10 cc. of methanol was added and the solution was diluted with 10 cc. of acetone. After standing for two weeks, small wart-like clusters of crystals appeared. By using these as seeds, calcium (−)-pantothenate could be crystallized readily from 10% solution in 99.5% methanol. The crystals were washed with methanol and dried *in vacuo* at 100°; m. p. 187.5–189°; $[\alpha]^{25}D$ −27.8° (*C*, 1% in H_2O). The biological potency was practically zero.

Anal. Calcd. for $Ca(C_9H_{16}O_5N)_2$: C, 45.35; H, 6.77. Found: C, 45.30; H, 6.55.

RESEARCH LABORATORY
MERCK & CO., INC.
RAHWAY, N. J.

RECEIVED AUGUST 2, 1941

The Preparation of 2-Bromonaphthalene

BY MELVIN S. NEWMAN AND PAUL H. WISE

Since the replacement of amino groups on the naphthalene nucleus by bromine according to the usual Sandmeyer technique often results in poor yields, we were interested in using the procedure of Schwechten[1] wherein the diazonium salt is treated with mercuric bromide and the solid complex thus produced is dried and heated with sodium bromide. Although Schwechten gave no details concerning the amount of mercuric bromide used, he represented the complex in the case of diazotized 2-naphthylamine as $(C_{10}H_7N_2Br)_2 \cdot HgBr_2$. A search of the literature revealed that investigators who have followed this procedure generally have used mercuric halides far in excess of that required by the formula.[2] In this communication we show that when the amount of mercuric bromide is reduced to that required for the formation of the complex $(C_{10}H_7N_2Br)_2 \cdot HgBr_2$ it is possible to obtain from 53 to 59% of pure 2-bromonaphthalene. Doubling the amount of mercuric bromide used raised the yield to 61–65%, and further increases had no effect.

Experimental

As the result of many experiments, we recommend the following procedure for the preparation of 2-bromonaphthalene. To the cold diazonium solution, prepared as usual from 50 g. (0.35 mole) of 2-naphthylamine, 670 cc. of water, 140 cc. of concentrated hydrochloric acid and 20% sodium nitrite solution, is added with stirring a cold suspension of mercuric bromide formed by treating 57 g. (0.175 mole) of mercuric nitrate with 83 g. of sodium bromide in a total volume of 250 cc. of water. The yellow insoluble complex which separates immediately is collected by filtration, washed with water and acetone, and air dried. The air-dried complex weighs from 137 to 149 g. (94–103% calculated on the basis of the formula $(C_{10}H_7N_2Br)_2 \cdot HgBr_2$). For decomposition, the complex is well mixed with 300 g. of finely ground sodium bromide and added in several portions through a wide rubber tube to a flask heated in a glycerol bath at 90° and fitted with a reflux condenser.[3] After each addition of complex a vigorous gas evolution occurs but no tendency to explode was ever noticed.

After the decomposition is complete, the organic matter is taken into benzene and washed with dilute acid and alkali. The 2-bromonaphthalene is twice vacuum distilled, b. p. 103–104° at 4 mm., and crystallized from 110 cc. of hot alcohol after addition of 4 cc. of hot water. In two crops, there is obtained 38.4–43.1 g. (53–59%) of almost colorless plates of 2-bromonaphthalene, m. p. 55.0–56.4°, cor. The remainder of the organic material is mostly accounted for as dark tar and high-boiling matter. Very little if any naphthol is produced.

Using a similar procedure, 1-chloro-2-bromonaphthalene, m. p. 55.0–56.5°, was obtained in 46% over-all yield from 1-chloro-2-acetylaminonaphthalene.[4]

(1) Schwechten, *Ber.*, **65**, 1605 (1932).

(2) For example, see Ruzicka and Mörgeli, *Helv. Chim. Acta*, **19**, 377 (1936); and Bachmann and Boatner, THIS JOURNAL, **58**, 2194 (1936).

(3) See sketch in Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1935, p. 287.

(4) Hodgson and Leigh, *J. Chem. Soc.*, 1352 (1937).

CHEMICAL LABORATORIES
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO

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The Action of *t*-Butylmagnesium Chloride on Propylene Oxide

BY PHILIP G. STEVENS[1] AND JAMES A. MCCOUBREY[2]

In view of the recent paper by Huston and Agett[3] on the reaction of the Grignard reagent with ethylene oxide, we wish to report briefly our work in the same field. As we were interested primarily in a stereochemical problem, we used propylene oxide and *t*-butylmagnesium chloride, hoping to obtain 4,4-dimethylpentanol-2.[4]

Our best results were obtained by allowing the oxide (220 g.) and the Grignard reagent (from 150 g. of magnesium) to stand at about 25° for seven weeks. The mixture was decomposed with ammonium sulfate, and most of the ether (5 liters) from the extractions, supernatant on one liter of 10% caustic, was removed by fractional distillation. To destroy the chlorhydrin, the residual liquor was refluxed with excess caustic for five hours and then steam-distilled. Thus a chlorine-free product was obtained. Fractional distillation yielded the following fractions boiling above 130° at 762 mm.: 1, 130–134, 0.5 g.; 2, 134–137, 11 g.; 3, 137–138, 39 g.; or a combined yield of 11%, and a residue of 42 g. Two grams of fraction 3 gave 4 g. of crude 3,5-dinitrobenzoate, which after repeated crystalliza-

(1) Present address: Chemistry Department, Yale University, New Haven, Conn.

(2) Present address: Research Laboratories, Shawinigan Chemicals, Ltd., Shawinigan Falls, Quebec, Canada.

(3) Huston and Agett, *J. Org. Chem.*, **6**, 123 (1941).

(4) Levene and Walti, *J. Biol. Chem.*, **94**, 367 (1931).

tions from ethyl and methyl alcohols melted at 92.5–93°. and showed no depression with the same derivative of 2,2-dimethylpentanol-3. A mixed melting point with the 3,5-dinitrobenzoate of 4,4-dimethylpentanol-2 (m. p. 95–96°) was 87–90°. The α-naphthylurethan of both our heptanol and 2,2-dimethylpentanol-3 melted at 107–108°. *Anal.* Calcd. for $C_{18}H_{23}NO_2$: C, 75.8; H, 8.1. Found: C, 75.4; H, 8.3. The distillation residue was treated with phthalic anhydride and pyridine in an attempt to extract therefrom any primary alcohol formed by reverse addition, however without success.

While we admit that the boiling point of fraction 3 was quite close to that of 4,4-dimethylpentanol-2,[5] yet from this we were able to isolate and identify only a derivative of 2,2-dimethylpentanol-3 (b. p. 133°). The only reaction we can prove then is another example of the well-known rearrangement of these oxides, or their halohydrins to (in this case) propionaldehyde, and thus by normal addition to 2,2-dimethylpentanol-3. A rearrangement to acetone instead would give 1,1,2,2-tetramethylpropanol-1, b. p. 130°. Inasmuch as this tertiary alcohol forms a readily recognized hydrate during ether extractions, and since we observed no such hydrate formation, we believe this isomeric heptanol was not formed in this reaction to any extent.

No reverse addition[6] resulting in the formation of 2,3,3-trimethylbutanol-1 was observed. This carbinol, hitherto unreported, was prepared by first adding hydrogen bromide in the presence of ascaridole at −78° to 2,3,3-trimethylbutene-1,[7] and then converting the primary bromide to the Grignard reagent, and treating this with oxygen.[8] It boiled at 159.5–162° (761 mm), $n^{25}D$ 1.4288.

(5) Whitmore and Homeyer, THIS JOURNAL, **55**, 4194 (1933), reported 137–137.5° at 736 mm.

(6) Kharasch and Clapp, *J. Org. Chem.*, **3**, 355 (1938).

(7) The primary bromide was formed exclusively; compare Michael and Weiner, *ibid.*, **4**, 531 (1939).

(8) Thanks are due Mr. J. Calder, Honor Student of McGill University, 1940, for the preparation of this carbinol.

McGILL UNIVERSITY
MONTREAL, CANADA

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The Preparation and Bioassay of Thiamine Hydriodide

BY JACOB G. TOLPIN, JOHN R. FOY AND LEOPOLD R. CERECEDO

We have observed that certain pyrimidine-thiazole combinations, linked together by a methylene group as in thiamine, are split when dissolved in glacial acetic acid and treated with sodium. Thiamine hydrochloride, however, resists this cleavage; instead, both chlorine atoms are removed by the sodium, and the vitamin base itself can be extracted from the reaction mixture with ether or chloroform. On addition of hydriodic acid to the extract, thiamine iodide hydriodide is obtained. Inasmuch as this compound is not described in the literature, its antineuritic potency has been studied.

Experimental[1]

Thiamine Iodide Hydriodide.—To a solution of 0.125 g. of thiamine hydrochloride in 9 cc. of glacial acetic acid and 2–3 drops of water, kept under a reflux condenser, was gradually added 0.126 g. of sodium under stirring or shaking. The mixture, which still showed an acid reaction, was then evaporated under reduced pressure and the residue extracted with 15 cc. of dry chloroform (or ether) for one to two hours. To the extract a 57% aqueous solution of hydriodic acid was added dropwise with stirring. (Addition of hydrogen iodide in absolute alcohol solution delays somewhat the precipitation of the crystals, but a purer product is produced thereby.) The crystalline precipitate was purified by solution in boiling methanol and precipitation with dry ether. Light yellow crystals, m. p. 230–231° (decomp.), were obtained in 49% yield.

Anal. Calcd. for $C_{12}H_{18}ON_4I_2S$: C, 27.69; H, 3.46; N, 10.77; I, 48.85; S, 6.15. Found: C, 27.81; H, 3.54; N, 10.83; I, 48.60; S, 6.07.

Similar treatment of an ether extract of the reaction product with a 40% solution of hydrogen bromide yielded thiamine bromide hydrobromide, m. p. 218–221°. Andersag and Westphal[2] give 220°.

Anal. Calcd. for $C_{12}H_{18}ON_4Br_2S$: N, 13.37. Found: N, 13.11.

Bioassay.—The antineuritic activity of thiamine hydroiodide was tested on rats according to the method of Chase and Sherman.[3] The material was injected in aqueous solution in doses of 7.7 μg. and 5 μg. daily (double doses on Saturdays). The results obtained are summarized in Table I. For comparison the data obtained with corresponding doses (on a molar basis) of thiamine hydrochloride have been included.

TABLE I

BIOASSAY OF THIAMINE HYDRIODIDE AND THIAMINE HYDROCHLORIDE

Substance	Dose, μg.	No. of rats	Mean increase in weight in 25 days, g.
Thiamine hydriodide	5	5	34
Thiamine hydrochloride	3.2	2	38
Thiamine hydriodide	7.7	5	45
Thiamine hydrochloride	5	5	39

The data show that on a molar basis the antineuritic potency of thiamine hydriodide is at least as high as that of thiamine hydrochloride.

(1) Microanalyses by Mr. Joseph Alicino of this Laboratory.

(2) Andersag and Westphal, *Ber.*, **70**, 2035 (1937).

(3) Chase and Sherman, THIS JOURNAL, **53**, 3506 (1931).

CHEMISTRY DEPARTMENT
FORDHAM UNIVERSITY
NEW YORK, N. Y.

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