placed particularly among the compounds examined by change from an aliphatic to an aromatic substituent.

EXPERIMENTAL

Sulfamyl chlorides. Diethylsulfamyl chloride was prepared as described by Binkley and Degering.[7] *N*-Pentamethylene sulfamyl chloride was prepared by Denivelle's procedure[8] as modified by Audrieth and von Brauchitsch.[9] The compounds boiled at 62°/0.02 mm. and 95°/1 mm., respectively.

N-Substituted sulfamides. Ammonolysis could be effected with liquid ammonia but not in the presence of a diluting solvent. As the procedure followed in all aminolysis reactions was essentially the same, only one synthesis of this type is described. With diethylsulfamyl chloride, chloroform is a suitable solvent; with pentamethylenesulfamyl chloride, benzene is better.

N,N-Diethylsulfamide. One hundred milliliters of liquid ammonia was placed in a three necked flask fitted with a mechanical stirrer, an outlet tube, and a small separatory funnel and immersed in a bath of Methyl Cellosolve and Dry Ice to maintain the temperature at −70°. Twenty grams (0.117 mole) of diethylsulfamyl chloride was added dropwise with vigorous agitation over a period of 2 hr. The resulting solution was stirred for 2 hr. and then kept at room temperature in order to permit evaporation of the excess of ammonia. The residue was dissolved in hot ether, the solution filtered, and the ether removed from the filtrate under vacuum. The product was recrystallized twice from ether.

N,N-Diethyl-N'-cyclohexylsulfamide. Seventeen and one-tenth grams (0.1 mole) of diethylsulfamyl chloride, 20.0 g. (0.2 mole) of cyclohexylamine, and 50 ml. of chloroform were placed in a flask equipped with a reflux condenser. The solution was then refluxed at 70° for 12 hr. The solvent was removed by distillation, and the dark residue was shaken with water and ether in a separatory funnel. The ether layer was dried over anhydrous calcium chloride. Removal of the ether by distillation left a dark oily residue which, upon fractional distillation, yielded a colorless, viscous oil. Upon standing, this solidified to a crystalline mass. Final purification was effected by recrystallization from *n*-heptane.

Infrared spectra. These were measured with a Perkin-Elmer Model 21 instrument, using a sodium chloride prism.

Acknowledgment. Support received for this investigation under Contract DA-11-022-ORD-2956 with the Feltman Research and Engineering Laboratory, Ordnance Corps, Picatinny Arsenal, Dover, N. J., is gratefully acknowledged.

URBANA, ILL.

(7) W. W. Binkley and E. F. Degering, *J. Am. Chem. Soc.*, 61, 3250 (1939).

(8) L. Denivelle, *Bull. soc. chim. France*, [5], 3, 2143 (1936).

(9) L. F. Audrieth and M. von Brauchitsch, *J. Org. Chem.*, 21, 426 (1956).

[CONTRIBUTION FROM SMITH KLINE AND FRENCH LABORATORIES AND TEMPLE UNIVERSITY RESEARCH INSTITUTE]

Synthesis of Phenothiazines. VI. Certain 2-Substituted Phenothiazines and Their 10-Aminoalkyl Derivatives

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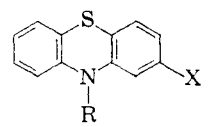
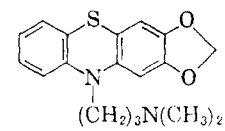
2-Dimethylaminophenothiazine, 2,3-methylenedioxyphenothiazine, 2-cyanophenothiazine and phenothiazine-2-carboxamides were synthesized. Several 10-aminoalkyl derivatives of these compounds and of 2-acetylphenothiazine and its oxime were prepared for pharmacological evaluation.

Various investigators have found that introduction of certain substituents such as chlorine or the trifluoromethyl group in the 2-position of 10-dimethylaminopropylphenothiazine (promazine) (Ia) produces agents having enhanced tranquilizing and antiemetic activities.[2] In the course of our studies on the chemistry and pharmacology of 2-substituted phenothiazines[3] related to Ia, we synthesized derivatives Ib–d, II and several compounds derived from 2-acetylphenothiazine listed in Table I.





II

Ia. X = H, R = $(CH_2)_3N(CH_3)_2$
b. X = $N(CH_3)_2$, R = $(CH_2)_3N(CH_3)_2$
c. X = $CON(CH_3)_2$, R = $(CH_2)_3N(CH_3)_2$
d. X = CN, R = $CH_2CH(CH_3)CH_2N(CH_3)_2$

2-Dimethylaminophenothiazine (IV) was prepared by the Ullman route starting with *N,N*-dimethyl-4-bromoaniline (III).[4]

An attempt to obtain IV by thionation of 3-dimethylaminodiphenylamine (Bernthsen method) was unsuccessful.

Alkylation of IV with 3-dimethylaminopropyl chloride was carried out in the usual way to yield

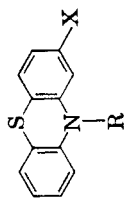
(1) Research Institute of Temple University.

(2) See E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.* 25, 60 (1960) (Paper III of this series) and references therein.

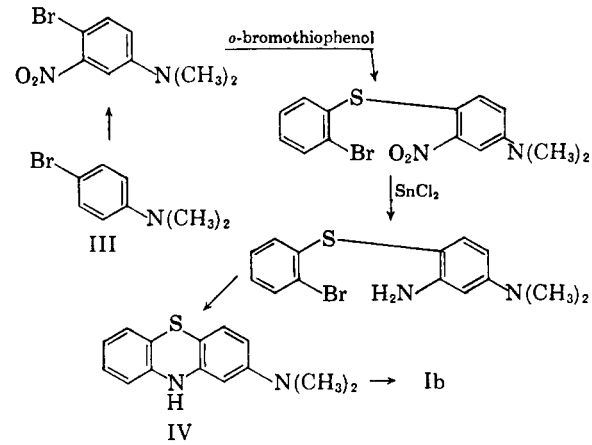
(3) Paper IV of this series: P. N. Craig, M. Gordon, J. J. Lafferty, B. M. Lester, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, 25, 944 (1960).

(4) G. R. Clemo and J. M. Smith, *J. Chem. Soc.*, 2414 (1928).

TABLE I DERIVATIVES OF 2-ACETYLPHENOTHIAZINE

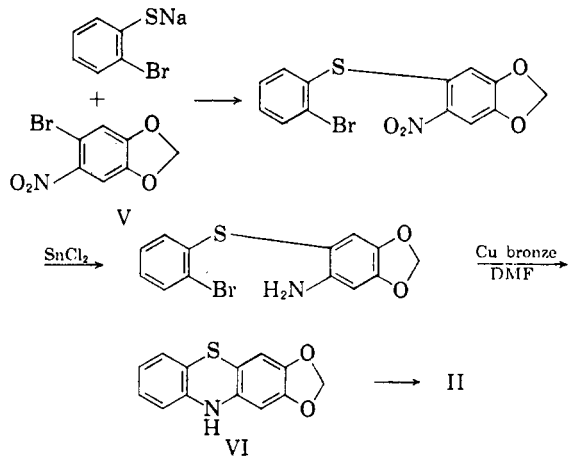


	X	R	Yield, %	B.P. Free base (mm.)	Salt	M.P.	Molecular Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XI	$COCH_3$	$(CH_2)_3N(CH_3)_2$	60	255–260° (0.75)	Dimaleate	179–180°	$C_{32}H_{37}N_3OS.2C_4H_4O_4$ $\frac{1}{2}H_2O$	57.95	5.71	—	57.86	5.83	—
XII	$COCH_3$	$CH_2CH(CH_3)CH_2N(CH_3)_2$	65	260–265° (0.1)	Dihydrochloride	249–50° (dec.)	$C_{23}H_{33}N_3OS.2HCl$	58.96	6.67	—	58.72	6.92	—
XIII	$COCH_3$	$CH_2CH(CH_3)CH_2N(CH_3)CH(CH_3)_2$	56	215–220° (0.1)	Hydrochloride	219–221°	$C_{10}H_{34}N_3OS.HCl$ $\frac{1}{4}H_2O$	62.97	6.74	—	62.99	6.99	—
XIV	$C(CH_3)_2OH$	$(CH_2)_2N(CH_3)_2$	—	—	Free base	107.5–109°	$C_{20}H_{24}N_2OS$	70.13	7.65	8.18	69.83	7.58	8.30
XV	$C(CH_3)=NOH$	$(CH_2)_3N(CH_3)_2$	65	—	Dimaleate	171–172° (dec.)	$C_{32}H_{33}N_4OS_2.C_4H_4O_4$	57.31	5.77	—	57.08	5.75	—

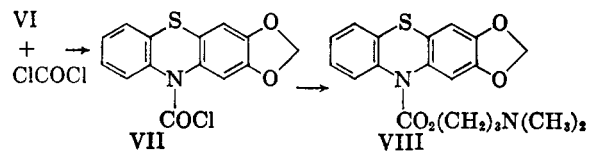


2 - dimethylamino - 10 - (3 - dimethylaminopropyl)-phenothiazine (Ib).

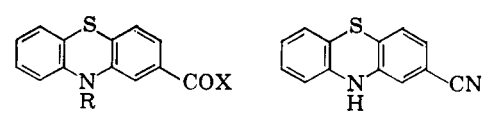
By a similar route 2,3-methylenedioxyphenothiazine (VI) was prepared from 4-nitro-5-bromocatechol methylene ether (V).[5]



From VI were obtained 2,3-methylenedioxy-10-(3 - dimethylaminopropyl) - phenothiazine (II) by aminoalkylation and 3-dimethylaminopropyl 2,3-methylenedioxyphenothiazine - 10 - carboxylate (VIII) *via* the carbamyl chloride VII.



Several derivatives (IX and X) of phenothiazine 2-carboxylic acid (IXa)[6] were prepared as indicated below.



IX. a. X = OH, R = H
b. X = Cl, R = H
c. X = NH_2, R = H
d. X = OH, R = $COCH_3$
e. X = Cl, R = $COCH_3$
f. X = $N(CH_3)_2$, R = $COCH_3$
g. X = $N(CH_3)_2$, R = H

X

The acid IXa was converted to its amide IXc *via* the acid chloride IXb which was obtained by treatment of IXa with phosphorus pentachloride. Dehydration of IXc with phosphorus oxychloride gave the 2-cyano derivative X. By alkylation of the latter compound with 3-dimethylamino-2-methylpropylchloride, 2-cyano-10-(3-dimethylamino-2-methylpropyl)phenothiazine (Id) was obtained.[7]

Starting with 10-acetylphenothiazine-2-carboxylic acid (IXd), the *N,N*-dimethylamide IXg was prepared *via* intermediates IXe and IXf. Alkylation of IXg with 3-dimethylaminopropyl chloride gave 2 - (*N,N* - dimethylcarboxamido) - (3- dimethylaminopropyl)phenothiazine (Ic).

Several 10-aminopropyl derivatives of 2-acetylphenothiazine were prepared by alkylation of its ethylene ketal derivative. This procedure was used after it was found that the ketone is not smoothly alkylated under the usual conditions employing sodamide as a condensing agent. The usual conditions gave large amounts of resinous material, probably resulting from base catalyzed condensation reactions involving the methyl ketone group. While this work was in progress Schmitt *et al.*[8] reported the synthesis of a number of these compounds by the same route. These workers also prepared 10-aminoalkyl derivatives of 2-acetylphenothiazine oxime.[9] In Table I are listed those derivatives (XI–XV) of 2-acetylphenothiazine prepared in this work that have not been previously reported. The oxime derivative XV was obtained by oximation of XI and compound XIV, 2 - (1 - hydroxy - 2 - propyl) - 10 - (3 - dimethylaminopropyl)phenothiazine,[10] was prepared by the action of methyl lithium on 2-acetyl-10-(3-dimethylaminopropyl)phenothiazine.[8,9]

The results of pharmacological studies on these compounds will be reported elsewhere.

EXPERIMENTAL

Analyses were performed by Analytical and Physical Chemistry Section of Smith Kline and French Laboratories.

Synthesis of 2-dimethylaminophenothiazine (IV). (a) *o-Bromothiophenol.* This preparation was successfully conducted from 1.5 moles *o*-bromoaniline according to the procedure described previously.[11] *o*-Bromothiophenol was obtained in 80% yield.

(b) *2'-Bromo-2-nitro-4-(n,N-dimethylamino)diphenylsulfide.* An aqueous ethanolic solution of sodium *o*-bromothiophenolate [57 g. (0.3 mole) *o*-bromothiophenol[11] in 300 ml. ethanol and 12 g. (0.3 mole) sodium hydroxide in 20 ml. water] was added dropwise to a stirred refluxing solution of 4-bromo-3-nitrodimethylaniline[4] (prepared from 4-bromo-*N,N*-dimethylaniline (III)[12] in 600 ml. of ethanol in a 2-l. three-neck flask. The solution was stirred and refluxed for 20 hr. It was then treated with Norit and filtered. The filtrate yielded two crops upon cooling. The first crop was orange crystals, m.p. 117.5–119°; the second yellow, m.p. 120–121°. A mixed melting point gave 118.5–120°. Recrystallization of the combined crops gave the sulfide (82.5 g., 78%) as yellow crystals, m.p. 120–121°. The analytical sample from methanol melted 120.5–121.5°. It is to be noted that the above sulfide was obtained at times as distinct yellow crystals, distinct orange crystals, and as an intimate mixture of both forms.

Anal. Calcd. for $C_{14}H_{13}BrN_2O_2S$: C, 47.60; H, 3.71. Found: C, 47.64; H, 4.00.

2'-Bromo-2-amino-4-(N,N-dimethylamino)diphenylsulfide. The nitro compound above (91.9 g., 0.26 mole) was added in portions to a stirred solution of stannous chloride dihydrate (235 g., 1.04 mole) in concd. hydrochloric acid (690 ml.) in a 2-l., three-neck flask at 50–60°. The white suspension was refluxed for 4 hr. after which time it was diluted with water and made alkaline with sodium hydroxide solution. A solid which formed on cooling was collected, dried *in vacuo* and extracted with hot benzene. Dilution with petroleum ether (b.p. 35–60°) gave the amino sulfide as white crystals, m.p. 126–127.5° in 65% yield. The analytical sample melted 126.5–127.5°.

Anal. Calcd. for $C_{14}H_{15}BrN_2S$: C, 52.01; H, 4.68. Found: C, 52.21; H, 4.94.

2-(N,N-Dimethylamino)phenothiazine (IV). 2'-Bromo-2-amino-4-(*N,N*-dimethylamino)diphenyl sulfide (49.5 g., 0.153 mole), anhydrous granular potassium carbonate (28.8 g., 0.208 mole), cuprous iodide (8 g.) and copper bronze powder (2.88 g.) were stirred and heated in refluxing dimethylformamide (500 ml.) for 21 hr. under a slow stream of prepurified nitrogen. There was no further indication of carbon dioxide evolution after this time. The mixture was filtered and the filtrate diluted with water. A light-purple precipitate was collected and dried *in vacuo* at 100°. Recrystallization from benzene with a Nuchar treatment gave 2-(*N,N*-dimethylamino)phenothiazine (IV) (24.1 g., 65%) as microscopic white needles, m.p. 157.5–158.5°.

Anal. Calcd. for $C_{14}H_{14}N_2S$: C, 69.38; H, 5.82; N, 11.56. Found: C, 69.27; H, 5.86; N, 11.63.

Two previous attempts to produce cyclization in the absence of a solvent were unsuccessful. After 1.5 hr. at 180–190° (the temperature was allowed to rise slowly from 120°), only some starting material was recovered from the black reaction mass. When the reaction tube was placed in a bath at 150° and the temperature raised to 155° vigorous effervescence occurred after 20 min. A low boiling liquid having a fishy odor escaped from the reaction tube. The products from this attempt were not identified.

Attempted synthesis of 2-dimethylaminophenothiazine via the Bernthsen thionation reaction N'Acetyl-N,N-dimethyl-m-phenylenediamine. 3-Nitrodimethylaniline[13] (49.8 g., 0.3 mole) was added in portions to a stirred solution of stannous chloride dihydrate (251 g., 1.2 moles) in concd. hydrochloric acid (300 ml.) at 50–60° in a 2-l., three-neck flask. The solution was refluxed for 4 hr. and diluted with water. It was then made alkaline with sodium hydroxide. The oil that

(5) T. G. H. Jones and R. Robinson, *J. Chem. Soc.*, 903 (1917).

(6) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).

(7) Since completion of this work several patents have appeared describing the synthesis of 2-cyanophenothiazine derivatives by a different route; Aust. Pat. **34,737/58**; July 24, 1958; Belgian Pat. **552,557**; May 15, 1957; South African Pat. Appl., **3595/56** June 19, 1957.

(8) J. Schmitt, A. Hallot, P. Comoy, M. Suquet, R. Fallard, and J. Boitard, *Bull. soc. chim. France*, 1474 (1957).

(9) J. Schmitt, J. Boitard, P. Comoy, A. Hallot, and M. Suquet, *Bull. soc. chim. France*, 938 (1957).

(10) We are indebted to W. S. Gump and E. Nikowitz of the Givaudan Corp. for preparing supplies of 2-acetylphenothiazine for us and for the synthesis of compound XIV (Table I).

(11) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **23**, 1906 (1958).

(12) Weber, A., *Ber.*, **8**, 714 (1875).

(13) H. M. Fitch, *Org. Syntheses*, **Coll. Vol. III**, 658 (1955).

formed was extracted from the cooled mixture with ether. The ether extracts were dried and the solvent distilled at atmospheric pressure. The residue was dissolved in pyridine. To this solution at 5° was added dropwise, with stirring, 27 g. acetic anhydride. After remaining overnight at room temperature the solution was thrown on to water. The precipitated solid was collected, washed and dried. Recrystallization from petroleum ether gave the acetylated product as white crystals (37.8 g., 70%) m.p. 86–87° (lit.[14] m.p. 87°).

3-Dimethylaminodiphenylamine. Bromobenzene (17.2 g., 0.11 mole), *N'*-acetyl-*N,N*-dimethyl-m-phenylene diamine (17.8 g., 0.10 mole), anhydrous granular potassium carbonate (8.5 g.) and copper-bronze powder (0.35 g.) were stirred at a bath temperature of 180° for 16 hr. and at 200° for 8 hr. The mixture was then extracted with acetone and filtered. The acetone was evaporated *in vacuo* and the residue refluxed with 250 ml. of 7*N* hydrochloric acid for 2 hr. The solution was made alkaline and then cooled. The oil that formed solidified. Recrystallization from petroleum ether (b.p. 35–60°) gave white crystals of the diphenylamine (8.4 g., 40%), m.p. 64–65° (lit.[15] m.p. 65–66°).

Attempted thionation of 3-dimethylaminodiphenylamine. An intimate mixture of 3-dimethylaminodiphenylamine (2.12 g., 0.01 mole), sulfur (0.61 g., 0.019 mole) and iodine (0.03 g.) was placed in an atmosphere of prepurified nitrogen in a scrupulously predried test tube. The reactor was fitted with a T-tube through which a stream of nitrogen was passed during the course of the reaction. The tube was placed in a bath at 140°. Hydrogen sulfide evolution commenced. After 0.5 hr., *ca.* 30% of the theoretical amount of hydrogen sulfide had been produced. Effervescence, however, had ceased. An additional 0.1 g. sulfur and a few iodine crystals were introduced into the reactor. The bath temperature was maintained at 170–185° until the theoretical amount of hydrogen sulfide was liberated. The reaction mass upon vacuum distillation gave a dark red oil which would not solidify. Attempted recrystallizations with alternate and combined alumina and Norit treatments from benzene-petroleum ether, high-boiling ligroin, carbon tetrachloride, chloroform, ethyl acetate, water, dilute hydrochloric acid, acetone-water and alcohol, were unsuccessful in producing any crystalline material.

10-(3-Dimethylaminopropyl)-2-dimethylaminophenothiazine dihydrochloride monohydrate (Ib). To a solution of 19.5 g. of 2-dimethylaminophenothiazine in 700 ml. of dry xylene was added 4.0 g. of sodamide. The mixture was stirred and refluxed under nitrogen atmosphere for 80 min. A solution of 12.4 g. of 3-chloro-1-dimethylaminopropane in 50 ml. of dry xylene was added. The mixture was refluxed and stirred under a nitrogen atmosphere for 6 hr. After cooling, 200 ml. of water was added. The xylene layer was extracted with four 50-ml. portions of 15% acetic acid. The acid extracts were made alkaline and extracted with benzene. The benzene extracts were combined and the solvent evaporated. The residue was distilled at 215–220°/0.3–0.5 mm., to give 21.1 g. (80%) of free base. The amine was dissolved in dry ether and treated with a solution of isopropyl alcohol containing 2 equivalent amounts of hydrogen chloride. The precipitated dihydrochloride salt was recrystallized from benzene-methanol and melted at 214–215°.

Anal. Calcd. for $C_{19}H_{25}N_3S.2HCl.H_2O$:C, 54.54; H, 6.91. Found: C, 54.41; H, 6.99.

Synthesis of 2,3-methylenedioxyphenothiazine. 6-Bromopiperonal. A stirred solution of piperonal (Eastman) (300 g., 2 moles) in glacial acetic acid (600 ml.) was gradually treated dropwise with a solution of bromine (120 ml., 4.6 moles) in glacial acetic acid (300 ml.). During the addition the reaction was cooled. After standing 48 hr. at room temperature, crystals of 6-bromopiperonal were filtered and water added to the filtrate. The precipitate that formed consisted of a mixture of 6-bromopiperonal and 4,5-dibromocatechol methylene ether. This mixture was stirred rapidly with a warm aqueous solution of sodium bisulfite. The latter dissolved the 6-bromopiperonal which was recovered from the filtrate after the addition of sodium carbonate. Both fractions of 6-bromopiperonal were recrystallized from hot ethanol to give 230 g., 50%, m.p. 127–128.5° (lit.[16] m.p. 129°).

4-Nitro-5-bromocatechol methylene ether (V). To stirred concentrated nitric acid (1400 ml., *d.* 1.42) in a 5-l., three-neck flask immersed in a water bath at 25°, was added gradually in portions over 1.5 hr., 6-bromopiperonal (210 g., 0.92 mole). The addition was conducted at such a rate as to maintain an internal temperature no greater than 25°. After 2 hr. the mixture was poured on to 4-l. ice water. The precipitated light yellow solid was collected and washed well with water. Recrystallization from ethanol gave V (136 g., 60%) as yellow needles, m.p. 88–89° (lit.[17] m.p. 89°).

4,5-Methylenedioxy-2-nitro-2'-bromodiphenylsulfide. To a stirred solution of the 4-nitro-5-bromocatecholmethylene ether (147.6 g., 0.6 mole) in hot ethanol (1250 ml.) in a 3-l., three-neck flask was added dropwise a solution of sodium *o*-bromothiophenolate (113.4 g., 0.6 mole, *o*-bromothiophenol in 500 ml. ethanol; 23.9 g., 0.6 mole, sodium hydroxide in 25 ml. water). During the addition the bright yellow product commenced to precipitate from the reddish-orange reaction solution. The mixture was allowed to reflux for 3 hr. It was then cooled to 0° and the precipitated product filtered. Several washings with cold ethanol afforded the sulfide (186 g., 88%) as bright yellow crystals, m.p. 149–150°.

Anal. Calcd. for $C_{13}H_8BrNO_4S$: C, 44.08; H, 2.28. Found: C, 44.29, 44.25, 44.29; H, 2.65, 2.32, 2.66.

2-Amino-4,5-methylenedioxy-2'-bromodiphenylsulfide. To a stirred solution of stannous chloride dihydrate (426.6 g., 1.89 moles) in concd. HCl (675 ml.) and ethanol (675 ml.) at 70–80° was added, in portions, the nitro compound above. The mixture was then allowed to reflux for 4 hr. The brown solution was subsequently poured on to 4-l. ice water. A gum formed which slowly solidified. The tan solid was collected and washed well with water. It was dried *in vacuo* at 100°. Recrystallization from benzene-petroleum ether with a Norit treatment yielded the amine (126 g., 74%) as white crystals, m.p. 142–143.5°. The analytical sample melted at 143–144°.

Anal. Calcd. for $C_{13}H_{10}BrNO_2S$: C, 48.16, H, 3.11. Found: C, 48.36; H, 2.85.

2,3-Methylenedioxyphenothiazine (VI). A mixture of the above amine (3.6 g., 0.0111 mole, m.p. 143–144°), anhydrous granular potassium carbonate (1.56 g., 0.0113 mole) and copper bronze powder (0.2 g.), was refluxed in 45 ml. dimethylformamide with stirring for 6 hr. The evolution of carbon dioxide had ceased at this time. The purple mixture was filtered and the filtrate diluted with warm water. The purple precipitate was collected and dried *in vacuo*. It was then extracted with benzene and the extracts treated with alumina and charcoal. Cooling the benzene filtrate gave VI as light purple platelets, m.p. 202–203°. The analytical sample was obtained by sublimation as white platelets from benzene, m.p. 202–203.5°. The estimated yield in this reaction on this scale is 50%.

Anal. Calcd. for $C_{13}H_9NO_2S$: C, 64.18; H, 3.73; N, 5.76. Found: C, 64.21; H, 3.96; N, 5.72.

3-Dimethylaminopropyl 2,3-methylenedioxyphenothiazine-10-carboxylate hydrochloride VIII. A solution of 7.3 g. of 2,3-methylenedioxyphenothiazine in 50 ml. of chlorobenzene was heated at 115–120° for 90 min. while a brisk stream of phosgene was bubbled through the mixture. On cooling to 100° a vigorous stream of nitrogen was passed through the solution for 30 min. Following the addition of 4.2 g. of 3-dimethylaminopropanol in 10 ml. of chlorobenzene, the solu-

(14) W. Staedel and H. Bauer, *Ber.* 19, 1939 (1886).

(15) A. Albert, *J. Chem. Soc.* 1225 (1948).

(16) A. M. B. Orr, R. Robinson, and M. M. Williams, *J. Chem. Soc.*, 946 (1917).

(17) T. G. H. Jones and R. Robinson, *J. Chem. Soc.*, 903 (1917).

tion was refluxed for 15 min. On cooling, the mixture was extracted with dilute hydrochloric acid. The acid extracts were made alkaline and taken up in ether. The ethereal solution was dried over magnesium sulfate and treated with an isopropanolic hydrogen chloride solution. The precipitated crude salt was removed by filtration and a small sample recrystallized from benzene-methanol which melted at 229–230°. The yield of crude product was 5.7 g. (48%). The salt appears to be light sensitive, darkening slowly to a deep blue.

Anal. Calcd. for $C_{19}H_{20}N_2O_4S.HCl$: C, 55.81; H, 5.18. Found: C, 56.14, 56.17; H, 5.96, 5.48.

10-(3-Dimethylaminopropyl)-2,3-methylenedioxyphenothiazine maleate II. A well stirred suspension of 1.17 g. of sodamide, 6.5 of 2,3-methylenedioxyphenothiazine VI and 110 ml. of dry xylene was refluxed for 70 min. under a nitrogen atmosphere and then treated with 4.3 g. of 3-dimethylaminopropyl chloride. The mixture was stirred and refluxed for 8 hr. On cooling, the mixture was treated cautiously with 60 ml. of water. The xylene layer was extracted with three 20-ml. portions of 10% hydrochloric acid. The acid extracts were made alkaline with 10% sodium hydroxide solution and extracted with benzene. The benzene solution was dried over magnesium sulfate and evaporated to dryness. The residue was distilled at 230–233°/0.5 mm. to give 4.1 g. (48%) of 10-(3-dimethylaminopropyl)-2,3-methylenedioxyphenothiazine. The base was converted to a maleate salt in ethylacetate and recrystallized from ethyl acetate-methanol solutions. The maleate salt melted at 151–152.5°.

Anal. Calcd. for $C_{18}H_{20}N_2.C_4H_4O_4$: C, 59.44; H, 5.44. Found: C, 59.24; H, 5.59.

2-Carboxamidophenothiazine IXc. A mixture of 67 g. phenothiazine-2-carboxylic acid[6] in 900 cc. of dry benzene was cooled to +5 to 7°. To the stirred mixture was added 62.8 g. of phosphorus pentachloride portionwise over a period of 30 min. The cooling bath was removed and the stirring was continued for 2 hr. The acid chloride mixture was poured onto excess concentrated ammonia and ice with stirring and then was allowed to stand for several hours. The greenish yellow crystals were filtered, washed with water and dried at +40 to 60°. The 46.0 g. of crude amide (69%) was recrystallized from ethanol-isopropyl alcohol and decolorizing carbon to give 24.0 g. of yellow needles, melting at 232.5–233.5°. Another 7.0 g. of amide was obtained from the mother liquor by concentration and cooling.

Preparation of 2-cyanophenothiazine X. Various dehydrating agents were investigated for the conversion of phenothiazine-2-carboxamide to the corresponding nitrile. Although phosphorus pentoxide, phosphorus oxychloride and a mixture of the two were tried, none of these procedures were very satisfactory. In one experiment 1.6 g. of the carboxamide was refluxed for 4 hr. in 10 ml. of phosphorus oxychloride. The mixture was poured onto ice and then the solution was made slightly basic. A product was filtered off (1.6 g.), which softened at 192–194° and melted at 198–205°. This material was characterized by its peak at 4.5 μ in the infrared spectrum, and by its alkylation to Id, which was identical with a sample of Id prepared by an alternate route.[7]

2 Cyano-10[3-dimethylamino-2-methylpropyl]phenothiazine maleate (Id). Alkylation of 1.6 g. of 2-cyanophenothiazine was accomplished as usual using 0.4 g. of sodamide and 1.2 g. of 3-dimethylamino-2-methylpropylchloride in 25 ml. toluene. Distillation of the free base gave 1.4 g. (64%) of a yellow oil; b.p. 205–220° (0.2–0.5 mm.).

This oil was converted to the maleate salt, which, after two recrystallizations from methanol-ethanol, gave 1.4 g. of pale yellow plates melting at 196–197°.

Anal. Calcd. for $C_{23}H_{25}N_3O_4S.{}^1/_4\ H_2O$: C, 62.21; H, 5.79. Found: C, 62.41; H, 5.65.

Infrared spectral data shows the presence of the cyano peak at 4.5 μ.

2-N,N-Dimethylcarboxamido-10-acetylphenothiazine (IXf) *Method A.* 2-Carboxy-10-acetylphenothiazine (10.0 g.) was treated with an equivalent amount of sodium carbonate solution. The water was removed by azeotroping with benzene and the benzene removed by freeze drying. To a stirred suspension of the salt in 100 cc. of dry benzene was added 7.6 g. of oxalyl chloride in 40 cc. of benzene. After warming for several minutes on a water bath the mixture was stirred for 7 hr. at room temperature and then allowed to stand for 2 days. The mixture was filtered and the filtrate was evaporated to an orange residue. The residue was dissolved in benzene and a solution of 19 g. of dimethylamine in benzene was added. After heating for 10 min. on the steam bath the mixture was cooled and filtered. Evaporation of the filtrate gave 12.2 g. of a yellow solid which melted over a wide range. A small sample of this solid (1.5 g.) was vacuum distilled but this did not improve the melting point. The remainder of the yellow solid was dissolved in hot benzene and extracted twice with very dilute sodium bicarbonate. The benzene was dried over magnesium sulfate, and after evaporation of the benzene there remained 8.3 g. of a yellow solid. This was subjected to deacetylation without further purification.

Method B. An intimate mixture of 2-carboxy-10-acetylphenothiazine (7.2 g.) and 10 g. of phosphorus pentachloride was heated for 5 min. After the addition of 25 cc. of benzene the mixture was filtered, and the filtrate was heated for 5 min. The cooled solution was treated with 50 cc. of 25% aqueous dimethylamine, and the mixture was stirred for 15 min. The layers were separated and the water layer was extracted twice with benzene. The combined benzene layers were washed three times with water, dried over magnesium sulfate, and the benzene evaporated. The residue was 7.9 g. (98%) of a thick brown oil. This material was subjected to deacetylation without further purification.

2-N,N-Dimethylcarboxamidophenothiazine (IXg). A mixture of 65.5 g. 31% hydrochloric acid and 20 g. glacial acetic acid was stirred at reflux with 8.3 g. of crude 2-(*N,N*-dimethylcarboxamido)-10-acetylphenothiazine. The mixture was poured into 400 cc. of water and the yellow solid which formed (6.9 g., 97%) was filtered. Upon recrystallization from acetone using decolorizing charcoal, 5.7 g. of yellow crystals melting at 161–163.5° were obtained.

2-N,N-Dimethylcarboxamido-10-(3-dimethylaminopropyl)-phenothiazine citrate (Ic). 2-*N,N*-Dimethylcarboxamido phenothiazine (7.6 g.) in 100 cc. xylene was refluxed and stirred with 1.4 g. sodamide for 1 hr. After the addition of 4.9 g. of 3-dimethylaminopropyl chloride in 25 cc. xylene, refluxing was continued for 4 hr. The cooled mixture was treated with 50 cc. of water and the layers were separated. The organic layer was taken through acid and base to give 6.7 g. of a dark brown oil. Upon distillation there was obtained 4.8 g. (35%) of an oil; b.p. 225–240° (0.06–0.09 mm.). There was also recovered 2.8 g. of neutral material.

The 4.8 g. of oil was converted to the citrate which was dried under a vacuum to give a foamy-looking solid melting at 94.5–96.5°.

Anal. Calcd. for $C_{20}H_{25}N_3OS.C_6H_8O_7.2H_2O$: C, 53.50; H, 6.39. Found: C, 53.73, 53.60; H, 6.23, 6.15.

This material was amorphous, rather than truly crystalline, and was hygroscopic.

10-[3-(4-Methyl-1-piperazinyl)propyl]-2-phenothiazinyl methyl ketoxime dimaleate (XV). To 5 g. of 10-[3-(4-methyl-1-piperazinyl)propyl]-2-phenothiazinyl methyl ketone in 200 ml. of dry pyridine was added 2 g. of hydroxylamine hydrochloride. The solution was refluxed 90 min. and the pyridine removed under vacuum. The residue was washed with 5% sodium carbonate solution and dissolved in ethyl acetate. This solution was added to another solution of ethyl acetate containing 2 equimolar amounts of maleic acid. The precipitated dimaleate salt was recrystallized from methanol; m.p. 171°–172° dec.; 5.2 g. (65%).

10-[3-(4-Methyl-1-piperazinyl)propyl]-2-phenothiazinyl methyl ketone dimaleate (XI). To a solution of 24.2 g. of 2-acetylphenothiazine in 450 ml. of dry toluene were added

6.2 g. of redistilled ethylene glycol and 0.2 g. of *p*-toluenesulfonic acid. The mixture was azeotroped for 3 hr. and washed with 40% sodium hydroxide solution. The toluene solution was azeotroped for 1 hr. over 2 g. of potassium hydroxide, filtered and added to a suspension of 4.5 g. of freshly prepared sodamide in 100 ml. of dry toluene. The mixture was refluxed and stirred under nitrogen for 20 min. To the mixture was added a solution of 4-methyl-4-(3-chloropropyl) piperazine (20 g.) in 50 ml. of dry toluene. The mixture was refluxed and stirred under nitrogen for 4 hr. On cooling, 150 ml. of water was added. The toluene layer was extracted with dilute hydrochloric acid. The acid extracts were made alkaline and extracted with benzene. The benzene was evaporated and the residual oil was distilled; b.p. 255°–260°/75 mm.; 23 g. (60%). The free base was dissolved in 100 ml. of ethyl acetate and added to a solution of ethyl acetate containing 2 equimolar amounts of maleic acid. The precipitated dimaleate salt was recrystallized from methanol; m.p. 179–180°.

2-(1-Hydroxyisopropyl)-10-dimethylaminopropylphenothiazine (XIV). To a solution of methyllithium prepared from 2 g. of lithium and 18.2 g. of methyl iodide in ether was added a solution of 41.7 g. of 2-acetyl-10-dimethylaminopropylphenothiazine[8] in 100 ml. of ether. The mixture was stirred and refluxed for 2.5 hr. and then poured into water. The organic layer was washed with water, dried and evaporated to give 43.5 g. of brown viscous oil. By trituration of 24 g. of this material with an ether-petroleum ether mixture 14.4 g. of yellow solid, m.p. 97.5–100.5°, was obtained. Further purification of the product by distillation, b.p. 203–210° (50 microns), followed by recrystallization from hexane gave pure carbinol (XIV), m.p. 107.5–109°.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, THE WELLCOME RESEARCH LABORATORIES]

5-Arylthiopyrimidines. I. 2,4-Diamino Derivatives

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Arylmercaptoacetonitriles are readily acylated with lower aliphatic esters. Their crude enol ethers, obtained by reaction with diazomethane, condense with guanidine to produce 2,4-diamino-5-arylmercaptopyrimidines. In contrast with the closely related 5-phenoxy- and 5-benzylpyrimidines, these compounds are practically devoid of activity *vs.* protozoan and bacterial infections. However, several members of the series are central nervous system depressants.

Derivatives of 2,4-diaminopyrimidine bearing weighty substituents in the 5-position are, in general, antimetabolites with considerable potency as antifolic acids.[2,3] Several subseries, the 5-phenyl-, 5-benzyl-, and 5-phenoxypyrimidines, were found to possess antimicrobial activity, which is most strikingly exemplified by the antimalarial activity of pyrimethamine, 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine.[4–6] It was of considerable interest, therefore, to prepare the isologous 5-phenylmercaptopyrimidines for comparison.

Very few 5-pyrimidyl aryl or alkyl sulfides have been reported in the literature. P. F. Hu[9] reported the synthesis of 2-amino-4-hydroxy-5-(4′-nitrophenylmercapto)-6-methylpyrimidine and the corresponding 4,6-dimethyl derivative. These were obtained by condensations of guanidine with ethyl α-(4′-nitrophenylmercapto)acetoacetate and 3-(4′-nitrophenylmercapto)-2,4-pentanedione, respectively. Johnson and Guest[10] prepared some 5-benzylmercaptopyrimidines by condensing *S*-ethylisothiourea with ethyl α-formylbenzylmercaptoacetate. Subsequent conversions yielded 5-benzylmercaptouracil and -cytosine. No 2,4-diamino derivatives were described, however.

It was found here that 2,4-diamino-5-arylmercaptopyrimidines could be obtained by the condensation of guanidines with α-arylmercapto-β-methoxyacrylonitriles. This procedure is similar to that reported by Russell and Hitchings[7] for the corresponding 5-phenyl derivatives. The intermediate arylmercaptoacetonitriles were most conveniently prepared by the reaction of arylmercaptans with chloroacetonitrile[11]; however, some of the nitriles employed here were obtained by dehydration of the corresponding amides. The nitriles were readily acylated by treatment of the esters in ethanol with two moles of sodium methylate. The resultant α-acylphenylmercaptoacetonitriles (I) failed to condense with guanidine to form pyrimidines, as was found earlier with the phenyl derivatives.[7] However, their crude enol ether derivatives (presumably of structure II),

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