Table III. Electronic Spectra of Substituted Thioureas

| Compd. No. | Absorption Band Maxima, mμ [Molar Extinction Coefficients × $10^{-3}$] | | | |
|---|---|---|---|---|
| 1[a] | 293[22.7] | 307[25.1] | 323[25.1] | |
| 2[a] | | 319[29.6] | | |
| 3[b] | | 304[14.8] | | |
| 4[b] | | 320[26.9] | | |
| 5[a] | | 315[28.6] | | |
| 6[b] | 313[14.4] | 323[14.1] | 355[14.8] | |
| 7[a] | 243[40.9] | 263[36.1] | 332[11.3] | |
| 8[b] | 307[13.0] | 323[15.8] | 338[11.1] | 357[5.2] |
| 9[b] | 271[17.8] | 323[15.7] | 342[16.9] | |
| 10[a] | 244[33.8] | 270[22.9] | 332[ 9.2] | |

[a] Measured in ethanol. [b] Measured in *p*-dioxane.

were measured on a Beckman DK-1 recording instrument.

The antimicrobial effectiveness of the compounds listed in Tables I and II were evaluated, at concentrations of 10, 100, and 1000 p.p.m., by the tube dilution method (*1*). The test organisms used in these screening experiments were *Aspergillus niger*, strain USDA 215-5373.16, and *Chaetomium globosum*, strain USDA 1-42.4. The criterion of effectiveness was the absence of growth after a 48-hour (*A. niger*) or a two-week (*C. globosum*) incubation period.

The aryl isothiocyanates, the 8-aminoquinoline, and the 4-aminobenzophenone were the purest grades obtainable from commercial sources, and were used without further purification.

**Preparation of 1-(4-Benzoylphenyl)-3-(Substituted)-2-Thioureas (I).** A solution of 4-aminobenzophenone (0.01 mole) in absolute ethanol (50 ml.) was added dropwise with stirring to a warm solution of aryl isothiocyanate (0.01 mole) in absolute ethanol (50 ml.). The resulting mixture was heated gently on the steam bath for 2 hours; water was then added until the onset of precipitation. The precipitate which formed during subsequent cooling to room temperature was collected, washed with cold 50% aqueous ethanol, and recrystallized to constant melting point.

The following major characteristic infrared bands (cm.$^{-1}$) were common to the spectra of compounds 1 to 5: 3360–3300, m (NH stretch); 1655–1635, s (C=O stretch); 1605–1600, s (phenyl ring stretch); 1535, s, 1325, s (NH deformation and CN stretch); 1080, w (NCN stretch, some C=S stretch); 800–795, m (C=S stretch).

**Preparation of 1-(8-Quinolyl)-3-(Substituted)-2-Thioureas (II).** To a warm solution of an aryl isothiocyanate (0.01 mole) in absolute ethanol (50 ml.) was added, with stirring, 8-aminoquinoline (0.01 mole) in absolute ethanol (50 ml.). The resulting mixture was refluxed for one-half hour. The precipitate which formed on cooling was collected, washed with cold absolute ethanol, and recrystallized to constant melting point.

The following important specific absorptions (cm.$^{-1}$) were observed in the infrared spectra of compounds 6 to 10: 3200–3180, s (NH stretch); 1630–1600, m (aromatic ring stretch); 1550, vs, 1325–1310, m (NH deformation and CN stretch); 1090, m (NCN stretch, some C=S stretch); 805–795, s (C=S stretch).

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# Preparation of *p*-bis(Dinitromethyl)benzene

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**The application of the ter Meer reaction to the synthesis of aromatic substituted *gem*-dinitromethyl compounds is reported. The preparation of *p*-bis(dinitromethyl)benzene by this method is given.**

THE SYNTHESIS of aliphatic *gem*-dinitro compounds from 1-nitro-1-haloalkanes by the displacement of halogen with nitrite ion in basic media is well known (*1, 2, 4*). The application of the ter Meer reaction to the synthesis of aromatic substituted *gem*-dinitromethyl compounds is now reported for the first time.

$$ArCH(NO_2)X \xrightarrow[2)\ H^+]{1)\ NO_2^-} ArC(NO_2)_2H$$

*Gem*-dinitromethyl aromatic compounds have been prepared by the oxidation and nitration of benzaldoximes (*3, 6*) and nitration of phenylnitromethane (*7, 8*) with dinitrogen tetroxide. In the present work, the ter Meer reaction was used to prepare the first aryl bis-*gem*-dinitromethyl compound.

Treatment of α,α′-dibromo-*p*-xylene (I) with sodium nitrite in dimethylformamide or silver nitrite in dichloromethane gave α,α′-dinitro-*p*-xylene (II). A second product, α-nitro-*p*-tolualdehyde (IV), was isolated from this reaction after sulfuric acid treatment. This compound probably originated from the decomposition of the expected by-product, nitrite ester (III). Bromination of II yielded *p*-bis(bromonitromethyl)benzene (V). Initial efforts to convert V to the dipotassium salt of *p*-bis(dinitromethyl)benzene (VI) using the usual ter Meer conditions or potassium nitrite

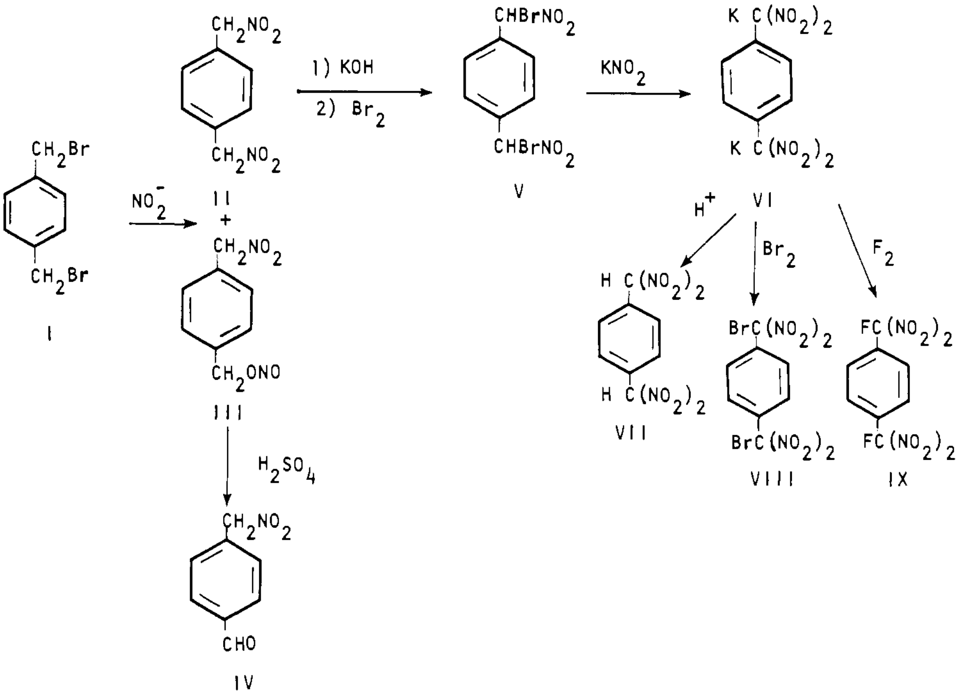

Figure 1. Reaction sequence for compounds I to IX

in a basic medium (potassium carbonate) were unsuccessful. Inhibition of the ter Meer reaction by excess strong base has been reported (5). The conversion of V to VI in 59% yield, using an excess of potassium nitrite and no base, was realized. Acidification of VI gave *p*-bis(dinitromethyl)benzene (VII). Bromination of VI yielded *p*-bis(bromodinitromethyl)benzene (VIII). Aqueous fluorination of VI caused neutralization to occur with the formation of VII. When the fluorination was carried out in acetonitrile at 0° to 5° C., the desired *p*-bis(fluorodinitromethyl)benzene (IX) was obtained. The reaction sequences for the preparation of these compounds are summarized in Figure 1.

## EXPERIMENTAL

Melting points are uncorrected. The infrared spectra were taken on mulled samples with a Perkin-Elmer Infracord.

CAUTION. Because of their explosive nature, reasonable care and precautions should be taken when handling polynitro compounds.

**$\alpha,\alpha'$-Dinitro-p-xylene (II).** WITH SILVER NITRITE. Over a period of 1 hour, $\alpha,\alpha'$-dibromo-*p*-xylene (66.0 grams, 0.250 mole) dissolved in 750 ml. of warm methylene chloride was added in small portions to a stirred slurry of silver nitrite (100 grams, 0.650 mole) in 150 ml. of methylene chloride cooled to 0° C. A small soxlet thimble sealed with calcium hydride (1.0 gram) was added. After the mixture was stirred in the dark for 17 hours at 0° C., the solids were filtered and washed with methylene chloride. The solvent was removed under reduced pressure, leaving 48.9 grams of pale yellow oily solid. Over a period of 15 minutes, the solid was added in small portions to 100 ml. of concentrated sulfuric acid stirred at −5° C. The mixture evolved nitrogen oxides and became black. After the final addition, the mixture was stirred for 15 minutes, then poured over 500 grams of ice. After the ice had melted, the brown solid was filtered, washed six times with copious amounts of water, and dried in vacuo to give 32.9 grams. The solid was digested in boiling 1,2-dichloroethane, charcoal added, filtered hot, and allowed to crystallize on cooling to yield 12.5 grams (26%) of pale yellow plates, m.p. 128° to 130.5° C. Major infrared bands were at 1530 and 1348 cm.$^{-1}$. Anal Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.54, 48.40; H, 3.91, 3.96; N, 14.35.

WITH SODIUM NITRITE. Using sodium nitrite and dimethylformamide as solvent, the yield of II was only 10%.

**$\alpha$-Nitro-p-tolualdehyde (IV).** The solvent was allowed to evaporate from the mother liquor obtained from crystallizing the $\alpha,\alpha'$-dinitro-*p*-xylene in the silver nitrite preparation, leaving 11.6 grams of residue. On sublimination of a 200-mg. sample of this residue at 0.5 mm. and 45° C., 150 mg. was volatile (indicated 21% yield). After discarding a low-melting forerun, a middle fraction (m.p. 55° to 57° C.) was resublimed to yield an analytical sample. Major infrared bands were at 1680, 1550, 1450, and 1360 cm.$^{-1}$. Anal. Calcd. for: $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.64, 57.98; H, 4.49, 4.45; N, 8.32.

**p-bis(Bromonitromethyl)benzene (V).** A stirred suspension of $\alpha,\alpha'$-dinitro-*p*-xylene (14.7 grams, 0.075 mole) in 75 ml. of methanol at 0° C. was treated with 150 ml. of methanolic potassium hydroxide (1*N*). The pale yellow precipitated dipotassium salt was dissolved by the addition of 75 ml. of water. This solution was chilled to 0° C., and 75 ml. of methanolic bromine (26.4 grams, 0.165 mole, 10% excess) was added dropwise simultaneously to 300 ml. of water stirred at 0° C. A white precipitate appeared immediately. An excess of bromine was maintained at all times, and the temperature was maintained at or somewhat below 0° C. Stirring was continued for an additional 15 minutes at 0° C., followed by pouring the mixture into 1000 ml. of water. The solid was filtered, washed with three 200-ml. portions of water, dissolved in warm methylene chloride, and separated from the aqueous phase. After the methylene chloride solution was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The resulting solid was dissolved in hot carbon tetrachloride, separated from a small amount of insoluble orange solid, and cooled to yield 22.33 grams (84%) of pale yellow needles, m.p. 121° to 123.5° C. In another preparation, the filtered white solid was dried in vacuo before crystallizing from carbon tetrachloride. Recrystallization from carbon tetrachloride yielded the analytical sample: m.p. 123.5° to 125° C. Major infrared bands were at 1560, 1340, and 750 cm.$^{-1}$. Anal. Calcd. for $C_8H_6Br_2N_2O_4$: C, 27.14; H, 1.71; N, 7.92. Found: C, 26.89, 27.00; H, 2.07, 1.84; N, 7.97.

**Dipotassium *p*-bis(Dinitromethyl)benzene (VI).** A solution of *p*-bis(bromonitromethyl)benzene (1.77 grams, 5 mmoles) in 35 ml. of methanol was poured into a stirred solution prepared by dissolving potassium nitrite (2.04 grams, 24 mmoles, 20% excess) in 4 ml. of water and adding 15 ml. of methanol. An orange precipitate appeared from the initial orange solution in 30 seconds and the temperature rose rapidly from 26° to 30° C. Stirring was continued for 1 hour, during which time the temperature slowly fell to 26° C. The solid was filtered, washed with two 10-ml. portions of methanol, and dried in vacuo to give 1.06 grams (59%) of crude dipotassium *p*-bis(dinitromethyl)benzene. The salt was purified by dissolving in 70 ml. of water, filtering out insoluble solid employing filter aide (Celite), concentrating the resulting solution to 2.5 ml. under reduced pressure, adding 5 ml. of methanol, and filtering the resultant bright yellow solid, 0.80 gram. Major infrared bands were at 1450, 1180, 1110, and 1080 cm.$^{-1}$.

***p*-bis(Dinitromethyl)benzene (VII).** A 5-ml. aqueous solution containing 0.6 ml. of concentrated hydrochloric acid (37%, 6.1 mmoles) was added dropwise to a stirred 70-ml. aqueous solution of dipotassium *p*-bis(dinitromethyl)benzene (0.39 gram, 1.08 mmoles) at 0° C. The yellow-orange color of the solution faded as a pale yellow solid precipitated. The solid was filtered, washed with two 5-ml. portions of water, and dried in vacuo to yield 0.30 gram (97%), m.p. 122° to 122.5° C. Crystallization from chloroform followed by recrystallization from 1,2-dichloroethane yielded the analytical sample: m.p. 127.5° to 128° C. The major infrared band was at 1580 cm.$^{-1}$ Anal. Calcd. for $C_8H_6N_4O_8$: C, 33.57; H, 2.11; N, 19.58. Found: C, 33.24, 33.23, 33.54; H, 2.55, 2.41, 2.54; N, 19.54.

***p*-bis(Bromodinitromethyl)benzene (VIII).** A 5-ml. methanolic bromine solution (0.53 gram, 3.3 mmoles) was slowly poured into a stirred aqueous solution of dipotassium *p*-bis(dinitromethyl)benzene (0.41 gram, 1.13 mmoles) at 0° C. The yellow-orange color of the solution faded as a white solid precipitated. The solid was filtered, washed with two 5-ml. portions of water, and dried in vacuo to yield 0.50 gram (99%), m.p. 125° to 127° C. Two recrystallizations from carbon tetrachloride yielded the analytical sample: m.p. 130° to 131° C. The major infrared band was at 1580 cm.$^{-1}$. Anal. Calcd. for $C_8H_4Br_2N_4O_8$: C, 21.64; H, 0.91; N, 12.62. Found: C, 21.83, 21.77; H, 0.71, 0.89; N, 12.50.

***p*-bis(Fluorodinitromethyl)benzene (IX).** A slurry of 0.2 gram (0.00055 mole) of the dipotassium salt of *p*-bis(dinitromethyl)benzene and 15 ml. of acetonitrile was cooled to −8° C. and purged with dry nitrogen. Then a 3 to 1 $N_2/F_2$ gas mixture was bubbled through the reaction mixture at a rate of 60 cc. per minute for 30 minutes. The mixture was purged with nitrogen, allowed to warm to ambient temperature, and filtered free of the precipitated potassium fluoride. Concentration of the filtrate in vacuo yielded 0.17 gram (quantitative yield) of yellow solid. Recrystallization from isopropyl alcohol resulted in colorless plates with a melting point of 86° to 88° C. Anal. Calcd. for $C_8H_4F_2N_4O_8$: C, 29.80; H, 1.24; N, 17.40. Found: C, 29.86, 30.02; H, 1.26, 1.26; N, 17.44.

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# Convenient Synthesis of 6-Hydroxycoumarin

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**6-Hydroxycoumarin was obtained in a 77% yield by treatment of 2,5-dimethoxycinnamic acid with boron tribromide in chloroform. The method is potentially useful for preparation of other hydroxylated coumarins.**

LARGE quantities of 6-hydroxycoumarin were prepared for biological evaluation. The method of Sastri *et al.* (*3*) was impractical for a large-scale synthesis. The procedure involved hydroxylation of 2-hydroxycinnamic acid with potassium persulfate in 35 to 40% yield, followed by treatment of the resulting 2,5-dihydroxycinnamic acid with mercuric chloride and hydrogen chloride. The resulting coumarin was purified by sublimation and obtained in approximately a 10% over-all yield.

The title compound can be prepared readily from commercially available 2,5-dimethoxycinnamic acid by treatment with boron tribromide. The reaction was conducted in chloroform solution with a two-fold excess of boron tribromide, and after 48 hours at room temperature, the coumarin