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

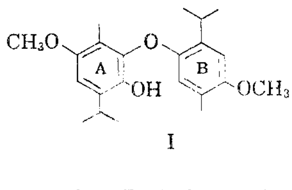
[9] The tetrahydrofuran was dried and purified by first shaking with sodium hydroxide pellets, refluxing over sodium metal for several hours, and finally distilling, immediately before use, from lithium aluminum hydride.

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

EUGENE ZAVARIN AND ARTHUR B. ANDERSON

Received February 22, 1957

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.



I

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It has long been known that alkaline ferricyanide solutions bring about the oxidation of phenolic compounds.[2,3] When *p*-methoxythymol was submitted to the ferricyanide reaction, a 49% yield of libocedrol was obtained with 20% recovery of the starting material. The identity of the synthetic material with the naturally occurring compound was established by examination of the infrared absorption spectra and by the mixed melting points of the compounds themselves as well as their *p*-methoxythymol addition complexes, *p*-nitrobenzoates, and benzoates.

It has been stated frequently that oxidative coupling of phenolic substances plays an important role in biosynthesis. Thus, it has been established that several lignans can be obtained by ferric chloride,[4-6] ammonium persulfate,[6] or enzymatic coupling[7,8] of the parent phenolic units, and it has been suggested that the lignans may be formed in a similar manner in wood.[9-11] It also has been demonstrated that the same reaction is very likely responsible for the formation of lignin in plants.[12] The formation of thyroxine[13] and of dehydrodigallic acid[14] was ascribed to similar biosynthetic paths.

Cousin and Herissey, working with mushroom dehydrogenase, established that carvacrol and thymol are able to undergo oxidation under these conditions. Dehydrodithymol was isolated from the reaction mixture in the second case.[15,16] However, so far as we are aware, no coupling product of phenolic compounds with *p*-cymene carbon skeleton has been isolated from a natural source. The structure of libocedrol suggests it is the first member of a new group of naturally occurring compounds that, as far as their biosynthesis is concerned, can be regarded as the products of the oxidative coupling of the *p*-cymene type phenols in the same way that lignans are regarded as derived from *n*-propylbenzene-type phenols. The occurrence of the mixed-type compounds represents another probability.

EXPERIMENTAL[17]

p-Methoxythymol.[18] Hydrothymoquinone (96.0 g., m.p. 142–143°C.) was added to a solution of 3.5 g. of sodium hydrosulfite in 400 ml. of 10% sodium hydroxide in a separatory funnel filled with nitrogen and equipped with a stirrer. To this mixture was added 90 g. of commercial dimethyl sulfate in 10 portions. The formation of the dimethylation product was minimized by extracting the monomethylated hydrothymoquinone from the reaction mixture. Thus, after addition of each portion, the mixture was stirred for 5 min., then 100 ml. of chloroform was added, stirred, and the organic phase removed. Hydrothymoquinone itself is not extractable under these conditions. After all of the dimethyl sulfate was added, the aqueous portion was acidified and extracted with 100 ml. of chloroform. The extracts were filtered from the unreacted hydrothymoquinone that separated at this point. The latter weighed 5 g. and melted at 144–145° C. All of the chloroform extracts were combined, dried over sodium sulfate, and filtered. The solvent was removed by evaporation. The residue was dissolved in 300 ml. of petroleum ether and extracted 6 times with 100 ml. portions of 10% sodium hydroxide. The organic phase was dried, the solvent removed by evaporation, and the residue distilled. The main fraction was collected between 70 and 90° C. at 0.03 mm. It weighed 11.1 g., n_D^{24} 1.5119, and was composed mainly of dimethylhydrothymoquinone.[19]

The sodium hydroxide extract was acidified and extracted with ethyl ether in several portions. The ether extract was dried, the solvent evaporated, and the residue crystallized from 400 ml. of petroleum ether at −5° C. to give 26.4 g. of *p*-methoxycarvacrol, m.p. 63–64° C. The filtrate was evaporated to dryness and the residue was benzoylated in the usual manner. Crystallization of the benzoate mixture from 250 ml. of methanol at −5° C. gave 37.4 g. of *p*-methoxythymol benzoate, m.p. 85–86° C. The filtrate was hydrolyzed by adding 7.0 g. of sodium hydroxide and refluxing for 1 hr. on a steam bath. The resulting mixture was cooled and neutralized with gaseous CO_2. The methanol was evaporated, the residue was dissolved in 150 ml. of water, and extracted with petroleum ether in several portions. The petroleum ether extract was dried over sodium sulfate, filtered, and upon evaporation of the solvent, the residue was crystallized from 125 ml. of petroleum ether at −5° C. to give an additional 9.5 g. of *p*-methoxycarvacrol, m.p. 65–66° C. Repetition of the benzoylation procedure gave an additional crop of 8.3 g. of *p*-methoxythymol benzoate, m.p. 84–85° C. Residue from benzoylation, weighed after removal of the solvent, was 19.0 g.; further separation was not attempted. Thus, there were obtained: 5 g. of unreacted hydrothymoquinone benzoate (5%), 35.9 g. *p*-methoxycarvacrol (34.5%), 45.7 g. *p*-methoxythymol benzoate (28%), 11.1 g. of dimethylhydrothymoquinone (10%), and 19.0 g. of unseparated monobenzoates (11.5%). To obtain *p*-methoxythymol, its benzoate was hydrolyzed with alcoholic alkali as described.[18]

Libocedrol. p-Methoxythymol (2.107 g., n_D^{24} 1.5228) was dissolved in 50 ml. of 8% sodium hydroxide solution. To the resulting liquid was added 50 ml. of carbon tetrachloride and the mixture was vigorously stirred. A solution of 5.0 g. of potassium ferricyanide in 100 ml. of water was then added dropwise to the point at which the aqueous phase assumed a yellowish color and no white emulsion formed around the drops of ferricyanide solution. The addition took about 1 hr. at the rate of 20 drops per min. The mixture was then trans-

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ferred into a separatory funnel, acidified with hydrochloric acid, and shaken. The slightly yellow organic phase was separated, the aqueous solution was washed with 60 ml. of chloroform, and the chloroform was combined with the carbon tetrachloride solution. The resulting liquid was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was crystallized from petroleum ether at −5° C. to give 1.273 g. of white crystals, m.p. 88–89° C. Further crystallization raised the melting point to 90–91° C. The melting point was undepressed upon admixture with libocedrol *p*-methoxythymol adduct. The material was separated using the previously described procedure[1] into libocedrol, m.p. 86–87° C., and *p*-methoxythymol characterized as its *p*-nitrobenzoate, m.p. 126–127° C.; both melting points were undepressed on admixture with authentic samples.

The filtrate was diluted to 30 ml. with petroleum ether and extracted with 150 ml. of 5% sodium hydroxide in 3 portions. The petroleum ether solution was dried and evaporated to dryness. The residue was heated on a steam bath with 1.0 g. of *p*-nitrobenzoyl chloride in 5 ml. of pyridine, cooled, and treated with 25 ml. of 10% bicarbonate solution and 50 ml. of ethyl ether. The ethyl ether solution was washed with 50 ml. of 10% sodium carbonate and 50 ml. of 10% hydrochloric acid, dried, and evaporated to dryness. The residue was crystallized from methanol to give 244 mg. of libocedrol *p*-nitrobenzoate, m.p. 165–170° C. (8%). Further crystallization from isooctane followed by crystallization from methanol raised the melting point to 174–175° C., undepressed on admixture with an authentic sample.

The sodium hydroxide extracts were combined, acidified with hydrochloric acid, and extracted with ethyl acetate. The extract was dried with anhydrous sodium sulfate, filtered, evaporated to dryness, and *p*-nitrobenzoylated in the usual manner to give a very small amount of material of indefinite melting point which was not further investigated.

Thus, the reaction gave 1.020 g. (49%) of libocedrol and 0.425 g. (20%) of the original material.

Comparison of the infrared spectra of the synthetic libocedrol and the naturally occurring material revealed that they were identical. Also the benzoylation of the synthetic libocedrol[11] gave a benzoate, m.p. 137–138° C., which did not depress the melting point of the naturally occurring libocedrol benzoate.

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Bromination Rates of Some Norcamphor Derivatives[1]

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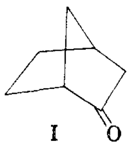
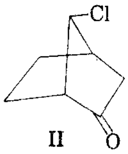
In continuation of earlier work on the effect of structure on reactivity in the norbornyl system,[3] a study has been made of the sodium acetate-catalyzed rates of bromination of norcamphor (I), *syn*- and *anti*-7-chloronorcamphor (II and III), *exo*-3-bromonorcamphor (IV), *d*-camphor (V) and *endo*-3-bromo-*d*-camphor (VI).

Ketones I, II, and III were prepared from the corresponding *exo*-norborneols by chromic acid oxidation, a method found to be superior to nitric acid oxidation.[4] I–III were purified by regeneration from their pure semicarbazones by steam distillation from oxalic acid solution. *d*-Camphor (V) was brominated under acid-catalyzed conditions[5] to give VI, whose structure has been unequivocally established by an x-ray crystal structure determination.[6,7] *exo*-3-Bromonorcamphor (IV) was prepared by a similar method. In addition to the kinetic argument given below, the *exo*-configuration assigned to the bromine atom of IV was consistent with a comparison of its ultraviolet absorption with those of VI and its *exo*-isomer (Table I).



I



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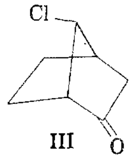

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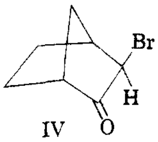

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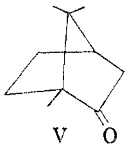

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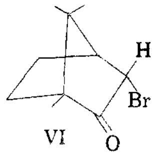

VI

TABLE I

ULTRAVIOLET SPECTRAL DATA[a]

Ketone	Solvent	λ_{max} Mμ	ϵ
d-Camphor(V)	95% EtOH	289.5[b]	32
	cyclo-C_6H_{12}	292[b]	23
exo-3-Bromo-*d*-camphor	*cyclo*-C_6H_{12}	312[b]	89
endo-3-Bromo-*d*-camphor(VI)	95% EtOH	306[b]	100
	cyclo-C_6H_{12}	307.5[b]	95.5
Norcamphor(I)	95% EtOH	287	30.9
exo-3-Bromonorcamphor(IV)	95% EtOH	312	84.4
	cyclo-C_6H_{12}	317	73.2

[a] Determined with a Cary Model 11M recording spectrophotometer using 1-cm. quartz cells. [b] R. C. Cookson, *J. Chem. Soc.*, **1954**, 282 and references cited therein.

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(1) Taken in part from the Ph.D. thesis of William G. Woods, California Institute of Technology, 1957.

(2) National Science Foundation Predoctoral Fellow, 1955–56. Present address: General Electric Research Laboratory, Schenectady, N. Y.

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