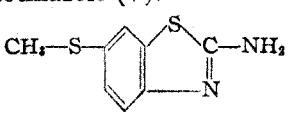
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Certain Derivatives of 2-Aminobenzothiazole

BY FLAVEN E. JOHNSON[1] AND CLIFF S. HAMILTON

Alkyl aryl and heterocyclic aryl sulfones containing a *p*-amino group have shown marked bacteriostatic[2] and antitubercular[3] activity. This is particularly true of derivatives containing the thiazole ring.[4] Sulfides and sulfoxides have also shown chemotherapeutical activity.[5] The present investigation was undertaken to embody the above characteristics in one compound by synthesizing sulfur containing derivatives of 2-aminobenzothiazole, for example 6-methylmercapto-2-aminobenzothiazole (V).



V

4-Methylmercaptonitrobenzene (II) was prepared by a series of conventional methods, reduced to the amine and converted to 4-methylmercaptophenylthiourea (IV). Oxidation of IV with bromine gave 2-amino-6-methylmercaptobenzothiazole (V) in good yields. After protecting the amino group compound V was oxidized to 2-amino-6-methylsulfonylbenzothiazole (VIII) in excellent yields.

2-Amino-6-methylsulfonylbenzothiazole was also prepared by oxidizing compound II to 4-methylsulfonylnitrobenzene (IX), reducing it to the amine and treating the compound obtained with ammonium thiocyanate, then with bromine to give a low yield of compound VIII. This synthesis proved that the mercapto sulfur and not the ring sulfur was undergoing oxidation.

Conversion of compound VIII to 2-chloro-6-methylsulfonyl-benzothiazole (XI) proceeded smoothly employing a modified Sandmeyer reaction. An attempt to use the same reaction on compound V produced two products, 2-chloro-6-methylsulfinylbenzothiazole (XVI) at 0° and 2-chloro-6-methylmercaptobenzothiazole (XXI) at −20°. Compounds XVI and XXI were later oxidized to XI by means of hydrogen peroxide.

Chloro compounds XI, XVI and XXI were all successfully condensed with benzylamine, piperidine, δ-diethylaminobutylamine and γ-diethylaminopropylamine to produce the remainder of the compounds shown in the accompanying tables.

All of the sulfone derivatives and a representative member of the sulfoxide and sulfide series have been submitted for pharmacological screen testing.

(1) Parke, Davis and Company fellow.

(2) Fourneau, *et al.*, *Compt. rend. soc. biol.*, **127**, 393 (1938); *C. A.*, **32**, 3901 (1938).

(3) Smirnova, *J. Gen. Chem. (U.S.S.R.)*, **17**, 284 (1947).

(4) Bambas, THIS JOURNAL, **67**, 671 (1945).

(5) Gibbs and Robinson, *J. Chem. Soc.*, 925 (1945).

Experimental

Sodium *p*-Nitrothiophenate (I).—This compound was prepared according to the procedure of Stacy[6] using a 75% ethanol–water solution as the reaction medium. The solution was kept at reflux temperature during the entire reaction to yield 84% of the desired salt.

4-Methylmercaptonitrobenzene (II).—The procedure as employed by Waldron and Reid[7] was used to prepare the compound in 70–75% yields; m. p., 68–69°, lit.[7] 67° and 71°.

4-Methylmercaptoaniline Hydrochloride (III).—4-Methylmercaptonitrobenzene (45 g., 0.32 mole) was reduced in three runs (15 g. each), by means of hydrogen and Raney nickel in acetone solution. Six hours were required for complete reduction and the product was isolated as a salt by passing dry hydrogen chloride gas through the solution. The product removed by filtration weighed 44.5 g. (94%) and was identified by formation of the benzoyl derivative; m. p. 176–178°, lit.[8] 177–178°.

4-Methylmercaptophenylthiourea (IV).—The method used was that of Wertheim[9]; yield 86%, m. p. 200–201°, lit.[9] 198–199°.

2-Amino-6-methylmercaptobenzothiazole (V).—4-Methylmercaptophenylthiourea (58 g., 0.29 mole) was suspended in 200 ml. of dry chloroform in a 500-ml. round-bottomed flask. Liquid bromine (58 g., 0.362 mole) in dry chloroform (100 ml.) was carefully added. The reaction flask was placed under a reflux condenser provided with a trap to catch hydrogen bromide vapors and carefully warmed for forty minutes. The solvent was then decanted and fresh chloroform added followed by twenty minutes of heating. The solid which remained was decanted free of solvent and dried. The yellow amorphous material was triturated with sulfurous acid solution and washed with water. The hydrobromide salt obtained was dissolved in 1.5 l. of hot water, filtered free of impurities and made alkaline with ammonium hydroxide. The solid separating on cooling was recrystallized from 50% ethanol–water solution; yield, 51.2 g. (89.5%) of light tan plates melting at 150–151°.

2-Acetamido-6-methylmercaptobenzothiazole (VI).—2-Amino-6-methylmercaptobenzothiazole (15 g., 0.8 mole) was dissolved by warming in technical grade acetic anhydride and treated in the conventional manner to obtain 18.1 g. (99%) of cream-colored crystals, which recrystallized from 95% ethanol and had a m. p. of 198–200°.

Anal. Calcd. for $C_{10}H_{10}N_2OS_2$: N, 11.75. Found: N, 12.03.

2-Acetamido-6-methylsulfonylbenzothiazole (VII).—2-Acetamido-6-methylmercaptobenzothiazole (18.1 g., 0.8 mole) was dissolved in 340 ml. of glacial acetic acid by warming on a steam-bath. Hydrogen peroxide solution (60 ml., 30%) in glacial acetic acid (40 ml.) was added and the mixture warmed to 80° on a steam-bath. After standing at room temperature for one hour the reaction solution was placed in the refrigerator overnight. The white fluffy crystals that separated were removed by filtration, washed with water and dried; yield 15.7 g. (76.5%), m. p. 305–307°.

Anal. Calcd. for $C_{10}H_{10}N_2O_3S_2$: N, 10.36. Found: N, 10.52.

2-Amino-6-methylsulfonylbenzothiazole (VIII) (Method I).—2-Acetamido-6-methylsulfonylbenzothiazole (15.7 g., 0.6 mole) was heated at reflux temperature with hydrochloric acid (4 *N*, 240 ml.) for thirty minutes. The white

(6) Price and Stacy, THIS JOURNAL, **68**, 498 (1946).

(7) Waldron and Reid, *ibid.*, **45**, 2399 (1923).

(8) Gattermann, *Ann.*, **393**, 230 (1912).

(9) Wertheim, THIS JOURNAL, **53**, 200 (1931).

TABLE I

6-METHYLMERCAPTOBENZOTHIAZOLE DERIVATIVES

	Compound	Yield, %	Formula	M. p., °C.	Analyses, % Calcd.	Found
V	2-Amino-	89.5	$C_8H_8N_2S_2$	150–151	N 14.27	14.16
					C 48.95	49.08
					H 4.11	4.08
XXI	2-Chloro-	28	$C_8H_6ClNS_2$	51–52	C 44.58	44.57
					H 2.80	2.83
XXII	2-(δ-Diethylaminobutylamino)-[a]	70	$C_{16}H_{27}Cl_2N_3S_2$	.....	C 48.47	48.64
					H 6.86	6.92
XXIII	2-(γ-Diethylaminopropylamino)-[a]	58	$C_{15}H_{25}Cl_2N_3S_2$	.....	N 10.99	10.79
XXIV	2-(Benzylamino)-	45	$C_{15}H_{14}N_2S_2$	175–176	N 9.78	9.90
XXV	2-(Piperidino)-	40	$C_{13}H_{16}N_2S_2$	75–76	C 59.05	59.13
					H 6.10	6.05

TABLE II

6-METHYLSULFINYLBENZOTHIAZOLE DERIVATIVES

	Compound	Yield, %	Formula	M. p., °C.	Analyses, % Calcd.	Found
XVI	2-Chloro-	34	$C_8H_6ClNO_2S$	112–113	N 6.04	6.34
					C 41.46	41.32
					H 2.61	2.62
XVII	2-(δ-Diethylaminobutylamino)-[a]	40	$C_{16}H_{27}Cl_2N_3OS_2$	.....	N 10.19	10.40
XVIII	2-(γ-Diethylaminopropylamino)-[a,b]	21	$C_{27}H_{29}N_9O_{15}S_2$	.....	N 16.08	15.91
XIX	2-(Benzylamino)-	65	$C_{15}H_{14}N_2OS_2$	158–160	N 9.27	9.41
XX	2-(Piperidino)-	23	$C_{13}H_{16}N_2OS_2$	109–110	N 9.99	9.78

TABLE III

6-METHYLSULFONYLBENZOTHIAZOLE DERIVATIVES

	Compound	Yield, %	Formula	M. p., °C.	Analyses, % Calcd.	Found
XI	2-Chloro-	48	$C_8H_6ClNO_2S_2$	189–190	N 5.65	5.77
					C 38.78	39.03
					H 2.44	2.42
VIII	2-Amino-	91	$C_8H_8N_2O_2S_2$	224–226	N 12.26	12.25
					C 42.09	42.18
					H 3.53	3.57
XII	2-(δ-Diethylaminobutylamino)-[a]	44	$C_{16}H_{27}Cl_2N_3O_2S_2$	.....	Cl 16.51	16.27
					N 9.81	9.83
XIII	2-(γ-Diethylaminopropylamino)-[a]	80	$C_{15}H_{25}Cl_2N_3O_2S_2$	.....	N 10.14	10.32
XIV	2-(Benzylamino)-	95	$C_{15}H_{14}N_2O_2S_2$	220	C 56.58	56.49
					H 4.43	4.29
XV	2-(Piperidino)-	94	$C_{13}H_{16}N_2O_2S_2$	150–151	C 52.69	52.61
					H 5.44	5.31

[a] Dihydrochlorides. [b] Analyzed as a dipicrate which has a m. p. of 163–165°.

solid was completely dissolved by this time so the solution was filtered and carefully neutralized with ammonium hydroxide while still hot. The crystals that separated were recrystallized from 95% ethanol; yield 12 g. (91%) of white needles, m. p. 224–226°.

4-Methylsulfonylnitrobenzene (IX).—4-Methylmercaptonitrobenzene (2.0 g., 0.012 mole) was placed in glacial acetic acid (15 ml.) and hydrogen peroxide (30%, 10 ml.) was added. The solution was warmed on a steam-bath until all the mercapto compound went into solution. The mixture was allowed to stand at room temperature for one hour and then placed in the refrigerator overnight. The long yellow needles that separated were filtered yielding 1.85 g. (79%), m. p. 142°, lit. 136° and 142.5°.[6]

4-Methylsulfonylaniline Hydrochloride (X).—4-Methylsulfonylnitrobenzene (7.1 g., 0.035 mole) was reduced using Raney nickel and hydrogen in acetone solution. After complete reduction the solution was filtered free of catalyst and saturated with dry hydrogen chloride; yield 6.3 g. (86.5%). Some of the hydrochloride was converted to the amine producing a light yellow solid; m. p. 136–137°.[6]

2-Amino-6-methylsulfonylbenzothiazole (VIII). (Method II).—4-Methylsulfonylaniline hydrochloride (4.05 g., 0.024 mole) was treated with ammonium thiocyanate (1.8 g., 0.024 mole) in a water solution analogous to the preparation of compound IV. The impure solid thus obtained was treated with bromine and chloroform in a manner analogous to the preparation of compound V; yield 0.5 g. (9.1%), m. p. 223–225°. A mixed melting point determination with compound VIII prepared by Method I gave no appreciable depression of the melting temperature.

2-Chloro-6-methylsulfonylbenzothiazole (XI).—2-Amino-6-methylsulfonylbenzothiazole (4 g., 0.02 mole) was dissolved by warming and stirring in 87% phosphoric acid (43 ml.). The solution was cooled externally to 0° and concentrated nitric acid (18 ml.) was added with stirring. A solution of sodium nitrite (1.43 g., 0.02 mole) in water (3.6 ml.) was added to the lower portion of the well-stirred mixture. After standing for ten minutes the viscous diazonium solution was poured in a thin stream into concentrated hydrochloric acid (75 ml.) containing cuprous chloride (3 g., 0.02 mole). After the evolution of

nitrogen had ceased, the mixture was diluted to three times its volume and allowed to stand for one hour. The solid which formed was removed by filtration and recrystallized using charcoal from 95% ethanol (100 ml.); yield 2.4 g. (48%) of white needles, m. p. 189–190°.

2-Chloro-6-methylsulfinylbenzothiazole (XVI).—2-Amino-6-methylmercaptobenzothiazole (5 g., 0.03 mole) was dissolved by heating in 87% phosphoric acid (75 ml.). The solution was then cooled to 0° by means of an ice-bath. Cold concentrated nitric acid (25 ml.) was added with rapid stirring. A solution of sodium nitrite (2 g. in 5 ml. of water, 0.03 mole) was then added to the lower portion of the well-stirred acid medium. The deep red viscous diazonium mixture which formed was then poured in a small stream into concentrated hydrochloric acid (100 ml.) containing cuprous chloride (5.0 g., 0.03 mole). As soon as evolution of nitrogen ceased the mixture was stirred for an additional fifteen minutes and diluted to three times its volume. The diluted solution was extracted four times with benzene (100-ml. portions). The benzene was dried over anhydrous sodium sulfate and evaporated to dryness. The resulting orange solid was recrystallized, employing charcoal, from hot water (150 ml.); yield 2 g. (34%) of white fluffy crystals, m. p. 112–113°.

2-Chloro-6-methylmercaptobenzothiazole (XXI).—Identical conditions and amounts were employed as in the preparation of compound XVI with the exception that the diazotization was carried out at −20 instead of 0° using an acetone–Dry Ice-bath. The product was extracted with benzene and obtained in the solid form as before. The yellow material was transferred in two portions to a small fractionating column and distilled under reduced pressure. A yellow oil distilled over at 138–142° (3 mm.). This product was recrystallized, using charcoal, from hot petroleum ether; yield 1.5 g. (28%) of white crystals, m. p. 51–52°.

The condensations of amines with chloro compounds were carried out in a slightly over two mole excess of the amine so that the excess amine would form a salt with the hydrogen chloride eliminated. The method employed for isolation of the product was based on the fact that all the amines reacting were more soluble in water than the condensed products. The following preparations illustrate the procedure used.

2-(Benzylamino)-6-methylsulfonylbenzothiazole (XIV).—2 - Chloro - 6 - methylsulfonylbenzothiazole (0.75 g., 0.003 mole) and benzylamine (0.86 g., 0.008 mole) reacted together in a 25-ml. round-bottomed flask equipped with a water condenser. Although some heat was evolved at once the mixture was heated at 150° for four hours in an oil-bath to complete the reaction. Upon cooling the reaction mixture solidified. The crystals which formed were washed thoroughly with dilute ammonium hydroxide and water to remove excess benzylamine. The solid that remained was recrystallized from ethyl acetate; yield 0.93 g. of fine white crystals, m. p. 220°.

2-(δ-Diethylaminobutylamino)-6-methylmercaptobenzothiazole Dihydrochloride (XXII).–2-Chloro-6-methylmercaptobenzothiazole (0.25 g., 0.001 mole) and δ-diethylaminobutylamine (0.43 g., 0.003 mole) reacted together on a steam-bath for twenty-two hours. The resulting liquid was mixed thoroughly with dilute ammonium hydroxide and extracted with three portions of diethyl ether (25 ml.). The combined solutions were washed three times with water (25 ml.), dried over anhydrous sodium sulfate and dry hydrogen chloride gas added until an oil separated. The oil was recrystallized, using charcoal, from methanol and anhydrous diethyl ether; yield 0.35 g. of a light brown solid.

Summary

1. 2 - Amino - 6 - methylsulfonylbenzothiazole and 2 - amino - 6 - methylmercaptobenzothiazole have been prepared from *p*-nitrochlorobenzene in good yields.

2. The above compounds were converted to the corresponding 2-chloro compounds producing in addition 2-chloro-6-methylsulfinylbenzothiazole.

3. All three chloro compounds were successfully condensed with benzylamine, piperidine, δ-diethylaminobutylamine and γ-diethylaminopropylamine.

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Some β-Amino-α-chloroacrylonitriles

BY JOHN G. ERICKSON

Except for a few β-aminoacrylonitriles prepared by Moureu and Lazennec,[1] no compounds of this class have been reported. The French workers prepared their compounds by the addition of various primary and secondary amines to several α,β-acetylenic nitriles.

Here we wish to report the preparation of a number of β-amino-α-chloroacrylonitriles (II) by the reaction of α,β-dichloroacrylonitrile (I) with ammonia and aliphatic and aromatic primary and secondary amines.

$$\underset{\text{I}}{\text{ClCH=}\overset{\text{Cl}}{\overset{|}{\text{C}}}\text{CN}} + \text{RR'NH} \longrightarrow \underset{\text{II}}{\text{RR'NCH=}\overset{\text{Cl}}{\overset{|}{\text{C}}}\text{CN}} + \text{HCl}$$

The reactions were carried out in alcohol or benzene solutions at or near room temperature. An acid acceptor, which was either a tertiary amine or an excess of the ammonia or amine being used in the reactions, was always present to neutralize the hydrogen chloride eliminated in the reactions.

The β-amino-α-chloroacrylonitriles are, in general, unstable. Although they may usually be distilled, even at high temperatures, without serious decomposition, those compounds which are liquids at room temperature slowly darken and decompose upon standing. The solid compounds appear to be relatively stable at room temperature. Of the liquid β-amino-α-chloroacrylonitriles, those derived from secondary amines are less stable than those derived from primary amines. The nature of the decomposition is not clear.

Attempts to confirm the structures of these compounds by conversion to known compounds failed, presumably because the chlorine in these

(1) Moureu and Lazennec, *Compt. rend.*, **143**, 553 (1906).