

Figure 1

Table I. It is clear then that the stereochemistry of Claisen rearrangement may be studied equally readily by optical methods³ or by a study of the geometric isomerism about the double bond. Utilizing the latter method we have prepared a sample of *cis*-4-phenoxy-pent-2-ene, b.p. 43–45° (0.6 mm.), n_D^{20} 1.5097 (Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.55; H, 8.58), infrared band at 718 cm^{-1} , by semihydrogenation of 4-phenoxy-pent-2-yne, b.p. 59.5–60° (0.65 mm.) n_D^{20} 1.5254 (Anal. Calcd. for $C_{11}H_{12}O$: C, 82.48; H, 7.55. Found C, 82.56; H, 7.56) over the Lindlar⁵ catalyst. A sample of *trans*-4-phenoxy-pent-2-ene, b.p. 48–48.5° (0.4 mm.), n_D^{20} 1.5101 (lit.³ n_D 1.5110), infrared band at 965 cm^{-1} , was also prepared by standard methods. Each isomer was free of the other geometric form as indicated by infrared spectroscopy.

TABLE I

Geometry		Config. Relation
Initial double bond	Final double bond	
<i>trans</i>	<i>trans</i>	Invert.
<i>trans</i>	<i>cis</i>	Reten.
<i>cis</i>	<i>trans</i>	Reten.
<i>cis</i>	<i>cis</i>	Invert.

Each ether was rearranged in a 1M solution in boiling mesitylene (b.p. 163°) and the unchanged ether as well as the rearrangement product recovered in each case. In each case the rearrangement product consisted of mainly (ca. 90%) *o*-(1-methyl-*trans*-but-2-enyl)phenol, b.p. 64–65° (0.2 mm.), n_D^{20} 1.5325. However in each case a small but significant amount of *cis* product was obtained and the amount was notably greater in the product from the *trans* ether. These results were reproduced in three separate runs, the analysis being by infrared spectroscopy. It is interesting that the *trans* ether was recovered as pure *trans* ether after partial reaction whereas the *cis* ether was slowly converted to the *trans* form. However, prolonged heating of the

(5) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

product from the rearrangement of either the *cis* or *trans* ether under the conditions of the rearrangement produced no change as indicated by infrared spectra.

These results can be consistently interpreted by assuming a cyclic transition state whose geometry resembles that of the chair form of cyclohexane (Fig. 1) and applying the principles of conformational analysis. This brings the stereochemistry of the Claisen rearrangement into accord with that of the S_Ni' process and shows that it occurs with high stereospecificity.

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New Synthesis of 4-Hydroxycoumarins¹

Sir:

The principal known methods for the synthesis of 4-hydroxycoumarins are: (a) condensation of acetyl salicyloyl chlorides with acetoacetic, cyanoacetic, or malonic ester and conversion of the resulting 3-substituted 4-hydroxycoumarins to the corresponding 4-hydroxycoumarins;² (b) cyclization of acetyl methyl salicylates in the presence of an alkali metal;³ (c) condensation of *o*-hydroxyacetophenones with diethyl carbonate in the presence of an alkali metal⁴ and (d) cyclization of diaryl malonates in the presence of anhydrous aluminum chloride at about 180°.⁵

We have evolved a new and simple process for the synthesis of 4-hydroxycoumarins in which a phenol is treated with an equimolecular proportion of a malonic acid in the presence of a mixture of 2–3 moles each of anhydrous zinc chloride and phosphorus oxychloride as the condensing agent at temperatures preferably between 60–75°. The success of this reaction is dependent upon the specific condensing action of the mixture of anhydrous zinc chloride and phosphorus oxychloride⁶ which are individually almost ineffective. Other condensing agents such as anhydrous aluminum chloride, stannic chloride, and ferric chloride and mixtures with phosphorus oxychloride are also ineffective. Lower alkyl esters of malonic acid or substituted malonic acid may also be used in the reaction, but usually

(1) V. R. Shah, J. L. Bose, and R. C. Shah (to Council of Scientific & Industrial Research, India), Indian Patent 62890, Jan. 20, 1958. Patents filed in U.S.A., U.K., Switzerland, and Germany.

(2) R. Anschütz, *Ber.*, **36**, 465 (1903).

(3) H. Pauly and K. Lockemann, *Ber.*, **48**, 28 (1915).

(4) J. Boyd, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 174 (1948).

(5) E. Ziegler and H. Junek, *Monatsh.*, **86**, 29 (1955).

(6) P. K. Grover, G. D. Shah, and R. C. Shah, *J. Chem. Soc.*, 3982 (1955).

poor yields of 4-hydroxycoumarins are then obtained.

The new method would appear to be of industrial significance for the production of 4-hydroxycoumarin which is a key intermediate for the synthesis of a number of leading anticoagulant drugs, like dicoumarol and tromexan, and also for the synthesis of modern anticoagulant rodenticides, warfarin and fumarin.

Small quantities of diaryl malonates were often isolated from the reaction product. The possibility of formation of diaryl malonates *in situ* and their further cyclization under the conditions of our method was, however, unlikely since no appreciable quantity of 4-hydroxycoumarins could be obtained when diaryl malonates such as diphenyl malonate were heated with a mixture of anhydrous zinc chloride and phosphorus oxychloride under the usual conditions of the new method.

We have condensed successfully by our method phenols such as phenol, thiophenol, *o*-, *m*-, and *p*-cresols, 2,5-xylene-1-ol, α - and β -naphthols, and resorcinol, with malonic acid to give, in most cases, good yields of the corresponding known 4-hydroxycoumarins. Thymol and *p,p'*-dihydroxydiphenyl with malonic acid yielded respectively 5-methyl-8-isopropyl-4-hydroxycoumarin, m.p. 223–224°, (*Anal.* Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.45; H, 6.19) and 4,4'-dihydroxy-6,6'-dicoumarin m.p. > 360°, difficult to combust and characterized through the diacetyl derivative, m.p. 229–230° (*Anal.* Calcd. for $C_{22}H_{14}O_8$: C, 65.03; H, 3.47. Found: C, 65.50; H, 3.77). We have also successfully condensed substituted malonic acids, such as *n*-propyl-, *n*-butyl-, *n*-hexyl-, and phenylmalonic acid with phenol to give good yields of the corresponding known 3-substituted 4-hydroxycoumarins. *n*-Octylmalonic acid with phenol yielded 3-*n*-octyl-4-hydroxycoumarin, m.p. 143–144° (*Anal.* Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.76; H, 8.21).

The following preparation of 4-hydroxycoumarin is typical: A mixture of phenol (225 g.), malonic acid (247.5 g.), anhydrous zinc chloride (979 g.), and phosphorus oxychloride (657 ml.) was heated with stirring at 60–65° for 35 hr., cooled and de-

composed with ice and water and allowed to stand. The resulting crude 4-hydroxycoumarin was collected, dissolved in 10% sodium carbonate and acidified. At about the neutral point some oily by-product separated out and was removed. Acidification of the remaining solution gave 4-hydroxycoumarin of m.p. 201–203° in 64% yield. On recrystallization from water or dilute alcohol pure 4-hydroxycoumarin of m.p. 209–210° was obtained.

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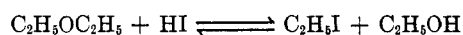
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Convenient Method for Splitting Diethyl Ether

Sir:

During the course of investigation of methods for the preparation of lanthanon iodides in which we were attempting to use diethyl ether as a solvent we discovered an unusual reaction. Anhydrous hydrogen iodide reacts immediately with diethyl ether at room temperature to produce ethyl alcohol and ethyl iodide.



A two layer system is obtained which can be separated by means of a separatory funnel. Undoubtedly hydrogen iodide reacts further with some of the ethyl alcohol to produce more ethyl iodide and some water.

Though we have not conducted a detailed investigation of this reaction it appears that it may be quite superior to the usual method of refluxing ethers with aqueous solutions of hydrogen iodide to split them. We have suggested that a student at another university study the general application of this reaction as a method for splitting ethers.

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