with polyphosphoric acid at 100° gave only unchanged starting material.

Apparently the nature of the solvent and the temperature have a marked influence on the reaction pathway. In toluene intramolecular attack of the carboxyl oxygen on carbon in V with expulsion of H_2S leads to VI which reacts further with anthranilic acid to give II. Attack of the carboxyl carbonyl on nitrogen on the other hand leading to I appears to be favored in alcohol.

It should be noted that the reaction of isocyanates with anthranilic acid provides a simple route to the ureas which avoids separating the mixtures obtained from the reaction of amines with isatoic anhydride.[4]

To our knowledge the internal cyclization reaction with removal of sulfur in thioureido anthranilic acid derivatives has not been observed before.

Experimental Section

N-[*o*-(3-Allylureido)benzoyl]anthranilic Acid (II). A mixture of 27.4 g (0.2 mole) of anthranilic acid and 21.8 g (10% excess) of allyl isothiocyanate in 250 ml of toluene was heated under reflux for 6 hr. The solid which formed was removed by filtration and recrystallized twice from a mixture of dimethylformamide and water to give 20.6 g (61%) of II, mp 194–196.5° dec.

Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38; S, 0.0. Found: C, 63.65; H, 5.14; N, 12.56; S, 0.0.

N-[*o*-(3-Ethylureido)benzoyl]anthranilic Acid (III).—A mixture of 27.4 g (0.2 mole) of anthranilic acid and 18 g of ethyl isothiocyanate was heated under reflux for 4 hr in 250 ml of toluene. Recrystallization of the product from ethanol gave 6.4 g (20%) of III, mp 191–192.5° dec.

Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.24; N, 12.84. Found: C, 62.27; H, 5.37; N, 12.84.

N-(Ethylcarbamoyl)anthranilic Acid.—A mixture of 54.8 g (0.4 mole) of anthranilic acid and 28.4 g (0.4 mole) of ethyl isocyanate in 500 ml of toluene was heated under reflux for 2 hr. Filtration gave 66.1 g (80%) of product. A 10-g sample recrystallized from a mixture of dimethylformamide and water gave 6.5 g of pure material, mp 171.5–173.5° dec.

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 58.07; H, 5.84; N, 13.39.

N-[*o*-(3-Ethylureido)benzoyl]anthranilic Acid (III).—To 4.16 g (0.02 mole) of N-(ethylcarbamoyl)anthranilic acid in dimethylformamide was added 2.38 g (0.02 mole) of thionyl chloride. The reaction was slightly exothermic. The mixture was stirred at room temperature for 2 hr and a solution of 2.74 g (0.02 mole) of anthranilic acid in dimethylformamide was added. The mixture was stirred at room temperature for 48 hr and poured into water. The solid was recrystallized from ethanol to give 1.4 g (21%) of III identical with the material prepared above.

N-(Allylcarbamoyl)anthranilic Acid.—To a suspension of 27.4 g (1.2 moles) of anthranilic acid in 250 ml of ethanol was added 19.8 g (10% excess) of allyl isocyanate. Heat was evolved and the mixture was stirred for several hours until this was dissipated and the mixture was heated under reflux for 6 hr. The solvent was removed *in vacuo* and the residue was warmed with benzene and filtered to give 15.7 g of white solid. Recrystallization twice from acetonitrile gave 6.8 g of product (15%), mp 160–163° dec.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.25; H, 5.59; N, 12.53.

3-Allyl-2,4(1H,3H)-quinazolinedione.—To a dimethylformamide solution of 3.8 g (0.0173 mole) of N-(allylcarbamoyl)anthranilic acid was added 2.1 g of thionyl chloride. The exothermic reaction was stirred for 2 hr at room temperature and then for 1 hr at 60°. At 30° a solution of 2.37 g of anthranilic acid in dimethylformamide was added and the mixture was warmed to 60° for 1.5 hr and poured into water. Recrystallization of the solid from dilute ethanol gave 1.1 g (31%) of 3-allyl-2,4(1H,3H)-quinazolinedione, mp 182–185°.

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.42; H, 4.85; N, 13.86.

N-[*o*-(3-Allylureido)benzoyl]anthranilic Acid (II).—To a solution of 3.5 g (0.016 mole) of N-(allylcarbamoyl)anthranilic acid in dimethylformamide was added 1.9 g (0.016 mole) of thionyl chloride. The mixture was stirred at room temperature for 2 hr and to it was added a dimethylformamide solution of 2.18 g (0.016 mole) of anthranilic acid. After stirring for 72 hr the mixture was poured into water. The solid which resulted was recrystallized from a mixture of dimethylformamide and water to give 1.3 g (24%) of II, mp 193–194.5° dec. This material was identical with that prepared above.

Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.77; H, 5.23; N, 12.53.

Acknowledgment.—Microanalytical determinations were by Mr. Charles Childs and staff. Spectra were determined by Mr. E. Schoeb and Mrs. Carola Spurlock. Miss Nancy Headen prepared several batches of II. The authentic sample of I was prepared by Miss Carolyn Hess. All were of these laboratories.

On the Bromination of 3-Phenylthiophene

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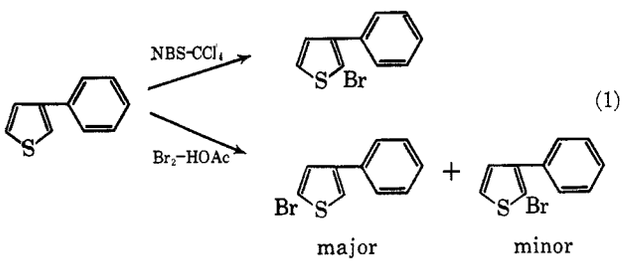
Bromination of 3-phenylthiophene with molecular bromine and with N-bromosuccinimide (NBS) has been investigated. These different reaction conditions furnished strikingly different isomer distributions as indicated in eq 1.[2]



(1)

Bromination with bromine in refluxing acetic acid yielded a monobrominated fraction consisting of two isomers in 1:2 ratio. These isomers were separated by preparative gas chromatography. By nmr spectroscopy[3] the minor component was identified as 2-bromo-3-phenylthiophene and the major as 5-bromo-3-phenylthiophene. This result was rather unexpected especially since the 5 position should be deactivated by the $-I$ effect of the phenyl group as is observed for the 3 position of biphenyl in electrophilic substitution reactions.[4,5] The preferential formation of the 5 isomer in

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(2) At the occasion of the Second Organic Sulfur Symposium, May 9–12, 1966, Groningen, The Netherlands, it was discovered that electrophilic bromination and NBS bromination of 3-phenylthiophene had been carried out at the University of Oslo, Norway, and the University of Groningen, The Netherlands, respectively.

(3) R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, **16**, 563 (1960).

(4) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

(5) Preliminary results indicate that acetylation and formylation of 3-phenylthiophene give predominantly the 2-substituted isomers: S. Gronowitz and N. Gjös, to be published.

the bromination of 3-phenylthiophene may indicate that the steric requirements of the brominating species are important. Bromination with molecular bromine is known to have a large selectivity factor[4] although biphenyl itself does not follow the selectivity rule, the reason for this being a matter of controversy.[6-8] Some authors consider the large *para*:*ortho* ratio (97.5:2.5)[9,10] in the bromination of biphenyl with molecular bromine to be mainly due to the greater importance of conjugative electron release with a neutral reagent in combination with increased stability of "*para*-quinoid" over "*ortho*-quinoid" transition states and not so much to the steric requirements of the brominating agent.[6,11] However, it is possible that the seeming discrepancies may be due to a difference in the mechanism of bromination of benzenes and thiophenes, an addition–elimination being involved in the latter case.

In contrast to the results cited above bromination using NBS in carbon tetrachloride with benzoyl peroxide initiator led exclusively to the 2 isomer. No 5 isomer could be detected gas chromatographically. Recent work has shown that benzylic bromination with NBS proceeds by a free-radical chain mechanism with a bromine radical as the hydrogen-abstracting agent,[12-14] the bromine radical being produced from molecular bromine formed from the reaction between NBS and hydrogen bromide. Much less appears to be known about the mechanism of nuclear bromination of activated aromatics by NBS. The quite different isomer distribution with 3-phenylthiophene makes it rather unlikely that molecular bromine could be the brominating agent in the NBS case unless the change in solvent (carbon tetrachloride in place of boiling acetic acid) has a great effect. A direct radicaloid substitution reaction as suggested for the bromination of naphthalene[15] under certain conditions is a possibility. More likely, perhaps, is the free-radical addition of bromine across the 2,3 positions followed by loss of hydrogen bromide. The report of Ross[16] that a rapid ionic path exists in polar media is interesting but doesn't seem applicable in this case.

Although further studies are necessary in order to elucidate the mechanistic details, the differences are very fortunate from the preparative point of view making both 2-bromo-3-phenylthiophene and 5-bromo-3-phenylthiophene available as possible useful synthetic intermediates.

Experimental Section

Nmr spectra were taken on a Varian A-60 instrument; gas chromatography was done on a F & M 810 with hydrogen flame detectors and an Aerograph Autoprep Model A-700.

Bromination of 3-Phenylthiophene with N-Bromosuccinimide.—A mixture of 1.6 g (10 mmoles) of 3-phenylthiophene, 1.8 g (10 mmoles) of N-bromosuccinimide (recrystallized from glacial acetic acid), a few milligrams of benzoyl peroxide, and 60 ml of carbon tetrachloride were refluxed for 49 hr after which time examination by glpc (diethylene glycol succinate, 6 ft, 190°) showed that the starting material had disappeared and a single product peak had appeared. The solution was filtered, washed three times with 5% potassium hydroxide solution and once with water, and dried over magnesium sulfate. The solvent was removed and the red residue was chromatographed on 2 × 20 cm of Grade 1 Merck alumina using 100 ml of reagent grade benzene as eluent. Removal of the benzene left 2.28 g. (95%) of a transparent liquid, bp 104–110° (0.25 mm). The nmr spectrum in acetone, in addition to the phenyl protons, showed two doublets centered at τ 2.56 and 2.94 (J_{45} = 5.4 cps) positively identifying the product as 2-bromo-3-phenylthiophene.[3] The material did not appear to be stable for long periods and repeated attempts at analysis gave erratic results. The bromide was thus converted to the solid carboxylic acid for analysis.

3-Phenyl-2-thiophenecarboxylic Acid.—Treatment of 0.68 g (2.84 mmoles) of freshly prepared 2-bromo-3-phenylthiophene with 0.20 g (8.2 mg-atoms) of magnesium in ether gave the Grignard reagent. Addition of solid carbon dioxide and work-up of the reaction mixture gave 0.56 g (88%) of 3-phenyl-2-thiophenecarboxylic acid, mp 201–204° (lit.[17] mp 205–206°). Its nmr spectrum (acetone) showed, in addition to the phenyl absorptions, two doublets at τ 2.35 and 2.90 (J_{45} = 5.2 cps).

Anal. Calcd for $C_{11}H_8O_2S$ (204.2): C, 64.68; H, 3.95; S, 15.70. Found: C, 64.92; H, 3.88; S, 15.38.

The same compound has also been obtained from the hypobromite oxidation of 2-acetyl-3-phenylthiophene.[5]

Bromination of 3-Phenylthiophene with Molecular Bromine.—Bromine (10.0 g, 0.063 g-atom) in 100 ml of glacial acetic acid was added dropwise to 10.0 g (0.063 mole) of 3-phenylthiophene in 130 ml of glacial acetic acid and the mixture was refluxed for 5 hr, cooled, and poured into water to yield 11.5 of crude product. Examination by glpc (30% Apiezon L 270°) showed four peaks. The first one had the same retention time as the starting material, the second (9.2 min) and third (12.7 min) had relative areas of 1:2, and finally a weak peak (18.1 min) probably owing to a dibromo derivative was observed. Through preparative gas chromatography the components with retention times of 9.2 and 12.7 min were obtained pure. The first component had the same infrared and nmr spectrum as 2-bromo-3-phenylthiophene, while the second component was 5-bromo-3-phenylthiophene, mp 75–77°, after recrystallization from aqueous ethanol. The nmr spectrum (dimethyl sulfoxide), in addition to the phenyl protons, showed two doublets centered at τ 2.13 and 2.29 (J_{24} = 1.8 cps). Pure 5-bromo-3-phenylthiophene could also be obtained by recrystallization from aqueous ethanol of the crude reaction product.

Anal. Calcd for $C_{10}H_7BrS$ (239.1): C, 50.23; H, 2.95; S, 13.41. Found: C, 50.54; H, 3.35; S, 13.36.

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Reactions of Certain Ferrocene Compounds Leading to a Ferrocenyl Ethyl Ether[1a]

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Recently, in connection with the proof of structure of the benzophenone adduct of lithiodimethylaminomethylferrocene, its methiodide (I) was converted

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