Analogues of Antipsychotic Phenothiazines. 10-(β-Dialkylamino)ethylaminophenothiazines

Carlos Corral, Jaime Lissavetzky and Gloria Quintanilla*

Instituto de Química Médica, Juan de la Cierva, 3, Madrid-6, Spain

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A series of 10-(β-dialkylamino)ethylaminophenothiazines III was obtained by lithium aluminum hydride reduction of 10-dialkylaminoacetylaminophenothiazines II. Compounds II were synthesized by intramolecular cyclization, *via* a Smiles rearrangement, of 2-nitro-2′-(β-dialkylaminoacetyl)hydrazinodiphenyl sulfides I and XI, which in turn were best prepared by condensation of the appropriate dialkylaminoacetic acid hydrochloride with the corresponding 2-nitro-2′-hydrazinodiphenyl sulfide in the presence of dicyclohexyl carbodiimide. Other attempted methods for the synthesis of compounds I are also described.

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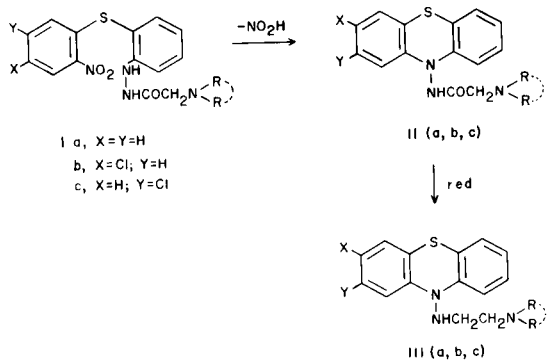
In a previous paper (1) it was shown that 2-nitro-2′-(β-acetyl)hydrazinodiphenyl sulfides cyclize in special reaction conditions, *via* a Smiles rearrangement, to give 10-acetylaminophenothiazines. It was therefore, expected that 2-nitro-2′-(β-dialkylaminoacetyl)hydrazinodiphenyl sulfides (I) should cyclize in a similar way to give the corresponding 10-dialkylaminoacetylaminophenothiazines (II), which could then be reduced to the title compounds (III) (Scheme I). Two of these last compounds (IIIa and IIIc, $N\langle^{R}_{R}$ = dimethylamino) were of special interest because they can be considered isosters of the known antipsychotic agents promazine and chlorpromazine.

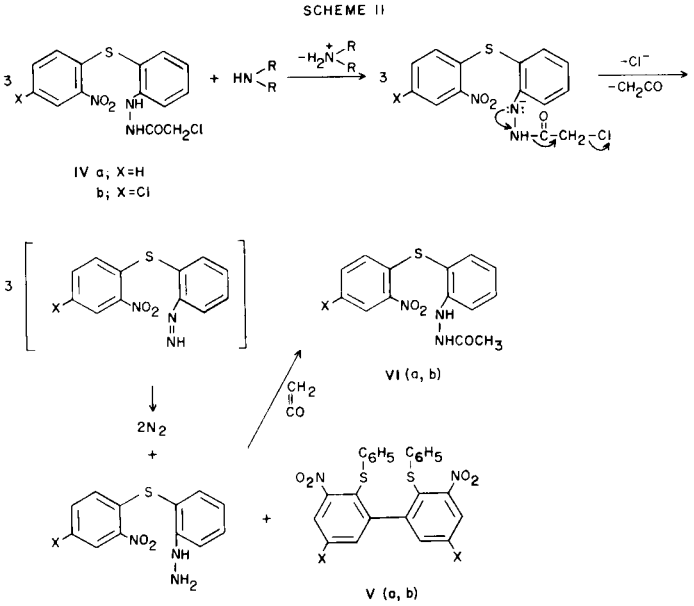
SCHEME I



Various approaches to the synthesis of compounds I were tried. Reaction of 2-nitro-2′-(β-chloroacetyl)hydrazinodiphenyl sulfides (IV) with secondary amines did not yield the corresponding compounds I but a mixture of the corresponding compounds VI and possibly V through a supposed heterolytic fragmentation reaction (2), as outlined in Scheme II.

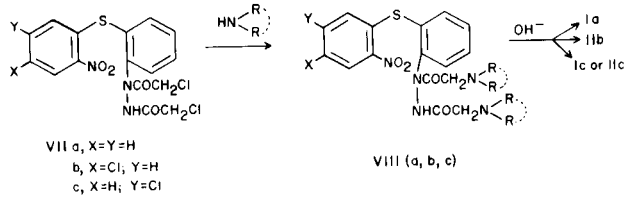
On the other hand, 2-nitro-2′-(α,β-dichloroacetyl)hydrazinodiphenyl sulfides (VII) which lack an α-hydrazinic hydrogen, reacted with secondary amines to give the expected compounds VIII. The last compounds may be selectively hydrolyzed by alkali, according to the literature (3), to give compounds I (Scheme III). This was also the

SCHEME II



case with compounds VIIIa, from which compounds Ia were easily obtained in fairly good yields by this method (see Table I, method A). However, compounds Ib and Ic could not be obtained in this manner. Hydrolysis of com-

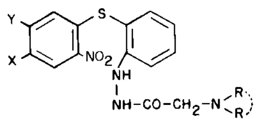
SCHEME III

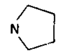
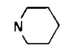
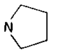
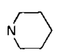
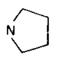
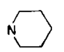


pounds VIIIb led directly to the corresponding cyclized compounds IIb, but in low yield even in the best conditions (2 equivalents of alkali), whereas hydrolysis of compounds VIIIc did not appear to be practical as a method for obtaining either compounds Ic or IIc.

Condensation at room temperature of 2-nitro-2′-hydrazinodiphenyl sulfides (IX) with dialkylaminoacetic acid

Table I

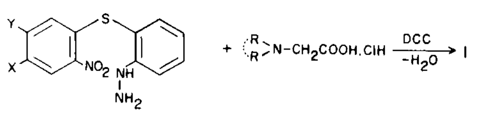


X	Y	$N{<}^{R}_{R}$	% Yield (Method)	M.p. (a)	Formula	Analysis Calcd. Found C	H	N
H	H	$N(CH_3)_2$	79 (A), 54 (B)	158-160	$C_{16}H_{18}N_4O_3S$	55.44 55.26	5.23 4.98	16.17 15.93
H	H	$N(C_2H_5)_2$	55 (B)	148-150	$C_{18}H_{22}N_4O_3S$	57.75 57.46	5.88 5.96	15.29 14.97
H	H		74 (A), 70 (B)	153-155	$C_{18}H_{20}N_4O_3S$	58.06 58.10	5.41 5.26	16.04 15.99
H	H		69 (A), 85 (B)	158-159	$C_{19}H_{22}N_4O_3S$	59.06 59.33	5.69 5.48	14.50 14.34
Cl	H	$N(CH_3)_2$	55 (B)	130-132	$C_{16}H_{17}ClN_4O_3S$	50.47 50.39	4.46 4.45	14.72 14.48
Cl	H	$N(C_2H_5)_2$	35 (B)	101-103	$C_{18}H_{21}ClN_4O_3S$	52.87 52.59	5.14 5.06	13.71 13.49
Cl	H		70 (B)	138-139	$C_{18}H_{19}ClN_4O_3S$	53.14 52.88	4.67 4.84	13.77 13.57
Cl	H		60 (B)	162-163	$C_{19}H_{21}ClN_4O_3S$	54.23 53.97	4.99 5.15	13.32 13.09
H	Cl	$N(CH_3)_2$	70 (B)	159-161	$C_{16}H_{17}ClN_4O_3S$	50.47 50.19	4.46 4.41	14.72 14.54
H	Cl	$N(C_2H_5)_2$	35 (B)	106-108	$C_{18}H_{21}ClN_4O_3S$	52.87 52.83	5.14 5.08	13.71 13.57
H	Cl		50 (B)	130-131	$C_{18}H_{19}ClN_4O_3S$	53.14 53.04	4.67 4.67	13.77 13.51
H	Cl		25 (A), 70 (B)	141-142	$C_{19}H_{21}ClN_4O_3S$	54.23 53.94	4.99 5.00	13.32 12.99

(a) Recrystallized from ethanol. All these compounds showed the following common ir and nmr spectral data; ir (nujol): ν 3390-3340; 3280-3240 (NH-NH); 1690-1660 (C=O); 1520, 1340 (NO_2); nmr (deuteriochloroform): δ 3.1-3.3 (s, 2H, CH_2); 6.8-6.85 (s, 1H, NH); 6.9-7.7 (m, 6 or 7H, aromatic protons); 8.20-8.35 (m, 1H, H-3, aromatic proton).

hydrochlorides in the presence of dicyclohexylcarbodiimide in a 1:1 mixture of tetrahydrofurane and acetonitrile as solvent (Scheme IV) proved finally to be the best method for the synthesis of compounds I (see Table I, method B).

SCHEME IV



IX a, X=Y=H
b, X=Cl, Y=H
c, X=H; Y=Cl

Cyclization of compounds I to the corresponding 10-aminophenothiazine derivatives (II), took place easily in the reaction conditions previously described (1). Reaction was complete in a short time (10-15 minutes) and only a breakdown secondary product, the corresponding phenothiazines, was identified by tlc. Yields of compounds IIa and IIb were fairly good and lower yields of compounds IIc were due to difficulties in the separation of a minute colored impurity (see Table II, method A). Compounds IIc were obtained in better yield by cyclization of the corresponding compounds XI as outlined in Scheme V

SCHEME V

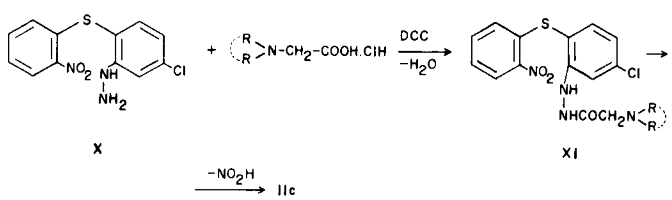
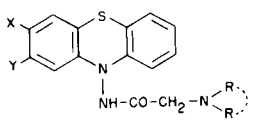


Table II



X	Y	N(R)(R)	% Yield (Method)	M.p. (a)	Formula	Analysis Calcd. Found C	H	N
H	H	$N(CH_3)_2$	70 (A)	180-182 dec.	$C_{16}H_{17}N_3OS$	64.21 64.37	5.68 5.88	14.04 14.26
H	H	$N(C_2H_5)_2$	67 (A)	168-170 dec.	$C_{18}H_{21}N_3OS$	66.03 65.98	6.46 6.28	12.83 13.07
H	H		60 (A)	172-173 dec.	$C_{18}H_{19}N_3OS$	66.46 66.54	5.84 6.01	12.92 13.02
H	H		66 (A)	187-189 dec.	$C_{19}H_{21}N_3OS$	67.23 67.46	6.23 6.24	12.28 12.46
Cl	H	$N(CH_3)_2$	75 (A)	180-182 dec.	$C_{16}H_{16}ClN_3OS$	57.57 57.42	4.79 4.71	12.59 12.46
Cl	H	$N(C_2H_5)_2$	40 (A)	102-103	$C_{18}H_{20}ClN_3OS$	59.76 59.70	5.53 5.43	11.62 11.52
Cl	H		75 (A)	179-180 dec.	$C_{18}H_{18}ClN_3OS$	60.10 60.03	5.00 4.94	11.68 11.49
Cl	H		75 (A)	194-196 dec.	$C_{19}H_{20}ClN_3OS$	61.06 60.93	5.35 5.24	11.24 10.99
H	Cl	$N(CH_3)_2$	45 (A) (b), 70 (B)	202-204 dec.	$C_{16}H_{16}ClN_3OS$	57.57 57.38	4.79 4.67	12.59 12.45
H	Cl	$N(C_2H_5)_2$	30 (A) (b), 55 (B)	154-155	$C_{18}H_{20}ClN_3OS$	59.76 59.62	5.53 5.47	11.62 11.56
H	Cl		45 (A) (b), 70 (B)	204-205 dec.	$C_{18}H_{18}ClN_3OS$	60.10 59.90	5.00 4.99	11.68 11.65
H	Cl		55 (A) (b), 60 (B)	210-212 dec.	$C_{19}H_{20}ClN_3OS$	61.06 61.12	5.35 5.29	11.24 10.98

(a) Recrystallized from acetonitrile. (b) Recrystallized first from acetonitrile, then from methylethylketone. All these compounds showed the following common ir and nmr spectral data; ir (nujol): ν 3280-3180 (NH); 1700-1685 (C=O); nmr (deuteriochloroform): δ 3.0-3.55 (s, 2H, CH_2); 6.7-7.4 (m, 7 or 8H, aromatic protons); 9.0-9.5 (bs, 1H, NH).

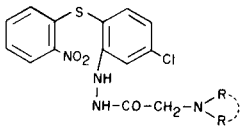
(see Table II, method B).

The identity of compounds IIc obtained by both methods is a proof of the existence of a Smiles rearrangement prior to the cyclyzation.

Some difficulties were encountered in reducing compounds II to compounds III. Although Kratz and Berger (4) reported that β-acylphenylhydrazines were easily reduced in high yields to the corresponding β-alkylphenylhydrazines with excess lithium aluminum hydride, when this reaction was carried out in methylal as solvent, reduction of compounds II took place very slowly, and some secondary products were produced. Soon after the beginning of the reaction, the spot of the corresponding phenothiazine appeared on tlc, possibly caused by cleavage of the N-N bond of compounds II by the hydrogen initially evolved. After heating under reflux for 72 hours reduction was not complete. Moreover, in the reduction of compounds IIc, small amounts of the corresponding compounds IIIa were produced by reductive dehalogenation.

Compounds III (Table IV) were isolated by preparative tlc on alumina plates, except compounds IIIb (N(R)(R) = diethylamino, pyrrolidino and piperidino) which underwent strong decomposition in this process and could not be purified otherwise. Compound IIIb (N(R)(R) = dimethylamino) was purified by recrystallization from ethanol. Compounds III were extremely sensitive to even weak acids.

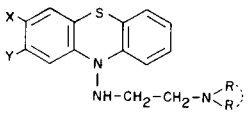
Table III



	% Yield	M.p. (a)	Formula	Analysis Calcd. Found		
				C	H	N
$N(CH_3)_2$	65	196-197	$C_{16}H_{17}ClN_4O_3S$	50.47	4.46	14.72
				50.71	4.48	14.73
$N(C_2H_5)_2$	60	119-120	$C_{18}H_{21}ClN_4O_3S$	52.87	5.14	13.71
				52.58	5.13	13.40
	70	170-172	$C_{18}H_{19}ClN_4O_3S$	53.14	4.67	13.77
				53.21	4.61	13.48
	40	162-164	$C_{19}H_{21}ClN_4O_3S$	54.23	4.99	13.32
				53.97	5.05	13.09

(a) Recrystallized from ethanol. All these compounds showed the following common ir and nmr spectral data; ir (nujol): ν 3320-3280 (-NH-NH); 1690-1700 (C=O); 1520, 1340 ($-NO_2$); nmr (deuteriochloroform): δ 3.1-3.3 (s, 2H, CH_2); 6.8-6.85 (s, 1H, NH); 6.9-7.7 (m, 6H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton).

Table IV



X	Y		% Yield	M.p. (Solvent)	Formula	Analysis Calcd. Found		
						C	H	N
H	H	$N(CH_3)_2$	37	74-75 (ethanol)	$C_{16}H_{19}N_3S$	67.36	6.66	14.73
						67.29	6.59	14.52
H	H	$N(C_2H_5)_2$	35	oil	$C_{18}H_{23}N_3S$	68.35	7.27	13.29
						68.21	7.23	13.09
H	H		40	70-72 (petroleum ether)	$C_{18}H_{21}N_3S$	69.54	6.75	13.50
						69.62	6.74	13.38
H	H		35	120-122 (ethanol)	$C_{19}H_{23}N_3S$	70.12	7.12	12.91
						69.87	6.92	12.80
Cl	H	$N(CH_3)_2$	35	80-82 (petroleum ether)	$C_{16}H_{18}ClN_3S$	60.11	5.63	13.14
						59.95	5.66	12.86
H	Cl	$N(CH_3)_2$	30	73.5-74 (petroleum ether)	$C_{16}H_{18}ClN_3S$	60.11	5.63	13.14
						59.91	5.84	13.19
H	Cl	$N(C_2H_5)_2$	30	oil	$C_{18}H_{22}ClN_3S$	61.12	6.22	13.58
						61.03	6.01	13.33
H	Cl		30	92-94 (petroleum ether)	$C_{18}H_{20}ClN_3S$	62.53	5.79	12.14
						62.63	5.79	11.85
H	Cl		40	114-116 (petroleum ether)	$C_{19}H_{22}ClN_3S$	63.43	6.12	11.68
						63.65	6.22	11.85

All these compounds showed the following common ir and nmr spectral data; ir (nujol): ν 3300-3260 (-NH); nmr (deuteriochloroform): 2.4-2.8 (t, 2H, CH_2- ); 2.9-3.2 (q, 2H, HN-CH_2); 4.2-4.6 (t, 1H, NH), 6.9-7.5 (m, 7 or 8H, aromatic protons).

EXPERIMENTAL

Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12 60 MHz spectrometer with TMS as internal reference.

Hydrazinic compounds IX and X were obtained as previously reported (1).

2-Nitro-2′-(β-chloroacetyl)hydrazinodiphenyl Sulfides (IV).

To an ice-cooled stirred mixture of 0.02 mole of the corresponding hydrazine in 40 ml. of anhydrous benzene and 0.02 mole of anhydrous sodium carbonate, 0.02 mole of chloroacetyl chloride was added gradually. The reaction mixture was left standing overnight with stirring. The salts so formed were filtered off, the filtrate was evaporated *in vacuo* to dryness and the residue was recrystallized.

The following compounds were obtained according to this procedure.

2-Nitro-2′-(β-chloroacetyl)hydrazinodiphenyl Sulfide (IVa).

This compound was obtained as a yellow solid in 74% yield, m.p. 116-117 (benzene); ir (nujol): ν 3330, 3240 (-NH-NH); (C=O); 1520, 1340 (-NO_2); nmr (deuteriochloroform): δ 4.2 1690 (s, 2H, CH_2); 6.8-6.9 (s, 1H, NH); 6.9-7.6 (m, 7H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton).

Anal. Calcd. for $C_{14}H_{12}ClN_3O_3S$: C, 49.74; H, 3.55; N, 12.44. Found: C, 50.00; H, 3.80; N, 12.23.

2-Nitro-4-chloro-2′-(β-chloroacetyl)hydrazinodiphenyl Sulfide (IVb).

This compound was obtained as a yellow solid in 78% yield, m.p. 173-175 (toluene); ir (nujol): ν 3300 (-NH-NH); 1690 (C=O); 1520, 1340 (-NO_2); nmr (deuteriochloroform): δ 4.2 (s, 2H, CH_2); 6.8-6.9 (s, 1H, NH): 6.9-7.7 (m, 6H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton).

Anal. Calcd. for $C_{14}H_{11}Cl_2N_3O_3S$: C, 45.16; H, 2.95; N, 11.29. Found: C, 45.25; H, 3.00; N, 11.02.

Reaction of Compounds IV with Secondary Amines.

To a stirred suspension of 0.005 mole of compounds IV in 50 ml. of anhydrous benzene, 0.011 mole of piperidine was added at room temperature. Evolution of bubbles was observed and the solid gradually dissolved in the reaction mixture which turned a red color. It was left standing overnight and the precipitate formed was filtered off and identified as the theoretical amount of piperidine hydrochloride. The filtrate was evaporated *in vauco* to dryness and the residue was chromatographed on preparative silica gel plates using 2:1 ethylacetate/petroleum ether as solvent. Thus, two main bands were separated. The slower-moving band afforded in the IVa reaction, a yellow solid (0.4 g.) identified as 2-nitro-2′-(β-acetyl)hydrazinodiphenyl sulfide (VIa) and in the IVb reaction, a yellow solid (0.6 g.) identified as 2-nitro-4-chloro-2′-(β-acetyl)hydrazinodiphenyl sulfide (VIb). These compounds have previously been described (1).

The faster-moving band afforded in the IVa reaction a yellow solid (Va) (0.5 g.), m.p. 158-158.5 (petroleum ether, b.p. 50-60°); ir (nujol): ν 1520, 1340 (-NO_2).

Anal. Calcd. for $C_{24}H_{16}N_2O_4S_2$: C, 62.60; H, 3.47; N, 6.08. Found: C, 62.57; H, 3.66; N, 6.05.

In IVb reaction, this band afforded a yellow solid (Vb) (0.7 g.), m.p. 201-202 (ethanol); ir (nujol): ν 1520, 1340 (-NO_2).

Anal. Calcd. for $C_{24}H_{14}Cl_2N_2O_4S_2$: C, 54.44; H, 2.64; N, 5.29. Found: C, 54.24; H, 2.74; N, 5.17.

2-Nitro-2′-(α,β-dichloroacetyl)hydrazinodiphenyl Sulfides (VII).

To a well-stirred suspension of 0.02 mole of the corresponding hydrazine in 40 ml. of anhydrous benzene, 0.04 mole of chloroacetyl chloride was added. The mixture was heated under reflux for 3 hours until no more hydrogen chloride gas was evolved. The reaction mixture was cooled to room temperature and the crystallized solid was filtered off. Since no crystalline compounds appeared in the case of VIIa, 40 ml. of diethyl ether were added to the solution with stirring. After a while, a small amount of a dark oil which appeared was removed and eventually the desired compound crystallized from the solution.

The following compounds were obtained according to this procedure.

2-Nitro-2′-(α,β-dichloroacetyl)hydrazinodiphenyl Sulfide (VIIa).

This compound was obtained as a yellow solid in 84% yield, m.p. 108-110 (benzene); ir (nujol): ν 3280 (-NH); 1740, 1690 (C=O); 1520, 1340 (-NO_2); nmr (deuteriochloroform): δ 4.05 (s, 2H, CH_2); 4.1 (s, 2H, CH_2); 6.8-7.8 (m, 7H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton); 9.3-9.6 (bs, 1H, NH).

Anal. Calcd. for $C_{16}H_{13}Cl_2N_3O_4S$: C, 46.37; H, 3.14; N, 10.14. Found: C, 46.22; H, 3.19; N, 10.21.

2-Nitro-4-chloro-2′-(α,β-dichloroacetyl)hydrazinodiphenyl Sulfide (VIIb).

This compound was obtained as a yellow solid in 82% yield, m.p. 145-147 (benzene); ir (nujol): ν 3280 (-NH); 1740 (C=O); 1520, 1340 (-NO_2); nmr (deuteriochloroform): δ 4.0 (s, 2H, CH_2); 4.05 (s, 2H, CH_2); 6.8-7.8 (m, 6H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton); 9.2-9.5 (bs, 1H, NH).

Anal. Calcd. for $C_{16}H_{12}Cl_3N_3O_4S$: C, 42.82; H, 2.67; N, 9.36. Found: C, 42.70; H, 2.72; N, 9.51.

2-Nitro-5-bhloro-2′-(α,β-dichloroacetyl)hydrazinodiphenyl Sulfide (VIIc).

This compound was obtained as a yellow solid in 77% yield, m.p. 132-134 (benzene); ir (nujol): ν 3260 (-NH); 1730, 1690 (C=O); 1520, 1340 (-NO_2); nmr (deuteriochloroform): δ 4.0 (s, 2H, CH_2), 4.05 (s, 2H, CH_2); 6.8-7.8 (m, 6H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton); 9.2-9.5 (bs, 1H, NH).

Anal. Calcd. for $C_{16}H_{12}Cl_3N_3O_4S$: C, 42.82; H, 2.67; N, 9.36. Found: C, 43.11; H, 2.74; N, 9.34.

2-Nitro-2′-(α,β-bis-dialkylaminoacetyl)hydrazinodiphenyl Sulfides (VIII).

General Procedure.

To a well-stirred solution of the corresponding compound VII (0.02 mole) in 60 ml. of anhydrous benzene, 0.08 mole of the suitable amine was added (0.016 mole of a benzenic solution in the case of *N,N*-dimethylamine). The reaction mixture was left standing overnight at room temperature. The solid formed was filtered and consisted of either the amine hydrochloride or a mixture of the amine hydrochloride and the corresponding compound VIII. In the latter cases, the two compounds were separated by treating with water. The benzenic filtrate was in all the cases evaporated to dryness, yielding the crude desired compounds VIII.

Only the reaction products obtained starting from piperidine are described. This is due to the fact that in the other cases a total purification of the compounds was unsuccessful and the crude products were used in the next step.

The following piperidine derivatives were obtained according to this procedure.

2-Nitro-2′-(α,β-dipiperidinoacetyl)hydrazinodiphenyl Sulfide.

This compound was obtained as a yellow solid in 84% yield, m.p. 129-130 (ethanol); ir (nujol): ν 3330 (-NH); 1690 (C=O); 1520, 1340 ($-NO_2$); nmr (deuteriochloroform): δ 1.3-1.7 (m, 12H, H-3, H-4 and H-5 piperidine rings); 2.3-2.8 (m, 8H, H-2 and H-6 piperidine rings); 2.9 (s, 2H, CH_2); 3.1 (2, 2H, CH_2); 6.8-7.8 (m, 7H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton); 9.5-9.8 (bs, 1H, NH).

Anal. Calcd. for $C_{26}H_{33}N_5O_4S$: C, 60.88; H, 6.52; N, 13.50. Found: C, 61.04; H, 6.50; N, 13.69.

2-Nitro-4-chloro-2′-(α,β-dipiperidinoacetyl)hydrazinodiphenyl Sulfide.

This compound was obtained as a yellow solid in 88% yield, m.p. 136 (benzene); ir (nujol): ν 3280 (-NH); 1700 (C=O); 1520, 1340 ($-NO_2$); nmr (deuteriochloroform): δ 1.3-1.7 (m, 12H, H-3, H-4 and H-5 piperidine rings); 2.4-2.8 (m, 8H, H-2 and H-6 piperidine rings); 2.9 (s, 2H, CH_2); 6.8-7.8 (m, 6H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton); 9.6-9.8 (bs, 1H, NH).

Anal. Calcd. for $C_{26}H_{32}ClN_5O_4S$: C, 57.19; H, 5.86; N, 12.83. Found: C, 56.98; H, 5.63; N, 13.02.

2-Nitro-5-chloro-2′-(α,β-dipiperidinoacetyl)hydrazinodiphenyl Sulfide.

This compound was obtained as a yellow solid in 90% yield, m.p. 107-109 (benzene); ir (nujol): ν 3300 (-NH); 1700 (C=O); 1520, 1340 ($-NO_2$); nmr (deuteriochloroform): δ 1.3-1.7 (m, 12H, H-3, H-4 and H-5 piperidine rings); 2.4-2.8 (m, 8H, H-2 and H-6 piperidine rings); 3.0 (s, 2H, CH_2); 3.1 (s, 2H, CH_2); 6.8-7.7 (m, 6H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton); 9.6-9.8 (bs, 1H, NH).

Anal. Calcd. for $C_{26}H_{32}ClN_5O_4S$: C, 57.19; H, 5.86; N, 12.83. Found: C, 57.47; H, 5.82; N, 12.54.

Hydrolysis of Compounds VIII.

Hydrolysis of Compounds VIIIa.

To a mixture of ethanol (100 ml.) and 30 ml. (0.03 mole) of an aqueous *N* solution of sodium hydroxide, 0.03 mole of compound VIIIa was added. The reaction mixture was heated under reflux for 8 hours. On cooling, the hydrolysis product crystallized as a yellow solid, which was filtered and recrystallized to give compounds Ia (see Table I, method A).

Hydrolysis of Compounds VIIIb.

To a mixture of ethanol (100 ml.) and 60 ml. (0.06 mole) of an aqueous *N* solution of sodium hydroxide, 0.03 mole of compounds VIIIb was added. The reaction mixture was heated under reflux for 8 hours. The solvent was evaporated *in vacuo* to dryness and the residue was treated with water and diethyl ether. The solid obtained on evaporation of the ethereal extracts was recrystallized from acetonitrile. Compound IIb (N  = dimethylamino) and compound IIb (N  = piperidino) were obtained in 18% and 31% yield, respectively, in this way.

Hydrolysis of compounds VIIIc.

To a mixture of ethanol (120 ml.) and 30 ml. (0.03 mole) of an aqueous *N* solution of sodium hydroxide, 0.03 mole of compound VIIIc (N  = piperidino), was added. The solvent was evaporated *in vacuo* to dryness and the residue was treated with water and diethyl ether. The ethereal extract was evaporated *in vacuo* and the residue was chromatographed on a silica-gel column using 2:1 ethylacetate/petroleum ether as solvent. Product-containing fractions gave after evaporation, compound Ic (N  = piperidino) in 25% yield.

When the reaction was carried out using a double amount of sodium hydroxide (60 ml., 0.06 mole), compound IIc (N  = piperidino) was isolated in ths same conditions as above, in 14% yield.

2-Nitro-2′-(β-dialkylaminoacetyl)hydrazinodiphenyl Sulfides (I, XI).

General Procedure.

To a stirred solution of the appropriate hydrazine (0.02 mole) in a 1:1 mixture of anhydrous tetrahydrofurane and acetonitrile (80 ml.), 0.02 mole of the corresponding *N,N*-dialkylaminoacetic acid hydrochloride (5) and 0.02 mole of *N,N′*-dicyclohexylcarbodiimide were added at room temperature.

The reaction mixture was stirred, in anhydrous conditions for 6 hours. The solid thus formed, which was a mixture of dicyclohexylurea and the desired compound hydrochloride was filtered and washed with the solvent mixture. The separation of these two compounds was made by treating with boiling water, in which the dicyclohexylurea was insoluble. The aqueous solution of the hydrochloride was cooled and stirred with a slight excess of a 2*N* solution of sodium hydroxide. The precipitated yellow solid was filtered, washed with water and recrystallized.

When this reaction was carried out with *N,N*-diethylaminoacetic acid hydrochloride, dicyclohexylurea was the only insoluble product in the solvent mixture. The desired compounds hydrochlorides were extracted with boiling water from the residue of the evaporation of the solvent mixture. Properties and yields of compounds I and XI are shown in Tables I (method B) and III, respectively.

10-Dialkylaminoacetylaminophenothiazines (II).

General Procedure.

Anhydrous potassium carbonate (0.01 mole) was added to a well-stirred solution of 0.01 mole of compounds I or XI in 30 ml. of *N,N*-dimethylformamide and the reaction mixture was heated under reflux for 10-15 minutes. After cooling to room temperature it was poured into water. The precipitate was filtered, washed with water, then with diethyl ether, dried and recrystallized from the adequate solvent. Properties and yields of compounds II are shown in Table II.

10-(β-Dialkylaminoethylamino)phenothiazines (III).

General Procedure.

Compound II (0.01 mole) was added at once to a stirred suspension of 0.04 mole of lithium aluminum hydride in freshly distilled anhydrous methylal (150 ml.). The reaction mixture was heated under reflux for 72 hours in anhydrous conditions. Once cooled, the excess of lithium aluminum hydride was destroyed with ethylacetate and the reaction mixture was hydrolyzed with the minimum amount of water. The inorganic solids were filtered

off and washed repeatedly with diethyl ether. The ethereal extracts together with the filtrate were evaporated *in vacuo*. The residue was extracted with petroleum ether (b.p. 50-60°) and the extract was evaporated to dryness to be purified by preparative alumina-gel tlc, using 1:2 ethylacetate/petroleum ether.

Compound IIIb (N  = dimethylamino) was purified by crystallization from ethanol of the residue of the petroleum ether extracts. The other compounds IIIb underwent a strong decomposition in all the attempted processes of purification. Properties and yields of the obtained compounds III are shown in Table IV.

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