TABLE I.—RESULTS OF THE ASSAY

Drug	No. Strips	Dose Range, mcg./ml.	ED_{50}, mcg./ml. (95% Confidence Limits)	Slope	95% Confidence Limits
Dibenamine	14	0.01 –1.0	0.05 (0.04–0.06)	2.4	±0.8
Tolazoline	11	1.0 –24.0	4.30 (3.37–5.50)	1.8	±0.5
Ergotamine	18	0.001–0.8	0.02 (0.01–0.03)	0.8	±0.2
Guanethidine	2	1.0 –200.0	>200	0.0	...

TABLE II.—EFFECT OF CONTACT TIME ON EPINEPHRINE INHIBITION

	Contact time	
	5 min.	10 min.
Tolazoline	52.8[a]	46.9[a]
Dibenamine	37.6	47.4

[a] Per cent inhibition.

from tissue receptors suggests that the binding forces involved are small and that removal from binding sites is dependent upon the distribution coefficient of the substance between tissue receptor and bathing medium. Brodie, *et al.* (16), have shown that tolazoline is only 23% plasma protein bound in the intact dog. These authors also found a relatively low degree of tissue localization of this agent and a relatively short biological half-life.

We have found this preparation to be an excellent tool for the investigation of drug action at adrenergic receptors. The relative ease in handling this tissue offers a distinct advantage over other methods. Investigations of the mechanism of action of a number of drugs on this organ are in progress.

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Synthesis of Some N- and S-Substituted Derivatives of 2-Aminobenzenethiol

By CHARLES S. DAVIS, GLENN L. JENKINS, ADELBERT M. KNEVEL, and CHARLES PAGET

N- and S-substituted derivatives of 2-aminobenzenethiol were prepared as intermediates in the synthesis of analogs of the phenothiazine tranquilizers. A new synthesis for the preparation of the benzothiazine ring is reported. The ring cleavage of 2,2-pentamethylenebenzothiazoline with alkylating agents is discussed.

IN RECENT years derivatives of 2-aminobenzenethiol have attracted attention in the development of medicinal agents. Gialdi and Baruffini (1) synthesized a series of 2-aminophenyl alkyl sulfides as potential fungicides. Burger, *et al.* (2), prepared N-substituted 2-aminophenyl aryl sulfides and found some of them to be radiation protective agents. We have undertaken the synthesis of analogs of the phenothiazine tranquilizers and found it necessary to prepare N- and S-substituted 2-aminobenzenethiols as intermediates. Bialdi and Baruffini (3) had prepared similar thiols by reducing 2,2′-dinitrodiphenyldisulfide with glucose to 2-nitrobenzenethiol. 2-Nitrobenzenethiol was then substituted with an alkyl bromide to give 2-nitrophenyl alkyl sulfide. This paper reports a one-step procedure of reacting commercial 2-aminobenzenethiol with alkyl halide in the presence of potassium hydroxide solution. Not only are the compounds prepared in fewer steps than those of Gialdi and Baruffini, but the yields of the corresponding products are

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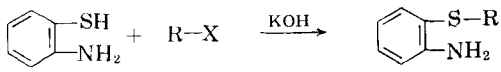
TABLE I.—2-AMINOPHENYL ALKYL SULFIDES



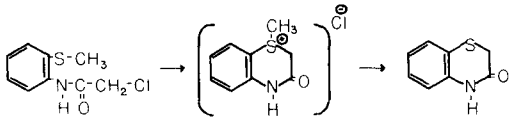
R	Yield, %	B.P., °C. (mm.)	M.P., °C.	Lit. M.p., °C. (3)
$-CH_2CH=CH_2$	75	84–86 (0.40)	142–143[g]	143–144
$-CH_2C_6H_5$	90	190–192 (0.15)	43–44	45
$-C_5H_{11}$-n	77	98–99 (0.45)	151–153[g]	152–153
$-CH_3$	95	121–123 (18)	189–190[g]	188–189
$-(CH_2)_3-NO$	67	165–166 (0.35)	54–55	[a]
$-(CH_2)_2-O-CH=CH_2$	50	109–110 (.35)	...	[b]
$-(CH_2)_2-N-(C_2H_5)_2$	78	130–132 (0.7)	...	[c]
$-(CH_2(CH_3)-CH-N-(CH_3)_2$	80	106–108 (0.5)	...	[d]
$-(CH_2)_2-N-(i-C_3N_7)_2$	75	120–122 (0.5)	...	[e]
$-CH_2)_3-N-(C_2H_5)_2$	76	162–164 (2.0)	198–200[g]	[f]

[a] *Anal.*—Calcd. for $C_{13}H_{20}N_2OS$: S, 12.71. Found: S, 12.57. [b] *Anal.*—Calcd. for $C_{10}H_{13}NOS$: S, 16.41. Found: S, 16.63. [c] *Anal.*—Calcd. for $C_{12}H_{20}N_2S$: S, 14.30. Found: S, 14.26. [d] *Anal.*—Calcd. for $C_{11}H_{18}N_2S$: S, 15.23. Found: S, 15.18. [e] *Anal.*—Calcd. for $C_{14}H_{24}N_2S$: S, 12.66. Found: S, 12.73. [f] *Anal.*—Calcd. for $C_{13}H_{22}N_2S$: S, 13.45. Found: S, 13.95. [g] Melting point of the hydrochloride salt.

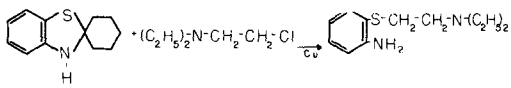
significantly higher. The compounds thus obtained are listed in Table I.

2-(2′-Diethylaminoethylamino)phenyl methyl sulfide (IV) was prepared by two methods. 2-Aminophenyl methyl sulfide (I) was alkylated directly with 2-diethylaminoethyl chloride hydrochloride in the presence of a copper catalyst. The compound IV was also synthesized by a method suggested by Burger (2). 2-Aminophenyl methyl sulfide (I) was reacted with chloroacetyl chloride to give 2-(2′-chloroacetamido)phenyl methyl sulfide (II) which was combined with diethylamine to give 2-(2′-diethylaminoacetamido)-phenyl methyl sulfide (III). This was reduced to 2-(2′-diethylaminoethylamino)phenyl methyl sulfide (IV) with lithium aluminum hydride.

2 - (2′ - Diethylaminoethylamino)benzenethiol (V) was synthesized by two procedures. The first was the alkaline hydrolysis of 2-oxo-3-(2′-diethylaminoethyl)benzothiazoline which gave a 50% yield of V. Alternately, the reduction of 2-(2′-diethylaminoethylamino)phenyl methyl sulfide (IV) with lithium in methylamine (4) gave 28% yield of V. In an attempt to purify 2-(2′-chloroacetamido)phenyl methyl sulfides (II) by distillation, methyl chloride was split out to produce 3-oxo-1,4-benzothiazine in 65–75% yields.



The spiro structure, 2,2-pentamethylenebenzothiazoline (VI) was prepared by a modification of the procedure outlined by Elderfield and McClenachen (5). The alkylation of VI was attempted with 3-diethylaminoethyl chloride and a copper catalyst. The major product was the corresponding sulfide and none of the N-alkylated material. Since this ring cleavage was not expected, VI was subjected to the copper catalyst alone. Starting material was recovered and none of the cleavage product could be found. Elderfield (5) reported the cleavage of the pentamethylene ring at high temperatures but not the heterocyclic ring.



EXPERIMENTAL[1]

2-Aminophenyl Methyl Sulfide (I).—To a solution of 34 Gm. (0.6 mole) of potassium hydroxide in sufficient water to just bring about solution, was added 37.5 Gm. (0.3 mole) of 2-aminobenzenethiol.[2] After cooling the mixture to room temperature, 43 Gm. (0.3 mole) of methyl iodide[3] was added slowly with rapid stirring. The rate of addition was such that the boiling temperature of methyl iodide was not exceeded. Water, 1000 ml., was added and an oil separated which was washed with 50 ml. of water and dried. The oil was distilled at 121–123° (18 mm.) to yield 95% of product.

The physical constants of the various 2-aminophenyl alkyl sulfides prepared by the above method are described in Table I.

2 - (2′ - Diethylaminoethylamino)phenyl Methyl Sulfide (IV).—*Method A.*—A suspension of 9.5 Gm. (0.25 mole) of lithium aluminum hydride in 30 ml. of dry ether was stirred and refluxed for 1 hour. To the above suspension was added, dropwise, a solution of 21.0 Gm. (0.1 mole) of 2-(2′diethylaminoacetamido)phenyl methyl sulfide (III) in dry ether over 25 minutes. The mixture was refluxed and stirred for 15 hours. The unreacted lithium aluminum hydride was then decomposed,

[1] All melting points are uncorrected. Analyses were performed by the Alfred Bernhardt, Mikroanalytisches Laboratorium in Max-Planck-Institut fur Kohlenforschung, Mulheim (Ruhr), Germany.

[2] 2-Aminobenzenethiol was supplied by American Cyanamid Co.

[3] It was found that the chloro or bromo compounds reacted as readily as the iodo compound.

with cooling, by dropwise addition of 2 ml. of ethyl acetate followed by 3 ml. of water. After vigorous stirring for 2 hours, the mixture was filtered by vacuum. The filtrate was treated with ethereal hydrogen chloride until the solution was neutral to litmus. The ethereal solution was made basic with 5% potassium hydroxide solution. The aqueous layer was extracted with ether and dried. The resulting oil was distilled at 106–107° (0.35 mm.) to yield 7.9 Gm. (40%).

Anal.—Calcd. for $C_{18}H_{22}N_2S$: S, 13.45. Found: S, 13.56.

Method B from 2-Aminophenyl Methyl Sulfide (I).—Twenty-one grams (0.15 mole) of I and 32 Gm. of anhydrous potassium carbonate were mixed with 20 ml. of dry benzene. To the slurry were added 18.6 Gm. (0.1 mole) of 2-diethylaminoethyl chloride hydrochloride and 0.5 Gm. of copper bronze[4] in 70 ml. of dry benzene. This mixture was stirred and refluxed for 10 hours. The brown mixture was filtered and the residue was washed with benzene. The product was distilled at 123–124° (1.5 mm.) to yield 4.2 Gm. (15%) of material identical to that prepared by method A.

2 - (2′ - Chloroacetamido)phenyl Methyl Sulfide (II). A solution consisting of 13.9 Gm. (0.1 mole) of 2-aminophenyl methyl sulfide (I) and 9.9 Gm. (0.125 mole) of dry pyridine in 200 ml. of dry ether was cooled to 0°. To this mixture was added an ethereal solution of 11.9 Gm. (0.105 mole) of chloroacetyl choride. After standing for 2 hours, the ethereal solution was washed twice with 100 ml. of 5% hydrochloric acid and then dried. The ether was removed and the orange oil crystallized upon standing. After recrystallization from aqueous ethanol, the waxy crystals melted at 43–44° to give 12.5 Gm. of product.

Anal.—Calcd. for $C_9H_{10}ClNOS$: S, 14.87. Found: S, 14.62.

When distillation of 5 Gm. (0.23 mole) of 2-(2′-chloroacetamido)phenyl methyl sulfide (II) was attempted, 3.5 Gm. (75%) of 3-oxo-1,4-benzothiazine resulted. The conversion was brought about by heating II in oil bath at 195° under 20 mm. pressure for 30 minutes. Upon cooling, the mixture solidified and 50 ml. of methanol was added. The alcoholic solution was boiled with Norite and filtered. Upon cooling the filtrate, pale yellow crystals were formed that melted at 177–178° [lit. (6) m.p. 179°.] The infrared spectrum was identical to an authentic sample.

2 - (2′ - Diethylaminoacetamido)phenyl Methyl Sulfide (III).—To a solution of 46 Gm. of 2-(2′-chloroacetamido)phenyl methyl sulfide (II) dissolved in 200 ml. of ether was added 31.2 Gm. of diethylamine in 40 ml. of ether. The ethereal solution was refluxed for 12 hours and then washed with 500 ml. of water. The ethereal solution was dried and distilled. The fraction distilling at 151–153° (3 mm.) was taken as product. The yield was 54 Gm. (85%); m.p. hydrochloride salt, 149–152°.

[4] No. 44 Bronze powder manufactured by Sunbrite Mfg. Co., St. Louis, Mo.

Anal.—Calcd. for $C_{13}H_{20}N_2OS$: S, 12.71. Found: S, 12.85.

2 - (2′ - Diethylaminoethylamino)benzenethiol (V).—A methylamine solution of 0.58 Gm. of lithium wire was added slowly to 10 Gm. of 2-(2′-diethylaminoethylamino)phenyl methyl sulfide (IV) in 150 Gm. of methylamine. To accomplish this, the methylamine was refluxed through a thimble containing the lithium wire cut into small pieces. The thimble was suspended above the reaction flask and under a dry ice condenser so that the methylamine vapors could travel from the reaction flask into the dry ice condenser. The thimble consisted of a 6-in. test tube tapered at the bottom and fitted with a length of glass tubing sufficiently long to extend well down into the neck of the reaction flask. [See (4) for a detailed description of apparatus used.] A small loose plug of glass wool placed in the bottom of the thimble kept small pieces of undissolved metal from dropping into the flask. After all of the lithium had dissolved, the methylamine was allowed to evaporate overnight and the residue was dissolved in water. The aqueous solution was neutralized with 10% acetic acid and extracted with ether. The ethereal solution was dried and concentrated to give an orange solid which melted at 103–105° [lit. (7) m.p. 100–102°]. Yield, 2.7 Gm. (28%).

Attempted Alkylation of 2,2-Pentamethylenebenzothiazoline.—In 200 ml. of dry toluene, 20.5 Gm. (0.1 mole) of 2,2-pentamethylenebenzothiazoline, 18.6 Gm. (0.1 mole) of diethylaminopropyl chloride hydrochloride, 40 Gm. of anhydrous potassium carbonate, and 0.1 Gm. of copper powder were refluxed with stirring for 24 hours. The reaction was allowed to cool and the solid residue filtered. The toluene was removed from the filtrate and the residue was distilled at 124–135° (0.1 mm.).

The distilled liquid mixed with petroleum ether (30:60) was allowed to pass through a column of alumina. The eluate was concentrated and the residue distilled at 162° (2 mm.). This material was found to be (3-diethylaminopropyl)-2-aminophenyl sulfide.

The product has an infrared spectrum identical to that of the material prepared from 2-aminobenzenenethiol, diethylaminopropyl chloride, and potassium hydroxide. The hydrochloride salt melted at 198–200° and gave no depression when mixed with authentic material.

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