

Syntheses of Some Aminonaphthylalanines¹

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In a study of amino acid transport and binding by ascites cells *in vivo* and *in vitro* of three isomeric β -(aminonaphthyl)- α -alanines, it was found that the separation of the enantiomers of two of these compounds could be achieved through paper chromatography.^{2,3} We are now reporting the syntheses of these new compounds (Table I).

Experimental Section⁴

The required methylnitronaphthalenes were prepared essentially accordingly to literature procedures.⁵⁻⁸ These compounds were found to be consistent with the proposed structures by nmr and infrared spectra; further they all showed single-spot thin layer chromatograms.⁹

1-Bromomethyl-4-nitronaphthalene.—A mixture of 3.9 g (0.0208 mole) of 1-methyl-4-nitronaphthalene, 3.72 g (0.0208 mole) of N-bromosuccinimide, 50 mg of benzoyl peroxide, and 100 ml of CCl₄ was refluxed by means of an ultraviolet lamp. After 5 hr, the NBS appeared to be consumed and thin layer chromatography showed the appearance of a new compound. The mixture was cooled and filtered, and the filtrate was evaporated *in vacuo* to give 5 g of a yellow semisolid. The material was recrystallized from cyclohexane.

Diethyl 4-Nitronaphthyl-1-methylformamidomalonate.—To a solution of sodium ethoxide [0.86 g (0.0376 g-atom) of sodium in 100 ml of ethanol] and 7.6 g (0.0376 mole) of diethyl formamidomalonate was added a solution of 10 g (0.0376 mole) of 1-bromomethyl-4-nitronaphthalene in 75 ml of ethanol and 75 ml of THF. A solid resulted on the addition of about half of the halo compound. After complete addition, the slurry was stirred for 3 hr at room temperature. The solid was collected and washed well with THF and water. There resulted 8.9 g of material, mp 217–219°. Evaporation of the reaction mother liquor gave an additional 3 g of solid, mp 180–219°. The combined crops were recrystallized from ethyl acetate.

3-(4-Nitro-1-naphthyl)alanine.—A mixture of 10.0 g (0.0758 mole) of diethyl 4-nitronaphthyl-1-methylformamidomalonate, 25 ml of glacial acetic acid, and 25 ml of 40% HBr was refluxed for 7 hr. The solution was cooled and the pH was adjusted to 5 with NH₄OH. There resulted a yellow solid which was collected, washed well with water, and air dried to give 5 g of material. The product was recrystallized from an aqueous acid solution by adjusting the pH of the solution to 5 with NH₄OH.

3-(4-Amino-1-naphthyl)alanine.—A mixture of 2.0 g (0.007 mole) of 3-(nitro-1-naphthyl)alanine, 100 ml of 2% NaOH, 0.1 g of 5% Pd-C, and 3.16 kg/cm² of hydrogen was shaken at room temperature until the calculated amount of hydrogen was absorbed (15 min). The reaction mixture was filtered through a Celite pad. The clear filtrate was adjusted to pH 5 with acetic acid and refrigerated overnight, and the resulting tan crystals were collected. The product was recrystallized by adjusting

TABLE I

Compound	Mp, °C	% yield	Calcd, %			Found, %			Ultraviolet, m μ	ϵ_{\max}
			C	H	Br	C	H	Br		
1-Bromomethyl-4-nitronaphthalene ^a	89–91	68	49.65	3.03	30.30	49.28	2.93	29.70		
3-Bromomethyl-1-nitronaphthalene	114–115	59	49.65	3.03	30.30	49.43	3.13	30.11		
1-Bromomethyl-3-nitronaphthalene	150–152	56	49.65	3.03	30.30	49.65	3.12	29.91		
Diethyl 4-nitronaphthyl-1-methylformamidomalonate	217–219	82	58.75	5.19		58.69	5.11			
Diethyl 1-nitronaphthyl-3-methylformamidomalonate	166–168	56	58.75	5.19		58.57	5.22			
Diethyl 3-nitronaphthyl-1-methylformamidomalonate	214–215 dec	71	58.75	5.19		58.54	5.13			
3-(4-Nitro-1-naphthyl)alanine	258–260 dec	75	60.00	4.65		59.72	4.93			
3-(1-Nitro-3-naphthyl)alanine	240–241 dec	70	60.00	4.65		60.08	4.77			
3-(3-Nitro-1-naphthyl)alanine	251–252 dec	88	57.04 ^b	4.97		56.86	4.98			
3-(4-Amino-1-naphthyl)alanine	273–275 dec	71	67.81	6.31		67.67	6.20			37,200, 22,200, 7550
3-(1-Amino-3-naphthyl)alanine/ ^c	286–288 dec	80	67.81	6.31		67.68	6.12			26,700, 24,800, 5300
3-(3-Amino-1-naphthyl)alanine ^c	303–305 dec	90	67.81	6.31		67.79	6.30			20,470, 21,350, 5210, 4118, 1850

^a Bromomethyl compounds gave positive Beilstein and NaI tests. ^b For 0.75H₂O. ^c 95% EtOH. ^d 85% EtOH. ^e 80% EtOH. ^f Refluxed for 12 hr. ^g Refluxed for 1.5 hr.

(1) These compounds were prepared for the Psychopharmacology Research Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Md., under research contract SA-43-ph-3021.

(2) P. Zaltzman-Nirenberg, J. Daly, G. Guroff, and S. Udenfriend, *Anal. Biochem.*, **15**, 517 (1966).

(3) S. Udenfriend, P. Zaltzman-Nirenberg, and G. Guroff, *Arch. Biochem. Biophys.*, in press.

(4) Infrared spectra were determined on a Perkin-Elmer Infracord, Model 137, and ultraviolet spectra on a Perkin-Elmer, Model 202, recording spectrophotometer. Melting points were determined on a Thomas-Hoover Uni-Melt Capillary apparatus and are corrected. Microanalyses were performed by Midwest Microlabs, Inc., of Indianapolis, Ind.

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an aqueous acetic acid solution of the material to pH 5 with NH_4OH .

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Some N-Substituted Derivatives of Bis(4-amino-3-nitrophenyl) Sulfone¹

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As part of a systematic study of the chemistry of bis(4-chloro-3-nitrophenyl) sulfone² several N-substituted derivatives of bis(4-amino-3-nitrophenyl) sulfone³ of potential physiological interest have been prepared.

N-Substituted derivatives of bis(4-amino-3-nitrophenyl) sulfone, listed in Table I, were prepared by two variations of the same procedure.

Procedure A.—To bis(4-chloro-3-nitrophenyl) sulfone (3.77 g, 0.01 mole) and 5.5 g (0.04 mole) of anhydrous K_2CO_3 , 0.025 mole of freshly distilled amine dissolved in 60 ml of absolute ethanol was added and the reaction mixture was refluxed for 3 hr with stirring. In some cases, after 2 hr of refluxing 6 ml of water was added and the refluxing was continued for an additional 1 hr. The cooled reaction mixture was poured into 200 ml of water. The precipitate was filtered, washed with water, and air dried. The crude product was treated with decolorizing carbon in the appropriate solvent, frequently glacial acetic acid or ethanol, and was recrystallized several times.

Procedure B was the same as procedure A except that 0.045 mole of amine dissolved in 200 ml of absolute ethanol was used in the absence of K_2CO_3 . If on slow cooling an oil separated, the reaction mixture was refluxed an additional 20 min and then cooled slowly. The precipitate was filtered, washed with water, air dried, treated with decolorizing carbon in alcohol solution, and finally recrystallized several times from the appropriate solvent. In a few cases where the product failed to separate, the reaction mixture was poured into 400 ml of water and worked up as in procedure A.

In some cases where products were obtained only as oils using procedure A, the use of procedure B resulted in crystalline products. In general better yields were obtained by the use of procedure B.

TABLE I
N-SUBSTITUTED DERIVATIVES OF BIS(4-AMINO-3-NITROPHENYL) SULFONE⁴

No.	R_1	R_2	Pro- ce- dure	Yield, ^b %	Mp, °C	Re- crystn solvent ^c	Formula	Calcd, %				Found, %			
								C	H	N	S	C	H	N	S
1	CH_3	H	A	70	249–250	AcOH	$\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_6\text{S}$	45.89	3.85	15.29	8.75	45.93	3.77	15.18	8.61
2	CH_3	CH_3	A	74	169–171	AcOH	$\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_6\text{S}$	48.72	4.60	14.21	8.12	49.21	4.72	14.98	8.08
3	<i>n</i> - C_4H_9	H	A	88	150–151	AcOH	$\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_6\text{S}$	53.32	5.32	12.43	7.11	53.53	5.26	12.44	7.11
4	<i>i</i> - C_4H_9	H	A	85	122–124	Et	$\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_6\text{S}$	53.32	5.32	12.43	7.11	53.62	5.20	12.33	7.06
5	<i>n</i> - C_6H_{13}	H	B	43	104–105	Et	$\text{C}_{24}\text{H}_{34}\text{N}_4\text{O}_6\text{S}$	56.91	6.78	11.06	6.33	56.98	6.92	11.29	6.54
6	<i>n</i> - C_7H_{15}	H	A	45	74–75	AcOH	$\text{C}_{26}\text{H}_{38}\text{N}_4\text{O}_6\text{S}$	58.40	7.16	10.48	5.99	58.61	7.23	10.37	6.04
7	<i>n</i> - C_8H_{17}	H	B	34	76–78	E-H	$\text{C}_{28}\text{H}_{42}\text{N}_4\text{O}_6\text{S}$	59.76	7.52	9.96	5.69	60.02	7.52	10.12	5.69
8	<i>n</i> - $\text{C}_{10}\text{H}_{21}$	H	B	56	87–88	Et	$\text{C}_{32}\text{H}_{50}\text{N}_4\text{O}_6\text{S}$	62.10	8.14	9.05	5.18	62.12	8.22	9.67	5.12
9	<i>n</i> - $\text{C}_{12}\text{H}_{25}$	H	B	36	84–85	Et	$\text{C}_{36}\text{H}_{58}\text{N}_4\text{O}_6\text{S}$	64.06	8.66	8.30	4.75	64.42	8.72	8.48	4.88
10	<i>n</i> - $\text{C}_{14}\text{H}_{29}$	H	A	29	82–83	A	$\text{C}_{40}\text{H}_{66}\text{N}_4\text{O}_6\text{S}$	65.71	9.10	7.66	4.38	65.67	8.98	7.74	4.46
11	<i>n</i> - $\text{C}_{16}\text{H}_{33}$	H	A	36	83–85	A	$\text{C}_{44}\text{H}_{74}\text{N}_4\text{O}_6\text{S}$	67.13	9.47	7.12	4.07	66.98	9.89	7.22	4.01
12	<i>n</i> - $\text{C}_{18}\text{H}_{37}$	H	A	17	91–92	A	$\text{C}_{48}\text{H}_{82}\text{N}_4\text{O}_6\text{S}$	68.36	9.80	6.64	3.80	68.36	9.49	6.76	3.87
13	<i>n</i> - $\text{C}_{18}\text{H}_{37}$	C_6H_{13}	B	75	81–83	Et	$\text{C}_{60}\text{H}_{98}\text{N}_4\text{O}_6\text{S}$	68.92	9.95	6.43	3.68	68.86	9.90	6.20	3.50
14	<i>m</i> - $\text{CH}_2\text{C}_6\text{H}_4$	H	B	23	196–198	An	$\text{C}_{26}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$	60.22	4.28	10.81	6.18	60.08	4.38	10.82	6.12
15	<i>p</i> - $\text{CH}_2\text{C}_6\text{H}_4$	H	A	44	221–223	B-P	$\text{C}_{26}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$	60.22	4.28	10.81	6.18	60.25	4.35	10.73	6.09
16	<i>p</i> - $\text{CH}_2\text{OC}_6\text{H}_4$	H	A	58	238–239	T	$\text{C}_{28}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$	56.72	4.03	10.18	5.82	56.94	4.17	10.25	6.02
17	<i>p</i> - $\text{C}_2\text{H}_5\text{OC}_6\text{H}_4$	H	A	65	216–217	T-P	$\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_6\text{S}$	58.12	4.53	9.68	5.74	58.34	4.59	9.54	5.46
18	$-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$	A	A	94	204–206	AcOH	$\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$	50.20	4.63	11.71	6.70	50.03	4.85	11.83	6.75
19	$-\text{CH}_2(\text{CH}_2)_2\text{CH}_2-$	A	A	44	227–229	A	$\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$	53.80	4.97	12.55	7.18	53.54	4.80	12.62	7.21

^a All compounds are yellow. ^b Yield calculated after one recrystallization. ^c A = acetone, An = acetonitrile, B = benzene, E = ether, Et = ethanol, H = heptane, AcOH = glacial acetic acid, P = petroleum ether, T = toluene.

Experimental Section¹

Bis(4-chloro-3-nitrophenyl) sulfone was prepared in 97% yield by the nitration of bis(4-chlorophenyl) sulfone by the method of Buehler and Masters.^{5,2}

(1) Abstracted in part from the theses of R. T. Enright and R. V. Mark, presented to the Graduate School of St. John's University in partial fulfillment of the requirements for the degree of Master of Science, June 1964 and June 1966, respectively.

(2) W. F. Hart and M. E. McGreal, *J. Med. Chem.*, **8**, 141 (1965).

(3) For previous literature see (a) F. Ullmann and J. Korselt, *Ber.*, **40**, 643 (1907); (b) R. J. LeFevre and E. E. Turner, *J. Chem. Soc.*, 1113 (1927).

(4) Melting points were taken in capillary tubes and are corrected. Elemental analyses were determined by Drs. Weiler and Strauss, Oxford, England.

The derivatives of methylamine and dimethylamine (**1** and **2**, Table I) were prepared by procedure A, using a large excess of the amine hydrochloride and anhydrous K_2CO_3 . The yields were not improved by procedure B employing pressure at 150° for 4 hr^{3a} but the products were more readily purified.

Several attempts to N-alkylate the products which were secondary amines using methyl iodide or dimethyl sulfate under various conditions were unsuccessful. Similarly, all attempts to quaternize the products which were tertiary amines using methyl iodide, dimethyl sulfate, benzyl chloride, or methyl *p*-toluenesulfonate were unsuccessful.

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