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The Synthesis of some Phenothiazinyl Ketones and their Derivatives

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The synthesis of a number of 2-chloro-8-acylphenothiazines via the Friedel-Crafts reaction has been reported. A series of dialkylaminoalkyl ketones have been derived from 2-chloroacetyl- and 2-chloro-8-chloroacetylphenothiazines. A number of dialkylaminoalkyl esters of 2-phenothiazinecarboxylic acid have also been synthesized.

Ring closure methods (1) and nuclear substitution reactions (2,3,4, and 5) are the two major approaches toward the syntheses of phenothiazine derivatives. In view of the physiological importance of the 2-position in the phenothiazine molecule and because of the ease of nuclear acylation via Friedel-Crafts reaction, it was of interest to investigate the utility of this acylation reaction to the 2-substituted phenothiazines.

Because of its ready availability, 2-chlorophenothiazine (VII) has been chosen and its 10-acetyl derivative (VIII) has been found to undergo acylation without difficulty, the second acyl group entering the 8-position. Evidence for this structure has been provided by the fact that generally a single substituent enters the 2-position and two substituents enter the 2- and 8-positions (2,3, and 5). Furthermore, 2-chloro-8-acetylphenothiazine has been converted to 2-chloro-8-phenothiazinylacetic acid by hydrolysis of the thioacetomorpholide obtained via the Willgerodt reaction, and decarboxylation of the acid has yielded 2-chloro-8-methylphenothiazine identical with a sample obtained by thionation of the appropriate diphenylamine (6).

In this paper is reported the acylation of 2-chloro-10-acetylphenothiazine (VIII) using acetyl, chloroacetyl and benzoyl chlorides; the respective 2-chloro-8-acyl derivatives (X) having been obtained by removal of the 10-acetyl group by hydrolysis. While the nuclear acetylation took place with ease, the benzoylation did not; and much of the starting material was recovered unchanged.

The simple acylphenothiazines serve as useful intermediates in the preparation of other phenothiazine derivatives. The availability of 2-phenothiazinecarboxylic acid (III) from 2-chloroacetyl-10-acetylphenothiazine (I) (4) has made possible the preparation of a number of simple alkyl esters of this acid (7). The syntheses of a series of dialkylaminoalkyl esters (IV), which might be physiologically active, are described in this paper. Also, the preparation of a number of dialkylaminoalkyl ketones (V, VI) of possible physiological value from 2-chloroacetyl- and 2-chloro-8-chloroacetylphenothiazines (II and Xb) by condensation reaction with dialkylamines is described here. In the esterifi-

cation reactions, if the dialkylaminoalkyl halides are used as their hydrochlorides, the esters are obtained in very poor yields and need much purification. However, by using the free bases, the esterifications are found to proceed smoothly, giving rise to pure esters in good yields.

EXPERIMENTAL (8)

Dialkylaminoalkyl Esters (IV).

The dialkylaminoalkyl esters were prepared by vigorously refluxing a mixture of 2-phenothiazinecarboxylic acid (III) (0.04 mole), the dialkylaminoalkyl halide (0.06 mole), an excess of anhydrous potassium carbonate (0.5 mole) and catalytic amounts of potassium iodide (1 g.) in dry acetone, for 24 hours. On cooling, the reaction mixture was poured into a large excess of cold water, when the dialkylaminoalkyl esters separated out as yellow solids. They were filtered, dried and recrystallized from acetone-ethanol mixture.

The dialkylaminoalkyl halides were obtained by reacting the respective hydrochlorides with potassium hydroxide and extracting the oily liquids that separated out with ether. The ether extracts were washed with water to remove alkali, dried over anhydrous magnesium sulfate and evaporated. The resulting oily residues were used directly for the esterification reactions.

β -Diethylaminoethyl 2-phenothiazinecarboxylate (IVa).

This compound was obtained as yellow needles, yield 62%, m.p. 113-114°.

Anal. Calcd. for $C_{19}H_{22}N_2O_2S$: C, 66.67; H, 6.43. Found: C, 67.11; H, 6.50.

β -Dimethylaminopropyl 2-phenothiazinecarboxylate (IVb).

This compound was obtained as yellow crystals, yield 38%, m.p. 148-150°.

Anal. Calcd. for $C_{18}H_{20}N_2O_2S$: C, 65.87; H, 6.09. Found: C, 66.10; H, 6.07.

β -Dimethylaminoisopropyl 2-phenothiazinecarboxylate (IVc).

This compound was obtained as shining yellow crystals, yield 71%, m.p. 148-150°. The mixture melting point of this with the β -dimethylaminopropyl ester was depressed considerably.

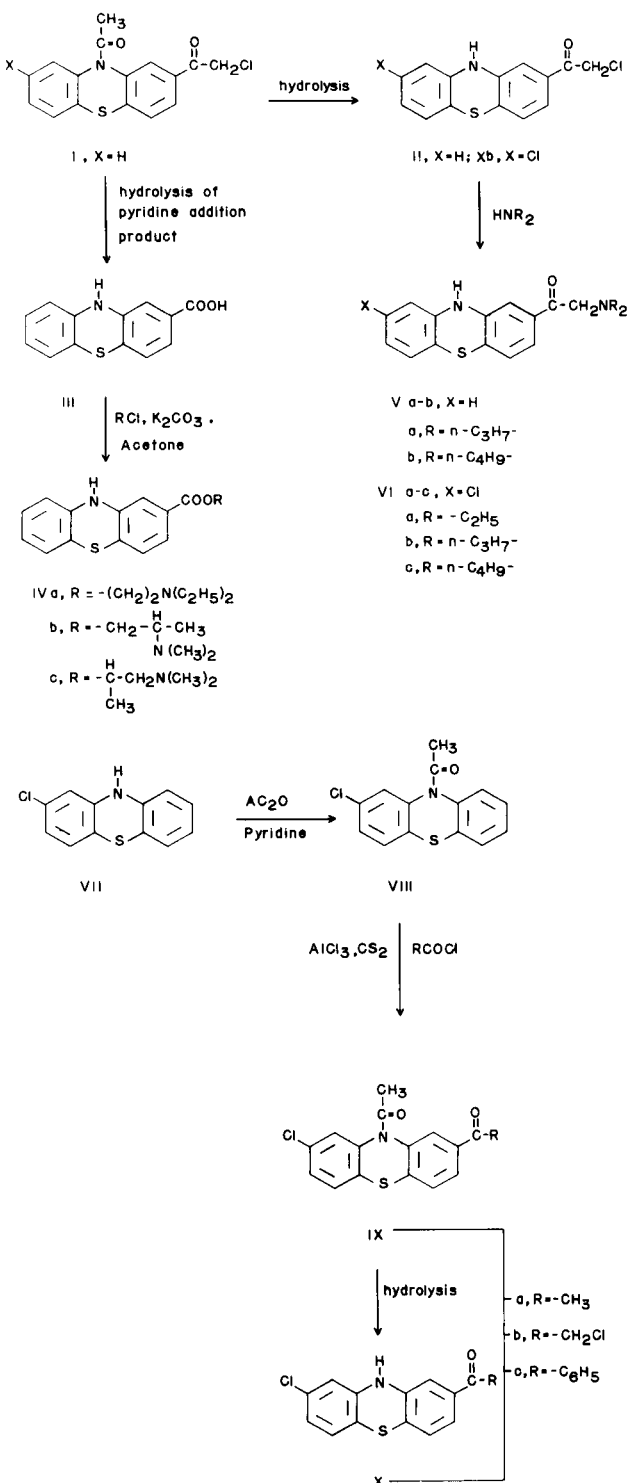
Anal. Calcd. for $C_{18}H_{20}N_2O_2S$: C, 65.87; H, 6.09. Found: C, 65.99; H, 5.98.

An attempt to prepare the β -diethylaminoethyl 2-phenothiazinecarboxylate by refluxing a mixture of the acid (0.02 mole), diethylaminoethyl chloride (0.03 mole) and anhydrous potassium carbonate (0.25 mole) in dry methyl ethyl ketone for 24 hours gave only a 43.2% yield of the ester, m.p. 114-115°.

Another attempt to prepare the ester by refluxing a mixture of the sodium salt of the acid (0.03 mole) and diethylaminoethyl chloride hydrochloride (0.05 mole) in dry toluene (200 ml.), for 18 hours yielded 19.4% of the impure ester, melting at 95-97° and clearing between 105-110°. There was also recovered 1.5 g. of the unchanged acid.

2-Chloro-10-acetylphenothiazine (VIII).

A mixture of 2-chlorophenothiazine (VII) (15 g., 0.07 mole), acetic anhydride (60 ml., 0.6 mole) and pyridine (2 ml.) was refluxed for 3-3.5 hours. After cooling, the reaction mixture was poured into cold water with vigorous stirring when the 2-chloro-10-acetylphenothiazine separated out as a white solid. It was filtered, dried and crystallized from ethanol, to give 14.5 g. (75%) of colorless crystals, m.p. 100-105°.



2-Chloro-8,10-diacetylphenothiazine (IXa).

2-Chloro-10-acetylphenothiazine (VIII) (14 g., 0.05 mole) and acetyl chloride (3.95 g., 0.05 mole) were placed in carbon disulfide (150 ml.) and anhydrous aluminum chloride (20 g., 0.15 mole) was then added and the mixture refluxed with stirring for 7 hours. After cooling, the carbon disulfide was decanted off, and the gummy residue poured into ice cold water, when the 2-chloro-8,10-diacetylphenothiazine separated out as a yellow solid. It was filtered, dried and crystallized from ethanol to give 9 g. (57%) of pale yellow crystals, m.p. 162-163.5°.

Anal. Calcd. for $\text{C}_{18}\text{H}_{12}\text{ClNO}_2\text{S}$: C, 60.46; H, 3.78. Found: C, 60.95; H, 3.98.

2-Chloro-8-acetylphenothiazine (Xa).

2-Chloro-8,10-diacetylphenothiazine (IXa) (8 g., 0.025 mole) was refluxed in a mixture of glacial acetic acid (80 ml.) and hydrochloric acid (20%, 20 ml.) for 10 minutes. Upon cooling, orange yellow shining crystals of 2-chloro-8-acetylphenothiazine separated out in pure form. Yield, 7 g. (99%), m.p. 235-236° (d). A sample was crystallized from acetone for analysis.

Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{ClNOS}$: C, 60.98; H, 3.63. Found: C, 60.87; H, 3.65.

2-Chloro-8-chloroacetylphenothiazine (Xb).

Anhydrous aluminum chloride (35 g., 0.24 mole) was slowly added to a suspension of 2-chloro-10-acetylphenothiazine (VIII) (20 g., 0.07 mole) and chloroacetyl chloride (7 ml., 0.07 mole) in carbon disulfide (240 ml.) and the mixture refluxed with stirring for 4 hours. It was worked up as before, when a light brown solid was obtained. This was refluxed with a mixture of glacial acetic acid (200 ml.) and hydrochloric acid (20%, 100 ml.) for 10 minutes. On cooling, 2-chloro-8-chloroacetylphenothiazine separated out as orange red crystals. These were filtered, washed well with ethanol and recrystallized from acetone to give 18 g. (82%) of product, m.p. 232-234°.

Anal. Calcd. for $\text{C}_{14}\text{H}_9\text{Cl}_2\text{NOS}$: C, 54.19; H, 2.90. Found: C, 54.59; H, 3.12.

2-Chloro-8-benzoylphenothiazine (Xc).

A mixture of 2-chloro-10-acetylphenothiazine (VIII) (14 g., 0.05 mole), anhydrous aluminum chloride (20 g., 0.15 mole) and benzoyl chloride (5.8 ml., 0.05 mole) in carbon disulfide (200 ml.) was refluxed with stirring for 7 hours. A soluble complex was formed in this reaction and was recovered by removing the solvent under reduced pressure. It was then decomposed with ice and hydrochloric acid when a sticky gum-like compound was obtained. The latter, on hydrolysis in the usual manner, yielded a product which appeared to be a mixture of a yellow and orange solid. The yellow solid was alcohol soluble and was washed off with this solvent; the residual orange material was recrystallized from acetone, in which it was quite sparingly soluble, to give 1.7 g. (10%) of 2-chloro-8-benzoylphenothiazine (Xc), bright orange crystals, m.p. 277-280°.

Anal. Calcd. for $\text{C}_{19}\text{H}_{12}\text{ClNOS}$: C, 67.55; H, 3.55. Found: C, 67.25; H, 3.75.

The yellow solid in alcohol solution, presumably the undecomposed complex, was refluxed with hydrochloric acid to ensure complete decomposition and then hydrolyzed to cleave off the 10-acetyl group, when pale yellow 2-chlorophenothiazine (VII) was obtained, m.p. and mixture m.p. 200°.

By increasing the reflux time to 44 hours and using excess aluminum chloride (6-7 times), it was found that no benzoyl derivative was formed.

Dialkylaminoalkyl Ketones.

A mixture of 2-chloroacetylphenothiazine (II) (5 g., 0.02 mole) and dialkylamine (0.05 mole) was refluxed in ethanol (95%, 25 ml.) for 6 hours. The reaction mixture was cooled immediately in an ice bath, when the dialkylaminoacetylphenothiazine (V) separated out as an orange yellow crystalline mass. If allowed to stand in solution for any length of time, the ketones underwent extensive decomposition. Decomposition also occurred by increasing the reflux time. The products were crystallized quickly from ethanol to prevent decomposition, and were obtained as shining orange yellow crystals.

2-Di-n-propylaminoacetylphenothiazine (Va).

This compound was obtained in a yield of 3.5 g. (51%), m.p. 107-111°.

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{OS}$: C, 70.58; H, 7.05. Found: C, 71.00; H, 7.20.

2-Di-n-butylaminoacetylphenothiazine (Vb).

This compound was obtained in a yield of 5 g. (68%), m.p. 115-118°.

Anal. Calcd. for $C_{22}H_{23}N_2OS$: C, 71.72; H, 7.60. Found: C, 72.12; H, 7.40.

2-Chloro-8-diethylaminoacetylphenothiazine (VIa).

A mixture of 2-chloro-8-chloroacetylphenothiazine (Xb) (2 g., 0.006 mole) and diethylamine (8 ml., 0.076 mole) in ethanol (50 ml.) was refluxed for 5 hours. On cooling, the amino ketone separated out as a deep orange solid and recrystallized from ethanol to give shining orange crystals, yield, 1.0 g. (49%), m.p. 195-196°.

Anal. Calcd. for $C_{18}H_{19}ClN_2OS$: C, 62.34; H, 5.48. Found: C, 61.95; H, 5.52.

2-Chloro-8-di-n-propylaminoacetylphenothiazine (VIb).

A mixture of 2-chloro-8-chloroacetylphenothiazine (Xb) (2.5 g., 0.008 mole) and di-n-propylamine (4 ml., 0.03 mole) in ethanol (25 ml.) was refluxed for 2.5 hours; longer heating resulted in decomposition of the product. The deep orange solid obtained on cooling recrystallized from ethanol to give 1.8 g. (60%) of shining orange crystals, m.p. 145-150°.

Anal. Calcd. for $C_{20}H_{23}ClN_2OS$: C, 64.07; H, 6.14. Found: C, 64.59; H, 6.30.

2-Chloro-8-di-n-butylaminoacetylphenothiazine (VIc).

The condensation reaction was carried out as above, but refluxed

for 5 hours. The deep orange product obtained on cooling crystallized from ethanol to give 1.5 g. (47%) of glistening orange yellow crystals, m.p. 134-139°.

Anal. Calcd. for $C_{22}H_{27}ClN_2OS$: C, 65.60; H, 6.71. Found: C, 66.30; H, 6.85.

REFERENCES

- (1) S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, **21**, 347 (1956); P. K. Kadaba and S. P. Massie, *ibid.*, **24**, 986 (1959).
- (2) R. Baltzly, M. Harfenist and F. J. Webb, *J. Am. Chem. Soc.*, **68**, 2673 (1946).
- (3) J. G. Michels and E. D. Amstutz, *ibid.*, **72**, 888 (1950).
- (4) A. Burger and J. Clements, *J. Org. Chem.*, **19**, 1113 (1954).
- (5) G. Cauquil and A. Casadevall, *Bull. Soc. Chim. France*, 768 (1955).
- (6) R. McKinley, Master's Thesis, Fisk University, 1958.
- (7) S. P. Massie, P. K. Kadaba, and C. Smith, *J. Org. Chem.*, **24**, 251 (1959).
- (8) All melting points are uncorrected. Microanalyses are by C. Beames, New Mexico Highlands University, Las Vegas, New Mexico, and by Kurt Eder, Laboratoire Microchimique, Ecole de Chimie, Geneve, Switzerland.

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