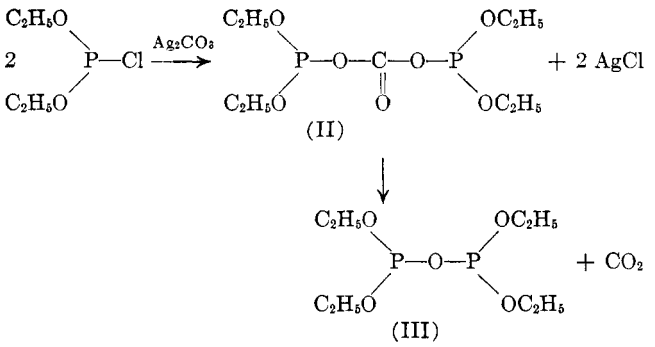
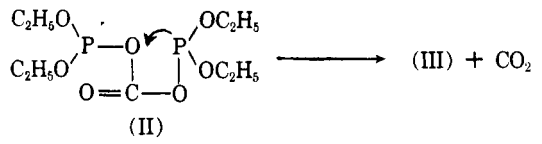
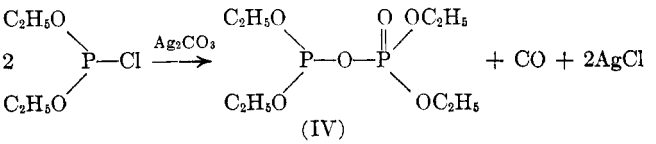


The reaction appears to proceed via the formation of a phosphorous carbonic anhydride (II). Whereas intermediate I is sufficiently stable to isolate and requires heating to effect decomposition, intermediate II is very unstable, as evidenced by the immediate evolution of gas (mainly CO_2) on mixing the reagents. This instability is probably a consequence of the ease with which a four centre cyclic mechanism may occur, such as is commonly found[2] in organophosphorus compounds.



This simple preparation (from two commercially available chemicals) appears to provide one of the easiest syntheses of the tetralkyl pyrophosphites, which are of importance in peptide synthesis[3] and the preparation of pyrophosphates specifically positionally labeled[4] with oxygen-18. Tetra-*n*-propyl pyrophosphite was prepared in the same way in both cases a yield of over 60% being obtained. The main side product accounting for *ca.* 15% of the yield based on phosphorochloridite is tetraethyl phosphorous phosphoric anhydride (IV).



The formation of this molecule from intermediate II implies the formation of carbon monoxide which in fact forms about 10% of the evolved gases.

Experimental

Tetraethyl pyrophosphite was prepared by the slow addition of diethyl phosphorochloridite (5 g.) to a stirred suspension of silver carbonate (3.5 g.) in dry benzene. An intermediate exothermic reaction occurs with the evolution of gas. The product is then fractionally distilled without separating the solid to give: (i) tetraethyl pyrophosphite (II), b.p. 87–89° (1 mm.) [lit.[5] b.p. 82–83° (2–3 mm.)] in about 60% yield; and (ii) tetraethyl phosphorous phosphoric anhydride (IV) b.p. 110–114° (1 mm.) [lit.[5] b.p. 116–117° (2 mm.)] in about 15% yield.

The gas was shown by mass spectrometry to be a mixture of carbon dioxide (about 90%) and carbon monoxide (about 10%). The identity of tetraethyl pyrophosphite (II) and tetraethylphosphorous phosphoric anhydride (IV) was confirmed by the oxidation equivalent of the hydrolyzed products (126 and 253, respectively) and by the infrared spectra in chloroform solution, maxima being observed at 1035 cm.$^{-1}$ (P—O—Et) and 945, 985 cm.$^{-1}$ (P—O—P) for both compounds with an additional peak at 1280 cm.$^{-1}$ (P—O) for the phosphoric phosphorous anhydride. An analogous reaction occurs with di-*n*-propyl phosphorochloridite.

The reaction mixture was distilled directly without filtering in order not to lose some of the product as the stable complex known to be formed between silver chloride and esters of phosphorous anhydride.[5]

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Levopimaramide and the Hofmann Reaction

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Isocyanates have been prepared from rosin by reaction of the amide with hypohalite by the Hofmann reaction.[3,4] The product from the reaction was the isocyanate rather than the amine or urea described by Wallis, *et al.*,[5] because of its unusual resistance to hydrolysis. In previous work the resin acid moiety was modified by either hydrogenation, dehydrogenation, disproportionation or aromatization which obviated reaction of the olefinic system with hypohalite as described by other workers. For example, Uraneck, *et al.*,[6] used hypohalite to modify rosin for use as soaps for emulsion polymerizations and Lombard, *et al.*,[7] reported the reaction of hypohalite on abietic acid. It was the purpose of the present investigation to determine if isocyanates containing the reactive conjugated diene system of levopimaric acid could be prepared.

The most reactive (and least thermodynamically stable) resin acid, levopimaric acid, is extremely sensitive to acidic conditions. Rapid rearrangement to abietic acid in the presence of 0.1 *N* ethanolic hydrochloric acid has been noted.[8,9] This sensitivity to acidic conditions precluded the preparation of the free acid chloride; however, in the presence of pyridine, the acid chloride, formed with phosphorus trichloride, was stable and pure levopimaramide was prepared without difficulty. Good yields of an isocyanate mixture were obtained by reaction of potassium hypobromite with pure levopimaramide in ether solution. Deviations from the preparative procedure resulted in large amounts of apparently isomeric and nondistillable compounds.

The crude product usually contained 10–30% of nonvolatile material which was conveniently removed by

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distillation. It has been shown previously that levopimaric acid is the only component of pine oleoresin which reacts appreciably with maleic anhydride at room temperature,[10] and that the change in rotation which occurs as a result of this reaction can be used as the basis of an analysis for the levopimaryl moiety.[11] This method was used to determine the levopimaryl isocyanate content of mixtures produced by the reaction. The results on one of the best runs, indicated that about 76% of the isocyanate (distilled) was levopimaryl isocyanate. The other 24% of the material was believed to be isomeric with the levopimaryl derivative because of elemental analyses, solubility, and presence of abietyl isocyanate which was separated and identified as its methylurethane.

The identity of the levopimaryl isocyanate was further established by isolation of crystalline maleic anhydride and tetracyanoethylene adducts. When the isocyanate was treated with alcoholic hydrochloric acid in accordance with Schuller and Lawrence[9] changes in optical rotation and ultraviolet absorbancies were similar to those reported for levopimaric acid by these authors. The isocyanate moiety was identified by strong infrared absorbancy at 4.5 μ which disappeared during formation of the methylurethane.

Experimental

Levopimaramide.—To a solution of 100 g. (0.33 mole) of levopimaric acid[12] in 300 ml. of pyridine was added 24 ml. (0.28 mole) of phosphorus trichloride. The reaction mixture was stirred occasionally for 0.5 hr.; the clear upper layer was then decanted slowly from the oily precipitate into 300 ml. of concentrated ammonium hydroxide. The hydroxide was stirred during the addition. The white precipitate which formed was collected on a Büchner funnel, then dissolved in ether. The ether solution was dried with sodium sulfate and concentrated to yield 89 g. (89%) levopimaramide, m.p. 175°, in an evacuated m.p. tube, 2 mm. Recrystallization from ethanol gave m.p. 182–183°, in evacuated m.p. tube, 2 mm., $[\alpha]^{25}D$ −282° (c = 2% in ethanol). (The oily layer which separated on the addition of the phosphorus trichloride gave 7 g. of levopimaramide on treatment with ammonia.) The product was insoluble in pentane and water.

Anal. Calcd. for $C_{20}H_{31}NO$: C, 79.69; H, 10.37; N, 4.65. Found: C, 79.70; H, 10.24; N, 4.68.

Levopimaryl Isocyanate.—A solution of 7.3 ml. (0.134 mole) of bromine in 220 ml. of cold 25% potassium hydroxide was added with stirring during a period of 20 min. to a slurry of 25 g. (0.083 mole) of levopimaramide in 80 ml. of ether in a 500 ml. round bottom flask cooled by an ice bath and equipped with stirrer, thermometer and addition funnel. The temperature in the flask was not allowed to go above 15° during the addition. Stirring was continued for 10 min. after the addition was completed, then 80 ml. of pentane was added and the organic layer separated, dried with sodium sulfate and concentrated in a rotary evaporator. The light yellow mobile oil, 23.9 g., 95%, $[\alpha]^{25}D$ −200° (c = 2% in ethanol), was distilled at 65° (0.005 mm). The product, 19.9 g., 80%, $[\alpha]^{25}D$ −220° (c = 2% in ethanol), $\lambda_{max}^{ethanol}$ 272 (ϵ 54,800), was analyzed by the method of Lloyd and Hedrick[11] and contained 76% of the levopimaryl moiety. The remainder of the material is believed to be isomeric with this. A strong infrared absorbancy characteristic of an isocyanate was observed at 4.5 μ.

Anal. Calcd. for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.18; H, 9.82; N, 4.63.

When an alcoholic solution of a portion of the material was treated with hydrochloric acid in accordance with Schuller and Lawrence[9] there was a change in observed rotation and ultraviolet absorbance, $[\alpha]^{25}D$ −68.5° (c = 2% in ethanol), $\lambda_{max}^{ethanol}$ 241 mμ with shoulders at 234 and 250 mμ. Separation of the isocyanate by vapor phase chromatography using silicone SE 30 column, was not successful.

Good yields of levopimaryl isocyanate depended on keeping the temperature at 15° or below. The concentration of hypobromite required for maximum yield was 1.7 to 2.0 moles per mole of amide. Otherwise, large amounts of apparently isomeric materials were isolated as well as nondistillable compounds. Hydrocarbon solvents, as recommended by Putman, *et al.*,[4] apparently did not give effective contact between the aqueous hypohalite and the solid amide. In the presence of such a solvent, the reaction required a very long time, moderately elevated temperature, vigorous stirring, and gave a product relatively low in levopimaryl isocyanate. These difficulties were overcome by the use of ether as a solvent. Thus, at 0° the amide was dispersed in the required amount of hypohalide solution and no reaction occurred. Upon the addition of a small amount of ether, the reaction became noticeably exothermic and proceeded to completion in about 3 min.

Maleopimaryl Isocyanate.—To a solution of 5 g. of crude levopimaryl isocyanate, 67% (0.011 mole based on levopimaryl isocyanate) in 10 ml. of ether was added 1.1 g. (0.011 mole) of maleic anhydride. The solution was allowed to stand at room temperature for 16 hr. then pentane was added, the supernatant liquid was decanted and the semicrystalline residue recrystallized four times from an ether and pentane mixture, giving 1.3 g. (39%) of maleopimaryl isocyanate, m.p. 138–139.5°, $[\alpha]^{25}D$ −25° (c = 2% in ethanol).

Anal. Calcd. for $C_{24}H_{31}NO_4$: C, 72.48; H, 7.86; N, 3.55. Found: C, 72.60; H, 7.91; N, 3.64.

Tetracyanoethylene Adduct of Levopimaryl Isocyanate.—Upon mixing 3.1 g. of the levopimaryl isocyanate as above (0.0078 mole based on levopimaryl isocyanate) and 1.0 g. of tetracyanoethylene (0.0078 mole) in 100 ml. of ether, a light green precipitate formed, 3.0 g. (90%), m.p. 235–245°. Recrystallization from benzene raised the melting point to 240–255°.

Anal. Calcd. for $C_{26}H_{29}N_5O$: C, 73.04; H, 6.84; N, 16.38. Found: C, 72.93; H, 6.69; N, 16.44.

N-Levopimaryl-O-methylurethane.—The isocyanate used for preparation of the methylurethane was prepared by a somewhat different method than the above. The synthesis is as follows: levopimaramide, 3.0 g., 0.01 mole was dispersed in 25 ml. of cold 25% potassium hydroxide containing bromine (1 ml., 0.018 mole). Upon the addition of 5 ml. of ether and shaking, the reaction warmed and the solid amide disappeared within 3 min. The ether was removed, then 20 ml. of pentane was added and the upper layer separated, washed with water, dried with sodium sulfate and concentrated to give 2.8 g. of crude isocyanate, $[\alpha]^{25}D$ −173° (c = 2% in ethanol), strong infrared absorbance at 4.5 μ.

A solution of 3 g. of crude levopimaryl isocyanate above in 15 ml. of absolute methanol was allowed to stand at room temperature for 15 hr. then 50 ml. of water was added and the oil which separated was extracted into ether, the ether solution was dried and concentrated to yield 0.3 g. of crystalline N-abietyl-O-methylurethane, m.p. 105°. Recrystallization from ether raised the melting point to 127–130°, $[\alpha]^{25}D$ −95° (c = 2% in ethanol), $\lambda_{max}^{ethanol}$ 241 mμ (ϵ 21,600).

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.07; H, 10.03; N, 4.25. Found: C, 76.24; H, 10.03; N, 4.28.

Crude levopimaryl isocyanate, 1.0 g. was treated with 10 ml. of methanol and after standing various periods of time, salt water was added and the oil was dissolved in ether. The ether was dried and concentrated. Conversion to urethane was determined by measuring infrared absorbancies at 4.5 μ. A reaction period of 10 min. gave 12% conversion, 70 min. gave 95% conversion, and 150 min. gave 100% conversion to urethane.

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