[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

The Preparation of Some Derivatives of β-(10-Phenothiazinyl)propionic Acid and β-(2-Chloro-10-phenothiazinyl)propionic Acid

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Received May 11, 1956

A number of derivatives of β-(10-phenothiazinyl)propionic acid and β-(2-chloro-10-phenothiazinyl)propionic acid have been prepared for pharmacological screening.

The increased importance of medicinal agents containing the phenothiazine nucleus such as Phenergan and Chloropromazine, active in allergic and psychiatric conditions, has suggested the preparation of additional phenothiazine derivatives. Thus Dahlbom and Willman[1] have prepared dialkylaminoalkyl esters, thioesters, and amides of β-(10-phenothiazinyl)propionic acid and found them to possess weak cholinergic and anti-histaminic activity. This paper describes the preparation of additional derivatives of this acid and related compounds, including those derived from 2-chlorophenothiazine. The suffix "a" after the Roman numerals in this article will refer to derivatives belonging to the "chloro series."

The intermediates, β-(10-phenothiazinyl)propionitrile (I) and β-(2-chloro-10-phenothiazinyl)propionitrile (Ia) required for this work were prepared in good yields by the addition of phenothiazine and 2-chlorophenothiazine to acrylonitrile using essentially the procedure of Smith.[2] The alkaline hydrolysis of the nitrile I to the corresponding acid, however, was not completely satisfactory, since it was accompanied to a considerable extent (20% or more) by the de-cyanoethylation reaction. A more suitable method which was used in the preparation of β-(2-chloro-10-phenothiazinyl)propionic acid consisted of the conversion of nitrile Ia to the methyl ester in 90% yield; a mild alkaline hydrolysis afforded the acid in essentially quantitative yield.

The reaction of β-(10-phenothiazinyl)propionitrile (I) with absolute alcoholic hydrogen chloride gave the iminoether hydrochloride VII. The insolubility of I at the low temperatures required for this conversion necessitated the use of more than one equivalent of alcohol as well as a large amount of dioxane and hydrogen chloride, coupled with a reaction time of several weeks. Under these conditions a 33% yield of VII could be obtained. Complete purification of this salt proved to be impractical and it was further characterized by conversion to the corresponding ethyl ester upon treatment with water, to the amidine VIII by the action of ammonia, and to the imidazoline IX by the reaction with ethylenediamine. It was not found possible to obtain the iminoether hydrochloride of β-(2-chloro-10-phenothiazinyl)propionitrile employing the conditions cited above, or by variations thereof, the main reaction product (56%) being the ethyl ester. By the use of methyl alcohol at higher temperatures the yield of methyl β-(2-chloro-10-phenothiazinyl)-propionate (IIa) could be increased to 85–90%. The inaccessibility of the iminoether VIIa and a desire to obtain imidazoline IXa prompted attempts to obtain the latter by alternative routes. However, the reactions of Ia, IIa, or IIIa with ethylene diamine, its hydrochloride or tosylate were found to be unsuccessful.

The reduction of nitriles I and Ia with lithium aluminum hydride (LAH) proceeded smoothly to yield the corresponding propyl amines IV and IVa. These amines then were cyanoethylated again.

In the case of 10-(3-aminopropyl)phenothiazine this reaction gave the bis-cyanoethylated product V, whereas with chloro-analog IVa the reaction halted after the introduction of only one cyanoethyl group to give Va. This nitrile was readily hydrolyzed to acid VIa.

The ester function in III was found to be remarkably inert. For example, whereas the reaction of III with hydrazine gave β-(10-phenothiazinyl)propionic acid hydrazide (X) after two hours of heating, the reaction with methyl hydrazine required at least 12 hours of heating, and the reaction of *unsym*-dimethylhydrazine failed even in a sealed vessel at 100° for 18 hours. Similarly attempted ammonolysis of the ester did not give the amide. The reaction of II with LAH proceeded to give 3-(10-phenothiazinyl)-1-propanol (XI); this compound had been previously prepared by Dahlbom[3] in comparable yields by reduction of the acid with LAH. Alcohol XI was further characterized by conversion to a phenylurethan.

Hydrazide X, upon treatment with 2-pyridinealdehyde gave hydrazone XII. Methyl isothiocyanate reacted with X to yield the thiosemicarbazide XIII which cyclized upon heating in the expected manner to give the mercaptotriazine XIV.

The inertness of ester II prompted us to reinvestigate the feasibility of preparing β-(10-phenothiazinyl)propionyl chloride, bearing in mind the instability of the phenothiazine nucleus towards the

(1) Dahlbom and Willman, *Acta Chem. Scand.*, **8**, 1952 (1954).

(2) N. L. Smith, *J. Org. Chem.*, **15**, 1129 (1950).

(3) R. Dahlbom, *Acta Chem. Scand.*, **6**, 310 (1952).

acidic reagents employed in preparation of acid chlorides. Thus, Burger[4] upon reacting 2-phenothiazinylcarboxylic acid with thionyl chloride followed by ammonolysis, obtained a tetrachloro-phenothiazinylcarboxamide. Furthermore, Mackie and Misra[5] observed that the treatment of β-(10-phenothiazinyl)propionic acid with either thionyl chloride or phosphorus oxychloride gave only intractable tars. A recent English patent[6] claims the conversion of β-(2-chloro-10-phenothiazinyl)propionic acid to the acid chloride by means of phosphorus pentachloride and phosphorus oxychloride at 50°. However, the acid chloride was not isolated and was converted *in situ* to various amides. Subsequent to the completion of this work Dahlbom and Willman[1] reported the conversion of the acid to the acid chloride by means of thionyl chloride and pyridine.

We have found that these acid chlorides can be prepared conveniently in two ways. First, when the sodium salt of III was added slowly to a solution of oxalyl chloride in ether the acid chloride could be obtained. However, this method left much to be desired particularly in view of erratic yields and variable quality of the product. Various analyses (infrared spectra, halogen analysis, estimation as amide) indicated a purity of 50–70%, the impurity consisting of unreacted acid. By the nature of amide formation this impurity was not found to be objectionable in the reaction with amines.

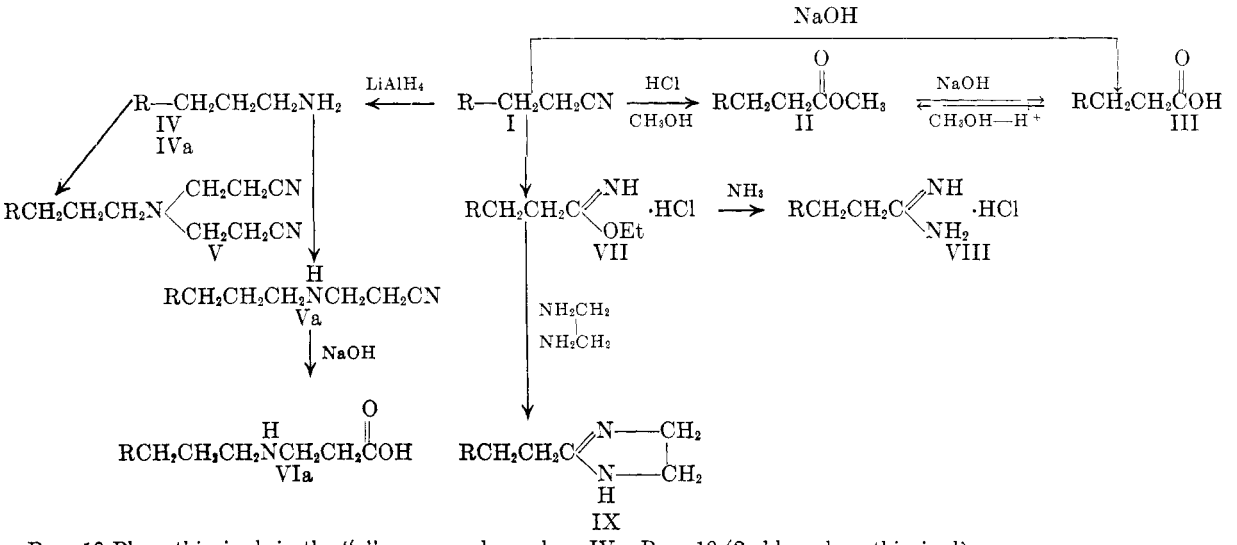
A second, more adaptable method was developed by allowing a benzene solution of phosphorus pentachloride to react with an ice-cold benzene slurry of the acid III. This result in excellent and reproducible yields of β-(10-phenothiazinyl)propionyl chloride (XV), which proved to be nearly analytically pure after one recrystallization from the system ether-benzene-ligroin. The compound was found to be relatively unstable but could be temporarily stored in the absence of moisture. Prolonged standing was found to result in the evolution of hydrogen chloride.

The acid chloride XV was further characterized by conversion to amides and hydrazides upon reaction with ammonia, dimethylamine, and *unsym*-dimethylhydrazine. In addition, a crystalline diazoketone was obtained by the treatment with diazomethane. The treatment of the acid chloride with dimethylaminoethanol gave the normal ester hydrochloride XVIII.

As was to be expected, XV exhibited a pronounced tendency to undergo ring closure to give 3-keto-2,3-dihydro-1-pyrido[3,2,1-*ll*]phenothiazine (XVI), previously reported by Smith.[2] This compound could be prepared by the action of stannic chloride or (unexpectedly) dimethylcadmium on XV. The latter, initially intended as a method to convert the acid chloride to the corresponding open-chained ketone, proved to be an excellent synthetic procedure for the preparation of XVI. Attempts to effect ring closure of acid III, other than the previously reported use of phosphorus pentoxide,[2] proved unsuccessful. Only the action of warm sulfuric acid resulted in cyclization but this was concomitant with the introduction of a sulfonic acid group into the nucleus.

In addition, the keto group of XVI was found to be readily reducible to the alcohol by means of LAH; a similar reduction of the ketone oxime yielded the corresponding amine.

CHART I



R = 10-Phenothiazinyl; in the "a" compounds, such as IVa, R = 10-(2-chlorophenothiazinyl).

(4) A. Burger and J. B. Clements, *J. Org. Chem.*, 19, 1113 (1954).
(5) A. Mackie and A. Misra, *J. Chem. Soc.*, 1281 (1955).
(6) British Patent 732,488 (June 22, 1955).

CHART II

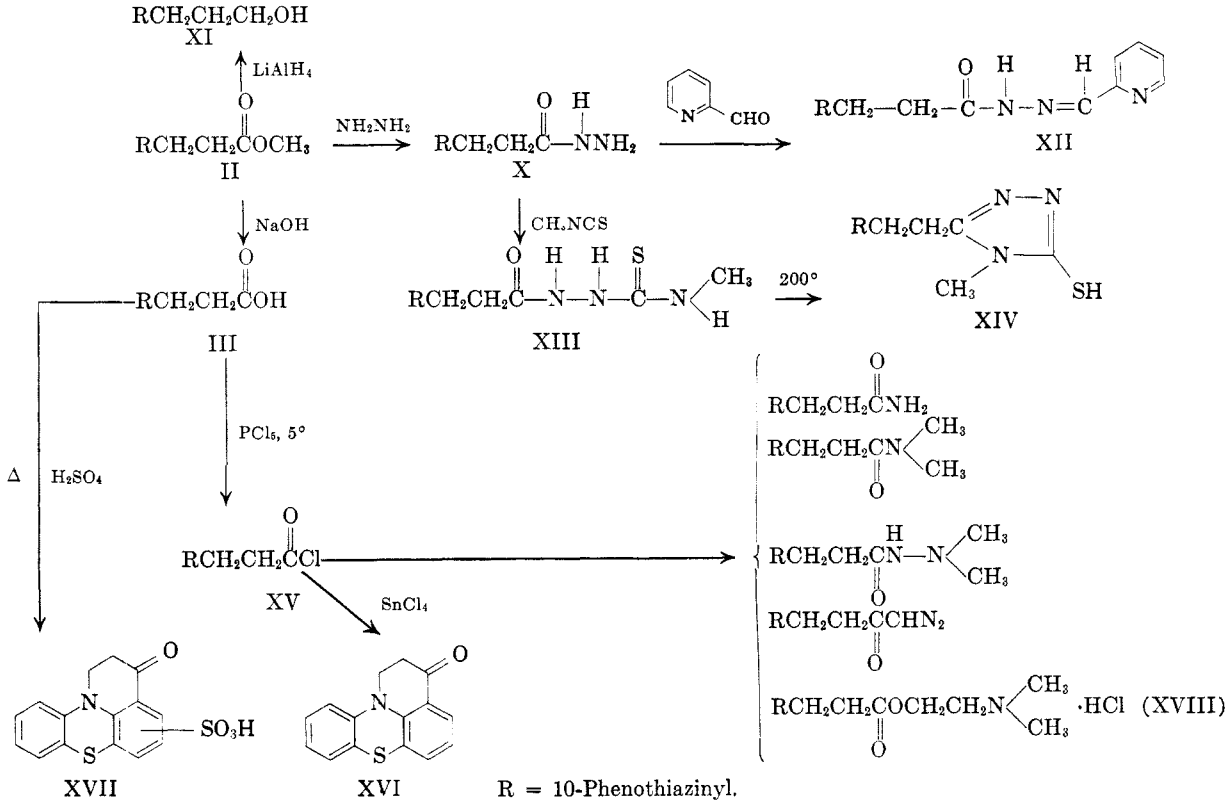
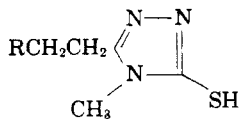


TABLE I

R = 10-(2-CHLOROPHENOTHIAZINYL)-

	Compound	M.p., °C.	Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
IVa	$RCH_2CH_2CH_2NH_2 \cdot HCl$	235–237	55.05	55.23	4.93	5.09
XIIIa	$RCH_2CH_2C(=O)NHNHC(=S)NHCH_3$	*ca.* 105	51.96	51.90	4.36	4.56
XIVa		205–206	54.47	54.20	4.03	4.34
XVa	RCH_2CH_2COCl[a]	114–116				
XVIIIa	$RCH_2CH_2COCH_2CH_2N(CH_3)_2 \cdot HCl$	167–168	55.20	55.36	5.37	5.62
	$RCH_2CH_2CONH_2$	147–148	59.11	58.76	4.30	4.47
Xa	$RCH_2CH_2CONHNH_2$	129.5–130	56.36	56.44	4.41	4.07
	$RCH_2CH_2CONHN(CH_3)_2$	156–157	58.69	58.35	5.22	5.29

[a] Calc'd for $C_{15}H_{11}Cl_2NOS$: Cl, 21.87. Found: Cl, 21.30.

EXPERIMENTAL[7]

β-(10-Phenothiazinyl)propionitrile (I). The preparation of this compound was based on the directions given by Smith.[2] A mixture of 798 g. (4.00 moles) of phenothiazine and 1200 ml. of acrylonitrile was cooled to 0–5°. To this was added, with efficient stirring and cooling, 8 ml. of Triton B. After a short induction period a vigorous reaction set in; external cooling and an efficient condenser were essential. When the reaction had subsided the product was taken up in 1200 ml. of dioxane and refluxed for one-half hour. The solution was poured on water and allowed to stand overnight. Filtration of the tan solid followed by washing with ice-cold acetone gave 930 g. of a snow-white product which melted at 156–157°. Yield, 92%.

This reaction can be run with dioxane as a diluent, but unless the dioxane is completely dry and pure the reaction is very difficult to initiate.

β-(10-Phenothiazinyl)propionic acid (III). A suspension of 750 g. (2.96 moles) of β-(10-phenothiazinyl)propionitrile, 4 l. of methyl alcohol, and 450 g. of sodium hydroxide in 1.5 l. of water was refluxed with stirring for 15 hours. The mixture was then poured on 10 l. of ice-water. Acidification with concentrated hydrochloric acid gave a very crude blue-grey product containing 20–30% phenothiazine. The material was suspended in an excess of 2 *N* sodium hydroxide solution, brought to the boil, and filtered while hot. The filtrate was brought to *p*H 3 and the acid was removed by filtration. Final purification was achieved by digesting the acid with 80% alcohol containing a trace of sodium hydrosulfite. This gave 480 g. (60% yield) of off-white material melting at 160–162°. The product was sensitive to direct light and was air-dried rapidly with the aid of an infrared heat lamp.

The *methyl ester* (II), m.p. 64–65°, was readily prepared by either the action of diazomethane on the acid or by direct esterification with methyl alcohol-sulfuric acid.

Anal. Calc'd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30. Found: C, 67.59; H, 5.55.

β-(10-Phenothiazinyl)propionitrile, iminoether, monohydrochloride (VII). A 50-g. portion (0.196 mole) of β-(10-phenothiazinyl)propionitrile was taken up in 750 ml. of sodium-dried dioxane containing 300 ml. of absolute ethyl alcohol. Dry HCl gas was bubbled into the ice-cold, stirred solution until 30 g. had been taken up. The reaction mixture then was refrigerated for 2 days, after which another 32 g. of HCl was run into the ice-cold suspension. After standing in the refrigerator for approximately two weeks the precipitated ammonium chloride was removed by filtration and the filtrate was taken to dryness *in vacuo* at 10–25°. The solid residue was taken up in 100 ml. of absolute alcohol at room temperature. This caused the precipitation of an additional amount of ammonium chloride which was filtered off. When the filtrate was progressively diluted with absolute ether, the product started to precipitate out as pale green crystals melting at 135–137°. The yield of crude product was 22 g. (33%); this contained some ammonium chloride impurities.

A small sample could be further purified by taking it up in alcohol-dioxane. The small amount of ammonium chloride was removed by centrifugation and the iminoether hydrochloride was slowly precipitated with ether. This gave a pale green crystalline product, melting at 134–136°. Attempts to carry purification beyond this point were not entirely successful.

Anal. Calc'd for $C_{17}H_{18}N_2OS \cdot HCl$: C, 60.97; H, 5.72. Found: C, 60.42; H, 5.89.

β-(10-Phenothiazinyl)propionamidine, monohydrochloride, monohydrate (VIII). Ice-cold ethyl alcohol (100 ml.) was saturated with ammonia gas and to it was added 3.35 g. (0.010 mole) of the iminoether hydrochloride described above. More ammonia was passed through the cooled solution for an additional 10 minutes after which time the reaction was allowed to stand at room temperature overnight.

The excess ammonia was removed by gently warming the solution to 60°. The solvent then was removed by vacuum-distillation. This left a residue which upon recrystallization from alcohol-ether melted at 226–228°. The yield of this amidine hydrochloride amounted to 2.6 g.

A small sample was recrystallized from alcohol-ether to give large plates, m.p. 228–230° (dec.). Analytical results indicate the presence of one molecule of water of hydration.

Anal. Calc'd for $C_{15}H_{15}N_2S \cdot HCl \cdot H_2O$: C, 55.63; H, 5.60; N, 12.98. Found: C, 55.63; H, 5.52; N, 13.12.

10-[2-(2-Imidazolin-2-yl)ethyl]phenothiazine (IX). To an ice-cold solution of 1.80 g. (0.0300 mole) of ethylenediamine in 25 ml. of absolute alcohol was added 3.35 g. (0.010 mole) of VII. After keeping the reaction for one hour at ice-bath temperature, the mixture was allowed to come to room temperature and then was warmed for a short time to 60°. The solvent was removed *in vacuo* and to the residue was added 25 ml. of methyl alcohol which in turn was distilled off *in vacuo*. The residual solid was recrystallized from alcohol-petroleum ether to give a product melting at 140–146°. Repeated recrystallizations from this solvent pair afforded 1.3 g. of a purified product melting at 144–146°.

Anal. Calc'd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.23. Found: C, 68.72; H, 5.97; N, 14.27.

A crystalline *hydrochloride* salt could be obtained, which was recrystallized from ether. It melted at 215–217°.

10-(3-Aminopropyl)phenothiazine, monohydrochloride (IV). The nitrile I (25.3 g., 0.100 mole) was placed in a Soxhlet extractor and was extracted into 500 ml. of ether containing 8.0 g. of lithium aluminum hydride (LAH). This required 72 hours after which time the mixture was decomposed by means of successive additions of 8 ml. of water, 6 ml. of 20% sodium hydroxide solution, and 28 ml. of water. The salts were removed by filtration and the amine hydrochloride was isolated by passing gaseous HCl into the ethereal filtrate. This gave 22 g. (75% yield) of product, melting at 226–229°. A small sample recrystallized from alcohol melted at 226–228°.

Anal. Calc'd for $C_{15}H_{16}N_2S \cdot HCl$: C, 61.52; H, 5.85; N, 9.57. Found: C, 61.56; H, 5.86; N, 9.76.

3-[(10-Phenothiazinyl)propylimino]dipropionitrile, monohydrochloride (V). To a solution of 11.8 g. (0.0405 mole) of IV in 25 ml. of dry, peroxide-free dioxane was added 1.7 ml. of Triton B and 6.0 g. (0.113 mole) of acrylonitrile. The mixture was allowed to stand for 3 hours at room temperature and then was warmed to 70° for 10 minutes. After allowing the reaction to cool, another 0.50 g. of acrylonitrile was added and the mixture was again brought to 70° for 10 minutes. Dilution with water brought down a basic oil from which the supernatant liquid was removed by decantation. The oil was taken up in 100 ml. of alcohol containing 4 ml. of concentrated hydrochloric acid. Removal of the solvent *in vacuo* left a solid which after one recrystallization from alcohol melted at 158–160°. A subsequent recrystallization failed to raise the melting point. A 62% yield (10 g.) of product was obtained.

Anal. Calc'd for $C_{21}H_{22}N_4S \cdot HCl$: C, 63.22; H, 5.81; N, 14.05. Found: C, 62.87; H, 6.00; N, 14.42.

3-[3-(2-Chloro-10-phenothiazinyl)propylamino]propionitrile, monohydrochloride (Va). This compound was prepared according to the directions given for V. It was purified by recrystallization from alcohol, m.p. 194–197° (dec.).

Anal. Calc'd for $C_{18}H_{18}ClN_3S \cdot HCl$: C, 56.84; H, 5.04; N, 11.04. Found: C, 56.48; H, 5.67; N, 11.04.

N-[3-(2-Chloro-10-phenothiazinyl)propyl]-β-alanine (VIa). A mixture of 0.500 g. (0.00131 mole) of Va, 5 ml. of alcohol, and 1.5 ml. of 5 *N* sodium hydroxide solution was refluxed for 15 hours. Removal of the solvents *in vacuo* left an oil which was dissolved in 5 ml. of water. The solution was brought to *p*H 7, which caused a viscous oil to come down. Cooling and scratching of this oil caused a partial solidification. The supernatant liquid was decanted and replaced with

(7) The melting points were determined on a Fisher-John block and are reported as read.

fresh water. Attempted filtration of the compound revealed a tendency of the product to revert back to an oil. However, this could be overcome by repeated rubbing in absolute alcohol. Final purification of the compound was effected by recrystallization from 20 ml. of alcohol containing 1 ml. of benzene. This gave 0.321 g. of long, slender needles, melting unreproducibly between 150° and 190° (dec.), depending upon the rate of heating. The product was soluble in both acid and base.

Anal. Calc'd for $C_{18}H_{19}ClN_2O_2S$: C, 59.58; H, 5.28. Found: C, 59.78; H, 5.67.

3-(10-Phenothiazinyl)-1-propanol (XI). A solution of 133 g. (0.467 mole) of methyl phenothiazinepropionate (II) in 300 ml. of ether was added dropwise to 1500 ml. of ether containing 40 g. of LAH. Decomposition of the complex as in IVa (*vide infra*) followed by filtration and stripping of the solvent left an oil. Vacuum distillation of this residue gave 70 g. (58% yield) of a straw-colored oil, b.p. 204–205° at 0.290 mm. The alcohol was made to crystallize by dissolving it in the minimum amount of ether followed by the addition of a large amount of ligroin. This gave an oil which slowly solidified to a white powder after prolonged rubbing.

Anal. Calc'd for $C_{15}H_{15}NOS$: C, 70.00; H, 5.88. Found: C, 70.06; H, 6.12.

The product was further characterized as a *phenylurethan*, platelets melting at 112–113° after recrystallization from alcohol.

Methyl-β-[10-(2-chlorophenothiazinyl)]propionate (IIa). A mixture of 115 g. (0.400 mole) of β-[10-(2-chlorophenothiazinyl)]propionitrile (which had been prepared according to directions for the synthesis of I), two liters of dry dioxane, and 1200 ml. of absolute methyl alcohol containing 140–250 g. of dry HCl was stirred at room temperature for 24 hours. To the almost clear solution was added 6 ml. of water after which time approximately one liter of solvent was removed *in vacuo*. The precipitated ammonium chloride was removed by filtration and the filtrate was further taken down to 500 ml. Some more ammonium chloride was filtered off and the filtrate then was completely stripped of solvent. The residual oil was made to crystallize by the addition of 300 ml. of absolute methanol. Filtration of the refrigerated mixture gave 115 g. of the ester melting at 71–72°. This represents a 90% yield. An analytical sample, recrystallized from methyl alcohol, melted at 71.5–72.5°.

Anal. Calc'd for $C_{16}H_{14}ClNO_2S$: C, 60.00; H, 4.42. Found: C, 60.28; H, 4.76.

β-[10-(2-Chlorophenothiazinyl)]propionic acid (IIIa). A solution of 115 g. (0.360 mole) of IIa (see above), 250 ml. of methyl alcohol, and 250 ml. of water containing 31 g. of sodium hydroxide was refluxed for 90 minutes. The mixture was poured on ice and was acidified to *p*H 3. The oily product was caused to solidify by cooling. It was filtered and digested from dilute ethyl alcohol, containing a trace of sodium hydrosulfite to give 103 g. of the acid, m.p. 150–152°. This represents a 94% yield.

A small analytical sample from benzene-ligroin melted at 152–153°.

Anal. Calc'd for $C_{15}H_{12}ClNO_2S$: C, 59.0; H, 3.96. Found: C, 59.01; H, 4.11.

β-(10-Phenothiazinyl)propionic acid, hydrazide (X). The ester II (7.0 g., 0.026 mole) was heated for 2 hours in the presence of 10 ml. of 85% hydrazine and 20 ml. of alcohol. The excess solvents were removed *in vacuo*. To the oil residue were added 20 ml. of ligroin and sufficient ethyl alcohol to effect solution at the boiling point. Cooling brought down 6.8 g. of a crystalline product melting at 98–99°. A recrystallized sample (alcohol-ligroin) melted at 98–99°.

Anal. Calc'd for $C_{15}H_{15}N_3OS$: N, 14.73. Found: N, 14.53.

β-(10-Phenothiazinyl)propionic acid, 2-(2-pyridylmethylene)hydrazide (XII). A mixture of 0.855 g. (0.003 mole) of hydrazide X, 5 ml. of alcohol containing one drop of glacial acetic acid, and 0.321 g. of 2-pyridinealdehyde was gently warmed. Cooling brought down the hydrazone, which upon recrystallization from alcohol melted at 162–163°.

Anal. Calc'd for $C_{21}H_{18}N_4OS$: C, 67.36; H, 4.85. Found: C, 67.48; H, 5.03.

4-Methyl-1-[3-(10-phenothiazinyl)propionyl]-3-thiosemicarbazide (XIII). Methyl isothiocyanate (0.80 ml.), 15 ml. of alcohol, and 2.85 g. (0.01 mole) of hydrazide Xa were refluxed for 24 hours. Scratching of the supersaturated solution initiated crystallization of the product, which solidified in perfectly spherical balls. The yield amounted to 3.1 g. A sample recrystallized from alcohol melted indefinitely between 90–100°.

Anal. Calc'd for $C_{17}H_{18}N_4OS_2$: C, 56.96; H, 5.06. Found: C, 56.66; H, 4.74.

4-Methyl-5-[2-(10-phenothiazinyl)ethyl]-4-H-1,2,4-triazole-3-thiol (XIV). Compound XIII (0.358 g., 0.001 mole) was heated to 200° for 10 minutes. The resulting oil was cooled and was taken up in hot dilute dimethylformamide. Cooling brought down 0.262 g. of product, m.p. 194–195°. An analytical sample was prepared from dilute dimethylformamide.

Anal. Calc'd for $C_{17}H_{16}N_4S$: C, 59.97; H, 4.74. Found: C, 59.68; H, 4.98.

β-(10-Phenothiazinyl)propionyl chloride (XV). (*a*). *By the action of oxalyl chloride on the sodium salt of the acid.* The sodium salt of the β-(10-phenothiazinyl)propionic acid was prepared by the addition of an equivalent amount of sodium hydroxide solution to the acid suspended in water, followed by filtration and lyophilization of the filtrate.

To a stirred solution of 3.7 g. (0.029 mole) of oxalyl chloride in 10 ml. of anhydrous ether was added in small portions 7.33 g. (0.025 mole) of the sodium salt described above. An immediate evolution of gasses took place and soon a thick solid began to separate from the solution. More ether was added as required and at the end of the reaction the total volume amounted to *ca.* 60 ml. The suspension was stirred for an additional hour and then was filtered through a sintered glass funnel. The precipitate (mostly sodium chloride and some acid chloride) was repeatedly extracted with boiling ether portions which then were added to the filtrate. Removal of the solvent *in vacuo* below a bath temperature of 30° followed by addition of 30 ml. of pet. ether to the residue gave 5.1 g. of a crude product. This material melted *ca.* 80–90° with the evolution of HCl. Chemical estimation (amide formation) indicated a purity of *ca.* 70%.

(*b*). *By the action of phosphorus pentachloride on the acid.* A suspension of 54.2 g. (0.200 mole) of the phenothiazinepropionic acid in 500 ml. of dry benzene was cooled to 5°. To this was added dropwise with stirring over a one-hour period a solution of 46 g. (0.220 mole) of phosphorus pentachloride in 250 ml. of benzene. The mixture, which had turned deep purple, was stirred for an additional hour while being allowed to come to room temperature. At that point approximately 20–30 g. of sodium hydrosulfite was added, which caused the color to be discharged within 15 minutes of stirring. Filtration of the yellow solution and removal of solvents *in vacuo* at bath temperature 30–40° left a solid residue. To this was added 500 ml. of pet. ether and the product was removed by filtration. This afforded 48 g. (84% yield) of a tan solid melting at 90–95°. The acid chloride was not stable at room temperature for more than several days and evolved HCl even in full, tightly stoppered vessels.

An analytical sample was prepared as follows. The acid chloride (2 g.) was suspended in 15 ml. of ether. Benzene then was added at the boiling point until complete solution occurred. The yellow solution was treated with charcoal and diluted with ligroin. Refrigeration for 24 hours yielded 1.2 g. of colorless plates, melting at 95–97° with the evolution of HCl and the formation of an orange melt.

Anal. Calc'd for $C_{15}H_{12}ClNOS$: Cl, 12.25. Found: Cl, 11.85.

The acid chloride was reacted with amines to give the following amides.

(*a*). *β-(10-Phenothiazinyl)propionamide,* melting at 125.5–126° upon recrystallization from alcohol-ligroin.

(*b*). *N,N-Dimethyl-β-(10-phenothiazinyl)propionamide* was recrystallized from alcohol to melt at 137.5–138°.

(*c*). *2,2-Dimethyl-β-(10-phenothiazinyl)propionic acid, hydrazide,* m.p. 147–148° was obtained by reacting the acid chloride with *unsym*-dimethylhydrazine.

Furthermore, the reaction of the acid chloride with diazomethane gave the diazoketone. Recrystallization of this derivative from ether (sol. 1 g./20 ml.) gave yellow needles, m.p. 71–72°.

Anal. Calc'd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.49. Found: C, 65.26; H, 4.69.

β-(10-Phenothiazinyl)propionic acid, 2-dimethylaminoethyl ester, monohydrochloride (XVIII). A solution of 0.725 g. (0.0025 mole) of acid chloride XV, 0.250 ml. (0.0025 mole) of dimethylaminoethanol, and 8 ml. of reagent-grade chloroform was refluxed for 90 minutes. The solvent was taken off *in vacuo* and the oily residue was rubbed with ether. This ether was discarded and the rubbing was continued with a fresh 5-ml. portion of ether containing one ml. of alcohol. After the mixture had stood for several days the oil began to solidify (rosettes). The solvents were replaced with acetone, which caused the remainder of the oil to solidify. The product was removed by filtration and was recrystallized from acetone in which it was sparingly soluble. A 41% yield of material (0.387 g.) was obtained, melting at 142.5–143°.

Anal. Calc'd for $C_{19}H_{21}N_2O_2S\cdot HCl$: C, 60.22; H, 5.85. Found: C, 60.19; H, 6.22.

The reaction of β-(10-phenothiazinyl)propionic acid with warm sulfuric acid to give XVII. To 20 ml. of ice-cold conc'd sulfuric acid was added portionwise 2.0 g. (0.0074 mole) of the acid (III). The mixture was warmed on the steam-bath for one hour, resulting in the evolution of sulfur dioxide. The dark liquid was poured on ice and an orange precipitate came down. This substance was filtered and was washed with successive portions of water, alcohol, and ether. The sulfonic acid was insoluble in most common organic solvents and did not melt below 300°. It was readily soluble in base.

An analytical sample was prepared as follows. The product was dissolved in hot 2 *N* sodium hydroxide solution. Cooling brought down a lemon-yellow sodium salt, which was removed by filtration. This was taken up in a fresh portion of warm water, and the sulfonic acid was reprecipitated by the addition of 1 *N* hydrochloric acid. Analysis indicated the product to be a sulfonated *3-keto-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine.*

Anal. Calc'd for $C_{15}H_{11}NO_4S_2$: C, 54.04; H, 3.33; S, 19.23. Found: C, 54.05; H, 3.05; S, 19.31.

3-Keto-2,3-dihydro-1-pyrido[3,2,1-kl]phenothiazine (XVI). (*a*). *By the reaction of acid chloride* XV *with dimethylcadmium.* To 64 ml. (0.196 mole) of commercial 3 *N* methylmagnesium bromide solution was added 260 ml. of dry ether and 18.3 g. (0.10 mole) of cadmium chloride. The mixture was refluxed for 30 minutes with stirring after which time 520 ml. of dry benzene were added. The ether then was removed by distillation.

A solution of 50 g. (0.172 mole) of the acid chloride (XVa) in 260 ml. of benzene was added dropwise to the solution of dimethylcadmium, which then was refluxed for an additional 1.5 hours. The dark red complex was decomposed by means of water and hydrochloric acid. The organic phase was washed repeatedly and was finally dried over sodium sulfate. Removal of the solvent *in vacuo* was impeded by severe foaming which could be overcome by either the use of a Kjeldahl-type distillation head or by the addition of one half volume of alcohol to the benzene solution. The residual red oil was allowed to crystallize to give 30.3 g. (69% yield) of yellow-orange product melting at 106–108°. One subsequent recrystallization from absolute alcohol gave 25.5 g. of intense yellow needles, melting at 112–113°, which is identical with the literature value. The yield of the pure material was 57%.

(*b*). *By the reaction of acid chloride* XV *with stannic chloride.* To a well stirred solution of 26.0 g. (0.090 mole) of phenothiazinepropionyl chloride in 500 ml. of dry benzene was added dropwise 26 ml. (0.235 mole) of stannic chloride in 100 ml. of benzene. A viscous red complex formed soon, which made stirring difficult. The mixture was allowed to sit for one-half hour after which time 300 ml. of ether was added. This solubilized the complex to some extent. The adduct was decomposed by the addition of 35 ml. of 12 *N* hydrochloric acid and 350 ml. of water. Washing of the organic phase with successive portions of water, dilute sodium hydroxide solution, and more water gave a yellow solution. After the solution had been dried the solvent was removed *in vacuo* (caution—foaming) which left a yellow residue. One recrystallization from alcohol afforded a pure product, m.p. 112–113°. Yield, 45–50%.

2,3-Dihydro-1H-pyrido[3,2,1-kl]phenothiazine-3-ol. The ketone XVI (5.06 g., 0.020 mole) was extracted from a Soxhlet apparatus into 300 ml. of ether containing 2.0 g. of LAH. The reaction was worked up according to directions for IV, to give, upon removal of the ether phase, a solid residue. When this was recrystallized from benzene-ligroin, needles melting at 124.5–125° were obtained. The yield amounted to 3.7 g. or 72%.

Anal. Calc'd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.15. Found: C, 70.59; H, 4.99.

A crystalline *acetate* could be obtained by refluxing the alcohol in acetic anhydride; recrystallization from ethyl alcohol yielded platelets, m.p. 105.5–106°.

1H-Pyrido[3,2,1-kl]phenothiazine-3(2H)-one, oxime. A mixture of 5.0 g. (0.0198 mole) of the ketone XVIa, 2.76 g. (0.040 mole) of hydroxylamine hydrochloride, and 50 ml. of 70% alcohol were refluxed for 5 hours. Within one-half hour a deep red solution had resulted, which was followed by precipitation of the oxime. The product was removed by filtration and was twice triturated with ice-cold alcohol to give 4.1 g. (78% yield) of pale yellow needles. An analytical sample from alcohol melted at 206.5–208°, with sublimation starting at 160°.

Anal. Calc'd for $C_{15}H_{12}N_2OS$: N, 10.44. Found: N, 10.59.

3-Amino-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine. The reduction of 8.70 g. (0.0324 mole) of the *oxime* by means of LAH according to directions of IV, yielded 6.2 g. of the amine, m.p. 120–122°. When recrystallized from alcohol the material melted at 122.5–123°.

Anal. Calc'd for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55. Found: C, 71.08; H, 5.55.

The amine gave a *hydrochloride* melting unreproducibly from 185–195°, as well as a well defined *acetyl* derivative which melted at 172–173°.

Acknowledgment. The authors are indebted to Mr. C. E. Childs and staff for the analytical data, and to Dr. J. M. Vandenbelt, and Messrs. B. Scott and E. Schoeb for their spectral interpretations. Furthermore, our thanks are due to Mr. T. Sulkowski for his preparation of a generous supply of 2-chlorophenothiazine.

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