[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

Reactions of 3-Thiocyano-2-butanone. II.[1] The Preparation of 2-Arylamino- and 2-Alkylamino-4,5-dimethylthiazoles

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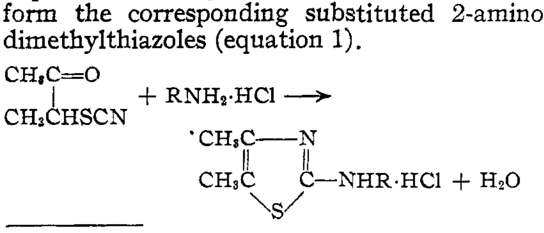
Seven different amines have been found to react with 3-thiocyano-2-butanone to form the corresponding N-substituted-2-amino-4,5-dimethylthiazoles. Ethylenediamine reacted to give N,N'-[(2)-4,5-dimethylthiazolyl]-ethylenediamine.

3-Thiocyano-2-butanone (I) has been shown[1] to react with ammonium chloride to form 2-amino-4,5-dimethylthiazole hydrochloride. For this reason it was of interest to determine whether I would react with amine hydrochlorides to form 2-substituted-amino-4,5-dimethylthiazoles. 2-Aminothiazoles have generally been prepared by the reaction of α-haloketones with monosubstituted thioureas.[2] There are a number of examples in the literature of the preparation of 2-arylamino-4-methylthiazoles[3] from thiocyanoacetone and aryl amines although the literature is somewhat confusing since Hantzsch and Weber[3a] state that the compounds were prepared by treating 2-hydroxy-4-methylthiazole with aryl amines. Later[3b] in a footnote Hantzsch states that the hydroxythiazole will not react with ammonia to form 2-amino-4-methylthiazole and that such a reaction is shown only by the thiocyanoacetone thereby implying that thiocyanoacetone was actually used in the reactions with aniline, *p*-toluidine and *m*-phenylenediamine.

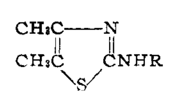
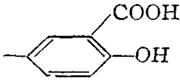
It has been found that a variety of aromatic and aliphatic amine hydrochlorides will react with I to form the corresponding substituted 2-amino-4,5-dimethylthiazoles (equation 1).



(1)

TABLE I

2-AMINO-4,5-DIMETHYLTHIAZOLES

	Yield,[a] %	Melting point,[d] °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
CH_3	77	125–128	50.65	50.56	7.09	6.99	19.70	19.63	22.54	22.42
C_6H_5	90	107–109.5	64.67	64.69	5.92	5.88	13.71	13.67	15.69	15.73
m-$C_6H_4SO_3H$	74	362 (dec.)	46.46	46.39	4.26	4.22	9.85	9.86	22.55	22.53
p-*t*-$C_6H_4C_5H_{11}$	91	123.5–125.5	70.03	70.27	8.08	8.04	10.21	10.25	11.68	11.59
p-C_6H_4COOH[b]	90	325–326	58.04	57.91	4.87	4.87	11.28	11.61	12.91	12.90
 [c]	79	286–287 (dec.)	54.53	54.52	4.58	4.48	10.60	10.55	12.13	12.11
β-$C_{10}H_7$	95	140.5–142.5	70.83	70.88	5.66	5.55	11.02	10.95	12.61	12.54

[a] Yield of crude product. [b] Recrystallized from formamide. [c] Diacetoxy derivative—m.p. 141–144°. [d] All melting points are uncorrected.

Table I lists a series of products formed by the reaction of I with the appropriate amine hydrochloride using conditions similar to those used for the preparation of 2-methylamino-4,5-dimethylthiazole. The reaction appears to be a general one for primary amines.

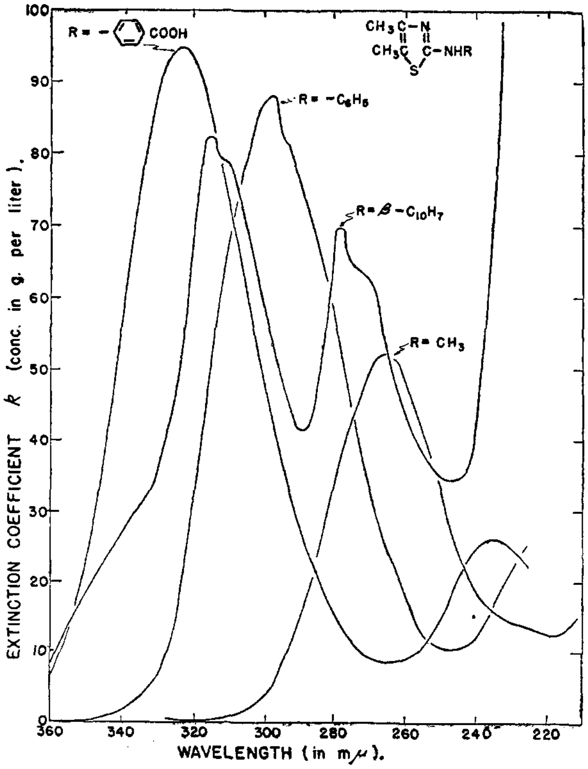


Fig. 1.—Absorption spectra of 2-amino-4,5-dimethylthiazoles in methanol.

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[1] For Paper I of this series see THIS JOURNAL, **74**, 1719 (1952).

[2] (a) A. Hantzsch and V. Traumann, *Ann.*, **249**, 31 (1888); (b) E. Naf, *ibid.*, **265**, 108 (1891); (c) R. H. Wiley, D. C. England and L. C. Behr, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 367–409.

[3] (a) A. Hantzsch and J. H. Weber, *Ber.*, **20**, 3118 (1887); **20**, 3336 (1887); (b) A. Hantzsch and L. Arapides, *Ann.*, **249**, 21 (1888); (c) A. Hantzsch, *Ber.*, **60B**, 2537 (1927); (d) A. Hantzsch and H. Swaneberg, *ibid.*, **61**, 1776 (1928); (e) J. Tcherniac, *ibid.*, **61**, 574 (1928).

Experimental[4]

2-Methylamino-4,5-dimethylthiazole.—A mixture of methylamine hydrochloride (27 g., 0.4 mole), water (100 ml.) and I (51.6 g., 0.4 mole) was heated at reflux temperature (103°) for 8 hr. The immiscible layer of I disappeared. After cooling the mixture to room temperature the solution was extracted three times with 50-ml. portions of ether to remove unreacted I. After treating with decolorizing carbon the solution was concentrated to one-fourth its volume. White crystals of the hydrochloride were obtained (8.4 g.—11.8%) which melted at 284–287° after recrystallization from ethanol. *Anal.* Calcd. for $C_6H_{11}ClN_2S$: Cl, 19.84; S, 17.94. Found: Cl, 20.00; S, 18.10. The rest of the product was isolated by neutralization to give the free base (37 g.—65.1%). The white crystalline solid melted at 125–128° after recrystallization from benzene and ethanol. *Anal.* (See Table I).

2-Anilino-4,5-dimethylthiazole. (a) **From I and Aniline.**—A solution of aniline (93 g., 1 mole), aniline hydrochloride (2.8 g.) and I (64.5 g., 0.5 mole) in benzene (200 ml.) was placed in a flask which was equipped with a 1 × 12-inch column, packed with berl saddles, and an esterification head. The esterification head was designed to separate the water removed by azeotropic distillation with benzene and to continuously return the benzene to the reaction flask. The solution was heated until 8.5 ml. (94.4% of theory) of water was isolated. The benzene and excess aniline (96% recovery) were removed by distillation at 30–50 mm. The residue was distilled at 0.1–0.4 mm. to give 72 g. (71% yield) of a crystalline solid; m.p. 101–105.5°. Recrystallization from ethanol–benzene and ethanol gave large crystals melting at 107–109.5°. *Anal.* (See Table I).

(b) **From 3-Chloro-2-butanone and Phenylthiourea.**—The reaction of these materials in water gave, after neutralization, a 77% yield of white crystals melting at 94.5–106°. After recrystallization from benzene the product melted at 107.5–109.8° and the mixture melting point with the product obtained in (a) showed no depression.

N,N'-[(2)-4,5-Dimethylthiazolyl]-ethylenediamine.—A solution of ethylenediamine (30 g., 0.5 mole), I (65 g., 0.5 mole), concd. hydrochloric acid (84 ml., 1 mole), water (200 ml.) and ethanol (100 ml.) was heated at the reflux temperature (87°) for 6 hours. After the ethanol was removed by distillation the solution was treated with decolorizing carbon and neutralized with sodium carbonate. The tan precipitate that formed weighed 27.7 g. (39%) and melted at 213–216°. After several recrystallizations from ethanol the white crystalline solid melted at 216–219°. *Anal.* Calcd. for $C_{12}H_{18}N_4S_2$: C, 51.03; H, 6.43; N, 19.84; S, 22.70; mol. wt., 282.4. Found: C, 50.97; H, 6.48; N, 19.77; S, 22.66; mol. wt., 288 (ebullioscopic—acetic acid). When the ethylenediamine and I reacted in a molar ratio of 1:2 this yield is increased to 88.5%.

Acknowledgment.—The analyses of all compounds were made by James R. Kubik, Arthur K. Kuder, and Huffman Microanalytical Laboratories. Sincere appreciation is expressed to Martin Smilek and James A. Early for their assistance with some of the experimental work reported here.

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[4] All melting points are uncorrected.

[Contribution from the Laboratory of Pharmaceutical Chemistry, University of Kansas School of Pharmacy]

Proof of Structures Derived from the Hydroxy- and Aminomethylation of Benzotriazole

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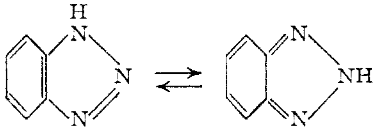
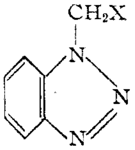
The products isolated from reactions involving benzotriazole and formaldehyde have been shown unequivocally to be substituted at position 1.

Although substitution reactions with benzotriazole are assumed to occur mainly at position 1, this assumption is not always justified.[1] Further, appreciable yields of both isomers, derivable from the following tautomeric forms, are often obtained.[2] Interest in the use of 1-dialkylaminomethylbenzotriazoles as possible alkylating agents induced us to attempt to establish unequivocally the structures Ia and IIa which have been assigned by others.[3,4]





X
Ia, NC_5H_{10}
b, $N(CH_3)_2$
c, NC_4H_8O

X
IIa, OH
b, Cl

Since the structures of 1- and 2-methylbenzotriazole have been definitely established,[5] attempts were made to confirm the structure of 1-hydroxymethylbenzotriazole (IIa) by its reduction to the methyl compound. With Raney nickel at high pressures and at 150°, hydrogen was absorbed but the only identifiable product was benzotriazole. At room temperature, 90% of IIa was recovered unchanged. Employing 5% palladium-on-charcoal as a catalyst at low pressure, a method used by others to effect reduction of benzyl alcohols to methyl derivatives,[6] the results were also negative. However, IIa was readily converted by means of thionyl chloride to the corresponding chloride (IIb) in yields exceeding 90%, and it was found that IIb could then be reduced by lithium aluminum hydride to 1-methylbenzotriazole, thus establishing unequivocally the structures IIa and IIb. The identity of the 1-methylbenzotriazole was confirmed by boiling point, mixed melting point with an authentic sample and preparation of a picrate.

1-Dimethylaminomethylbenzotriazole (Ib) and 1-(4-morpholinylmethyl)-benzotriazole (Ic), with

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(1) N. O. Cappel and W. C. Fernelius, *J. Org. Chem.*, **5**, 40 (1940).

(2) F. R. Benson and W. L. Savell, *Chem. Revs.*, **46**, 59 (1950).

(3) G. B. Bachman and L. V. Heisey, This Journal, **68**, 2496 (1946).

(4) K. Fries, H. Guterback and H. Kuhn, *Ann.*, **511**, 218 (1934).

(5) (a) F. Krollpfeiffer, A. Rosenberg and C. Mühlhausen, *ibid.*, **515**, 124 (1935); (b) A. Reissert, *Ber.*, **47**, 676 (1914).

(6) W. G. Dauben, C. F. Hiskey and A. H. Markhart, This Journal, **73**, 1398 (1951); R. Baltzly and J. S. Buck, *ibid.*, **65**, 1984 (1943); R. Baltzly and P. B. Russell, *ibid.*, **72**, 3410 (1950).