velocities of organometallic reactions, and dioxane may function significantly in this manner.

It should be stated that even in the absence of dioxane, phenylmagnesium bromide in ether adds to quinoline at room temperature to give a 7.5% yield of 2-phenylquinoline at the end of two days. Accordingly, forced conditions[7] are not required to effect addition of RMgX compounds to quinoline.

Finally, a combination of phenylmagnesium bromide and phenyllithium was used in a reaction with quinoline. The purpose of this experiment was to determine whether the onium-complex[13] with the RMgBr compound and quinoline might affect the course of addition of phenyllithium to give phenylquinolines other than 2-phenylquinoline.[14] However, the only product isolated when phenyllithium was added to the quinoline–phenylmagnesium bromide complex was 2-phenylquinoline.

Experimental

Benzalquinaldine and Phenyllithium.—The benzalquinaldine was prepared in almost quantitative yield in essential accordance with the procedure of Skraup and Bothm.[15] However, instead of crystallizing the crude product from ethanol, any residual benzaldehyde and quinaldine were removed by washing the powdered crude crystalline product with boiling petroleum ether (b. p., 60–68°) in which the benzalquinaldine is essentially insoluble.

To a stirred solution of 23.1 g. (0.1 mole) of benzalquinaldine dissolved in a minimum of dry benzene to which was then added an equal volume of anhydrous ether, was added (dropwise) 0.1 mole of phenyllithium in ether. The solution immediately assumed a blood-red color; refluxing occurred; and after stirring for one hour hydrolysis was effected by pouring into water. Evaporation of the dried ether extract gave a quantitative yield of α-benzohydrylquinaldine melting over the range 115–119°. A mixed melting point determination of a recrystallized sample and an authentic specimen[6] showed no depression.

Quinoline and Phenylmagnesium Bromide.—On the addition of 20 cc. of dry, freshly distilled dioxane to an ether solution of 0.166 mole of phenylmagnesium bromide, a pure white precipitate formed immediately. To the stirred suspension was added 21.5 g. (0.166 mole) of quinoline in an equal volume of ether, and a tan-colored precipitate formed. The suspension was stirred, without refluxing, for forty-eight hours. Subsequent to hydrolysis by saturated ammonium chloride solution, evaporation of the ether extract, oxidation of the dihydro intermediate by nitrobenzene, and distillation there was obtained 15 g. (44%) of 2-phenylquinoline (mixed m. p.).

When the above procedure was repeated without the use of dioxane, there was obtained from a 0.1 mole run 4 g. (20%) of a crude product (b. p., 145–160° (0.3 mm.)) which yielded after crystallization from benzene-petroleum ether (b. p., 60–68°) 1 g. (5%) of pure 2-phenylquinoline. A small quantity of the picrate of 2-phenylquinoline (corresponding to 0.5 g. or 2.5% of 2-phenylquinoline) was obtained from the picrates of the mother liquor.

Quinoline, Phenylmagnesium Bromide and Phenyllithium.—To 0.2 mole of the tan-colored ether-insoluble quinoline-phenylmagnesium bromide complex was added 0.2 mole of phenyllithium in ether. The mixture was stirred without refluxing for twelve hours, and during this time the complex dissolved completely. Hydrolysis by water and subsequent working up by customary procedures (including the nitrobenzene oxidation) gave 24 g. (58.5%) of 2-phenylquinoline (mixed m. p.).

Acknowledgment.—The authors are grateful to Dr. R. G. Jones for assistance.

Summary

1. Phenyllithium adds to benzalquinaldine to give α-benzohydrylquinaldine. This reaction very probably takes place by a 1,4-addition.

2. Phenylmagnesium bromide adds, in ether and at room temperature, to quinoline to give 2-phenylquinoline. The rate of addition under these mild conditions is markedly accelerated in an ether–dioxane medium, possibly because of the intermediate formation of coördination complexes.

AMES, IOWA RECEIVED JANUARY 19, 1949

---

[13] Sachs and Sachs, *Ber.*, **37**, 3091 (1904); **38**, 1087 (1905).

[14] Ziegler and Zeiser, *Ann.*, **485**, 182 (1931); see, also, ref. 5 in this paper.

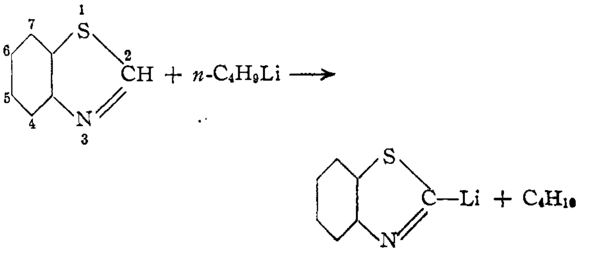
[15] Skraup and Bothm, *Ber.*, **59**, 1013 (1927).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Reactions of Organometallic Compounds with Benzothiazoles

BY HENRY GILMAN AND JOHN A. BEEL

Since it has been shown that certain benzothiazole derivatives are physiologically active,[1] some compounds containing this nucleus were considered to be of interest in the chemotherapy of tuberculosis. Feasible methods of preparing the desired compounds seemed to be through the addition of the proper organometallic compound to the azomethine grouping in benzothiazole and through the preparation of an organometallic compound of benzothiazole itself.



[I]

Courtot[2] had previously prepared 2-benzothiazolylmagnesium bromide (in yields not stated)

---

[1] (a) Bogert and Hess, *Rec. trav. chim.*, **48**, 904 (1929); (b) Newberry and Viaud, British Patent 517,272 (January 25, 1940) [*C. A.*, **35**, 6741 (1941)]; (c) Rose, Shonle and Chen, *Pharm. Arch.*, **11**, 81 (1940); (d) Ballowitz, *Arch. exptl. Path. Pharmakol.*, **163**, 687 (1931).

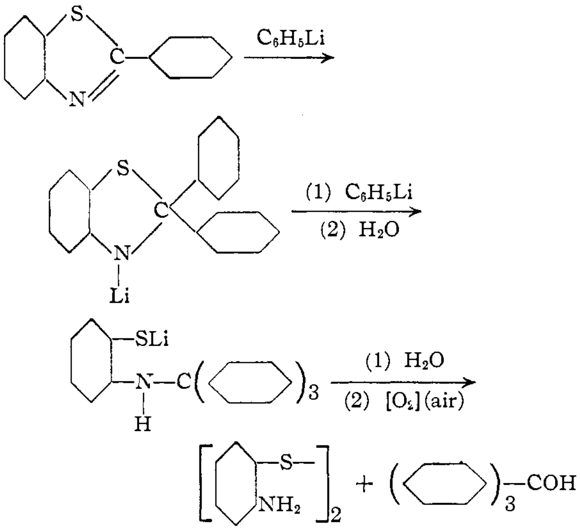
[2] Courtot and Tchelitcheff, *Compt. rend.*, **217**, 231 (1943).

by metalation of benzothiazole with ethylmagnesium bromide. We found it possible to metalate benzothiazole in the 2-position in 90% yield (determined by carbonation) by employing *n*-butyllithium at low temperatures, so no attempt was made to prepare the corresponding Grignard reagent. 2-Benzothiazolyllithium (I) is not stable above −35°, which somewhat restricts its use. However, it undergoes many of the reactions of organolithium compounds in good yield,[3] providing the reactions occur below the decomposition temperature. It has been found possible to add the RLi compound to nitriles, aldehydes, ketones and carbon dioxide. Color Test I,[4] which depends on the addition of I to Michler's ketone, is normal except that 20 drops of the second reagent (1% iodine in glacial acetic acid) have to be added instead of the usual one or two drops. Apparently the iodine is used up in some other reaction before it can develop the color of the test.

Reaction with benzoyl chloride produced only a small amount of ketone, and no 2-benzylbenzothiazole could be isolated from the reaction with benzyl chloride. Attempts to add I to the azomethine grouping in quinoline were unsuccessful though inconclusive. In most of the unsuccessful reactions the temperature was allowed to go above −35° because there was no evidence of reaction below that temperature. If the temperature of I goes above −35°, 2,2′-bibenzothiazole can be isolated from the reaction mixture, indicating intermolecular addition.

Addition to the azomethine grouping of benzothiazole does not proceed so smoothly as with quinoline. Because of the ease of metalation of benzothiazole a sufficient amount of the organometallic compound must be added to effect the metalation and subsequently the addition. Apparently there is no appreciable addition to the azomethine grouping at low temperatures, and at higher temperatures the decomposition of the metalated benzothiazole is a competitive reaction. Some 2-phenylbenzothiazole has been obtained from phenyllithium and benzothiazole, if hydrolyzed by ammonium chloride solution, but the yield is not high. The fact that most of the reaction mixture is soluble in the aqueous layer on hydrolysis with water indicates that something more than addition takes place, *i. e.*, the addition may be followed by rupture of the ring to form a thiophenol. This solubility might possibly be explained by postulating a direct cleavage of the sulfur–carbon bond in benzothiazole by the phenyllithium. Several procedures have been attempted to isolate products from the base soluble layer, but none has succeeded.

By treating 2-phenylbenzothiazole with phenyllithium we obtained bis-(*o*-aminophenyl) disulfide and triphenylmethanol, indicating addition to the azomethine grouping and then cleavage of the 1,2-dihydro compound as follows:



Of course, the cleavage may precede the addition to yield the same products, depending on the reactivity of the functional groupings to the organometallic compound.

Experimental

2-Benzothiazolyllithium.—Several attempts to prepare an organometallic compound of benzothiazole were made. Reactions between lithium and 2-chlorobenzothiazole and magnesium and 2-chlorobenzothiazole, even using an activated Cu–Mg–I catalyst,[5] were unsuccessful. All reactions employing benzothiazole and methyl-, butyl- or phenyllithium were successful, but the yields varied. The following is a description of the preparation under optimum conditions.

To 0.078 mole of *n*-butyllithium in 235 ml. of ether (0.33 *M*), cooled to −78° (bath temperature) was added slowly 10.5 g. (0.078 mole) of benzothiazole. Immediately after the addition the entire reaction mixture was poured into a slush of ether and Dry Ice. Hydrolysis and neutralization of the water layer produced 12.5 g. (89.7%) of benzothiazole-2-carboxylic acid. This melted with decomposition at 105° (with carbon dioxide evolution), corresponding to values found in the literature.[6] *Anal.* Calcd. for $C_8H_5O_2NS$: neut. equiv., 179.2. Found: neut. equiv., 182.0.

A small amount (1.3 g.) of yellow oil was found in the ether layer.

Compound I was not stable above −35°. At this temperature the solution began to turn color and decomposed. 2,2′-Bibenzothiazole was found after allowing a solution of I to warm up, and oxidizing the product with nitrobenzene. The 2,2′-bibenzothiazole was identified by melting point (310°) and mixed melting point with an authentic specimen prepared by heating acetanilide with sulfur.[7]

Benzothiazolyl Phenyl Ketone.—To 0.158 mole of I at −75° (bath temperature) was added 20.0 g. (0.19 mole) of benzonitrile. After stirring forty minutes the bath temperature was −58°, and a Color Test I was negative. Hydrolysis was effected by the addition of 100 ml. of water, and the mixture was made distinctly acid with hydrochloric acid. The ether layer was separated, dried over sodium sulfate, and the ether was removed and replaced with 40 ml. of 95% ethanol. Cooling yielded 31.5 g. of solid which melted at 95–101°. Recrystallization from

---

[3] Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 524–542.

[4] Gilman and Schulze, THIS JOURNAL, **47**, 2002 (1925).

[5] Gilman, Peterson and Schulze, *Rec. trav. chim.*, **47**, 19 (1928).

[6] Bogert and Stull, THIS JOURNAL, **48**, 250 (1926).

[7] Hunter, *J. Chem. Soc.*, **127**, 1318 (1925).

TABLE I

TERTIARY BENZOTHIAZOLEMETHANOLS PREPARED FROM I AND KETONES

2-Benzothiazole-methanol	Crystallization solvent	M. p., °C.	Yield, %	Analyses, % Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
α,α-Diphenyl-	Ethanol	150	95	4.42	4.33	10.12	10.22
α-Methyl-α-phenyl-	Pet. ether (b. p., 60–70°)	89	67	5.49	5.52	12.54	12.20
α-(*p*-Chlorophenyl)-α-methyl-	Ethanol (95%)	134–136	72	4.84	4.88	11.08	10.95
α-Methyl-α-(*p*-tolyl)-	Pet. ether (b. p., 77–115°)	100.5	63	5.19	5.02	11.87	11.27
α,α-Di-(*p*-dimethylaminophenyl)-	Benzene	195	64	10.40	10.28	7.94	7.50

TABLE II

SECONDARY BENZOTHIAZOLEMETHANOLS PREPARED FROM I AND ALDEHYDES

2-Benzothiazolemethanol	Crystallization solvent	M. p., °C.	Yield, %	Analyses, % Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
α-Phenyl-	Ethanol (95%)	121.5	80	5.80	5.63	13.28	12.76
α-(*n*-Propyl)-	Pet. ether (b. p., 77–115°)	82	56	6.78	6.68	15.57	15.36
α-(*p*-Dimethylaminophenyl)-	Benzene	157	60	9.84	9.68	11.28	11.24

95% ethanol gave 26.8 g. (71.1%) of material melting at 102.5°. *Anal.* Calcd. for $C_{14}H_9ONS$: N, 5.86; S, 13.39. Found: N, 5.96; S, 12.92.

Phenylhydrazone of Benzothiazolyl Phenyl Ketone.—This was prepared in the usual way by adding phenylhydrazine to a 95% ethanol solution of the ketone. The material which crystallized out melted at 93–135°. One recrystallization from alcohol raised the melting point to 149°. Further recrystallization did not raise the melting point. *Anal.* Calcd. for $C_{20}H_{15}N_3S$: N, 12.76; S, 9.73. Found: N, 12.92; S, 9.53.

Di-2-benzothiazolylphenylmethanol.—To 0.054 mole of I at −75° was added slowly 13.5 g. (0.054 mole) of benzothiazolyl phenyl ketone in 200 ml. of ether. A Color Test I was negative at the end of the addition. The stirring was continued for twenty minutes before hydrolyzing with 100 ml. of water. Some material was insoluble on hydrolysis. This was removed by filtration and added to the material obtained by replacing the ether with anhydrous alcohol and cooling. A total of 12.8 g. (63.6%) of product (m. p., 158°) was obtained after repeated alternate crystallization from benzene and anhydrous alcohol. *Anal.* Calcd. for $C_{21}H_{14}ON_2S_2$: N, 7.51; S, 17.12. Found: N, 7.47; S, 16.89.

Other methanols prepared in essentially the same manner by adding I to aldehydes and ketones are listed in Tables I and II.

Reaction with Benzoyl Chloride.—A solution of 0.11 mole of I in 250 ml. of ether was prepared in the usual way. To this solution at −75° was slowly added 16 g. (0.12 mole) of freshly-distilled benzoyl chloride. The mixture turned red and finally cream-colored and at the end of forty minutes gave a negative Color Test I.[4] The mixture was hydrolyzed by pouring into a beaker of cracked ice. The ether layer yielded 3.4 g. of an unidentified material which melted at 210°. Treatment of the alcoholic mother liquor with phenylhydrazine produced a small quantity of needle-shaped crystals which melted at 149°. This gave no depression of melting point when mixed with a pure sample of the phenylhydrazone of benzothiazolyl phenyl ketone prepared by adding I to benzonitrile.

Phenyllithium and Benzothiazole.—To 0.235 mole of phenyllithium in 200 ml. of ether was added 14.3 g. (0.155 mole) of benzothiazole. The reaction mixture was kept at 0° during the addition (fifteen minutes) and for two hours after the addition. Hydrolysis was effected by the addition of 100 ml. of 10% ammonium chloride. The layers were separated, and the ether layer was dried over sodium sulfate before removing the ether. The resulting residue was distilled to yield 3.7 g. of benzothiazole (b. p., 85–90° at 0.5 mm.) identified by means of its picrate (m. p., 167°) and mixed melting point with an authentic specimen. This is a 26.9% recovery of benzothiazole. The second fraction (b. p., 165–170° at 0.5 mm.) weighed 10.2 g. and was mostly 2-phenylbenzothiazole (41.9% crude yield). This was recrystallized from 95% ethanol to yield 7.7 g. (31.7% yield) of pure 2-phenylbenzothiazole (m. p., 114°) which showed no depression in a mixed melting point with an authentic specimen.

Phenyllithium and 2-Phenylbenzothiazole.—A solution of 0.118 mole of phenyllithium in 124 ml. of ether was added to 24.2 g. (0.115 mole) of 2-phenylbenzothiazole. The color darkened, and a gentle reflux occurred during the addition and for ten minutes thereafter. After stirring for one hour at room temperature a Color Test I was still positive, and the reaction mixture was poured into a slush of ether and Dry Ice. Hydrolysis was effected by the addition of 100 ml. of water. The water layer was acidified to congo red, but no acid was obtained. The ether was distilled from the ether layer, and the residue was dissolved in toluene. This toluene solution was extracted with concentrated hydrochloric acid. These extracts, poured into water, yielded 13.9 g. of material (m. p., 80–95°). As much of this as possible was dissolved in 95% ethanol and cooled to yield 5.6 g. of amorphous material (m. p., 108–111°). This is a 23.3% recovery of 2-phenylbenzothiazole, identified by mixed melting point with an authentic specimen.

The extracts of concentrated hydrochloric acid which had been hydrolyzed and filtered were neutralized with potassium hydroxide, yielding 3.2 g. of a greenish precipitate. On recrystallizing from 95% ethanol this yielded 1.1 g. (7.70%) of bis-(*o*-aminophenyl) disulfide (m. p., 93–94°).[8] *Anal.* Calcd. for $C_{12}H_{12}N_2S_2$: N, 11.23; Found: N, 11.17.

From the toluene layer 3.6 g. of crude material (m. p., 157° with softening at 144°) was obtained. Recrystallized from toluene and petroleum ether (b. p. 77–115°) it yielded 2.5 g. (8.36%) of material (m. p. 162°) which gave no depression of melting point when mixed with an authentic specimen of triphenylmethanol.

Summary

1. Benzothiazole can be metalated in the 2-position by *n*-butyllithium in 90% yield.
2. Although good yields of expected products are obtained from some reactions of 2-benzothiazolyllithium, its decomposition above −35° complicates other reactions.
3. Several new methanols containing the 2-benzothiazolyl grouping are reported.
4. Phenyllithium in excess reacts with 2-phenylbenzothiazole to cleave the sulfur–carbon bond.

---

(8) Hofmann, *Ber.*, **12**, 2346 (1879).

5. A 31.7% yield of 2-phenylbenzothiazole results from the reaction between phenyllithium and benzothiazole.

AMES, IOWA RECEIVED MARCH 7, 1949

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and its Derived Compounds. VIII.[1] The Ultraviolet Absorption of Vanillic Acid and Related Acids and their Esters[2,3]

BY IRWIN A. PEARL

A large number of esters of vanillic acid and related acids have been prepared recently and their toxicities toward representative microörganisms have been reported.[1,4] In addition, their use as food preservatives has been described.[5] Preliminary observations which indicated that certain compounds in this series possessed marked absorption in the ultraviolet region of the spectrum led to a comprehensive study of the ultraviolet absorption characteristics of vanillic acid, its esters, and its related compounds, and of possible uses for these materials.

The esters of vanillic, orthovanillic and 5-chlorovanillic acids previously described were employed as samples in this study. The ultraviolet absorption spectra of these compounds were determined in specially purified dioxane solution with the model DU Beckman quartz spectrophotometer employing 1.0-cm. quartz cells. Each reading was made at minimum slit width and, therefore, at minimum sensitivity. The narrow slit width was used, with the corresponding sacrifice in sensitivity, in order to obtain more accurately the exact shape of the absorption curve.

Vanillic Acid.—The ultraviolet absorption spectrum of vanillic acid is given in Curve 2 of Fig. 1. Three primary absorption bands are indicated. These have their maxima at 2900, 2590 and approximately 2200 Å., respectively. In addition, secondary maxima appear at 2630, 2530 and 2470 Å. The three primary absorption bands were expected on the basis of recorded data, but the positions of these bands are not in accord with that expected from a knowledge of the literature.

In a comprehensive study of the ultraviolet absorption characteristics of pure compounds related to lignin, Patterson and Hibbert[6] found that compounds possessing the guaiacyl structure exhibited three absorption bands in the ultraviolet, characterized by maxima at 3060, 2800 and 2305 Å., these being due, respectively, to the presence of a side chain chromophore in conjugation with the ring, to freedom of the position meta to the point of attachment of the side chain, and to some unexplained characteristic of the aromatic nucleus. These authors examined vanillin, eugenol, isoeugenol, coniferin, and many derivatives of propylguaiacol, but did not examine any derivatives of vanillic acid. The spectrum of α-hydroxypropiovanillone obtained by Aulin-Erdtman[7] concurs with spectra obtained by Patterson and Hibbert. All these spectra were obtained in ethanol.

We have obtained the ultraviolet absorption spectrum of vanillin in purified dioxane. This curve (Curve 1 of Fig. 1) has maxima at 3090, 2740 and 2275 Å. and, when compared with curves in the literature for vanillin in other solvents (see Table I), clearly indicates the effect of solvent on the ultraviolet absorption spectrum, and the variation in spectra determined by different experimenters employing the same solvent.

It is evident from a comparison of Curves 1 and 2 of Fig. 1 that the presence of a –CO–O– group attached to a ring para to the hydroxyl group has caused hypsochromic shifts of the principal maxima. In addition three secondary maxima have appeared. These secondary maxima have never been recorded in previous studies of guaiacyl derivatives.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF VANILLIN IN VARIOUS SOLVENTS

Solvent	Maxima, Å.		
Hexane[a]	3000	2670	2230
Ethanol[a]	3080	2810	2290
Ethanol[b]	3120	2780	
Ethanol[c]	3080	2780	2320
Water[a]	3310	2910	
Dioxane[d]	3040	2740	2275

[a] Herzog and Hillmer, *Ber.*, **64B**, 1288 (1932). [b] Russell, Todd and Wilson, *J. Chem. Soc.*, 1940 (1934). [c] Ref. 6. [d] Present paper.

Ultraviolet absorption curves were obtained for a large number of esters of vanillic acid. These curves (see Table II) for the most part are almost identical with that of vanillic acid, except for actual specific extinction values. In several instances, some of the secondary maxima have been reduced to breaks in the curve. In others, the presence of new groupings in the non-vanillic acid portion of the molecule has resulted in shifts of the principal maxima, as well as changes in the secondary maxima.

The spectrum for ethyl vanillate is illustrative of a case in which the 2470 Å. maximum has been reduced to a break in the curve. The spectrum for phenyl vanillate represents a case in which a principal maximum is shifted to a higher wavelength and three secondary maxima have been reduced to breaks in the curve.

The presence of halogen in the ester grouping exerts a different effect, depending upon the type of ester group and the position of the halogen in the group. 2-Chloroethyl vanillate has a break in the curve at 2650 Å. The principal maximum is at 2630 Å. as in vanillic acid, ethyl vanillate, etc. In the spectra of all the other halogenated derivatives, a bathochromic shift takes place and this maximum occurs at a slightly higher wave length. The

---

[1] For paper VII of this series, see THIS JOURNAL, **71**, 1066 (1949).

[2] Presented before the Division of Organic Chemistry at the 113th meeting of The American Chemical Society, Chicago, Illinois, April 19–23, 1948.

[3] This paper represents a portion of the results obtained in the research program sponsored by The Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

[4] Pearl and McCoy, THIS JOURNAL, **69**, 3071 (1947).

[5] Pearl and McCoy, *Food Industries*, **17**, 1458 (1945).

[6] Patterson and Hibbert, THIS JOURNAL, **65**, 1862 (1943).

[7] Aulin-Erdtman, *Svensk Papperstidn.*, **47**, 91 (1944).