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The synthesis of various 3-substituted derivatives of 7-fluorophenothiazin-3-ol and their 5-oxides is described. The ir, uv and mass spectral data are also included.

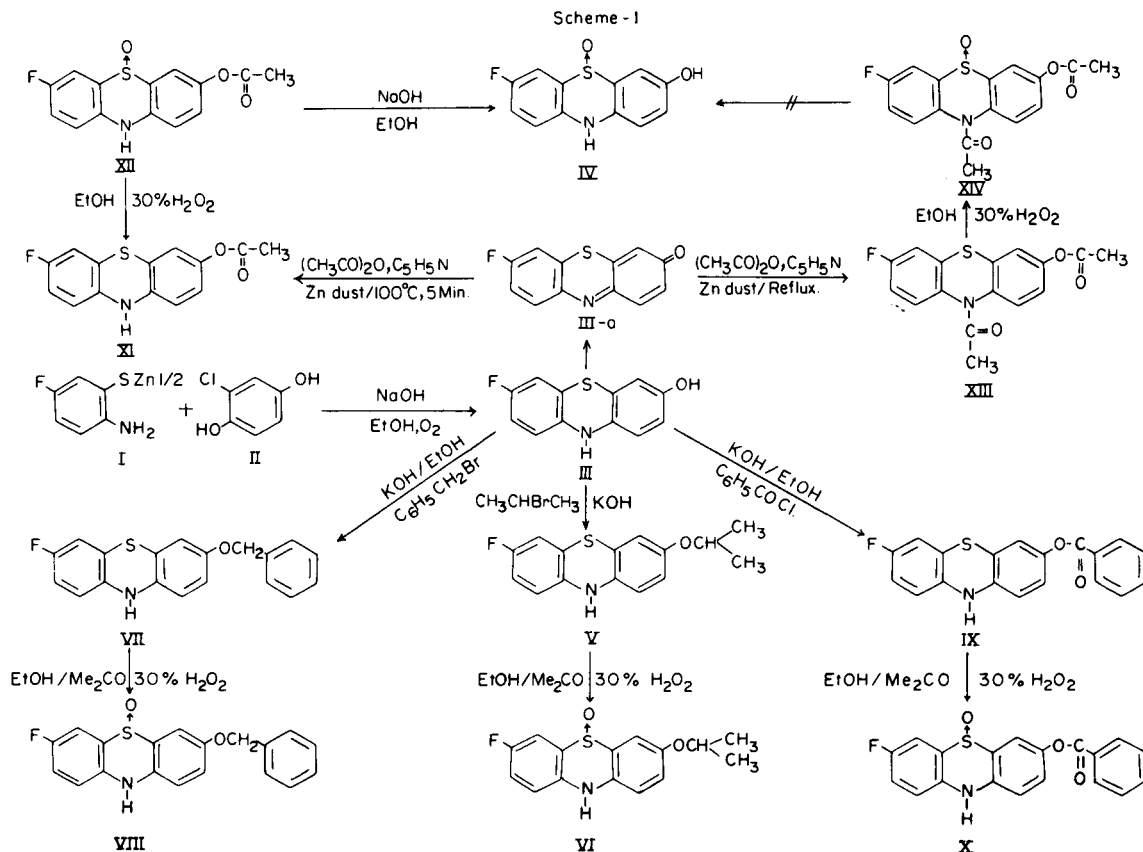
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Only a few fluorophenothiazines have been reported in the literature (1,2), although a great amount of work has been done in various phenothiazines (3-7). During the last few years a growing number of useful applications of fluorinated organic compounds (8,9) has increased the desirability of the preparation of fluorinated compounds and therefore the fluorophenothiazines were selected for the present investigation. In continuation of our work (10-12), we synthesized various 3-substituted derivatives of 7-fluorophenothiazin-3-ol and their 5-oxides.

The preparation of 7-fluorophenothiazin-3-ol (III) (Scheme I) was initiated with the condensation of zinc salt of 2-amino-5-fluorobenzenethiol (I) (13,14) and 2-chloro-4-hydroquinone (II) by adaptation of the procedure reported by Nodiff and Hausman (15). The isopropylation of III

with 2-bromopropane provided 7-fluoro-3-isopropoxyphenothiazine (V). Similarly the benzylation of III with benzyl bromide (alcoholic potassium hydroxide), and the benzylation with benzoyl chloride furnished 3-benzyloxy-7-fluorophenothiazine (VII) and 3-benzyloxy-7-fluorophenothiazine (IX). Acetylation of III-a with acetic anhydride and pyridine with an excess of zinc dust provided 3-acetoxy-7-fluorophenothiazine (XI) under mild conditions while under more vigorous conditions the 3-acetoxy-10-acetyl-7-fluorophenothiazine (XIII) was obtained. The oxidation of all of these compounds with 30% hydrogen peroxide furnished the corresponding sulphoxides.

The structure of all these compounds were confirmed by their analytical and spectral data. The ir spectra of the compounds shows some characteristic peaks, indicating



the presence of a particular functional group and the nature and shape of the uv spectra is characteristic of this tricyclic π -system. All the phenothiazines show three λ max, whereas the corresponding sulphoxides exhibit four λ max. In the mass spectra, the molecular ion peak suggests a high stability of the phenothiazine ring due to a high degree of conjugation. The fragments $M^+ - 1$ and $M^+ - 32$ are always present with varying intensity in all phenothiazines due to the loss of the H radical from a heterocyclic nitrogen atom and the loss of an S atom whereas in phenothiazine sulphoxides, $M^+ - 48$ and $M^+ - 17$ fragments suggests the loss of SO and OH radical due to the transannular hydrogen rearrangement in 5-oxides.

EXPERIMENTAL

Melting points were determined in sealed evacuated capillary tubes and are uncorrected. All the reactions were mechanically stirred under dry nitrogen and in absence of strong light. Infrared spectra were taken as Nujol mulls on a Perkin-Elmer Model 137B Infracord spectrophotometer. The uv spectra were taken on a Perkin-Elmer 202 UV-Visible spectrophotometer and the mass spectra were recorded on a Hitachi Mass Spectrometer RMU-6E instrument operating at 70 eV and a source temperature of 130-150°.

7-Fluorophenothiazin-3-ol (III).

A mixture of 9.1 g (0.026 mole) of I, 7.514 g (0.052 mole) of II (Aldrich Chemical Co), 100 ml of ethanol and 2.1 g of sodium hydroxide in 5 ml of water was heated under reflux for one hour during which time oxygen was passed through the solution. The solution was filtered and filtrate was poured into 1 litre of ice cold water containing 9.0 g of sodium dithionite. After standing overnight, the pale yellow suspension was extracted with ether and the extracts were dried and concentrated under reduced pressure. The unreacted II was removed by evacuating the residue at 120-125° and 0.05 mm. The resulting solid tar was stirred for 15 minutes with 100 ml of benzene, allowed to cool and was filtered. The solid was dried in vacuum and 8.84 g (73%) of III was obtained. Crystallization by sublimation provided an analytical sample, mp 198°; ir (nujol): ν 3330 (-NH), 3550 (-OH), 1260 (C-F); uv (benzene): λ max $m\mu$ (ϵ) 207 (26,378), 255 (34,506), 307 (4,371); ms: (m/e) 233 (100), 232 (16), 206 (10), 205 (14), 201 (4), 200 (6), 191 (4), 189 (2), 186 (12), 185 (4), 184 (2), 181 (2), 178 (8), 173 (2).

Anal. Calcd. for $C_{17}H_8FNOS$: C, 61.80; H, 3.43; N, 6.00. Found: C, 61.74; H, 3.44; N, 6.03.

7-Fluoro-3-isopropoxyphenothiazine (V).

To a solution of 1.16 g (0.005 mole) of III in 25 ml of acetone, 0.25 g of sodium dithionite and 5 ml of 10% ethanolic potassium hydroxide were added and heated under reflux for half an hour. To this solution then added 0.88 g (0.007 mole) of 2-bromopropane and again refluxed for 7-8 hours. The resulting green suspension was poured into ice cold water. The brown solid obtained was filtered, dried and crystallized from benzene to give 0.89 g (65%) of V, mp 118°; ir (Nujol): ν 3275 (-NH), 1405, 1375 (gem dimethyl group), 1255 (C-F); uv (benzene): λ max $m\mu$ (ϵ) 204 (21,185), 255.5 (29,353), 306 (3,573).

Anal. Calcd. for $C_{17}H_{14}FNOS$: C, 65.45; H, 5.09; N, 5.09. Found: C, 65.38; H, 5.05; N, 5.02.

7-Fluoro-3-isopropoxyphenothiazine 5-Oxide (VI).

To a solution of 11 g (0.004 mole) of V in 25 ml of ethanol and 50 ml of acetone was added 0.57 g (0.005 mole) of 30% hydrogen peroxide and heated under reflux for 7 hours. The solution was concentrated over steam bath and solid obtained was washed with acetone to give 1.00 g

(86%) of VI as an analytical sample mp 140°; ir (Nujol): ν 3260 (-NH), 1270 (C-F), 1035 (S=O); uv (benzene): λ max $m\mu$ (ϵ) 216 (23,165), 234 (28,535), 273 (12,372), 301 (8,424).

Anal. Calcd. for $C_{15}H_{14}FNO_2S$: C, 61.85; H, 4.81; N, 4.81. Found: C, 61.88; H, 4.80; N, 4.78.

3-Benzoyloxy-7-fluorophenothiazine (VII).

A mixture of 2.33 g (0.01 mole) of III, 0.05 mole of potassium carbonate and 50 ml of acetone was heated under reflux for half an hour. After adding 2.22 g (0.013 mole) of benzyl bromide, the reaction mixture was again refluxed for 8 hours and then poured into ice cold water. The resulting solid was extracted with ether and the extracts were dried and concentrated under vacuum. Complete removal of the solvent provided purple solid which was crystallized from benzene to provide 2.22 g (69%) of shining pink crystals of VII as the analytical sample, mp 147°; ir (Nujol): ν 3450 (-NH), 1255 (C-F); uv (benzene): λ max $m\mu$ (ϵ) 207 (24,239), 254.5 (32,723), 307 (4,040).

Anal. Calcd. for $C_{19}H_{14}FNOS$: C, 70.58; H, 4.33; N, 4.33. Found: C, 70.49; H, 4.37; N, 4.31.

3-Benzoyloxy-7-fluorophenothiazine (VIII).

To a solution of 2.26 g (0.007 mole) of VII in 25 ml of ethanol and 50 ml of acetone was added 0.8 g (0.007 mole) of 30% hydrogen peroxide and heated under reflux for 3 hours. The solvent was evaporated on a water bath to give a pink solid which was crystallized from ethanol to provide 1.42 g (60%) of VIII, mp 134°; ir (Nujol): ν 3260 (-NH), 1270 (C-F), 1015 (S=O); uv (ethanol): λ max $m\mu$ (ϵ) 239 (36,119), 273.5 (11,760), 298.5 (7,980), 341.5 (5,880).

Anal. Calcd. for $C_{19}H_{14}FNO_2S$: C, 67.25; H, 4.12; N, 4.12. Found: C, 67.28; H, 4.10; N, 4.09.

3-Benzoyloxy-7-fluorophenothiazine (IX).

To a mixture of 2.33 g (0.01 mole) of III in 50 ml of acetone was added 0.5 g of sodium dithionite and 100 ml of 10% ethanolic potassium hydroxide solution and the mixture was heated for 1 hour. Benzoyl chloride (1.967 g, 0.014 mole) was added to this solution and it was refluxed for 6 hours and then poured into 1 litre of ice cold water. The resulting solid was filtered, dried and crystallized from benzene to give 1.51 g (45%) of the desired compound IX, mp 200°; ir (Nujol): ν 3360 (-NH), 1275 (C-F), 1760 (C=O); uv (benzene): λ max $m\mu$ (ϵ) 204.5 (20,131), 255.5 (28,779), 206 (3,507).

Anal. Calcd. for $C_{19}H_{12}FNO_2S$: C, 67.65; H, 3.56; N, 4.15. Found: C, 67.58; H, 3.51; N, 4.11.

3-Benzoyloxy-7-fluorophenothiazine 5-Oxide (X).

Compound X (2.35 g, 0.007 mole) was dissolved in a hot mixture of 25 ml of ethanol and 50 ml of acetone and then added 0.8 g (0.007 mole) of 30% hydrogen peroxide. The solution was heated under reflux for 3 hours. The solvent was evaporated on a steam bath and the compound obtained was crystallized from ethanol to furnish 1.48 g (60%) of X, mp 180°; ir (Nujol): ν 3290 (-NH), 1270 (C-F), 1755 (C=O), 1025 (S=O); uv (ethanol): λ max $m\mu$ (ϵ) 216 (22,837), 234 (26,510), 272.5 (12,262), 301 (8,092).

Anal. Calcd. for $C_{19}N_{12}FNO_3S$: C, 64.58; H, 3.39; N, 3.96. Found: C, 64.54; H, 3.36; N, 3.95.

3-Acetoxy-7-fluorophenothiazine (XI).

Compound III-a (23.1 g, 0.01 mole) was dissolved in 50 ml of acetic anhydride and 2.5 ml of pyridine and stirred with excess of zinc dust for 45 minutes at room temperature and then heated on water bath for 5 minutes. The pale yellow solution was decanted from the zinc dust and poured into 150 ml of cold water. A yellow oil separated which soon solidified. The solid was dissolved in chloroform and this solution was washed with saturated aqueous sodium bicarbonate and then dried over anhydrous sodium sulphate. The solution was decolorized with Darco G-60 and concentrated under vacuum to provide 1.37 g (50%) of XI as shining yellow crystals, mp 125°; ir (Nujol): ν 3300 (-NH), 1260 (C-F), 1740 (C=O); uv (ethanol): λ max $m\mu$ (ϵ) 205 (26,553), 242.5 (25,668), 278.5

(18,296).

Anal. Calcd. for $C_{14}H_{10}FNO_2S$: C, 61.09; H, 3.63; N, 5.09. Found: C, 61.02; H, 3.59; N, 5.03.

3-Acetoxy-7-fluorophenothiazine 5-Oxide (XII).

Compound XI (1.92 g, 0.007 mole) in a mixture of 25 ml of ethanol and 50 ml of acetone together with 5.8 ml of 30% hydrogen peroxide was heated under reflux for 3 hours. The resulting reddish yellow solution was concentrated on a water bath and the solid obtained was crystallized from ethanol to provide 0.81 g (40%) of XII, mp 211°; ir (Nujol): ν 3290 (-NH), 1265 (C-F), 1765 (C=O), 1060 (S=O); uv (ethanol): λ max $m\mu$ (ϵ) 207 (25,220), 252.5 (37,830), 267 (27,284), 361 (4,127).

Anal. Calcd. for $C_{14}H_{10}FNO_2S$: C, 57.73; H, 3.43; N, 4.81. Found: C, 57.64; H, 3.40; N, 4.82.

3-Acetoxy-10-acetyl-7-fluorophenothiazine (XIII).

Compound III-a (1.61 g, 0.007 mole) was stirred with 40 ml of acetic anhydride, 4 ml of pyridine and an excess of zinc dust for 45 minutes at room temperature and then heated under reflux for 1 hour. The solution was poured into ice cold water and the solid so obtained was then taken up in chloroform. The extracts were washed with saturated sodium bicarbonate, dried and concentrated. The solid obtained was crystallized from benzene to afford 0.99 g (45%) of the dark yellow compound XIII, mp 128-130°; ir (Nujol): ν 1665 (N-acetyl), 1255 (C-F), 1745 (C=O).

Anal. Calcd. for $C_{16}H_{12}FNO_3S$: C, 60.56; H, 3.78; N, 4.41. Found: C, 60.51; H, 3.76; N, 4.36.

3-Acetoxy-10-acetyl-7-fluorophenothiazine 5-Oxide (XIV).

To a solution of 4.75 g (0.015 mole) of XIII in 75 ml of ethanol was added 2.38 g of 30% hydrogen peroxide and the solution was heated under reflux for 7 hours. The solution was concentrated on a steam bath and the solid obtained was dried and crystallized from ethanol to give 2.79 g (56%), of XIV, mp 220°; ir (Nujol): ν 1665 (N-acetyl), 1260 (C-F), 1760 (C=O), 1025 (S=O).

Anal. Calcd. for $C_{16}H_{12}FNO_4S$: C, 57.65; H, 3.60; N, 4.20. Found: C, 57.67; H, 3.62; N, 4.13.

7-Fluoro-3-hydroxyphenothiazine 5-Oxide (IV).

Compound XII (1.30 g, 0.0045 mole) in 75 ml of ethanol was refluxed for 30 minutes after adding 10 ml of a solution of 0.05 N ethanolic sodium hydroxide. It was cooled and poured into 500 ml of cold water. The aqueous layer was acidified to pH 2 with 10% hydrochloric acid and extracted with chloroform. The chloroform extracts were discarded and

the aqueous phase was adjusted to pH-8 with solid sodium carbonate. A white precipitate thus obtained was extracted with chloroform. The extracts were dried, decolorized and concentrated to give a white solid. Crystallization from ethanol provided 0.73 g (65%) of IV as white needles, ir (Nujol): ν 3320 (-NH), 1260 (C-F), 3550 (-OH); uv (ethanol): λ max $m\mu$ (ϵ) 239 (36,385), 274 (12,421), 299 (8,148), 342 (6,031); ms: (m/e) 249 (95), 233 (30), 232 (15), 221 (32), 201 (98), 200 (32), 193 (4), 192 (100), 174 (15), 173 (12), 166 (8), 160 (4).

Anal. Calcd. for $C_{12}H_8FNO_2S$: C, 57.83; H, 3.21; N, 5.62. Found: C, 57.77; H, 3.18; N, 5.60.

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