boxylation, in thioether cleavage, and in other enzymatic reactions. Crystalline sodium[1,2] and acridine[3] salts have been reported. We should like to describe here the preparation of a crystalline monoprocaine salt of the coenzyme.

Pyridoxamine dihydrochloride was phosphorylated with a mixture of phosphoric acid and phosphorus pentoxide,[4] and the product was isolated in crystalline form[5] by means of ion-exchange chromatography on Amberlite resin IRC-50. The pyridoxamine phosphate was oxidized to pyridoxal phosphate by manganese dioxide in aqueous solution at *p*H 6. The coenzyme was separated from inorganic compounds and was obtained as a bright yellow solid[2] by drying its aqueous solution in the frozen state.

The procaine salt was prepared by dissolving pyridoxal phosphate in water and adding to the solution an ethanolic solution of one equivalent of procaine. The procaine salt of pyridoxal phosphate crystallized in the form of orange needles.

Bioassay of the crystalline monoprocaine salt of pyridoxal phosphate by Dr. W. W. Umbreit of the Merck Institute for Therapeutic Research using a tyrosine-decarboxylase system indicated that the theoretical amount of coenzyme was present.

The procaine salt of pyridoxal phosphate is more stable than the calcium salt. The calcium salt, kept in a desiccator in the dark for 4$^1/_2$ years, lost 60% of its codecarboxylase activity; the procaine salt, stored under similar conditions for 1$^1/_2$ years, retained full codecarboxylase activity.

EXPERIMENTAL

Pyridoxal phosphate. One g. of pyridoxamine phosphate was dissolved in 84 ml. of 0.1*N* sulfuric acid. Manganese dioxide (0.4 g.) was added, and the mixture was stirred and heated at 65–75° for 1 hr. The reaction mixture was cooled and filtered. The filtrate was passed through a column of Amberlite resin IR-120 (H^+ cycle), and the column was washed with water. The eluate was treated with enough barium hydroxide to neutralize the sulfuric acid, and the precipitate of barium sulfate was removed. The filtrate was concentrated to about 100 ml. at reduced pressure and at a temperature below 40°. The concentrate was filtered through Super-Cel and was dried in the frozen state, giving 0.75 g. of pyridoxal phosphate.

Pyridoxal phosphate procaine salt. One hundred mg. of pyridoxal phosphate was dissolved in 3 ml. of water. To this solution was added 96 mg. (1 equivalent) of procaine, dissolved in 3 ml. of ethanol. The reaction mixture was chilled for several days in the refrigerator, and 120 mg. (60%) of the procaine salt of pyridoxal phosphate separated. Two recrystallizations from 50% water-ethanol (85% recovery) provided a sample of m.p. 150° (dec.), $\lambda_{max}^{0.1N\ NaOH}$ 275 mμ (ϵ16,000) and 390 mμ (ϵ6800). The sample was dried at 25°/0.1 mm. for analysis.

Anal. Calcd. for $C_{21}H_{30}N_3O_8P$: C, 52.17; H, 6.26, N, 8.69; P, 6.41. Found: C, 51.72; H, 6.32; N, 8.81; P, 6.24.

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Direct Preparation of Aryllithium Compounds from Aryl Fluorides

HENRY GILMAN AND THEODORE S. SODDY

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The investigation of Wittig and coworkers, which was concerned with the preparation of organolithium derivatives from aryl fluorides, was confined to the metalation of fluoroaromatics with phenyllithium.[1–4] More recently, some success in the preparation of fluoroaryllithium derivatives from the halogen-metal interconversion reaction has been reported from this laboratory.[5] The attempts, however, to prepare the aryllithium compound directly from an aryl fluoride and lithium met with some success. By refluxing lithium ribbon and fluorobenzene in diethyl ether for 24 hours, 0.7% of benzoic acid was obtained on carbonation.[6] Benzoic acid was obtained in 0.5% yield when fluorobenzene and lithium dispersion were refluxed in diethyl ether for 5 hours and then carbonated.[6]

The first attempt to prepare aryllithium compounds from aryl fluorides and lithium in tetrahydrofuran under reflux conditions was unsuccessful.[6] Recently, it was reported that benzoic acid was obtained in a yield of 54% from chlorobenzene and lithium in tetrahydrofuran on carbonation.[7] The preparation of α-naphthyllithium from α-fluoronaphthalene and lithium wire in tetrahydrofuran illustrated the importance of solvent and temperature control in these reactions. On carbonation of α-naphthyllithium, 23% of crude α-naphthoic acid was obtained. Although the initiation of this reaction did not require a catalyst, the reaction which involved fluorobenzene and *p*-fluorotoluene would not commence until their respective bromo analogs were added. The yields of phenyl- and *p*-tolyllith-

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[1] G. Wittig, G. Pieper, and G. Fuhrmann, *Ber.*, **73**, 1193 (1940).

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ium, which were based on the crude acids that were obtained on carbonation, averaged 50%, and one preparation of *p*-tolyllithium was 80%. In this particular run the higher yield may have been due to a better initiation of the reaction.

Since other experiments were run which gave little or no acid, the authors are led to believe that the conditions which are presented in the experimental should be followed carefully in order to insure successful preparation of the aryllithium compounds from aryl fluorides.

EXPERIMENTAL[8]

α-Fluoronaphthalene and lithium in tetrahydrofuran. Method A. Into a 500-ml., 3-necked, round-bottomed flask were placed 100 ml. of anhydrous tetrahydrofuran[9] and 0.22 g.-atom of lithium wire. This suspension was cooled by means of an ice bath to 2°, and 14.5 g. (0.1 mole) of α-fluoronaphthalene in 50 ml. of tetrahydrofuran was added dropwise. After the addition of 10 ml. no reaction occurred. A few drops of bromobenzene were added as a catalyst. When the reaction still failed to begin, the reaction mixture was warmed to room temperature, 3 more drops of bromobenzene and the remainder of the α-fluoronaphthalene were added, but no indication of a reaction was discernible. The reaction mixture was warmed to 45°. The color turned yellow, green, and then black. The lithium wire became bright, and the reaction flask had to be cooled with an ice bath to prevent the reaction from becoming too violent. When the vigorous reaction had ceased, the reaction mixture was carbonated by pouring it jetwise onto a Dry-Ice–ether slurry. The basic extract on acidification yielded no acid. The neutral layer was concentrated, and the residue was sublimed under reduced pressure. Naphthalene was obtained in a yield of 1.5 g. (10%). A mixture melting point with an authentic speciman was undepressed.

Method B. Into a 500-ml. flask were placed 50 ml. of tetrahydrofuran, 0.22 g.-atom of lithium wire and 4 g. of α-fluoronaphthalene. After 5 min. the color became light green. The temperature of the reaction mixture rose from 24° to 28° over a period of 10 min. The color became darker green and a small amount of black particles separated. The reaction mixture was cooled to −10° as the remaining 10 ml. of α-fluoronaphthalene, which had been diluted with 10 ml. of tetrahydrofuran, were added. The color became black, and the lithium wire coated. After the addition was completed, the reaction mixture was stirred for about 25 min. at the same temperature and then carbonated. The basic extract on acidification yielded 4 g. (23%) of crude α-naphthoic acid which melted between 120–140°. The pure acid on recrystallization from an ethanol-water pair melted at 158–159°. (lit. value 159–160°). The yield was 1 g. (6%).

Fluorobenzene and lithium in tetrahydrofuran. Method A. Into a flask, which contained 50 ml. of tetrahydrofuran and 0.22 g.-atom of lithium wire at 24°, was placed 4 g. of fluorobenzene. A few drops of bromobenzene were added as a catalyst, and after being stirred for 15 min., a noticeable increase was observed in the temperature of the reaction mixture. When the temperature had risen to 28°, a Dry-Ice–acetone bath was employed to lower the temperature to −10°. The color of the reaction mixture became red as the remaining 6 g. (6 ml.) of fluorobenzene was added dropwise over a 5-min. period. The temperature was kept between 0 and −10°. When the reaction was completed, the reaction mixture was so viscous that 50 ml. of tetrahydrofuran was added to insure sufficient fluidity for carbonation purposes. The carbonation was carried out in the usual manner. On acidification of the basic extract, the crude benzoic acid was obtained in a yield of 6 g. (50%). The melting point was 115–117°. The pure acid on crystallization from water melted at 119–120°, and the yield was 4 g. (33.3%). A mixed melting point with an authentic sample of benzoic acid was undepressed.

Method B. The reaction was repeated again under the same conditions as that described above except that, after the reaction was initiated, the remaining 6 g. of fluorobenzene was diluted to twice its volume with the solvent, prior to addition. The yield of crude acid was only 29%.

p-Fluorotoluene and lithium in tetrahydrofuran. This reaction was run in the same manner as described in Method A for fluorobenzene. The yield of crude acid was 10.8 g. (80%) and melted between 171–174°. The pure acid melted at 176–177°, and the yield was 9.1 g. (70%). A triple melting point with an authentic sample of *p*-toluic acid was undepressed. This reaction was repeated under the same conditions, but the yield in this case was only 50%. In another run, the conditions that were used were identical with those employed in Method B for fluorobenzene. The yield of crude acid was 50%.

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Extractive Components from Incense Cedar Heartwood. V. (*Libocedrus decurrens* Torrey.) Synthesis of Libocedrol

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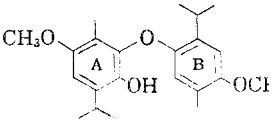
In determining the structure of libocedrol,[1] 2-hydroxy-4′,5-dimethoxy-5′,6-dimethyl-2′,3-di-*iso*-propyldiphenyl ether (I), the question of which one of the two hydroxy groups was methylated was resolved by assuming that libocedrol was formed by oxidative coupling of two parent phenolic units. Since this takes place *ortho* or *para* to hydroxyl, the libocedrol molecule was held to be composed of two *p*-methoxythymol units, *i.e.*, the 2- hydroxy group was assumed to be methylated. It was felt desirable to substantiate the above deduction by synthesis.



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(8) All melting points are uncorrected, and all reactions were carried out in an atmosphere of dry, oxygen-free nitrogen.

(9) The tetrahydrofuran was dried and purified by first shaking with sodium hydroxide pellets, refluxing over sodium metal for several hours, and finally distilling, immediately before use, from lithium aluminum hydride.

(1) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, 20, 788(1955).