The Stereochemistry of the Claisen Rearrangement of Optically Active *trans*-α,γ-Dimethylallyl Phenyl Ether[1,2]

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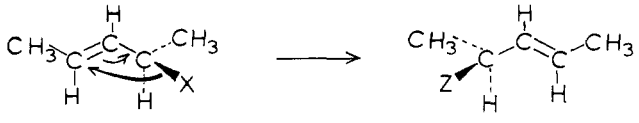
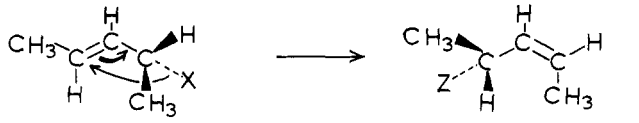
The relative and absolute configurations of reactant and product for the ortho Claisen rearrangement of optically active trans-α,γ-dimethylallyl phenyl ether (IV) have been determined by the relationships outlined in Chart I. Rearrangement of IV gives a mixture of cis- (Vb) and trans-2-(α,γ-dimethylallyl)phenol (Va) consisting mainly of the trans isomer. Hydrogenation of this mixture gives 2(2-pentyl)phenol (VI) in which the configuration of the asymmetric center is opposite that of the asymmetric center in the trans-α,γ-dimethylallyl ether IV. The present results show that the stereochemistry of the ortho Claisen rearrangement of IV corresponds to that predicted on theoretical grounds and to that observed for other intramolecular allylic rearrangements of α,γ-dimethylallyl derivatives.

Introduction

The stereochemical relationship (optical and geometric) between reactant and product for intramolecular allylic rearrangements[4] and SNi′ reactions[5] of *trans*-α,γ-dimethylallyl derivatives (I) is determined by the configuration of the allyl moiety in the transition state.[4a] As illustrated for (*R*)-I, if the transition state is related to conformation Ia geometric configuration is preserved and the optical configuration of the product is opposite that of the reactant, *i.e.*, (*R*)-*trans* → (*S*)-*trans*.[6] On the other hand, the transition state related to conformation Ib leads to the *cis* isomer and the optical configuration of the product is the same as that of the reactant, *i.e.*, (*R*)-*trans* → (*R*)-*cis*.

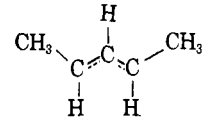


Ia

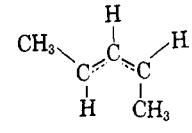


Ib

As pointed out earlier,[4a] IIa is a more stable configuration for the α,γ-dimethylallyl moiety than IIb (for the same reason that *trans*-2-butene is more stable than the *cis* isomer) and thus the transition state related to Ia would be expected to be favored over that related to Ib. With one exception, reactions involving rearrangements[4] or SNi′ reactions[5] of *trans*-α,γ-dimethylallyl systems have been reported to proceed with the expected stereochemistry (*i.e.*, preservation of geometric configuration and change of optical configuration). The exception is the *ortho* Claisen rearrangement of *trans*-α,γ-dimethylallyl phenyl ether (III).[7,8] For this case X (in Ia and Ib) is the phenoxy substituent and Z is the 2-hydroxyphenyl substituent.



IIa



IIb

It has been reported[7] that rearrangement of (−)-*trans*-α,γ-dimethylallyl phenyl ether (−IV), $\alpha^{25}D$ −0.10°,[9] gives (+)-(?)-2-(α,γ-dimethylallyl)phenol (+V), $\alpha^{25}D$ +0.48°. From this, and the observation that direct C-alkylation of phenol with the active α,γ-dimethylallyl chloride used to prepare (−)-IV gave (+)-V,[7] it was concluded[8] that the optical configuration of the product V is the same as that of the reactant IV. In an earlier paper[10] we pointed out the inconsistency of this conclusion with apparently analogous transformations and mentioned that we were undertaking a reinvestigation of the stereochemistry of the rearrangement of optically active IV. In the meantime two investigations have been reported[11,12] which have an important bearing on this subject. As outlined above, there are two stereochemical consequences of the configuration of the allyl moiety in the transition state: the relative optical and geometric configurations of reactant and product. The other workers[11,12] have approached this problem by determining the relative geometric configurations of reactant and product and have observed that 2-(α,γ-dimethylallyl)-phenol (V) derived from *trans*-α,γ-dimethylallyl phenyl ether (IV) is mainly, but not exclusively,[11] the *trans*

(1) Taken from the Ph.D. Thesis of W. I. Kimoto, University of Wisconsin, 1961.

(2) This work was supported in part by the Research Committee of the Graduate School of the University of Wisconsin with funds provided by the Wisconsin Alumni Research Foundation and in part by the National Science Foundation (G6285).

(3) Du Pont Summer Research Fellow 1957 and 1960.

(4) (a) H. L. Goering and R. W. Greiner, *J. Am. Chem. Soc.*, **79**, 3464 (1957); (b) H. L. Goering and M. M. Pombo, *ibid.*, **82**, 2515 (1960); H. L. Goering, *Record Chem. Progr.* (Kresge–Hooker Sci. Lib.), **21**, 109 (1960); (c) H. L. Goering, M. M. Pombo, and K. D. McMichael, *J. Am. Chem. Soc.*, **85**, 965 (1963).

(5) F. F. Caserio, G. E. Dennis, R. H. DeWolfe, and W. G. Young, *ibid.*, 77, 4182 (1955).

(6) In reactions of this type asymmetry is lost at one allylic carbon atom and created at the other. In some cases (*e.g.*, rearrangements of esters)[4] the migrating group is bonded in the same way in the reactant and product, *i.e.*, X = Z, and rearrangement results in reversible interconversion of enantiomers. In other cyclic processes (*e.g.*, Claisen rearrangement and SNi′ collapse of the chlorosulfinate[5]) the allylic substituent in the product Z differs from that in the reactant X.

(7) E. R. Alexander and R. W. Kluiber, *J. Am. Chem. Soc.*, **73**, 4304 (1951).

(8) H. Hart, *ibid.*, **76**, 4033 (1954).

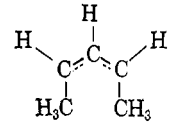
(9) Except as noted, rotations are for neat samples (*l* = 1 dm.).

(10) H. L. Goering and R. R. Jacobson, *J. Am. Chem. Soc.*, **80**, 3277 (1958).

(11) E. N. Marvell and J. L. Stephenson, *J. Org. Chem.*, **25**, 676 (1960); E. N. Marvel, J. L. Stephenson, and J. Ong, *J. Am. Chem. Soc.*, **87**, 1267 (1965).

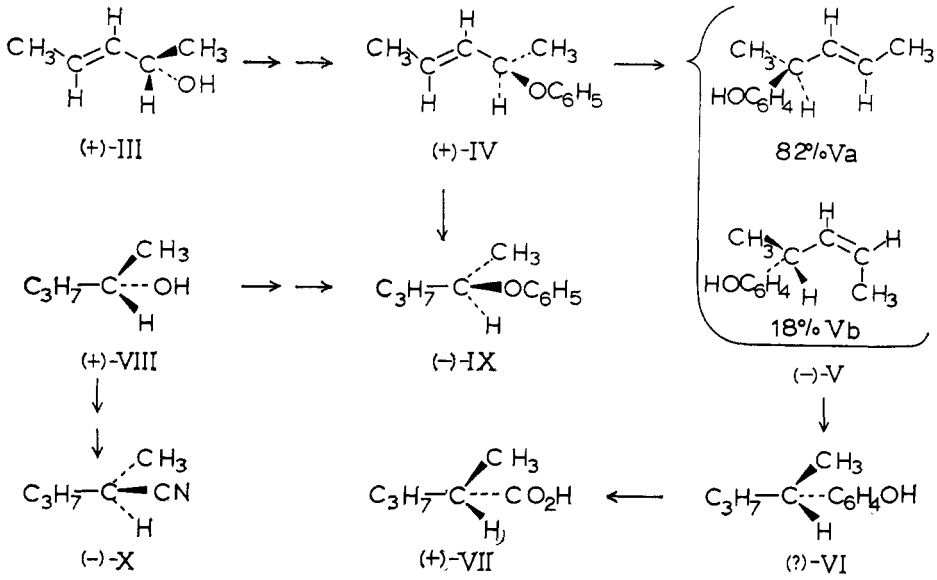
(12) A. W. Burgstahler, *ibid.*, **82**, 4681 (1960).

isomer Va. Similarly, rearrangement of *trans*-α,γ-dimethylallyl vinyl ether (I, X = $OCH{=}CH_2$) gives *trans*-3-methyl-4-hexenal (Z = CH_2CHO).[12,13] These results show that, contrary to the earlier proposal,[8] rearrangement of the *trans* ether IV proceeds for the most part *via* the transition state related to Ia as would be expected.[10] It is interesting to note that the α,γ-dimethylallylphenol derived from *cis*-α,γ-dimethylallyl phenyl ether contains less of the *cis* phenol Vb than that derived from the *trans* ether IV.[11] This also can be accounted for on the basis of the preferred configuration of the allyl moiety in the transition state. The two possible configurations for rearrangement of the *cis* ether are IIb (*cis* ether → *trans* phenol) and IIc (*cis* ether → *cis* phenol). Scale models indicate that the difference in stability for IIb and IIc is larger than for IIa and IIb. Thus the *cis* ether would be expected to give less *cis* phenol than the *trans* ether.



IIc

Chart I



In the present work a new synthesis of active *trans*-α,γ-dimethylallyl phenyl ether (IV) was developed which gives product some 70 times more active than that used in the earlier work.[7] The geometric configurational composition of the rearrangement product V was determined by gas chromatography and optical configurations were related by the transformations outlined in Chart I. In earlier work active 2-pentanol[14] and α-methylvaleric acid[15] were related to compounds for which absolute configurations are now known. This makes possible the assignment of the absolute configurations shown in Chart I.

Results and Discussion

The preparation of *trans*-α,γ-dimethylallyl phenyl ether (IV) by alkylation of phenol (homogeneous or heterogeneous reactions[16]) with α,γ-dimethylallyl chloride derived from optically active *trans*-α,γ-dimethylallyl alcohol (III)[4,17] results in almost complete loss of optical configuration. Alexander and Kluiber[7] used this method (heterogeneous alkylation) and obtained (−)-IV, $\alpha^{25}D$ −0.10°,[9] from (+)-III[18] of unspecified optical purity. The most successful effort[19] in our laboratory using this approach (homogeneous alkylation) gave (−)-IV, $\alpha^{25}D$ −1.0°, from >95% optically pure[4c] (+)-III. The extensive loss of configuration associated with this two-step process is not unexpected as this would result from racemization of the chloride prior to alkylation[20] or ionization of the chloride during alkylation (*i.e.*, an SN1 reaction).

In the present work optically active *trans*-α,γ-dimethylallyl phenyl ether was prepared by alkylation of phenoxide ion in diglyme (homogeneous reaction) with *trans*-α,γ-dimethylallyl 2,4-dinitrophenyl ether

(13) R. K. Hill and A. G. Edwards, *Tetrahedron Letters*, No. 44, 3239 (1964), have recently related the configurations of reactant and product for the thermal rearrangement of optically active cyclopenten-3-yl vinyl ether to cyclopentene-3-acetaldehyde: (*R*)-(+)-ether gives (*R*)-(−)-aldehyde (*i.e.*, bond making is *cis* to bond breaking). In cyclic systems of this type rotation about the C_α–C_β bond is precluded and thus the occurrence of rearrangement in itself establishes the relative configurations beyond reasonable doubt; see A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, 83, 198 (1961).

(14) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, 81, 703 (1929).

(15) S. Stallberg-Stenhagen and E. Stenhagen, *Arkiv Kemi Mineral. Geol.*, B24, No. 9 (1947); S. Stallberg-Stenhagen, *ibid.*, A23, No. 15 (1946).

(16) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, 81, 2705 (1959).

(17) H. W. J. Hill, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 576 (1936).

(18) As first noted by Kenyon, *et al.*,[17] optically active III has unusual optical properties—the rotation is small and the magnitude and sign vary with time. In other work[33] it was shown that the time dependence of sign and magnitude of the rotation is not due to optical instability of the alcohol—samples of the same preparation having different rotations (sign and magnitude) gave solid acid phthalate derivatives of the same optical purity as that from which the active III was derived. Evidently this anomalous behavior is due to formation of trace amounts of highly active contaminants, *e.g.*, peroxides. To avoid ambiguities the optical purity and configuration of active III should be based on the rotation of the acid phthalate derivative (high and reproducible) rather than on that of the alcohol—the alcohol can be derived from this derivative without change in optical purity.[4] In this and other papers dealing with active III we refer to the optical isomer derived from the (+)-acid phthalate derivative as the (+)-isomer. Levene and Haller[14] refer to this same isomer as the (−)-isomer.

(19) R. R. Jacobson, Ph.D. Thesis, University of Wisconsin, 1960.

(20) For examples of racemizations of allylic chlorides of this type under mild conditions, see H. L. Goering, T. D. Nevit, and E. F. Silversmith, *J. Am. Chem. Soc.*, 77, 4042, 5026 (1955).

derived from optically active III. The advantages of using this alkylating agent are that (a) it is prepared (from III and 2,4-dinitrofluorobenzene[21]) with preservation of optical configuration and (b) it is less likely to racemize or react by an SN1 process than the chloride. By this procedure (+)-IV, $\alpha^{25}D$ +7.80°,[9] was obtained from 87% optically pure (+)-III.[18] This product is about eight times as active (and of opposite configuration) as that obtained by the alternate route and 78 times more active than that used in the earlier investigation.[7] That (+)-IV obtained in this manner is the *trans* isomer was shown by the infrared spectrum[22] (strong absorption at 962 cm.$^{-1}$ and none in the 720, 953, or 1006-cm.$^{-1}$ regions[11]); capillary gas chromatography gave a single sharp peak which also indicates the absence of the *cis* isomer.

It has been shown[14] that (+)-III (the isomer derived from the (+)-acid phthalate[18]) has the same configuration as (+)-2-pentanol (reduction) and (+)-lactic acid (oxidation). Thus (+)-III and (+)-VIII have the absolute configurations shown in Chart I. Another investigation by Levene and Haller,[23] in which they showed that (−)-2-pentanol is related to (−)-γ-hydroxybutyric acid, which has the same configuration as (−)-lactic acid, serves as a double check of these assignments.

The assignment of the (*R*) configuration to (+)-*trans*-α,γ-dimethylallyl phenyl ether (+IV) is based on the stereospecific synthesis (conversion of (*S*)-(+)-III to the 2,4-dinitrophenyl ether without involvement of the asymmetric center and alkylation with inversion[24] of configuration) and reduction to (*R*)-(−)-2-pentyl phenyl ether (−IX). The configuration of the latter was established by stereospecific synthesis from active 2-pentanol (VIII) of known configuration. In this synthesis (*S*)-(+)-VIII, $\alpha^{20}D$ +10.30° (92% optically pure[25]), was converted to the *p*-toluenesulfonate derivative (retention) which when treated with phenoxide ion (inversion[24]) gave (−)-IX, $\alpha^{25}D$ −33.0°.[22] On another occasion[19] it was observed that (+)-VIII, $\alpha^{21}D$ +8.84°, gave (−)-IX, $\alpha^{21}D$ −29.90°, by this sequence of reactions. Assuming that the optical purity of the ether IX is the same as that of the alcohol—the agreement for the two preparations indicates this is the case—the rotation of optically pure IX is $\alpha^{21-25}D$ 37 ± 1.5°.[9]

Reduction of (+)-IV, $\alpha^{25}D$ +7.80°, over platinum oxide gave (−)-IX, $\alpha^{25}D$ −16.0°.[22] This rotation corresponds to an optical purity of 43 ± 2% which represents a lower limit for the optical purity of the (+)-IV from which it was derived. This is a lower limit because of the possibility that some activity is lost in the hydrogenation step. However, there is evidence that little, if any, activity is lost in the conversion of (+)-IV to (−)-IX. In other work[19] it was observed that (+)-IV, $\alpha^{25}D$ +0.50°, gave (−)-IX, $\alpha^{25}D$ −0.96°, when hydrogenated over 10% palladium-on-carbon catalyst. The ratio of these rotations is about the same as for the above experiment which means that the two catalyst systems give similar results. Evidence has been presented elsewhere[26] that catalytic hydrogenation (palladium on carbon) of optically active allylic acetates and acid phthalates results in little, if any, loss of configuration. From these observations it seems unlikely that activity is lost during hydrogenation and thus it appears that the optical purity of (+)-IV, $\alpha^{25}D$ 7.80°, is close to the limiting value of 43 ± 2%. These findings show that the active IV used in the earlier investigation was <1% optically pure and that the three-step transformation of the allylic alcohol +III to the phenyl ether −IV results in about 50% loss of configuration. Presumably most, if not all, of this occurs in the alkylation step.

Rearrangement of *trans*-α,γ-dimethylallyl phenyl ether (IV) to 2-(α,γ-dimethylallyl)phenol (V) was carried out by heating neat samples at 200° for 1 hr. Under these conditions (+)-IV, $\alpha^{25}D$ +7.40°, gave (−)-V, $\alpha^{25}D$ −15.0°. The infrared spectrum of the phenolic fraction V[22] indicated that it was primarily the *trans* isomer Va (strong absorption of 967 cm.$^{-1}$ [11]), with a lesser amount of the *cis* isomer Vb (weak absorption at 710 and 1265 cm.$^{-1}$ [11]). Capillary gas chromatography (g.c.) (only two peaks) showed the composition to be 82% Va and 18% Vb. That the peaks corresponded to the geometric isomers was shown by hydrogenation to a single product (one peak). These results are in qualitative agreement with the earlier reports[11,12] that the product derived from IV is mostly, but not entirely,[11] the *trans* phenol. It should be noted that the composition observed in the present work may differ somewhat from that of the reaction product because of possible fractionation during isolation (extractions) and purification (distillation)—our primary concern was to obtain pure samples for polarimetric measurements.

The configuration of (−)-V (82% Va, 18% Vb) was determined by a two-step conversion to (+)-α-methylvaleric acid. The first step involved hydrogenation of the allylic side chain to give 2-(2-pentyl)-phenol (VI). Cram[27] has observed that catalytic hydrogenation of a similar substrate, (−)-3-phenyl-1-butene, results in from 1 to 11% loss of optical configuration, depending on the conditions, and that this loss occurs before, and not after hydrogenation. In the present work we used conditions (Raney nickel and low pressure) which would be expected[27,28] to result in least loss of optical activity. It is likely that V is more susceptible to racemization (by formation of radical intermediates[28]) than 3-phenyl-1-butene and that this step results in some loss of configuration, *vide infra*.

The hydrogenation product VI was shown to be homogeneous (g.c.) and the infrared spectrum was the same as that of an authentic sample. The observed rotation of this product was zero. However, it was shown to be optically active by conversion to (+)-α-methylvaleric acid (+VII), $\alpha^{25}D$ +2.36° (for one experiment); $\alpha^{25}D$ +2.80° (average value for several

(21) W. B. Whalley, *J. Chem. Soc.*, 2241 (1950).

(22) In all cases infrared spectra of liquid samples or solutions of active samples were indistinguishable from those of authentic racemic samples.

(23) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **81**, 425 (1929).

(24) H. Hart and H. S. Eleuterio, *J. Am. Chem. Soc.*, **76**, 516, 519 (1954).

(25) D. H. Brauns, *J. Res. Nat. Bur. Std. A.*, **31**, 83 (1943), reports $\alpha^{20}D$ +11.26° (neat) for presumably optically pure (+)-VIII.

(26) H. L. Goering and U. Mayer, *J. Am. Chem. Soc.*, **86**, 3753 (1964).

(27) D. J. Cram, *ibid.*, **74**, 5518 (1952).

(28) W. A. Bonner, C. E. Stehr, and J. R. de Ameral, *ibid.*, **80**, 4732 (1958); W. A. Bonner and J. B. McKay, *ibid.*, **82**, 5350 (1960).

experiments).[9,22] The ethyl ester and amide of (+)-VII were dextrorotatory. In earlier work Levene and Mikeska[29] observed that rotations of active VII and the corresponding ethyl ester and amide have the same sign.

The absolute configuration of (+)-α-methylvaleric acid (+VII) can be assigned on the basis of two independent correlations. It has been shown[15] that (+)-VII has the same configuration as (−)-methylsuccinic acid which in turn has been related to (−)-malic acid by the quasi-racemate method.[30] This means that (+)-VII has the *S*-configuration as indicated. The alternate correlation involves relating active VII and 2-pentanol (VIII). Conversion of (*S*)-(+)-VIII, $\alpha^{25}D$ +10.30°, to the *p*-toluenesulfonate derivative (retention) followed by reaction with sodium cyanide in diethylene glycol gave (−)-α-methylvaleronitrile (−X), $\alpha^{25}D$ −28.0°. The displacement step involves inversion of configuration and thus (−)-X must have the indicated *R*-configuration.[31] It has been shown that (−)-X has the same configuration as (−)-α-methylvaleric acid (−VII).[29] Thus (−)-X and (+)-VII have opposite configurations which confirm the indicated assignments.

The correlation of the rearrangement product with α-methylvaleric acid shows that (−)-V (82% Va, 18% Vb) has the *S*-configuration which is opposite that of the ether +IV from which it was derived. Thus the relative optical configurations are in accord with the relative geometric configurations.[11,12]

For reasons outlined in the introduction the *trans* Va and *cis* Vb phenols have opposite configurations and thus hydrogenation converts these isomers to enantiomers. This means that the maximum optical purity of the hydrogenation product VI derived from (−)-V (82% Va, 18% Vb) is 64% that of the reactant (+IV)—this is an upper limit because activity may be lost in the hydrogenation step.[27,28] The estimated lower limit for the optical purity of the reactant, (+)-IV, $\alpha^{25}D$ +7.40°, is 41 ± 2% (*vide supra*) and, if optical configuration were fully preserved in the three-step conversion of (+)-IV to (+)-α-methylvaleric acid (+VII), the minimum optical purity of the latter would be 26 ± 2%.

Rotations of $\alpha^{16}D$ 17.2°[15] and $\alpha^{25}D$ 16.90°[9,32] have been reported for presumably optically pure α-methylvaleric acid. Thus the maximum optical purity of the (+)-VII, $\alpha^{20}D$ 2.80°, obtained from (−)-V, is 16%. This indicates that about 40% of the optical purity is lost in the two-step conversion of V to VII.

The present results show that contrary to the earlier suggestion[8] the optical configuration of the product is opposite that of the reactant for the *ortho* Claisen rearrangement of *trans*-α,γ-dimethylallyl phenyl ether (IV). Thus, as anticipated,[10] the stereochemistry for this reaction is similar to that of other allylic rearrangements of *trans*-α,γ-dimethylallyl derivatives.[4,5]

(29) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **84**, 571 (1929).
(30) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 5.
(31) *Cf.* conversion of (*S*)-(+)-2-butanol to (*R*)-(−)-α-methylbutyronitrile by same reaction sequence: J. A. Mills and W. Klyne, "Progress in Stereochemistry I," W. Klyne, Ed., Butterworth and Co. (Publishers) Ltd., London, 1954, p. 197.
(32) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **98**, 1 (1932).

Experimental[9]

(+)-*trans*-α,γ-*Dimethylallyl Alcohol* (+*III*). (+)-*trans*-α,γ-Dimethylallyl acid phthalate, m.p. 79–82°, $[\alpha]^{25}D$ +33.90° (ether), was prepared and resolved as described earlier.[4,17] The rotation of optically pure material has been determined[4c] by an isotope dilution method and on this basis the estimated optical purity is 87%. The acid phthalate was saponified by a method[17,33] that does not result in loss of configuration and the resulting (+)-*trans*-α,γ-dimethylallyl alcohol (+III)[18] had b.p. 118–121°, $n^{25}D$ 1.4250.[22] In another study[34] it was found that (+)-III, derived from 92% optically pure acid phthalate, $[\alpha]^{25}D$ 35.4° (*l*, 4; *c* 1.1, ethanol)—reduction ($LiAlH_4$)[4] or saponification[33] give (+)-III with full preservation of optical activity[34]—had $\alpha^{25}D$ +0.413° immediately upon isolation, $\alpha^{25}D$ −0.07° 1 hr. later, $\alpha^{25}D$ 0.00° several hours later, and $\alpha^{25}D$ +0.16° 2 days later.[18] Each of these samples gave acid phthalate derivatives having the original optical rotation.

(+)-*2-Pentanol* (+*VIII*). 2-Pentyl acid phthalate was resolved by the method used for the resolution of *trans*-α,γ-dimethylallyl acid phthalate except that the brucine salt was recrystallized from acetone instead of acetone–chloroform mixtures. After several recrystallizations the brucine salt had m.p. 155–157°, $[\alpha]^{20}D$ −4.6° (*l*, 4; *c* 3.7, ethanol); lit.[35] m.p. 155–156°, $[\alpha]^{20}D$ −3.91° (ethanol). The resolved acid phthalate derivative was not isolated because of its low melting point (34°).[35] Saponification[33] gave (+)-2-pentanol (+VIII), b.p. 118.5°, $n^{25}D$ 1.4045, $\alpha^{20}D$ +10.3[22] (lit. $\alpha^{20}D$ +11.1°[35] and +11.26°[25]).[9] The highest reported[25] rotation is presumably for optically pure material. Thus the product obtained in the present work was about 92% optically pure. Capillary g.c.[36] showed this product to be homogeneous.

(+)-α,γ-*Dimethylallyl Phenyl Ether* (+*IV*). In a typical experiment a mixture of 43 g. (0.5 mole) of (+)-III (87% optically pure), 93 g. (0.5 mole) of 2,4-dinitrofluorobenzene, and 50.5 g. (0.5 mole) of triethylamine was warmed on a steam bath for a few minutes and then allowed to stand at room temperature for 2 hr.[21] The dark mixture was diluted with ether and then extracted with 5% hydrochloric acid, 5% sodium bicarbonate solution, and water. After drying (Na_2SO_4) the solvent was removed (steam bath) and the *trans*-α,γ-dimethylallyl 2,4-dinitrophenyl ether was obtained as a viscous, red-orange residue. This material, without attempted purification, was dissolved in 200 ml. of diglyme and the resulting solution was added to a stirred solution of 0.75 mole of sodium phenoxide (prepared from 71 g. of phenol and 18 g. of sodium hydride) in 300 ml. of diglyme. The dark colored mixture was stirred and heated (55°) for 48 hr. after which it was diluted with 1.5 l. of water. The resulting mixture was extracted with four 250-ml. portions of pentane. The organic extracts were combined and extracted four times with 200-ml. portions of 10% sodium hydroxide. After washing with water the organic layer was dried (K_2CO_3) and

(33) H. L. Goering and J. P. Blanchard, *J. Am. Chem. Soc.*, **76**, 5405 (1954).
(34) R. W. Greiner, Ph.D. Thesis, University of Wisconsin, 1957.
(35) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).
(36) Column (300-ft.) with a polypropylene 550 (Ucon) coating.

concentrated on a steam bath. Distillation gave 24 g. (28% yield) of (+)-*trans*-α,γ-dimethylallyl phenyl ether (+IV), b.p. 65° (0.5 mm.), $n^{25}D$ 1.5083, $\alpha^{25}D$ +3.70° (*l*, 0.5, neat). The infrared spectrum[22] showed strong absorption at 962 cm.$^{-1}$ (*trans* isomer[11]) and none at 720, 953, and 1006 cm.$^{-1}$ (*cis* isomer[11]). Capillary g.c.[36] showed this material to be homogeneous.

(−)-2-Pentyl Phenyl Ether (−IX). A. By Reduction of (+)-trans-α,γ-Dimethylallyl Phenyl Ether (+IV). Hydrogenation of 2.0 g. of (+)-IV, $\alpha^{25}D$ +7.80°, over 200 mg. of PtO_2 in 50 ml. of absolute ethanol at atmospheric pressure resulted in rapid uptake of 1 equiv. of hydrogen. After removal of the catalyst, the solvent was removed under reduced pressure (aspirator). Distillation of the residue gave 1.0 g. (50% yield) of (−)-2-pentyl phenyl ether (−IX), b.p. 55–56° (0.2 mm.), $n^{25}D$ 1.4891, $\alpha^{25}D$ −8.00° (*l*, 0.5, neat). Capillary g.c.[36] showed this material to be homogeneous and the infrared spectrum was indistinguishable from that of an authentic analytical sample.[19]

B. From (+)-2-Pentanol (+VIII). A solution of 32 g. (0.36 mole) of (+)-2-pentanol (+VIII), $\alpha^{20}D$ +10.30°, in 450 ml. of dry pyridine was chilled in an ice–salt bath and 76 g. (0.40 mole) of *p*-toluenesulfonyl chloride was added. The mixture was shaken until all of the acid chloride dissolved and then was placed in a freezer overnight. Small pieces of ice were added to consume the excess acid chloride and then the reaction mixture was diluted with 1 l. of ice water. The mixture was extracted with three 200-ml. portions of ether and the ether extracts were combined and washed with dilute hydrochloric acid, potassium carbonate solution, and water. After drying (Na_2SO_4) the ether was removed under reduced pressure and 65 g. (74%) of (+)-2-pentyl *p*-toluenesulfonate was obtained as a pale orange residual oil, $\alpha^{25}D$ +8.20°, $n^{25}D$ 1.4950.[22] Racemic liquid 2-pentyl *p*-toluenesulfonate isolated by this method has been shown to be 98–99% pure.[37]

The *p*-toluenesulfonate derivative of (+)-VIII was converted to the phenyl ether (−)-IX as follows. To a stirred solution of 23 g. of sodium phenoxide (0.2 mole) in 200 ml. of diglyme was added a solution of 25 g. (0.1 mole) of the above described (+)-2-pentyl *p*-toluenesulfonate in 50 ml. of diglyme. The resulting solution was stirred for 4 days at room temperature after which 800 ml. of water was added and the solution extracted with four 150-ml. portions of pentane. The organic extracts were combined and washed with 10% sodium hydroxide and water. After drying (K_2CO_3), the solvent was removed. Distillation gave 9.2 g. (56%) of (−)-2-pentyl phenyl ether, b.p. 57–58° (0.2 mm.), $n^{25}D$ 1.4892, $\alpha^{25}D$ −33.0°.[22] Capillary g.c.[36] showed this product to be homogeneous. Except for the magnitude of the rotation the physical and spectral properties of samples prepared by methods A and B were indistinguishable.

Rearrangement of (+)-α,γ-Dimethylallyl Phenyl Ether (+IV). In a typical experiment 18 g. of (+)-IV, $\alpha^{25}D$ 3.70° (*l*, 0.5, neat) was heated to 200° for 1 hr. After cooling, the yellow product was diluted with 100 ml. of pentane and the resulting solution was extracted with four 50-ml. portions of 10% aqueous sodium hydroxide. The basic extracts were combined, washed with pentane, and acidified with carbon dioxide. Extraction with pentane followed by distillation gave 9 g. (50%) of (−)-2-(α,γ-dimethylallyl)phenol (−V), b.p. 85–87° (0.5 mm.), $n^{25}D$ 1.5341, $\alpha^{25}D$ −7.50° (*l*, 0.5, neat).[22] The infrared spectrum (liquid film) showed strong absorption at 967 cm.$^{-1}$ (*trans* isomer[11]) and weak absorption at 710 and 1265 cm.$^{-1}$ (*cis* isomer[11]). Capillary g.c.[36] showed this product to be a binary mixture consisting of 82% of the *trans* isomer Va (first peak) and 18% of the *cis* isomer Vb. Catalytic reduction resulted in these peaks being replaced by a single new peak.

Conversion of (−)-2-(α,γ-Dimethylallyl)phenol (−V) to (+)-α-Methylvaleric Acid (+VII). A. Reduction of (−)-V. Reduction of 6.5 g. of (−)-V, $\alpha^{25}D$ −7.50° (*l*, 0.5, neat) in 100 ml. of absolute ethanol over 2 teaspoonfuls of Raney nickel resulted in rapid uptake of from 86 to 99% (for a number of runs) of 1 equiv. of hydrogen (hydrogenation was terminated when the rate dropped to about 5% of the initial value). After removal of the catalyst the product was distilled and 2-(2-pentyl)phenol (VI) was obtained in yields of from 77 to 89%. This material was homogeneous (g.c.)[36] and had $n^{25}D$ 1.5150, zero rotation at the sodium D and mercury 4358 and 5460 lines (lit.[19] $n^{25}D$ 1.5149). Infrared spectra of samples prepared in this manner were indistinguishable from that of an authentic analytical sample.[19]

B. Oxidation of 2-(2-Pentyl)phenol (VI) to (+)-α-Methylvaleric Acid (+VII). This transformation involved ozonization followed by oxidation of the ozonide. The reported procedure[38] for the conversion of cyclohexene to adipic acid was used and VI, derived from (−)-V (82% Va, 18% Vb), $\alpha^{25}D$ −15.0°, gave (+)-α-methylvaleric acid (+VII). The yield of distilled product (+)-VII was from 32 to 55%. The (+)-VII had $n^{25}D$ 1.4123 and 1.4130, $\alpha^{25}D$ +1.18° and +1.40° (*l*, 0.5, neat).[22]

A sample of (+)-VII, $\alpha^{25}D$ +2.80°, was converted[29] to (+)-ethyl α-methylvalerate, $n^{25}D$ 1.4017, $\alpha^{25}D$ +1.43 (*l*, 0.5, neat).[22] This ester was shown to be homogeneous by capillary g.c.[36]

Another sample of (+)-VII, $\alpha^{25}D$ 2.36°, was converted[29] to (+)-α-methylvaleramide, m.p. 78–79.4°, $[\alpha]^{25}D$ +1.34° (75% ethanol). Levene and Mikeska[29] have reported the conversion of (−)-VII to the levorotatory ethyl ester and amide.

Conversion of (+)-2-Pentanol (+VIII) to (−)-Valeronitrile (−X). Solutions of (a) 23 g. (0.47 mole) of sodium cyanide in 190 ml. of freshly distilled diethylene glycol and (b) 48.5 g. (0.2 mole) of the *p*-toluenesulfonate derivative of (+)-VIII, $\alpha^{25}D$ +10.30°, described above, $\alpha^{25}D$ +8.2°, in 30 ml. of pure diethylene glycol were mixed and the resulting solution was stirred at room temperature for 7 days. The dark reaction mixture was diluted with 2 l. of water and extracted with three 200-ml. portions of ether. The ether extracts were combined and washed with water and dried (Na_2SO_4). After removal of solvent (steam bath) the dark residue was distilled and 6 g. of a frac-

(37) E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.*, **76**, 791 (1954).

(38) P. S. Bailey, *Ind. Eng. Chem.*, **50**, 993 (1958); *Chem. Rev.*, **58**, 925 (1958).

tion boiling at 140–144° was collected. Redistillation of this fraction gave 2.0 g. (10%) of (−)-α-methylvaleronitrile, b.p. 145–147°, $n^{25}D$ 1.3938, $\alpha^{25}D$ −28.0° (lit.[39] b.p. 146.6°, $n^{30}D$ 1.3959 for racemic material). Capillary g.c.[36] showed this product to be homogeneous.[22]

(39) C. de Hoffmann and E. Barbier, *Bull. soc. chim. Belges*, **45**, 565 (1936).

Azomethine Chemistry. III. Reduction of N-Pyruvylamino Acid Azomethines[1,2]

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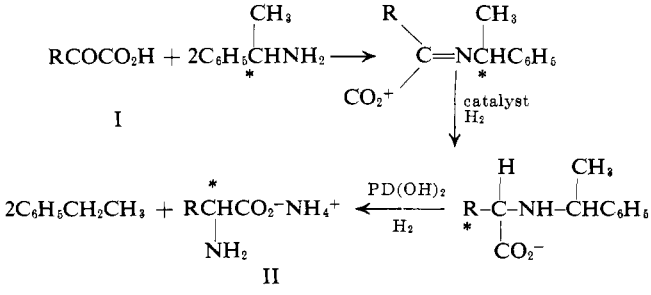
Contribution from the Venable Chemical Laboratory, The University of North Carolina, Chapel Hill, North Carolina. *Received July 13, 1964*

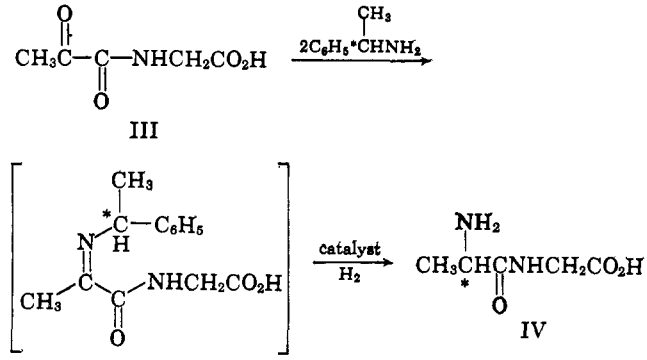
Reductive amination of N-pyruvylglycine with D-(+)- *and* L-(−)-*α-methylbenzylamine provided* D- *and* L-*alanylglycine in optical yields of approximately 50%. When the procedure was applied to N-pyruvyl-*L-*alanine using* D-(+)-*α-methylbenzylamine the ratio of* D-*alanyl-*L-*alanine to the* LL-*isomer was 74:26; with benzylamine the ratio was 67:33; with* L-(−)-*α-methylbenzylamine the ratio was 36:64. These results are discussed in terms of the Prelog rule of asymmetric induction.*

An earlier report[4] on the formation of optically active α-amino acids, by catalytic hydrogenation of the azomethines derived from resolved α-methylbenzylamine and various α-keto acids, described several features of the over-all process. The most striking aspect of the conversion of I to II was the fact that the configuration of the α-amino acid produced depended on the configuration of α-methylbenzylamine employed, *i.e.*, L-amine gave L-amino acid; D-amine gave D-amino acid. The yield and optical purity of the α-amino acids prepared by this route were compared with the size of the side chain, R, present in I. In general the yield of II was found to decrease as the size of R increased from methyl to *t*-butyl. The reduction



also became less selective as the size of the side chain increased, *i.e.*, the optical yield[5] decreased from 82% for alanine (II, R = CH_3–) to 63% for butyrine (II, R = CH_3CH_2–), to 28% for valine (II, R = $(CH_3)_2CH$–). A logical extension of this reaction sequence would involve a study of the hydrogenation of several N-pyruvylamino acids in the presence of optically active α-methylbenzylamine. The present report concerns the results of such an investigation.

The reductive amination of N-pyruvylglycine (III), by analogy with the previous experiments,[4] would be expected to provide alanylglycine (IV). The optical yields of IV should be similar to those previously obtained with α-keto acids. Thus, any asymmetry observed in IV would arise from the influence of the asymmetric center in the α-methylbenzyl portion of



the molecule on the hydrogenation.

A similar experiment using N-pyruvyl-L-alanine (V) as a substrate would present a somewhat different stereochemical situation. That is, the azomethine VII derived from V and optically active α-methylbenzylamine contains two asymmetric centers, both of which would be expected to influence the stereochemistry of the reduction.

The effect of the asymmetric center in the L-alanine portion of V, on the reduction of the azomethine, can be evaluated in the following manner. The structure of the azomethine VII is formally analogous to the substrates studied by Prelog, *et al.* Catalytic hydrogenation of α-keto esters of optically active alcohols has been discussed[6] and adherence to the "Prelog rule" was found, provided the substrate contained a single asymmetric center in the alcohol portion of the molecule.

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(2) Part II of this series: R. G. Hiskey and J. M. Jung, *J. Am. Chem. Soc.*, **85**, 578 (1963).

(3) Abstracted in part from a dissertation submitted by R. C. Northrop to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. Degree, Dec. 1963.

(4) R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.*, **83**, 4798 (1961).

(5) Defined as ($[\alpha]^{25}D$ observed/$[\alpha]^{25}D$ literature) × 100.

(6) V. Prelog, *Bull. soc. chim. France*, 987 (1956).