Heterocyclic Compounds

Synthesis of 7,14-Diacetyl-3,10-dioxy-6,13-dihalo-triphenodithiazine and Derivatives

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(Z. Naturforsch. 32b, 821-825 [1977]; received March 8, 1977)

7-Ethoxy-1,2,4-trihalo-3H-phenothiazin-3-one, 3,10-Dioxy-6,13-dihalo-triphenodithiazine, 3,10-Dioxy-6,13-dihalo-7,14-diacetyl-triphenodithiazine, 7-Ethoxy-1,2,4-trihalo-phenothiazin-3-ol, 7-Ethoxy-1,2,4-trihalo-3-acetoxy-phenothiazine

7,14-Diacetyl-6,13-dihalo-3,10-dioxytriphenodithiazines have been synthesised by reductive acetylation of 6,13-dihalo-3,10-dioxytriphenodithiazine with Zn dust (Ac2O) pyridine. Attempts to synthesis 7,14-dihydro-6,13-dihalo-3,10-dioxytriphenodithiazine is failed. Oxidation with 30% H2O2 in AcOH of 7,14-diacetyl-6,13-dihalo-3,10-dioxytriphenodithiazine did not produce its S,S-dioxide. 3-Acetoxy-7-ethoxy-1,2,4-trihalo-phenothiazin-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 stuff', antioxidants for polycarbonates3 and in the preparation of oxidation and corrosion resistant articles with good high temperature stability4. Triphenodithiazine (A) and 7,14-dihydro-6,13-dioxytriphenodithiazine5,6 (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 unsuccessful7. In the present paper we have reported the synthesis of 7,14-diacetyl derivatives of C.

Several attempts to synthesis A via Smiles rearrangements have been reported to be unsuccessful7.5 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-dioxy-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

Second method

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 nitrogenous 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. Cone. H2SO4 was used as spray reagent in all cases. Bromamil 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. Analytical data of 1a, b–6a, b.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent of m.p. yield* crystallization</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>282 87 Benzene Violet 0.65 0.67 0.54 — 1640 s — — —</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-Ethoxy-1,2,4-tribromo-3H-phenothiazin-3-one (1b)</td>
<td>278 82 Toluene Violet 0.70 0.70 0.57 — 1625 s — — —</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,10-Diethoxy-6,13-dichlorophenodithiazine (2a)</td>
<td>&gt;365 60 Nitro-benzene Violet 0.67 0.72 0.77 1145 w 1112 m — — —</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,10-Diethoxy-6,13-dibromophenodithiazine (2b)</td>
<td>&gt;365 65 Nitro-benzene Violet 0.67 0.72 0.77 1145 w 1112 m — — —</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7,14-diacetyltriphenodithiazine (4a)</td>
<td>172 52 Benzene-petroleum ether, 60–80 Yellow 0.77 0.71 0.73 1155 m 1115 s 1780 m — —</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7,14-diacetyltriphenodithiazine (4b)</td>
<td>198 51 Benzene-petroleum ether, 60–80 Yellowish 0.60 0.62 0.61 1180 w 1110 m — 1760 m — —</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-Ethoxy-1,2,4-trichlorophenothiazin-3-ol (5a)</td>
<td>161 99 -do- Silvery white 0.66 0.65 0.53 — — — 3400 b 3350 s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-Ethoxy-1,2,4-tribromophenothiazin-3-ol (5b)</td>
<td>162 99 -do- -do- 0.73 0.66 0.58 — — — 3380 b 3340 s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-Ethoxy-3-acetoxy-1,2,4-trichlorophenothiazine (6a)</td>
<td>173 85 Benzene Light yellow 0.77 0.66 0.61 — — 1752 s 3355 s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-Ethoxy-3-acetoxy-1,2,4-tribromophenothiazine (6b)</td>
<td>87 84 Benzene Yellow 0.75 0.64 0.59 — — 1760 s 3350 b</td>
<td></td>
<td></td>
<td></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 vC=O stretching frequency, c acetate vC=O stretching vibrations, d v-OH stretching frequency, e free v-NH stretching vibrations.

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

and 60.9 g (0.8 mole) of ammonium thiocynate 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
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 sodium bicarbonate (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.

Regression 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 color from pale yellow color. 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-trihalophenothiazine-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 steam 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-trihalophenothiazine (6)

Method A: by acetylation of 5: A mixture of 0.01 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 $R_f$ values of IR spectra.

The authors wish to express their sincere thanks to U. G. C., New Delhi for a J. R. F. to one of us (to S. K. Jain).

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