3,7-DIAMINO-10-ACETYLPHENOTHIAZINE*

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In continuation of our investigations into the synthesis of substituted phenothiazines, in a search for pharmacologically active substances, we have synthesized 3,7-diamino-10-acetylphenothiazine as a starting material. This choice was considered advisable on the grounds that phenothiazine-2-carmamate esters substituted in the 10 position by aminopropionyl chains exhibit high pharmacological activity. Thus, methyl 10-(β-diethylaminopropionyl)phenothiazine-2-carbamate has a more pronounced antiarrhythmic action than quinidine and novocainamide [1]. Ethyl 10-(β-morpholinopropionyl)phenothiazine-2-carbamate has entered medical practice under the name of ethmozine as a drug for treating extrasystole, heart flutter, and auricular and paroxysmal tachycardia [2, 3].

In the synthesis, we started from the 3,7-dinitro-10-acetylphenothiazine which we prepared in [4]. This was reduced to 3,7-diamino-10-acetylphenothiazine with hydrazine hydrate in a stream of nitrogen on a nickel catalyst [5]. Owing to the presence of the acetyl group, the latter was more resistant to oxidation than 3,7-diaminophenothiazine [6] and did not give colored compounds. However, 3,7-diamino-10-acetylphenothiazine hydrochloride (I) has better storage stability, so we used this in our work.

Hydrochloride I reacts readily with aromatic aldehydes to form Schiff's bases. Reaction of (I) with benzaldehyde or salicylaldehyde leads to 3,7-dibenzylidenamino-10-acetylphenothiazine (II) or 3,7-di(o-hydroxybenzylidenamino)-10-acetylphenothiazine (III). By reacting (I) with methyl, ethyl, and isobutyl chloroformate, we obtained the dimethyl (IV), diethyl (V) and diisobutyl (VI) esters of 10-acetylphenothiazine-3,7-dicarbamic acid, which were readily converted into the dimethyl (VII), diethyl (VIII), and diisobutyl (IX) esters of phenothiazine-3,7-dicarbamic acid by acid hydrolysis [7]. Treatment of the latter with methyl iodide led to the corresponding methylated derivatives (X)-(XII). (See scheme on following page.)

By reacting diesters (VII), (VIII), and (IX) with β-chloropropionyl chloride we obtained the dimethyl (XIII), diethyl (XIV) and diisobutyl (XV) esters of 10-(β-chloropropionyl)phenothiazine-3,7-dicarbamic acid. The latter were converted into the 10-(diethylamino-, morpholino- and pyridono-) derivatives of the phenothiazine-3,7-dicarbamate diesters (XVI)-(XXIV) by reaction with secondary amines, and these were isolated in the form of their hydrochlorides for pharmacological investigation. (See scheme on following page.)

Pharmacological investigations showed that compounds (XVI)-(XXIV) have antiarrhythmic activity but are less effective than ethmozine.

EXPERIMENTAL METHOD

3,7-Diamino-10-acetylphenothiazine Hydrochloride (I). A mixture of 9.9 g of 3,7-dinitro-10-acetylphenothiazine and 12 g of moist nickel catalyst in 200 ml of alcohol was vigorously stirred in a nitrogen atmosphere while added 9 g of hydrazine hydrate over 30 min at a temperature no higher than 50°. The reaction mixture was stirred for about 2 h until the starting material had dissolved, and was then rapidly filtered from the catalyst

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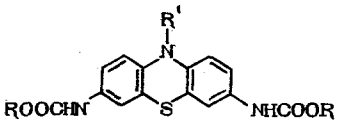
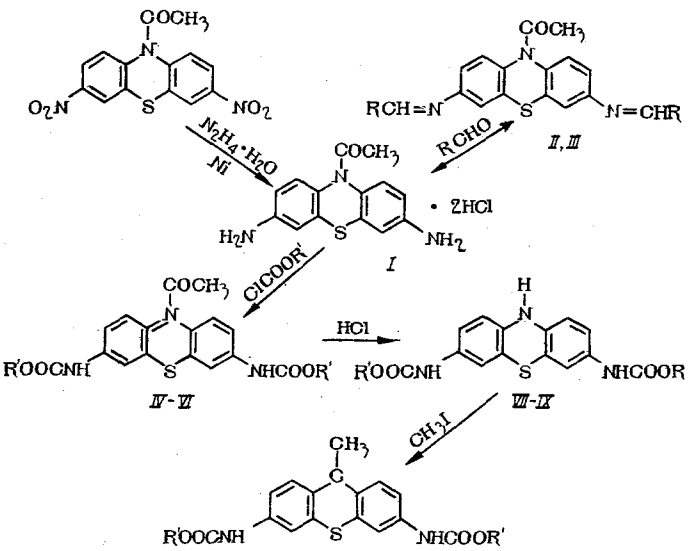
TABLE 1

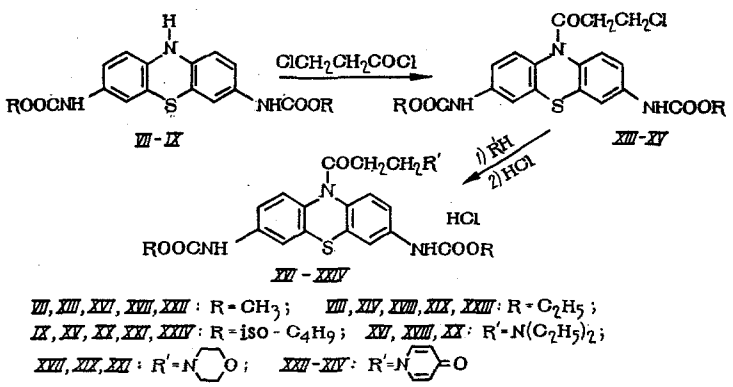


Compound	R	R′	Yield (%)	Melting point (deg)*	Found (%) N	Found (%) S	Empirical formula	Calculated (%) N	Calculated (%) S
V	C_2H_5	$COCH_3$	87	187—189	9,96	7,90	$C_{20}H_{21}N_3O_5S$	10,12	7,72
VI	iso-C_4H_9	$COCH_3$	85	138—140	8,85	6,99	$C_{24}H_{29}N_3O_5S$	8,91	6,80
VIII	C_2H_5	H	93	196—197	11,37	8,47	$C_{18}H_{19}N_3O_4S$	11,26	8,58
IX	iso-C_5H_9	H	90	217—219	9,68	7,51	$C_{22}H_{27}N_3O_4S$	9,78	7,46
XI	C_2H_5	CH_3	93	225—227	10,71	8,37	$C_{19}H_{21}N_3O_4S$	10,82	8,25
XII	iso-C_4H_9	CH_3	90	196—197	9,32	7,28	$C_{23}H_{29}N_4O_4S$	9,48	7,19
XIV	C_2H_5	$COCH_2CH_2Cl$	92	213—214	—†	7,12	$C_{21}H_{22}ClN_3O_5S$	—†	7,25
XV	iso-C_4H_9	$COCH_2CH_2Cl$	89	207—209	—‡	6,02	$C_{25}H_{30}ClN_3O_5S$	—‡	6,15

*Compounds (V), (VI), (VIII), (IX), (XIV), and (XV) were crystallized from toluene, and (XI) and (XII) from dioxane.
†Found, %: Cl 8.01. Calculated, %: Cl 8.03.
‡ Found, %: Cl 6.38. Calculated, %: Cl 6.16.



I: R=C_6H_5; II: R=C_6H_4OH
IV: R′=CH_3; V: R′=C_2H_5; VI: R′=iso-C_4H_9
VII: R′=CH_3; VIII: R′=C_2H_5; IX: R′=iso-C_4H_9
X: R′=CH_3; XI: R′=C_2H_5; XII: R′=iso-C_4H_9



VII, XIII, XVI, XVIII, XXII: R=CH_3; VIII, XIV, XVII, XIX, XXIII: R=C_2H_5;
IX, XV, XX, XXI, XXIV: R=iso-C_4H_9; XVI, XVIII, XX: R′=$N(C_2H_5)_2$;
XVII, XIX, XXI: R′=N⟨O⟩; XXII-XIV: R′=N⟨=O

into a vessel containing alcohol or ether saturated with hydrogen chloride. This was done with the minimum exposure of the reaction solution to the light. After cooling, the pre-

cipitated dihydrochloride I was filtered off and washed with ether to give 9.3 g (90%) of a product which darkened at a temperature above 230°. Found, %: Cl 20.55; N 9.35. $C_{14}H_{15}ClN_3OS$. Calculated, %: Cl 20.63; N 9.28.

3,7-Benzylidenamino-10-acetylphenothiazine (II). A solution of 1.5 g of I in 50 ml of 80% alcohol was treated with 1.8 ml of benzaldehyde, stirred for 30 min, and left overnight. The reaction solution was poured into 300 ml of water, and the precipitate separated to give 1.4 g (75%) of (II), mp 187-189° (isopropanol). Found, %: N 9.21; S 7.16. $C_{28}H_{21}N_3O$. Calculated, %: N 9.38; S 7.16.

3,7-(o-Hydroxybenzylidenamino)-10-acetylphenothiazine (III). This was prepared analogously to (II) from (I) and salicylaldehyde with a yield of 80%: mp 201-204° (from toluene). Found, %: N 8.53; S 6.68. $C_{28}H_{21}N_3O_3S$. Calculated, %: N 8.76; S 6.68.

Dimethyl 10-Acetylphenothiazine-3,7-dicarbamate (IV). A solution of 1.72 g of (I) in 50 ml of anhydrous alcohol was treated with a solution of 0.4 g of sodium hydroxide in 2 ml of water, rapidly cooled to 5-7°, and 0.66 g of methyl chloroformate added over 10 min, the temperature being kept below 10°. Then, 0.75 g of methyl chloroformate and a solution of 0.93 g of sodium carbonate in 4 ml of water were added simultaneously in 15 min at the same temperature. The reaction mixture was stirred for 1 h, 200 ml of water added, and the precipitate separated. Yield 1.33 g (70%), mp 224-277° (from dichloroethane). IR spectrum (in mineral oil), cm^{-1}: 3324 (NH), 1690 (CO). Found, %: N 10.98; S 8.39. $C_{18}H_{17}N_3O_5S$. Calculated, %: N 10.84; S 8.27.

Compounds (V) and (VI) were prepared analogously (Table 1).

Dimethyl Phenothiazine-3,7-dicarbamate (VII). A solution of 1 g of IV in 7 ml of methanol and 3 ml of acetone was treated with 6 ml of concentrated hydrochloric acid and boiled for 4 h. After cooling, the precipitate was separated and washed with water, to give 0.8 g (80%) of (VII), mp 242-243° (from dichloroethane). Found, %: N 12.24; S 9.23. $C_{16}H_{15}N_3O_4S$. Calculated, %: N 12.17; S 9.28.

Compounds (VIII) and (IX) were obtained analogously (Table 1).

Dimethyl 10-Methylphenothiazine-3,7-dicarbamate (X). A mixture of 1.5 g of (VII), 1.5 ml of methanol, and 1.5 ml of methyl iodide was heated for 10 h in a steel vessel on a boiling-water bath. After cooling, the precipitate was filtered off, washed with methanol, and crystallized from dioxan to give 1.2 g (80%) of X, mp 254-255° (from dioxan). Found, %: N 11.50, S 8.97. $C_{17}H_{17}N_3O_4S$. Calculated, %: N 11.69; S 8.92.

Compounds (XI) and (XII) were prepared analogously (Table 1).

Dimethyl 10-(β-Chloropropionyl)phenothiazine-3,7-dicarbamate (XIII). A solution of 1.8 g of (VII) in 20 ml of dry toluene was treated with 0.76 g of β-chloropropionyl chloride and boiled for 2 h. After cooling, the precipitate was filtered off and washed with petroleum ether to give 2.0 g (92%) of (XIII), mp 232-233° (from a mixture of toluene and dichloroethane). Found, %: Cl 7.97; S 7.46. $C_{19}H_{18}ClN_3O_5S$. Calculated, %: Cl 8.13; S 7.35.

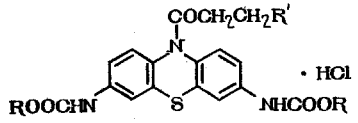
Compounds (XIV) and (XV) were prepared analogously (Table 1).

Dimethyl 10-(β-Diethylaminopropionyl)phenothiazine-3,7-dicarbamate Hydrochloride (XVI). A solution of 1.7 g of (XIII) in 40 ml of toluene was treated with 0.8 g of diethylamine and boiled for 4 h. The hot solution was filtered and diethylamine hydrochloride separated. The filtrate was evaporated down to half volume, cooled, and the oily precipitate isolated the next day. The precipitate was dissolved in dry toluene, and ether saturated with hydrogen chloride added to pH 2.0. The oily precipitate was triturated with ether and the hydrochloride (XVI) isolated. Yield 1.47 g (70%), mp 161-164° (decomp., from dichloroethane). Found, %: Cl 7.15; N 11.09; S 6.37. $C_{23}H_{29}ClN_4O_5S$. Calculated, %: Cl 6.96; N 11.00; S 6.32.

Compounds (XVII) and (XXI) were prepared analogously (Table 2).

Dimethyl 10-(β-Pyridonopropionyl)phenothiazine-3,7-dicarbamate Hydrochloride (XXII). A solution of 1.7 g of (XIII) in 25 ml of toluene and 25 ml of chloroform was treated with 0.76 g of 4-pyridone, boiled for 8 h, cooled, and the precipitate separated, dried and treated with 5 ml of water to remove 4-pyridone. The precipitate was dissolved in methanol and treated with ether saturated with hydrogen chloride to pH 2.0. The hydrochloride (XXII) was precipitated with ether. Yield 1 g (50%). The product was crystallized from methanol

TABLE 2



Compound	R	R'	Yield (%)	Melting point (deg)*	Found (%)			Empirical formula	Calculated (%)		
					Cl	N	S		Cl	N	S
XVII	CH_3		74	177—180	6,84	10,67	6,38	$C_{23}H_{26}N_4O_6S \cdot HCl$	6,78	10,71	6,13
XVIII	C_2H_5	$N(C_2H_5)_2$	69	150—152	6,58	10,43	6,15	$C_{25}H_{32}N_4O_5S \cdot HCl$	6,60	10,43	5,97
XIX	C_2H_5		72	207—211	6,40	10,29	—	$C_{25}H_{30}N_4O_6S \cdot HCl$	6,44	10,16	—
XX	iso C_4H_9	$N(C_2H_5)_2$	71	135—138	5,82	9,71	5,18	$C_{29}H_{40}N_4O_5S \cdot HCl$	5,97	9,44	5,44
XXI	iso C_4H_9		68	117—120	5,71	9,40	5,27	$C_{29}H_{38}N_4O_6S \cdot HCl$	5,84	9,21	5,38
XXIII	C_2H_5		57	218—220	6,09	9,82	5,98	$C_{26}H_{26}N_4O_6S \cdot HCl$	6,34	10,02	5,73
XXIV	iso C_4H_9		52	178—180	5,52	8,76	5,47	$C_{30}H_{34}N_4O_6S \cdot HCl$	5,76	8,94	5,21

*All the compounds melt with decomposition. (XVIII) was crystallized from isopropanol, (XVIII)-(XXI) from dichloroethane, (XXIII) from 80% ethanol, and (XXIV) from 90% isopropanol.

by adding ether, mp 194-195° (decomp.). Found, %: Cl 6.81; N 10.70; S 5.87. $C_{24}H_{23}ClN_4O_6S$. Calculated, %: Cl 6.66; N 10.52; S 6.02.

Compounds (XXIII) and (XXIV) were prepared analogously (Table 2).

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