together with a small amount of impurity probably resulting from reduction of the sulfonamide by *n*-butyllithium.

Only unchanged starting material was obtained from a reaction carried out at −70°.

***p*-Bromobenzonitrile and *n*-Butyllithium.**—Terephthalic acid, isolated after interconversion at −70° and carbonation (Table I), owes its formation to hydrolysis of *p*-carboxybenzonitrile, for on working up the carbonation product the ether suspension was extracted with dilute potassium hydroxide solution and the basic extract was heated on the steam plate for about one hour to remove dissolved ether.

Neither *p*-carboxybenzonitrile nor terephthalic acid was obtained from a second experiment in which the *p*-bromobenzonitrile, dissolved in a mixture of benzene and ether (rather than suspended in ether alone), was added to a solution of *n*-butyllithium in ether at −70°. It was shown earlier[11] that no acidic fraction (exclusive of valeric acid formed from *n*-butyllithium) was obtained from carbonation of an attempted interconversion reaction in which *p*-bromobenzonitrile, dissolved in a mixture of toluene and ether, was added to a solution of *n*-butyllithium in ether at 0°. It is probable, on the basis of other studies,[12] that benzene and toluene suppress the interconversion reactions.

Summary

In connection with studies concerned with physiological action, it has been shown that the halogen-metal interconversion reaction can be used for the preparation of organolithium compounds containing the alcoholic hydroxyl (as $-OLi$), nitrilo, and sulfonamido (as $-SO_2NHLi$ or $-SO_2NLi_2$) groups. Incidental to the hydroxyl studies, there was developed a satisfactory synthesis of *p*-bromobenzyl alcohol.

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[11] W. A. Gregory, unpublished studies. Iowa State College.

[12] Gilman and Moore, THIS JOURNAL, **62**, 1843 (1940); Gilman, Langham and Moore, *ibid.*, **62**, 2327 (1940); Gilman, Moore and Baine, *ibid.*, **63**, 2479 (1941).

AMES, IOWA RECEIVED JULY 17, 1947

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Catalytic Hydrogenation of 2-Naphthol to 1,2,3,4-Tetrahydro-2-naphthol

BY HYP J. DAUBEN, JR.,[1a] BLAINE C. MCKUSICK[1b] AND GEORGE P. MUELLER[1c,d]

During a search for compounds with favorable insect repellent properties,[2] it became apparent that alcohols as a group and 2-phenethanols in particular possessed appreciable repellency times. Of the 2-phenethanols prepared and tested, 1,2,3,4-tetrahydro-2-naphthol represented not only the most effective repellent in this class but one of the few compounds of any type with the requisite properties of low irritancy, low toxicity and complete protection from mosquito bites for many hours even under tropical conditions.[3]

In response to requests from different investigators[3] in the repellency field, large quantities of 1,2,3,4-tetrahydro-2-naphthol were prepared. By repeated preparations of this material it became possible to define, within narrow and reproducible limits, the conditions for rapid production of a pure product in good yields and to determine the nature and amounts of by-products.

Partial catalytic hydrogenation of 2-naphthol has been shown to furnish 1,2,3,4-tetrahydro-2-naphthol and 5,6,7,8-tetrahydro-2-naphthol in varying relative amounts depending on the catalyst and conditions used. Stork[4] and Adkins and Krsek[5] have demonstrated recently that hydrogenation, using Raney nickel catalysts, gives yields of 66–87% of 5,6,7,8-tetrahydro-2-naphthol and 6–33% of 1,2,3,4-tetrahydro-2-naphthol. The same authors showed that the addition of small amounts of basic promoters altered the relative rates so that 65% yields of the 1,2,3,4-tetrahydro isomer could be realized. Earlier work by the Adkins group[6] with copper–chromium oxide catalyst led to the isolation of 1,2,3,4-tetrahydro-2-naphthol as the major product in 76–88% yields. Purification of this product was performed by fractional distillation and no mention was made of the formation of other products. The present studies, using copper–chromium oxide catalyst and improved methods of purification, confirm the yield but indicate the formation of 5,6,7,8-tetrahydro-2-naphthol and naphthalene as minor by-products.

Hydrogenation of purified 2-naphthol was conducted at 200° without solvent and reaction ceased with the absorption of 2 moles of hydrogen. Total impurities in the crude hydrogenation product were estimated by cryoscopic determination. Approximately 8.5 mole per cent. total impurities were indicated and this value agrees fairly well with those obtained by actual isolation; purified 2-naphthol (14.90 kg.) gave 79.0% (11.76 kg.) of pure 1,2,3,4-tetrahydro-2-naphthol, 5.1% (0.76 kg.) of pure 5,6,7,8-tetrahydro-2-naphthol and

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[1] Present locations: (a) Department of Chemistry, University of Washington, Seattle 5, Wash.; (b) Chemical Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington 99, Del.; (c) Department of Chemistry, University of Tennessee, Knoxville, Tenn.; (d) The assistance of Sidney D. Ross, Samuel Siegel and G. Forrest Woods is gratefully acknowledged.

[2] This work was carried out as part of the program at Harvard University with Paul D. Bartlett as official investigator under contracts NDCrc-136 and OEMsr-1304 with the Office of Scientific Research and Development.

[3] Testing was done at the Experiment Station of U. S. Department of Agriculture. Bureau of Entomology and Plant Quarantine, Orlando, Florida. Extensive evaluation of the compound was made by this group and by Jachowski and Pijoan at the Naval Medical Research Institute, Bethesda, Maryland, *cf. Science*, **104**, 266–269 (1946).

[4] Stork, THIS JOURNAL, **69**, 576 (1947).

[5] Adkins and Krsek, *ibid.*, **70**, 412 (1948).

[6] Musser and Adkins, *ibid.*, **60**, 665 (1938); Adkins and Reid, *ibid.*, **63**, 741 (1941).

6.8% (1.04 kg.) of forerun material which was difficult to purify but contained largely 1,2,3,4-tetrahydro-2-naphthol mixed with about 1% naphthalene. Naphthalene must have been formed by hydrogenolysis since the 0.04% naphthalene present in the commercial 2-naphthol used had been largely removed in the preliminary distillation from Raney nickel.[7]

The practice of topical application of insect repellents to large areas of perspiring skin requires absence of irritant and toxic impurities. Demand for kilogram quantities of 1,2,3,4-tetrahydro-2-naphthol of this purity necessitated the development of a simple, effective method of purification.[8] Extraction of the phenolic 5,6,7,8-tetrahydro-2-naphthol was complicated by the fact that its sodium salt is soluble only in relatively dilute (2%) sodium hydroxide solution and also soluble in the ether–tetrahydronaphthol layer.[9] Aqueous extraction of the organic layer removed only part of the soluble sodium tetrahydronaphthoxide and caused sufficient hydrolysis of the remainder to contaminate the final distilled product. Complete separation of the two isomers was performed conveniently by shaking the crude product, diluted with benzene, several times with 10% aqueous sodium hydroxide to convert all of the phenolic isomer to its sodium salt. The organic layer retained most of the sodium 5,6,7,8-tetrahydro-2-naphthoxide and gave on distillation, without further washing or drying, pure 1,2,3,4-tetrahydro-2-naphthol and a solid residue of the phenolic sodium salt. Pure 5,6,7,8-tetrahydro-2-naphthol was isolated from the 10% sodium hydroxide washings and from the sodium salt distillation residue.

Experimental

Hydrogenation of 2-Naphthol.—U.S.P. grade 2-naphthol (Mallinckrodt or Sherwin-Williams) was distilled from 2 weight per cent. Raney nickel[10] in nine-pound lots using stirring and water-aspirator reduced pressure; recovery, 95%. Naphthalene content in the small forerun, collected separately, was estimated after steam distillation and alkali extraction at about 0.04%.

Molten, redistilled 2-naphthol was poured into large, high pressure rocking hydrogenators (1–4 l.) and 5 weight per cent. copper-chromium oxide[11] added. Hydrogen was admitted to a pressure of 3000–5000 lb. per sq. in. at 200° and maintained at this temperature and above 1000 lb. per sq. in. pressure by repeated additions of hydrogen for two to five hours until absorption essentially ceased. The catalyst was allowed to settle and the liquid product decanted from the bulk of the catalyst. The next charge of molten 2-naphthol was then added along with about 20% of the original quantity of catalyst to compensate for loss incurred in the decantation of the previous charge. Fourteen successive charges of naphthol were so reduced in one series of hydrogenations with no apparent change in rate of hydrogenation. The crude product was diluted with an equal volume of benzene and the suspended catalyst removed by filtration through a bed of Hyflo-Supercel in a steam-heated Büchner funnel. The catalyst-free product varied from colorless to light brown in color depending on length of exposure to air and heat.

Separation of Products.[12]—The crude filtered product was shaken three or four times with the total of an equal volume of 10% sodium hydroxide solution. Without further washing or drying, the mixture was concentrated under water-aspirator vacuum until most of the benzene and dissolved water had been removed. Distillation was then continued through a short Vigreux column at 5 mm. pressure. Fractions collected were: (1) about 1% naphthalene, (2) about 5% forerun with high refractive index, (3) about 50% pure 1,2,3,4-tetrahydro-2-naphthol before crystallization of sodium 5,6,7,8-tetrahydro-2-naphthoxide began, (4) about 25% pure 1,2,3,4-tetrahydro-2-naphthol collected at gradually decreasing pressure down to 1 mm. and (5) remainder of the material that distils at 1 mm. with the bath temperature up to 200°. Crystallization of the sodium tetrahydronaphthoxide as a cake slowed distillation and required reduction of pressure and elevation of temperature to maintain the distillation rate. Typical data obtained on a 1510-g. batch of hydrogenation product are shown in Table I.

TABLE I

Fraction	Temp., °C.	Bath, °C.	Pressure, mm.	Weight, g.	Per cent.	$n^{25}D$
2	-121	160	5.0	98.2	6.5	1.5673[a]
3	120.5–121.2	162	5.0	827.5	54.8	1.5630[b]
4	119.5–106.8	162–202	4.8–1.1	337.3	22.4	1.5630[b]
5	107–103	202	1.0	102.5	6.8	1.5637[c]
Residue of 147 g.				(128)[d]	(8.5)[d]	

[a] Combined foreruns of several batches furnished additional 1,2,3,4-tetrahydro-2-naphthol on redistillation. [b] Purity indicated by flat melting curve at 22.8–22.9° for fifteen minutes. [c] Combined after runs of several batches reprocessed to furnish additional 1,2,3,4-tetrahydro-2-naphthol. [d] Calculated as 5,6,7,8-tetrahydro-2-naphthol on basis of weight of dry sodium salt residue.

The bright yellow distillation residue of sodium 5,6,7,8-tetrahydro-2-naphthoxide turned brown or gray on admission of air. Recovery of the free phenol was effected by acidification, ether extraction, and distillation of the dark brown liquid; b. p. 128–129° at 10 mm., $n^{25}D$ 1.5674 ± 0.0005, yield 6.6%. Crystallization from 40–60° petroleum ether gave 5,6,7,8-tetrahydro-2-naphthol as white needles, m. p. 60–61°. Similar treatment of the 10% sodium hydroxide washings furnished additional phenolic isomer in about one per cent. yield.

The purification procedure could not be altered to include either water or saturated sodium chloride washings after the shaking with 10% sodium hydroxide solution. Even under the more favorable conditions of aqueous sodium chloride washing the major distillation fraction had a sloping melting point curve with a maximum at 21.3° which in-

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[7] "Organic Syntheses," **21**, 15 (1941).

[8] Methods recorded in the literature were lengthy and not adaptable to large-scale preparations. Bamberger and Lodter (*Ber.*, **23**, 205 (1906)) removed the phenolic isomer by the sequence of alkali extraction, steam distillation from aqueous alkali, and extraction with alkaline benzenediazonium-*p*-sulfonate solution. Pickard and Kenyon (*J. Chem. Soc.*, **101**, 1431 (1912)) recommended the isolation of sodium 1,2,3,4-tetrahydro-2-naphthol phthalate.

[9] Support for these conclusions is found in the work of Bamberger and Lodter[7] and by the solubility of sodium 2-naphthoxide in ether. Stork,[4] subsequent to our work, reached similar conclusions and successfully used repeated extraction with 2% sodium hydroxide for purification.

[10] Preliminary distillation of commercial U. S. P. grade 2-naphthol from Raney nickel was necessary to remove catalyst poisons which otherwise retarded or stopped hydrogenation before completion; *cf.*, Adkins and Reid.[6]

[11] Adkins, "Reactions of Hydrogen with Organic Compounds over Copper–Chromium Oxide and Nickel Catalysts," University of Wisconsin Press, Madison. 1937, p. 12.

[12] Total impurities in the crude undiluted product were estimated by cryoscopic determination using the cryoscopic constant of 1.06° per mole determined for a synthetic mixture of naphthalene in pure 1,2,3,4-tetrahydro-2-naphthol of melting point 22.9°. Typical batches of the product had melting points of about 14.3° which corresponded to about 8.5 mole per cent. impurity. Cryoscopic determinations were performed by Dr. A. S. Schneider.

dicated contamination by at least 1.5% of 5,6,7,8-tetrahydro-2-naphthol.

Physical constants found for the two tetrahydronaphthols were: 1,2,3,4-tetrahydro-2-naphthol, b. p. 120.5–121.5° (5.0 mm.), m. p. 22.9°, $n^{25}\text{D}$ 1.5630 ± 0.0002; 5,6,-7,8-tetrahydro-2-naphthol; b. p. 128–129° (10.0 mm.), m. p. 60–61° (34–35°), $n^{25}\text{D}$ 1.5674 ± 0.0005. Melting point determination afforded the best criterion of purity since refractive index differences were small and diazonium color reactions detected only phenolic impurities. Pure 1,2,3,4-tetrahydro-2-naphthol is a colorless, hygroscopic, very viscous liquid with a fluorescent cast and shows little tendency to become colored on standing.

Labile Form of 5,6,7,8-Tetrahydro-2-naphthol.—Crystalline material was separated from a commercial sample[13] of tetrahydro-2-naphthol by filtration and recrystallized from petroleum ether to give platy crystals, m. p. 34–35°.

Anal. Calcd. for $C_{10}H_{18}O$: C, 81.06; H, 8.17. Found: C, 80.58; H, 7.72.

The tetrahydronaphthol indicated by analysis was identified as 5,6,7,8-tetrahydro-2-naphthol by preparing the *p*-nitrobenzoate derivative; m. p. and m. m. p. 113–114°, from acetic acid or ethanol. 5,6,7,8-Tetrahydro-2-naphthol usually crystallized as needles, m. p. 60–61°, but on recrystallization from petroleum ether selective seeding enables isolation of either the stable needle form, m. p. 60–61°, or the labile plate form, m. p. 34–35°. No mention of the labile form was found in the literature.

Autoxidation of 1,2,3,4-Tetrahydro-2-naphthol.—Enhanced repellency times were found for samples of pure 1,2,3,4-tetrahydro-2-naphthol which had been exposed to air.[14] The ready autoxidizability of tetralin[15] and the substituted tetralin structure of 1,2,3,4-tetrahydro-2-naphthol suggested autoxidation as cause of increased repellent times. Negligible oxidation occurs, as judged by peroxide tests and refractive index changes, on passage of oxygen through pure 1,2,3,4-tetrahydro-2-naphthol in Pyrex vessels even at 70° in the presence or absence of strong artificial light irradiation. Samples of 1,2,3,4-tetrahydro-2-naphthol in quartz flasks in a shaking, volumetric hydrogenation apparatus absorbed oxygen at the rate of approximately 0.4 cc. per hr. per g. at 65° on exposure to ultraviolet light irradiation. Rates of absorption were dependent on intensity of ultraviolet irradiation and decreased gradually after absorption of about 0.1 molar equivalent. The yellow-colored product had increased refractive index and contained hydroperoxide groups, as indicated by iodimetric titration, to the extent of about 15% of oxygen absorbed. No definite oxidation product could be isolated by direct crystallization, either before or after treatment with dilute alkali, nor any derivatives obtained on treatment with carbonyl reagents.

Summary

Hydrogenation of 2-naphthol over copper-chromite catalyst yields at least 77% of pure 1,2,-3,4-tetrahydro-2-naphthol, 7–8% of 5,6,7,8-tetrahydro-2-naphthol and about 13% of slightly impure 1,2,3,4-tetrahydro-2-naphthol from which more pure material may be isolated. Simple separation of the mixture was accomplished by conversion of the phenol constituent to its non-volatile sodium salt and distillation of the alcoholic constituent from the mixture.

A new labile crystalline form of 5,6,7,8-tetrahydro-2-naphthol and the melting point of *dl*-1,2,3,4-tetrahydro-2-naphthol are reported. Autoxidation of 1,2,3,4-tetrahydro-2-naphthol occurs in the presence of oxygen and ultraviolet light.

CAMBRIDGE 38, MASS. RECEIVED JULY 15, 1948

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[13] Material was prepared on order by a commercial hydrogenation company with a catalyst purported to be similar to copper chromite. The hydrogenated material supplied contained at least 62% 5,6,7,8-tetrahydro-2-naphthol. Considerable crystalline material had separated in shipment during the cold winter months.

[14] Private communication from M. Pijoan.

[15] Hock and Süsemihl, *Ber.*, **66**, 61 (1933).

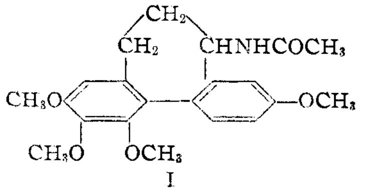
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Cyclization of β-2-(3-Bromo-4,5,6,4′-tetramethoxybiphenyl)-propionic Acid[1]

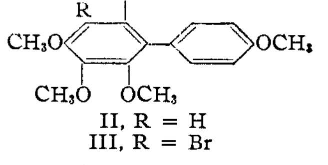
BY H. T. HUANG, D. S. TARBELL AND H. R. V. ARNSTEIN

A recent paper[2] reported experiments on a projected synthesis of compound I, which is a probable structure for an important degradation product of colchicine, N-acetylcolchinol methyl ether.[3] The synthesis of the latter is highly desirable in order to establish the position of the acetamino group and to confirm the structure of ring B in colchicine.

The proposed synthesis involved cyclization of the bromo acid III to the ketone IV, followed by debromination and conversion of the carbonyl group of IV to an acetamino group. In the previous work[2] the bromo acid III had been synthesized, and it had been found that it could be cyclized, although in poor yield, to a bromo ketone.



I



II, R = H
III, R = Br

A further study of the cyclization of III, which is now reported, has shown the cyclization to be accompanied by halogen migration, with the formation of a five-membered ring instead of a seven-membered one. The final product of the

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[1] Aided by a grant from the National Institute of Health.

[2] Frank, Fanta and Tarbell, THIS JOURNAL, **70**, 2314 (1948).

[3] *Cf.* Cohen, Cook and Roe, *J. Chem. Soc.*, 194 (1940), and later papers; also Tarbell, Frank and Fanta, THIS JOURNAL, **68**, 502 (1946).