M. K. Humphrey, E. Thornton and M. Mc Gregor, and Mrs. Edith Meiss for the microanalyses reported in this paper.

Summary

dl-Biotin has been converted by the Raney nickel hydrogenolysis reaction into *dl*-desthiobiotin. *dl*-Allobiotin and *dl*-*epi*-allobiotin have been converted to a common desthio derivative, *dl*-desthioallobiotin, which differs from *dl*-desthiobiotin. These desthio derivatives were obtained also by an alternative series of reactions starting with the 3-acetamido-4-benzamidotetrahydro-2-thiophenevaleric acid methyl esters which were treated with Raney nickel catalyst to give the ζ-acetamido-η-benzamidopelargonic acids. These acids were hydrolyzed and treated with phosgene to yield *dl*-desthiobiotin and *dl*-desthioallobiotin.

dl-Biotin was stable toward boiling dilute sulfuric acid while *dl*-allobiotin was quickly hydrolyzed to give the corresponding diamino acid sulfate and carbon dioxide.

These results indicate that *dl*-biotin has the *cis* configuration in respect to its nitrogen atoms, and that *dl*-allobiotin and *dl*-*epi*-allobiotin both have the *trans* configuration in respect to their nitrogen atoms.

RAHWAY, NEW JERSEY RECEIVED AUGUST 18, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Rearrangement in the Reaction of α-Halogenonaphthalenes with Lithium Diethylamide

BY HENRY GILMAN, N. N. CROUNSE, S. P. MASSIE, JR., R. A. BENKESER AND S. M. SPATZ

It has been shown that sodamide in liquid ammonia reacts with aryl halides, in which the halogen is *ortho* to an ether[1] or sulfide[2] linkage, to give a rearrangement product in which the amino group is *meta* to the oxygen or sulfur group.

$$o\text{-}ClC_6H_4OCH_3 + NaNH_2 \longrightarrow m\text{-}H_2NC_6H_4OCH_3 + NaCl$$

In extension of those studies it has been observed[3] that related rearrangements occur with lithium dialkylamides in ether solution.

$$o\text{-}IC_6H_4OCH_3 + LiN(C_2H_5)_2 \longrightarrow m\text{-}(C_2H_5)_2NC_6H_4OCH_3 + LiI$$

However, from the particular reaction just given as an illustration there was isolated 22% of anisole. This suggested that a halogen–metal interconversion reaction may have been responsible for most of the anisole.

$$o\text{-}IC_6H_4OCH_3 + LiN(C_2H_5)_2 \longrightarrow o\text{-}LiC_6H_4OCH_3 \xrightarrow{HOH} C_6H_5OCH_3$$

It appeared that one of the better ways of establishing the possibility of a halogen–metal interconversion reaction was by means of α-bromonaphthalene, for α-bromonaphthalene is known[4] to undergo the halogen–metal interconversion reaction with *n*-propyllithium almost quantitatively (97%). Any intermediately formed α-naphthyllithium could be readily characterized by carbonation to α-naphthoic acid.

$$\alpha\text{-}C_{10}H_7Br + LiN(C_2H_5)_2 \longrightarrow \alpha\text{-}C_{10}H_7Li \xrightarrow[HOH]{CO_2} \alpha\text{-}C_{10}H_7CO_2H$$

Only a trace of acidic material was isolated from these reactions, and α-naphthoic acid has not as yet been identified. However, the basic fraction was found to be composed largely of β-diethylaminonaphthalene. This demonstrated that rearrangements with alkali amide types are not confined to aryl halides in which the halogen is *ortho* to an oxygen or sulfur linkage.

A rearrangement reaction of this type is not novel, for Bergstrom and Urner[5] obtained a good yield of β-naphthylamine from reaction of α-chloronaphthalene with an excess of potassium amide in liquid ammonia. However, the same authors observed no rearrangement in a corresponding reaction with α-fluoronaphthalene from which α-naphthylamine was isolated. Accordingly, this suggested an examination of the reaction of lithium diethylamide in ether with α-fluoronaphthalene and with α-chloronaphthalene. We have found that these two halonaphthalenes, as well as the α-bromonaphthalene, undergo rearrangement. There appear, then, to be significant differences between the reactions of simple alkali amides in liquid ammonia from those of the alkali dialkylamides in ether.

The reaction of lithium dialkylamides with RX compounds proceeds quite satisfactorily in some cases.[6] However, direct reaction of the RX compound with the secondary amine may be preferred at times. For example, we have shown that 2-dimethylaminoquinoline is obtainable in 91% yield by reaction of dimethylamine with 2-chloroquinoline. By contrast, the reaction of 2-chloroquinoline with potassium amide in liquid ammonia gave largely tars.[6] It seemed of interest to determine whether the reaction of 2-chloroquinoline with lithium dimethylamide in ether

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[1] Gilman and Avakian, THIS JOURNAL, **67**, 349 (1945).

[2] Gilman and Nobis, *ibid.*, **67**, 1479 (1945).

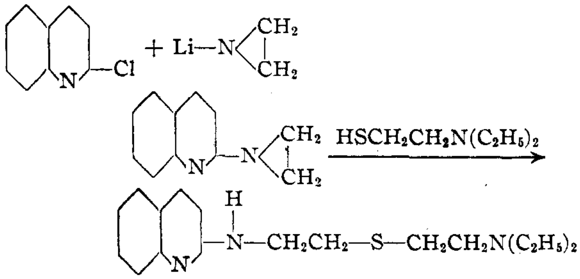
[3] Unpublished studies by R. H. Kyle.

[4] Gilman and Moore, THIS JOURNAL, **62**, 1843 (1940).

[5] Unpublished results privately communicated by Dr. F. W. Bergstrom.

[6] Unpublished studies by E. C. Horning. See Bergstrom and Fernelius, *Chem. Rev.*, **20**, 437 (1937).

might have some advantage over the corresponding reaction with alkali amides in liquid ammonia. Actually, this is the case for 2-dimethylaminoquinoline is formed in satisfactory yield from lithium dimethylamide in ether. This type of reaction was extended, and 2-chloroquinoline with lithium ethyleneimide in ether gave a 73% yield of 2-ethyleneiminoquinoline. The ethyleneiminoquinoline types have been found useful in studies on compounds of physiological interest. One reaction, reported at this time, is with β-diethylaminoethyl mercaptan to give β-(2-quinolylamino)-ethyl β'-diethylaminoethyl sulfide dihydrochloride.



Experimental

Bromobenzene and Iodobenzene with Lithium Diethylamide.—These reactions were carried out incidental to an examination of the preparation of lithium diethylamide from naphthalene, lithium, and diethylamine.[7] The yields of diethylaniline from bromobenzene, in diethyl ether or in benzene as media, were in the range of 30–40%; and the yield from iodobenzene in ether was 31%. Unquestionably, it is better to prepare the lithium dialkylamides,[6] for laboratory scale operations, from the secondary amines and RLi compounds in ether.

α-Halonaphthalenes with Lithium Diethylamide.—In a typical experiment, lithium diethylamide was prepared in ether by reaction of 18.3 g. (0.25 mole) of diethylamine in 100 cc. of ether with 0.2 mole of methyllithium in 100 cc. of ether. Then 32.6 g. (0.2 mole) of α-chloronaphthalene in 75 cc. of ether was added, and the mixture was stirred and refluxed for twenty-four hours. The color changes in the mixture during reaction were from brown to green to brownish-yellow, and a small amount of solid formed. Subsequent to hydrolysis by dilute hydrochloric acid, the ether layer was extracted with dilute hydrochloric acid. From the ether layer after drying there was obtained by distillation 2.2 g. (8.5%) of pure naphthalene (mixed m. p.) and 9 g. (27.5%) of recovered α-chloronaphthalene which was identified by a mixed m. p. determination of its picrate with an authentic specimen of the picrate. From the hydrochloric acid solutions, subsequent to being made alkaline by sodium hydroxide solution, there was obtained a crude yield of 13.3 g. (33%) of β-diethylaminonaphthalene which on redistillation yielded 10.8 g. (27%) of pure product. Identification was completed by formation of the *sym*-trinitrobenzene complex which melted at 114–115° and showed no depression in mixed m. p. with an authentic specimen.[8]

From related experiments using 0.2 mole of α-bromonaphthalene there were isolated and identified, 2.2 g. (8.5%) of naphthalene, 10 g. (24%) of α-bromonaphthalene, and 10.5 g. (27%) of β-diethylaminonaphthalene.

Under corresponding conditions, experiments with 0.18 mole of α-fluoronaphthalene gave 14.3 g. (40%) of β-diethylaminonaphthalene, and 6.2 g. of a mixture of what appears to be napththalene and α-fluoronaphthalene (which have essentially the same boiling points).

The products obtained from two runs with α-fluoronaphthalene and α-chloronaphthalene, respectively, and from three runs with α-bromonaphthalene, were identified by comparison with authentic specimens (mixed m. p.). In some other experiments involving α-chloronaphthalene and α-bromonaphthalene, respectively, the reaction mixtures were carbonated prior to hydrolysis and only a very small quantity of an as yet unidentified acidic material was isolated.

2-Chloroquinoline and Dimethylamine.—A mixture of 22.9 g. (0.14 mole) of 2-chloroquinoline and 18.9 g. (0.42 mole) of anhydrous dimethylamine was heated in a sealed tube at 150–158° for sixteen hours. The cold reaction mixture was dissolved in dilute hydrochloric acid, and then made alkaline. After boiling off the excess dimethylamine, the oily residue crystallized to yield 24 g. (99%) of 2-dimethylaminoquinoline. Recrystallization from petroleum ether (b. p., 60–68°) gave 21.8 g. (91%) of long needles melting at 70–71°. This melting point agrees with a previous preparation[9] of the compound by heating quinoline-2-sulfonic acid and dimethylamine in the presence of zinc chloride at 135°.

2-Chloroquinoline and Lithium Dimethylamide.—Gaseous dimethylamine was passed, against a pressure of 40 mm. of mercury, through a solution of 0.15 mole of methyllithium in 100 cc. of ether at room temperature for about one hour. A heavy white precipitate formed immediately, and after three-quarters of an hour an additional 50 cc. of anhydrous ether was added to facilitate stirring. After about one hour the solution gave a negative color test I,[10a] the gas flow was cut off, the mixture was refluxed for fifteen minutes, and a color test IV[10b] made at this stage was positive. Then 16.4 g. (0.1 mole) of 2-chloroquinoline in 50 cc. of ether was added over a thirty-five-minute period. A dark red solution resulted at the end of this time, and a slight precipitate of what appeared to be lithium chloride was evident. Subsequent to stirring at room temperature for one and three-quarter hours and then refluxing for twenty minutes, the mixture was carefully hydrolyzed. From the ether layer, after drying over sodium sulfate, was obtained a 90% yield of crude product melting over the range 57–63°. Crystallization from petroleum ether (b. p., 60–68°) gave a 58% yield of 2-dimethylaminoquinoline (mixed m. p.).

2-Ethyleneiminoquinoline.[11]—A solution of 0.22 mole of methyllithium in 120 cc. of ether was added, during a one-hour period, to a stirred solution of 9.5 g. (0.22 mole) of ethyleneimine in 100 cc. of ether. A voluminous precipitate formed, and the mixture gave a negative color test I[10a] and a positive color test IV.[10b] To the stirred suspension was added a solution of 30 g. (0.183 mole) of 2-chloroquinoline in 80 cc. of ether. The mixture turned deep red in color, and no gas was evolved. After stirring for two hours at room temperature and then refluxing for twenty minutes, the cooled mixture was hydrolyzed by water. The ether layer was separated, dried, and then the ether was removed under reduced pressure. The residue was dissolved in 150 cc. of boiling ether, heated with Norite, filtered, and the process was repeated. On concentrating the brownish-red solution to about 25 cc., crystals were deposited. The total yield of tan-colored crystals, melting at 62.5–64°, was 22.6 g. (73%). Recrystallization of a portion of the product from ether gave a product melting at 64–65°. The compound is soluble in methanol, ethanol, chloroform, acetone, benzene, and somewhat soluble in petroleum ether fractions.

Anal. Calcd. for $C_{11}H_{10}N_2$: N, 16.46. Found: N, 16.58.

β-(2-Quinolylamino)-ethyl β'-Diethylaminoethyl Sulfide Dihydrochloride.[12]—A solution of 3.6 g. (0.021 mole) of 2-ethyleneiminoquinoline and 3.2 g. (0.025 mole) of

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[7] Ziegler, U. S. Patent 2,141,058 [*C. A.*, **33**, 2538 (1939)].

[8] Hibbert and Sudborough, *J. Chem. Soc.*, **83**, 1340 (1903).

[9] Zerweck and Kunze, German patent, 615,184 [*Chem. Zentr.*, **106**, II, 2284 (1935)].

[10] (a) Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925); (b) Gilman and Woods, *ibid.*, **65**, 33 (1943).

[11] By L. A. Woods and R. A. Benkeser.

[12] By L. A. Woods.

β-diethylaminoethyl mercaptan[13] in 10 cc. of ether containing two drops of 9 molar alcoholic hydrogen chloride was heated slowly to 70° in an oil-bath, and then kept at about this temperature for twenty hours. The product was treated with a mixture of 25 cc. of 10% sodium hydroxide and 80 cc. of ether. The ether layer was removed, washed with 15 cc. of water, dried, and then filtered. An excess of ethereal hydrogen chloride was added; the ether was decanted; the precipitate was dissolved in 20 cc. of absolute ethanol; and 25 cc. of ether was added. From the cooled solution there separated slowly 4.8 g. (61%) of product which softened at 160° and melted at 169–172°. Recrystallization gave the same melting point range.

Anal. Calcd. for $C_{17}H_{27}Cl_2N_3S$: N, 11.16; S, 8.51. Found: N, 11.15 and 10.95; S, 8.19 and 8.35.

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[13] See Albertson and Clinton, THIS JOURNAL, **67**, 1222 (1945); Gilman and Woods, *ibid.*, **67**, 1843 (1945); and Gilman, Plunkett, Tolman, Fullhart and Broadbent, *ibid.*, **67**, 1845 (1945), for the preparation of this mercaptan.

Summary

Lithium diethylamide reacts with α-fluoro-, α-chloro- and α-bromonaphthalene in ether solution to give the rearrangement product, β-diethylaminonaphthalene. One of the products isolated from these reactions is naphthalene, which apparently does not owe its formation to a halogen–metal interconversion reaction.

The lithium dialkylamide reaction in ether proceeds smoothly with 2-chloroquinoline to give 2-dialkylaminoquinolines. One of the types formed by this method is 2-ethyleneiminoquinoline, which when treated with β-diethylaminoethyl mercaptan gives β-(2-quinolylamino)-ethyl β-diethylaminoethyl sulfide dihydrochloride.

AMES, IOWA RECEIVED JULY 30, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF STANFORD UNIVERSITY]

The Action of Bases on Organic Halogen Compounds. III. The Reaction of Potassium Amide with the Naphthyl Halides

BY ROBERT S. URNER AND F. W. BERGSTROM[1]

The action of the alkali amides on the phenyl halides (the fluoride excepted) leads to the formation, in varying amounts, of aniline, diphenylamine, triphenylamine and *p*-aminobiphenyl.[2] Other aromatic halides sometimes give the expected amine, but a rearrangement to the ortho position is often noted, as in the experiments of Gilman and Avakian.[3] The present work is a continuation of investigations of Wright, Chandler, Gilkey and Horning of this Laboratory, and deals with the action of a liquid ammonia solution of potassium amide on the naphthyl halides.

An excess of potassium amide, dissolved in liquid ammonia, removes halogen almost quantitatively from 1-chloronaphthalene, 1-bromonaphthalene and 1-iodonaphthalene with the formation of 2-naphthylamine in 40–55% yields, together with smaller amounts (2–3%) of 1-naphthylamine. The same results are obtained when potassium amide solution is added to an excess of the naphthyl halide. Both reactions follow the equation

$$C_{10}H_7Cl + 2KNH_2 = C_{10}H_7NHK + KCl + NH_3 \quad (1)$$

When hydrolyzed, $C_{10}H_7NHK + H_2O = C_{10}H_7NH_2 + KOH$.

Although fluorobenzene is attacked only to a very slight extent by potassium amide at 20 or 80°,[2a] 1-fluoronaphthalene and potassium amide react slowly at −33° to form 1-naphthylamine; the yield is somewhat improved by carrying out the reaction at room temperatures. A by-product melting at 111° has not yet been identified. Liquid ammonia solutions of the 2-naphthyl halides react with potassium amide to give 2-naphthylamine almost exclusively, with very minor quantities of 1-naphthylamine. Rearrangement therefore does not always occur in the reaction between potassium amide and an aryl halide. It is interesting in this connection that Gilman and co-workers[4] have found that 2-diethylaminonaphthalene is formed in the reaction of lithium diethylamide with 1-fluoronaphthalene, 1-chloronaphthalene and 1-bromonaphthalene. The reaction between potassium amide and 1-fluoronaphthalene may also involve a rearrangement, but to the 4-position of the nucleus.

Experimental

The naphthyl halides were all refractionated white-label preparations of the Eastman Kodak Company, with the exception of 2-fluoro- and 2-chloronaphthalenes, which were made from 2-naphthylamine by known methods. The description of a typical run is given.

Potassium amide was prepared in about 200 ml. of liquid ammonia in a 3-necked 500-ml. flask, by the catalytic action of superficially (flame) oxidized iron wire upon dissolved metallic potassium free from oxide. One neck of the flask was stoppered, one was loosely plugged with cotton and the center neck was closed with a rubber stopper through which passed a glass delivery tube, bent externally at right angles, and reaching almost to the bottom of the flask. The delivery tube was connected by means of a short length of rubber tube (which could be clamped shut if desired) to a tube passing through one of the small necks of a 1000-ml. 3-necked flask. The center opening carried a mercury sealed stirrer, and the third neck was plugged with cotton. This second flask contained 300–500 ml. of liquid ammonia, in which the naphthyl halide was dissolved, at times incompletely. Potassium amide was transferred slowly to the stirred solution and suspen-

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[1] Abstracted from Part II of the Doctor's thesis of R. S. Urner, Stanford University, 1940.

[2] (a) Bergstrom, Wright, Chandler and Gilkey, *J. Org. Chem.*, **1**, 170–178 (1936); (b) Wright and Bergstrom, *ibid.*, **1**, 179–188 (1936).

[3] Gilman and Avakian, THIS JOURNAL, **67**, 349–351 (1945).

[4] Gilman, Crounse, Massie, Benkeser and Spatz, THIS JOURNAL, **67**, 2106 (1945).