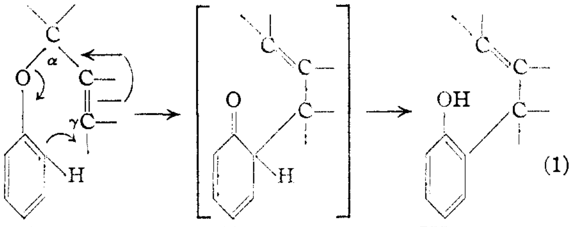
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Studies on the Mechanism of the Claisen Rearrangement. The Ortho Rearrangement of (−)α,γ-Dimethylallyl Phenyl Ether and the Para Rearrangement of (−)α,γ-Dimethylallyl 2,6-Xylyl Ether

BY ELLIOT R. ALEXANDER[1] AND RUDOLPH W. KLUIBER

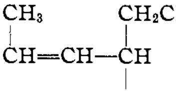
The ortho Claisen rearrangement of (−)α,γ-dimethylallyl phenyl ether (α^{25}D −0.10 ± 0.02°) gives +2-(α,γ-dimethylallyl)-phenol (α^{23}D +0.48 ± 0.02°). The para Claisen rearrangement of (−)α,γ-dimethylallyl 2,6-xylyl ether (α^{28}D −0.63 ± 0.02°) gives 4-(α,γ-dimethylallyl)-2,6-xylol (α^{29}D −0.08 ± 0.02°). The retention of optical activity in these reactions is consistent with the cyclic mechanisms which have been proposed for such rearrangements.

In the rearrangement of allyl ethers of enols and phenols to C-allyl derivatives, commonly known as the Claisen rearrangement,[2] it is generally accepted that the ortho rearrangement involves the *concerted* bonding of the γ-carbon atom to the benzene ring and the cleavage of the C_α-oxygen bond (equation 1).



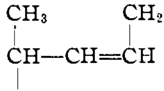
I II III

Hurd and Pollack[3] have suggested that the para rearrangement involves two cyclic steps similar to that postulated for the ortho rearrangement. It was the object of this work to learn whether the ortho and para Claisen rearrangements of suitably substituted optically active phenyl allyl ethers would lead to optically active phenols when the α-carbon atom was the only asymmetric center in the molecule. Such a result would require the simultaneous destruction of one asymmetric center and the creation of another. Although this possibility does not seem to have been investigated in the Claisen rearrangement, reactions of this kind are known. Airs, Balfe and Kenyon, for example, have shown that on standing (+)γ-methyl-α-ethylallyl alcohol (IV) rearranges to (+)α-methyl-γ-ethylallyl alcohol (V) with 73% retention of optical activity.[4]



$$\underset{\substack{|\\ \mathrm{CH_3}}}{} \mathrm{CH{=}CH{-}CH(CH_2CH_3)OH}$$

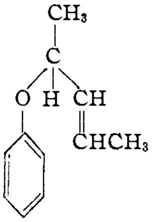
IV



$$\mathrm{CH_3{-}CH(OH){-}CH{=}CH{-}CH_2CH_3}$$

V

For the study of the ortho Claisen rearrangement α,γ-dimethylallyl phenyl ether (VI) was selected since both the resolution of α,γ-dimethylallyl alcohol[5a] and the preparation[5b] and rearrangement[5b,6] of racemic α,γ-dimethylallyl phenyl ether are known.



VI

Results and Discussion

(−)α,γ-Dimethylallyl phenyl ether (α^{25}D − 0.10°) upon heating at 200° for one hour gave 2-(α,γ-dimethylallyl)-phenol (α^{25}D + 0.48°). Thus optical activity is retained in an ortho Claisen rearrangement when the only center of asymmetry in the ether is the *alpha* carbon atom of the allyl group.

It was found that α,γ-dimethylallyl 2,6-xylyl ether was a suitable model compound for the study of the *para* rearrangement. It could be prepared in an optically active form [α^{29}D − 0.63 ± 0.02° (l = 1, no solvent)] by the reaction of (−)4-chloro-2-pentene with 2,6-xylol in acetone solution, using potassium carbonate as a condensation agent. 2,6-Dimethoxyphenol and 2-carbomethoxy-6-cresol were also investigated as possible starting points for di-ortho substituted phenyl allyl ethers, but in acetone, methanol, acetone–water, acetone–methanol or absolute ethanol, reaction with *rac*-4-chloro-2-pentene led only to ring-alkylated phenols regardless of whether the catalyst employed was potassium carbonate, sodium ethoxide, sodium hydroxide or potassium hydroxide.

Rearrangement of (−)α,γ-dimethylallyl 2,6-xylyl ether was carried out by heating the compound at 200° for one hour. There was formed in 23% yield 4-[α,γ-dimethylallyl]-2,6-xylol [α^{29}D − 0.08 ± 0.02° (l = 1, no solvent)], 2,6-xylol (23% yield) and *trans*-1,3-pentadiene.

Since the optical rotations of both phenols obtained by rearrangement of the corresponding ethers are small, there is immediately a question as to whether the observed rotations are due to a true asymmetric synthesis or to the presence of impurities carried through the scheme of isolation. To remove any traces of neutral material remaining in the rearrangement product, the phenol was extracted with aqueous sodium hydroxide. The water solution of the sodium salt was washed with petroleum ether and the substituted phenol subsequently regenerated with dilute acid. This process would remove any unrearranged ether remaining in the phenol.

---

(1) Deceased October 23, 1950.

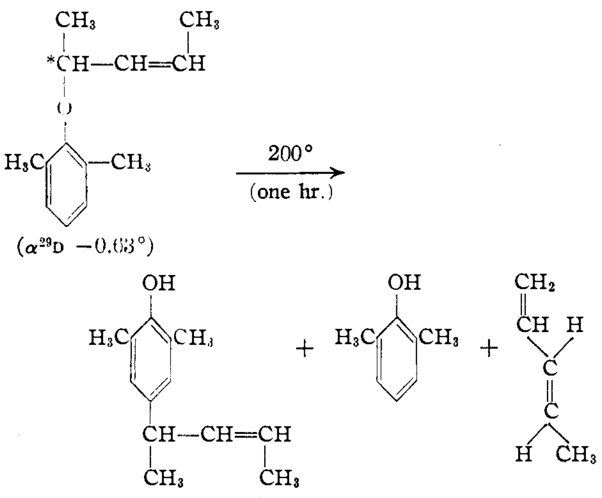
(2) For a review of the Claisen rearrangement see S. Tarbell in R. Adams' "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 1.

(3) C. D. Hurd and M. A. Pollack, *J. Org. Chem.*, **3**, 550 (1939).

(4) R. S. Airs, M. P. Balfe and J. Kenyon, *J. Chem. Soc.*, 18 (1942).

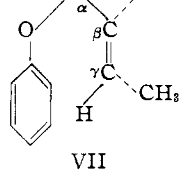
(5) (a) H. W. J. Hills, J. Kenyon and H. Phillips, *ibid.*, 582 (1936); (b) L. Claisen, *Ann.*, **442**, 225 (1925).

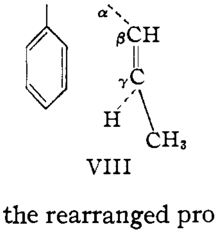
(6) C. D. Hurd and F. L. Cohen, THIS JOURNAL, **53**, 1917 (1931).



Retention of optical activity can also be explained by assuming that the starting ethers may have contained small amounts of the corresponding optically active phenols (formed by C-alkylation, during the ether synthesis). To eliminate this possibility, the phenols produced by C-alkylation were isolated and their rotations determined. In the study of the ortho Claisen rearrangement, the 2(?)-α,γ-dimethylallyl phenol isolated during the ether synthesis gave a rotation $\alpha^{25}\text{D}$ + 0.15°, whereas the corresponding phenol obtained from the rearrangement had a rotation $\alpha^{25}\text{D}$ + 0.48°. Likewise in the study of the para Claisen rearrangement, the 4-(α,γ-dimethylallyl)-2,6-xylol from the ether synthesis had $\alpha^{29}\text{D}$ + 0.19° compared with $\alpha^{29}\text{D}$ − 0.08° for the corresponding xylol obtained by rearrangement. It thus seems that both the ortho and para Claisen rearrangements proceed with at least partial retention of optical activity.

It is not yet possible to present an unequivocal mechanism to account for the above facts. However, if the ortho Claisen rearrangement is considered to proceed through an intramolecular quasi six-membered ring,[3] steric considerations could account for the retention of activity. Structures VII and VIII represent the configuration of the ether molecule at the moment of rearrangement. (The dotted bonds around the ethylenic linkage indicate that the groups project downward. Also a *trans* configuration is shown because the original crotonaldehyde used was *trans*.) If both forms were equally likely to occur, the rearranged product formed would be optically inactive. However, models indicate that the methyl group on the alpha carbon atom and the hydrogen on the beta carbon atom tend to interfere with one another. This interference varies in the two forms thus giving rise to partial or total asymmetric synthesis.[7]


VII


VIII

Similarly the retention of optical activity in the para Claisen rearrangement can be considered in accord with the intramolecular cyclic mechanism proposed by Hurd and Pollack.[3] In any case, retention of optical activity involves a concerted mechanism of some sort rather than the separate formation of ions or radicals.

Experimental[8]

***rac*-α,γ-Dimethylallyl Alcohol.**[5a]—This material was prepared by the addition of methylmagnesium iodide to crotonaldehyde. Thus, from 170 g. (7.0 moles) of clean magnesium turnings, 1 kg. (7.05 moles) of methyl iodide, 490 g. (6.9 moles) of freshly distilled crotonaldehyde and a total of 4 liters of ether was obtained 380 g. (63%) of α,γ-dimethylallyl alcohol, b.p. 116–121°, $n^{20}\text{D}$ 1.4280.

***rac*-α,γ-Dimethylallyl Acid Phthalate.**[5a]—From 148 g. (1.0 mole) of phthalic anhydride, 86 g. (1.0 mole) of *rac*,α,γ-dimethylallyl alcohol and 86 g. (1.1 moles) of pyridine was obtained 207 g. (89%) of crude *rac*-α,γ-dimethylallyl acid phthalate, m.p. 79–86°. This ester was found to be difficult to recrystallize and it was used without further purification for the preparation of the brucine salt.

(−)Brucine Salt of (+)α,γ-Dimethylallyl Acid Phthalate.[5a]—From 200 g. (0.86 mole) of the crude phthalate and 340 g. (0.88 mole) of brucine was obtained (after three recrystallizations from a 2:1 mixture of acetone and chloroform) 219 g. (83%) of the (−)brucine salt, m.p. 168.5–169.5° (reported, 169–169.5°).

(+)α,γ-Dimethylallyl Acid Phthalate.[5a]—Hydrolysis of 570 g. (0.923 mole) of the brucine salt with 1.2 liters of cold 4 *N* hydrochloric acid gave 162 g. (75%) of (+)α,γ-dimethylallyl acid phthalate,m.p. 81–84° (reported, 82–84°).

(+)α,γ-Dimethylallyl Alcohol.[5a]—From 162 g. (0.693 mole) of (+)α,γ-dimethylallyl acid phthalate was obtained on treatment with 8 *N* sodium hydroxide solution, 49.6 g. (83%) of the optically active α,γ-dimethylallyl alcohol, b.p. 67° (70 mm.), $\alpha^{25}\text{D}$ −0.07 ± 0.02° (l = 1, no solvent). Another resolution carried out in the same way gave an alcohol of $\alpha^{25}\text{D}$ +0.16 +0.02° (l = 1, no solvent).

Although these rotations seem conflicting, (+)α,γ-dimethylallyl alcohol apparently undergoes mutarotation from a positive to a negative value and its optical rotation is extremely sensitive to temperature.[5a] One batch of the alcohol prepared by Hills, Kenyon and Phillips,[5a] for example, was reported to be dextrorotatory at 20° ($\alpha^{20}\text{D}$ +0.50°) and levorotatory at 30° ($\alpha^{30}\text{D}$ −0.10°). That our two resolutions produced the same optical isomer is shown by the fact that (−)4-chloro-2-pentene was obtained from each (see below).

(−)4-Chloro-2-pentene.—The chloro compound was prepared by the method of Levene and Haller[9] which consists in the treatment of the alcohol with phosphorus trichloride in the presence of pyridine. From 25 g. (0.29 mole) of (+)α,-γ-dimethylallyl alcohol ($\alpha^{25}\text{D}$ 0.16°), 5 ml. (0.063 mole) of dry pyridine and 15 g. (0.11 mole) of phosphorus trichloride was obtained 26 g. (83%) of (−)4-chloro-2-pentene, b.p. 19–25° (20 mm.), $n^{20}\text{D}$ 1.4337, $\alpha^{25}\text{D}$ −9.88 ± 0.02° (l = 1, no solvent).

The other batch of α,γ-dimethylallyl alcohol ($\alpha^{25}\text{D}$ −0.07°) gave (−)4-chloro-2-pentene of $\alpha^{25}\text{D}$ −7.35 ± 0.02° (l = 1, no solvent). For the same compound rotations of $\alpha^{32}\text{D}$ −8.25°[6] and $\alpha^{12}\text{D}$ −12.10°[3] have been reported.

(−)α,γ-Dimethylallyl Phenyl Ether.—After considerable exploratory work the following procedure, adapted from that of Claisen,[5b] was employed for the preparation of the optically active ether.

To a cooled mixture of 16.3 g. (0.188 mole) of phenol, 26.5 g. (0.192 mole) of potassium carbonate and 30 ml. of acetone was added 27 ml. (24.4 g., 0.235 mole) of (−)4-chloro-2-pentene ($\alpha^{25}\text{D}$ −9.88°). The mixture was then heated under reflux for one hour on a steam-bath. Upon cooling, 150 ml. of water was added and the mixture was extracted with two 50-ml. portions of low boiling petroleum

---

[7] W. v. E. Doering and R. W. Young, THIS JOURNAL, **72**, 631 (1950).

[8] All melting points and boiling points are uncorrected.

[9] P. A. Levene and H. S. Haller, *J. Biol. Chem.*, **81**, 706 (1929).

ether. The petroleum ether extracts were then washed five times with 10% sodium hydroxide solution and then two times with 50-ml. portions of water. After drying over magnesium sulfate and removing the excess solvent, distillation gave fraction 1, 8.7 g., b.p. 83–86° (1 mm.), and fraction 2, b.p. 110–115° (1 mm.), n^{20}_{D} 1.5164, α^{23}_{D} $-0.22 \pm 0.02°$ ($l = 1$, no solvent). Fraction 2 appeared to be 2-(α,γ-dimethylallyl)-phenyl α,γ-dimethylallyl ether.[10]

Redistillation of fraction 1 gave 7.9 g. (25%) of α,γ-dimethylallyl phenyl ether, b.p. 72° (0.8 mm.), n^{20}_{D} 1.5110, α^{23}_{D} $-0.10 \pm 0.02°$ ($l = 1$, no solvent).

Acidification of the alkaline extracts caused the separation of an oil. After extraction with ether, drying over magnesium sulfate, and removal of the solvent, 1 g. (3%) of material showing the following physical properties was obtained: b.p. 104–106° (2 mm.), n^{20}_{D} 1.5360, α^{25}_{D} $0.15 \pm 0.02°$ ($l = 1$, no solvent). This material appeared to be 2-(or a mixture of 2 and 4)-α,γ-dimethylallylphenol (see the following reaction).

Of the preliminary experiments carried out, this procedure appeared to be the most satisfactory. At room temperature practically no reaction took place and longer periods of heating caused no appreciable improvement in yield. Attempted etherification in absolute ethanol utilizing sodium ethoxide rather than potassium carbonate resulted principally in the direct formation of a ring alkylated phenol.

Rearrangement of (−)α,γ-Dimethylallyl Phenyl Ether.[6]—In a 10-ml. distilling flask, the side arm of which extended into a test-tube cooled in an ice-bath, was placed 6.3 g. (0.039 mole) of (−)α,γ-dimethylallyl phenyl ether (α^{32}_{D} -0.10). The distilling flask was then immersed for one hour in an oil-bath maintained at 200°. Upon removal of the flask approximately 0.5 ml. of distillate was observed in the test-tube, n^{20}_{D} 1.4317. The refractive index, volatility and odor indicated it to be 1,3-pentadiene.[11]

The pyrolysis mixture was then dissolved in high boiling petroleum ether (90–110°) and extracted with two 50-ml. portions of cold 2.5 N sodium hydroxide solution. The alkaline extracts were washed once with 50 ml. of petroleum ether and then acidified with cold, dilute hydrochloric acid. A yellow oil separated which was extracted with two 50-ml. portions of high boiling petroleum ether. The extracts were then combined and dried over anhydrous magnesium sulfate. After removing the solvent, distillation from a modified Claisen flask gave 1.5 g. (24%) of 2-(α,γ-dimethylallyl)-phenol, b.p. 87° (0.3 mm.), n^{20}_{D} 1.5360, α^{25}_{D} $0.48 \pm 0.02°$ ($l = 1$, no solvent). The forerun, 2.0 g. (31%), b.p. 60–87° (0.3 mm.), n^{20}_{D} 1.5361, appeared to be principally 2-(α,γ-dimethylallyl)-phenol also.

(−)α,γ-Dimethylallyl 2,6-Xylyl Ether.—A mixture of 23.6 g. (0.194 mole) of 2,6-dimethylphenol, 26.0 g. (0.25 mole) of (−)4-chloro-2-pentene (α^{26}_{D} $-7.35°$), 27.6 g. (0.20 mole) of anhydrous potassium carbonate and 50 ml. of dry acetone was heated under reflux for ten hours. The mixture was then cooled, poured into water and extracted with low boiling petroleum ether. The petroleum ether extracts were washed three times with 10% sodium hydroxide and then with water. After drying over anhydrous magnesium sulfate and removing the solvent, distillation gave fraction 1 (4 g., b.p. 68–80°, n^{20}_{D} 1.5010), fraction 2 (3 g., b.p. 80–85°, n^{20}_{D} 1.5054), fraction 3 (2 g., b.p. 85–100°, n^{20}_{D} 1.5112) and fraction 4 (3 g., b.p. 100–110°, n^{20}_{D} 1.5252) all of which were distilled at 0.6 mm. Fractions 1 and 2 were combined and redistilled yielding 4.3 g. (12%) of (−)α,γ-dimethylallyl 2,6-xylyl ether, b.p. 70–75° (0.8 mm.), n^{20}_{D} 1.5043, α^{29}_{D} $-0.63 \pm 0.02°$ ($l = 1$, no solvent).

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.14; H, 9.81.

The alkaline extracts were acidified, extracted with petroleum ether and dried over anhydrous magnesium sulfate. After removal of the solvent, distillation gave 12 g. (52% recovery) of 2,6-dimethylphenol, b.p. 70–80° (1 mm.),[12] and 1.7 g. (4.6%) of 4-[α,γ-dimethylallyl]-2,6-xylylphenol, b.p. 100–110° (0.8 mm.), n^{20}_{D} 1.5333, α^{29}_{D} $+0.19 \pm 0.02°$ ($l = 1$, no solvent).

Rearrangement of (−)α,γ-Dimethylallyl 2,6-Xylyl Ether.—In a 10-ml. distilling flask, the side arm of which extended into a test-tube cooled in a Dry Ice–acetone-bath, was placed 4.0 g. (0.021 mole) of (−)α,γ-dimethylallyl 2,6-xylyl ether (α^{29}_{D} -0.63). The flask was then immersed in an oil-bath heated to and maintained at 200° for one hour. During this time approximately 0.5 ml. of a liquid distilled into the test-tube. The rearrangement mixture was then cooled, dissolved in low boiling petroleum ether, and extracted repeatedly with 10% sodium hydroxide solution until a small portion of the aqueous extract gave only a slight opalescence on acidification. The alkaline extracts were combined, washed once more with 50 ml. of petroleum ether and acidified with cold, dilute hydrochloric acid. The resulting oil was separated and the aqueous layer was extracted with two 50-ml. portions of low boiling petroleum ether. The oil and the petroleum ether extracts were then combined, dried over anhydrous magnesium sulfate and the solvent removed. Distillation gave 0.6 g. (23%) of 2,6-xylol, b.p. 50–80° (0.6 mm.), and 0.9 g. (23%) of 4-[α,γ-dimethylallyl]-2,6-xylol, b.p. 90–100° (0.6 mm.), n^{20}_{D} 1.5343.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.88; H, 9.82.

Unfortunately the smallest polarimeter tube available required about 0.9 ml. of liquid and our sample of 4-[α,γ-dimethylallyl]-2,6-xylol did not quite fill it. Accordingly the rotation of this substance was determined by adding two drops of the same inactive phenol prepared during earlier exploratory work. The observed rotation (29°) was $-0.08° \pm 0.02$ ($l = 1$, no solvent).

The low boiling material which was collected in the Dry Ice trap during rearrangement was diluted with 5 ml. of dry benzene and cooled to 5°. To this solution was added 0.5 g. of maleic anhydride dissolved in 5 ml. of dry benzene, also cooled to 5°. The mixture was then frozen in a Dry Ice–acetone-bath for one hour and finally allowed to stand at room temperature for ten days. Removal of the benzene and recrystallization from low boiling petroleum ether gave a derivative melting at 60.5–61.5°. This is the value reported for the Diels–Alder adduct of maleic anhydride and *trans*-1,3-pentadiene.[13] A mixture of this derivative and maleic anhydride melted at room temperature.

URBANA, ILLINOIS RECEIVED MARCH 12, 1951

---

(10) From a number of exploratory runs these high boiling alkali insoluble residues were combined and redistilled for analysis. The purified material, b.p. 113–115° (0.3 mm.), n^{20}_{D} 1.5188, gave the correct analysis for 2-(α,γ-dimethylallyl)-phenyl α,γ-dimethylallyl ether. *Anal.* Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.57; H, 9.72.

(11) N. J. Demjanow and M. Dojarenko, *Ber.*, **55**, 2726 (1922), found the refractive index at 15° to be 1.4340.

(12) These fractions solidified completely on addition of a crystal of 2,6-xylol.

(13) E. H. Farmer and F. L. Warren, *J. Chem. Soc.*, 3221 (1931).