A. Lower Molecular Weight Aliphatic Aldehydes with Ethyl Cyanoacetate.—A mixture of ethyl cyanoacetate[6] (56.6 g., 0.5 mole), the freshly distilled aldehyde (0.6 mole), 1.0 g. of palladinized charcoal[7] and 80 ml. of glacial acetic acid was placed in a 500-ml. Pyrex bottle later to be used for the reduction. To this was added a solution of piperidine (2.0 ml., 0.02 mole) in 20 ml. of glacial acetic acid and hydrogenation at a pressure of 1 to 2 atmospheres was begun immediately.[8] Reduction was rapid and exothermic. In one to three hours the theoretical amount of hydrogen (0.5 mole) was taken up, and absorption ceased.

The ethyl alkylcyanoacetates were purified readily by distillation. The reaction mixture was filtered, 50 ml. of benzene was added, and the solution was washed with two 50-ml. portions of 10% sodium chloride solution followed by three 25-ml. portions of water. If emulsions were formed at this point, they were broken by the addition of a few ml. of ether. The washings were extracted with two small portions of benzene and the combined benzene solutions were distilled through a Widmer column under reduced pressure. No ethyl cyanoacetate was recovered in the forerun, and only a small distillation residue remained.

When aldol was the aldehyde used, 0.7 mole of hydrogen was absorbed (calcd., 0.5 mole) and 55.5 g. (66%) of ethyl *n*-butylcyanoacetate was obtained. The identity of this ester was established by analysis (*Anal.* Calcd. for $C_9H_{15}O_2N$: C, 63.98; H, 8.94. Found: C, 64.29; H, 8.88), and conversion into the amide, m. p. and mixed m p. with a known sample 125.5–126.5°.[9]

(6) Obtained from the Dow Chemical Company, Midland, Michigan.

(7) Hartung, THIS JOURNAL, **50**, 3372 (1928), subsequently modified by Dr. Hartung as follows. Ten ml. of a commercial palladium chloride solution containing 0.1 g. of palladium and approximately 0.05 g. of hydrogen chloride per ml. (obtained from the J. Bishop Company, Malvern, Pennsylvania) is added to a solution of 27 g. of sodium acetate trihydrate in 100 ml. of water. Norite (9 g.) is added and the mixture is hydrogenated until absorption ceases. The catalyst (10 g.) is filtered on a Büchner funnel, washed with water, dried by drawing air through the funnel for about thirty minutes and stored in a desiccator over calcium chloride.

(8) With propionaldehyde the yield of ethyl *n*-propylcyanoacetate dropped from 94 to 61% when the solution was allowed to stand for one hour before reduction was commenced. The yield of ethyl *n*-butylcyanoacetate was 87% when the reaction mixture stood for three hours before hydrogenating.

(9) Guareschi, *Atti Accad. sci. Torino*, **37**, 15 (1901); *Chem. Zentr.*, **73**, II, 700 (1902).

B. Branched Chain, Higher Molecular Weight Aliphatic Aldehydes, and Benzaldehyde.—A mixture of ethyl cyanoacetate (56.6 g., 0.5 mole), the aldehyde (0.6 mole), glacial acetic acid (6.0 g., 0.05 mole) and 150 ml. of dioxane[10] was placed in a 500-ml. Pyrex bottle later to be used for the reduction and cooled in an ice–salt mixture to 4°. Piperidine (2.0 ml., 0.02 mole) was added dropwise to this solution during approximately ten minutes with occasional swirling. The temperature rose to 20° and the solution became turbid. When the addition was complete, 1.0 g. of palladinized charcoal was added and the mixture was hydrogenated as before. With the aliphatic aldehydes, heat was evolved and reduction was complete in about four hours. With benzaldehyde, hydrogen absorption was very slow even when the reaction was carried out at 60°. The esters were purified as in method A. In the reactions employing aliphatic aldehydes, no ethyl cyanoacetate was recovered and only small distillation residues were left. With benzaldehyde there was a forerun of ethyl cyanoacetate (8.0 g.) and considerable residue (35 g.).

C. Aliphatic Ketones with Ethyl Cyanoacetate.—Ethyl cyanoacetate (56.6 g., 0.5 mole), the ketone (0.55 mole), ammonium acetate (3.9 g., 0.05 mole), glacial acetic acid (6.0 g., 0.1 mole), 100 ml. of 95% ethanol and 1.0 g. of palladinized charcoal were placed in a 500-ml. Pyrex bottle and hydrogenated as before. These reductions were exothermic but to a lesser degree than those mentioned under methods A and B. The esters were purified as in method A.

Summary

Experimental conditions are described whereby a number of aldehydes and aliphatic ketones can be condensed with ethyl cyanoacetate and simultaneously hydrogenated in the presence of palladinized charcoal to obtain pure ethyl monoalkylcyanoacetates in good yield. Ammonium acetate and acetic acid were employed as the condensing agents with ketones, and piperidine acetate and acetic acid with aldehydes.

(10) Purified by boiling over sodium for forty-eight hours and redistilling.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Derivatives of Phenothiazine

BY HENRY GILMAN AND DAVID A. SHIRLEY

The first attempt to apply a phenothiazine derivative as an antimalarial agent was made by Guttman and Ehrlich[1] in 1891, when they showed that methylene blue was an active chemotherapeutic agent against human malaria, and later work[2,3] substantiated this claim. As a part of the extensive antimalarial research carried out by the I. G. Farbenindustrie, Schuleman[4] modified the structure of methylene blue by replacing an N-methyl group with alkylaminoalkyl groupings. More recently Holcomb and Hamilton[5] prepared 3,7-di-(6′-methoxy-2′-methyl-4′-quinolyl)-thionine as a possible antimalarial, but no report is available of its pharmacological value.

These prior studies have been concerned with the oxidized or methylene blue types of phenothiazine. It seemed of interest to prepare some appropriately substituted, non-oxidized phenothiazines for testing in avian malaria. Phenothiazine and some of its simple derivatives have a significantly low toxicity for animals. The toxicity is still further reduced by the introduction of

(1) Guttman and Ehrlich, *Berlin klin. Wochschr.*, **28**, 953 (1891).

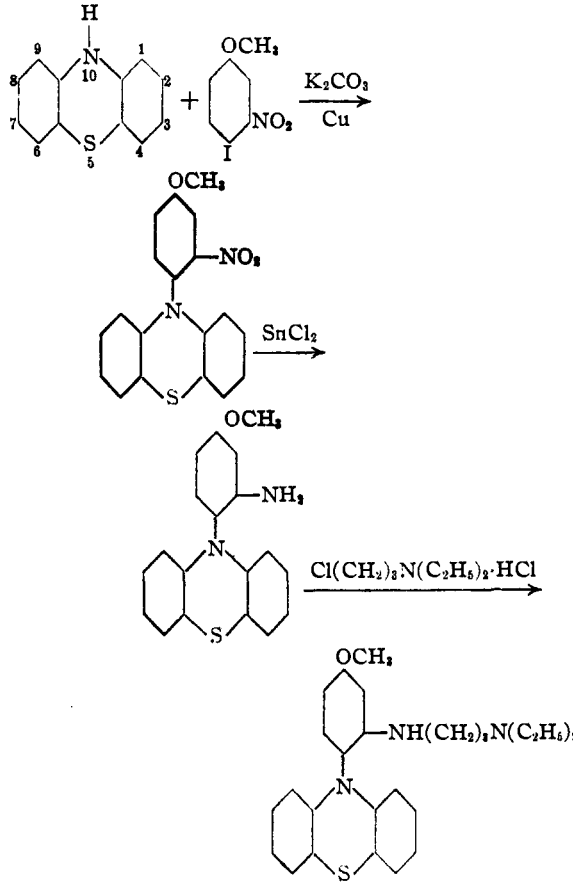
(2) Couto, *Arch. Schiffs- u. Tropen-Hyg.*, **30**, 275 (1926).

(3) Fourneau, Trefouel, Bovet and Benoit, *Ann. inst. Pasteur*, **46**, 520 (1931).

(4) Schuleman, *Proc. Roy. Soc. Med.*, **25**, 897 (1932); German Patent 688,945 [*C. A.*, **24**, 2242 (1930)]; German Patent 490,275 [*C. A.*, **24**, 2241 (1930)].

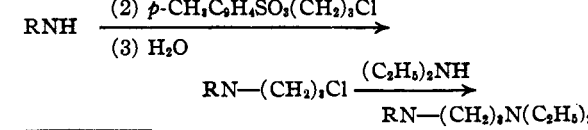
(5) Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).

substituents in the 10-position.[6] For this reason, and also because of the opportunity of introducing some nuclear substituents like chlorine and methoxy groups which are present in atabrine, some substituted 10-phenylphenothiazine derivatives were prepared. Some of these had the generally desirable dialkylaminoalkylamino group, and the following typical series of reactions illustrates the synthesis of 10-(2′-γ-diethylaminopropylamino-4′-methoxy)-phenylphenothiazine



None of these compounds showed antimalarial activity with the exception of 10-(4′-γ-diethylaminopropylamino)-phenylphenothiazine, which had a doubtful activity at a daily dosage of twelve and one-half milligrams.

A series of phenothiazine derivatives was prepared which contained a basic alkylaminoalkyl group attached to the nitrogen of phenothiazine. These compounds were prepared by the following reactions in which the synthesis of 10-γ-diethylaminopropylphenothiazine is an illustration (RN- is the phenothiazyl radical).



(6) Schaffer, Haller and Fink, *J. Econ. Entomol.*, **30**, 361 (1937).

There were also prepared two derivatives of this type which contained a methoxyl group in the 3-position. These compounds were prepared by the same series of reactions shown above, starting with 3-methoxyphenothiazine which was prepared from 4-methoxydiphenylamine by ring closure with sulfur. None of these derivatives showed any activity.

In addition, tests were carried out on a miscellany of phenothiazine derivatives which were prepared either during the course of the investigation on the metalation of phenothiazine[7] or as intermediates in the synthesis of the compounds containing groups likely to impart or increase antimalarial action. This group of compounds, listed in the Experimental Part, was also without activity.

Experimental

10-(2′-Nitro)-phenylphenothiazine.—Twenty grams (0.1 mole) of phenothiazine, 37 g. (0.15 mole) of *o*-iodonitrobenzene, 100 ml. of xylene, 15 g. of potassium carbonate, and 1 g. of copper bronze were refluxed with stirring for ten hours. The mixture was cooled, filtered and the residue extracted with water. The residue was recrystallized from a mixture of benzene and petroleum ether (b. p. 80–110°) to give 14 g. (44%) of yellow-brown prisms which melted at 156–157°.

Anal. Calcd. for $C_{18}H_{12}O_2N_2S$: N, 8.75. Found: N, 8.66.

10-(2′-Amino)-phenylphenothiazine.—Five grams (0.015 mole) of 10-(2′-nitro)-phenylphenothiazine, 10 g. of granulated tin, and 20 ml. of water were stirred and refluxed for one-half hour during which 75 ml. of concd. hydrochloric acid was added. The mixture was stirred and heated for an additional one-half hour. The organic matter was removed by filtration and recrystallized from alcohol. Another recrystallization from petroleum ether (b. p. 80–110°) gave 4.5 g. (95%) of light yellow needles melting at 139–139.5°.

Anal. Calcd. for $C_{18}H_{14}N_2S$: N, 9.65. Found: N, 9.66.

γ-Diethylaminopropyl Chloride Hydrochloride.—The general procedure for the preparation of γ-diethylaminopropyl chloride hydrochloride was kindly furnished by Dr. R. R. Burtner and represents a modification of the procedure of Slotta and Behnisch.[8]

A mixture of 1200 ml. of chloroform and 290 g. (2.43 moles) of thionyl chloride was immersed in an ice-bath, and to this was added (one hour) a solution of 157 g. (1.20 moles) of γ-diethylaminopropanol in 260 ml. of chloroform. The mixture was refluxed for three hours, after which the solvent and excess thionyl chloride were removed by distillation. The residue was treated cautiously with 300 ml. of 40% sodium hydroxide solution and extracted with 2 liters of ether. The ethereal solution was dried over anhydrous sodium sulfate and then evaporatively distilled. The residue distilled as a colorless oil at 73–75° (20 mm.). The yield was 131 g. (73%).

The hydrochloride is a white, extremely hygroscopic powder which melts at 66–68°. Magidson and Strukov[9] reported the compound to melt at 62–64°.

10-(2′-γ-Diethylaminopropylamino)-phenylphenothiazine.—Four grams (0.013 mole) of 10-(2′-amino)-phenylphenothiazine and 2.5 g. (0.014 mole) of γ-diethylaminopropyl chloride hydrochloride were heated for fifteen hours in a test-tube immersed in a metal bath at 130–140°. The dark red viscous product was extracted with hot 2% hydrochloric acid. The acidic extracts were made alkaline

(7) Gilman, Shirley and Van Ess, THIS JOURNAL, **66**, 625 (1944); Gilman, Van Ess and Shirley, *ibid.*, **66**, in press (1944).

(8) Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

(9) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933).

with concentrated sodium hydroxide solution and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and evaporatively distilled. The residual oil was distilled at less than 0.5 mm. pressure. It boiled at 215–230° and was a yellow-green, fluorescent, highly viscous oil. The yield was 2.7 g. or 49%.

Anal. Calcd. for $C_{25}H_{29}N_3S$: N, 10.41. Found: N, 10.54.

TABLE I

10-(γ-DIETHYLAMINOPROPYLAMINO)-PHENYLPHENOTHIAZINES AND THEIR PRECURSORS

10-Substituent	M. p., °C.	Yield, %	N Analyses, % Calcd.	Found
-(4'-nitro)-phenyl-[a]	157	33	8.75	8.77
-(4'-amino)-phenyl-[b]	132–133	85	9.65	9.41
-(4'-γ-diethylaminopropyl amino)-phenyl	[c]	42	10.41	10.50
-(2'-nitro-4'-methyl)-phenyl-[d]	179.5–180	36	8.40	8.47
-(2'-amino-4'-methyl)-phenyl-[e]	140–140.5	81	9.20	9.45
-(2'-γ-diethylaminopropyl-amino-4'-methyl)-phenyl	[f]	45	10.08	10.09
-(2' nitro-4'-methoxy)-phenyl-[g]	184–186	26	8.00	7.85
-(2'-amino-4'-methoxy)-phenyl[h]	180–181	57	8.75	8.74
(2'-γ-diethylaminopropyl-amino-4'-methoxy)-phenyl	[i]	47	9.70	9.60
-(2'-methoxy-4'-nitro)-phenyl-[j]	159–160	36	8.00	8.06
(2'-nitro-4'-chloro)-phenyl-[k]	185–186.5	21	7.90	8.10
-(2'-amino-4'-chloro)-phenyl-[l]	125.5–126	38	8.65	8.45
-(2'-γ-diethylaminopropyl-amino-4'-chloro)-phenyl-	[m]	47	9.61	9.62

[a] Prepared from phenothiazine (0.1 mole) and *p*-iodonitrobenzene (0.15 mole); crystallized first from ethanol, then from benzene; yellow prisms. [b] The nitro compound was reduced by tin and hydrochloric acid. Crystallization from petroleum ether (b. p., 80–110°) gave yellow prisms; yield in first run was 46%. [c] The product was distilled at less than 0.5 mm. with a bath temperature of 350°, and was a yellow "glass." [d] Prepared from phenothiazine (0.1 mole) and 3-nitro-4-iodotoluene (0.12 mole). The 3-nitro-4-iodotoluene was prepared in 88% yield by treating the diazotized 3-nitro-4-aminotoluene with potassium iodide in accordance with some general directions of Beilstein and Kuhlberg, *Ann.*, **158**, 344 (1872). The brownish crystals of the product were obtained from glacial acetic acid, and a mixed m. p. with phenothiazine (m. p. 180–181°) was below 150°. [e] Reduction was effected by adding a hot solution of stannous chloride in concd. hydrochloric acid to a hot glacial acetic acid suspension of the nitro compound. Crystallization was from petroleum ether (b. p., 80–110°). [f] The product distilled at a bath temp. of 270° under a pressure of less than 0.5 mm., and was a yellow oil with a green fluorescence. [g] Prepared (first in 24% and then in 26% yield) from phenothiazine (0.1 mole) and 3-nitro-4-iodoanisole (0.12 mole). The latter was prepared in 92% yield from diazotized 3-nitro-4-aminoanisole in general accordance with the directions of Reverdin, *Ber.*, **29**, 2595 (1896). [h] Reduction was effected by stannous chloride and concd. hydrochloric acid; the yield in a first preparation was 53%. Crystallization from benzene gave small olive-green prisms. [i] The product distilled at 220–235° at a pressure less than 0.5 mm., and was a yellow-red oil. [j] Prepared from phenothiazine (0.1 mole) and 2-iodo-5-nitroanisole (0.15 mole). The orange-red plates were obtained by first crystallizing from acetic acid and then from a mixture of benzene and petroleum ether (b. p., 80–110°). The m. p. of 5-nitro-2-iodoanisole (prepared by diazotization) was 130–131° instead of 127–128° reported previously by Meldola and Eyre, *Proc. Chem. Soc.*, **17**, 131 (1901). An attempted reduction of 10-(2'-methoxy-4'-nitro)-phenylphenothiazine by stannous chloride gave a mixture which has not been resolved by crystallization. [k] Prepared from phenothiazine (0.1 mole) and 2-nitro-4-chloroiodobenzene (0.125 mole). Crystallization from acetic acid gave brown prisms. The 2-nitro-4-chloroiodobenzene was obtained in 96% by the procedure of Körner, *Gazz. chim. ital.*, **4**, 381 (1874). [l] Reduction was by stannous chloride, and there was appreciable tar formation. Crystallization was from benzene and then from pet. ether (b. p., 80–110°). [m] The product distilled over the range 270–280° (2 mm.) as a yellow oil.

Preparation of 10-(γ-Diethylaminopropylamino)-phenylphenothiazines.—The nitro-, the amino- and the γ-diethylaminopropylamino-phenylphenothiazines described in Table I were prepared in general accordance with the directions just given for the preparation of 10-(2'-γ-diethylaminopropylamino)-phenylphenothiazine and its necessary precursors.

No reaction was observed in an attempted condensation of phenothiazine with either *m*-iodonitrobenzene or 2-iodo-5-nitrotoluene; and with 2-iodo-3-nitrotoluene, 24% of the nitro compound was recovered in the tarry reaction product. There was also marked tar formation in a reaction between 3-methylphenothiazine and *o*-iodonitrobenzene, and in a reaction between 3-methoxyphenothiazine and *o*-iodonitrobenzene.

10-β-Chloroethylphenothiazine.—The preparation of 10-β-chloroethylphenothiazine was carried out in essential accordance with directions kindly provided by S. M. Spatz and M. J. Kolbezen.

To 600 ml. of an ethereal solution of *n*-butyllithium containing 0.69 mole of the organometallic compound was added slowly 137 g. (0.69 mole) of phenothiazine. A solution of 151 g. (0.69 mole) of freshly distilled β-chloroethyl *p*-toluenesulfonate in 100 ml. of ether was added over a period of one hour to the iced 10-lithiophenothiazine solution. The mixture was hydrolyzed by the slow addition of water. The ether layer was separated and the ether allowed to evaporate. The yellow solid, which remained after evaporation of the ether, was recrystallized once from ethyl alcohol to give 85 g. of light yellow needles which melted at 96–97°. This corresponds to a yield of 47%. Spatz and Kolbezen gave the melting point of the compound as 97–98°, and their yield was 62%.

10-β-Chloroethylphenothiazine-5-oxide.—Fifteen grams (0.057 mole) of 10-β-chloroethylphenothiazine was dissolved in 500 ml. of warm alcohol, and 50 ml. of 30% hydrogen peroxide[10] was added. The mixture was allowed to stand at room temperature for two days. The clear wine-red solution was poured into an excess of water, which precipitated a white solid. This solid was removed by filtration and recrystallized from a 1:1 mixture of benzene and pet. ether (b. p., 80–110°) to yield 10 g. (63%) of white prisms which melted at 154–155°.

Anal. Calcd. for $C_{14}H_{12}OClNS$: N, 5.04. Found: N, 4.80.

10-β-Diethylaminoethylphenothiazine.—Ten grams (0.038 mole) of 10-β-chloroethylphenothiazine was refluxed with 30 ml. of diethylamine in the presence of 1.0 g. of copper bronze for sixty hours. The reaction mixture was dissolved in dilute hydrochloric acid and this solution was made strongly alkaline with sodium hydroxide. The mixture was extracted with ether and the combined extracts dried over sodium sulfate. Evaporative distillation of the dried ethereal solution followed by a vacuum distillation of the residue gave a yellow oil boiling at 161–165° at a pressure of less than 0.5 mm. The yield was 7.6 g. (67%).

Anal. Calcd. for $C_{18}H_{22}N_2S$: N, 9.40. Found: N, 9.46.

Table II lists other 10-β-aminoethylphenothiazines prepared in an analogous manner.

The condensation of β-chloroethylphenothiazine (0.038 mole) and 8-amino-6-methoxyquinoline (0.114 mole) was effected by heating with 1.0 g. of copper powder for five hours in a nitrogen atmosphere at 140–150°.

10-γ-Chloropropylphenothiazine.—10-γ-Chloropropylphenothiazine was prepared in a manner analogous to the preparation of 10-β-chloroethylphenothiazine from 10-lithiophenothiazine and γ-chloropropyl *p*-toluenesulfonate.

(10) Kehrmann and Diserens, *Ber.*, **48**, 318 (1915).

TABLE II

10-(β-AMINOETHYLPHENOTHIAZINES)

10-Substituent	B. p., °C.	Yield, %	N Analyses, % Calcd.	Found
-β-dipropylaminoethyl-[a]	225–230 (1 mm.)	77	8.59	8.50
-β-morpholinoethyl-[b]	198–201 (< 0.5 mm.)	71	8.97	8.95
-β-(6′-methoxy-8′-quinolyl)-aminoethyl-	[c]	12	10.53	10.82

[a] The product was a light yellow oil. [b] The light yellow, viscous oil solidified to a white crystalline mass which melted at 74.5–75.5°. [c] The red, viscous oil distilled over the range 310–330° at a pressure less than 0.5 mm. This oil was extracted several times with pet. ether (b. p., 80–110°), and evaporation of the solvent gave a mixture of oil and yellow crystals. Recrystallization from a mixture of benzene and pet. ether, and then from pet. ether (b. p., 80–110°), gave light yellow prisms melting at 118.5–119.5°.

The product crystallized from methanol in the form of white prisms melting at 60°. The yield was 32%.

Anal. Calcd. for $C_{15}H_{14}ClNS$: N, 5.08. Found: N, 5.23.

10-γ-Diethylaminopropylphenothiazine.—The reaction of 10-γ-chloropropylphenothiazine and diethylamine was carried out as previously described under the preparation of 10-β-diethylaminoethylphenothiazine. The product was a yellow oil boiling at 170–182°/< 0.5 mm. and was obtained in a yield of 68%.

Anal. Calcd. for $C_{19}H_{24}N_2S$: N, 8.97. Found: N, 9.18.

The *dipicrate* derivative separated from the alcohol as yellow prisms which melted at 103–104°.

Anal. Calcd. for $C_{31}H_{30}O_{14}N_8S$: N, 14.56. Found: N, 14.80.

It was attempted to prepare 10-γ-diethylaminopropylphenothiazine by the condensation of γ-diethylaminopropyl chloride or its hydrochloride with phenothiazine, but only unchanged phenothiazine or tarry product was isolated in two attempts. Also unsuccessful was an attempt to use γ-diethylaminopropyl bromide hydrobromide in the preparation of this compound.

Table III lists other 10-γ-aminopropylphenothiazines prepared by a corresponding procedure.

TABLE III

10-(γ-AMINOPROPYLPHENOTHIAZINES)

10-Substituent	B. p., °C.	Mm.	Yield, %	N Analyses, % Calcd.	Found
-γ-dipropylaminopropyl-[a]	257–262	2	57	8.25	8.17
-γ-diallylaminopropyl-[b]	245–260	1	53	8.34	8.57
γ-piperidylpropyl-[c]	255–265	1–2	33	8.65	8.90

[a] Reaction was effected by refluxing, in the presence of copper powder, for twenty hours. The product was a light yellow oil. [b] The reflux period was twenty-six hours, and the product was a yellow oil. [c] The reflux period for this condensation with piperidine was fifty hours, and the product was a dark yellow, viscous oil.

3-Methoxyphenothiazine.—This compound was prepared by the action of sulfur on 4-methoxydiphenylamine.

4-Methoxydiphenylamine was prepared by treating acetyl-*p*-anisidine with excess bromobenzene in the presence of sodium carbonate and copper powder, followed by treatment with dilute hydrochloric acid in order to remove the acetyl group. The yields in two runs were 31 and 48%. The product was separated as steel-gray needles which melted at 106°. Wieland and Wecker[11] gave 105° as the melting point.

An intimate mixture of 37.5 g. (0.189 mole) of 4-methoxydiphenylamine, 12.5 g. (0.378 g. atom) of sulfur, and 1 g. of iodine as a catalyst was placed in a distilling flask immersed in a metal bath. The temperature of the bath was raised to 140–150°. Evolution of hydrogen sulfide began at this temperature and continued for thirty minutes. The reaction mixture was then heated to 175° over a period of fifteen minutes as the evolution of hydrogen sulfide slackened. The black fluid was poured into a mortar and allowed to solidify. The solid cake was then ground up to a yellow powder, which was placed in a Soxhlet extractor and extracted with pet. ether (b. p., 80–110°) for fifty hours. Nineteen and one-half grams of yellow powder melting at 158–159° separated from the pet. ether, which corresponded to a yield of 45%. A second run gave a yield of 51%. Pummerer and Gassner[12] gave 163° as the melting point of 3-methoxyphenothiazine; however, Kehrmann,[13] who later prepared the same compound, reported the melting point as 159°.

3-Methoxy-10-γ-di-*n*-propylaminopropylphenothiazine.—Four grams (0.0131 mole) of crude 3-methoxy-10-γ-chloropropylphenothiazine[14] was refluxed with 15 ml. of di-*n*-propylamine and 0.2 g. of copper bronze for eight hours. The reaction mixture was treated as previously described under the preparation of 10-γ-diethylaminopropylphenothiazine. The product distilled over the range 250–265° (2 mm.). The yield of red oil was 3.2 g. (66%).

Anal. Calcd. for $C_{22}H_{30}ON_2S$: N, 7.56. Found: N, 7.72.

3-Methoxy-10-γ-diethylaminopropylphenothiazine.—Eight grams (0.0262 mole) of the crude 3-methoxy-10-γ-chloropropylphenothiazine was refluxed for ten hours with 30 ml. of diethylamine and 0.2 g. of copper bronze. The product distilled at 220–225° at a pressure of less than 0.5 mm. as a dark yellow oil with a strong green fluorescence. The yield was 4.4 g. (49%).

Anal. Calcd. for $C_{20}H_{26}ON_2S$: N, 8.20. Found: N, 8.46.

3-Methoxy-10-acetylphenothiazine.—Two grams (0.0087 mole) of 3-methoxyphenothiazine was refluxed for four and one-half hours with 50 ml. of acetic anhydride. The solution was poured into excess water, which precipitated a white solid. The solid was removed by filtration and refluxed with enough petroleum ether (b. p. 80–110°) to effect solution. Cooling the petroleum ether solution precipitated two crops of oil from which the clear supernatant solution was decanted. The solution then deposited 0.5 g. (22%) of white rosets which melted at 121–121.5°.

Anal. Calcd. for $C_{15}H_{13}O_2NS$: N, 5.16. Found: N, 5.24.

3-Methylphenothiazine.—3-Methylphenothiazine was prepared by the action of sulfur on 4-methyldiphenylamine.

The preparation of 4-methyldiphenylamine was carried out by the method of Weston and Adkins,[15] in yields of 27 and 28%.

For the conversion of 4-methyldiphenylamine to 3-methylphenothiazine, an intimate mixture of 72 g. (0.394 mole) of 4-methyldiphenylamine, 25.3 g. (0.788 g. atom) of sulfur, and 1 g. of iodine were heated to a temperature of 280° over a period of twenty minutes. The liquid melt was allowed to solidify before being ground up in a mortar to a green powder. This material, which was obtained in a quantitative yield, melted at 160–162°. Two recrystallizations from benzene raised the melting point to 166–168°.

Anal. Calcd. for $C_{13}H_{11}NS$: N, 6.57. Found: N, 6.66.

3,7-Dinitro-10-acetylphenothiazine-5-oxide.—10-Acetylphenothiazine was prepared according to Bernthsen.[16]

(11) Wieland and Wecker, *Ber.*, **43**, 708 (1910).

(12) Pummerer and Gassner, *ibid.*, **46**, 2325 (1913).

(13) Kehrmann, *ibid.*, **48**, 327 (1915).

(14) This was prepared from the 3-methoxy-10-lithiophenothiazine and γ-chloropropyl *p*-toluenesulfonate as a viscous orange oil which was intractable to both distillation and crystallization.

(15) Weston and Adkins, THIS JOURNAL, **50**, 862 (1928).

(16) Bernthsen, *Ann.*, **230**, 77 (1885).

The nitration of 10-acetylphenothiazine was attempted according to the directions of Bernthsen,[16] and it was found that no reaction occurred under these conditions. The following procedure was found satisfactory for the preparation of 3,7-dinitro-10-acetylphenothiazine-5-oxide.

Fifty grams (0.25 mole) of phenothiazine was suspended in 400 ml. of glacial acetic acid and 125 ml. of concd. nitric acid was added over a period of fifteen minutes. Upon standing the solution precipitated 40 g. (46%) of yellow-tan powder which melted with decomposition at 265–267°. Bernthsen[16] gives no melting point for his nitration product.

Anal. Calcd. for $C_{14}H_9O_6N_3S$: N, 12.03. Found: N, 12.21.

3-Nitro-10-ethylphenothiazine-5-oxide.—Kehrmann and Zybs[17] nitrated 10-methylphenothiazine and obtained 3-nitro-10-methylphenothiazine-5-oxide. 10-Ethylphenothiazine was nitrated using the general procedure developed by these workers. The 10-ethylphenothiazine was prepared by the reaction of ethyl bromide and phenothiazine in a steel bomb.[18]

Ten grams (0.044 mole) of 10-ethylphenothiazine was dissolved in 250 ml. of glacial acetic acid, and to this solution was added 10 ml. of concd. nitric acid dissolved in 40 ml. of glacial acetic acid. The mixture was allowed to stand for two days, and the clear yellow solution was poured into excess water. A bright yellow powder which melted at 202–204° was precipitated in a quantitative yield. One recrystallization of the product from a 1:1 mixture of alcohol and glacial acetic acid gave minute canary-yellow crystals which melted at 204.5–205°. Analysis showed this to be a mononitro-10-ethylphenothiazine-5-oxide, and by analogy to the nitration of 10-methylphenothiazine, it was assumed that nitration had occurred in the reactive 3-position of phenothiazine.

Anal. Calcd. for $C_{14}H_{12}O_3N_2S$: N, 9.72. Found: N, 9.82.

10-Allylphenothiazine.—A mixture of 50 g. (0.25 mole) of phenothiazine, 60 g. (0.50 mole) of allyl bromide, 50 ml. of benzene, 20 g. of sodium carbonate, and 2 g. of copper powder was stirred and refluxed for six hours. The hot mixture was filtered and the filtrate was distilled to remove the benzene and excess allyl bromide. The residual oil was distilled at 187–195° (1 mm.), and 37 g. (62%) of product was collected as a light brown oil.

Anal. Calcd. for $C_{15}H_{13}NS$: N, 5.86. Found: N, 5.91.

10-Decylphenothiazine.—A mixture of 50 g. (0.25 mole) of phenothiazine, 55 g. (0.25 mole) of *n*-decyl bromide, 25 g. of sodium carbonate, and 2 g. of copper powder was stirred and heated in an oil-bath at 170–180° for eleven hours. The cooled reaction mixture was extracted with ether, and the combined ether extracts were dried over anhydrous sodium sulfate and the ether removed by evaporative distillation. The residue was distilled at 1 mm. pressure and 21.5 g. of yellow oil was collected at 225–235°. This was redistilled at less than 0.5 mm. pressure, and 8.0 g. (9.4%) of yellow oil was collected at 183–185°.

Anal. Calcd. for $C_{22}H_{29}NS$: N, 4.13. Found: N, 4.16.

3-Nitro-10-decylphenothiazine-5-oxide.—Ten grams (0.295 mole) of 10-decylphenothiazine was dissolved in 75 ml. of glacial acetic acid and 10 ml. of concd. nitric acid in 75 ml. of acetic acid was added with shaking over a period of ten minutes. The mixture was allowed to stand for two days, and was then poured into excess water. The precipitated yellow solid was recrystallized from pet. ether (b. p. 60–68°) to give 4.0 g. (34%) of bright yellow prisms which melted at 102.5–103°.

Anal. Calcd. for $C_{22}H_{28}O_3N_2S$: N, 7.00. Found: N, 7.34.

(17) Kehrmann and Zybs, *Ber.*, **52**, 130 (1919).

(18) Gilman, Van Ess and Shirley, THIS JOURNAL, **66**, in press (1944).

10-Octadecylphenothiazine.—A mixture of 30 g. (0.09 mole) of *n*-octadecyl bromide, 17.9 g. (0.09 mole) of phenothiazine, 10 g. of anhydrous sodium carbonate, and 1 g. of copper powder was heated at 170–180° for twelve hours. The mixture was extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and then evaporatively distilled. The residual oil was distilled at a pressure of less than 0.5 mm., and gave 18 g. of yellow oil boiling at 290–300°. Upon cooling, this oil solidified to a waxy solid which was recrystallized from ethanol to give 8.2 g. (20%) of minute, white needles which melted at 53°.

Anal. Calcd. for $C_{30}H_{45}NS$: N, 3.11. Found: N, 3.06.

10-Octadecylphenothiazine-5-oxide.—Five grams (0.011 mole) of 10-octadecylphenothiazine was dissolved in 600 ml. of hot alcohol and 30 ml. of 30% hydrogen peroxide solution was added to the mixture. The solution was heated to boiling for several minutes, and then allowed to stand at room temperature for two days. Pouring the reaction mixture into water precipitated 4.2 g. of a pink powder which upon recrystallization from pet. ether (b. p. 80–110°) gave 2.7 g. (53%) of light pink to white plates which melted at 98°.

Anal. Calcd. for $C_{30}H_{45}ONS$: N, 3.00. Found: N, 3.07.

10-Phenylphenothiazine-5-oxide.—Two grams (0.0073 mole) of 10-phenylphenothiazine was dissolved in 50 ml. of hot alcohol and treated with 5 ml. of 30% hydrogen peroxide as in the preparation of 10-octadecylphenothiazine-5-oxide. The product melted at 170–171° after recrystallization from a mixture of benzene and pet. ether (b. p. 80–110°) and consisted of white prisms. The yield was 1.5 g. (71%).

Anal. Calcd. for $C_{18}H_{13}ONS$: N, 4.81. Found: N, 4.66.

3-Nitro-10-phenylphenothiazine-5-oxide.—Ten grams (0.036 mole) of 10-phenylphenothiazine was suspended in 75 ml. of glacial acetic acid, and a solution of 10 ml. of concd. nitric acid in 75 ml. of acetic acid was added. The mixture was allowed to stand for two days and then was poured into water. The precipitated yellow solid was recrystallized once from ethanol and once from a mixture of ethanol and acetic acid to yield 8.5 g. (70%) of yellow minute crystals melting at 223.5–224.5°.

Anal. Calcd. for $C_{18}H_{12}O_3N_2S$: N, 8.33. Found: N, 8.51.

Pharmacological Tests.—The authors are grateful to Parke, Davis and Company for arranging for the tests on experimental avian malaria. In addition to the compounds mentioned in the Introduction, the following phenothiazine derivatives were tested, and showed no activity: 10-(4′-carboxy)-phenyl-; 3-methyl-; 1-carboxy-; 3-nitro-10-phenyl-5-oxide; 10-methyl-; 10-β-chloroethyl-; 10-phenyl-; 10-allyl-; 10-decyl-; 10-octadecyl-; and phenothiazine.

In connection with the decrease in toxicity of some derivatives substituted in the 10-position, the following information on the lethal dose for canaries in milligrams (in parentheses) is of interest: phenothiazine (20), 3-methylphenothiazine (50), 10-phenylphenothiazine (>50), and 10-phenyl-3-nitrophenothiazine-5-oxide (100).

The relatively low toxicity of phenothiazine and many of its derivatives suggests an examination of some non-oxidized types containing, in addition to a basic side chain, two nuclear substituents drawn from groups like methyl, methoxyl, chloro, or diethylamino. In particular, a compound patterned somewhat after atabrine and containing a methoxyl and a chlorine might help provide more decisive information on the possibilities of effective non-oxidized phenothiazine types.

Summary

The relatively low toxicity of phenothiazines suggested an examination in avian malaria of a miscellany of non-oxidized phenothiazine derivatives containing a basic side-chain and, parti-

cularly, substituents on the nitrogen. Of the compounds synthesized and tested, only one had any activity [10-(4′-γ-diethylaminopropylamino)-phenylphenothiazine], and this was of a doubtful nature.

AMES, IOWA RECEIVED FEBRUARY 1, 1944

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF THE ETHYL CORPORATION]

Zinc Alkyls from Secondary Alkyl Halides

BY HAROLD SOROOS AND MORLEY MORGANA

Of zinc alkyls derived from secondary alkyl halides, the literature reports the preparation of only one, diisopropylzinc.[1] In the reported preparations of this compound, isopropyl iodide was added all at once to zinc or zinc–copper couple, and heat was applied. The yields were low, and mainly gaseous products were obtained. Recent attempts to repeat and confirm this work, by methods known to be successful for the preparation of zinc alkyls from primary halides, were unsuccessful.[2]

Recently, in studies conducted in this Laboratory, it was found that both diisopropylzinc[3] and di-*s*-butylzinc could be obtained in essentially as good yields as the zinc alkyls derived from primary alkyl halides, by a modification of Noller's procedure.[2] The method consists simply of adding a mixture of the secondary alkyl bromide and iodide slowly with stirring under controlled temperature conditions to an excess of zinc–copper couple, followed by distillation of the reaction mixture at as low a temperature and pressure as possible.

In contrast to the preparation of zinc alkyls from primary alkyl halides, the reaction with the secondary halides starts easily and proceeds smoothly if properly controlled. Only a trace of gas is formed, and the reaction mixture consists of a clear oily liquid[4] and the excess couple. Distillation of the reaction mixtures under reduced pressure gives the zinc alkyls in good yield.

Both compounds are spontaneously inflammable and somewhat less stable than the primary analogs, decomposing slowly in diffused daylight with the deposition of metallic zinc.

(1) Bohm (*J. Russ. Phys.-Chem. Soc.*, **31**, 46 (1899): *Chem. Zentr.*, **70**, 1, 1067 (1899)) reports obtaining diisopropylzinc in 25% yield from isopropyl iodide and zinc; Gladstone and Tribe (*J. Chem. Soc.*, **26**, 961 (1873)) obtained the compound in 13% yield from isopropyl iodide and zinc-copper couple; Ragosin (*J. Russ. Phys.-Chem. Soc.*, **24**, 549 (1892); *Ber.*, **26** (Ref.), 380 (1893)) obtained the compound by interaction of isopropyl iodide in ether with zinc and a small amount of sodium–zinc alloy.

(2) Noller, THIS JOURNAL, **51**, 594 (1929).

(3) The preparation of this compound was investigated in a study sponsored and supported by the National Advisory Committee for Aeronautics.

(4) The oily liquid is apparently the RZnX compound, which on subsequent heating disproportionates to R_2Zn and ZnX_2. It was necessary to heat the reaction mixtures at 1 mm. to considerably higher temperatures than required for distillation of the zinc alkyls alone before the latter distilled from the reaction mixtures. Also, the liquid was observed to be considerably more stable toward oxidation on exposure to air than the zinc alkyls.

Experimental

Zinc–Copper Couple.—A wrought-iron alloy pot, flushed with nitrogen, was charged with 3319 g. (51 g. atoms) of zinc and 369 g. (3.55 g. atoms Cu, 2.11 g. atoms Zn) of Tobin bronze brazing rod, and loosely covered. The mass was heated to 600° with an oxy-acetylene torch and shaken vigorously for five minutes, maintaining the temperature at 600°. The melt was discharged into a one-inch iron pipe mold, cooled in air, and finally quenched in water. The rod was machined into turnings without the use of cutting oil. *Anal.*[5] Zn, 94.5; Cu, 5.86.

Diisopropylzinc.—To a 500-ml., 3-neck flask, equipped with a reflux condenser, an efficient stirrer, and a Hershberg dropping funnel, was added 104.5 g. (98.9 g. Zn, 1.5 g. atom) of zinc–copper couple turnings. The system was evacuated to 1 mm. while stirring and warming gently with a free flame, and then flushed several times with dry nitrogen. A trap cooled in dry-ice was connected to the outlet of the reflux condenser and a mixture of 61.5 g. (0.5 mole) of isopropyl bromide and 85.0 g. (0.5 mole) of isopropyl iodide was added to the dropping funnel. A water-bath at 50° was raised around the flask and the stirrer started. About 2 ml. of the alkyl halide mixture was added rapidly. Within two minutes, reaction had started as shown by a trace of white fumes, a darkening of the couple, and the oily appearance of the liquid on the walls of the flask. The 50° bath was replaced by a water-bath at 20°, and dropwise addition of the halides was started. The drop rate was adjusted so that addition was complete in five and one-half hours. At this rate not more than 0.5 ml. of liquid collected in the trap; a faster rate caused undue gas formation as shown by liquid in the dry-ice trap. After addition, stirring was continued for 30 minutes. The reaction mixture consisted of a clear, colorless, liquid and the almost black excess zinc–copper couple.

For distillation of the diisopropylzinc, one neck of the three-neck flask was stoppered, the other was equipped with a simple distillation head and thermometer, and the rubber sleeve of the stirrer was wired to the shaft. Three traps were placed in series, the first two being equipped with Vaseline-lubricated stopcocks, all being large enough so that freezing of the distillate would not cause plugging. With the first two traps at room temperature and the third in liquid nitrogen, the system was slowly evacuated to 1 mm. Low-boiling material was collected in the cold trap until ebullition ceased in the flask. The first two traps were then cooled in a dry-ice mixture at −65° and an oil-bath, placed around the flask, was heated rapidly to about 100°. The oil-bath was maintained at 90–140° for forty-five minutes until distillation was almost complete, at the end of which time it was raised to 200° to remove the last trace of product. It was necessary to maintain the oil pump on the system throughout, owing to some pyrolytic decomposition. Without the liquid nitrogen trap, an oil pump would not maintain a pressure of 1 mm. and the yield was lowered. The residue was a

(5) Spectrographic analysis of the zinc used in this preparation, kindly obtained for us by Dr. F. L. Howard of the National Bureau of Standards, showed the metal to contain trace amounts (less than 0.01%) of Au, Ba, Cd, Cu, Fe, Mg, Mn, Ni, Pb, and Si.