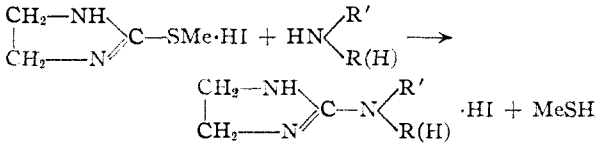
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WILLIAMS COLLEGE]

A Synthesis of 2-Alkylamino-4,5-dihydroimidazoles

BY SAMUEL R. ASPINALL* AND ERNEST J. BIANCO

As part of a continuing study[1] of derivatives of ethylenediamine, we report herewith a synthesis of certain 2-alkylamino-4,5-dihydroimidazoles. Such compounds, which may also be regarded as N-alkylated-N′,N″-ethyleneguanidines, seem not to have been reported except as noted below.[2]

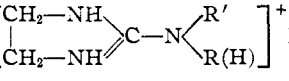
Briefly, the method was to heat 2-methylmercapto-4,5-dihydroimidazole hydriodide with a moderate excess of a primary or secondary amine in an inert solvent until the evolution of mercaptan was complete.



The solvent was removed, if necessary, and upon cooling the reaction mixture the pure guanidinium iodide was isolated in good yield by filtration. Water, acetone or methanol may be used as the solvent, although methanol has the advantage of the lowest solubility for the guanidinium salt, a situation which may be improved further by the addition of absolute ether. Time of reaction varies with the amine used, but usually development of mercaptan is essentially complete after 30 minutes reflux, and no improvement in yield is obtained by increasing reaction time over 2 hours. The use of excess amine, particularly for the lower homologs, is desirable because of volatility losses, and in no case is it disadvantageous if methanol is the solvent, for the unreacted portion remains in solution and does not interfere with the isolation of the product; however, no significant improvement in yield is obtained by using more than a 100% excess of amine. The reaction appears to be of general applicability to primary or secondary amines of various types and to diamines. The use of 2-benzylmercapto-4,5-dihydroimidazole hydrochloride in lieu of the corresponding methyl iodide offers no advantages and suffers from the fact that the benzyl mercaptan produced remains in the reaction mixture.

The guanidinium iodides are well defined, nonhygroscopic, sharply melting salts which show the expected solubilities in the common solvents; their water solutions are essentially neutral to litmus. The free bases may be obtained by treating the hydriodides with a large excess of alkali, but not by using sodium carbonate. For purposes of further characterization the hydriodides or free bases may be converted quantitatively to well-defined picrates. The benzenesulfonguanidides also may be obtained in excellent yield by the usual procedures. Further work on this synthesis is in progress.

TABLE I

SALTS OF 2-ALKYLAMINO-4,5-DIHYDROIMIDAZOLES 

		Hydriodides						Picrates[i]			
Amine used[b]	Reactn. solv.[c]	% Yield	Recrystn. solv.	M.p., °C. (cor.)	Formula	Nitrogen, % Calcd.	Kjeld.	M.p., °C. (cor.)	Nitrogen, % Calcd.	Found
Methylamine[d]	H_2O	80.3	Abs. EtOH	178–180	$C_4H_{10}N_3I$	18.51	18.45	193–194	24.61	25.42[e]
Benzylamine	Ace.[k]	78.5	MeOH–Ace.	146–148	$C_{10}H_{14}N_3I$	13.91	13.86	149–150	20.89	20.90[f]
Cyclohexylamine	MeOH	95.0	[g]	164–165	$C_9H_{18}N_3I$	14.24	14.24	225–226	21.21	21.61[f]
Ethanolamine	Ace.	39.0	MeOH–Ace.	104–106	$C_5H_{12}ON_3I$	16.34	16.41	163–164	23.42	23.83[f]
Piperidine	H_2O	78.2	Abs. EtOH	214–215	$C_8H_{16}N_3I$	14.95	14.89	151–153	21.99	21.64[f]
Morpholine	MeOH	80.2	MeOH	256–257	$C_7H_{14}ON_3I$	14.84	15.07	195–196	21.88	21.94[e]
Ethylenediamine	MeOH	68.5	MeOH–Ace.	178–180[h]	$C_8H_{18}N_6I_2$	18.58	18.63	259–261[i]	25.75	25.66[e]

[a] X^- represents the iodide or picrate ion. [b] Two-tenths mole of amine was used per 0.1 mole of thiouronium iodide except in the case of ethylenediamine, which was used in 0.05-mole amount. [c] 50 cc. [d] 33⅓% solution. [e] Kjeldahl. [f] Dumas, Tiedcke Laboratory. [g] Dissolved in abs. ethanol, precipitated with abs. ether. [h] Dihydriodide. [i] Dipicrate. [j] Recrystallized from water or dilute ethanol. [k] Acetone.

Experimental[3]

2-Methylmercapto-4,5-dihydroimidazole Hydriodide.—One-half mole (51 g.) of ethylenethiourea[4] is refluxed two hours with 0.55 mole (78 g.) of methyl iodide dissolved in 100 cc. of absolute methanol. An equal volume of absolute ether is added to the cool reaction mixture and 90 g. (74%) of 2-methylmercapto-4,5-dihydroimidazole hydriodide collected by filtration. After recrystallization from absolute methanol, the product melts at 142°.[5]

2-Benzylmercapto-4,5-dihydroimidazole Hydrochloride.—This compound melting at 172° after recrystallization from absolute ethanol is obtained in quantitative yield using a method analogous to that of Donleavy[6] for S-benzylthiouronium chloride. Calcd. for $C_{10}H_{13}N_2SCl$: N, 12.25. Found: N (Kjeld.), 12.18.

2-Morpholinyl-4,5-dihydroimidazole Hydriodide.[7]—In a flask equipped with a reflux condenser leading to a dry safety trap and thence to an absorption tower containing 20% sodium hydroxide, there are placed 24.4 g. (0.1 mole) of 2-methylmercapto-4,5-dihydroimidazole hydriodide, 17.4 g. (0.2 mole) of morpholine and 50 cc. of absolute methanol. Upon refluxing the solution, methyl mercaptan is evolved

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(1) S. R. Aspinall *J. Org. Chem.*, **6**, 859 (1941).

(2) In U. S. Patent 1,912,849, one derivative (the cyclohexyl) is claimed, although the sketchy description therein of this compound does not coincide with our data.

(3) All melting points corrected.

(4) Commercial ethylenethiourea, which was generously supplied by the Rohm and Haas Co., was recrystallized from water.

(5) Schacht, *Archiv für Pharmazie*, **235**, 451 (1911).

(6) J. J. Donleavy, THIS JOURNAL, **58**, 1004 (1936).

(7) This description is typical for all the guanidinium iodides herein reported.

vigorously for about 15 minutes and then more slowly for another 15 minutes, after which time the sodium hydroxide solution usually sucks back into the dry safety trap. After an additional 90 minutes of heating, the reaction mixture is cooled in an ice-bath and the product removed by filtration, washed twice with cold methanol and dried. The yield is 22.7 g. (80%). Some of the guanidinium iodides do not precipitate on cooling the reaction mixture, but do so after most of the solvent, water, acetone or methanol, is removed by distillation.

2-Cyclohexylamino-4,5-dihydroimidazole Picrate.—A quantitative yield of this compound precipitates immediately when a water solution of either the free base or its hydriodide is added to one molecular equivalent of picric acid dissolved in 95% ethanol.

2-Morpholinyl-3-benzenesulfonyl-4,5-dihydroimidazole.—2-Morpholinyl-4,5-dihydroimidazole hydriodide dissolved in a small quantity of water is treated without cooling with alternate portions of benzenesulfonyl chloride (1.5 equivalents) and 20% sodium hydroxide (3 equivalents). The mass of crystals which separates on slight cooling represents a quantitative yield and after recrystallization from water melts at 128–129°. Calcd. for $C_{14}H_{19}N_3O_3S$: H, 14.24. Found: N (Kjeld.), 14.09.

Summary

1. 2-Alkylamino-4,5-dihydroimodazoles are obtained in excellent yield by treating 2-methylmercapto-4,5-dihydroimidazoles with a primary or secondary amine.

2. The compounds are best isolated as their hydriodides and may be further characterized as picrates or benzenesulfonguanidides.

3. The free guanidines may be isolated from the hydriodides by treatment with excess alkali.

4. A study has been made of the effect of solvent, ratio of reactants and time on the yield.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Monomagnesium Derivatives of Dibromotoluenes

BY ALLEN S. HUSSEY AND JOHN R. DYER

The monomagnesium derivative obtained from the reaction of equimolar quantities of magnesium and 2,4-dibromoanisole has been shown to be a mixture of both isomers[1] contrary to previous reports.[2] One would expect the monomagnesium derivative of 2,4-dibromotoluene to consist of a similar mixture of isomers even though hydrolysis is reported to produce only 4-bromotoluene.[2]

We have investigated the monomagnesium derivatives of the four unsymmetrical dibromotoluenes, (2,3-, 2,4-, 2,5- and 3,4-), and have found all of them to be mixtures of both isomers. Ether solutions of the magnesium derivatives of each purified dibromotoluene were hydrolyzed with dilute acid and the products were examined for toluene, monobromotoluene and recovered dibromotoluene. The compositions of the several monobromotoluene fractions were determined by ultraviolet absorption. These results are summarized in Table I.

TABLE I

HYDROLYSIS OF MAGNESIUM DERIVATIVES OF DIBROMOTOLUENE

Dibromotoluene[a]	Toluene,[b] yield, %	Bromotoluene[b] Yield, %	Bromotoluene[b] Composition, %
2,3-	10–11	57–58[c]	91 ± 2 2-bromo
2,4-	11–12	73–74	70 ± 2 2-bromo
2,5-	12–14	76–78	70 ± 2 2-bromo
3,4-	9–13	58–62[c]	90 ± 2 3-bromo

[a] In all reactions, 2–3% of dibromotoluene was recovered. [b] Representative results of several experiments with each dibromotoluene. [c] *Ca.* 20% of high-boiling side-reaction product observed, presumably biphenyl compounds, but not identified.

The precision of the analysis of two of the monobromotoluene fractions is limited by the similarity of the absorption spectra of 2- and 3-bromotoluene. However, the precision can be increased considerably by making observations of the optical density of both of the pure monobromotoluene solutions and of the unknown solution simultaneously at the same wave length and slit-width setting of the spectrophotometer.[3]

The relative reactivities of bromine atoms in 2,4- and 3,4-dibromotoluene as determined in this way are consistent with what is already known about the activating effect of a methyl group. The steric effect of an adjacent methyl group is apparent in the case of 2,5-dibromotoluene, (where the bromine atom meta to the methyl group is predominately involved), and the pronounced steric effect when both methyl group and bromine atom are adjacent is apparent with 2,3-dibromotoluene.

Experimental[4]

Monobromotoluenes.—Samples of Eastman Kodak Co. monobromotoluenes were purified by washing with sulfuric acid, followed by three alternate fractional distillations and crystallizations. All three isomers distil at 74° at 19 mm. Other physical constants are given in Table II.

TABLE II

PHYSICAL CONSTANTS OF MONOBROMOTOLUENES

	F. p., °C.	$n^{25}D$	d^{25}_4	(95% ethyl alc.) at 235, 236, 240, 270 mμ
2-Bromo	−26.60	1.55375	1.4170	525 438 234 202
3-Bromo	−38.40	1.55025	1.4022	650 540 256 230
4-Bromo	+26.80	1.54864	1.3971	1254 ... 512 397

2,3-Dibromotoluene.—2-Amino-3-bromo-5-toluenesulfonic acid[5] was prepared by adding 64 g. (0.4 mole) of liquid bromine over 2 to 3 hours to a vigorously stirred mixture of 200 cc. of carbon tetrachloride and 50 g. (0.27 mole) of 2-amino-5-toluenesulfonic acid[6] dissolved in 2500 cc. of water. The bulk of the water and carbon tetrachloride was removed under reduced pressure and 58 g. (80%) of crystalline product was collected by filtration.

(1) Hussey and Wilk. THIS JOURNAL, **72**, 830 (1950).

(2) Paty and Quelet. *Bull. soc. chim.*, **11**, 505 (1944).

(3) This procedure was suggested by R. L. Burwell, Jr., L. G. Maury and R. B. Scott, who have used the same technique in analysis in the infrared; R. L. B., Jr., private communication.

(4) All m.p.'s corrected unless otherwise specified. Microanalyses by Miss Virginia Hobbs and Miss Joyce Sorensen.

(5) Wynne, *J. Chem. Soc.*, **61**, 1036 (1892).

(6) Nevile and Winther, *Ber.*, **13**, 1941 (1880).