denser. Two liters of benzene were added, and the mixture was refluxed until no more water separated.

The flask was then equipped with a mechanical stirrer, reflux condenser, and dropping funnel. Dry pyridine (200 ml.) was added, followed by dropwise addition of 342 g. (1.8 mole) of chrysanthemumic acid chloride. After the mixture had stood overnight, water was added to dissolve the pyridine hydrochloride. The upper benzene layer was washed consecutively with dilute hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution, and then dried with sodium sulfate overnight. The benzene was removed and the residue distilled under high vacuum. A small forerun was obtained and then the main fraction; b.p. 183–200°/1.1 mm., n_D^{25} 1.5496; yield 593 g. (78% based on piperonyl alcohol).

The over-all 4-step synthesis for the chloro derivative was similar to the bromo except that chlorination took place at 50° instead of 15–25°.

6-Chloropiperonyl acetate (VI, X = Cl). Hydrolysis of V (X = Cl) in glacial acetic acid and anhydrous sodium acetate in the usual manner gave VI in 83% yield melting at 84–85°.

Anal. Calcd. for $C_{10}H_9ClO_4$: Cl, 15.48%. Found: Cl, 15.17%.

6-Chloropiperonyl alcohol in 93% yield was prepared from this acetate by sodium hydroxide hydrolysis in methanol; m.p. (from ethanol) 69–70°, mixed melting point with that prepared by reduction of 6-chloropiperonal 69–70.5°.

Anal. Calcd. for $C_8H_7ClO_3$: Cl, 18.84%. Found: Cl, 18.97%.

6-Chloropiperonyl ester of chrysanthemumic acid by transesterification (I, X = Cl). One molar amount of ethyl chrysanthemumate[7] and 6-chloropiperonyl alcohol were heated to 150° in a flask, equipped with a Dean-Starke trap and thermometer. Shortly after addition of 0.25 g. of sodium, ethanol began to distil. When this liberation of ethanol ceased, another 0.25 g. of sodium was added and more alcohol liberated. This procedure was repeated (about eight additions), the temperature being maintained between 150–160°, until the theoretical quantity of ethanol was collected. The mixture was then cooled and dissolved in ether. The solution was washed with dilute hydrochloric acid, saturated sodium bicarbonate, saturated sodium chloride solution, and finally dried over sodium sulfate. After removal of the ether and some forerun of unreacted ethyl chrysanthemumate and 6-chloropiperonyl alcohol, the product distilled; b.p. 155–171°/0.2 mm., n_D^{25} = 1.5375; yield 65%.

BELTSVILLE, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Preparation of Some *N*-Substituted Phenothiazines in Tetrahydrofuran

HENRY GILMAN AND RALPH O. RANCK

Received January 15, 1958

Tetrahydrofuran was found to be an excellent solvent for the preparation of some *N*-substituted phenothiazine derivatives. 10-(*n*-Decyl)phenothiazine, 10-(*n*-octadecyl)phenothiazine, and 10-(*o*-bromobenzyl)phenothiazine were prepared in high yields using this technique. The sulfoxides and sulfones of 10-(*n*-decyl)phenothiazine and 10-(*n*-octadecyl)phenothiazine were also prepared in very good yields.

N-Substitutions of phenothiazine can be accomplished by a number of techniques. These include the sealed tube reaction such as was used for the preparation of 10-phenothiazinecarbonyl chloride using a mixture of phenothiazine and phosgene in toluene;[1–3] reactions between phenothiazine and a halogen compound in a solvent such as toluene or xylene using a basic condensing agent (*e.g.*, sodium carbonate or sodium hydroxide) and a copper powder catalyst as in the preparation of 10-(*p*-methoxyphenyl)phenothiazine from phenothiazine, *p*-iodoanisole, potassium carbonate, and copper powder in refluxing xylene;[4] reactions similar to that just described in the absence of solvent as in the preparation of 10-phenylphenothiazine by heating a mixture of iodobenzene, phenothiazine, sodium carbonate, and copper powder;[4] and reactions between 10-sodiophenothiazine and an appropriate halide in anhydrous liquid ammonia as in the preparation of 10-ethylphenothiazine from 10-sodiophenothiazine (prepared from phenothiazine and sodium amide in liquid ammonia) and ethyl bromide.[5,6]

10-(*n*-Decyl)phenothiazine and 10-(*n*-octadecyl)-phenothiazine have both been prepared in low yield (10% and 20%, respectively).[7] In these preparations, a mixture of phenothiazine, sodium carbonate, copper powder, and the appropriate alkyl bromide was heated for 11–12 hr. at 180°. Purification was accomplished by extraction with ether, vacuum distillation of the residue after removal of the ether, and, in the case of the *n*-octadecyl derivative, recrystallization of the distilled material from absolute ethanol.

Champaigne[8] prepared 10-(*n*-decyl)phenothiazine

(1) N. Fraenkel, *Ber.*, **18**, 1843 (1885).
(2) S. Paschkowezky, *Ber.*, **24**, 2905 (1891).
(3) R. Dahlbom, *Acta Chem. Scand.*, **7**, 879 (1953).
(4) H. Gilman, P. R. Van Ess, and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 1214 (1944). For general references on the chemistry of phenothiazine see the excellent article by S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).
(5) H. Gilman, R. D. Nelson, and J. F. Champaigne, Jr., *J.Am. Chem. Soc.*, **74**, 4205 (1952).
(6) H. Gilman, R. K. Ingham, J. F. Champaigne, Jr., J. W. Diehl, and R. O. Ranck, *J. Org. Chem.*, **19**, 560 (1954).
(7) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 888 (1944).
(8) J. F. Champaigne, Jr., M.S. thesis, Iowa State College (1952).

in a high crude yield (86.7%) using the liquid ammonia procedure. However, he was unable to get this in a pure form, the product being contaminated with phenothiazine and an unidentified red component even after attempted chromatographic purification (using benzene as the solvent and eluent on a column of activated alumina) and distillation of the chromatographed material. Champaigne[8] also attempted the preparation of the 10-*n*-octadecyl derivative by the addition of either a toluene or xylene solution of *n*-octadecyl bromide to a mixture of 10-sodiophenothiazine in liquid ammonia. This work was unsuccessful.

In the work reported herein, both 10-(*n*-decyl)-phenothiazine and 10-(*n*-octadecyl)phenothiazine were prepared successfully by several techniques. Using the liquid ammonia procedure, 10-(*n*-decyl)-phenothiazine was prepared pure in yields between 60 and 80%. The procedure used was similar to that described by Champaigne[8] except that a greater concentration (five to ten times as great) of 10-sodiophenothiazine in ammonia was used, and petroleum ether (b.p. 60–70°) was substituted for benzene in the chromatographic purification. The chromatographed material was also vacuum-distilled to give a product free of phenothiazine and the red component.

Experiments utilizing ether as a solvent for the *n*-decyl bromide and liquid ammonia as a solvent or carrier for the 10-sodiophenothiazine showed no outstanding advantage over the above technique except, perhaps, a slight advantage in yield of the final product. The same purification procedure [chromatography using petroleum ether (b.p. 60–70°) as the solvent and eluent followed by vacuum distillation] was used here.

A definite advantage was indicated by the use of tetrahydrofuran alone as a solvent for this reaction. Using this technique, a tetrahydrofuran solution of *n*-decyl bromide was added to a solution of 10-sodiophenothiazine in tetrahydrofuran to give an 87% yield of pure product. The purification required only simple vacuum distillation of the crude product.

10-(*n*-Octadecyl)phenothiazine was also prepared successfully by several techniques. Using the liquid ammonia procedure and adding molten *n*-octadecyl bromide under conditions of high concentration a 17% crude yield or 12.9% pure yield of product was obtained. Variations of this procedure, which are described under Experimental, gave lower yields of product.

The use of various solvents for the *n*-octadecyl bromide and addition of these solutions to 10-sodiophenothiazine in liquid ammonia enabled yields of product ranging between 40 and 50%. Solvents used were ether, ethylene glycol dimethyl ether, and tetrahydrofuran. When pentane was used as a solvent for the halogen compound, a yield of less than 5% was obtained. In this series of experiments, the order of addition did not seem to be critical.

When the tetrahydrofuran procedure was used, a yield of 91% of pure 10-(*n*-octadecyl)phenothiazine was obtained. The use of ether in place of tetrahydrofuran was not adequate, a lower yield (estimated) being obtained.

Since tetrahydrofuran had been so successful in the above alkylations, it was investigated for the preparation of other *N*-substituted phenothiazine derivatives. 10-Phenylphenothiazine failed to form either at room temperature or in refluxing tetrahydrofuran when iodobenzene was used. Even when the halogen was activated by a nitro group, as in *o*- and *p*-iodonitrobenzene, no product was obtained. No 10-(2-pyridyl)- or 10-(2-quinolyl)phenothiazine formed in tetrahydrofuran when using 2-bromopyridine and 2-chloroquinoline, respectively. Compounds having a very reactive halogen such as triphenylmethyl chloride, *o*-bromobenzyl chloride, and *p*-nitrobenzyl bromide were also investigated. The *o*-bromobenzyl chloride gave a high crude yield of 10-(*o*-bromobenzyl)phenothiazine, but the material was very difficult to purify. The triphenylmethyl chloride gave an unidentified product while the *p*-nitrobenzyl bromide gave a product tentatively indentified as *p,p'*-dinitrobibenzyl.

Tetrahydrofuran was selected as a solvent for the *N*-alkylations and attempted *N*-arylations because of its higher polarity (1.68 Debye units)[9] compared to ether (1.22 Debye units).[10] In the mixed solvent systems, ether-ammonia has shown a definite advantage over such combinations as pentane-ammonia, toluene-ammonia,[8] and xylene-ammonia.[8] These hydrocarbon solvents are much lower in polarity than ether, ranging from zero Debye units for pentane[11] to 0.1 to 0.58 Debye units for xylene.[12] The tetrahydrofuran did not show any advantage over ether in the mixed solvent technique but did show a decided advantage over ether when used as a solvent for both the 10-sodiophenothiazine and the halogen compound in the preparation of 10-(*n*-octadecyl)phenothiazine. This could possibly be attributed to the higher polarity of tetrahydrofuran over ether, but since compounds such as *o*-iodo- and *p*-iodonitrobenzene failed to react with 10-sodiophenothiazine it is believed that this solvent has little effect on the leaving group or at least not appreciably more than ether itself.

(9) L. G. Wesson, *Tables of Electric Dipole Moments*, The Technology Press, Massachusetts Institute of Technology, Cambridge, Mass., 1949, p. 21.

(10) L. G. Wesson, *Tables of Electric Dipole Moment*, The Technology Press, Massachusetts Institute of Technology, p. 22.

(11) L. G. Wesson, *Tables of Electric Dipole Moments*, The Technology Press, Massachusetts Institute of Technolcgy, p. 25.

(12) L. G. Wesson, *Tables of Electric Dipole Moments*, The Technology Press, Massachusetts Institute of Technology, p. 40.

The success of tetrahydrofuran in the preparation of 10-(*n*-decyl)-phenothiazine and 10-(*n*-octadecyl)-phenothiazine has been attributed partially to the increased solubility of 10-sodiophenothiazine and the halogen compound in this solvent as compared to ammonia, pentane, xylene, toluene, and ether. Both *n*-decyl bromide and *n*-octadecyl bromide are solid in liquid ammonia. If they were liquid in liquid ammonia they would probably give nearly quantitative yields of their corresponding phenothiazine derivatives since their reactivity is comparable to that of ethyl bromide.[13] Ethyl bromide remains liquid in liquid ammonia, or may dissolve to some extent, and gives a quantitative yield of 10-ethylphenothiazine.[5,6] When using molten undiluted *n*-decyl bromide or *n*-octadecyl bromide most of the reaction in liquid ammonia must occur before the halogen compound solidifies. This is supported by those experiments involving the preparation of 10-(*n*-octadecyl)phenothiazine in which both molten and finely ground *n*-octadecyl bromide were used. The first of these gave a 17% crude yield and the latter, less than 5% crude yield.

Both the 10-(*n*-decyl)phenothiazine and 10-(*n*-octadecyl)phenothiazine were oxidized to the monoxides and dioxides. These oxidations were accomplished by well known procedures, the monoxides being formed by oxidation with 30% hydrogen peroxide in refluxing ethanol and the dioxides by treatment with 30% hydrogen peroxide in warm (80°), glacial acetic acid. The preparation 10-(*n*-octadecyl)phenothiazine-5-oxide in 53% yield using hydrogen peroxide in ethanol has been reported previously.[7] The use of a greater concentration of unoxidized product in absolute ethanol and an extension of the reaction time in the work reported here, provided a 96% yield of product. The other oxidized compounds, 10-(*n*-decyl)phenothiazine-5-oxide and -5,5-dioxide, and 10-(*n*-octadecyl)phenothiazine 5,5-dioxide, have not been reported previously. In the preparation of 10-(*n*-decyl)phenothiazine-5-oxide, the use of a higher concentration of unoxidized compound and hydrogen peroxide also proved advantageous.

10-(*n*-Decyl)phenothiazine-4-carboxylic acid was prepared by the reductive metalation of 10-(*n*-decyl)phenothiazine-5-oxide with *n*-butyllithium followed by carbonation and hydrolysis. A similar procedure has been described for the preparation of 10-ethylphenothiazine-4-carboxylic acid from 10-ethylphenothiazine-5-oxide.[6] The 10-(*n*-decyl) derivative was obtained in a lower yield than was reported for 10-ethylphenothiazine-4-carboxylic acid.

(13) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 316.

EXPERIMENTAL[14]

10-(n-Decyl)phenothiazine. (*a*) *In anhydrous liquid ammonia.* Two and six-tenths grams (0.11 g.-atom) of sodium was added to 150 ml. of anhydrous liquid ammonia contained in a flask equipped with a Dewar-type Dry Ice condenser. Immediately after the first few pieces of sodium were added, a crystal of ferric nitrate was introduced as a catalyst. Stirring was continued for approximately 1 hr. or until the gray color of the sodium amide was very evident. Twenty grams (0.1 mole) of phenothiazine was then added and stirring was continued for another hour during which time the color of the reaction became orange-yellow. Thirty-three grams (0.15 mole) of *n*-decyl bromide was added and stirring was continued for 6 hr. The ammonia was evaporated and the residue was extracted with petroleum ether (b.p. 60–70°). This extract was chromatographed on a column of activated alumina, the column being eluated with additional petroleum ether (b.p. 60–70°). The solvent was stripped from the eluate and the material which remained was vacuum distilled to give 28.5 g. (84%) of a yellow oil boiling at 175–180° (0.5 mm.). The reported boiling point for this compound is 183–185° (0.5 mm.).

Other similar experiments in which the concentration of 10-sodiophenothiazine was varied (0.1 mole in 100 ml. to 200 ml. of liquid ammonia) gave yields ranging from 60–80%.

The use of high speed agitation showed no advantages.

(*b*) *Using ether as a solvent for the halogen compound.* One-tenth mole of 10-sodiophenothiazine in 150 ml. of liquid ammonia was prepared as in the experiment above. A solution of 33 g. (0.15 mole) of *n*-decyl bromide in 100 ml. of ether was added and agitation was continued for 6 hr. The solvents were then evaporated and the residue was extracted with petroleum ether (b.p. 60–70°). This extract was chromatographed on a column of activated alumina and the column was eluted with additional petroleum ether (b.p. 60–70°). The solvent was stripped from the eluate and the remaining material was vacuum-distilled to give 28.5 g. (84%) of pure product boiling at 175–180° (0.5 mm.).

Using this same procedure but with high speed agitation, and shorter reaction times, (1, 2, and 3 hr.) yields of about 75% were obtained.

(*c*) *Using tetrahydrofuran.*[15] One-tenth mole of 10-sodiophenothiazine was prepared in 150 ml. of liquid ammonia by the procedure described in part (*a*) of this section. One hundred and fifty milliliters of tetrahydrofuran was then added and the ammonia was permitted to evaporate. Before all of the ammonia had escaped, the contents were placed under an atmosphere of nitrogen and kept this way until the reaction was complete. A solution of 33 g. (0.1 mole) of *n*-decyl bromide in 150 ml. of tetrahydrofuran was added over a period of 15–20 min. and stirring was continued at room temperature for 12 hr. The tetrahydrofuran was removed by distillation and the remaining residue was extracted with benzene. This was filtered, the benzene was distilled from the filtrate, and the oily compound which remained was subjected to vacuum distillation. Twenty-nine and one-half grams (86.5%) of material boiling at 175–180° (0.5 mm.), n_D^{25} 1.5853, d_{25}^{25} 1.0442 was obtained.

Anal. Calcd. for $C_{22}H_{29}NS$: MR_D, 110.84. Found: MR_D, 111.57.

10-(n-Octadecyl)phenothiazine. (*a*) *In liquid ammonia.* One-tenth mole of 10-sodiophenothiazine was prepared in the usual manner by the addition of 20 g. (0.1 mole) of phenothiazine to 0.11 mole of sodium amide (prepared from 2.6 g. of sodium using a ferric nitrate catalyst) in 150 ml. of liquid ammonia. Fifty grams (0.15 mole) of molten *n*-

(14) All melting points reported herein are uncorrected.

(15) The tetrahydrofuran which was used in these experiments was Eastman Kodak Co. White Label. This was dried and further purified by refluxing over sodium for several hours and then distilling just prior to use.

octadecyl bromide was added and stirring with a high-speed counter-rotating agitator was continued for 3 hr. The ammonia was evaporated and the residue was extracted with petroleum ether (b.p. 60–70°). This extract was filtered and then chromatographed on a column of activated alumina, the column being eluted with additional petroleum ether (b.p. 60–70°). Evaporation of the solvent from the eluate left 7.5 g. (17%) of crude material melting at 42–44°. Recrystallization of this from an ethanol-water system gave 5.8 g. (12.9%) of white material having a melting point of 52–52.5° and which showed no depression in melting point when mixed with an authentic sample (53°).[7]

A few variations, which gave lower yields, were made in this procedure. These included the addition of 10-sodiophenothiazine in liquid ammonia to a dispersion of *n*-octadecyl bromide in liquid ammonia (5% crude yield), 10-sodiophenothiazine in liquid ammonia added to molten (40–50°) *n*-octadecyl bromide (10% crude yield), and ground (28 mesh) *n*-octadecyl bromide added to 10-sodiophenothiazine in liquid ammonia (5% crude yield).

(*b*) *Using various solvents for the halogen compound.* One-tenth mole of 10-sodiophenothiazine was prepared as above in 150 ml. of liquid ammonia. A solution of 50 g. (0.15 mole) of *n*-octadecyl bromide in 150 ml. of ether was added and stirring was continued for 7 hr. A four-bladed propeller-type agitator run at about 1200 r.p.m. was used for this. Evaporation of the solvents left 25 g. (55%) of crude material which on recrystallization from an ethanol-water system gave 11.5 g. (25%) of material melting at 42–43°.

When 100 ml. of liquid ammonia was used for the 10-sodiophenothiazine and 200 ml. of ether for the halogen compound, 32.8 g. (72.5%) of crude material melting at 40–43° was obtained. Recrystallization of this from an ethanol-water system gave a 40% yield of pure material melting at 53°. When an inverse addition was employed with these same amounts of material, a 53% yield of white product melting at 53.5° resulted. A higher ratio of ether to ammonia offered no advantages.

When the ammonia-10-sodiophenothiazine mixture was added to an *n*-pentane solution of *n*-octadecyl bromide a 6% crude yield of product was obtained. Using this inverse addition with tetrahydrofuran as a solvent for the halogen compound, a 36% yield of pure material was obtained and with ethylene glycol dimethyl ether, again with the inverse addition, a 49% yield of pure material resulted. When normal addition was made using ethylene glycol dimethyl ether as a solvent for the halogen compound, a 54% yield of material melting at 53–54° was produced.

(*c*) *Using tetrahydrofuran.* One-tenth mole of 10-sodiophenothiazine was prepared in 150 ml. of liquid ammonia using the procedure described in part (*a*) of this section. One hundred and fifty milliliters of tetrahydrofuran was added and the ammonia was permitted to evaporate. Before all of the ammonia had escaped, the contents of the flask were placed under an atmosphere of nitrogen. When the reaction mass had warmed to room temperature, a solution of 50 g. (0.15 mole) of *n*-octadecyl bromide in 150 ml. of tetrahydrofuran was added over a period of 2 hr. and stirring was continued for 32 hr., the temperature being maintained at 20–25°. The tetrahydrofuran was removed by distillation and the residue was extracted with benzene. This extract was filtered and the benzene was stripped from the filtrate. The excess *n*-octadecyl bromide was removed by vacuum distillation. The remaining undistilled portion weighed 47 g. and had a melting point of 44–45°. Recrystallization of this from an ethanol-water system gave 40.5 g. (90%) of white material having a melting point of 53–54°. A repeat of this experiment gave the same results.

Refluxing the tetrahydrofuran solution of the reactants showed no advantages.

When ether was substituted for tetrahydrofuran as a solvent for both the halogen compound and the sodiophenothiazine a much cruder product was formed. This was not purified, but it is estimated that the amount of pure product which would have formed would have been between 50–60%.

10-(o-Bromobenzyl)phenothiazine. One-tenth mole of 10-sodiophenothiazine was prepared by adding 20 g. (0.1 mole) of phenothiazine to 0.11 mole of sodium amide (prepared from 2.6 g. of sodium using a ferric nitrate catalyst) in 100 ml. of liquid ammonia. One hundred and fifty milliliters of tetrahydrofuran was added and the ammonia was permitted to evaporate. Before all of the ammonia had escaped, the contents of the flask were put under an atmosphere of nitrogen. A solution of 27 g. (0.132 mole) of *o*-bromobenzyl chloride in 150 ml. of tetrahydrofuran was added to the 10-sodiophenothiazine at room temperature over a period of 15 min. and stirring was continued for a period of 6 hr. at this same temperature. The reaction mass was filtered and the solvent removed by distillation. Thirty-six grams of a brown viscous oil remained.

Attempted chromatographic purification by passing a benzene solution of the crude material through a column of activated alumina, elution with benzene and evaporation of the solvent from the eluate left a viscous oil which failed to solidify. Recrystallization of a portion of this from an ethanol-water system gave material having a melting point range of 91–93° but the crystal formation was poor.

Further purification of the chromatographed material by vacuum distillation was also inadequate since a large portion of the material tended to pyrolyze. Material boiling at 190–200° (0.005 mm.) was collected. This was also resinous in nature and crystallized with difficulty from an ethanol-water system. Two recrystallizations from this solvent system gave a white product melting at 90–92°. The infrared spectrum showed an absorption band characteristic of *ortho* disubstitution and had no absorption band in the region characteristic of N–H.

Anal. Calcd. for $C_{19}H_{15}BrNS$: S, 8.71. Found: S, 8.99, 9.01.

A sulfur analysis was also run on some of the chromatographed material to determine how its quality compared to the recrystallized material. The analysis was quite marginal but it did indicate that it was the desired material. This quality material was produced in 88% yield.

Anal. Calcd. for $C_{19}H_{15}BrNS$: S, 8.71. Found: S, 9.20, 9.34.

10-(n-Decyl)phenothiazine-5-oxide. Ten grams (0.0295 mole) of 10-(*n*-decyl)phenothiazine was dissolved in 600 ml. of refluxing absolute ethanol. Twenty-five milliliters (0.24 mole) of 30% hydrogen peroxide was added and stirring was continued at reflux for 6 hr. Three hundred and fifty milliliters of the solution was removed by distillation and the remainder was poured into 1250 ml. of water previously heated to 75°. After refrigeration, 10.1 g. (93%) of material crystallized from the solution. This was recrystallized from an ethanol-water system to give 9.2 g. (90%) of white material melting at 97–98°. Another recrystallization from this same solvent system failed to increase the melting point.

The infrared spectrum showed the characteristic sulfoxide absorption band.

Anal. Calcd. for $C_{22}H_{29}NOS$: S, 9.02. Found: S, 8.87, 9.00.

In another experiment in which a greater concentration of reactants was employed (102 g. of 10-(*n*-decyl)phenothiazine in 2250 ml. of absolute ethanol oxidized with 93 ml. of 30% hydrogen peroxide followed by removal of 1500 ml. of solvent and pouring into 3700 ml. of water previously heated to 75°) 99 g. (93%) of material melting at 97–98° and 5 g. (5%) of material melting at 91–92° were obtained, this last portion after concentration of the filtrate.

10-(n-Octadecyl)phenothiazine-5-oxide. Ninety grams (0.2 mole) of 10-(*n*-octadecyl)phenothiazine was dissolved in 2000 ml. of refluxing absolute ethanol. Sixty milliliters (0.59 mole) of 30% hydrogen peroxide was added and stirring was continued at reflux for 5 hr. Fifteen hundred milliliters of the solvent was removed by distillation and the remaining undistilled portion was poured into 2500 ml. of water previously heated to 80°. Upon cooling to room temperature,

92 g. (98%) of cream colored material having a melting point range of 90–95° separated. Recrystallization of this from an ethanol-water system gave 90 g. (96%) of material melting at 95–96°. Additional recrystallizations failed to raise the melting point further. A mixture melting point with an authentic specimen (98°)[7] showed no depression. A 53% yield of this material made by a somewhat similar procedure has been reported.[7]

10-(n-Decyl)phenothiazine-5,5-dioxide. Seventeen grams (0.05 mole) of 10-(*n*-decyl)phenothiazine was dissolved in 290 ml. of glacial acetic acid at 70°. Sixteen milliliters (0.154 mole) of 30% hydrogen peroxide was added causing the formation of a deep red color. Stirring was continued for 1.5 hr. at 80° after which an additional 5 ml. (0.048 mole) of 30% hydrogen peroxide was added. This caused no apparent change in the reaction. One hundred and ninety milliliters of the solvent was removed by distillation. Upon cooling, 13.5 g. (73%) of pink-brown material having a melting point of 93–95.5° separated. Recrystallization of this from an ethanol-water system produced 12.1 g. (67%) of tan material having a melting point of 95.5–96.5°. Additional recrystallization did not raise the melting point.

The infrared spectrum showed the characteristic sulfone absorption bands.

Anal. Calcd. for $C_{22}H_{29}NO_2S$: S, 8.65. Found: S, 8.49, 8.50.

An additional 4.7 g. of a brown semisolid material was recovered by dilution of the acetic acid filtrate from the reaction mixture with water. No effort was made to purify this.

10-(n-Octadecyl)phenothiazine-5,5-dioxide. Twenty-two and one-half grams (0.05 mole) of 10-(*n*-octadecyl)phenothiazine was dissolved in 300 ml. of glacial acetic acid at 80°. Fifteen milliliters (0.147 mole) of 30% hydrogen peroxide was added and the reaction was stirred for 1.5 hr., the temperature being maintained at 80°. An additional 10 ml. (0.098 mole) of 30% hydrogen peroxide was added, causing no change in the reaction. Upon cooling to room temperature, 22 g. (91.5%) of cream colored material melting at 93–93.5° separated. Recrystallization of this from absolute ethanol failed to increase the melting point. The infrared spectrum showed an absorption band characteristic of a sulfone.

Anal. Calcd. for $C_{30}H_{45}NO_2S$: S, 6.63. Found: S, 6.64, 6.71.

10-(n-Decyl)phenothiazine-4-carboxylic acid. Seventeen and one-quarter grams (0.05 mole) of 10-(*n*-decyl)phenothiazine-5-oxide was suspended in 250 ml. of anhydrous ether under an atmosphere of nitrogen. The suspension was cooled to −20° by means of a Dry Ice–acetone bath and 0.05 mole of *n*-butyllithium[16] in 45 ml. of ether was added at such a rate as to maintain the temperature at −20°. After stirring for 2 hr. at −20° another 0.1 mole of *n*-butyllithium in 90 ml. of ether was added and the mixture was permitted to warm to 0° where it was maintained for 4 hr. The reaction mass was then poured jet-wise into an agitated Dry Ice-ether slurry. After this mixture had warmed to room temperature, the ether was extracted with 100 ml. (0.262 mole) of 10% sodium hydroxide in several portions. Acidification of the basic extract with hydrochloric acid caused the separation of a yellow oil which gradually solidified on standing. This weighed 7 g. (36%) and had a melting point of 124–125°. Recrystallization of this from glacial acetic acid gave 6.2 g. (32%) of bright yellow material melting at 128–129°. Additional recrystallizations failed to increase the melting point. The infrared spectrum showed characteristic absorptions bands for the carbonyl group and 1,2,3 trisubstitution.

Anal. Calcd. for $C_{23}H_{29}NO_2S$: S, 8.36. Found: S, 8.21, 8.33.

The sodium salt of this compound was prepared by adding an excess of 10-(*n*-decyl)phenothiazine-4-carboxylic acid to a solution of dilute sodium hydroxide. When the maximum amount of material had dissolved, the solution was filtered and the filtrate was allowed to evaporate slowly. Yellow plate-like crystals having a melting point of 253–254° formed. A flame test indicated the presence of sodium.

Acknowledgment. We wish to thank Mr. E. Miller Layton, Jr., of the Ames Laboratory of the Institute for Atomic Research for the determination of the infrared spectra.

AMES, IOWA

(16) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

A New Synthesis of 10-(3-Dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine Hydrochloride[1] and 7-Substituted Derivatives[2]

K. FLOREY AND A. R. RESTIVO

Received January 27, 1958

The zinc salt of 2-amino-4-(trifluoromethyl)benzenethiol reacted with 2,4-dinitrochlorobenzene to give 2-amino-4-(trifluoromethyl)-2′,4′-dinitrodiphenylsulfide. The formamido derivative of the latter was cyclized *via* the Smiles Rearrangement to 7-nitro-2-(trifluoromethyl)phenothiazine. By alkylation with dimethylaminopropyl chloride, 10-(3-dimethylaminopropyl)-7-nitro-2-(trifluoromethyl)phenothiazine was obtained. Reduction to the 7-amino analog and reductive deamination *via* the diazonium compound led to 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine in 35% over-all yield. The diazotization of aminophenothiazines is discussed.

The current interest in 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine (VIII) as an ataractic agent[3] prompted us to seek new synthetic approaches to this compound.

VIII has been synthesized in two laboratories[4,5] by alkylation of 2-(trifluoromethyl)phenothiazine (V). V had been prepared by Smith[6] by thionation of 3-(trifluoromethyl)diphenylamine which led to

(1) The Olin Mathieson Chemical Corp. trademark of this compound is VESPRIN.

(2) Presented at the 132nd Meeting of the American Chemical Society, New York, September 1957.