Heterocyclic Compounds
Synthesis of 7,14-Diacetyl-3,10-diethoxy-6,13-dihalo-triphenodithiazine and Derivatives

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7-Ethoxy-1,2,4-trihalo-3H-phenothiazin-3-one, 3,10-Diethoxy-6,13-dihalotriphenodithiazine, 3,10-Diethoxy-6,13-dihalo-7,14-diacetyltriphenodithiazine, 7-Ethoxy-1,2,4-trihalophenothiazin-3-ol, 7-Ethoxy-1,2,4-trihalo-3-acetoxyphenothiazine

7,14-Diacetyl-6,13-dihalo-3,10-diethoxytriphenodithiazines have been synthesised by reductive acetylation of 6,13-dihalo-3,10-diethoxytriphenodithiazine with Zn dust (AC₂O) pyridine. Attempts to synthesis 7,14-dihydro-6,13-dihalo-3,10-diethoxytriphenodithiazine is failed. Oxidation with 30% H₂O₂ in AcOH of 7,14-diacetyl-6,13-dihalo-3,10-diethoxytriphenodithiazine did not produce its S,S-dioxide. 3-Acetoxy-7-ethoxy-1,2,4-trihalo-phenothiazine on treatment with 30% H₂O₂ in AcOH regenerated 7-ethoxy-1,2,4-trihalo-3H-phenothiazine-3-one by oxidative deacetylation. Their Rf values and IR spectral data have been recorded.

Little information is available on the chemistry of triphenodithiazines¹,² (1,4-benzothiazino-[2,3-a] phenothiazines) which is used as vat dye stuff⁶, antioxidants for polycarbonates⁷ and in the preparation of oxidation and corrosion resistant articles with good high temperature stability⁸. Triphenodithiazine (A) and 7,14-dihydro-6,13-dioxytriphenodithiazine (B) derivatives are well known as the basic compounds, but compounds of the type 7,14-dihydrotriphenodithiazine (C) (where X = H or monovalent substituent) are not known. Attempts to synthesis C remains unsuccessful⁹. In the present paper we have reported the synthesis of 7,14-diacetyl derivatives of C.

![Heterocyclic Compounds](image)

Several attempts to synthesis A via Smiles rearrangements have been reported to be unsuccessful⁷,⁸. In a search for a simple synthesis of A, we have synthesised some new 7-ethoxy-1,2,4-trihalo-3H-phenothiazin-3-ones (1) by the condensation of zinc

salt of 2-amino-5-ethoxythiophenol (AET) with chloranil and bromanil. The condensation reaction proceeds in the same fashion with the zinc thiol as with the free thiol, but the use of the zinc salt is superior, since it is more stable. 1 obtained were again condensed with zinc salt of AET (1 mole equivalent) in AcOH to give 6, 13-dihalo-3,10-diethoxy-triphenodithiazine (2) which has identical mixed mpts and Rf values with those obtained directly by condensing zinc salt of AET (2 mole equivalent) with chloranil and bromanil in AcOH (see Scheme 1).

First method

![Scheme 1](image)

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Scheme 1.
Reduction of 2 with sodium dithionite in acetone produces yellow coloured solution of 7,14-dihydro-6,13-dihalo-3,10-diethoxytriphenodithiazine (3) which when poured in ice-cooled water containing sodium dithionite gave light yellow precipitate of 3, but it immediately turns to violet colour of 2. Several attempts fails to isolate 3. Thus, we have obtained its 7,14-diacetyl derivative (4) without isolating 3, by reductive acetylation of 2 with zinc dust -Ac₂O-pyridine under vigorous condition. 4 on treatment with acid or base afforded again the starting material i.e. 2. 4 on oxidation with 30% H₂O₂ in acetic acid gave back 2 instead of its S,S-dioxide (see Scheme 2).

1 on reduction with sodium dithionite in acetone or with zinc dust in glacial acetic acid afforded 7-ethoxy-1,2,4-trihalophenothiazin-3-ol (5) which on acetylation, with Ac₂O/pyridine gave 3-acetoxy-7-ethoxy-1,2,4-trihalophenothiazine (6). 6 were also obtained from 1 on reductive acetylation with zinc dust/Ac₂O in presence of pyridine as a catalyst under mild condition, 1 on reductive acetylation with zinc dust/Ac₂O/pyridine under vigorous condition gave 3-acetoxy-10-acetyl-7-ethoxy-1,2,4-trihalophenothiazine as a yellow mixture which on pour in water gave 6. It may be due to the presence of electron withdrawing halogen at position one which weakens the >N-COCH₃ bond and gets hydrolysed in aqueous medium (see Scheme 3).

6 on oxidation with 30% H₂O₂ in acetic acid medium afforded 1, instead of expected S,S-dioxide. It may be due to the oxidative deacetylation of 6. The probable mechanism of the reaction may be shown as follows:

Acetic acid and H₂O₂ gave peracetic acid and water molecule. Due to acidic medium 6 is hydrolysed to 5 and acetic acid. 5, thusformed, is immediately oxidised by peracetic acid to 1.

2-Amino-6-ethoxythiophenol was prepared by the alkaline hydrolysis of 2-amino-6-ethoxybenzothiazole, which was obtained in good yields by the modification of earlier reported methods.

The structure of all these compounds have been confirmed by their elemental analysis and IR spectral data.

**Experimental**

All reactions were carried under nitrogeneous atmosphere. All melting points are uncorrected. IR spectra were recorded with a Perkin-Elmer IR-4 spectrophotometre for KBr pellets using Nujol. The purity of compounds were tested by tlc on silica gel ‘G’ (E. Merck) in various solvent systems. Con. H₂SO₄ was used as spray reagent in all cases. Bromanil was purified by sublimation under reduced pressure. The % yield for the crystallized products have been reported in all cases. Satisfactory elemental analysis were obtained for all the compounds.

Modified procedure for the synthesis of 2-amino-6-ethoxybenzothiazole

To a solution of 13.7 g (0.1 mole) of p-phenetidine
<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent of</th>
<th>m.p. [°C]</th>
<th>Yield [%)</th>
<th>Colour</th>
<th>Rf value**</th>
<th>IR spectral data*** frequency [cm⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-Ethoxy-1,2,4-trichloro-3H-phenothiazin-3-one (1a)</td>
<td>Benzene</td>
<td>282</td>
<td>87</td>
<td>Violet</td>
<td>0.65</td>
<td>1640 s</td>
</tr>
<tr>
<td>7-Ethoxy-1,2,4-tribromo-3H-phenothiazin-3-one (1b)</td>
<td>Toluene</td>
<td>278</td>
<td>82</td>
<td>Violet</td>
<td>0.70</td>
<td>1625 s</td>
</tr>
<tr>
<td>3,10-Diethoxy-6,13-dichlorophenodithiazine (2a)</td>
<td>Nitrobenzene</td>
<td>&gt; 365</td>
<td>60</td>
<td>Violet</td>
<td>0.66</td>
<td>1150 m</td>
</tr>
<tr>
<td>3,10-Diethoxy-6,13-dibromophenodithiazine (2b)</td>
<td>Nitrobenzene</td>
<td>&gt; 365</td>
<td>65</td>
<td>Violet</td>
<td>0.67</td>
<td>1145 w</td>
</tr>
<tr>
<td>7,14-diacetyltriphenodithiazine (4a)</td>
<td>Benzene-petroleum ether, 60-80</td>
<td>172</td>
<td>52</td>
<td>Yellow</td>
<td>0.77</td>
<td>1115 s</td>
</tr>
<tr>
<td>7,14-diacetyltriphenodithiazine (4b)</td>
<td>Benzene-petroleum ether, 60-80</td>
<td>198</td>
<td>51</td>
<td>Yellowish</td>
<td>0.60</td>
<td>1110 m</td>
</tr>
<tr>
<td>7-Ethoxy-1,2,4-trichlorothiazin-3-ol (5a)</td>
<td>-do-</td>
<td>161</td>
<td>99</td>
<td>Silvery white</td>
<td>0.66</td>
<td>3400 b</td>
</tr>
<tr>
<td>7-Ethoxy-1,2,4-tribromophenothiazin-3-ol (5b)</td>
<td>-do-</td>
<td>162</td>
<td>99</td>
<td>Silvery white</td>
<td>0.73</td>
<td>3380 b</td>
</tr>
<tr>
<td>7-Ethoxy-3-acetoxy-1,2,4-trichlorophenothiazine (6a)</td>
<td>Benzene</td>
<td>173</td>
<td>85</td>
<td>Light yellow</td>
<td>0.77</td>
<td>3355 s</td>
</tr>
<tr>
<td>7-Ethoxy-3-acetoxy-1,2,4-tribromophenothiazine (6b)</td>
<td>Benzene</td>
<td>87</td>
<td>84</td>
<td>Yellow</td>
<td>0.75</td>
<td>1760 s</td>
</tr>
</tbody>
</table>

Satisfactory C, H, N and S analysis have been obtained in all cases.

* The % yield of the crystallized product is reported.
** Solvent system A = benzene-n-butanol (80:15); B = benzene-1,4-dioxane (80:20); C = toluene-n-butanol (80:20).
*** IR spectral data: a characteristic bond for 6,13-disubstituted triphenodithiazine, b νC=O stretching frequency, c acetate νC=O stretching vibrations, d νOH stretching frequency, e free ν-NH stretching vibrations.

Key: s = sharp, m = medium, w = weak, b = broad.

and 60.9 g (0.8 mole) of ammonium thiocyanate in 100 ml 96% AcOH was added dropwise, with stirring. 32 g (0.2 mole) of Br₂ dissolved in 50 ml of glacial AcOH at 0-5 °C. After all the bromine solution had been added, the mixture was stirred for 3 h and kept overnight. It was filtered and the benzo-thiazole hydrobromate salt was dissolved in hot water. The filtrate was neutralized with sodium carbonate solution. The yield of product, melting at 160-161 °C, was 85-90%. This material is pure enough for subsequent reactions. It may be further purified by ethanol, m.p. 162 °C (ref. 12, m.p. 161 °C).

**Synthesis of 2-amino-5-ethoxythiophenol (AET)**

A mixture of 2-amino-6-ethoxybenzothiazole (53 g, 0.27 mole), KOH (85 g, 1.5 mole) and water (250 ml) was refluxed until ammonia (70% yield) was no longer evolved (9 h). The solution was cooled at 0-5 °C after filtration, neutralized with AcOH (3 N) and filtered. The precipitate was washed well with cold water (2 l), dissolved in minimum amount
of warm 95% ethanol (75-80 ml) and filtered. The filtrate on cooling provided fine yellow crystals of AET, m.p. 104 °C.

Anal. for C₈HuNOS:
Caled N 8.28,
Found N 8.16%.

Zinc salt of 2-amino-5-ethoxythiophenol
0.1 mole of AET was dissolved in 50-70 ml of 95% ethanol and added to a solution containing 4 g (0.1 mole) NaOH in 15 ml H₂O and 5 ml ethanol. The volume of the mixture increased to 100 ml with water, warmed for 5 min and filtered to remove any insoluble material. The filtrate was poured into a solution of 7.5 g (0.55 mole) of zinc chloride in 25 ml glacial AcOH and 150 ml H₂O. A white solid precipitated immediately as a fine suspension, which was boiled for 10-15 min to facilitate filtration and the solid was collected and dried. Drying in vacuum at 80-100 °C was found to be more satisfactory.

Synthesis of 7-ethoxy-1,2,4-trihalo-3H-phenothiazin-3-one (1)
A mixture of zinc salt of AET (0.005 mole) and halogeno-p-benzoquinone (chloranil and bromalni) (0.01 mole) in 95% ethanol (35 ml) was stirred for 1 h at ambient temperature and then heated under gentle reflux for 80 min. The solid, which was formed on cooling, was filtered off, washed with ethanol, hot aqu. 7% HCl (ca. 200 ml), water and ethanol. Crystallization with benzene or toluene provided analytical sample. Analytical data are reported in the Table.

Synthesis of 3,10-diethoxy-6,13-dihalotriphenodithiazine (2)

Method A: by condensation of 1 with zinc salt of AET: A mixture of 1 (0.01 mole) and the zinc salt of AET (0.011 mole) in 50 ml glacial AcOH was stirred for 1 h and then refluxed for 6 h. The solid was filtered off after cooling. The crude product was worked as above. 2 was extracted with nitrobenzene and purified by column chromatography using Al₂O₃ gel and toluene as eluent. M.P., Rf values and IR spectral data are given in the Table.

Method B: by condensation of halogeno-p-benzoquinone with zinc salt of AET: An intimate mixture of chloranil or bromanil (0.01 mole) and zinc salt of AET (0.01 mole) in 40 ml glacial AcOH was refluxed for 6 h. After cooling at room temperature, the solid which separated was filtered off and worked as in Method A. The compound has identical m.p., Rf values and IR spectra as of authentic sample.

Synthesis of 7,14-diacetyl-3,10-diethoxy-6,13-dihalotriphenodithiazine (4)
0.456 g (0.001 mole) of 2 in Ac₂O (30-35 ml) and pyridine (2 ml) was stirred with zinc dust (4 g) at room temperature for 30 min. The pale yellow reaction mixture, after heating under reflux for 45 min was filtered on ice-cold water, when a yellowish solid precipitated. The solid was collected by filtration, washed well with water containing sodiumbicarbonate (2%) and finally with water. The solid was crystallized from benzene-petroleum ether, 60-80, gave the desired product as yellow crystals. Analytical datum are reported in the Table.

Regeneration of 2 from 4
0.5 g of 4 in AcOH (10 ml) was refluxed under gentle heating. Calculated amount of 30% H₂O₂ was added, immediately reaction mixture changed to violet colour from pale yellow colour. After 15 min the reaction mixture cooled and the solid was collected by filtration. After crystallization from nitrobenzene, it gave the same melting point as of 2 and gave no depression in melting point when mixed with 2. It has identical Rf values as well as IR spectra.

Synthesis of 7-ethoxy-1,2,4-trihalo phenothiazin-3-ol (5)

Method A: by reduction with sodium dithionite: A mixture of 1 g of 1, 1.2 g sodium dithionite, 5 ml of distilled water and 7 ml acetone or 10 ml methanol was heated under gentle reflux for 80 min. The mixture, which had turned from violet to colourless was allowed to cool and poured into a solution of 3.5 g sodium dithionite in 200 ml H₂O. The resulting white solid was washed with water, dried in vacuum at 100 °C and crystallized from benzene-petroleum ether to give desired product. Additional crystallization from benzene provided the analytical sample. Analytical datum are reported in Table.

Method B: by reduction with zinc dust in AcOH: A solution of 1 g of 1 in a mixture of 50 ml acetone and 5 ml glacial AcOH was heated on a stream bath for 1 h, under addition of zinc dust. When the solution became colourless, it was not filtered and the acetone removed by distillation. On cooling, 5 separated in pure state, as a silvery white needles having identical mixed m.p., Rf values and IR spectra as obtained by method A.

Synthesis of 3-acetoxy-7-ethoxy-1,2,4-trihalo phenothiazine (6)

Method A: by acetylation of 5: A mixture of 0.1 mole of 5, 3.8 ml pyridine, 0.1 g sodium dithionite and 1-2 drops of Ac₂O was stirred for 3 h at ambient temperature, and poured into 100 ml of cooled water. The resulting solid was washed with water, dried and crystallized from benzene to give the desired product. Analytical datum are given in the Table.

Method B: by reductive acetylation of 1: 0.0033 mole of 1 in 25 ml Ac₂O and 0.5 ml pyridine was stirred with zinc dust (0.5 g) at room temperature for 15 min. The colourless solution was filtered and poured into ice cooled water. The resulting solid
was purified as above. Mixed melting point determination gave no depression in melting point with authentic sample obtained by method A.

**Regeneration of 1 from 6**

0.5 g of 6 in 5 ml glacial AcOH was refluxed and a calculated amount of 30% H$_2$O$_2$ was added, immediately, reaction mixture changed to violet colour from pale yellow. After 15 min the reaction mixture cooled and the solid was collected by filtration and worked as before. It had the same m.p. as of 1 and gave no depression for mixed m.p. and have identical $Rf$ values of IR spectra.

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