oximino ketones generally exhibit signals in the range 11.7 to 12.5 ppm; glyoximes, 11.0 to 11.9 ppm; formamidoxime and acetamidoxime, 8.61 and 8.86 ppm (both broad), respectively; ethyl acetohydroximate, 9.25 ppm; acetonitrolic acid, 12.80 ppm; and ethyl α-oximinoacetoacetate, *ca.* 13.1 ppm (very broad). In the case of glyoximes the number of hydroxy proton signals observed is equal to the number of nonequivalent oxime groupings present in the molecule.

Studies are in progress to elucidate more fully the effects of substituent groups upon the OH chemical shift of oximes.

An Example of Sulfur Elimination. The Reaction of Alkyl Isothiocyanates with Anthranilic Acid

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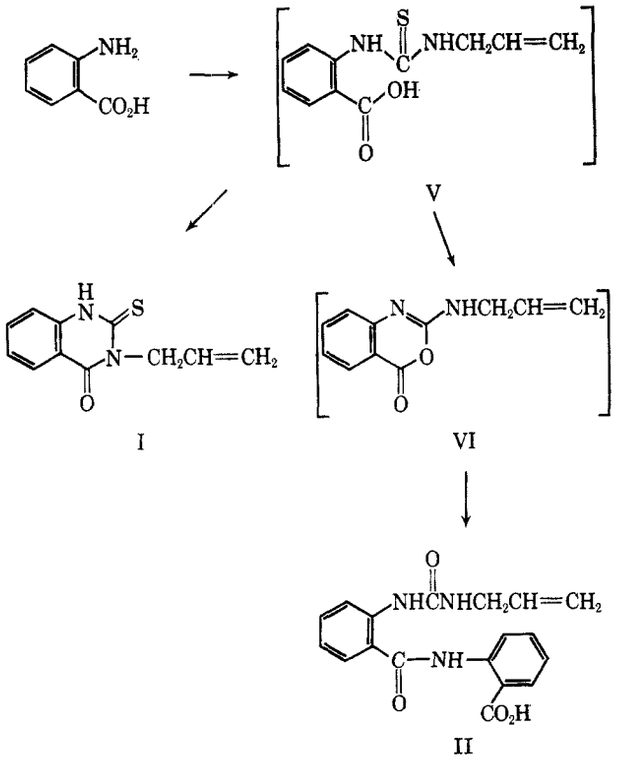
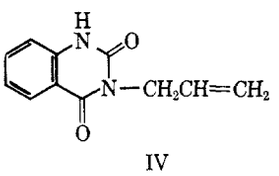
Received August 22, 1966

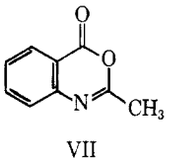
There has been little information available regarding the reaction of isocyanates or isothiocyanates with anthranilic acid. Recently[1] a series of arylureas was prepared from anthranilic acid and aryl isocyanates in refluxing benzene.

In an attempt to prepare 3-allyl-2-thio-2,4-(1H,3H)-quinazolinedione (I)[2] the melt procedure of Dhami, *et al.*,[3] was modified by heating anthranilic acid under reflux in toluene with a 10% excess of allylisothiocyanate. The material which resulted had a melting point close to that reported for I. The microanalytical data however indicated that the material formed contained no sulfur and was not the desired I. The microanalytical values, solubility in aqueous base, and spectral data suggested structure II, N-[*o*-(3-allylureido)benzoyl]anthranilic acid, for the compound obtained. Ethyl isothiocyanate similarly gave a material which was found to be N-[*o*-(3-ethylureido)benzoyl]anthranilic acid (III). Independent synthesis confirmed the proposed structures of these anomalous reaction products. Thus ethyl isocyanate was condensed with anthranilic acid in toluene to give N-(ethylcarbamoyl)anthranilic acid.[4] Conversion of the latter into the acid chloride with thionyl chloride in N,N-dimethylformamide at room temperature, followed by treatment with anthranilic acid, gave the desired III identical with the material obtained by the action of ethyl isothiocyanate on anthranilic acid. The reaction of allyl isocyanate with anthranilic acid was more complicated. An initial attempt to form the urea in toluene led only to the isolation of II in poor yield. When the reaction was carried out in ethanol the desired N-(allylcarbamoyl)anthranilic acid[4] was formed in low yield. Treatment of this material with thionyl chloride in N,N-dimethylformamide at 60° and then with anthranilic acid led to ring closure and afforded only a material which appears to be the quinazolinedione IV. This was surprising since Staiger and Wagner[4] reported N-(allylcarbamoyl)anthranilic acid to be resistant to cyclization with mineral acid. Repetition of this procedure at room temperature afforded a product identical (mixture melting point, infrared, ultraviolet) with the material obtained from allyl isothiocyanate and anthranilic acid.





IV



VII

When allyl isothiocyanate and anthranilic acid were heated under reflux in ethanol, the desired quinazolinedione I was obtained without difficulty. Recently a series of 3-aryl derivatives of I was obtained similarly.[5]

The reaction sequence may involve an intermediate containing an activated carbonyl function such as 2-(allylamino)-4H-3,1-benzoxazin-4-one (VI). Such an intermediate could conceivably arise from the thiourea derivative V. Attack by anthranilic acid at the carbonyl function in VI would then give the product II. Similar activated intermediates derived from anthranilic acid have been reported. Thus acetyl anthranilic anhydride VII formed by the action of acetic anhydride on anthranilic acid[6] undergoes nucleophilic attack to give 2-acetamidobenzamides.[7,8] Although compounds similar to VI have recently been reported[9] an attempt to isolate an intermediate of the type VI by treatment of N-(ethylcarbamoyl)anthranilic acid

(1) Netherlands Patent 6,407,915 (1965); *Chem. Abstr.*, **63**, 1742*d* (1965).
(2) This investigation was supported in part by U. S. Army Medical Research and Development Command, Contract DA-49-193-MD-2754.
(3) K. S. Dhami, H. S. Sachdev, and K. S. Narang, *J. Sci. Ind. Res.* (India), **15B**, 690 (1956).
(4) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **18**, 1427 (1953).
(5) K. M. Muraveva and M. N. Shchukina, *Biol. Atkiun. Suedin, Akad. Nauk SSSR*, 54 (1965); *Chem. Abstr.*, **63**, 16347*c* (1965).
(6) J. Kacker and S. H. Zaheer, *J. Indian Chem. Soc.*, **28**, 344 (1951).
(7) M. T. Bogert and R. A. Gortner, *J. Am. Chem. Soc.*, **32**, 119 (1910).
(8) Z. Ecsery and I. Kosa, *Chem. Ber.*, **97**, 302 (1964).
(9) M. Kurihara and N. Yoda, *Tetrahedron Letters*, 2597 (1965).

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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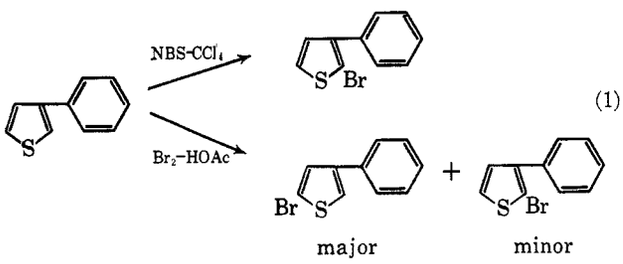
Received September 1, 1966

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

(1) Chemical Institute, University of Lund, Sweden.

(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.