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In this paper it is shown that 2-nitro-2'-(β -acetyl)hydrazinodiphenyl sulfides cyclize, *via* a Smiles rearrangement, to 10-acetylaminophenothiazines, which are inert to alkalis and suffer a strong decomposition by acids. 10-Aminophenothiazine has been obtained by ring closure of 2-bromo-2'-hydrazinodiphenyl sulfide *via* an assumed benzyne intermediate.

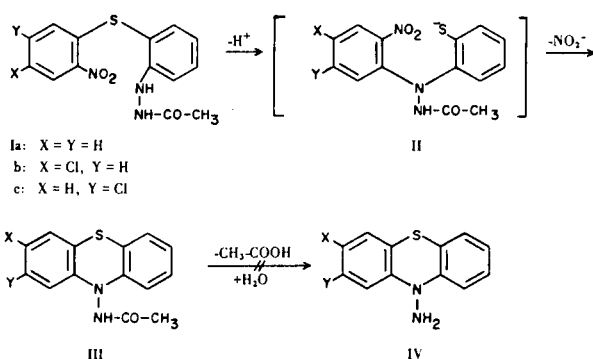
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In connection with ongoing work on the synthesis of analogs of antipsychotic phenothiazines, we were interested in the preparation of the hitherto unknown 10-aminophenothiazine and nuclear substitution derivatives thereof.

Since attempts of *N*-nitrosation of phenothiazine have been unsuccessful (1), only a cyclization route would lead to the synthesis of the desired compounds. It is known (2) that the base-catalyzed Smiles rearrangement of 2-nitro-2'-acylamino diphenyl sulfides gives *N*-acyl-2-(2'-nitrophenylamino)phenyl sulfides, which then cyclize to the corresponding *N*-acylphenothiazines. It was thought (Scheme I), that 2-nitro-2'-(β -acetyl)hydrazinodiphenyl sulfides (I), in which the acidity of the α -NH group is enhanced and the nucleophilicity of the α -N⁻ anion is not lowered by a β -acetyl group, should rearrange in a similar way to the *N,N*-diphenylhydrazine derivatives, (II) and that the latter should cyclize to the corresponding 10-acetylaminophenothiazines (III). Hydrolysis of compounds III should afford the desired compounds IV.

Compounds I, obtained from the corresponding amines by routine methods, did not yield the corresponding 10-aminophenothiazine derivatives (IV) when submitted to the customary experimental conditions used in the Smiles synthesis of phenothiazines. However, when solutions of compounds I in *N,N*-dimethylformamide were refluxed for a short time in the presence of an equimolar amount of anhydrous potassium carbonate, compounds III were obtained in fairly good yield. The only secondary breakdown products in these reactions were the corresponding phenothiazines.

Scheme I

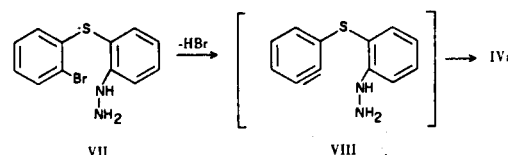


ir spectra of compounds III the bands assigned to the nitro group had disappeared. In addition, in the nmr spectra of compounds III, the signal due to the H-3 had been displaced towards the region of the rest of the aromatic protons ($\delta = 6.8-7.4$). This signal appeared at $\delta = 8.2-8.4$ in the starting materials, due to the deshielding effect of the *ortho* nitro group.

In order to prove the existence of an intermediate Smiles rearrangement product, compounds Va and Vb were cyclized under the same conditions as above to yield compounds identical to IIIc and IIIb, respectively (Scheme II).

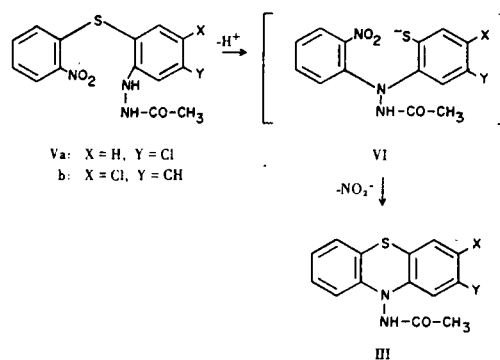
Hydrolysis of compounds III to compounds IV could not be accomplished since they were unreactive towards alkalyne hydrolysis conditions. On the other hand, they showed an excessive liability towards acid hydrolysis which led to black decomposition products.

The synthesis of 10-aminophenothiazines was at last achieved in low yield (18%) as outlined below.



Compound IVa showed an infrared spectrum very similar to that of *N*-amino carbazol and gave, by acetylation, a compound identical to compound IIIa. *N*-Aminophenothiazine underwent rapid acidic decomposition giving black products even in the presence of weak acids.

Scheme II



The fact that cyclization had taken place could be deduced from the analytical and spectral data. Thus, in the

EXPERIMENTAL

Melting points were determined on a Gallenbamp capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12 60 MHz spectrometer with TMS as internal reference.

Aminodiphenyl Sulfides.

The following compounds were obtained according to the literature: 2-nitro-2'-aminodiphenyl sulfide (3), 2-nitro-4-chloro-2'-aminodiphenyl sulfide (4), 2-nitro-5-chloro-2'-aminodiphenyl sulfide (5), 2-nitro-2'-amino-4'-chlorodiphenyl sulfide (6) and 2-bromo-2'-aminodiphenyl sulfide (7).

2-Nitro-2'-amino-5'-chlorodiphenyl Sulfide.

This compound was obtained in 55% yield starting from 2-amino-5-chlorobenzenethiol hydrochloride (8), following an above mentioned method (6), m.p. 144-145° (ethanol); ir (nujol, ν): 3420, 3330 (-NH₂); 1510, 1330 (-NO₂); nmr (deuteriochloroform, δ): 4.61 (s, 2H, NH₂); 6.8-7.6 (m, 7H, aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton).

Anal. Calcd. for C₁₂H₉ClN₂O₂S: C, 51.33; H, 3.20; N, 9.98. Found: C, 51.60; H, 3.33; N, 10.08.

Hydrazinodiphenyl Sulfides.

General Procedure.

The powdered corresponding amine (0.4 mole) was added gradually, under vigorous stirring, to 560 ml. of hydrochloric acid. The mixture was stirred at room temperature for 2 hours, whereupon sodium nitrite (0.44 mole) in 160 ml. of water was added dropwise, keeping the temperature between 0° and 5°. After stirring for 1 hour at this temperature, the reaction mixture was cooled to -15° (salt-ice bath) and a solution of stannous chloride dihydrate (0.88 mole) in 140 ml. of hydrochloric acid cooled at -15° was added at once with stirring. The reaction mixture was left standing overnight, and the solid was filtered off and treated with an excess of a 20% solution of sodium hydroxide. After two hours stirring, the solid was filtered off, washed with water and dried over calcium chloride *in vacuo*.

The following compounds were obtained according to this procedure:

2-Nitro-2'-hydrazinodiphenyl Sulfide.

This compound was obtained as a yellow solid in 53% yield, m.p. 138-139° (benzene and then ethanol); ir (nujol, ν): 3330, 3320 (-NH-NH₂); 1520, 1340 (-NO₂); nmr (DMSO-*d*₆, δ): 3.2-3.8 (bm, 2H, NH₂); 6.65-6.95 (m, 3H, H-3', H-4', and H-5', aromatic protons); 7.2-7.6 (m, 4H, H-4, H-5, H-6 and H-6', aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton).

Anal. Calcd. for C₁₂H₁₁N₃O₂S: C, 55.17; H, 4.21; N, 16.09. Found: C, 55.46; H, 4.41; N, 16.29.

2-Nitro-4-chloro-2'-hydrazinodiphenyl Sulfide.

This compound was obtained as a yellowish solid in 51% yield, m.p. 128.5-129° (benzene); ir (nujol, ν): 3340, 3300 (-NH-NH₂); 1520, 1340 (-NO₂); nmr (DMSO-*d*₆, δ): 3.2-3.7 (bm, 2H, NH₂); 6.7-7.6 (m, 6H, H-5, H-6, H-3', H-4', H-5', and H-6', aromatic protons); 8.30-8.35 (m, 1H, H-3, aromatic proton).

Anal. Calcd. for C₁₂H₁₀ClN₃O₂S: C, 48.74; H, 3.38; N, 14.21. Found: C, 48.69; H, 3.63; N, 14.00.

2-Nitro-5-chloro-2'-hydrazinodiphenyl Sulfide.

This compound was obtained as a yellow solid in 58% yield,

m.p. 138-139° (benzene and then ethanol); ir (nujol, ν): 3340, 3300 (-NH-NH₂); 1520, 1340 (-NO₂); nmr (DMSO-*d*₆, δ): 3.0-3.6 (bm, 2H, NH₂); 6.7-7.6 (m, 6H, H-4, H-6, H-3', H-4', H-5' and H-6', aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton).

Anal. Calcd. for C₁₂H₁₀ClN₃O₂S: C, 48.74; H, 3.38; N, 14.21. Found: C, 49.00; H, 3.32; N, 14.18.

2-Nitro-2'-hydrazino-4'-chlorodiphenyl Sulfide.

This compound was obtained as a yellow solid in 65% yield, m.p. 152-154° (benzene); ir (nujol, ν): 3350, 3290 (-NH-NH₂); 1520, 1340 (-NO₂); nmr (DMSO-*d*₆, δ): 3.0-3.7 (bm, 2H, NH₂); 6.70-6.95 (m, 2H, H-3' and H-5', aromatic protons); 7.2-7.5 (m, 4H, H-4, H-5, H-6 and H-6', aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton).

Anal. Calcd. for C₁₂H₁₀ClN₃O₂S: C, 48.74; H, 3.38; N, 14.21. Found: C, 48.72; H, 3.54; N, 13.97.

2-Nitro-2'-hydrazino-5'-chlorodiphenyl Sulfide.

This compound was obtained as a yellow solid in 37% yield, m.p. 132-133° (benzene); ir (nujol, ν): 3360, 3320 (-NH-NH₂); 1520-1340 (-NO₂); nmr (DMSO-*d*₆, δ): 3.3-4.0 (bm, 2H, NH₂); 6.75-6.95 (m, 2H, H-3' and H-4', aromatic protons); 7.3-7.6 (m, 4H, H-4, H-5, H-6 and H-6', aromatic protons); 8.2-8.4 (m, 1H, H-3, aromatic proton).

Anal. Calcd. for C₁₂H₁₀ClN₃O₂S: C, 48.74; H, 3.38; N, 14.21. Found: C, 49.00; H, 3.45; N, 14.25.

2-Bromo-2'-hydrazinodiphenyl Sulfide.

The compound was extracted with diethyl ether. Evaporation of the organic extracts afforded a reddish solid, which was recrystallized from ethanol (charcoal) to give a colorless solid in 64% yield, m.p. 116-117°; ir (nujol, ν): 3340, 3260 (-NH-NH₂); nmr (DMSO-*d*₆, δ): 3.0-3.6 (bm, 2H, NH₂); 6.7-7.5 (m, 8H, aromatic protons).

Anal. Calcd. for C₁₂H₁₁BrN₂S: C, 48.82; H, 3.75; N, 9.49. Found: C, 48.72; H, 3.76; N, 9.72.

2-Nitro-2'-(β -acetyl)hydrazinodiphenyl Sulfides.

General Procedure.

To a cooled solution (0°) of 0.1 mole of the corresponding hydrazine in 120 ml. of tetrahydrofuran, 9.40 ml. (0.1 mole) of acetic anhydride were added dropwise. The reaction mixture was left overnight and the solvent concentrated to dryness *in vacuo*. The residue was treated with a small amount of diethyl ether and filtered to give the desired products which were chromatographically pure.

The following compounds were obtained according to this procedure:

2-Nitro-2'-(β -acetyl)hydrazinodiphenyl Sulfide (Ia).

This compound was obtained as a yellow solid in 91% yield, m.p. 144-145° (ethanol); ir (nujol, ν): 3330, 3300 (-NH-NH₂): 1670 (C=O); 1520, 1340 (-NO₂); nmr (deuteriochloroform, δ): 1.90 (s, 3H, CH₃); 6.85-7.10 (m, 3H, H-4', H-5' and H-6', aromatic protons); 7.40-7.70 (m, 4H, H-4, H-5, H-6 and H-3', aromatic protons); 7.95 (s, 1H, -NH-), 8.30-8.45 (m, 1H, H-3, aromatic proton); 9.95 (s, 1H, -NH-).

Anal. Calcd. for C₁₄H₁₃N₃O₃S: C, 55.44; H, 4.32; N, 13.86. Found: C, 55.25; H, 4.54; N, 13.64.

2-Nitro-4-chloro-2'-(β -acetyl)hydrazinodiphenyl Sulfide (Ib).

This compound was obtained as a yellow solid in 96% yield, m.p. 170-172° (ethanol); ir (nujol, ν): 3330, 3300 (-NH-NH₂);

1670 (C=O); 1520, 1340 (-NO₂); nmr (deuteriochloroform, δ): 1.90 (s, 3H, CH₃); 6.85-7.05 (m, 2H, H-4' and H-5', aromatic protons); 7.35-7.75 (m, 4H, H-4, H-5, H-6 and H-3', aromatic protons); 7.90 (s, 1H, NH); 8.30-8.35 (m, 1H, H-3, aromatic proton); 9.95 (s, 1H, NH).

Anal. Calcd. for C₁₄H₁₂ClN₃O₃S: C, 49.79; H, 3.55; N, 12.44. Found: C, 49.69; H, 3.38; N, 12.24.

2-Nitro-5-chloro-2'-(β -acetyl)hydrazinodiphenyl Sulfide (Ic).

This compound was obtained as a yellow solid in 84% yield, m.p. 175-176° (ethanol); ir (nujol, ν): 3340, 3250 (-NH-NH-); 1660 (C=O); 1510, 1340 (-NO₂); nmr (deuteriochloroform, δ): 1.90 (s, 3H, CH₃); 6.85-7.05 (m, 2H, H-4' and H-5', aromatic protons); 7.30-7.75 (m, 4H, H-4, H-6, H-3' and H-6', aromatic protons); 7.85 (s, 1H, NH); 8.20-8.40 (m, 1H, H-3, aromatic proton); 9.95 (s, 1H, NH).

Anal. Calcd. for C₁₄H₁₂ClN₃O₃S: C, 49.79; H, 3.55; N, 12.44. Found: C, 49.57; H, 3.49; N, 12.22.

2-Nitro-2'-(β -acetyl)hydrazino-4'-chlorodiphenyl Sulfide (Va).

This compound was obtained as a yellow solid in 89% yield, m.p. 195-197° (toluene); ir (nujol, ν): 3320, 3270 (-NH-NH-); 1660 (C=O); 1510, 1340 (-NO₂); nmr (deuteriochloroform, δ): 1.90 (s, 3H, CH₃); 6.85-7.0 (m, 2H, H-4' and H-6', aromatic protons); 7.4-7.7 (m, 4H, H-4, H-5, H-6 and H-3', aromatic protons); 7.95 (s, 1H, NH); 8.25-8.40 (m, 1H, H-3, aromatic proton); 9.95 (s, 1H, NH).

Anal. Calcd. for C₁₄H₁₂ClN₃O₃S: C, 49.79; H, 3.55; N, 12.44. Found: C, 49.55; H, 3.73; N, 12.53.

2-Nitro-2'-(β -acetyl)hydrazino-5'-chlorodiphenyl Sulfide (Vb).

This compound was obtained as a yellow solid in 86% yield, m.p. 156-158° (toluene); ir (nujol, ν): 3320, 3290 (-NH-NH-); 1660 (C=O); 1510, 1340 (-NO₂); nmr (deuteriochloroform, δ): 1.90 (s, 3H, CH₃); 6.85-7.0 (m, 2H, H-4' and H-6', aromatic protons); 7.45-7.65 (m, 4H, H-4, H-5, H-6 and H-3', aromatic protons); 7.85 (s, 1H, NH); 8.30-8.45 (m, 1H, H-3, aromatic proton); 9.95 (s, 1H, NH).

Anal. Calcd. for C₁₄H₁₂ClN₃O₃S: C, 49.79; H, 3.55; N, 12.44. Found: C, 49.68; H, 3.69; N, 12.59.

10-Acetylaminophenothiazines (III).

General Procedure.

Anhydrous potassium carbonate (0.01 mole) was added to a solution of the corresponding β -acetylhydrazino compounds (0.01 mole) in 30 ml. of *N,N'*-dimethylformamide, and the vigorously stirred reaction mixture was heated under reflux for 15 minutes. After cooling to room temperature it was poured into water. The precipitate was filtered, washed with diethyl ether and recrystallized from acetonitrile.

The following compounds were obtained according to this procedure:

10-Acetylaminophenothiazine (IIIa).

This compound was obtained as a colorless solid in 71% yield, m.p. 219-221° dec.; ir (nujol, ν): 3180 (-NH-); 1680 (C=O); nmr (DMSO-*d*₆, δ): 2.15 (s, 3H, CH₃); 6.8-7.3 (m, 8H, aromatic protons); 10.5 (s, 1H, NH).

Anal. Calcd. for C₁₄H₁₂N₂OS: C, 65.61; H, 4.72; N, 10.93. Found: C, 65.35; H, 4.90; N, 11.04.

3-Chloro-10-acetylaminophenothiazine (IIIb).

This compound was obtained as a colorless solid from Ib in 71% yield and Vb in 40% yield, m.p. 223-224° dec.; ir (nujol, ν): 3200 (-NH-); 1670 (C=O); nmr (DMSO-*d*₆, δ): 2.15 (s, 3H, CH₃);

6.8-7.3 (m, 7H, aromatic protons); 10.7 (s, 1H, NH).

Anal. Calcd. for C₁₄H₁₁ClN₂OS: C, 57.85; H, 3.78; N, 9.64. Found: C, 58.04; H, 3.87; N, 9.44.

2-Chloro-10-acetylaminophenothiazine (IIIc).

This compound was obtained as a colorless solid from Ic in 25% yield and from Va in 60% yield, m.p. 220-222° dec.; ir (nujol, ν): 3200 (NH); 1680 (C=O); nmr (DMSO-*d*₆, δ): 2.15 (s, 3H, CH₃); 6.8-7.4 (m, 7H, aromatic protons); 10.65 (s, 1H, NH).

Anal. Calcd. for C₁₄H₁₁ClN₂OS: C, 57.85; H, 3.78; N, 9.64. Found: C, 57.84; H, 3.85; N, 9.61.

10-Aminophenothiazine (IVa).

2-Bromo-2'-hydrazinodiphenyl sulfide (VII) (8 g., 0.027 mole) in 200 ml. of anhydrous diethyl ether was added dropwise to a solution of sodium amide in liquid ammonia, prepared from 2.6 g. (0.11 mole) of sodium and 600 ml. of ammonia. The reaction mixture was stirred at room temperature for 4 hours. After the ammonia had been removed, water was added to destroy the excess sodium amide. It was then extracted with diethyl ether and the organic extracts were concentrated to dryness *in vacuo*. Recrystallization of the residue from ethanol afforded 1.1 g. (18%) of IVa as light grey plates, m.p. 119-121°; ir (nujol, ν): 3370, 3420 (NH₂).

Anal. Calcd. for C₁₂H₁₀N₂S: C, 67.28; H, 4.70; N, 13.07. Found: C, 67.07; H, 4.57; N, 13.08.

10-Acetylaminophenothiazine (IIIa).

The crude product of another run of the above reaction was dissolved in diethyl ether and treated with an excess of acetic anhydride. The precipitate which then appeared was filtered, washed with diethyl ether and recrystallized from ethanol, yield 20%. This compound was identical in all respects to that obtained from 2-nitro-2'-(β -acetyl)hydrazinodiphenyl sulfide (Ia).

10-Benzoylaminophenothiazine.

The crude residue of another run was dissolved in anhydrous pyridine and treated with an excess of benzoyl chloride. The reaction mixture was left standing overnight and then diluted with water to yield a colorless solid in 16% yield, m.p. 197-199° (ethanol); ir (nujol, ν): 3330 (-NH); 1690 (C=O); nmr (DMSO-*d*₆, δ): 6.8-7.4 (m, 13H, aromatic protons); 10.6 (s, 1H, NH).

Anal. Calcd. for C₁₉H₁₄N₂OS: C, 71.68; H, 4.43; N, 8.80. Found: C, 71.62; H, 4.34; N, 8.56.

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