1,3-Benzoxathioles. Electrophilic Aromatic Substitution

Salvatore Cabiddu (a), Giovanni Cerioni (b), Maria Teresa Cocco (b),

Antonio Maccioni (b) and Antonio Plumitallo (b)

(a) Istituto di Chimica Organica, Università,
09100 Cagliari, Italy

(b)Istituto di Chimica Farmaceutica e Tossicologica,
Università, 09100 Cagliari, Italy
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Some electrophilic substitution reactions on 1,3-benzoxathiole derivatives are described. Bromination and acylation reactions take place in position 5, *i.e.*, *para* to the oxygen atom. 1,3-Benzoxathiole nitration yields a mixture of the corresponding sulfoxide and of the 6-nitro derivative when performed with 33% nitric acid, while, using a mixture of 40% nitric acid and acetic acid or acetyl nitrate, the 6-nitroderivative is obtained together with large amounts of gummy products. 2,2-Dimethyl-1,3-benzoxathiole nitration with 33% nitric acid yields disulfide XI, while with 33% nitric acid and acetic acid or with acetyl nitrate a mixture of disulfide XI and XII is obtained. The structure of the products have been determined by spectroscopic methods.

In previous works some methods for obtaining 1,3-benzoxathioles have been reported and their reactions with organomagnesium, organocalcium and organolithium compounds have been studied (1). This last type of reaction showed the possibility of introducing functional groups in positions 2 and 7 (1e).

Bearing in mind the potential pharmaceutical activity of this heterocyclic ring due to its isology with 1,3-benzodioxole, we have tested some electrophilic substitution reactions with the purpose of functionalizing the other possible positions of the benzene ring. We have examined bromination, acylation and nitration reactions; in all these cases we tried to minimize the medium acidity or the oxidizing power to avoid heterocyclic ring opening.

The reaction of equimolar amounts of Ia-b with bromine in acetic anhydride at low temperatures (-5°) in a strictly anhydrous medium, or with *N*-bromosuccinimide in warm carbon tetrachloride, gives (Scheme 1) compounds IIa-b in good yields. They have been identified by elemental analysis and ir and nmr spectroscopy. The halogen atom position has been determined by examining the aromatic region of their nmr spectra. In fact, in the spectrum of IIa, it is possible to observe an AMX system with this set of parameters: δ_A 7.25, δ_M 7.07 and δ_X 6.65 ppm and $J_{MX} = 8.4$ Hz, $J_{AM} = 2.0$ Hz and $J_{AX} \cong 0.5$ Hz. These coupling constants are of the type *ortho, meta* and *para,* respectively, and both structure "A" and "B", which have the halogen atom in the *para* position respective to the oxygen or the sulfur atom, could satisfy these spectral requirements.
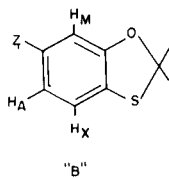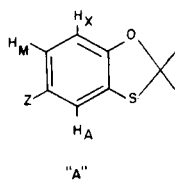
To distinguish between these two possibilities for the halo derivatives, IIa has been transformed in the corresponding sulfoxide IVa. The analysis of the aromatic region of the nmr spectrum showed again a group of signals centered at δ 7.97, δ 7.64 and δ 7.10 ppm. Doping the solution with increased quantities of tris(dipivaloylmethanato)europium, one of the signals moves gradually to low fields, from δ 7.97 to δ 8.15 ppm, with a clearly greater rate than the others. This signal shows one *meta* ($J_{AM} = 2.0$ Hz) and one *para* ($J_{AX} \cong 0$ Hz) coupling constants, which univocally demonstrates the rightness of the type "A" structure.

Compounds IIIa-b have been obtained in good yields by acylation with acetic anhydride (Scheme 1). In this case, because of the fact that the carbonyl group is a very good complexation site for the tris(dipivaloylmethanato)europium (2), it has not been possible to determine the substituent position *via* sulfoxide. On the other side, because of the molecular symmetry of both form "A" and "B", to perform measures with tris(dipivaloylmethanato)europium exploiting the carbonyl group would not have solved the structural problem. For this reason, IIIa-b has been desulfurated with Raney nickel catalyst (3) and the reaction mixture has been compared with authentic samples by glc; the presence of only compounds VI and VIIa-b allows us to assign the substituent the position *para* to the oxygen atom.

Remarkable difficulties have been met for the synthesis of the nitroderivatives from Ia-b. In fact, starting from Ia and 33% nitric acid, the reaction yields mostly the sulfoxide VIII besides some small quantities (10%) of the nitroderivative IX (Scheme 2). The latter has, surprisingly, the nitro group *meta* to the oxygen atom. It is possible to increase slightly (20%) the yields of IX operating at -10° or below with a mixture of 40% nitric acid and acetic acid or with acetyl nitrate. Operating with these two last modalities, the sulfoxide VIII is not obtained, but notable

"A"   "B"

Scheme 1

a: R= H

b: R=CH$_3$
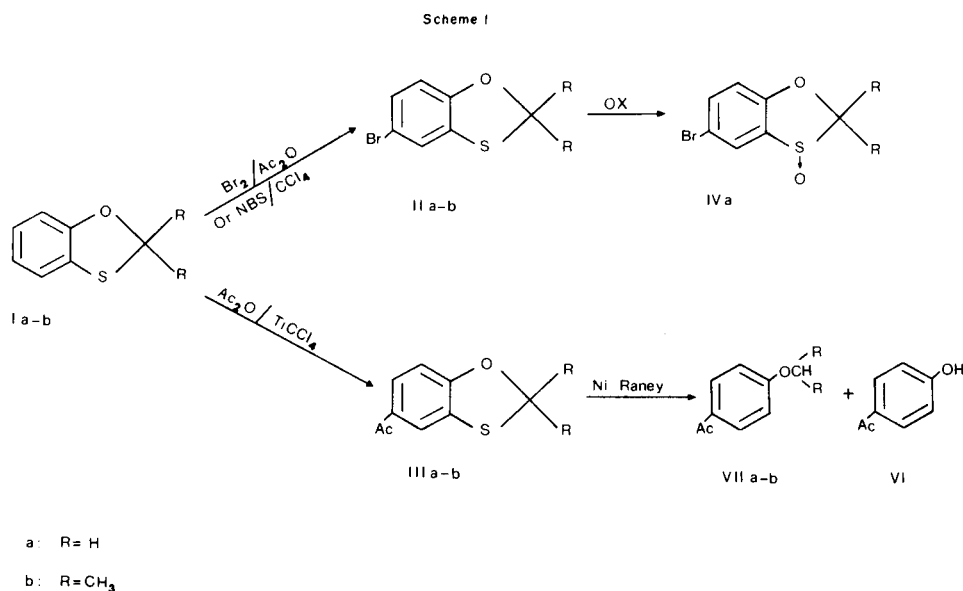
amounts of gummy products are formed and a complete analysis of this mixture has not been possible.

The nitration of Ib was even more complicated. Starting from this substrate, we could not obtain the corresponding nitro derivative because, regardless of the conditions which we tried, we always observed cleavage of the heterocyclic ring. So, with 33% nitric acid we have obtained the disulfide XI (Scheme 3), while with a mixture of 33% nitric acid and acetic acid or with acetyl nitrate, the reaction gives both XI and XII. Carrying out the reactions at very low temperatures yields the same results; besides in every case, the reaction products are obtained together with fair amounts of gummy products of unknown structures.

Scheme 2
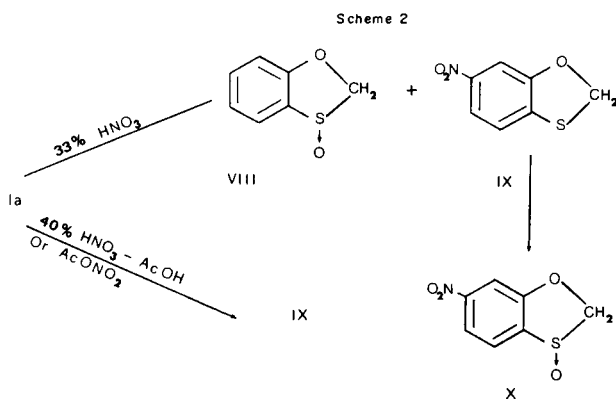
The difference of stability of Ia with respect to Ib towards the nitration reaction can be justified by observing that the first one is the cyclic acetal of formaldehyde, more stable than the latter to the hydrolysis reaction (4). On the other hand, Ib, the cyclic acetal of acetone, will be easily hydrolyzed to 2-hydroxybenzenethiole XIII, which

will first undergo an oxidation to the disulfide and then will be nitrated to mono XII and in a second step, to the dinitro XI derivative. The fact that, under the same reaction conditions, XIII yields XI and XII, and XI is obtained from XII confirmed our hypotheses.

The fact that VIII is obtained is explained by the oxidative capabilities of aqueous nitric acid, while surprisingly, the formation of IX, whose nitro group is para to the sulfur atom, is in contrast to that which happens in the case of acylation and bromination reactions. Further research is in progress to explain this fact and to find the reagents and the reaction conditions which will yield the nitro derivative of Ib.

The structure of VIII has been unambiguously demonstrated by analytical and spectral data. The nitro group position in IX has been determined by comparison of the aromatic region of its nmr spectrum with the one of the corresponding sulfoxide X, obtained without or with increasing amounts of tris(dipivaloylmethanato)europium. In fact, the spectrum of IX is of the AMX type, like that of a 1,2,4-trisubstituted aromatic ring, with the signals centered at δ 7.74, δ 7.54 and δ 7.16 ppm and the three coupling constants J$_{ortho}$, J$_{meta}$ and J$_{para}$ equal to J$_{AX}$ = 8.4 Hz, J$_{AM}$ = 2.1 Hz and J$_{MX}$ $\cong$ 0.5 Hz. The aromatic region of X is formed, before doping the solution with tris-(dipivaloylmethanato)europium, by a singlet centered at δ 8.05 ppm because of the casual isochronism of the three aromatic protons. Increasing amounts of tris(dipivaloyl-methanato)europium remove the isochronism and produce also, in this case, a system of the AMX type. The proton which undergoes the major shift to δ 10.01 ppm is characterized by an ortho coupling constant (J$_{AX}$ = 8.6 Hz). A more detailed analysis of the system is unnecessary

Scheme 3
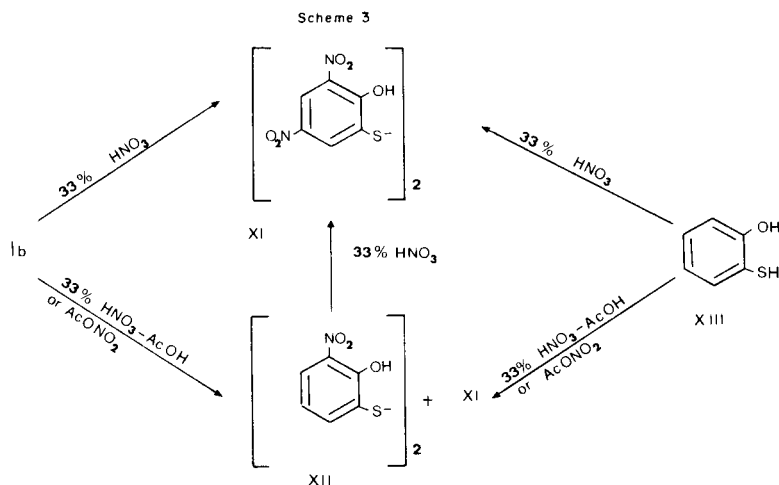
and the large amounts of tris(dipivaloylmethanato)-europium required would tend to lose the fine structure of the spectrum because of the braodening of the signals. As a matter of fact, we could determine at least a *meta* coupling constant ($J_{AM} = 1.7$ Hz).

Also the correct position of the nitro group of XII has been determined by nmr analysis. The system has three signals centered at δ 8.00, δ 7.89 and δ 6.98 ppm (ABX type) in agreement with an aromatic trisubstituted ring and the coupling constants are only of the type *ortho* and *meta* ($J_{AX} = 8.9$ Hz, $J_{BX} = 7.9$ Hz, $J_{AB} = 1.6$ Hz). The analysis of the spectrum has been checked by computer simulation. The nitro group can so be either *ortho* to the oxygen atom or to the sulfur atom. Since the OH proton lies at very low fields (δ 11.1 ppm), we have been able to choose the correct structure with the nitro group *ortho* to the oxygen atom. In a similar manner we have determined the positions of the nitro groups for the disulfide XI (AB system with signals centered at δ 8.96 and δ 8.79 ppm *meta* type $J_{AB} = 2.6$ Hz, the OH group signal at very low fields δ 11.50 ppm).

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus (capillary method) and are uncorrected. All boiling points were uncorrected and obtained from distillation or with a boiling point apparatus. Infrared spectra were determined on a Perkin Elmer model 157 G spectrophotometer using either potassium bromide mulls or neat liquids between sodium chloride plates. The nmr spectra were determined on a Varian FT 80A spectrometer using tetramethylsilane as the internal reference. The glc analyses were performed on a Carlo Erba GV instrument equipped with SE-30 column (2 m × 0.5 cm, 10% on carbowax 20M). Microanalyses for CHN were carried out on a Perkin Elmer model 240 Elemental Analyzer; analyses for Br and S were performed according to literature procedures (5).

Starting Materials.

1,3-Benzoxathiole (Ia) and 2,2-dimethyl-1,3-benzoxathiole (Ib) were prepared by reported methods (1a,6).

5-Bromo-1,3-benzoxathiole (IIa).

A solution of Ia (5 g, 0.036 mole) in acetic anhydride (25 ml), enough to give a clear solution, was treated dropwise with bromine (5.8 g, 0.036 mole) with rapid stirring at -5°. The reaction was set aside for 1 hour and then poured into 10% sodium carbonate and extracted with diethyl ether. The combined extracts were washed with water, dried over sodium sulfate and evaporated to afford IIa a pale yellow oil, yield 70%, bp 133-135° (3 mm); n$\overset{25}{D}$ 1.6390; ir (neat): 810 cm^{-1} (1,2,4-trisubstituted benzene); nmr (deuteriochloroform): δ 6.99 (m, 3H aromatic, AMX, $\nu_A = 7.25$, $\nu_M = 7.07$, $\nu_X = 6.65$, $J_{MX} = 8.4$ Hz, $J_{AM} = 2.0$ Hz, $J_{AX} \cong 0.5$ Hz) and 5.68 ppm (s, 2H, >CH$_2$).

Anal. Calcd. for C$_7$H$_5$BrOS: C, 38.73; H, 2.32; Br, 36.81; S, 14.77. Found: C, 38.55; H, 2.25; Br, 36.70; S, 14.58.

The same result was obtained performing the reaction with equimolar amounts of N-bromosuccinimide in carbon tetrachloride, yield 66%.

5-Bromo-1,3-benzoxathiole S-Oxide (IVa).

To a well stirred mixture of IIa (0.3 g, 0.0014 mole) in dry chloroform (30 ml), kept at 0°, a solution of 3-chloroperoxybenzoic acid (0.24 g, 0.0014 mole) in dry chloroform (30 ml) was added dropwise. When the addition was complete, the mixture was stirred for almost 24 hours at room temperature, and then washed (in turn) with 10% aqueous potassium carbonate, water and dried over anhydrous sodium sulfate. After solvent evaporation *in vacuo*, the crude product was crystallized from benzene, yield 92%, mp 122°; ir (potassium bromide): 1050 (S=O), 810 cm^{-1} (1,2,4-trisubstituted benzene); nmr (deuteriochloroform): δ 7.57 (m, 3H aromatic, AMX, $\nu_A = 7.97$, $\nu_M = 7.64$, $\nu_X = 7.10$, $J_{MX} = 8.8$ Hz, $J_{AM} = 2.0$ Hz, $J_{AX} \cong 0$ Hz) and 5.24 ppm (q, 2H, >CH$_2$, J = 11.2 Hz).

Anal. Calcd. for C$_7$H$_5$BrO$_2$S: C, 36.07; H, 2.16; Br, 34.29; S, 13.75. Found: C, 36.20; H, 2.23; Br, 34.14; S, 13.62.

5-Bromo-2,2-dimethyl-1,3-benzoxathiole (IIb).

This compound was obtained by a similar method described for IIa, starting from Ib (5 g, 0.03 mole) acetic anhydride (20 ml) and bromine (4.8 g, 0.03 mole), yield 63%; bp 126-127° (2 mm); n$\overset{25}{D}$ 1.5950; ir (neat): 815 cm^{-1} (1,2,4-trisubstituted benzene); nmr (deuteriochloroform): δ 6.71 (m, 3H aromatic, AMX, $\nu_A = 7.00$, $\nu_M = 6.87$, $\nu_X = 6.27$, $J_{MX} = 8.2$ Hz, $J_{AM} = 1.8$ Hz, $J_{AX} \cong 0$ Hz) and 1.69 ppm (s, 6H, (CH$_3$)$_2$C<).

Anal. Calcd. for C$_9$H$_9$BrOS: C, 44.09; H, 3.70; Br, 32.60; S, 13.08. Found: C, 44.20; H, 3.61; Br, 32.49; S, 12.95.

5-Acetyl-1,3-benzoxathiole (IIIa).

To a well stirred mixture of Ia (6.9 g, 0.05 mole), carbon tetrachloride (50 ml) and titanium tetrachloride (13 g, 0.07 mole) was added acetic anhydride (5.1 g, 0.05 mole) maintaining the temperature at 0°. After stirring for an additional 15 hours at 0°, the mixture was poured onto 100 g of ice and extracted with chloroform. The extract was washed (in turn) with 10% sodium carbonate, water and dried over anhydrous

sodium sulfate. After solvent evaporation *in vacuo*, the crude product was recrystallized from ethanol, yield 83%, mp 124-125°; ir (potassium bromide): 1660 (C=O), 815 cm^{-1} (1,2,4-trisubstituted benzene); nmr (deuteriochloroform): δ 7.42 (m, 3H aromatic, AMX, ν_A = 7.79, ν_M = 7.64, ν_X = 6.83, J_{MX} = 8.4 Hz, J_{AM} = 1.8 Hz, $J_{AX} \cong$ 0 Hz), 5.76 (s, 2H, >CH$_2$) and 2.52 ppm (s, 3H, CH$_3$-CO-).

Anal. Calcd. for C$_9$H$_8$O$_2$S: C, 59.98; H, 4.47; S, 17.79. Found: C, 60.11; H, 4.56; S, 17.61.

Action of Raney Nickel Catalyst on IIIa.

A solution of IIIa (0.5 g, 0.003 mole) in 95% ethanol (3 ml) was refluxed for 2 hours with Raney nickel (3) (0.6 g). The mixture was filtered, evaporated *in vacuo* and the residue diluted with diethyl ether. The glc analysis showed two peaks with the same retention time as VI and VIIa, respectively.

5-Acetyl-2,2-dimethyl-1,3-benzoxathiole (IIIb).

Acetic anhydride (2.6 g, 0.025 mole) was added dropwise at 0° to a mixture of Ib (4.1 g, 0.025 mole), carbon tetrachloride (50 ml) and titanium tetrachloride (6.6 g, 0.035 mole). The resulting mixture was worked up in the same manner described for the synthesis of IIIa, giving an oil, which was purified by distillation *in vacuo*, yield 68%, bp 138-140° (3 mm); n$_D^{25}$ 1.5780; ir (neat): 1680 (C=O), 815 cm^{-1} (1,2,4-trisubstituted benzene); nmr (deuteriochloroform): δ 7.37 (m, 3H aromatic, AMX, ν_A = 7.72, ν_M = 7.63, ν_X = 6.77, J_{MX} = 8.3 Hz, J_{AM} = 2.0 Hz, $J_{AX} \cong$ 0.3 Hz), 2.49 (s, 3H, CH$_3$-CO-) and 1.84 ppm (s, 6H, (CH$_3$)$_2$C<).

Anal. Calcd. for C$_{11}$H$_{12}$O$_2$S: C, 63.43; H, 5.81; S, 15.39. Found: C, 63.31; H, 5.73; S, 15.17.

Action of Raney Nickel Catalyst on IIIb.

A solution of IIIb (0.05 g, 0.0024 mole) in 95% ethanol (2.5 ml) was refluxed for 2 hours with Raney nickel (0.5 g). The resulting mixture was worked up in the same manner described above. The glc analysis showed two peaks with the same retention time as VI and VIIb (7), respectively.

Reaction of Ia with 33% Nitric Acid.

Ia (6.9 g, 0.05 mole) was added to 33% nitric acid (60 g, 0.31 mole) over a period of 30 minutes while stirring and maintaining the temperature at 0°. After stirring for an additional 2 hours the mixture was filtered and the product washed with ice-water and *vacuum* dried. After recrystallization from ethanol, this product had mp 167-168° and was identified as 6-nitro-1,3-benzoxathiole (IX); ir (potassium bromide): 1320 and 1500 (NO$_2$), 810 cm^{-1} (1,2,4-trisubstituted benzene); nmr (deuteriochloroform): δ 7.48 (m, 3H aromatic, AMX, ν_A = 7.74, ν_M = 7.54, ν_X = 7.16, J_{AX} = 8.4 Hz, J_{AM} = 2.1 Hz, $J_{MX} \cong$ 0.5 Hz) and 5.78 ppm (s, 2H, >CH$_2$).

Anal. Calcd. for C$_7$H$_5$NO$_3$S: C, 45.89; H, 2.75; N, 7.65; S, 17.50. Found: C, 45.78; H, 2.81; N, 7.55; S, 17.36.

The solution was added to 500 g of ice and extracted with chloroform. The extract was washed (in turn) with 20% aqueous sodium carbonate and water and dried over anhydrous sodium sulfate. After solvent evaporation *in vacuo*, the crude product was chromatographed on a silica gel column, using benzene-petroleum ether (10:1) as eluent. Initial elution gave 0.5 g of pure IX. The entire amount of IX was 1 g, yield 11%. Subsequent elution afforded 4 g (52%) of a product which was identified as 1,3-benzoxathiole-*S*-oxide (VIII), mp 97-98°; ir (potassium bromide): 1040 cm^{-1} (S=O); nmr (deuteriochloroform): δ 7.50 (m, 4H aromatic) and 5.20 ppm (q, 2H, >CH$_2$, J = 11.3 Hz).

Anal. Calcd. for C$_7$H$_6$O$_2$S: C, 54.53; H, 3.92; S, 20.79. Found: C, 54.41; H, 3.83; S, 20.59.

Reaction of Ia with 40% Nitric Acid.

To a stirred mixture of 40% nitric acid (40 g, 0.254 mole) in glacial acetic acid (27 ml), Ia (6.9 g, 0.05 mole) was added over 30 minutes maintaining the internal temperature below -10°. After stirring for an additional two hours at -10°, the mixture was added to 500 g of ice. The product was then filtered, washed with water and dried *in vacuo* The crude material, which was identified as IX, crystallized from ethanol, yield 19%, mp 167-168°. The compound isolated from this reaction was iden-

tical to an authentic sample obtained above (mixed mp, ir and nmr data).

Reaction of Ia with Acetyl Nitrate.

Acetyl nitrate (prepared from 4.5 g of 100% nitric acid and 35 g of acetic anhydride) was added dropwise to a solution of Ia (4.2 g, 0.025 mole) in acetic anhydride (35 ml) while stirring and maintaining the internal temperature below -15°. After stirring for an additional 4 hours at -15°, the solution was added to 400 g of ice and the product worked up in the same manner described above. The compound was identified as IX and gave no depression in mixture melting point determination with an authentic sample of the product obtained above, yield 20%, mp 167-168°.

6-Nitro-1,3-benzoxathiole-*S*-oxide (X).

To a mixture of IX (0.3 g, 0.0016 mole) in dry chloroform (30 ml) kept at 0°, a solution of 3-chloroperoxybenzoic acid (0.28 g, 0.0016 mole) in dry chloroform (30 ml) was added dropwise with stirring. When the addition was complete, the mixture was worked up in the same manner described for IVa. The crude product was crystallized from benzene, yield 90%, mp 151°; ir (potassium bromide): 1515 and 1350 (NO$_2$), 1055 (S=O), 815 cm^{-1} (1,2,4-trisubstituted benzene); nmr (deuteriochloroform): δ 8.05 (s, 3H aromatic) and 5.39 ppm (q, 2H, >CH$_2$, J = 11.4 Hz).

Anal. Calcd. for C$_7$H$_5$NO$_4$S: C, 42.21; H, 2.53; N, 7.03; S, 16.10. Found: C, 42.18; H, 2.44; N, 6.91; S, 15.96.

Reaction of Ib with 33% Nitric Acid.

Ib (10 g, 0.06 mole) was added dropwise to 33% nitric acid (66 g, 0.346 mole) while stirring and maintaining the temperature at -10°. After stirring for an additional 1 hour at -10°, the precipitate was filtered off, washed thoroughly with water and dried. The crude material, which was identified as bis(2-hydroxy-3,5-dinitrophenyl) disulfide (XI), crystallized from dioxane-ethanol (4:1); yield 70%, mp 205°; ir (potassium bromide): 3260 (OH), 1545 and 1345 cm^{-1} (NO$_2$); nmr (DMSO-d$_6$): δ 11.50 (s, 1H, OH, deuterium oxide exchanged) and 8.87 ppm (m, 2H aromatic, AX, ν_A = 8.96, ν_X = 8.79, J_{AX} = 2.6 Hz).

Anal. Calcd. for C$_{12}$H$_6$N$_4$O$_{10}$S$_2$: C, 33.49; H, 1.41; N, 13.02; S, 14.90. Found: C, 33.39; H, 1.47; N, 12.94; S, 14.74.

Reaction of Ib with 33% Nitric Acid in Glacial Acetic Acid.

To a well stirred solution of Ib (8.3 g, 0.05 mole) in glacial acetic acid (27 ml) 33% nitric acid (38.4 g, 0.2 mole) was added dropwise over 1 hour while maintaining the temperature below -10°. After stirring for an additional 1 hour at -10°, the solution was poured onto 500 g of ice and extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. After solvent evaporation *in vacuo*, the crude product was chromatographed on a silica gel column, using benzene-acetone (4:1) as eluent. Initial elution gave 3 g of a product which was identified as bis(2-hydroxy-3-nitrophenyl)disulfide (XII), yield 36%, mp 139-140°; ir (potassium bromide): 3250 (OH), 1510 and 1350 (NO$_2$), 750 cm^{-1} (1,2,3-trisubstituted benzene); nmr (deuteriochloroform): δ 11.1 (s, 1H, OH, deuterium oxide exchanged) and 7.62 ppm (m, 3H aromatic, ABX, ν_A = 8.0, ν_B = 7.89, ν_X = 6.98, J_{AX} = 8.9 Hz, J_{BX} = 7.9 Hz, J_{AB} = 1.6 Hz).

Anal. Calcd. for C$_{12}$H$_8$N$_2$O$_6$S$_2$: C, 42.35; H, 2.37; N, 8.23; S, 18.84. Found: C, 42.50; H, 2.41; N, 8.17; S, 18.68.

Subsequent elution afforded 2.8 g of pure XI, yield 26%, mp and mixed mp 205°.

Reaction of Ib with Acetyl Nitrate.

A solution of Ib (4.15 g, 0.025 mole) in acetic anhydride (10 ml) was added dropwise to acetyl nitrate, prepared from 4.5 g of 100% nitric acid and 35 g of acetic anhydride. The addition was carried out at -20° while stirring rapidly. Stirring was continued and the temperature was maintained for an additional hour. The solution was then poured onto 500 g of ice and extracted with chloroform. The extracts were washed with water and dried over anhydrous sodium sulfate. After solvent evaporation *in vacuo*, the crude product was chromatographed on a silica gel column using benzene-acetone (4:1) as eluent. Initial elution gave starting material;

subsequent elution afforded XII and XI in the percentage ratio of 3:1, total yield 71%.

Reaction of XIII with 33% Nitric Acid.

Compound XIII (6) (6.3 g, 0.05 mole) was added dropwise to 33% nitric acid (5.5 g, 0.29 mole) while stirring and maintaining the temperature at -10°. The resulting mixture was then treated in the same manner described above for the reaction of Ib with 33% nitric acid, to furnish the compound XI, yield 81%. The ir and nmr spectra and melting point were identical with those of the above product.

Reaction of XIII with 33% Nitric Acid in Glacial Acetic Acid.

The same procedure described above was employed, starting from XIII (4 g, 0.032 mole), glacial acetic acid (17 ml) and 33% nitric acid (24.6 g, 0.13 mole). The crude product was chromatographed on a silica gel column using benzene-acetone (4:1) as eluent. The elution afforded XII and XI in the percentage ratio of 1:1, total yield 68%.

The same products XII and XI, in the percentage ratio of 2.8:1, were obtained starting from XIII and acetyl nitrate. Total yield 63%.

Reaction of XII with 33% Nitric Acid.

To 33% nitric acid (6.6 g, 0.035 mole), XII (2 g, 0.006 mole) was added while stirring and maintaining the temperature at -10°. The resulting mixture was worked up in the same manner described above to furnish the compound XI, yield 71%, mp and mixed mp 205°.

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