[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE MUNICIPAL UNIVERSITY OF WICHITA]

Derivatives of 2-Amino-6-methoxybenzothiazole[1]

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p-Substituted anilines are readily converted to 2-amino-6-substituted benzothiazoles by reaction with alkali thiocyanates in the presence of bromine.[2] By modification of procedure we have obtained 2-amino-6-methoxybenzothiazole from *p*-anisidine in 87% yield.

In a search for types of compounds that might exhibit antimalarial activity several derivatives of 2-amino-6-methoxybenzothiazole were prepared.[3] Details are given in the experimental section.

Experimental

2-Amino-6-methoxybenzothiazole.—To a solution of 24.6 g. (0.2 mole) of *p*-anisidine and 77.6 g. (0.8 mole) of potassium thiocyanate in 360 ml. of 96% acetic acid was added dropwise, with stirring, 32 g. (0.2 mole) of bromine dissolved in 150 ml. of glacial acetic acid while the temperature was kept below 35°. After all the bromine solution had been added the mixture was stirred for ten hours and was then filtered and the residue washed with water. The combined filtrate and washings were neutralized with ammonium hydroxide. The precipitate was collected on a filter and dried. The yield of product melting at 158–161° was 31.5 g. or 87%. This material is pure enough for subsequent reactions. Larger runs do not affect the yield.

Further purification is most readily carried out by crystallization from a mixture composed of equal volumes of concentrated hydrochloric acid and 95% ethanol. The hydrochloride thus obtained is dissolved in water and the free base is precipitated with sodium carbonate. The recovery of 2-amino-6-methoxybenzothiazole, melting at 161–162°,[4] is nearly quantitative. An alternate method of purification is crystallization from benzene.

2-Chloro-6-methoxybenzothiazole.—A solution of 18 g. (0.1 mole) of 2-amino-6-methoxybenzothiazole in 50 ml. of formic acid, 20 ml. of glacial acetic acid and 40 ml. of concd. hydrochloric acid was cooled to −5° and then 7 g. of sodium nitrite in 10 ml. of water was added dropwise with stirring. After addition was complete, stirring was continued for fifteen minutes at 0°. The mixture was then added slowly to an ice-cold vigorously stirred solution of 0.13 mole of cuprous chloride in 59 ml. of hydrochloric acid (sp. gr. 1.14). After one-half hour the mixture was heated to 60° on a steam-bath. When evolution of nitrogen ceased, the mixture was diluted with water and the solid was filtered off and extracted with hot ethanol. The alcohol extract was poured into water and the precipitated material collected on a filter and dried. Crystallization from dilute methanol gave 6 g. or 30% of 2-chloro-6-methoxybenzothiazole, m. p. 43–44°.

Anal. Calcd. for C_8H_6ONClS: Cl, 17.8. Found: Cl, 17.7.

TABLE I

SOME 2-SUBSTITUTED-6-METHOXYBENZOTHIAZOLES

Substituent	M. p., °C.	Solvent	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1-Pyrryl[a]	117–118	Ethanol	28	62.6	62.4	4.25	4.39	12.17	12.00
2,5-Dimethyl-1-pyrryl[b]	125–126	Ethanol	40	65.1	65.0	5.42	5.52	10.85	10.78
Piperidino[c]	72–72.5	Methanol	66	62.9	62.6	6.41	6.49	11.29	11.34
Morpholino[c]	127.5–129	Methanol	58	57.6	57.7	5.61	5.70	11.21	11.27
Morpholinoacetylamino[d]	129–130	Ethanol	36	57.5	57.3	5.48	5.46	9.55	9.72
m-Nitrobenzoylamino[e]	235	Pyridine	76	54.7	54.8	3.34	3.41	12.77	12.62
m-Aminobenzoylamino[f]	147–148	Acetic acid	90	60.2	59.9	4.35	4.24	14.38	14.46
p-Dimethylaminophenylazo[g]	225–227	Acetic acid	44	61.5	61.3	5.13	5.18	17.95	17.77

[a] A mixture of 8 g. of mucic acid and 6 g. of 2-amino-6-methoxybenzothiazole was distilled from a 50-ml. Claisen flask evacuated to 2 mm. (Bell, *Ber.*, 10, 1861 (1877)). [b] 2-Amino-6-methoxybenzothiazole and acetonylacetone were heated for five hours at 135°. [c] 2-Chloro-6-methoxybenzothiazole was refluxed with the requisite amine for two hours. [d] A mixture of 2-amino-6-methoxybenzothiazole, chloroacetyl chloride and dimethylaniline was heated on a steam-bath for an hour and was then poured into 500 ml. of dilute hydrochloric acid. The yellow precipitate was collected on a filter and dried. The crude material was heated with morpholine at 135° for four hours. [e] 2-Amino-6′-methoxybenzothiazole was condensed with *m*-nitrobenzoyl chloride in pyridine solution. [f] The corresponding nitro compound was reduced with tin and acetic acid. [g] 2-Amino-6-methoxybenzothiazole was diazotized as previously described and then coupled with N,N-dimethylaniline.

Summary

1. A procedure for the preparation of 2-amino-6-methoxybenzothiazole has been described.

2. Several derivatives of 2-amino-6-methoxybenzothiazole have been prepared.

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(1) Presented before the Organic Division of the Fifteenth Midwest Regional Meeting of the American Chemical Society, Kansas City, Missouri, June, 1947.

(2) British Patent 295,295, March 30, 1927.

(3) A number of 2-amino-6-alkoxybenzothiazoles have been tested as antimalarials. *Cf.* "Survey of Antimalarial Drugs 1941–1945," Wiselogle, Editor, Edwards Bros., Ann Arbor, Mich., 1946, Vol. II, Part I, pp. 1938, *et seq.*

(4) Dyson, Hunter and Morris, *J. Chem. Soc.*, 186 (1927), report a melting point of 147°. Tubs and Fox, U. S. Patent 1,931,077 (1934), report a melting point of 161–162.5°.