A thick, brown oil separated at the bottom of the separatory funnel. The oil and the water layer were combined and extracted with ether to remove ether soluble material. The mixture was then made alkaline with diluted sodium hydroxide and the resulting oil extracted with ether. The ether layer was dried over calcium chloride, the solvent was distilled off and the residue distilled in vacuum. B. p. 190—200°/0.3—0.4 mm. Yield 11.2 g of a colourless, very viscous oil. On treatment with light petroleum the oil solidified, giving crystals (6.1 g) melting at 98—102°. After four recrystallisations from light petroleum: acetone m. p. 119—120°.

$C_{20}H_{24}N_2S$ (324.5)	Calc.	C 74.0	H 7.45	N 8.6
	Found	» 73.6	» 7.4	» 8.4

The great loss of material in treating the oily base with light petroleum and the difficulty of obtaining a constant m. p. suggested the presence of the isomeric reaction product. No attempts were made at the present to isolate any remaining isomer.

From the base the hydrochloride was obtained in the usual way. M. p. 256—257° after recrystallisation from ethanol.

$C_{20}H_{24}N_2S \cdot HCl$ (360.9)	Calc.	C 66.55	H 7.0	Cl 9.8
	Found	» 65.6	» 7.0	» 9.8

B. Crude 10-(β-bromopropyl)-phenothiazine (6.1 g) and piperidine (10 g) were dissolved in benzene (25 ml). A little copper powder was added and the mixture was heated in a sealed glass vessel at 100° for 48 hours. After cooling the separated piperidine hydrobromide was filtered off and the filtrate washed thoroughly with water. The benzene solution was dried over calcium chloride, and oxalic acid in ether was added until no more precipitate was formed. The crude oxalate (4.0 g) was suspended in water and the base liberated with N sodium hydroxide. The oily base was extracted with ether and an ethereal solution of hydrogen chloride added. The hydrochloride obtained in this way melted at 256°—257° after crystallisation from ethanol. Mixed m. p. with the hydrochloride prepared according to (A) showed no depression.

The base obtained from the hydrochloride melted at 120—121° after recrystallisation from light petroleum: acetone. Mixed m. p. with base from (A) 119—120°.

For further comparison the picrate was prepared. After crystallisation from ethanol m. p. 172.5—173° with decomposition.

$C_{20}H_{24}N_2S \cdot C_6H_3N_3O_7$	Calc.	C 56.4	H. 4.9	
	Found	» 56.6	» 5.1	

The picrate obtained from the base from (A) melted at 172.5—173° with decomposition. Mixed m. p. 172.5—173° with dec.

10-[β-(N-Morpholino)-propyl]-phenothiazine

A. α-(N-Morpholino)-β-chloropropane hydrochloride, which was to be used as starting material, did not seem to have been reported in the literature. It was prepared in the following way.

Morpholine (60.0 g) and propylene chlorohydrine (31.6 g) were heated on the water bath for three hours. After cooling, the mixture was poured out into water and made strongly alkaline with 40 % sodium hydroxide. The amino alcohol was extracted with chloroform, the solvent was evaporated and the residue distilled in vacuum. The pure *α-(N-morpholino)-β-hydroxypropane* (36.0 g) boiled at 99—101°/16 mm.

$C_7H_{15}NO_2$ (145.2)	Calc.	C 57.9	H 10.4
	Found	» 58.2	» 10.2

α-(N-Morpholino)-β-hydroxypropane (35.0 g) was dissolved in chloroform (25 ml) and thionyl chloride (25 ml) in chloroform (25 ml) was cautiously added. The mixture

was then refluxed for an hour. On cooling, *α-(N-morpholino)-β-chloropropane hydrochloride* (37.0 g) separated. M. p. 177—177.5° after recrystallisation from acetone.

$C_7H_{14}ClNO \cdot HCl$ (200.1)	Calc.	C 42.0	H 7.6	Cl 35.4
	Found	» 42.2	» 7.5	» 34.8

The reaction between phenothiazine (19.9 g) and α-(N-morpholino)-β-chloropropane hydrochloride (19.8 g) was carried out in the usual way. The base was isolated from the reaction mixture by means of oxalic acid. The crude oxalate (24.2 g) was recrystallised twice from acetone. M. p. 195—196° with decomposition.

$C_{19}H_{22}N_2OS \cdot (COOH)_2$ (416.5)	Calc.	C 60.55	H 5.8
	Found	» 60.7	» 6.0

The base prepared from the oxalate distilled at 0.2—0.3 mm at a bath temperature of 240° giving a light yellow very viscous oil. By dissolving the material in hot light petroleum and cooling the solution, white crystals melting at 92—93° were obtained.

$C_{19}H_{22}N_2OS$ (326.5)	Calc.	C 69.9	H 6.8	N 8.6
	Found	» 70.3	» 6.9	» 8.6

The hydrochloride prepared in the usual manner melted at 250—252° after repeated recrystallisations from acetone: light petroleum.

$C_{19}H_{22}N_2OS \cdot HCl$ (362.9)	Calc.	C 62.9	H 6.4
	Found	» 62.4	» 6.4

B. The reaction between 10-(β-bromopropyl)-phenothiazine (6.1 g) and morpholine (10 g) was carried out as described for the piperidino compound. The crude oxalate (2.5 g) was recrystallised from acetone. M. p. 194.5—196° with decomposition. No depression was obtained with oxalate from (A). The base prepared from the oxalate melted at 91.5—92° after recrystallisation from light petroleum. Mixed m. p. with base from (A) 91.5—92.5°.

SUMMARY

Four piperidino- and morpholinoalkyl derivatives of phenothiazine have been prepared.

It has been shown that α-(N-piperidino)-β-chloropropane and α-(N-morpholino)-β-chloropropane undergo rearrangements similar to that observed in other α-alkylamino-β-chloropropanes.

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Received March 9, 1949.