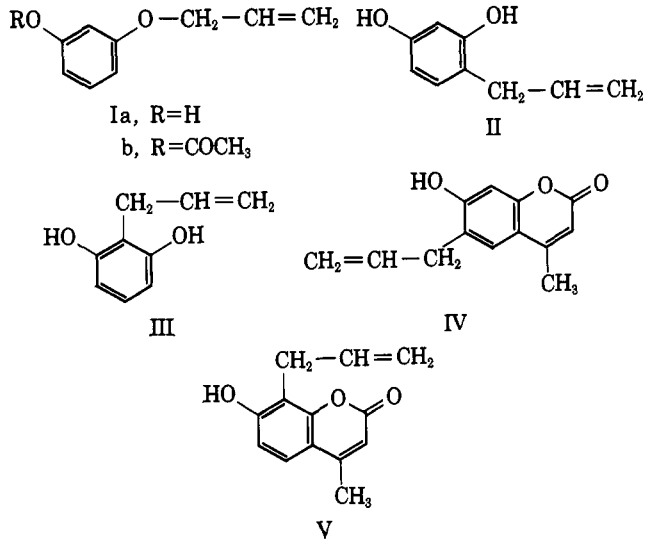
This reaction has been reinvestigated with the aid of a spinning-band fractionating column and vapor phase chromatography. Pure resorcinol monoallyl ether (Ia) was obtained by alkaline hydrolysis of 3-allyloxyphenyl acetate[2] (Ib), which is readily obtained by allylation of resorcinyl monoacetate. To avoid complications due to the exothermic nature of the reaction,[1a] the Claisen rearrangement of Ia was carried out in refluxing diethylaniline, and a red oil was obtained in 94% yield. Distillation through a spinning-band column facilitated the isolation of small crystalline samples of 4-allylresorcinol (II), m.p. 68–69°, and 2-allylresorcinol (III), m.p. 48–52°. The identity of both compounds was confirmed by condensation of each with ethyl acetoacetate to obtain 6-allyl-4-methylumbelliferone (IV) and 8-allyl-4-methylumbelliferone (V). The latter compound was shown to be identical (mixture melting point and infrared spectra) with an authentic sample.[2]



In order to estimate its percentage composition, a small portion of the crude Claisen rearrangement product was subjected to simple distillation, to remove traces of colored impurities, and analyzed by vapor phase chromatography. Estimation of the areas under the curves showed that the mixture was 57% 2-allylresorcinol (III) and 43% 4-allylresorcinol (II).

In contrast with the results of earlier workers[1], who emphasize 4-allylresorcinol as the product of Claisen rearrangement of resorcinol monoal yl ether, this study indicates that the 2-allyl isomer is also formed, and in slightly larger amounts. It should be mentioned that the 4-allyl isomer crystallizes more readily and hence is more easily isolated.

Experimental[3]

Resorcinol Monoallyl Ether (Ia).—Crude, undistilled 3-allyloxyphenyl acetate[2] (20 g., 0.104 mole) was refluxed in a stirred, 10% aqueous sodium hydroxide solution under a nitrogen atmosphere for 2 hr. The cooled solution was shaken with ether (*ca.* 150 ml.) and then poured into a stirred mixture of ice and concentrated hydrochloric acid (100 ml.). A brown oil separated and was isolated with ether. Vacuum distillation gave 9.24 g. (59.2%) of a yellow oil, b.p. 102° at 0.7 mm. Evaporation of the first ether extract led to the recovery of 4.0 g. of unreacted starting material.

Claisen Rearrangement.—A mixture of resorcinol monoallyl ether (62.89 g.) and diethylaniline (125 ml.) was refluxed for 1 hr. An ether solution of the reaction mixture was extracted with 5% aqueous sodium hydroxide and the acidified (concentrated hydrochloric acid) alkaline layer was extracted with ether. The ether layer was washed with 5% aqueous sodium bicarbonate (to remove traces of hydrochloric acid, which cause extensive decomposition during distillation), dried ($MgSO_4$), and concentrated to a red oil (59.09 g., 94%). A portion of this oil (16.77 g.) was carefully distilled through an 18-in., stainless steel, spinning-band column.[4] After a negligible forerun, a fraction (5.108 g., b.p. 88–90.5° at 0.15 mm.) was obtained and it crystallized after standing for several days. Repeated crystallization of a portion of this fraction from a mixture of benzene and petroleum ether (b.p. 30–60°) gave 2-allylresorcinol, m.p. 48–52° (lit.[1b] m.p. 52°). A later fraction (5.135 g., b.p. 99–100° at 0.15 mm.) also crystallized, and a portion of it was recrystallized twice from a mixture of benzene and petroleum ether (b.p. 30–60°) to give 4-allylresorcinol, m.p. 68–69° (lit.[1b] m.p. 67°).

8-Allyl-4-methylumbelliferone (IV).—Dry hydrogen chloride gas was passed through a solution of 2-allylresorcinol (50 mg.) and ethyl acetoacetate (0.04 ml.) in glacial acetic acid (*ca.* 3 ml.) for 45 min. After standing in a closed container for 14 hr., the reaction mixture was poured into water (*ca.* 30 ml.) and the precipitate was recrystallized once from 95% ethanol and twice from benzene to give colorless prisms, m.p. 196–197°. A mixture of this compound and a sample of 8-allyl-4-methylumbelliferone (m.p. 200–201°)[2] had m.p. 197–198°. The infrared spectra of the two samples were identical.

6-Allyl-4-methylumbelliferone (V).—Dry hydrogen chloride gas was passed through a solution of 4-allylresorcinol (0.20 g.) and ethyl acetoacetate (0.17 ml.) in glacial acetic acid (*ca.* 8 ml.) for 45 min. After standing in a closed container for 12 hr., the reaction mixture was poured into water (*ca.* 80 ml.) and the cream-colored precipitate was recrystallized from a mixture of ethanol and water to give colorless needles (0.201 g., 69%), m.p. 174–175° (lit.[2] m.p. 175–176°).

Vapor Phase Chromatography.—The crude reaction product from the Claisen rearrangement of resorcinol monoallyl ether was purified by simple distillation at 125° at 0.4 mm. to give a colorless oil (95% recovery). A 20% solution in ethanol (2 μl.) was introduced at an injection port temperature of 245° on a 2 ft. × 0.125 in. stainless steel column of SE-30 silicone rubber suspended on firebrick as supplied with an F and M (Model 500) gas chromatograph. The column temperature was maintained at 175° and helium flowed continuously through the column at a rate of 80 ml./min. Under these conditions, pure 2-allylresorcinol was retained on the column for 2.7 min. and 4-allylresorcinol for 3.5 min. The areas under the curves were estimated by multiplying the height of a peak by its half-width.

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(4) Nester and Faust, Box 565, Newark, Del.

Preparation and Resolution of Cyclopentaneglycine[1]

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The synthesis and microbiological properties of the isoleucine analog DL-cyclopentaneglycine have

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been reported.[2] This paper describes the synthesis of this compound by a different route, which conveniently provides an intermediate which can be used in its resolution. The D and L isomers of cyclopentaneglycine are needed for use in the synthesis of peptides containing amino acid analogs.

Diethyl acetamidomalonate was allowed to react with cyclopentyl bromide in dimethylformamide to yield diethyl cyclopentylacetamidomalonate. The crude product, which proved difficult to crystallize, was refluxed with sodium carbonate and decarboxylated with acid[3] to obtain the resolvable intermediate, N-acetyl-DL-cyclopentaneglycine. Enzymatic resolution[4] with hog kidney acylase 1 (Sigma Chemical Co., St. Louis, Mo.) resulted in L-cyclopentaneglycine and N-acetyl-D-cyclopentaneglycine. The D isomer was obtained by acid hydrolysis of the N-acetyl-D-cyclopentaneglycine. N-Acetyl-L-cyclopentaneglycine was prepared by the method described by Sheehan and Bolhofer[5] and used for characterization.

Growth inhibition by cyclopentaneglycine in *E. coli* ATCC strain 9723 is apparently due to the L isomer. Complete growth inhibition occurred at a concentration of 30 μg./5 ml. with the L isomer; the D isomer had no inhibitory effect when added at a concentration of 300 μg./5 ml. Growth studies employed a salts–glucose medium in a previously described procedure.[6]

Experimental

Diethyl Cyclopentylacetamidomalonate.—In a 3-l. flask fitted with a drying tube, sodium hydride (12.5 g., 0.52 mole) was suspended in 1 l. of dimethylformamide,[8] and diethyl acetamidomalonate (108.5 g., 0.5 mole) was added in small portions; the exothermic reaction was controlled by cooling in an ice bath. After about 2 hr. the mixture was filtered through glass wool. The filtrate was added in one portion to 100 g. (0.66 mole) of dry cyclopentyl bromide (Eastman) contained in a 2-l. flask equipped with a magnetic stirring bar and drying tube. The solution was stirred at 60° for a period of 24 hr., whereupon an additional 25 g. of cyclopentyl bromide was added; stirring was then continued for 12 hr. The solvent was removed under reduced pressure at a temperature below 60°, and the residue was partitioned between water and ethyl acetate. The ethyl acetate solution was washed with three portions of a 5% solution of potassium bicarbonate and three portions of water and dried. Removal of the solvent left an oily residue which partially solidified after several days. This intermediate was used without further purification in the subsequent preparation.

N-Acetyl-DL-cyclopentaneglycine.—The total yield of diethyl cyclopentylacetamidomalonate was allowed to reflux for 36 hr. in a mixture of 900 ml. of 95% ethanol, 200 ml. of water, and 110 g. of Na_2CO_3. The solution was concentrated to a volume of about 500 ml. and adjusted to pH 3.5 with concentrated HCl while the temperature was maintained at about 50°. After decolorizing the solution with Darco G-60, the N-acetyl-DL-cyclopentaneglycine was extracted into ethyl acetate. Recrystallization of the product from hot ethanol–water resulted in a yield of 51 g. (55%), m.p. 173–175°.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.55. Found: C, 58.57; H, 8.11; N, 7.36.

L-Cyclopentaneglycine.—In 900 ml. of water were suspended 18.5 g. (0.1 mole) of N-acetyl-DL-cyclopentaneglycine, and the pH was adjusted to 7.6 with 4 *N* lithium hydroxide. The volume was increased to 1 l. with water, and hog kidney acylase 1 (100 mg.) was added. After 18 hr. of incubation at 37° hydrolysis was complete, as determined by titration of liberated amino acid.[9] The solution was carefully acidified to pH 5 and decolorized with Darco G-60 at a temperature of 50°. Removal of the solvent under reduced pressure at 40° resulted in a sirup which was taken up in a mixture 200 ml. of water and 800 ml. of ethanol. Upon cooling, L-cyclopentaneglycine crystallized. The crystals were harvested and washed successively with ethanol and ether. The filtrates were concentrated to 50 ml. and treated with 200 ml. of ethanol to obtain a second crop; total yield 5.9 g. (82%), m.p. 280–284° dec., $[\alpha]^{22}D$ +14.26° (*c* 2.0, 2 *N* HCl). The filtrate containing N-acetyl-D-cyclopentaneglycine was reserved for the following step.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.71; H, 9.14; N, 9.78. Found: C, 58.52; H, 9.06; N, 9.87.

N-Acetyl-D-cyclopentaneglycine.—The filtrate obtained after removal of L-cyclopentaneglycine was concentrated to a sirup, and the residue was dissolved in water. The pH of the solution was lowered to 2 with concentrated HCl, and the N-acetyl-D-cyclopentaneglycine was extracted into diethyl ether. The solution was taken to dryness, and the residue was recrystallized from hot ethanol–water to obtain 6.5 g. (70%) of N-acetyl-D-cyclopentaneglycine; m.p. 172–174°, $[\alpha]^{22}D$ +5.61° (*c* 2.0, 95% ethanol).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.55. Found: C, 58.17; H, 7.94; N, 7.38

D-Cyclopentaneglycine.—N-Acetyl-D-cyclopentaneglycine (1.0 g.) was hydrolyzed with 6 *N* HCl. Neutralization of the hydrochloride in ethanol with NH_4OH resulted in a yield of 0.45 g. (57%) of amino acid; m.p. 282–286° dec., $[\alpha]^{22}D$ −14.20° (*c* 2.0, 2 *N* HCl).

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.71; H, 9.14; N, 9.78. Found: C, 58.58; H, 8.99; N, 9.92

DL-Cyclopentaneglycine.—N-Acetyl-DL-cyclopentaneglycine (0.5 g.) was hydrolyzed by refluxing for 6 hr. in 10 ml. of 6 *N* HCl. The hydrochloride obtained was dissolved in ethanol and neutralized with NH_4OH. DL-Cyclopentaneglycine was recrystallized from hot ethanol–water; m.p. 284–286° dec. (lit.[1] m.p. 286–288°).

N-Acetyl-L-cyclopentaneglycine.—L-Cyclopentaneglycine (572 mg., 4.0 mmoles) was allowed to react with acetic anhydride (500 mg., 4.4 mmoles) in the presence of 8.0 mmoles of $NaHCO_3$ to obtain 425 mg. (75%) of N-acetyl-L-cyclopentaneglycine; m.p. 173–174°, $[\alpha]^{22}D$ −5.59° (*c* 2.0, 95% ethanol).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.55. Found: C, 57.80; H, 8.05; N, 7.50.

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The Synthesis of Unsymmetrical Aliphatic Phosphine Oxides *via* Diphenyl Alkylphosphonates and Grignard Reagents

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The preparation of unsymmetrical aryl-substituted phosphine oxides by reaction of diphenyl esters of phenyl-[1,2] and methylphosphonic[3] acids with Grignard reagents has been reported. The synthesis of purely aliphatic phosphine oxides of the type, $RP(O)R'_2$, *via* diphenyl alkylphosphonates has not been reported, al-

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