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Note

The Oxidation of 10-Acylphenothiazines with Lead Tetraacetate

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The oxidation of 10-acetylphenothiazine, 10-chloroacetylphenothiazine and 10-dichloroacetylphenothiazine with lead tetraacetate was attempted. The former two compounds were oxidized to the corresponding oxides whereas the oxidation was unsuccessful in the case of the last named compound.

Various oxidizing reagents have been used for the oxidation of the sulfide sulfur in 10-substituted derivatives of phenothiazine. In phenothiazine derivatives it can be oxidized to the sulfoxide or sulfone stage depending on the nature of the oxidation reagent and on the reaction conditions. Thus the oxidation to sulfoxide has been accomplished with the folowing reagents: potassium permanganate[1,2], sodium nitrite in acetic acid[3,4], nitric acid (sp. g. 1.42 and 1.50) in acetic acid[5–8], 30% hydrogen peroxide in ethanol[4,5,7,9–12], 30% hydrogen peroxide in methanol in the presence of oxalic acid[12], *m*-cloroperbenzoic acid in chloroform at $< 10^0$C[8] and alkylhydroperoxides[13,14]. For the oxidation to the sulfone the following reagents have been used: potassium permanganate[2], 30% hydrogen peroxide in glacial acetic acid [5,7,8,14–16], 30% hydrogen peroxide in hot absolute ethanol[5], 30% hydrogen peroxide in dioxane[4], hypochlorous acid[15], and chromium trioxide[17].

In the present work, which represents a part of our investigation on the oxidation of sulfur containing compounds, we report the oxidation of some 10-acylphenothiazines with lead tetraacetate.

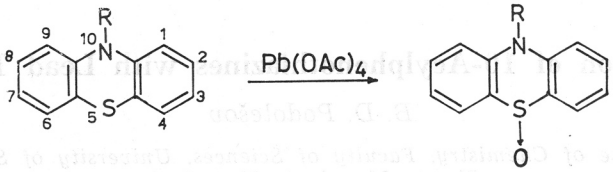
The oxidation reaction was carried out in 99% acetic acid at room temperature with constant shaking for 5 hrs. Equimolar quantities of 10-acylphenothiazines and of lead tetraacetate were used.

Under such conditions the oxidation of 10-acetylphenothiazine, 10-chloroacetylphenothiazine and 10-dichloroacetylphenothiazine has been attempted. It was found that 10-acetylphenothiazine and 10-chloroacetylphenothiazine were oxidized to the corresponding sulfoxides, whereas 10-dichloroacetylphenothiazine was not affected under these conditions.

The formation of 10-acetylphenothiazine-5-oxide and 10-chloroacetylphenothiazine-5-oxide in these oxidations was confirmed by elemental analysis as well as by subsequent saponification to phenothiazine-5-oxide.

The presence of strong bands in the 1100—1000 cm^{-1} region of the infrared spectra of the reaction products also confirms that the oxidations here described lead to sulfoxides. The above region is, in fact, identical with the region characteristic for alkyl and aryl sulfoxides[18] and for phenothiazine sulfoxides[19]. The IR spectra showed no evidence for the presence of sulfones.

To the contrary, the oxidation of 10-dichloroacetylphenothiazine, as mentioned above, could not be affected under the same reaction conditions. Both the elemental analysis and the infrared spectra confirmed this and only the starting material could be recovered from the reaction mixture.



$R = CH_3CO-$, CH_2ClCO-

The foregoing discussion shows that the success of the oxidation of sulfur in the phenothiazine derivatives is not only dependent on the oxidizing agent and the reaction conditions, but also on the nature of the *N*-substitutent. This finding is in agreement with those of some other investigators[2,5,20].

Small quantities of a by-product were formed in the course of all the reactions that were carried out.

Further investigations on the application of lead tetraacetate as an oxidant of phenothiazine derivatives and other sulfur-containing compounds is presently under way and the results will be reported in due time.

EXPERIMENTAL

The IR spectra were run as Nujol mulls on a Perkin Elmer model 521 Infrared-spectrophotometer. Melting points are uncorrected.

10-Acetylphenothiazine-5-oxide

A suspension of 2.4 g. (0.01 mole) of 10-acetylphenothiazine[3] and 4.44 g. (0.01 mole) of powdered lead tetraacetate in 60 ml. 99% acetic acid was shaken at room temperature for 2 hrs. A red colored solution was obtained and shaking was continued for additional 3 hrs. Then a few drops of ethyleneglycol were added to the reaction mixture to remove any traces of unreacted lead tetraacetate. The main part of acetic acid was evaporated under reduced pressure and the residue was poured into water. The separated precipitate was filtered off, washed with water and dried. The pink colored precipitate was dissolved in benzene and the solution was extracted with a dilute aqueous solution of sodium carbonate to remove the by-product. The extraction was repeated until the sodium carbonate solution remained blue. The benzene solution was then washed several times with water and dried over anhydrous sodium sulfate. The benzene was removed by distillation and the solid residue washed several times with small portions of absolute ethanol to remove the pink colored products.

The first recrystallization from absolute ethanol gave pale pink crystals, m. p. 172°. The yield was 1,8 g. (70%). The recrystallization was repeated three times to yield colorless crystals of 10-acetylphenothiazine-5-oxides, m. p. 173°.

The IR spectrum showed a strong band around 1050 cm^{-1} attributable to S = 0 group.

Anal. $C_{14}H_{11}NO_2S$ (257.31) calc'd.: C 65.33% H 4.31% N 5.45%
found: C 65.26% H 4.26% N 5.38%

10-Chloroacetylphenothiazine-5-oxide

The oxidation of 10-chloroacetylphenothiazine was carried out in the same way as described above. 10-Chloroacetylphenothiazine[21] (1.38 g., 0.005 mole) and 2.22 g.

(0.005 mole) of lead tetraacetate suspended in 30 ml. 99% acetic acid gave 1.25 g. (85.6%) of the crude product. Five recrystallizations from acetic acid-ethanol-water gave colorless crystals, m. p. 186° (188° dec.).

The IR spectrum showed a strong band around 1040 cm^{-1}.

Anal. $C_{14}H_{10}ClNO_2S$ (291.77) calc'd.: C 57.64% H 3.45% N 4.80%
found: C 57.36% H 3.29% N 5.11%

Hydrolysis of 10-Acetylphenothiazine-5-oxide

To a solution of 1.0 g. (0.0039 mole) of 10-acetylphenothiazine-5-oxide in 20 ml. ethanol, 2 ml. of 10% sodium hydroxide were added. After 10 minutes of refluxing a brown solution was obtained. After cooling, crystalline platelets separated and were filtered off. Recrystallization from ethanol gave 0.6 g. (72%) of phenothiazine-5--oxide m. p. 258° dec.

The m. p. of the product mixed with an authentic sample of phenothiazine-5--oxide showed no depression. The IR spectrum showed a strong band at around 1065 cm^{-1}.

Anal. $C_{12}H_9NOS$ (215.87) calc'd.: C 66.96% H 4.21% N 6.05%
found: C 66.84% H 4.34% N 5.83%

10-chloroacetylphenothiazine-5-oxide was hydrolyzed as described above to give phenothiazine-5-oxide.

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ИЗВОД

Оксидација на 10-ацилфенотиазински деривати со оловен тетраацетат

Б. Д. Подолешов

Утврдено е дека при оксидација на 10-ацетилфенотиазин и 10-хлорацетилфенотиазин со оловен тетрацетат во 99% оцетна киселина и при собна температура се добиваат соответни сулфоксиди.

Наспроти тоа, при оксидација на 10-дихлорацетилфенотиазин, при истите услови, не можеше да се добие соответниот сулфоксид.

Врз основа на добиените резултати, утврдено е дека оксидацијата на сулфурот во фенотиазинските деривати зависи и од природата на 10-супституентот.

ХЕМИСКИ ИНСТИТУТ
ПРИРОДНО-МАТЕМАТИЧКИ ФАКУЛТЕТ
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