commonly performed *via* the 2-chloro compound. Replacement of 2-OH by 2-Cl is somewhat objectionable, however, because high temperature exposure to severe reagents is required.[8,12] The *p*-toluenesulfonate ester employed in this study was made under milder conditions, was obtained in higher yield than the 2-chloro compound, and was easier to purify. Although the yields of products of substitution in the lepidine nucleus are poorer from the *p*-toluenesulfonate ester (Table I), it is conceivable that syntheses *via* the ester might be preferable when sensitive groups were present elsewhere in the system.

Experimental

Materials were purified by methods previously described,[4] except as otherwise mentioned. *2-Chlorolepidine*, m.p. 55–57°, was obtained from 2-hydroxylepidine[13] by the method of Krahler and Burger[12] in 89% yield.

2-(*p*-Toluenesulfonoxy)lepidine.—The general method of Cavalito and Haskell[14] was utilized, but with important modifications. To 25 cc. of pyridine, dried by refluxing over sodium metal for several hours and then distillation from sodium, 5.00 g. (0.031 mole) of 2-hydroxylepidine[13] and 6.80 g. (0.036 mole) of *p*-toluenesulfonyl chloride were added. A tight-fitting glass stopper was inserted, and the flask was warmed slightly on the steam bath and shaken thoroughly. As soon as all the solid material had dissolved, the solution was placed in a cold cabinet at about −20° and left there 12 hr. It was removed and its contents poured into about 250 cc. of water and ice. The mixture was stirred thoroughly. The gray crystals which formed were collected, pressed dry and dissolved in hot benzene. The benzene solution was heated with decolorizing charcoal for about 10 min. To the hot filtered solution ligroin was added until a faint turbidity appeared, and then a little hot benzene to restore clarity. The mixture was cooled in an ice bath. 2-(*p*-Toluenesulfonoxy)lepidine, m.p. 122–124°, separated as white crystals that weighed 9.3 g. (96%). Three recrystallizations from benzene–ligroin raised the m.p. to 125–126°. The ester is stable in storage.

Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82. Found[15]: C, 64.75; H, 4.82.

2-Thiophenoxylepidine was prepared by reaction of 2-chlorolepidine with sodium thiophenoxide in 75% dioxane–25% water at 46° for 24 hr. The product, isolated by standard methods and crystallized from benzene–petroleum ether, consisted of white crystals of m.p. 81–82°. The yield was 68%.

Anal. Calcd. for $C_{16}H_{13}NS$: C, 76.45; H, 5.21. Found[15]: C, 76.76; H, 4.94.

2-Piperidinolepidine was prepared by reaction of 2-chlorolepidine with excess piperidine at 46° for 24 hr. The product, isolated by standard methods and crystallized from benzene–petroleum ether, consisted of white crystals of m.p. 72–73°. The yield was 76%.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02. Found[15]: C, 79.88; H, 8.10.

2-Anilinolepidine was prepared by condensation of 2-chlorolepidine with excess aniline after Knorr.[16] The yield was 69%, and the m.p. 128–130° (lit.,[16] 129–130°).

2-Chlorolepidine was recovered unchanged from exposure to ethyl sodioacetoacetate in refluxing tetrahydrofuran for 26 hr.

Reactions Summarized in Table I.—One gram of 2-(*p*-toluenesulfonoxy)lepidine was allowed to react with 5 cc. of each of the amine reagents, with or without addition of the amine hydrochloride. The reaction mixture for the sodium thiophenoxide experiment was prepared by combining 1.00 g. of the ester, in 15 cc. of dioxane, with 1.10 g. of thiophenol and 5 cc. of a 6% aqueous solution of sodium hydroxide. Products of all reactions were isolated by standard techniques, but principally by chromatography on alumina. They were the 2-lepidyl derivative of the nucleophile I, 2-hydroxylepidine II, and the *p*-toluenesulfonyl derivative of the nucleophile III. All products were identified by their melting points and by mixture melting points with authentic samples. In the case of the sodium thiophenoxide reaction, diphenyl disulfide was isolated as III rather than phenyl *p*-toluenethiolsulfonate; the disulfide is presumed to be a secondary product resulting from the action of thiophenoxide ion on the thiolsulfonate ester.[4]

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Stabilities and Some Reactions of Benzyllithium and α-Methylbenzyllithium

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An important property of an organometallic compound is its ability to effect metalation.[1] In the use of dibenzofuran (I) as a model heterocycle, the extent to which metalation takes place depends significantly upon the organometallic compound. *n*-Butylsodium[2a] and benzylsodium[2b] metalated (I) to give, after carbonation, dibenzofuran-4,6-dicarboxylic acid in yields of about 70%. However, benzylpotassium[2b] did not metalate (I) even after refluxing for forty-eight hours in toluene. *n*-Butyllithium gave monometalation in yields of 1–76% using diethyl ether as the solvent.[2b,3] Monometalation also has been accomplished using ethyl-,[2b,4a] *n*-propyl-,[3d] *n*-butyl-,[4b–d] isobutyl-,[3b] *sec*-butyl-,[3b] *tert*-butyl,[3b] 4-dibenzothienyl-,[4e] and 2,4,6-triphenylphenyllithium,[1] generally in less than 50% yield. The metalating abilities of *n*-butyl-, phenyl-, 1-naphthyl-, and *p*-anisyllithium in diethyl ether have been compared.[5] A recent

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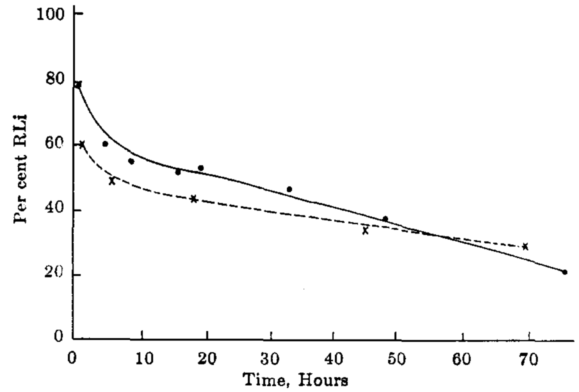
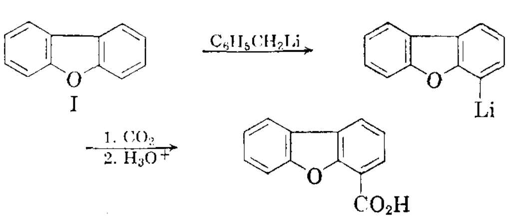


Fig. 1.—Stability of benzyllithium in tetrahydrofuran
—— 0°
---- Room temperature

study[6] in which I was metalated under comparable conditions by methyl-, *n*-butyl-, and phenyllithium in diethyl ether, a mixture of diethyl ether and tetrahydrofuran, and in tetrahydrofuran alone, revealed that tetrahydrofuran is the most satisfactory solvent, and *n*-butyllithium is the best metalating agent of those examined. Benzyllithium can now be placed in this series. The stabilities of some alkyllithium compounds measured as the rate of disappearance in solution have been determined by analyzing by the double-titration method.[7,8] A related procedure has now been used for measuring the stability of benzyllithiums in tetrahydrofuran and tetrahydropyran (Figures 1, 2, and 3). The following stabilities at room temperature (−%/hr.) and metalating abilities (%) were found: benzyllithium, −0.44%/hr.; 27%: methyllithium,[6,7b] −1.41%/hr.; 29.2%: α-methylbenzyllithium, −2.14%/hr.; 38%: phenyllithium,[6,7b] −3.3%/hr.; 55.3%. It will be noted that there is an apparent increase in



metalating ability with decreasing stability. This information considered in conjunction with other studies[9,10] indicates that the decomposition might possibly involve a preliminary metalation of the solvent, as well as cleavage.

In a reaction of benzyllithium with benzophenone, the blue color of the ketyl was observed,[11] but no benzopinacol has as yet been found in either of two experiments.

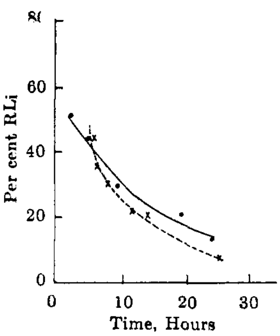


Fig. 2.—Stability of benzyllithium in tetrahydropyran
—— 0°
---- Room temperature

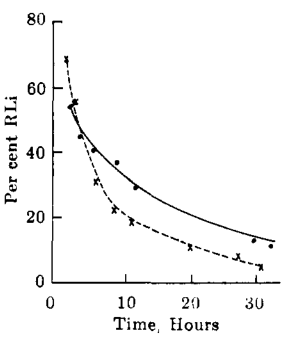


Fig. 3 —Stability of α-methylbenzyllithium in tetrahydrofuran
—— 0°
---- Room temperature

The first reported reactions between organolithium reagents and aza-aromatic heterocycles were by Ziegler and Zeiser,[12] in which they found that an organolithium compound reacts with pyridine, quinoline, and isoquinoline to give 1,2-dihydro intermediates which, upon oxidation, form derivatives substituted in the position adjacent to the nitrogen atom. When pyridine was treated with benzylmagnesium chloride,[13] the primary product was 4-benzylpyridine, although some 2-benzylpyridine was isolated.[13b] Benzyllithium was found to be more reactive and to exhibit apparently greater selectivity in its reaction with pyridine so that 4-benzylpyridine is the only product (17.5%) so far isolated.

Experimental

Stability Determinations. General Procedure.—The organolithium reagents used in these experiments were prepared by a published procedure.[14] In measuring the time for the decomposition, the zero point was chosen as the time at which the mixing of reactants was complete. When the titer[8] for the organolithium reagent ceased to increase, the mixture was filtered under nitrogen into an addition funnel and stored under nitrogen throughout the determination. Aliquots were taken at varying intervals for analysis by the double-titration method[8] until the decomposition curve was established (Fig. 1, 2, and 3).

Metalations of Dibenzofuran. General Procedure.—In a typical reaction, 84 ml. of a 0.12 *N* solution of benzyllithium prepared from dibenzyl ether in tetrahydrofuran (THF) was added dropwise at 0° to a stirred solution of 1.51 g. (0.0089 mole) of dibenzofuran in THF to give a total volume of 99

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[14] H. Gilman and H. A. McNinch, *J. Org. Chem.*, **26**, 3723 (1961); H. Gilman, H. A. McNinch, and D. Wittenberg, *J. Org. Chem.*, **23**, 2044 (1958).

ml. The solution was allowed to warm to room temperature and was stirred for 5 hr. before it was carbonated. The carbonation mixture was hydrolyzed, and the layers were separated. The organic layer was washed with 5% aqueous sodium hydroxide. The combined aqueous solution was boiled to remove any dissolved organic solvent, acidified with concd. hydrochloric acid, and filtered while hot to give 0.74 g. (39.1%) of dibenzofuran-4-carboxylic acid, m.p. 195–205°. Recrystallization from ethanol-water gave 0.51 g. (27%) of product, m.p. 203–207° (mixed melting point).

The results of this and other metalation experiments are listed in Table I.

Table I

Metalations of Dibenzofuran

RLi	Solvent	Time, Hr.	Acid, %[a] Crude	Acid, %[a] Pure
$PhCH_2Li$[b]	THF	5	39.1	27.0
			31.8	24.0
$PhCH_2Li$[b]	THF	46	41.3	34.7
$PhCH(CH_3)Li$[c]	THF	5	46.0	38.8
$PhCH_2Li$[b]	THP	5	10.9	8.0
			6.0	...

[a] The acid isolated was dibenzofuran-4-carboxylic acid. [b] The benzyllithium was prepared from dibenzyl ether. See ref. 14. [c] The α-methylbenzyllithium was prepared from bis(α-methylbenzyl) ether. See ref. 14.

Reaction of Benzyllithium with Benzophenone.—To 95 ml. of a 0.156 *N* solution of benzyllithium prepared from dibenzyl ether in THF there was added dropwise, at the temperature of an ice bath, a solution of 2.95 g. (0.016 mole) of benzophenone in 40 ml. of diethyl ether. The resulting blue solution gave a negative Color Test I[15] within 10 min. after the addition was complete. The solution was hydrolyzed and then extracted with diethyl ether. The combined organic solution was dried and evaporated to leave a yellow residue which was distilled under reduced pressure to give 0.89 g. of benzyl alcohol, b.p. 60–62.5° at 2.5 mm., $n^{20}D$ 1.5442. The distillation residue was rinsed from the flask with boiling petroleum ether (b.p. 60–70°) and filtered while hot to liberate 0.88 g. (25%) of 1,1,2-triphenylethanol, m.p. 84–89.5°. Recrystallization from benzene-petroleum ether gave 0.80 g. (22.9%) of pure product, m.p. 91–92° (mixed melting point).

The filtrate from the above separation was poured onto a column of dry alumina. Elution with petroleum ether (b.p. 60–70°) afforded 0.33 g. (26.6%) of bibenzyl, m.p. 50–54° (mixed melting point). Elution with benzene led to the isolation of an additional 0.75 g. (21.5%) of 1,1,2-triphenylethanol, m.p. 90–91° (mixed melting point) giving a total of 1.63 g. (46.5%) of this product. Continued washing of the alumina column with benzene gave a cloudy oil which was subsequently distilled under reduced pressure to yield 0.31 g. (10.5%) of recovered benzophenone, m.p. 47–50° (mixed melting point).

In a second experiment using benzyllithium prepared from benzyl methyl ether there was isolated 23.1% of bibenzyl, mixed m.p. 52–54°, and 54.2% of 1,1,2-triphenylethanol, m.p. 91–93° (mixed melting point).

Reaction of Benzyllithium with Pyridine. To 220 ml. of a 0.15 *N* solution of benzyllithium prepared from dibenzyl ether in tetrahydrofuran (THF) there was added rapidly with vigorous stirring 3.30 g. (0.041 mole, 10% excess) of dry pyridine in 25 ml. of THF at room temperature. Color Test I was negative after 1 hr. although the solution remained reddish brown. After stirring overnight under reflux, the solution was poured slowly upon crushed ice. The separated water layer was extracted with diethyl ether, and the combined organic solvent was dried and distilled under reduced pressure giving an almost colorless liquid boiling over the range 100–145° at 15 mm. A second distillation of the product afforded 1.11 g. (17.5%) of 4-benzylpyridine, boiling over the range 146–153°/14 mm.

The picrate of the 4-benzylpyridine melted at 142–143.5° after crystallization from ethanol. A mixture melting point with the picrate prepared from an authentic sample of 4-benzylpyridine (K and K Laboratories, Inc., Lot No. 6696) also was 142–143.5° A mixture melting point with the picrate from an authentic sample of 2-benzylpyridine (K and K Laboratories, Inc., Lot No. 6695) was depressed to 119–125°. This is almost identical with the melting point range observed for a mixture of the picrates prepared from the authentic samples of 2- and 4-benzylpyridine.

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Synthesis of 1,2,6-Tris(2-cyanoethoxy)hexane

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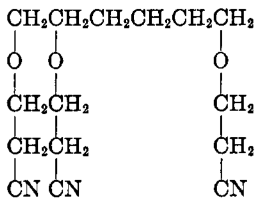
In connection with the use of extremely sensitive ionization detectors in gas chromotography, a polar liquid phase having a very low vapor pressure was required. To fill this need 1,2,6-tris(2-cyanoethoxy)hexane (I) was prepared from acrylonitrile and 1,2,6-hexanetriol by the method of Bruson and Riener.[1,2]

Acrylonitrile condenses readily with the labile hydrogen atoms of the polyalcohol with the formation of a molecule containing three very polar cyanoethyl groups as shown in I.



$$\begin{array}{lll} CH_2 & CH_2CH_2CH_2CH_2 & CH_2 \\ | & | & | \\ O & O & O \\ | & | & | \\ CH_2 & CH_2 & CH_2 \\ | & | & | \\ CH_2 & CH_2 & CH_2 \\ | & | & | \\ CN & CN & CN \end{array}$$

I

The compound is easily purified by molecular distillation, provided the alkaline condensing agent is first destroyed by acidification in order to prevent the β-alkoxynitrile to the corresponding β-alkoxypropionic acid.[3]

Experimental

Preparation of 1,2,6-Tris(2-cyanoethoxy)hexane (I).—Three moles (159.2 g.) of acrylonitrile was gradually added to a mixture of 1 mole (134.2 g.) of 1,2,6-hexanetriol and 9.4 g. (7% by weight) of 40% aqueous potassium hydroxide solution. The mixture was stirred and maintained at a temperature of 15–20° during the addition of the acrylonitrile. Subsequently, the mixture was stirred overnight while being allowed to warm to room temperature. After this time, the mixture was diluted with 200 ml. of distilled water and made acid to litmus with hydrochloric acid. The

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