[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF FISK UNIVERSITY]

Ring Derivatives of Phenothiazine. II. 2-Phenothiazinyl Ketones and Their Derivatives[1]

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Some 2-phenothiazinyl ketones have been prepared by the Friedel-Crafts method from 10-acetylphenothiazine. The infrared spectra and derivatives of these ketones are described.

The two broad approaches to ring-substituted derivatives of phenothiazine are ring-closure methods and nuclear substitution.[4] In regard to nuclear substitution, the sulfur atom in the phenothiazine nucleus renders the molecule susceptible to oxidation, and, therefore, the common aromatic substitution methods of nitration, sulfonation, and halogenation are not as feasible as acylation *via* the Friedel-Crafts reaction.

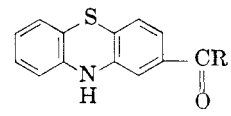
The Friedel-Crafts acylation of 10-acetylphenothiazine has been studied by several workers who acylated it with acetyl chloride,[5,6,7] β-carbomethoxypropionyl chloride,[5] chloroacetyl chloride,[7] and acetic anhydride.[8]

A single substituent was shown to enter the 2-position,[5,6,8] and two substituents to enter the 2- and 8-position. Unsubstituted phenothiazine gave only disubstituted derivatives, believed to be the 3,7-derivative in the case of phthaloyl chloride,[9] and shown not to be the 2,8-derivative in the case of acetic anhydride.[10,11] 10-Methylphenothiazine was also shown to give only the disubstituted 3,7-diacetyl-10-methylphenothiazine.[12] However, 10-acylated phenothiazines gave 2-acetylphenothiazine with acetic anhydride.[13]

Because of the differences in orientation and the physiological interest in the 2-position of phenothiazine, due to the activity of chlorpromazine [(2-chloro-10-(3-dimethylaminopropyl)phenothiazine], it was of interest to prepare several 2-phenothiazinyl

TABLE I

2-PHENOTHIAZINYL KETONES



Substituent, R	M. P., °C.	Yield, %	Color	Formula	Anal. Calc'd	Found
CH_3	193–194[5]		Yellow-orange			
CH_3CH_2	170	45	Yellow-orange	$C_{15}H_{13}NOS$	5.49	5.40
CH_3CH_2 Ketoxime[b]	175–176		Greenish-yellow	$C_{15}H_{14}N_2OS$	10.35	10.14
$CH_3(CH_2)_{10}$	150–152	32	Yellow-orange	$C_{24}H_{31}NOS$	3.67	3.50
$ClCH_2$	199–200[7]	90	Red			
Cl_2CH	175–176	95	Dark red	$C_{14}H_9Cl_2NOS$	4.15	4.50
Cl_3C	Not obtained					
C_6H_5	181–182	68	Dark red	$C_{19}H_{13}NOS$	4.62	4.67
C_6H_5 Ketoxime[b]	231–232		Yellow	$C_{18}H_{14}N_2OS$	8.80	8.55
$C_6H_5CH_2$	Not obtained					
$BrCH_2$[a]	188–190	93	Red	$C_{14}H_{10}BrNOS$	4.38	4.56
ICH_2[a]	179–180	93	Red	$C_{14}H_{10}INOS$	3.81	4.12
$CNCH_2$[a]	246–247	74	Red	$C_{15}H_{10}N_2OS$	10.53	10.20

[a] These compounds were prepared by metathetical reactions from 2-chloroacetylphenothiazine and the corresponding potassium salts. [b] These oximes were prepared by the conventional method using hydroxylamine and pyridine.

(1) A portion of this material was presented before the Fourteenth International Congress of Pure and Applied Chemistry, Zurich, Switzerland, July, 1955.

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(3) A portion of this material is from the master's thesis of William A. Hills, Fisk University, 1956.

(4) Massie, *Chem. Revs.*, **54**, 800 (1954).

(5) Baltzly, Harfenist, and Webb, *J. Am. Chem. Soc.*, 68, 2673 (1946).

(6) Michels and Amstutz, *J. Am. Chem. Soc.*, **72**, 888 (1950).

(7) Burger and Clements, *J. Org. Chem.*, **19**, 1113 (1954).

(8) Cauquil and Casadevall, *Bull. soc. chim. France*, 768 (1955).

(9) Scholl and Seer, *Ber.*, **44**, 1233 (1911).

(10) Massie, Doctoral Dissertation, Iowa State College (1946).

(11) A comparison of the infrared spectra of a sample of 2,8-diacetylphenothiazine, kindly furnished by Dr. E. D. Amstutz, with the unknown diacetylphenothiazine showed that they were different.

(12) Cauquil and Casadevall, *Bull. soc. chim. France*, 1061 (1955).

(13) Cauquil and Casadevall, *Compt. rend.*, 240, 538 (1955).

ketones by the Friedel-Crafts method and to convert these ketones to other derivatives.

In this study the following acid chlorides were used: CH_3COCl, CH_3CH_2COCl, $CH_3(CH_2)_{10}COCl$, $ClCH_2COCl$, Cl_3COCl, $Cl_2CHCOCl$, $C_6H_5CH_2COCl$, and C_6H_5COCl. The results are given in Table I.

It is readily observed that the ease of acylation depends on the nature of the radical of the acyl halide. Electropositive groups decrease the yield, while electronegative groups increase the yield. The attempted synthesis of 2-trichloroacetylphenothiazine yielded a compound which could not be hydrolyzed to the carboxylic acid by the action of alkali and presented no absorption in the infrared spectrum characteristic of an N—H function or a carbonyl function.

It is also of interest that the ketones are colored and that substituents sharply modify the color. When the amides of these compounds are prepared this color is lost and these amides are either colorless or light yellow.

The infrared spectra of some of these ketones are given in Table II.

TABLE II

INFRARED SPECTRA OF 2-PHENOTHIAZINYL KETONES

Substituents	(N—H)	C=O
CH_3	3340 cm.$^{-1}$	1667 cm.$^{-1}$
CH_3CH_2	3300	1678
$CH_3(CH_2)_{10}$	3340	1668
$ClCH_2$	3340	1683
Cl_2CH	3340	1680

Although there are insufficient data for any theoretical discussion to be made on these frequencies, it can be noted that the nature of the acyl group has no effect on the N—H stretching frequency and very little on the carbonyl stretching frequency. Our laboratories are engaged in a continuing study of the spectra of ring derivatives of phenothiazine.

2-Acetylphenothiazine was converted to several derivatives of theoretical and physiological interest. It underwent several of the typical reactions of ketones. 2-Acetylphenothiazine was found to undergo the Wolff-Kishner reduction in 65 per cent yield to give 2-ethylphenothiazine.[7] Partial reduction to the alcohol by the use of aluminum isopropoxide in the Meerwein-Pondorf reaction gave 1-(2-phenothiazinyl)ethanol in 67 percent yield.

In the Willgerodt reaction, the condensation of 2-acetylphenothiazine, sulfur, and morpholine has been shown to give β-(2-phenothiazinyl)thioacetomorpholide,[7] but no further studies were reported. The hydrolysis of the thiomorpholide to 2-phenothiazinylacetic acid and conversion to the methyl ester with diazomethane has been carried out. Decarboxylation of the acid gave 2-methylphenothiazine, identical with a sample prepared by the thionation of N-phenyl-*m*-toluidine, thus adding further confirmation to the fact that the position of the acetyl group obtained by the Friedel-Crafts reaction of 10-acetylphenothiazine is the 2-position.

The Leuckhardt reaction gave 1-(2-phenothiazinyl)ethylamine in 66 percent yield. It is of interest to note that in an attempted proof of the structure of this amine by the reduction of the oxime of 2-acetylphenothiazine, lithium aluminum hydride gave a mixture which could not be characterized.[14,15] Zinc and acetic acid or sodium and ethanol hydrolyzed the oxime back to the ketone.

It was also of interest to convert 2-chloroacetylphenothiazine into several derivatives. Reduction by the Wolff-Kishner method caused reduction of the halogen as well as the carbonyl group, yielding 2-ethylphenothiazine. The reduction to the chlorohydrin with lithium aluminum hydride in 32 percent has been previously reported.[7] The use of aluminum isopropoxide gave the chlorohydrin in 72 percent yield.

The chlorine in 2-chloroacetylphenothiazine was replaced by bromo, iodo, and cyano groups to yield 2-bromoacetylphenothiazine, 2-iodoacetylphenothiazine, and 2-cyanoacetylphenothiazine. 2-Cyanoacetylphenothiazine on hydrolysis in both acid and base yielded 2-carboxyphenothiazine. Thiourea reacted with 2-chloroacetylphenothiazine to give 2-amino-4-(2-phenothiazinyl)thiazole in 62 percent yield.

However, 2-dichloroacetylphenothiazine did not react under similar conditions with potassium bromide or iodide.

These compounds were tested for anti-carcinogenic activity by the Sloan-Kettering Institute. Results will be reported elsewhere, but no significant activity was shown. Likewise antibacterial tests carried out by the Upjohn Company showed no significant activity.

EXPERIMENTAL[16,17,18]

2-Phenothiazinyl ketones. These compounds, described in Table I, were prepared by the addition of 4 molar-equivalents of anhydrous aluminum chloride to one equivalent of 10-acetylphenothiazine and the acid chloride in carbon disulfide. These mixtures were stirred and refluxed for seven hours with the exception of the benzoyl derivative which required 24 hours. After reaction the carbon disulfide was poured off, and the residue, which was a sticky mass, was hydrolyzed in the usual manner with ice and dilute

(14) Burger and Schmalz, *J. Org. Chem.*, 19, 1842 (1954) also reported obtaining a gum in the attempted reduction of 10-methylphenothiazine-3-aldoxime with lithium aluminum hydride.

(15) N. Bolden, Senior Paper, Langston University, 1953.

(16) The analyses for nitrogen were carried out by Mrs. Helen Peoples of these laboratories, using the semi-micro Kjeldahl technique.

(17) The infrared spectra described were carried out using a Nujol mull technique in a Perkin-Elmer 21 spectrophotometer, courtesy, Dr. J. R. Lawson, Tennessee A and I State University.

(18) All melting points are uncorrected.

hydrochloric acid. The residue was extracted with acetone and, after removal of the acetone by distillation, the acetone residues were hydrolyzed with dilute alcoholic hydrogen chloride to give the ketone. Again the benzoyl compound was different in that the complex was soluble in the carbon disulfide layer, and was obtained there, whereas the unreacted 10-acetylphenothiazine formed the gummy complex.

β-(2-Phenothiazinyl)thioacetomorpholide.[7] This compound, prepared in the usual manner from 2-acetylphenothiazine, sulfur, and morpholine, was obtained in 46 percent yield and melted at 193–194°.

2-Phenothiazinylacetic acid. A mixture of 18 g. (0.05 mole) of β-(2-phenothiazinyl)thioacetomorpholide and 300 ml. of 10 percent alcoholic potassium hydroxide was refluxed for 14 hours. The mixture was diluted with twice its volume of water and acidified. The acid mixture was extracted with two 50-ml. portions of ether. The ether was evaporated and the solid residue was recrystallized from ethanol yielding 4 g. (34%) of grayish-white crystals, melting at 156–157°.

Anal. Calc'd for $C_{14}H_{12}NO_2S$: N, 5.44. Found; N, 5.21.

The *methyl ester*, prepared using diazomethane, on recrystallization from methanol formed small, light-yellow crystals, melting at 106–108°.

Anal. Calc'd for $C_{15}H_{14}NO_2S$: N, 5.17. Found: N, 4.80.

2-Methylphenothiazine. One gram of 2-phenothiazinylacetic acid was sublimed, giving yellow crystals, melting at 184–185°. This compound was also prepared by the thionation of N-phenyl-*m*-toluidine[19] and a mixture melting point showed no depression.

Anal. Calc'd for $C_{13}H_{11}NS$: N, 6.57. Found: N, 6.52.

1-(2-Phenothiazinyl)ethylamine. A mixture of 24.1 g. (0.1 mole) of 2-acetylphenothiazine and 24.1 g. (0.32 mole) of ammonium formate was heated slowly to 150°. The temperature then was slowly raised to 189–185° where it was maintained for three hours. The mixture was cooled and extracted several times with water. The remaining solid was hydrolyzed with a mixture of 100 ml. of 95 percent ethanol and 20 ml. of concentrated hydrochloric acid. The solution was diluted with water and made basic with concentrated ammonium hydroxide. The resulting solid was recrystallized from ethanol-water using Norit as the adsorbent to give 16 g. (65%) of white needles, melting at 79–80°.

Anal. Calc'd for $C_{14}H_{15}N_2OS$: N, 10.6. Found: N, 10.49.

The amine is very susceptible to oxidation and turns purple very quickly. Attempts to acetylate the amine gave an uncrystallizable gum.

2-Amino-4-(2-phenothiazinyl)thiazole. A mixture of 18.8 g. (0.5 mole) of 2-chloroacetylphenothiazine and 7.5 g. (0.1 mole) of thiourea in 200 ml. of 95% ethanol was refluxed for two hours.[20] The mixture was poured into water and made alkaline with sodium hydroxide solution, wherein a light greenish-yellow precipitate was obtained. This precipitate was washed well with water and dried to give a crude product melting at 200–205°. The product was recrystallized from ethyl acetate–hexene with the addition of Norit to give 18.5 g. (63%) of a yellow powder, melting at 212–213°.

Anal.[21] Calc'd for $C_{15}H_{11}N_3S_2$: N, 14.16; S, 21.56. Found: N, 13.53, 13.77; S, 21.35.

2-Carboxyphenothiazine. A mixture of 3 g. of 2-cyanoacetylphenothiazine in 25 ml. of 10 percent alcoholic potassium hydroxide was refluxed for four hours. The mixture was cooled and the solution was acidified with dilute hydrochloric acid. The resulting yellow precipitate was recrystallized from 95 percent ethanol to yield yellow crystals, melting at 274–275°. The reported melting point of the acid is 276–277°.[5]

1-(2-Phenothiazinyl)ethanol. Reduction of 24.1 g. (0.1 mole) of 2-acetylphenothiazine with aluminum isopropoxide in isopropyl alcohol yielded, after recrystallization from aqueous ethanol, 16 g. (67%) of yellowish-green flakes, m.p. 130–136°. The compound underwent decomposition on attempted purification by distillation under reduced pressure.

Anal. Calc'd for $C_{14}H_{14}NOS$: N, 5.77. Found: N, 5.54.

2-Chloro-1-(2-phenothiazinyl)ethanol. A 27.5-g. portion (0.1 mole) of 2-chloroacetylphenothiazine was reduced as described under 1-(2-phenothiazinyl)ethanol to give on recrystallization from alcohol–benzene, 19 g. (72%) of white flaky crystals, melting at 180–182°. The previously reported melting point was 170–171°.[7]

Anal. Calc'd for $C_{14}H_{13}ClNOS$: N, 5.06. Found: N, 5.06.

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(20) Dodson and King, *J. Am. Chem. Soc.* **67**, 2242 (1945).

(21) These analyses were carried out in the Upjohn Drug Research Laboratories, courtesy, Dr. R. V. Heinzelman.