shown by the solid–liquid phase diagrams of the binary system.

2. Diphenyl selenoxide and selenone give a continuous series of mixed crystals of the type with minimum (type III).

3. Dibenzyl selenide forms with the corresponding selenoxide a simple eutectic system. Dibenzyl sulfide and selenide form a continuous series of mixed crystals with minimum.

These results prove that selenoxides have the same steric configuration as the corresponding sulfoxides, having therefore a tetrahedral configuration, the same as attributed to the sulfoxides.

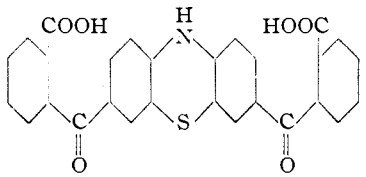
SÃO PAULO, BRAZIL RECEIVED AUGUST 14, 1946

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Some Phenothiazine Derivatives. The Course of the Friedel–Crafts Reaction

BY RICHARD BALTZLY, MORTON HARFENIST AND FREDERICK J. WEBB

In the course of synthetic experiments with phenothiazines, in which the primary object was to prepare water-soluble, N-unsubstituted derivatives, recourse was had to the Friedel–Crafts reaction. The only reference on this subject is a paper by Scholl and Seer[1] who employed phthalic anhydride and reported rather poor yields of a dipthaloyl derivative for which they proposed the formula (I). The substance was cyclized by sulfuric acid to a bis-quinone which Scholl and Seer regarded as linear.



(I)

It seemed probable to us that under Friedel–Crafts conditions orientation would be due mainly to the sulfur rather than the nitrogen, since the latter should either be acylated rapidly or maintained in the cationic state. This supposition has proved to be correct, both as to the priority of N-acylation and the dominant orientation by sulfur. In most cases we found it best to operate with N-acetylphenothiazine (thereby avoiding any doubt as to N-acylation) but it was found that phenothiazine itself underwent substitution by acetyl chloride and succinic anhydride in the same position as the N-acetyl compound although with considerably worse yield. These differences may well have been due to fortuitous influences of solubility since in all these reactions the reaction-complex, which usually forms a second layer, came out as a thick gum and largely frustrated attempts at stirring.

When N-acetylphenothiazine reacted with acetyl chloride and aluminum chloride an N,x-diacetylphenothiazine was obtained in fair yield. With succinic anhydride the primary product was undoubtedly an N-acetyl-x-succinyl derivative but in the isolation the acetyl group was intentionally hydrolyzed and the x-succinylphenothiazine was obtained. The position of the acyl groups was in doubt, but it is reasonable to assume that in both compounds the same position had been substituted. In the acetylation product it has been possible to locate the acetyl group in position 2, and the transformations shown in Chart I are formulated on that basis.

The N,2-diacetylphenothiazine (II) was degraded by the haloform reaction to the carboxylic acid (IV). Treatment of IV either with boiling hydriodic acid[2] or with Raney nickel[3] removed the sulfur with the formation of a diphenylamine carboxylic acid melting at 142–143°. Gilman, Van Ess and Shirley[2] had prepared diphenylamine-3-carboxylic acid for which they reported the m. p. as 140°. A sample of our acid was sent to Professor Gilman who found the preparations to be identical (mm. p.). It was thus apparent that the acetyl group had entered at either position 2 or position 4 and in either case had been oriented by the sulfur.

Gilman, Van Ess and Shirley[2] had obtained, by metalation of N-ethylphenothiazine with lithium, an N-ethylphenothiazine carboxylic acid in which the carboxyl group occupied one of the positions, 2 and 4. The melting point of this acid was given as 178–179°, that of its methyl ester as 111–112°. Our acid, IV, was converted to an N-ethyl acid (V), m. p. 184–185°, giving a methyl ester that melted at 84.5–85.5°. Direct comparison with a sample generously furnished by Professor Gilman showed that the acids (and their esters) were different. Thus the two series of phenothiazine derivatives capable of being degraded to diphenylamine-3-carboxylic acid are represented by Gilman's acid and by ours, and the unambiguous orientation of one must also determine the structure of the other.

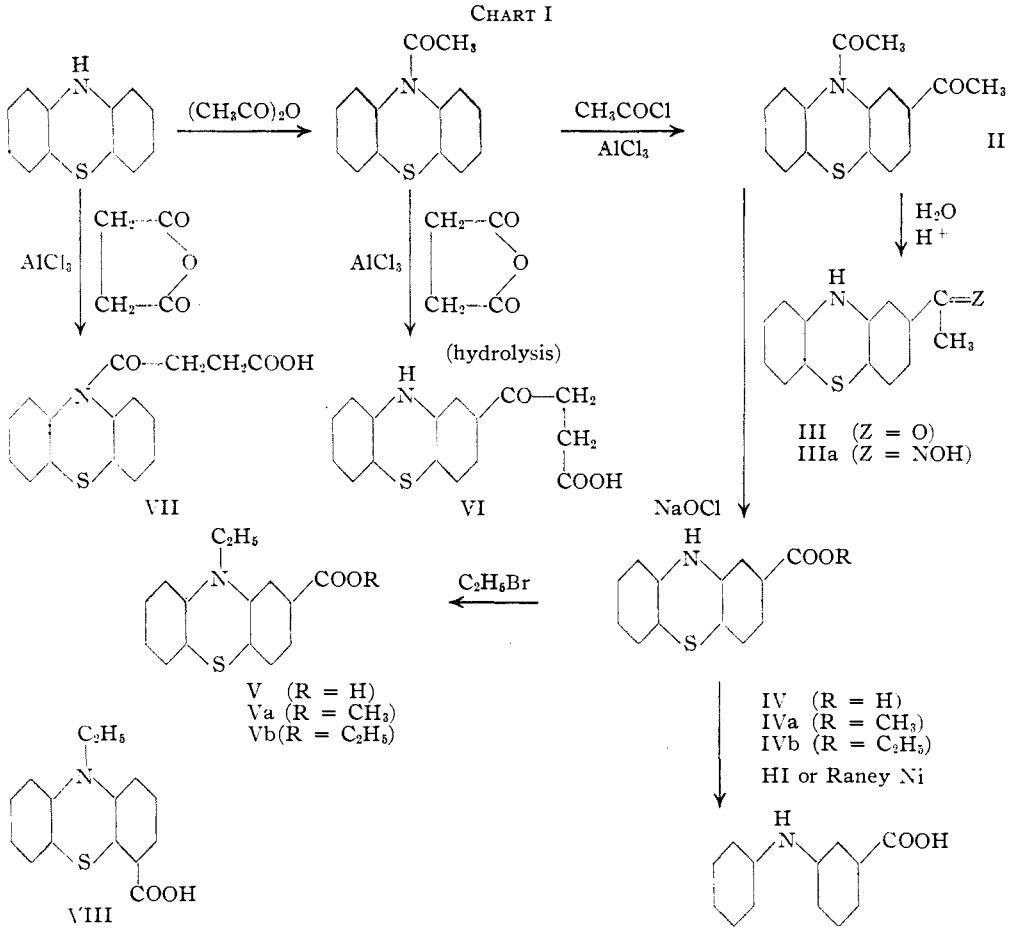
On the basis of his extensive experience with metalation reactions, Gilman considered that N-ethylphenothiazine would be most likely to metalate *ortho* to the sulfur and provisionally assigned to his acid the structure VIII. In agreement with this, we felt that the Friedel–Crafts reaction, which has a marked tendency to *para* sub-

(1) Scholl and Seer, *Ber.*, **44**, 1243 (1911).

(2) Gilman, Van Ess and Shirley, THIS JOURNAL, **66**, 1214 (1944).

(3) Roblin, Lampen, English, Cole and Vaughan, *ibid.*, **67**, 290 (1945).

CHART I



stitution, would probably have afforded 2-substituted phenothiazines. Two attempts at an unambiguous synthesis were made along the lines developed by Smiles[4] and outlined in Chart II. The first of these broke down when compound XI failed to undergo the Smiles rearrangement and cyclization. The second line of attack went as far as 2-bromo-7-aminophenothiazine (XV) from which it was hoped to obtain compound IV by removal of the amino group and exchange of the bromine for lithium followed by carbonation. Unfortunately the diazotization and reduction of XV yielded only traces of crystalline material and this project also was abandoned.

Since the prospects for a chemical identification appeared unpromising, and the dimensions of the alternative structures should differ considerably, it decided to submit the compounds IV and VIII to a preliminary X-ray examination. (Both substances were studied in the hope that at least one would give manageable results.) The X-ray studies were made by Mr. Milton Schneider[5] in the laboratories of Dr. I. Fankuchen of the Polytechnic Institute of Brooklyn. Summaries of Mr. Schneider's results are presented in the experimental section.

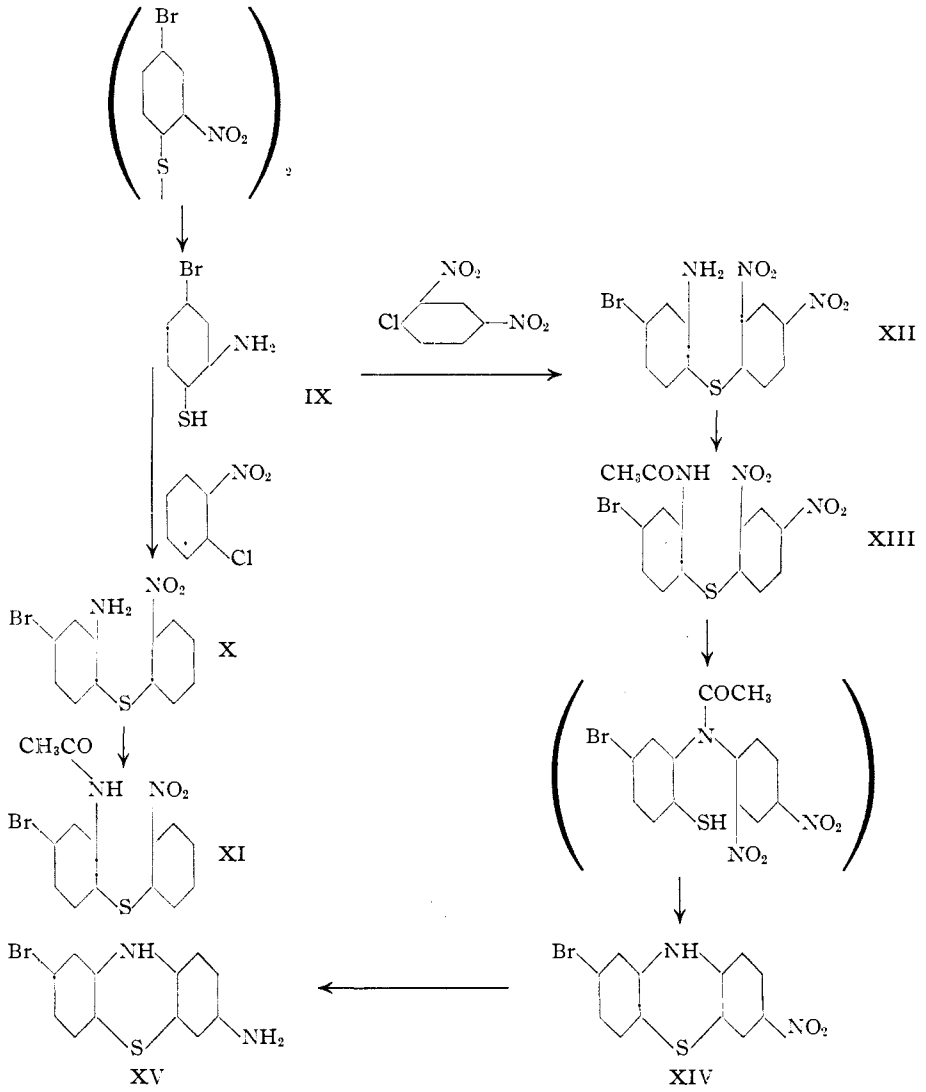
The unit cell dimensions and symmetry found for VIII were inadequate to decide between the alternative molecular structures, especially in view of the uncertainty as to the relative location of the N-ethyl group. For crystals of IV, on the other hand, the cell size, shape and symmetry data, combined with optical observations, furnish some evidence that this substance is phenothiazine-2-carboxylic acid, rather than the 4-acid. Assuming generally accepted interatomic distances and planar or nearly planar molecules,[6] several spatial arrangements of the former are possible, without placing atoms of different molecules too close together, whereas molecules of the latter type can be fitted into the unit cell (in accordance with the size, shape and symmetry requirements) only by inclining them all at small angles (14–18°) to the plane containing the *a* and *c* axes. Such an arrangement would be in disagreement with the optical observations, which indicate that the molecule widths are more nearly parallel to the plane containing the *b* and *c* axes than to the *a c* plane. The initial probability that IV is phenothiazine-2-carboxylic acid is thus strongly reinforced.

(4) Wight and Smiles, *J. Chem. Soc.*, 342 (1935); Evans and Smiles, *ibid.*, 1263 (1935).

(5) Solid Phase Research, 84 Livingston St., Brooklyn 2, N. Y.

(6) Wood, McCale and Williams, *Phil. Mag.*, **31**, 71 (1940).

CHART II



Since it seems unlikely that a further publication will issue from this laboratory on the phenothiazine series, opportunity is taken here to summarize certain other results obtained in the course of this work; the reactions are indicated in chart III. The compound XVII, 3-nitro-4-(2-acetamidophenylmercapto)-benzoic acid was prepared with the intention of cyclizing it to phenothiazine-3-carboxylic acid. So far the cyclization has not succeeded. The cyclization of *p*-anilinophenoxyacetic acid (XVIII) to compound (XIX) was successful, but the methyl ester (XVIIIa) yielded no isolable product.

p-Methoxydiphenylamine, prepared most advantageously by decarboxylation of 5-methoxy-2-anilinobenzoic acid, was cyclized to 3-methoxyphenothiazine. Metalation of this, followed by carbonation, yielded a carboxylic acid (XX) in which the carboxyl group is probably at position 4 or perhaps position 1. An attempt to prepare 3-methoxy-4′-bromodiphenylamine by decarboxylation of 4-methoxy-2-(4-bromophenylamino)-benzoic acid gave only tar.

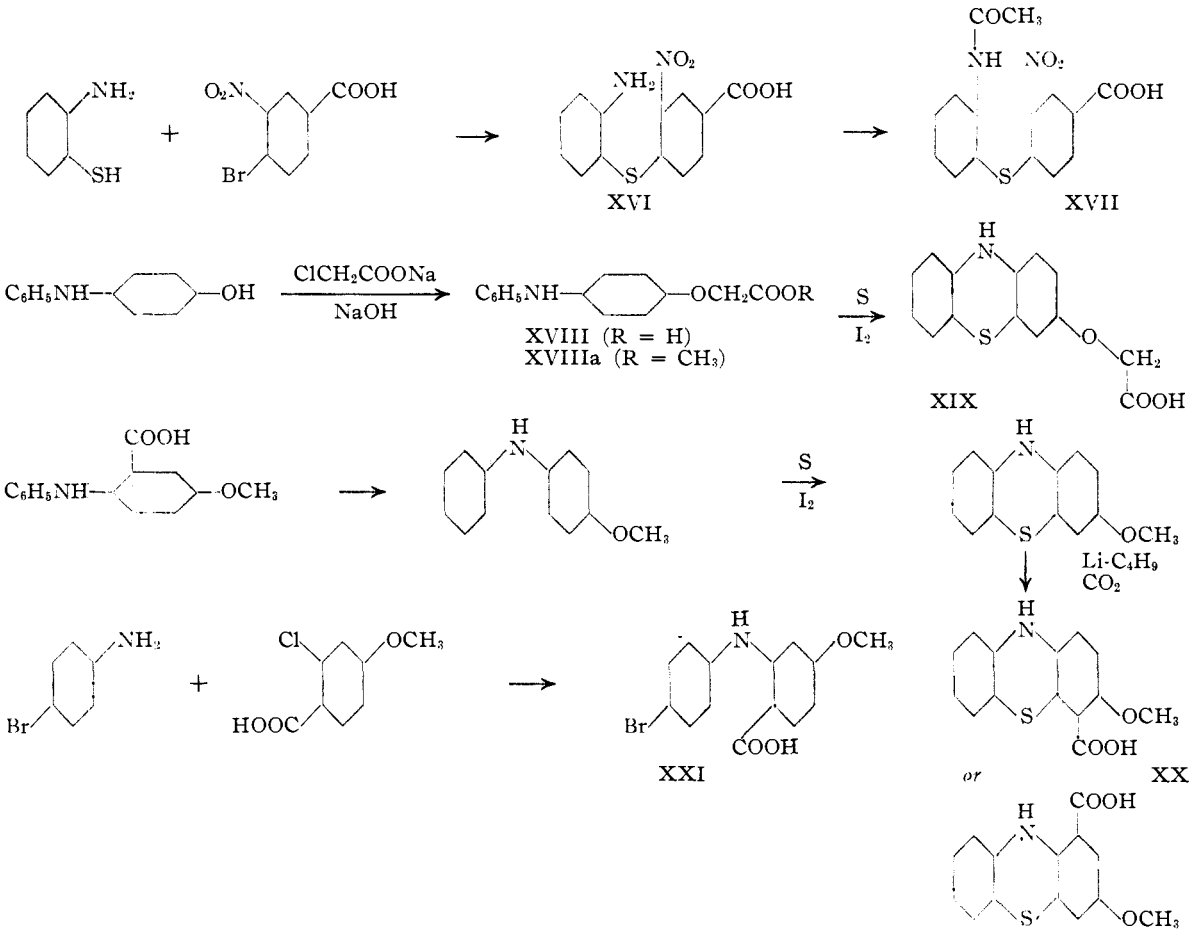
None of the phenothiazines here reported has shown activity against plasmodia or trypanosomes

Experimental

Analytical data and physical properties of the phenothiazine derivatives are presented in Table I. Similar data for the new intermediates are in Table II. Where the substances were prepared by familiar procedures, those are mentioned in the footnotes.

N,2-Diacetylphenothiazine (II).—The Friedel-Crafts reaction of acetyl chloride with N-acetylphenothiazine was studied under a variety of conditions. Substitution of *sym*-tetrachlorethane as solvent for the more usual carbon bisulfide was found to give very low yields. The best results were obtained by using a rather large volume of carbon bisulfide (*ca.* 2 liters for a 0.5-mole run) and adding a 100% excess of aluminum chloride to the other ingredients. Variations in yield were probably due to an irregular tendency of N-acetylphenothiazine together with the reaction-complex to precipitate as a gum enclosing much of the

CHART III



aluminum chloride. As a result, rather long reaction times (six to seven hours of refluxing) were considered necessary. At the end of the reaction, the supernatant carbon bisulfide could be decanted; it contained no significant amount of product. The gummy residues were decomposed in the usual way with ice and hydrochloric acid, and the mixtures were extracted with ether. At this point considerable amounts of N-acetylphenothiazine remained undissolved and were filtered off. The ethereal solutions were dried over sodium sulfate and evaporated leaving gummy residues which corresponded to 60–75% of the starting material. Crystallization of these crude products from alcohol–hexane mixtures gave, in 40–50% yield, N,2-diacetylphenothiazine melting in the range 90–100° and sufficiently pure for use in the haloform reaction. Repeated crystallizations from alcohol–hexane accomplished complete purification when this was desired.

A Friedel–Crafts reaction on phenothiazine itself using 2 mols of acetyl chloride and 1 mol of aluminum chloride (added last) gave a 41% yield of crude N,2-diacetylphenothiazine (m. p., 85–95°) and a 50% yield of N-acetylphenothiazine. When the acetyl chloride was added last, the yield of diacetyl compound was 22%, the balance being found as N-acetylphenothiazine.

Phenothiazine-2-carboxylic Acid (IV).[7]—A solution in 250 cc. of dioxane of 27.3 g. (0.1 mole) of diacetylphenothiazine (m. p. 95°) was cooled to 5° with stirring. During twenty minutes there was added an aqueous solution containing 0.3 mole of sodium hypochlorite. Stirring was continued thirty minutes in the cold and an additional hour without cooling. The dioxane was then removed *in vacuo* and the residue partitioned between water and ether. On acidification of the aqueous layer, 21.3 g. of yellowish green acidic material was obtained. This crude acid melted in the range 240–250° and was quite impure. After extraction with ether in a Soxhlet apparatus nearly half of the material remained as an ether-insoluble substance not melted at 300° and probably consisting of halogenated products. The ether-soluble fraction melted at 261–263° and was recrystallized several times from benzene or ethyl acetate for analysis.

A sample of this material was examined optically and by X-ray methods by Mr. Milton Schneider, who reported the following results: crystal system, monoclinic; density, 1.497; sign of optical birefringence, negative; number of molecules in the unit-cell, 8; space group, $A2/a$. The dimensions of the unit-cell are: a = 7.93 Å. (approximately along α); b = 6.04 Å. (along β); c = 47.27 Å. (along γ), β = 105°. The X-ray molecular weight is 247 (calcd., 243.3).

Reduction of IV to Diphenylamine-3-carboxylic Acid.[2]—Thirty cc. of hydriodic acid (d. 1.7) and 1.9 g. of phenothiazine-2-carboxylic acid were refluxed for twenty-one hours. The resulting pale-brown solution was cooled, filtered and diluted to 500 cc. with water. There separated 0.9 g. of a pale-yellow powder melting at 139–140°. Recrystallization from hexane raised the m. p. to 142–143°.

The same cleavage was accomplished in 65% yield by means of Raney nickel.[3] The melting point of the once-recrystallized product was 141–142°.

X-Ray Study of VIII and Comparison with V.—A sample of methyl-N-ethylphenothiazine-4-carboxylate obtained

(7) *Cf.* Bogert and Davidson, THIS JOURNAL, **54**, 336 (1932).

TABLE I

PHENOTHIAZINE DERIVATIVES

Chart no.	Substituents	Appearance	Crystg. solvent[a]	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
II	N, 2-$(CH_3CO)_2$	Colorless needles	A	105–106	$C_{16}H_{13}O_2NS$	67.84	4.62	67.68	4.75
III	2-CH_3CO[b]	Yellow-orange needles	Æ-H	192–193	$C_{14}H_{11}ONS$	69.66	4.60	69.75	4.74
IIIa	2-CH_3—C=NOH	Yellow plates	A-Aq	242–243 (dec.)	$C_{14}H_{12}ONS$	65.58	4.72	65.79	4.76
IV	2-COOH	Yellow plates	B or Æ	276–277 (dec.)	$C_{13}H_9O_2NS$	64.13	3.73[c]	64.01	4.00
IVa	2-COOMe[d]	Flat yellow prisms	H	167–168	$C_{14}H_{11}O_2NS$	65.36	4.31	65.65	4.00
IVb	2-COOEt[e]	Yellow needles	Æ-H	152–152.5	$C_{15}H_{13}O_2NS$	66.39	4.83	66.30	4.88
V	N-Et, 2-COOH[f]	Yellow prisms	B-H	184–185	$C_{15}H_{13}O_2NS$	66.39	4.83[g]	66.60	4.78
Va	N-Et, 2-$COOCH_3$[h]	Pale yellow needles	M-Aq	84.5–85.5	$C_{16}H_{15}O_2NS$	67.37	5.30	67.38	5.49
Vb	N-Et, 2-$COOC_2H_5$[i]	Yellow needles	H	62.5–63.5	$C_{17}H_{17}O_2NS$	68.20	5.72	68.08	5.50
VI	2-CO—CH_2CH_2COOH	Brownish-orange platelets	HAc	251–252	$C_{16}H_{13}O_3NS$	64.19	4.39	64.18	4.39
VII	10-$COCH_2CH_2COOH$	Colorless needles	A	181–182 (dec.)	$C_{16}H_{13}O_3NS$	64.19	4.39	64.12	4.32
XIV	2-Br-7-NO_2[j]	Purple needles	Ac-Aq	224–225 (dec.)	$C_{12}H_7O_2N_2SBr$	44.59	2.18	44.58	2.28
XV	2-Br-7-NH_2[k]	Pale yellow plates	B-H	237–238	$C_{12}H_9N_2SBr$	49.15	3.09	49.32	3.02
XIX	3-OCH_2COOH	Colorless plates	Æ-H	217–218 (dec.)	$C_{14}H_{11}O_3NS$	61.54	4.06	61.51	3.90
XX	3-OMe,4-(or 1)-COOH	Greenish-yellow needles	Æ-H	203–204 (dec.)	$C_{14}H_{11}O_3NS$	61.54	4.06	61.63	4.27

[a] A = ethanol, Æ = ethyl acetate, Aq = water, B = benzene, E = ether, H = hexane, M = methanol, HAc = acetic acid, Ac = acetone. [b] Prepared by acid hydrolysis of II. [c] Calcd.: N, 5.76. Found: N, 5.87. [d] From action of diazomethane on IV. [e] From silver salt of IV with ethyl iodide. [f] By hydrolysis of Vb. [g] Calcd.: neut. equiv., 271.3. Found: neut. equiv., 271.7. [h] From V with diazomethane. [i] From IVa by heating with ethyl bromide in ethanol thirteen hours at 120–135°. Separated by fractional crystallization from considerable amounts of IVb and IVa. [j] By a Smiles cyclization (ref. 4) of XIII. The crude product is best purified by a Soxhlet extraction using acetone. The yield was 64%. [k] By reduction of XIV with tin and hydrochloric acid in alcohol.

TABLE II

INTERMEDIATES IN CHARTS II AND III

Chart no.		Appearance	Crystg. solvent[a]	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
IX	2-SH-5-Br-$C_6H_3NH_2Cl$[b]	Colorless needles	A-E	218–219	$C_6H_7NSBrCl$	29.96	2.93	30.12	2.94
	Substituents		Diphenylamine Derivatives						
XVIII	4-OCH_2COOH[c]	Colorless needles	Æ-H	146–147	$C_{14}H_{13}O_3N$	69.12	5.39	69.28	5.40
XVIIIa	4-OCH_2COOMe[d]	Feathery needles	H	90–91	$C_{15}H_{15}O_3N$	70.05	5.88	70.30	5.90
XXI	5-OMe-2-COOH-4′-Br[e]	Yellow needles	A-Aq	201–202	$C_{14}H_{12}O_3NBr$	52.19	3.76	52.28	4.08
			Diphenyl Sulfide Derivatives						
XII	2-NH_2-4-Br-2′,4′-$(NO_2)_2$[f]	Yellow needles	A-Aq	182–183	$C_{12}H_8O_4N_3SBr$	38.93	2.18	39.33	2.13
XIII	2-$NHCOCH_3$-4-Br-2′,4′-$(NO_2)_2$[g]	Yellow needles	A-Aq	208–209	$C_{14}H_{10}O_5N_3SBr$	40.78	2.45	40.55	2.29
X	2-NH_2-4-Br-2′-NO_2[f]	Yellow plates	A-Aq	109–110	$C_{12}H_9O_2N_2SBr$	44.31	2.79	44.60	3.13
XI	2-$NHCOCH_3$-4-Br-2′-NO_2[g]	Yellow needles	A-Aq	185–186	$C_{14}H_{11}O_2N_2SBr$	45.78	3.02	45.86	3.02
XVI	2-NO_2 4-COOH-2′-NH_2[f]	Yellow powder	A-Aq	199–200	$C_{13}H_{10}O_4N_2S$	53.77	3.47	53.35	3.50
XVII	2-NO_2-4-COOH-2′-$NHCOCH_3$[g]	Yellow needles	Æ-H	241–242	$C_{15}H_{12}O_5N_2S$	54.24	3.64	54.38	3.80

[a] Solvent symbols as in Table I. [b] Prepared in 70% yield by the method of Lankelma and Knauf, (THIS JOURNAL, **53**, 309 (1931)) from 2-nitro-5-bromophenyl disulfide (Blanksma, *Rec. trav. chim.*, **20**, 132 (1901)). [c] Prepared from chloroacetic acid and *p*-hydroxydiphenylamine in alkaline solution (*cf.* Shriner and Fuson, "The Identification of Organic Compounds," John Wiley and Sons, N. Y., 1935, p. 148.) [d] From XVIII with diazomethane. [e] By refluxing *p*-bromoaniline with 2-bromo-5-methoxybenzoic acid (Pschorr, *Ann.*, **391**, 25 (1912)) in *n*-amyl alcohol solution in the presence of anhydrous potassium carbonate and copper powder. *Cf.* ref. 10. [f] By the method of Bost, Turner and Norton, THIS JOURNAL, **54**, 1985 (1932). In the preparation of XII there was no heating. [g] From the corresponding amino compound with acetic anhydride in acetone.

from Professor Gilman, was recrystallized from hexane, m. p. 112–113°. A portion was hydrolyzed with alcoholic potassium hydroxide solution to give the acid (VIII) which melted at 182–183° after recrystallization from ben-

zene. A mixture of this with 10-ethylphenothiazine-2-carboxylic acid (V) (m. p. 184–185°) melted at 148–150°.

A specimen of VIII was submitted to Mr. Milton Schneider for X-ray study. His findings were: crystal system, monoclinic; density, 1.3707; number of molecules in the unit-cell, 4; space group, $P_{2_1/c}$. The dimensions of the unit-cell are: a = 8.67 Å.; b = 8.02 Å.; c = 21.65 Å.; β = 120°. The X-ray molecular weight = 271 (calcd. 271.3).

2-Succinylphenothiazine (VI).—To a stirred, refluxing solution in 1800 cc. of carbon bisulfide of 54 g. (0.22 mole) of N-acetylphenothiazine and 33.7 g. (0.22 mole) of β-carbomethoxypropionylchloride[8] was added 97 g. (0.73 mole) of aluminum chloride. Refluxing was continued for six hours and the mixture was allowed to stand overnight. After decantation of the carbon bisulfide layer, the reaction mixture was decomposed with ice and hydrochloric acid. The product was taken into chloroform, washed with dilute hydrochloric acid and the solvent evaporated. The residue, boiled two hours with dilute sodium hydroxide solution and filtered, yielded, after acidification, 38.8 g. (58%) of crude 2-succinylphenothiazine. The same substance was prepared in 9% yield by a Friedel-Crafts reaction using succinic anhydride.

N-Succinylphenothiazine (VII).—The direct reaction of succinic anhydride with phenothiazine was rather unsatisfactory. Fusion without solvent, refluxing of the reactants in toluene and xylene with and without addition of mineral acid, and refluxing in glacial acetic acid gave yields of 4–15%. Yields up to 50% were obtained in Friedel-Crafts reactions of succinic anhydride with phenothiazine when the aluminum chloride was added last.

Friedel-Crafts Reaction of Phenothiazine and Phthalic Anhydride.—Forty grams (0.2 mole) of phenothiazine and 88.8 g. (0.6 mole) of phthalic anhydride were stirred and refluxed in 1500 cc. of carbon bisulfide until most of the solid had dissolved. During five minutes 100 g. (0.75 mole) of aluminum chloride was added. Stirring and refluxing were continued for seven hours. After standing overnight, the carbon bisulfide layer was decanted and the residue was decomposed in the usual manner. Extraction with hot water removed 36 g. of phthalic acid. The material insoluble in hot water was boiled thirty minutes with 400 cc. of 5% sodium hydroxide solution and filtered from a precipitate of 8 g. of phenothiazine. On cooling, the filtrate deposited crystals of a sodium salt which was collected and converted to the corresponding acid, N-phthaloylphenothiazine. This fraction accounted for 72% of the phenothiazine used. The filtrate from the sodium salt yielded, on acidification, a brick-red solid weighing 5.3 g. Further boiling with alkali accomplished some purification and it was possible to isolate by crystallization from alcohol 1.6 g. of small orange plates melting at 311–313° and giving correct analytical figures for a diphthaloylphenothiazine. This presumably is the same as the substance reported by Scholl and Seer.[1]

When N-acetylphenothiazine was subjected to Friedel-Crafts reaction under similar conditions, no product could be isolated and virtually all of the starting material was recovered.

(8) Robinson and Robinson, *J. Chem. Soc.*, **127**, 180 (1925).

3-Phenothiazoxyacetic Acid (XIX).—A mixture of 4.9 g. of *p*-anilinophenoxyacetic acid (XVIII), 1.28 g. of sulfur and 0.2 g. of iodine was heated at 160–170° for two hours, the temperature being raised to 200° during the last five minutes. The black melt was extracted with sodium bicarbonate solution, and the extract was charcoaled and acidified giving 1.9 g. of a dark solid. By extraction with ether in a Soxhlet apparatus there was obtained 1 g. of a gray powder, m. p. 199–200°, which was purified by recrystallization.

An attempted cyclization of methyl *p*-anilinophenoxyacetate gave no isolable product.

3-Methoxyphenothiazine.—2-(4-Methoxyanilino)-benzoic acid[9] was prepared in 86% yield by the method of Ullmann.[10] The acid was decarboxylated[10] by heating three hours at 220–260° giving a 99% yield of *p*-methoxydiphenylamine,[11] m. p. 105–106°.

A mixture of 21.8 g. (0.16 mole) of *p*-methoxydiphenylamine, 10.3 g. (0.32 at.) of sulfur and 1 g. of iodine was heated at 150–160° for forty-five minutes, then at 175° for fifteen minutes. The powdered product weighed 36.5 g. and melted at 150–155°. One crystallization from ethyl acetate–hexane mixture gave 25.2 g. melting at 160–161°.[12]

3-Methoxyphenothiazine-4-(or 1)-carboxylic Acid (XX).—In an atmosphere of dry, oxygen-free, nitrogen a stirred, filtered solution of *n*-butyllithium, prepared from 4.9 g. (0.7 at.) of lithium and 44.5 g. (0.35 mole) of *n*-butyl bromide was treated with 20 g. (0.088 mole) of 3-methoxyphenothiazine. The resulting orange-brown solution was refluxed two hours, let stand overnight and refluxed an additional two hours prior to carbonation on Dry Ice. The mixture was hydrolyzed with ice and hydrochloric acid and extracted with ether. Extraction with sodium bicarbonate solution yielded 8.3 g. (35%) of acidic material melting at 192–194°. From the neutral fraction 12.4 g. (62%) of 3-methoxyphenothiazine was recovered.

Acknowledgment.—The authors wish to express their gratitude to Mr. Samuel Blackman for the microanalyses here recorded, to Professor Henry Gilman for his generous loan of specimens, to Mr. Milton Schneider for the X-ray examination of samples and to Dr. I. Fankuchen for advice in interpreting the X-ray results.

Summary

1. The Friedel–Crafts reaction has been applied to phenothiazine with production of monoacylated derivatives.

2. It has been shown that substitution by the acetyl group, and presumably by other acyl groups, is in the 2-position, or *para* to the sulfur atom.

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(9) Borsche, Runge and Trautner, *Ber.*, **66**, 1315 (1933).

(10) Ullmann, *Ann.*, **355**, 323 (1907).

(11) Wieland and Wecker, *Ber.*, **43**, 718 (1910).

(12) Gilman and Shirley, THIS JOURNAL, **66**, 891 (1944).