rum albumin. This would appear likely since it has been shown that the interaction of 4-aminoazobenzene and bovine serum albumin involves the amino group of the dye.[5] It was found, however, that 4'-methyl-4-aminoazobenzene was the strongest base of the three dyes examined and that 3'-methyl-4-aminoazobenzene and 4-aminoazobenzene had similar basicities (Table IV).

TABLE IV

pK_a's FOR DYES

Dye[a]	No. of detmn.	Mean pK_a	Standard error
AB	5	2.90	0.0132
3'-Me-AB	4	2.88	.0123
4'-Me-AB	4	3.04	.0230

[a] Abbreviations: same as in Table I. The lit. values for the pK_a of AB include 2.90 as calculated from the k_a of 1.25×10^{-3} reported by Farmer and Warth[19] and 2.80 as reported by Hammett and Paul.[20]

Thus if a relationship exists between basicity and the extent of interaction, one would expect 4-aminoazobenzene and 3'-methyl-4-aminoazobenzene to be bound to the protein in similar quantities. This was not observed and thus it was concluded that basicities could not be directly correlated to the binding observed in these cases.

Another suggested explanation for the binding observed might be the possible existence of a relationship between solubility and the extent of interaction. It was found that 3'-methyl-4-aminoazobenzene and 4'-methyl-4-aminoazobenzene were much less soluble than 4-aminoazobenzene when the phosphate buffer was used as a solvent (Table V). Thus if solubility were related to the extent of binding then one would expect that 3'-methyl-4-aminoazobenzene and 4'-methyl-4-aminoazobenzene both would be bound to bovine serum albumin in nearly equal quantities. This was observed and thus it was concluded that in this case solubility could be related to the extent of binding in an inverse manner.

TABLE V

SOLUBILITIES OF DYES IN PHOSPHATE BUFFER (pH 6.8, 25°)

Dye[a]	Time of agitation, hr.	Solubility (mole/l.)
AB	48	1.39×10^{-4}
	84	1.37×10^{-4}
3'-Me-AB	48	1.79×10^{-5}
	84	1.79×10^{-5}
4'-Me-AB	48	1.59×10^{-5}
	84	1.58×10^{-5}

[a] Abbreviations: same as Table I.

The fact that solubility and extent of binding can be related to each other may not be the only way in which the observed data can be explained. The solubility of a molecule can be attributed to a number of factors among which is the weight of the molecule involved. The weight of the molecule may not only affect the solubility of the molecule but it might also affect the ability of the molecule to engage in protein binding through van der Waals forces. Since it was observed that the two methylated dyes were bound to the protein in equal (or nearly equal) and larger quantities than 4-aminoazobenzene, it was concluded that in this study the extents of interaction also could be related to the molecular weights of the dyes. Thus it appears that factors such as solubility, or molecular weight, or van der Waals forces are more important than basicity in determining the abilities of these three dyes to form complexes with bovine serum albumin.

Acknowledgment.—The authors are indebted to Dr. Holly C. Fryer, Department of Mathematics, Kansas State College, for advice regarding the statistical analysis of the observed data.

DEPARTMENT OF CHEMISTRY
KANSAS STATE COLLEGE
MANHATTAN, KANSAS

(19) R. C. Farmer and F. J. Warth, *J. Chem. Soc.*, **85**, 1713 (1904).
(20) L. P. Hammett and M. A. Paul, THIS JOURNAL, **56**, 827 (1934).

The Halogenation of Some 2- and 3-Amino Derivatives of Dibenzothiophene

BY HENRY GILMAN AND GENE R. WILDER

RECEIVED JULY 5, 1955

Earlier work on the halogenation[1] and nitration[2-5] of amino derivatives of dibenzothiophene indicate that isomers formed during electrophilic attack on the amino derivative are influenced both by the size of the group attached to the amine, *i.e.*, the carbonyl component, and the size of the electrophile.

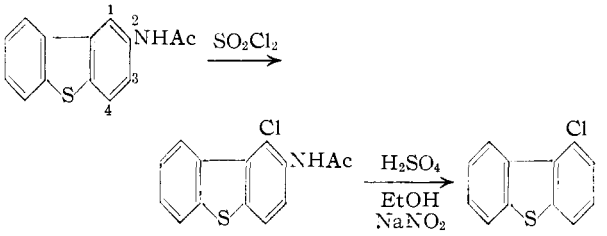
The bromination of 2-acetamidodibenzothiophene[1,6] yields 2-acetamido-3-bromodibenzothiophene[1] as has been shown by deamination followed by oxidation to the known 3-bromodibenzothiophene-5-dioxide.[7] Also reported was the chlorination of 2-acetamidodibenzothiophene with sulfuryl chloride to give a chloro-2-acetamidodibenzothiophene which was believed by analogy to be the 3-isomer.[1] This material was actually 1-chloro-2-acetamidodibenzothiophene as was shown in the present work by deamination and comparison with an authentic specimen of 1-chlorodibenzothiophene.[4]

In the nitration of 3-acetamido- and 3-benzamidodibenzothiophene,[5] good yields of the 4-nitro isomer were obtained in both cases. Chlorination, however, affords mixed isomers in both cases, namely, the 2- and 4-chloro isomers. The 2-chloro isomer was identified by deamination and oxidation to the 2-chlorodibenzothiophene-5-dioxide which corresponds to the 2-chlorodibenzothiophene-5-dioxide reported by Courtot,[8] who obtained it by treating 2-nitrodibenzothiophene with thionyl chloride followed by oxidation.

Chlorination appears to follow nitration in the cases of the 2-acetamido- and 2-benzamidodibenzothiophene,[5] *i.e.*, chlorination of 2-benzamidodibenzothiophene goes in the 3-position as does bromination. The bromo-2-benzamidodibenzothiophene was identified by hydrolysis to the known 3-bromo-

(1) H. Gilman and S. Avakian, THIS JOURNAL, **68**, 1514 (1946).
(2) E. Sawicki, *J. Org. Chem.*, **18**, 1942 (1953).
(3) E. Sawicki, *ibid.*, **19**, 608 (1954).
(4) H. Gilman and G. Wilder, THIS JOURNAL, **76**, 2906 (1954).
(5) H. Gilman and G. Wilder, *ibid.*, **77**, 3920 (1955).
(6) H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1938).
(7) H. Gilman, A. L. Jacoby and H. A. Pacevitz, *ibid.*, **3**, 120 (1938).
(8) M. Courtot, *Compt. rend.*, **198**, 2260 (1934).

2-amidodibenzothiophene,[1] and the chloro-2-benzamidodibenzothiophene by the similarity of the infrared spectra of the two.



Experimental[9]

2-Bromo-3-acetamidodibenzothiophene.—Into a 200-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer and reflux condenser leading to an acid trap, were placed 3.0 g. (0.0125 mole) of 3-acetamidodibenzothiophene[10] and 75 ml. of chloroform. To this solution were added 2.1 g. (0.013 mole) of bromine dissolved in 25 ml. of chloroform and a small crystal of iodine. The mixture was warmed to near reflux and stirred for a period of 2 hr. The solvent was then stripped from the reaction mixture affording 4.5 g. of crude residue melting over the range of 202–220°. This material was crystallized from methyl Cellosolve to yield a total of 3.4 g. (76.5%) of 2-bromo-3-acetamidodibenzothiophene melting at 222–223°.

Anal. Calcd. for $C_{14}H_{10}BrNOS$: S, 10.02. Found: S, 10.30.

2-Bromo-3-aminodibenzothiophene.—Into a 125-ml. erlenmeyer flask equipped with a reflux condenser were placed 1.1 g. (0.0034 mole) of 2-bromo-3-acetamidodibenzothiophene, 2.0 g. of potassium hydroxide, 45 ml. of ethanol and 15 ml. of water. The mixture was refluxed for a period of one hour and then allowed to cool. There was deposited 0.55 g. (57.6%) of long, white needles of 2-bromo-3-aminodibenzothiophene melting at 132–133°. Recrystallization from methanol did not raise the melting point of the compound.

Anal. Calcd. for $C_{12}H_8BrNS$: S, 11.53. Found: S, 11.83.

A small sample of this material was deaminated[4] by the use of ethanol, sulfuric acid and sodium nitrite to give a compound which gave no depression in mixed melting point with authentic 2-bromodibenzothiophene, prepared essentially in accordance with the method of Courtot.[11]

2-Bromo-3-benzamidodibenzothiophene.—Into a 500-ml. round-bottomed, three-necked flask equipped with a mechanical stirrer and reflux condenser fitted to an acid trap were placed 8.0 g. (0.0264 mole) of 3-benzamidodibenzothiophene[5] and 200 ml. of chloroform. A small crystal of iodine was then added to the system and followed by 4.7 g. (0.029 mole) of bromine dissolved in 35 ml. of chloroform. The reaction mixture was heated at reflux for a period of 4 hr., at the end of which time the evolution of hydrogen bromide appeared to cease. The solution was washed with water and dilute sodium hydroxide, dried over sodium sulfate and filtered. The chloroform was stripped from the residue leaving 8.1 g. of material which melted between 161–170°. This product was crystallized from methyl Cellosolve to afford a total of 4.8 g. (47.2%) of 2-bromo-3-benzamidodibenzothiophene melting at 179–180°.

Anal. Calcd. for $C_{18}H_{12}BrNOS$: S, 8.39. Found: S, 8.11.

A sample of this material was hydrolyzed to yield 2-bromo-3-aminodibenzothiophene which gave no depression in melting point when admixed with the 2-bromo-3-aminodibenzothiophene prepared by the bromination and hydrolysis of 3-acetaminodibenzothiophene.

The Chlorination of 3-Acetamidodibenzothiophene.—Into a 500-ml. three-necked, round-bottomed flask, equipped with a mechanical stirrer and reflux condenser fitted with an acid trap, were placed 11.0 g. (0.0456 mole) of 3-acetamidobenzothiophene[10] and 250 ml. of chloroform. There were then added to the solution 6.35 g. (0.047 mole) of sulfuryl chloride, dissolved in 50 ml. of chloroform, and a small crystal of iodine. The mixture was heated to reflux and stirred for 6 hr. at the end of which time the evolution of hydrogen chloride appeared to cease. The solvent was then stripped from the reaction mixture yielding 11.2 g. of material which melted over the range of 157–167°. Fractional crystallization from methyl Cellosolve afforded 3.8 g. (28.8%) of material which melted at 219–220° and whose infrared spectrum was almost identical with that of 2-bromo-3-acetamidodibenzothiophene, and 2.8 g. (21.2%) of material which melted at 193–194° and which is assumed to be the 4-isomer.

Anal. 2-Chloro-3-acetamidodibenzothiophene. Calcd. for $C_{14}H_{10}ClNOS$: S, 11.63. Found: S, 11.81.

Anal. 4-Chloro-3-acetamidodibenzothiophene. Calcd. for $C_{14}H_{20}ClNOS$: S, 11.63. Found: S, 11.72.

A small sample of 2-chloro-3-acetamidodibenzothiophene was deaminated and then oxidized with hydrogen peroxide to give 2-chlorodibenzothiophene-5-dioxide which melted at 245–246°, and corresponds to the product obtained by Courtot[8] from the treatment of 2-nitrodibenzothiophene with thionyl chloride followed by oxidation to the sulfone.

The Chlorination of 3-Benzamidodibenzothiophene.—Into a 500-ml. three-necked, round-bottomed flask, equipped with a mechanical stirrer and reflux condenser fitted with an acid trap, were placed 5.0 g. (0.0165 mole) of 3-benzamidodibenzothiophene[5] and 200 ml. of chloroform. To this were then added 2.3 g. (0.017 mole) of sulfuryl chloride, dissolved in 30 ml. of chloroform, and a small crystal of iodine. This mixture was heated and stirred at reflux for a period of 3 hr. at which time the solvent was stripped from the reaction mixture. The residue was fractionally crystallized from an ethanol–methyl Cellosolve pair to give two fractions. There was obtained 1.6 g. (29.2%) of material melting at 198–200° and 2.0 g. (36.4%) of material melting at 173–174°. The infrared spectrum of the material melting at 173–174° was quite similar to that of 2-chloro-3-acetamidodibenzothiophene and affords the same amine upon hydrolysis. The 2-chloro derivative has a broad band between 11.4 and 11.8 μ which is not present in the 4-isomer, and the 4-isomer has a band at 11.2 μ which is not present in the 2-isomer.

Anal. 2-Chloro-3-benzamidodibenzothiophene. Calcd. for $C_{19}H_{12}ClNOS$: S, 9.49. Found: S, 9.40.

Anal. 4-Chloro-3-benzamidodibenzothiophene. Calcd. for $C_{19}H_{12}ClNOS$: S, 9.49. Found: S, 9.36.

2-Chloro-3-aminodibenzothiophene.—Into a 125-ml. erlenmeyer flask equipped with a reflux condenser were placed 1.0 g. (0.0036 mole) of 2-chloro-3-acetamidodibenzothiophene, 2.0 g. of potassium hydroxide, 40 ml. of ethanol and 20 ml. of water. The mixture was refluxed for a period of one hour at which time the contents were cooled and the precipitate filtered and dried to yield 0.76 g. of material which melted between 129–132°. This was crystallized from methanol to afford 0.51 g. (60.1%) of 2-chloro-3-aminodibenzothiophene melting at 132–133°.

Anal. Calcd. for $C_{12}H_8ClNS$: S, 13.75. Found: S, 13.49.

3-Bromo-2-benzamidodibenzothiophene.—Into a 500-ml. round-bottomed, three-necked flask, equipped with a mechanical stirrer and reflux condenser fitted with an acid trap, were placed 5.0 g. (0.0165 mole) of 2-benzamidodibenzothiophene[5] and 200 ml. of chloroform. To this solution were added 2.7 g. (0.017 mole) of bromine dissolved in 30 ml. of chloroform and a small crystal of iodine. The mixture was heated to near reflux for a period of 4 hr. The solvent was then stripped from the reaction mixture and the residue crystallized from methyl Cellosolve to yield 4.7 g. (74.5%) of 3-bromo-2-benzamidodibenzothiophene melting at 201–202°.

Anal. Calcd. for $C_{19}H_{12}BrNOS$: S, 8.39. Found: S, 8.21.

A small sample of this material was hydrolyzed to give the same 2-amino-3-bromodibenzothiophene as that obtained previously from this Laboratory[1] identified by the method of mixed melting points.

1-Chloro-2-acetamidodibenzothiophene.—This material was made essentially as described previously[1] by treating 2-acetamidodibenzothiophene with sulfuryl chloride in chloroform. The deamination product of this material was

(9) All melting points are uncorrected.

(10) H. Gilman and J. F. Nobis, THIS JOURNAL, **67**, 1479 (1945).

(11) C. Courtot, L. Nicolas and T. H. Liang, *Compt. rend.*, **186**, 1624 (1928).

shown to be 1-chlorodibenzothiophene, rather than the 3-isomer by the method of mixed melting points with an authentic sample of 1-chlorodibenzothiophene.[4]

3-Chloro-2-benzamidodibenzothiophene.—Into a 500-ml. round-bottomed, three-necked flask, equipped with a mechanical stirrer and reflux condenser fitted with an acid trap, were placed 5.0 g. (0.0165 mole) of 2-benzamidodibenzothiophene[5] and 200 ml. of chloroform. To the reaction mixture were then added 2.3 g. (0.017 mole) of sulfuryl chloride, dissolved in 30 ml. of chloroform, and a small crystal of iodine. The reaction mixture was heated at reflux for a period of 3 hr. and the solvent was stripped from the residue. Crystallization from methyl Cellosolve gave 3.7 g. (67.5%) of material which melted at 211–212°. The infrared spectrum of this compound was almost identical with that of 2-benzamido-3-bromodibenzothiophene.

Anal. Calcd. for $C_{19}H_{12}ClNOS$: S, 9.49. Found: S, 9.35.

Acknowledgments.—The authors wish to express their thanks to Dr. V. A. Fassel and Mr. Robert McCord of the Institute for Atomic Research for the infrared analyses.

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

The Aminolysis of N-Nitrotoluenesulfonamides[1]

BY WILLIAM D. EMMONS AND JEREMIAH P. FREEMAN

RECEIVED MAY 2, 1955

In connection with other investigations we have observed an extremely facile cleavage of the sulfonamide linkage. Substituted N-nitrotoluenesulfonamides are readily aminolyzed by secondary amines at room temperature to produce primary nitramines and the corresponding disubstituted toluene amide. This reaction has proved to be a general

$$p\text{-}CH_3C_6H_4SO_2\underset{\displaystyle NO_2}{\underset{|}{N}}R + R_2'NH \longrightarrow p\text{-}CH_3C_6H_4SO_2NR_2' + RNHNO_2$$

one for the preparation of mono- and dialkylcarbinyl nitramines. The reactions were carried out in acetonitrile as a solvent and piperidine was used most generally as the aminolytic agent. The experimental results are summarized in Table I. The nitrotoluenesulfonamides were prepared by the method of Gillibrand and Lamberton.[2]

TABLE I

CONVERSION OF TOLUENESULFONAMIDES TO PRIMARY NITRAMINES

Toluenesulfonamide	Yield, % of N-nitrotoluenesulfonamide	Yield,[a] % nitramine
n-Butyl	92	81
s-Butyl	54	86
n-Amyl	81	90
Isoamyl	95	96
n-Hexyl	84	86

[a] Based on N-nitrotoluenesulfonamide.

This rapid and nearly quantitative cleavage of the sulfur–nitrogen bond is remarkable in view of the resistance toward alkaline hydrolysis exhibited by sulfonamides as a class. A recent review has pointed out that there appear to be no examples of alkaline hydrolysis of sulfonamides involving, as a first step, breaking of the sulfur–nitrogen bond.[3] Hydrolysis of these compounds is universally carried out under strongly acid conditions at elevated temperatures. Indeed the resistance of sulfonamides to bases prompted our investigation of nitrosulfonamides as alkaline nitrating agents. It was thought that nucleophilic attack might possibly occur at the nitro group rather than at the sulfonyl group producing a secondary nitramine (eq. 1).

$$R_2'NH + p\text{-}CH_3C_6H_4SO_2\underset{\displaystyle NO_2}{\underset{|}{N}}R \longrightarrow R_2'NNO_2 + p\text{-}CH_3C_6H_4SO_2NHR \quad (1)$$

It is possible that the direction of cleavage is controlled by the stability of the leaving group. Attack on the sulfonyl group produces the resonance-stabilized nitramine anion whereas attack at the nitro group would yield a sulfonamide ion stabilized by the interaction of adjacent opposite charges and d-orbital resonance.[4] The nitramine anion is probably the more stable species, as it has been demonstrated that the nitromethane anion is more stable than a sulfonylmethyl anion.[5] In the case under study here the nitrogen analogs of these two species are involved

Carbon[6]	Nitrogen
$RSO_2CH_2^-$	RSO_2NR^-
$CH_2{=}NO_2^-$	$RN{=}NO_2^-$

Whatever the cause, the reaction must be initiated by nucleophilic attack at the sulfonyl group and probably involves expansion of the sulfur octet. Another example of this reaction is known. Gillibrand and Lamberton[2] have reported the hydrolysis of N-nitrotoluenesulfonamides by boiling caustic. The comparative slowness of their method was probably due to the insolubility of the nitramides in water.

This reaction could not be applied to the preparation of trialkylcarbinylnitramines as the corresponding N-nitrotoluenesulfonamides could not be prepared. The tosyl derivatives of *t*-carbinamines cleaved very readily in the acidic nitration medium to produce toluenesulfonamide and, presumably, the tertiary carbonium ion. Only the amide and various nitration and degradation products of the olefins corresponding to the carbonium ion were obtained. A similar acid-catalyzed solvolysis of tertiary toluenesulfonamides has been reported recently.[6]

Experimental[7]

Toluenesulfonamides.—The following sulfonamides were prepared in the manner described by Shriner and Fuson:[8]

(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) M. I. Gillibrand and A. H. Lamberton, *J. Chem. Soc.*, 1883 (1949).

(3) H. R. Snyder and R. E. Heckert, THIS JOURNAL, **74**, 2006 (1952).

(4) W. von E. Doering and L. K. Levy, *ibid.*, **77**, 509 (1955), *et seq.*

(5) R. G. Pearson, D. H. Anderson and L. L. Alt, *ibid.*, **77**, 527 (1955).

(6) R. H. Wiley, C. C. Ketterer and S. F. Reed, *ibid.*, **76**, 4996 (1954).

(7) We are indebted to Miss Annie Smelley for the microcombustion data.

(8) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, Ed. 3, p. 178.