tared reaction flask, and about 1.0 g. of triethylammonium chloride was added as well as 100 ml. (30°) of freshly prepared triethylamine–benzene solution or triethylamine-phenol–benzene stock solution. The resulting mixture was held in the thermostat for six hours to allow the solution to become saturated with the amine hydrochloride. The proper amount of trityl chloride was rapidly weighed and added to the solution (zero time), complete solution of the halide occurring within one minute. An aliquot was immediately taken and analyzed for triethylamine. The reaction flask was held in the thermostat and its contents sampled at appropriate intervals. In runs where the initial amine concentration exceeded that of the trityl chloride, an aliquot was added to a few drops of water and allowed to stand while stoppered for one hour. Acetone was then added to give 25 ml. of homogeneous solution which was titrated for triethylamine to obtain the infinity titer. In the cases where the triethylamine was not present in excess, the calculated infinity titer was used in the calculation of the percentage reaction. The change in titer between zero and infinity time obtained by the hydrolysis method agreed with the calculated change within 2%.

In the runs that utilized no alcohol but only phenol, the same procedure was used.

In one run 0.0278 *M* triethylamine was allowed to react with 0.0278 *M* trityl chloride in dry benzene at 30°. After 10,080 minutes only 6.2% of the halide had been consumed.

Product Analysis. Procedure Used in Absence of Phenol.—Approximately 40 ml. of the reaction mixture which had been allowed to stand at room temperature for several weeks was thoroughly washed with water and dried. The benzene was evaporated, the residue was dissolved in boiling pentane, and the solution was allowed to cool slowly. The crystals that separated were collected, washed, weighed and the melting point determined. This material was recrystallized from pentane to constant m.p.

Product Analysis. Procedure Used in Presence of Phenol.—The procedure was the same as above except that after the benzene was evaporated, the low molecular weight compounds were removed from the residue by distillation at 100–125° at 5 mm.

Phenyl Trityl Ether.—A benzene solution of 0.0546 *M* triethylamine, 0.0521 *M* phenol and 0.0507 *M* trityl chloride was allowed to react at 30° until titration of the triethylamine indicated that the reaction was 67% complete. A 40-ml. aliquot of the solution was then washed with water, dried and the solvent was evaporated to give a 10-ml. residue. This solution was absorbed on a 30 × 3 cm. column of activated neutral alumina and eluted with 750 ml. of a 4:1 pentane–benzene solution. The column filtrate produced 374 mg. (82% yield) of phenyl trityl ether, m.p. 101–102° (pentane), lit. m.p. 103°.[3b]

Acknowledgment.—The authors wish to thank Dr. George Hammond for helpful discussions of this problem.

LOS ANGELES 24, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WYOMING]

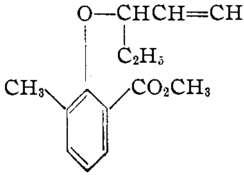
The *para*-Claisen Rearrangement. I. The Preparation and Rearrangement of the α- and γ-Ethylallyl Ethers of Methyl *o*-Cresotinate. A Reinvestigation[1,2]

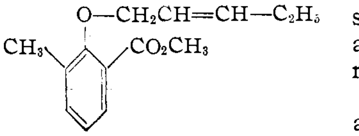
BY SARA JANE RHOADS, REBECCA RAULINS AND ROSALIE D. REYNOLDS[3]

RECEIVED JANUARY 25, 1954

The preparation and rearrangement of the α- and γ-ethylallyl ethers of methyl *o*-cresotinate have been restudied. Evidence is presented which establishes that both ethers undergo the *para*-Claisen rearrangement *without* inversion.

The original report of Mumm, Hornhardt and Diederichsen[4] that the isomeric α- and γ-ethylallyl ethers of methyl *o*-cresotinate (I and II) rearranged to the same *p*-allylated phenol (III) led to the postulation of two mechanisms which would permit equilibration of the migrating allylic system in the *para*-Claisen rearrangement, a free radical process[4] and a "pi complex" mechanism.[5] The "double-cyclic, semi-ionic" picture proposed by Hurd and Pollack[6] in analogy to the well-established mechanism for the *ortho*-rearrangement received scant attention since it required non-inversion in all cases.


I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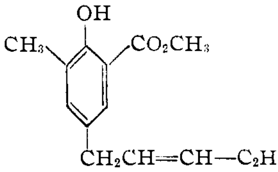
III

Dissatisfied with the evidence offered by Mumm, Hornhardt and Diederichsen for the structures of their isomeric ethers[4,7,8] and dissuaded of the idea that the *ortho*- and *para*-rearrangements should show such differences in mechanism, we undertook a complete reinvestigation of the preparation and rearrangement of this pair of ethers.

Preparation and rearrangement of the γ-ethylallyl ether, II, according to the procedure of the earlier workers gave results essentially in agreement with their report, although we were unable to duplicate their yields of ether or to succeed with their purification method. The reaction mixture from the ether preparation, consisting of unreacted

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(1) Taken from the dissertations of Rebecca Raulins and Rosalie D. Reynolds submitted in partial fulfillment of the requirements for the Ph.D. degree, May, 1953. A preliminary announcement of this work appeared in THIS JOURNAL, **75**, 2531 (1953).

(2) Presented before the Division of Organic Chemistry of the American Chemical Society, March, 1954, in Kansas City, Missouri.

(3) Soroptimist Fellow, Rocky Mountain Region, 1952–1953.

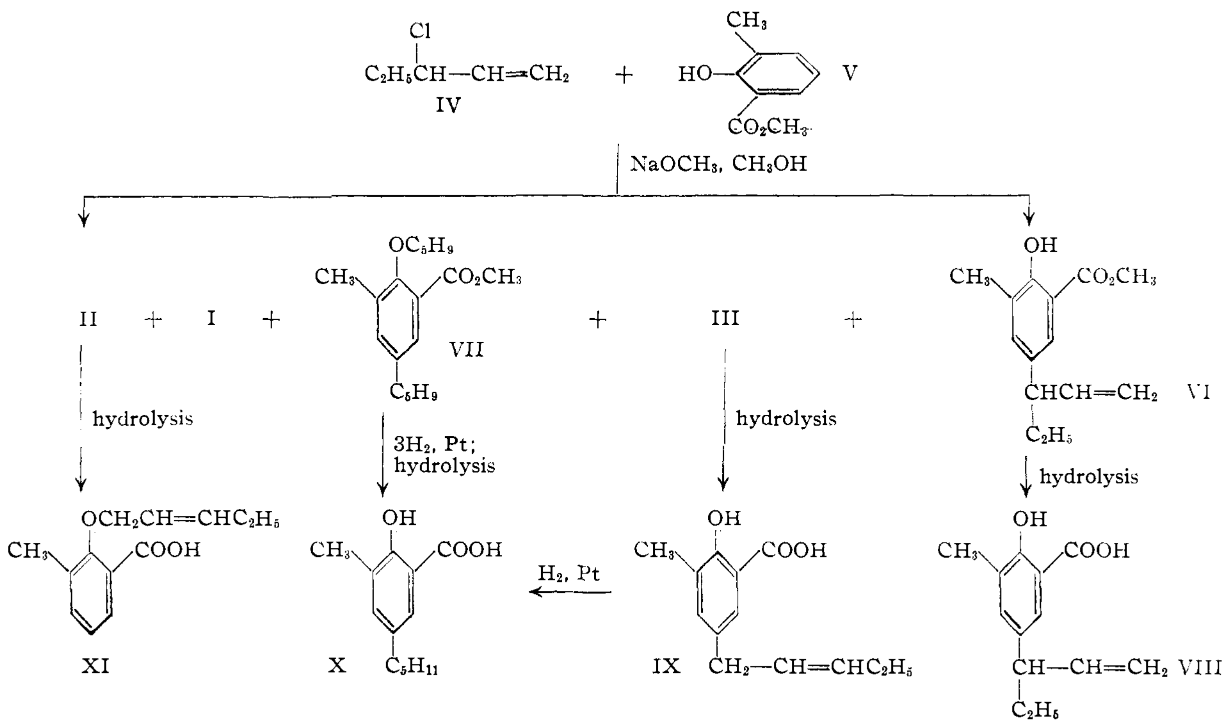
(4) O. Mumm, H. Hornhardt and J. Diederichsen, *Ber.*, **72**, 100 (1939); O. Mumm and J. Diederichsen, *ibid.*, **72**, 1523 (1939).

(5) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, p. 230.

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

(7) The sole distinction noted between the two ethers lay in their strikingly different behavior toward methanolic potassium hydroxide; the γ-ether saponified normally while the α-ether underwent rearrangement and saponification.

(8) Serious doubt concerning the homogeneity of the α-ether preparation was prompted by the recent recognition of the prevalence of abnormal products in displacement reactions of allylic halides. *Cf.* (a) R. E. Kepner, S. Winstein and W. G. Young, THIS JOURNAL, **71**, 115 (1949); (b) W. G. Young, I. D. Webb and H. L. Goering, *ibid.*, **73**, 1076 (1951).



methyl *o*-cresotinate and II, was not cleanly separable by the 2 *N* sodium hydroxide extractions which they employed but required the use of Claisen alkali.[9] A substantial improvement in yield and reduction in reaction time were realized by adapting the potassium *t*-butoxide, *t*-butyl alcohol system to this preparation in lieu of sodium methoxide and methanol.

The preparation of the α-ether, on the other hand, gave results which contrasted sharply with the original report. The reaction between α-ethylallyl chloride (IV) and the sodium salt of methyl *o*-cresotinate (V) proceeded quite sluggishly in methanol, 20 hours at reflux being required to realize a 25% yield of ethereal product.[10] The reaction mixture, in this experiment, consisted of at least six components, unreacted V, the α-ethylallyl ether (I), the γ-ethylallyl ether (II), the (α-ethylallyl)-phenol (VI), the (γ-ethylallyl)-phenol (III) and diallylated material (VII). Separation of the reaction mixture into an ethereal fraction containing I, II and VII and a phenolic fraction containing III, V and VI was, again, possible only with Claisen alkali.[11] Partial separation of the components of the phenolic fraction was accomplished by fractional distillation under reduced pressure. After a forerun of V the allylated phenolic material was separated into arbitrarily cut fractions. Subsequent hydrolysis of the first fraction and fractional recrystallization of the crude acids obtained permitted the isolation of a small quantity of 2-carboxy-4-(α-ethylallyl)-6-methylphenol (VIII), m.p. 101.5–103°, identical by mixed m.p. with an authentic sample (*vide infra*). Hydrolysis of subsequent fractions produced 2-carboxy-4-(γ-ethylallyl)-6-methylphenol (IX), m.p. 115–116°, in good yield.

Separation of the components of the ethereal fraction was more difficult. The thermal sensitivity of the allylic ethers eliminated the possibility of a slow fractional distillation but rapid distillation at low pressures could be carried out on small quantities without rearrangement. In this manner the ethereal material was split into low boiling fractions A-1 and A-2 and a high boiling fraction B. Fraction B was identified as the diallylated substance(s), VII, by elementary analysis and by hydrogenolysis followed by hydrolysis to 2-carboxy-4-pentyl-6-methylphenol (X).

Fraction A was subjected to careful scrutiny. Evidence that it was a mixture of the α- and γ-ethers, I and II, was forthcoming from several sources. The presence of II was early established by hydrolysis of A-2 to the corresponding acid, XI, m.p. 63.5–64°, identical with that obtained from authentic II.[12] When the same hydrolytic conditions were imposed on A-1, saponification occurred *without* rearrangement, contrary to the original report, to yield an acidic oil which crystallized at minus 5°. Ozonolysis of fraction A-1 produced formaldehyde in yields corresponding to 40 ± 4% of a compound with a terminal methylene group. Ozonolysis of this same material followed by oxidation furnished 2-carboxy-6-methylphenoxyacetic acid (XII), identical with that obtained by similar treatment of authentic II and by independent synthesis. Fi-

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[9] L. Claisen, *Ann.*, **418**, 96 (1919). The weakly acidic nature of methyl *o*-cresotinate and similarly constituted phenols was fully appreciated by Claisen in his pioneering work in this field.

[10] Significantly, the use of potassium *t*-butoxide and *t*-butyl alcohol did not improve the situation here, as it did with the γ-ether preparation (*vide supra*); indeed, the allylation proceeded even more slowly, 45 hours being required to achieve a comparable yield.

[11] The failure of Mumm, Hornhardt and Diederichsen to completely separate the ethereal and phenolic materials undoubtedly accounts for the later appearance of methyl *o*-cresotinate in the rearrangement product, which fact they cite as support for a radical mechanism. *Cf.* ref. 4.

[12] This fact was first noted in a preliminary investigation of this preparation by Erskine E. Harton in these laboratories in 1951.

nally, infrared spectral studies indicated the presence of a mixture.

Figure 1 shows the significant 9–11 μ region of the infrared spectra for fraction A-1 of the α-ether preparation, the γ-ethylallyl ether (II) and a model compound, the allyl ether of methyl *o*-cresotinate (XIII).[13] The two curves at the top of the figure represent the spectra of the α-ether preparation and II superimposed for comparison. The lower pair of curves shows the spectrum of the α-ether preparation superimposed on that of the model compound. The strong band at 10.31 μ present in the spectra of II and the α-ether preparation but absent in that of the model compound is attributable to the internal *trans* double bond of II.[14] The broad absorption in the region 10.6–10.75 μ which is present in the α-ether preparation but absent in II and corresponds approximately to the 10.78 μ band of the model compound (*cf.* lower pair of curves) is believed to be due to the terminal double bond of the α-ether, displaced somewhat from its usual position (10.9–11.0 μ) by structural features at the adjacent carbon.[14a]

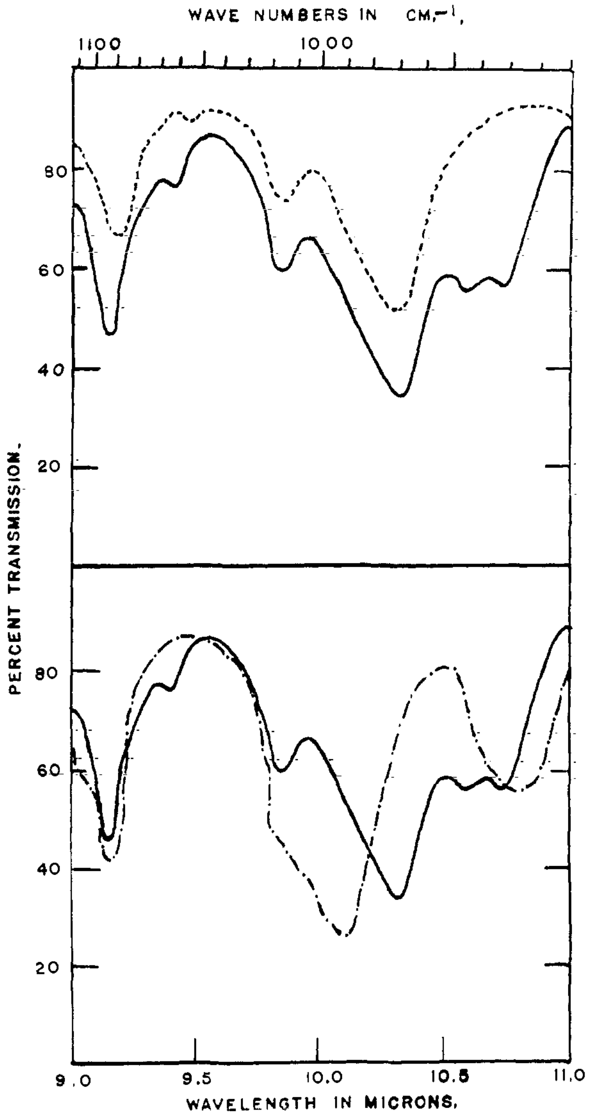
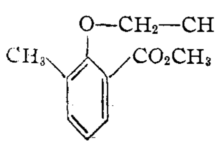
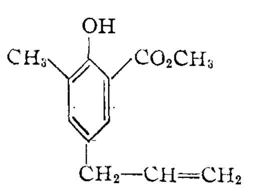


Fig. 1.—Infrared absorption spectra: upper curves, —, α-ether preparation, ------, γ-ethylallyl 2-carbomethoxy-6-methylphenyl ether (II); lower curves, —, α-ether preparation, -·-·-, allyl 2-carbomethoxy-6-methylphenyl ether (XIII).

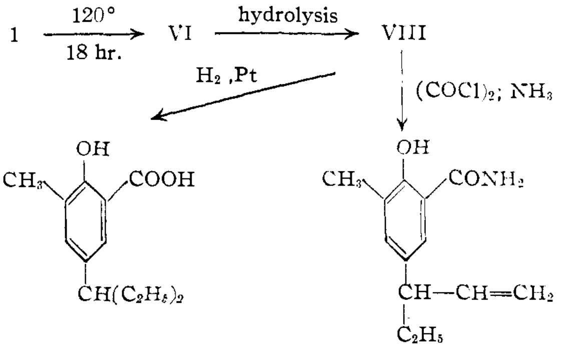


XIII



XVII

Thwarted in our efforts to obtain a reasonably pure sample of I for rearrangement studies, we turned to the possibility of a preferential rearrangement. Earlier observations had indicated that the α-ether preparation was markedly more prone to rearrangement than II. Mere standing at room temperature for several days sufficed to produce enough phenolic product in the α-ether preparations to be detected by a ferric chloride test; II, in contrast, was completely stable under these conditions. Further investigations indicated that a temperature of 120° brought about a reasonably rapid rearrangement of I without an appreciable effect on II over a period of 18 hours. Claisen alkali extraction of the preferentially rearranged α-ether preparation yielded relatively pure rearranged product, VI, in 17% yield from the ether. Hydrolysis of VI furnished the acid VIII in good yield, m.p. 102.5–103°, which was *not identical* with the corresponding γ-isomer, IX, m.p. 115–116°. For further comparison, the acids VIII and IX were converted to the amides, XIV and XV (m.p. 123–124° and 101–101.5°, respectively), and reduced to the saturated acids XVI and X (m.p. 117–118° and 82–83°, respectively). Ozonolysis of VI produced formaldehyde in amounts corresponding to 84 ± 8% of a compound with a terminal methylene group. Authentic III gave no formaldehyde under the experimental conditions.



XVI XIV

Figure 2 shows the 9.5–11.5 μ region of the infrared spectra of the three phenolic products, VI, III

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[13] The complete infrared and ultraviolet spectra for these compounds are contained in the Ph.D. dissertation of Rebecca Raulins, obtainable from the University of Wyoming Library through Interlibrary loan.

[14] (a) D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, 915 (1950); (b) A. C. Cope, D. E. Morrison and L. Field, THIS JOURNAL, **72**, 59 (1950).

and XVII, obtained by rearrangement of the related ethers I, II and XIII.[13] At the top of the figure the two curves corresponding to the phenols III and VI, now show quite significant differences. The 10.32 μ band, characteristic of the internal *trans* double bond of the γ-structure is still detectable in the spectrum of VI indicating that some of III may be present in the preferentially rearranged product. However, two intense bands appear in VI which are lacking or much less intense in III, one at 10.10 μ and one at 10.93 μ. Moreover, these bands find very close correspondence in the spectrum of the model compound (see lower curves) and show good agreement with previously reported values[14,15] for terminal double bonds. The change in position of the terminal double bond absorption from 10.74–10.78 μ in the ethers to 10.93 μ in the phenols may reasonably be attributed to differences in rotational and vibrational influences accompanying the structural change from carbon to oxygen to carbon to carbon bonding.[16,17]

Clearly, the rearrangement of the α-ethylallyl ether of methyl *o*-cresotinate (I) gives material which is not identical with that obtained from the isomeric γ-ethylallyl ether (II), but rather possesses an allylic group of *uninverted* structure. The findings of Mumm, Hornhardt and Diederichsen can, then, be rationalized on the grounds that their "α-ether" was, in fact, predominantly II and that their purification method was ineffective in removing phenolic products from the neutral material.

The origin of the γ-substituted ether II and phenol III in the α-ether preparation requires comment. Preliminary rearrangement of the α-ethylallyl chloride to the γ-ethylallyl chloride does not seem to be involved. All starting materials were carefully purified and dried prior to use to reduce the likelihood of isomerization of the halide. That the α-ethylallyl chloride is stable toward thermal isomerization under the conditions of the reactions is shown by the fact that it could be recovered unchanged after being heated alone for 45 hours at 80°. Since II rearranges very slowly to III even at 120° it is quite unlikely that any appreciable amount of III could be formed in this manner during the preparation. There remain two possible explanations. The γ-substituted products II and III could have arisen *via* an S_N2′ process[8] involving displacement by the phenoxide ion (giving either C- or O-allylation) at the γ-carbon of the secondary allylic chloride; alternatively, a slow preliminary ionization of the halide followed by rapid reaction with the phenoxide ion could account for the abnormal products.[18] A rough calculation based on the method of Winstein[19] indicates that under the conditions of the reaction in methanol approximately 31% of the α-ethylallyl chloride used could have reacted *via* a preliminary ionization step during the 20-hour reflux period. This could well account for the abnormal products formed. A concurrent S_N2′ displacement is, of course, still admissible.

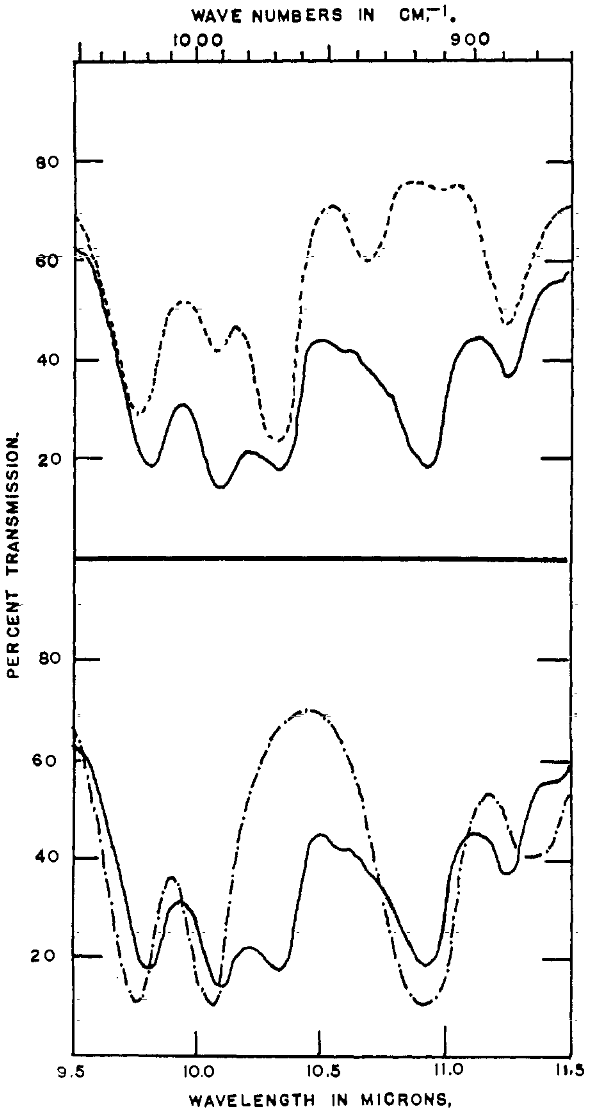

Fig. 2.—Infrared absorption spectra: upper curves, —, 2-carbomethoxy-4-(α-ethylallyl)-6-methylphenol (VI), ------, 2-carbomethoxy-4-(γ-ethylallyl)-6-methylphenol (III); lower curves, —, VI, ------, 2-carbomethoxy-4-allyl-6-methylphenol (XVII).

Recent activity[20] in this field has established, beyond reasonable doubt, that the "rule of non-inversion" applies to both substituted and unsubstituted allylic ethers in the *para*-rearrangement. The intramolecular nature of the rearrangement,

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[15] D. S. Tarbell and M. A. McCall, THIS JOURNAL, **74**, 48 (1952).

[16] F. A. Miller in "Organic Chemistry, An Advanced Treatise," Vol. III, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, p. 144.

[17] Absorption evidence in the 6.10μ region used by Cope, *et al.*,[14b] to distinguish the two types of double bonds was not available in the compounds studied here because of interfering absorption by other groups.

[18] We favor the latter explanation in view of the marked difference in rates of allylation experienced when we changed from the solvent methanol to *t*-butyl alcohol—a solvent of much poorer ionizing power. *Cf.* footnote 10 and Experimental.

[19] E. Grunwald and S. Winstein, THIS JOURNAL, **70**, 846 (1948); S. Winstein, E. Grunwald and R. W. Jones, *ibid.*, **73**, 2700 (1951).

[20] (a) E. R. Alexander and R. W. Kluiber, *ibid.*, **73**, 4304 (1951); (b) J. P. Ryan and P. R. O'Connor, *ibid.*, **74**, 5866 (1952); (c) H. Schmid and K. Schmid, *Helv. Chim. Acta*, **35**, 1879 (1952); **36**, 489 (1953); (d) H. Conroy and R. A. Firestone, THIS JOURNAL, **75**, 2530 (1953); (e) K. Schmid, W. Haegele and H. Schmid, *Experientia*, **9**, 414 (1953); (f) D. Y. Curtin and H. W. Johnson, Jr., THIS JOURNAL, **76**, 2276 (1954); (g) E. N. Marvell, A. V. Logan, L. Friedman and R. W. Ledeen, *ibid.*, **76**, 1922 (1954).

suggested by the work of Alexander and Kluiber,[20a] has found confirmation in the carefully executed tracer experiments of Schmid and Schmid.[20c,21] The isolation of a 2,2,6-trisubstituted-dienone[20d] together with the very recent demonstrations of allylic exchange at the *ortho*-carbon[20e,20f] indicate clearly that the *para*-rearrangement proceeds through a dienone stage in which the migrating allylic fragment is bound to an *ortho*-carbon.

The Hurd–Pollack mechanism for the Claisen rearrangements[6] not only accommodates all the known facts, but also offers an attractive stereopath for the reaction. In this connection, the mechanism proposed in the paper by Young, Webb and Goering for abnormal displacements in allylic systems (SN2′)[8b,22] is of interest since the Claisen rearrangements may be considered as *intramolecular* versions of the same reaction. As Bartlett[23] has pointed out, the geometry of an allyl aryl ether is such that the approach of the γ-carbon of the allylic group to an *ortho*-carbon atom of the ring is quite facile (Fig. 3, A). In such a position, the allylic group lies in a plane below and almost parallel with that of the ring. The displacing electron pair (at the *ortho*-carbon) and the departing oxygen are *cis* with respect to the plane defined by the three carbons of the allylic system—precisely the steric disposition required by the Young mechanism. Additional stabilization of the transition state T_1 is afforded by coulombic attraction of the partially charged centers. Passing from the first intermediate I_1, the reaction can follow one of two paths. If R is an easily removed group, enolization (or its equivalent) can occur with the formation of the *ortho*-rearrangement product. In the event that R cannot be removed, reorientation of the allylic group may be effected by pivoting on the *ortho*-carbon to place the terminal carbon of the side chain directly beneath the *para*-carbon, the three carbon allylic system again occupying a plane below and parallel to that of the ring (Fig. 3, B). A new transition state, T_2, analogous to T_1, leads to I_2 and finally to the *para*-rearrangement product.

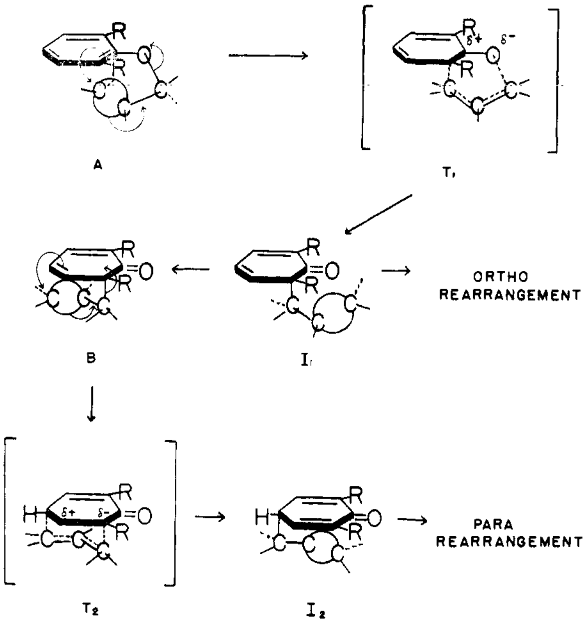

Fig. 3.

Acknowledgment.—This research was supported by grants from the Research Corporation, the American Academy of Arts and Sciences and the Research Council of the University of Wyoming. We are also indebted to the Bureau of Mines Petroleum and Oil-Shale Experiment Station, Laramie, for making available to us certain spectrographic facilities. The technical advice of Mr. C. W. Bailey and Mr. C. E. Johannsen and the preparative assistance of Mr. John Rogan are gratefully acknowledged.

Experimental[24]

Materials.—The isomeric ethylallyl chlorides were prepared from α-ethylallyl alcohol[25] according to the method of Kepner, Winstein and Young.[8a] Properties: α-ethylallyl chloride, b.p. 51.8–52.0° at 182 mm. (reported 55° at 200 mm.[8a]), n^{20}_D 1.4253 (reported, n^{20}_D 1.4253[8a]); γ-ethylallyl chloride, b.p. 68.3–68.5° at 182 mm. (reported 71.8° at 200 mm.[8a]), n^{20}_D 1.4403 (reported n^{20}_D 1.4404[8a]).

Methyl *o*-cresotinate (V) was prepared by esterification of *o*-cresotinic acid. A mixture of 200 g. (1.31 moles) of *o*-cresotinic acid, 317 g. (9.91 moles) of dry methanol and 60 ml. (1.08 moles) of concentrated sulfuric acid was refluxed for 18 hours. The reaction mixture was poured into 800 ml. of water, and the resulting oily suspension was extracted with benzene. After thorough extraction with 5% sodium carbonate solution and several water washes, the benzene solution was distilled to give 109.5 g. (50.5% yield) of colorless oil, b.p. 220–225° at 585 mm.[26] Further purification was accomplished by fractionation *in vacuo*. The pure ester had the following properties: b.p. 145–146° at 54 mm. (reported, 119.0–121.5° at 14 mm.[27]), m.p. −1.2 to −0.5° (reported −0.5°[27]), n^{20}_D 1.5347, n^{16}_D 1.5351 (reported $n^{16.8}_D$ 1.53538[27]).

Allyl 2-carbomethoxy-6-methylphenyl ether (XIII) was prepared from V and allyl bromide using the sodium methoxide–methanol method.[28] Unreacted V was removed with Claisen alkali; properties of the purified ether: b.p. 95–96° at 0.65 mm., n^{20}_D 1.5184, ferric chloride test, negative.

2-Carbomethoxy-4-allyl-6-methylphenol (XVII)[28] was prepared by the rearrangement of XIII in diethylaniline. Properties: b.p. 107–108° at 0.8 mm., n^{20}_D 1.5367, ferric chloride test, blue-purple.

Ether Preparations.—Various conditions were employed for preparing and isolating the ethereal products. Results from representative experiments are summarized in Table I. Specific details are recorded below.

Reaction of Methyl *o*-Cresotinate with γ-Ethylallyl Chloride; Preparation of γ-Ethylallyl 2-Carbomethoxy-6-methylphenyl Ether (II). A. Sodium Methoxide–Methanol Method (Expt. 1).—When the reaction was carried out according to Mumm, Hornhardt and Diederichsen[4] achievement of neutrality in the reaction mixture required a 13-hour reflux period. Distillation of the sodium hydroxide extracted product gave the following results: recovered V, b.p. 74–76° at 1.7 mm., 17.2%; II, b.p. 123–124° at 0.8 mm. (reported 125° at 1.1 mm.[4]), n^{20}_D 1.5148, 31.2%

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(21) The point has also been demonstrated in these laboratories in "crossing experiments" with substituted allylic ethers by Robert L. Crecelius, unpublished work.

(22) *Cf.* also G. Stork and W. N. White, THIS JOURNAL, **75**, 4120 (1953).

(23) P. D. Bartlett in "Organic Chemistry, An Advanced Treatise," Vol. III, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, p. 72.

(24) All melting points are corrected. The elementary analyses were performed by the Clark Microanalytical Laboratory, Urbana, Illinois.

(25) C. Prevost, *Ann. chim.* (*Paris*), [10] **10**, 147 (1928).

(26) The yield of ester can be substantially improved (72%) by extending the reflux period to 35 hours (R. L. Crecelius, unpublished work).

(27) C. Guillaumin, *Bull. soc. chim.*, [4] **7**, 375 (1910).

(28) L. Claisen and O. Eisleb, *Ann.*, **401**, 21 (1913).

TABLE I

DATA FROM REPRESENTATIVE PREPARATIONS OF THE ISOMERIC ETHYLALLYL ETHERS OF METHYL *o*-CRESOTINATE

Expt. No.[a]	Conditions: Solvent	Catalyst	Excess chloride %	Reflux, hr.	Extracting solvent	Methyl *o*-cresotinate recovered, %	Yield products, %: Ethereal	Phenolic
1	MeOH	NaOMe	35	13.0	2 *N* NaOH	17.2	31.2	. .
2	*t*-BuOH	K-*t*-BuO	0	8.5	Claisen alkali	3.0	52.7	. .
3	MeOH	NaOMe	40	11.0	2 *N* NaOH	16.0	32.4	
4	MeOH	NaOMe	50	32.0	2 *N* NaOH	17.6	34.8	
5	MeOH	NaOMe	40	20.0	Claisen alkali	34.4	26.1	20.3
6	*t*-BuOH	K-*t*-BuO	11	45.0	Claisen alkali	34.0	25.8	8.1

[a] In experiments 1 and 2 the chloride used was γ-ethylallyl chloride; in experiments 3–6, α-ethylallyl chloride.

yield.[29] The two fractions were identified by hydrolysis with 30% methanolic potassium hydroxide solution to the corresponding acids, *o*-cresotinic acid, m.p. 166–166.5° and γ-ethylallyl 2-carboxy-6-methylphenyl ether (XI), m.p. 63.5–64.0° (reported 63–64°[4]). XI was further characterized by conversion to the corresponding amide via the oxalyl chloride–ammonia method described later, m.p. 97–98.5° from hexane, negative ferric chloride test.

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.3; H, 8.0; N, 6.4.

B. **Potassium *t*-Butoxide–*t*-Butyl Alcohol Method (Expt. 2).**—To a refluxing solution of potassium *t*-butoxide in dry *t*-butyl alcohol contained in a reaction vessel equipped with a dropping funnel, condenser and stirrer and protected from atmospheric moisture, was added an equivalent amount of V, followed after ten minutes by an equivalent amount of γ-ethylallyl chloride. Stirring and refluxing were continued for 8.5 hours at which time the reaction mixture tested neutral and gave only a weak ferric chloride test. The *t*-butyl alcohol was removed under vacuum on the steam-bath. After the addition of water, the reaction mixture was extracted three times with low boiling petroleum ether. The water-washed petroleum ether solution was twice extracted in the *cold* (all solutions were kept well-iced to minimize hydrolysis of the ester) with Claisen alkali to remove phenolic material. The extracted petroleum ether solution was washed well with water, dried over magnesium sulfate and distilled to give 52.7% of II, b.p. 109–111° at 0.2 mm., n^{20}_{D} 1.5142, n^{25}_{D} 1.5120, d^{25}_{0} 1.0355, ferric chloride test, negative.

Reaction of Methyl *o*-Cresotinate with α-Ethylallyl Chloride. A. Sodium Methoxide–Methanol Method According to Mumm, Hornhardt and Diederichsen (Expt. 3 and 4).—When the procedure outlined by Mumm, Hornhardt and Diederichsen[4] was followed in detail, the sodium hydroxide-extracted material yielded on distillation a product boiling over the range 76–142° at 0.3 mm., together with a high boiling residue. (The original report[4] indicates a single fraction, b.p. 125–128° at 0.8–1.2 mm.) Attempted fractionation of this material through a 3-foot Podbielniak-type column was unsuccessful. All fractions were characterized as containing phenolic material by their intense ferric chloride reactions. Extension of the reaction time and addition of excess halide did not alter these results (Expt. 4).

B. **Sodium Methoxide–Methanol Method. Modified Treatment of Reaction Mixture (Expt. 5).**—The best yields of products from the reaction of V with α-ethylallyl chloride in the presence of sodium methoxide and methanol were obtained by the following procedure.

To dry methanol, distilled under nitrogen directly into the reaction flask, sodium was added through the condenser. Shortly after reaction was complete, V was added dropwise and the mixture was heated to reflux. After the system, cooled to 0°, was flushed with nitrogen, slightly more than one equivalent of α-ethylallyl chloride was added. The mixture was allowed to warm to room temperature and then heated to gentle reflux. Additional halide was added in small portions during the 20-hour reflux period which followed. Excess chloride used amounted to 40%.

Treatment of the reaction mixture was the same as that described above for the reaction mixture of V and γ-ethylallyl chloride by the potassium *t*-butoxide–*t*-butyl alcohol method. Separation into phenolic and ethereal fractions was again achieved with Claisen alkali extractions in the cold. Removal of solvent from the ethereal material left an almost colorless oil (negative ferric chloride test) which was purified either by molecular distillation or by ordinary vacuum distillation. When the latter method of purification was employed, it was necessary to distil the material in relatively small quantities (no more than 9 g.) to avoid partial rearrangement. Three fractions were cut in each distillation, the first arbitrarily: fr. A-1, b.p. 92–112° at 0.2 mm., n^{25}_{D} 1.5072; fr. A-2, b.p. 112–120° at 0.2 mm., n^{25}_{D} 1.5119; fr. B, b.p. 138–140° at 0.2 mm., n^{25}_{D} 1.5128. Each fraction represented *ca.* $^1/_3$ of the total charge; each gave a negative ferric chloride test. The low boiling ethereal fraction A (A-1 and A-2) was obtained in yields of 22 to 26%.

The phenolic material was liberated from the Claisen alkali extracts by neutralization with dilute sulfuric acid and ice, extracted with petroleum ether, washed, dried and finally distilled. A mixture of phenolic products boiling over the range 68–158° at 0.35 mm. was obtained. Identification of the components of this mixture is described below.

C. **Potassium *t*-Butoxide–*t*-Butyl Alcohol Method (Expt. 6).**—When the method described above for the preparation of II was applied to the α-ethylallyl ether preparation, a 26% yield of crude ethereal material was obtained after a reflux period of 45 hours. The material had essentially the same composition as that obtained by the sodium methoxide–methanol method. The phenolic fraction again consisted of recovered V, III and VI.

Characterization and Identification of Ethereal Material from α-Ether Preparation.—Methanolic potassium hydroxide hydrolysis of fraction A-1 produced an almost colorless oil in yields of 85–88%. Crystallization was induced by trituration with hexane at −70°. The resultant fine white needles were stable at −5° but melted when warmed to room temperature.

Hydrolysis of fraction A-2 gave, after trituration in hexane at −70°, an 82% yield of impure white crystals, melting after two recrystallizations from hexane at 62.5–63.5°; admixture with authentic XI caused no depression.

The high boiling fraction B (VII) produced only oily material on hydrolysis. Hydrogenation of VII over Adams catalyst proceeded rapidly with the absorption of 3 mole equivalents of hydrogen, indicating hydrogenolysis of the allylic ether as well as reduction of two double bonds.[30] The reaction product was directly saponified with methanolic potassium hydroxide to yield 2-carboxy-4-pentyl-6-methylphenol (X), m.p. 80–82°, not depressed when mixed with authentic X.

Anal. of VII. Calcd. for $C_{19}H_{26}O_3$: C, 75.5; H, 8.7. Found: C, 76.1; H, 8.9.

Identification of Phenolic Material from α-Ether Preparation.—The phenolic fraction removed by the Claisen alkali extraction was subjected to a vacuum fractional distillation through a 3-foot Podbielniak-type column equipped with a tantalum wire packing and a partial reflux head.[31] The

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[29] Mumm, Hornhardt and Diederichsen[4] report an excellent yield of II in this preparation but make no mention of a forerun of V. In addition, they report their product II to have a "so gut wie negativ" ferric chloride test. V gives an intense purple color with ferric chloride; repeated distillation of II, isolated in this way, is necessary to obtain a sample with a negative test. The substitution of Claisen alkali for the 2 *N* sodium hydroxide extractions completely removes the unreacted V and gives uncontaminated II directly.

[30] *Cf.* ref. 4, 15 and E. Bergmann and H. Heimhold, *J. Chem. Soc.*, 1365 (1935). The allylic ethers I and II also undergo hydrogenolysis with the absorption of exactly 2 mole equivalents of hydrogen and regeneration of V.

[31] J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1950, p. 237.

original charge amounted to 49 g. The following fractions were cut (0.5 mm. pressure): fr. 1, b.p. 68–75°, n^{20}D 1.5331, 20.6 g., ferric chloride test, deep purple; fr. 2, b.p. 112–117°, n^{20}D 1.5234, 1.1 g., ferric chloride test, royal blue; fr. 3, b.p. 117–119°, n^{20}D 1.5236, 5.8 g., ferric chloride test, pure blue; fr. 4, b.p. 119–122°, n^{20}D 1.5257, 5.1 g., ferric chloride test, pure blue; fr. 5, b.p. 122–123.5°, n^{20}D 1.5276, 12.4 g., ferric chloride test, pure blue; fr. 6, b.p. 126–158° (forced), n^{20}D 1.5231, 1.8 g., ferric chloride test, blue. Fraction 1 was identified as V by physical properties and hydrolysis to *o*-cresotinic acid. Fractions 2 and 3, representing *ca*. 25% of the total phenolic fraction, exclusive of V, yielded, on hydrolysis, white crystalline material, the melting ranges of which (81–90°, 86–106°) indicated both were mixtures. Fractions 4 and 5, on hydrolysis, furnished good yields of 2-carboxy-4-(γ-ethylallyl)-6-methylphenol (IX), m.p. 115–116°, thereby identifying these fractions as essentially pure III. Fraction 6 was not further examined.

Fractional recrystallization from hexane of the acid mixture obtained from fr. 2 permitted the isolation of a small quantity of the more soluble component, 2-carboxy-4-(α-ethylallyl)-6-methylphenol (VIII), m.p. 101.5–103°, undepressed on admixture with a sample obtained from the preferential rearrangement (*vide infra*). Mixed with authentic IX it melted 77–92°.

Rearrangement of γ-Ethylallyl 2-Carbomethoxy-6-methylphenyl Ether (II).—Rearrangement of II in diethylaniline by the procedure of Mumm, Hornhardt and Diederichsen[4] led to the isolation of 2-carbomethoxy-4-(γ-ethylallyl)-6-methylphenol (III) in 60% yield, b.p. 115–117° at 0.25 mm. (reported 170–175° at 17 mm.[4]), n^{20}D 1.5290, n^{25}D 1.5275, ferric chloride test, pure blue. III was characterized by hydrolysis to IX, m.p. 115–116° and conversion to the amide XV. No methyl *o*-cresotinate forerun was observed when III was distilled.

The amide **XV** was prepared from the acid chloride obtained by the oxalyl chloride method of Wilds and Shunk.[32] The crude acid chloride was decomposed with a large excess of cold, concentrated ammonia solution. The deep yellow solid which formed instantly was decomposed by gentle heating on the steam-bath. Partial acidification of the alkaline solution with concentrated hydrochloric acid produced the separation of colorless crystals of the amide, XV, m.p. 101–101.5°, from hexane.

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.2; H, 7.7; N, 6.7.

Preferential Rearrangement of α-Ethylallyl 2-Carbomethoxy-6-methylphenyl Ether (I). Isolation of 2-Carbomethoxy-4-(α-ethylallyl)-6-methylphenol (VI).—Samples of pure II and fraction A-1 of the low boiling ether fraction were placed in test-tubes fitted with air condensers and introduced into an oil-bath held at 120°. After three hours at this temperature, the ethereal mixture containing I showed a blue-green color when tested with ferric chloride while II still showed a negative reaction. Eighteen hours at 120° were required before II showed a slightly positive, light green ferric chloride test. By that time the mixture originally containing I gave a deep bluec olor when treated with ferric chloride. The heating was immediately discontinued and the preferentially rearranged material from the ether fraction A-1 was isolated by extraction with Claisen alkali. Distillation furnished a colorless oil in 17% yield, b.p. 95–96° at 0.18 mm., n^{20}D 1.5266, n^{25}D 1.5234, ferric chloride test, deep blue.

2-Carboxy-4-(α-ethylallyl)-6-methylphenol (VIII).—Methanolic potassium hydroxide hydrolysis of the distilled phenolic material from the preferential rearrangement gave rise in excellent yield (87–89%) to well formed needles crystallizing in spherical clusters from hexane; m.p. 102.5–103.0°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 70.7; H, 7.6.

The phenolic acid VIII was further characterized by conversion to the amide, **XIV**, by the method already described for XV, crystals from hexane, m.p. 123–124°.

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.0; H, 7.9; N, 6.5.

2-Carboxy-4-(3-pentyl)-6-methylphenol (XVI).—Reduction of 31.4 mg. of VIII dissolved in alcohol was accomplished in a microhydrogenation apparatus over Adams catalyst. The sample rapidly absorbed one equivalent of hydrogen. Removal of the catalyst and solvent and recrystallization from hexane afforded fine clustered needles, m.p. 117–118°.[33]

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2. Found: C, 70.3; H, 8.4.

Ozonolysis Procedure. Ozonization.—Ozonizations were carried out at −5 to 0° on samples varying in size from 2.5 to 4.1 mmoles. The solvent was purified ethyl bromide (Matheson Co.), used as supplied. Ozone was furnished by a Welsbach Model T-19 ozonator at a concentration of *ca*. one mole per cent. and at a flow rate of 9–10 liters/hour. The ozonization train consisted of three gas absorption bottles, a flow meter and a wet test meter. The solution of the sample to be ozonized was placed in the first bottle; the second bottle served as water-trap to catch any formaldehyde produced by spontaneous cleavage.[34] The third bottle contained a 0.5% sodium iodide–starch indicator solution. Quantitative determinations of ozone concentration were made preceding each run. Conditions of ozone concentration, temperature and flow rate were maintained as uniformly as possible in all ozonizations.

Formaldehyde Determination.—After ozonization was complete the pale yellow ethyl bromide solution of the ozonide was poured into 60–75 ml. of water containing 0.6 g. of zinc dust and 15–20 drops of glacial acetic acid. The mixture was allowed to stand 2 hours at room temperature and then refluxed for an additional 2 hours. After removal of the zinc the aqueous layer was separated, and, combined with three 25-ml. water-washes of the ethyl bromide solution, was distilled (to a volume of 15–20 ml.) into 80 ml. of ice-cooled water. The total aqueous distillate was immediately treated with a 10% excess of the theoretical quantity of methone dissolved in 15 ml. of 95% alcohol and the whole heated to boiling. The solution was maintained at the boiling point for 10 minutes, cooled to 70°[35,36] and filtered through a tared sintered glass crucible. The white formaldimethone was dried to constant weight in one-hour periods[37] at 60°, m.p. 188–191°, undepressed when mixed with an authentic sample. The formaldehyde in the water trap was isolated directly by precipitation of the methone derivative, m.p. 190–191°.

The allyl ether of methyl *o*-cresotinate, XIII, and its rearrangement product, 2-carbomethoxy-4-allyl-6-methylphenol (XVII) were studied as model compounds in the ozonolysis. Under the conditions described, XIII gave formaldehyde in yields of 56 ± 5% while XVII gave yields of 50 ± 5%. Taking these values as representing the maximum formaldehyde yields obtainable under these conditions,[38] the following estimates of terminal methylene structure present in the compounds and mixtures studied were made.

Sample	Actual formaldimethone, % yield	% Terminal methylene cpd.
XIII and XVII	56 ± 5; 50 ± 5	100
II	0	0
α-Ether preparation, fraction A-1	20, 23, 25[a]	36 ± 4 to 45 ± 4
III	0	0
VI (from preferential rearrangement)	42	84 ± 8

[a] These figures represent results on three different ether preparations.

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[32] A. L. Wilds and C. H. Shunk, THIS JOURNAL, **70**, 2427 (1948).

(33) Reduction of the isomeric IX gave 2-carboxy-4-pentyl-6-methylphenol (X), m.p. 82–83° (reported 84°[4]).

(34) In actual runs formaldehyde in amounts of 3–11% of theory was found here. *Cf.* (a) L. Ruzicka, C. F. Seidel, H. Schinz and C. Tavel, *Helv. Chim. Acta*, **31**, 257 (1948); (b) A. Henne and W. Perilstein, THIS JOURNAL, **65**, 2183 (1943).

(35) W. R. Nummy and D. S. Tarbell, *ibid.*, **73**, 1504 (1951).

(36) Because of a marked difference in the rates of formation of the methone derivatives, these conditions permit the determination of formaldehyde in the presence of other aldehydes. Preliminary experiments indicated that as little as 10% formaldehyde in a formaldehyde-propionaldehyde mixture could successfully be determined.

(37) This is necessary to prevent loss of the methone derivative by sublimation.

(38) *Cf.* ref. 34a; W. Oroshnik, G. Karmas and A. D. Mebane, THIS JOURNAL, **74**, 295 (1952); and G. R. Clemo and J. M. MacDonald, *J. Chem. Soc.*, 1294 (1935).

Oxidative Cleavage of Ozonide. Silver Oxide Method.[39]—The ethyl bromide solution of the ozonide was hydrolyzed with 70 ml. of water by refluxing 30 minutes. To the cooled mixture were added double molar quantities of freshly prepared silver oxide and sodium hydroxide. After a three-hour reflux period, the alkaline solution was filtered to remove silver and evaporated *in vacuo* on the steam-bath. The solid residue was taken up in a minimum amount of water, acidified with dilute sulfuric acid and thoroughly extracted with ether. Removal of the solvent from the dried ether extracts left a dark yellow, semi-solid residue of acids. A positive ferric chloride test indicated the presence of *o*-cresotinic acid.[40] The latter was cleanly removed from the dibasic acid by sublimation *in vacuo* at 90–95°. The unsublimed crude 2-carboxy-6-methylphenoxyacetic acid (XII) was purified by treatment with Norite and repeated recrystallization from acetonitrile, m.p. 200–203°, undepressed on admixture with an authentic sample. The dibasic acid XII was obtained in very poor yield (6–9%) by this method from samples II, XIII and the α-ether preparation.

Hydrogen Peroxide–Acetic Acid Method.[41]—In a typical case, a 0.6-g. sample of ether was ozonized and hydrolyzed in the presence of zinc. After removal of the zinc by filtration, the ethyl bromide was evaporated *in vacuo* and the remaining oil and water mixture treated with equal volumes (8 ml. each) of 20% hydrogen peroxide and 25% acetic acid. The oxidizing mixture was refluxed 3 hours. Cloudiness and an oily layer appeared on cooling. The cooled solution was thoroughly extracted with ether. Evaporation of the ether left a pale yellow liquid which was heated with excess 30% methanolic potassium hydroxide for 5 minutes in a water-bath to hydrolyze the ester. The cooled yellow solution was treated with an equal volume of water, extracted once with ether and acidified with 6 *N* sulfuric acid. The yellow-white solids which separated were taken up in ether and the ethereal solution was filtered through anhydrous sodium sulfate and dried over anhydrous magnesium sulfate. Removal of the ether left a yellow solid which was freed of cresotinic acid by sublimation as described above. The unsublimed material was of sufficient purity that recrystallization was generally not necessary. The m.p. of unrecrystallized XII ranged from 195 to 204°. XII was obtained in yields of 25–38% from samples of II, XIII and the α-ether preparation. No evidence for the more soluble, lower melting α-(2-carboxy-6-methylphenoxy)-butyric acid (see below), the expected oxidation product of I, could be found.

2-Carboxy-6-methylphenoxyacetic Acid (XII).—Alkylation of V with ethyl bromoacetate was accomplished with sodium methoxide in methyl alcohol using conventional alkylation methods. Unreacted starting materials were removed by distillation *in vacuo*. The residue was evaporatively distilled at a bath temperature of 150–180° and pressure of 0.08 mm. to give a 30% yield of ethyl 2-carbomethoxy-6-methylphenoxyacetate. The diester was directly hydrolyzed with methanolic potassium hydroxide to give XII, fine short needles from acetonitrile, m.p. 205–206.5° (reported 203–204°[42]).

Anal. Calcd. for $C_{10}H_{10}O_5$: neut. equiv., 105. Found: neut. equiv., 106.

α-(2-Carboxy-6-methylphenoxy)-butyric Acid.—This acid was prepared by saponification of the diester, ethyl α-(2-carbomethoxy-6-methylphenoxy)-butyrate, formed from V and ethyl α-bromo-*n*-butyrate in a manner analogous to that described for the diester of XII. Recrystallized from ethyl acetate the acid melted at 127.5–128.5°.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9; neut. equiv., 119. Found: C, 60.4; H, 5.9; neut. equiv., 120.

Stability of α-Ethylallyl Chloride (IV).—A 10-g. sample of α-ethylallyl chloride protected from atmospheric moisture was heated for 45 hours at 80°. Fractionation through a 3-foot Podbielniak column at 195 mm. gave 85.3% recovery, $n^{20}D$ 1.4254. The residual material was a brown polymer. No γ-ethylallyl chloride could be detected.

Infrared Spectra.—The infrared spectra were secured with a Perkin–Elmer Model 12C spectrophotometer, using sodium chloride cells of 0.025 mm. and 0.005 ± 0.001 mm. thickness.

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[39] W. G. Young, A. C. McKinnis, I. D. Webb and J. D. Roberts, THIS JOURNAL, **68**, 293 (1946).

[40] In all the ozonolyses of these compounds *o*-cresotinic acid was found in appreciable amounts in the acid fractions from oxidative cleavages. This has been established as a product of abnormal ozonolysis, which subject will be treated in a forthcoming paper. *Cf.* also ref. 39.

[41] G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgstahler, THIS JOURNAL, **75**, 384 (1953).

[42] R. Meyer and C. Duczmal, *Ber.*, **46**, 3374 (1913). These authors report the preparation of XII in poor yield from *o*-cresotinic acid and chloroacetic acid in concentrated sodium hydroxide solution. We were unable to obtain satisfactory results with this method.

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

Cyclic Aminoacyloins. II. F-Strain Limitation of Transannular Interaction between N and C_{CO}

BY NELSON J. LEONARD AND MICHINORI ŌKI

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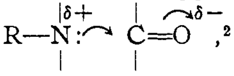
It has been demonstrated, by determination of the infrared absorption spectra and comparison of the pK'_a values in different solvents for a series of 1-alkyl-1-azacyclononan-5-ol-6-ones (II), that steric strain (F-strain) places a limitation on transannular interaction between N and C_{CO} in cyclic aminoacyloins. In the series IIa, b, c, d, as the bulk of the N-alkyl group increases, the extent of transannular N → C_{CO} bonding decreases. It has also been shown that the physical state of the compounds (solid or solution) and the nature of the solvent employed for solutions of these compounds may influence the extent to which steric interference prevents transannular bonding.

In a previous communication from this Laboratory,[1] we indicated the probable limits of ring size within which appreciable transannular interaction,



$R{-}\overset{\delta+}{N}{:}\curvearrowright C{=}\overset{\delta-}{O}$

,[2] will occur in cyclic aminoketones and aminoacyloins. It seemed reasonable to expect that an additional limitation of transannular interaction would be found in steric hindrance.

Accordingly, we have extended our synthesis of nine-membered ring aminoacyloins (II) to include the N-isopropyl (IIc) and N-*t*-butyl (IId) derivatives. Together with the N-methyl (IIa) and N-ethyl (IIb) compounds previously reported,[1] these constitute an excellent series in which to compare progressive changes in properties with increasing bulk of the alkyl group attached to nitrogen. As

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[1] N. J. Leonard, R. C. Fox, M. Ōki and S. Chiavarelli, THIS JOURNAL, **76**, 630 (1954).

[2] (a) F. A. L. Anet, A. S. Bailey and Sir Robert Robinson, *Chemistry and Industry*, 944 (1953); (b) E. H. Mottus, H. Schwarz and L. Marion, *Can. J. Chem.*, **31**, 1144 (1953); (c) R. Huisgen, H. Wieland and H. Eder, *Ann.*, **561**, 193 (1949); (d) see also H. C. Brown and E. A. Fletcher, THIS JOURNAL, **73**, 2808 (1951).