

When 24.0 g. of *d,l*-erythro-1,2-diphenyl-1-propyl chloride was submitted to the above procedure, 96% of the starting material was recovered, m.p. 139–140°, undepressed by admixture with an authentic sample.

When a mixture of 5.0 g. of *d,l*-threo-1,2-diphenyl-1-propyl chloride, 10 g. of lithium iodide and 75 ml. of benzene was held at reflux for 48 hours, a 94% recovery of starting mate-

rial was realized, m.p. 53–54° (undepressed by admixture with an authentic sample).

Acknowledgment.—The authors wish to acknowledge the value of conversations about portions of this paper with Dr. R. L. Scott.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Studies in Stereochemistry. XV. Effect of Configuration on Steric Inhibition of Resonance in Diastereomerically Related Compounds

BY FRED HAWTHORNE¹ AND DONALD J. CRAM²

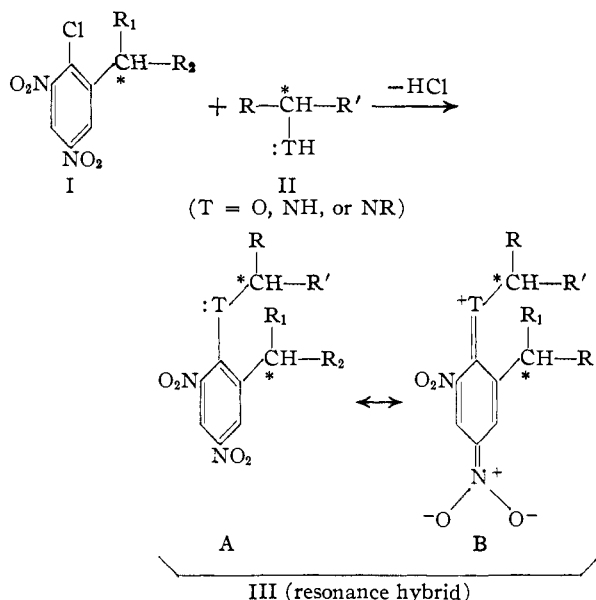
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This investigation has demonstrated the feasibility of using differences between the ultraviolet absorption spectra of certain diastereomerically related compounds to determine the relative configurations of the asymmetric carbon atoms involved.

The four stereoisomers of Compound VIII have been prepared, and the configurations of the two asymmetric carbon atoms in each have been related to D-glyceraldehyde by chemical transformations. Comparisons of the spectra of the diastereomers of VIII, and of model compounds and VIII indicate that different degrees of steric inhibition of resonance exist in the diastereomers. The direction of this difference is in agreement with the direction predicted from a comparison of molecular models of the diastereomers. The relative rates of the reaction of the enantiomers of 2-s-butyl-4,6-dinitrochlorobenzene with (+)- α -phenylethylamine to form diastereomers of VIII have been determined. The qualitative relationship between these rates has been correlated with the differences in spectra in the products, and the differences in the steric situations found in hypothetical models for the diastereomerically related transition states for the two reactions.

Correlations between the signs of rotations of optically active molecules and the configurations about the asymmetric centers responsible for the activity have been of great value in making configurational assignments to substances whose stereochemical structures are unknown. The use of other physical properties in relating the configurations about two or more asymmetric carbon atoms within the same molecule has occasionally been of value,³ but has never received widespread attention. This investigation was undertaken to explore the possibility of determining the configurations of optically active amines and alcohols relative to D-glyceraldehyde through the use of ultraviolet absorption spectral techniques.

If an optically active reagent of structure I is allowed to react with an optically active amine or alcohol such as II, then compound III is capable of existing in either of two diastereomeric forms. It has long been recognized that the damping of resonance through steric effects in systems similar to III decreases the intensity and usually the wave length of the major absorption peak in the ultra-



violet absorption spectrum.⁴ Therefore that diastereomer of III in which the two asymmetric carbon atoms come closest to becoming coplanar with the benzene ring should absorb light at the longer wave length and higher intensity. Since the way in which R₁, R₂, R and R' fit together sterically is a function of the configurations about the two asymmetric carbon atoms, then differences in molecular models of the two diastereomers of III should correlate in an *a priori* predictable fashion with the

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(3) Differences in dipole moments [A. Weissberger, *THIS JOURNAL*, **67**, 778 (1945)], and dielectric constants [S. Winstein and R. E. Wood, *ibid.*, **62**, 548 (1940)] between diastereomerically related compounds have been found, and might in some cases prove useful in making configurational assignments. The use of X-ray diffraction techniques has been of great value in a few cases in assigning configurations in such complicated molecules as cholesterol iodide [C. H. Carlisle and D. Crowfoot, *Proc. Roy. Soc. (London)*, **A184**, 64 (1945)] and penicillin [D. Crowfoot, C. W. Bunn, B. W. Rogers-Low and A. Turner-Jones, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 310]. Recently N. H. Cromwell, *et al.*, [*THIS JOURNAL*, **73**, 1044 (1951)] made provisional assignments of configuration to two diastereomerically related iminoketones based on differences in ultraviolet absorption spectra due to differences in steric inhibition of resonance in the two diastereomers.

(4) (a) G. Wheland, "Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 160 (numerous references); (b) W. R. Remington, *THIS JOURNAL*, **67**, 1838 (1945); (c) N. J. Leonard, *et al.*, *ibid.*, **72**, 484, 5388 (1950); (d) R. T. Arnold and P. N. Craig, *ibid.*, **72**, 2728 (1950).

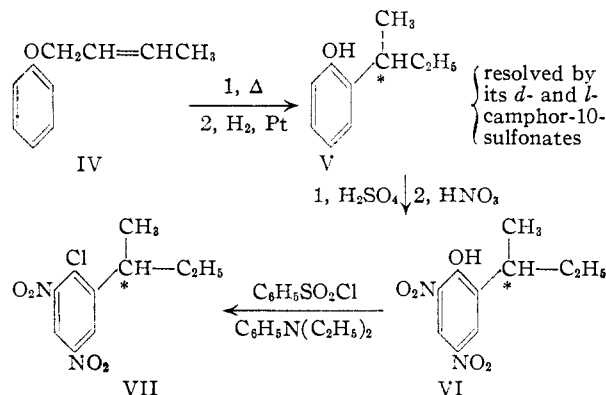
TABLE I
 PHYSICAL PROPERTIES AND ANALYSES OF 2-*s*-BUTYLPHENOL AND DERIVATIVES

Compound	Number	M.p., °C.	[α] ²⁵ _D	Formula	Analyses, %			
					Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
DL-2- <i>s</i> -Butylphenol	V ^a	C ₁₀ H ₁₄ O	79.96	79.90	9.39	9.36
L-(+)-2- <i>s</i> -Butylphenol	L-V ^a	+18.1 ^b	C ₁₀ H ₁₄ O	...	79.88	..	9.46
D-(-)-2- <i>s</i> -Butylphenol	D-V ^a	-16.7 ^c	C ₁₀ H ₁₄ O	...	79.86	..	9.52
L-(+)-2- <i>s</i> -Butylphenyl- <i>d</i> -camphor-10-sulfonate	71-72.5	+42.4 ^d	C ₂₀ H ₂₈ O ₄ S	65.90	65.79	7.74	7.86
D-(-)-2- <i>s</i> -Butylphenyl- <i>l</i> -camphor-10-sulfonate	70-71	-40.3 ^d	C ₂₀ H ₂₈ O ₄ S	...	65.85	..	8.04
DL-2- <i>s</i> -Butylphenyl phenylurethan	86	C ₁₈ H ₁₉ O ₂ N	75.81	75.57	7.11	7.12
DL-2- <i>s</i> -Butyl-4,6-dinitrophenol	VI	40-41	C ₁₀ H ₁₂ O ₆ N ₂	49.99	50.00	5.04	5.14
L-(+)-2- <i>s</i> -Butyl-4,6-dinitrophenol	L-VI	30-31	+13.7 ⁱ	C ₁₀ H ₁₂ O ₆ N ₂	...	50.29	..	5.29
D-(-)-2- <i>s</i> -Butyl-4,6-dinitrophenol	D-VI	29-30	-11.90 ^{d,e}	C ₁₀ H ₁₂ O ₆ N ₂	...	50.10	..	5.30
DL-2- <i>s</i> -Butyl-4,6-dinitrochlorobenzene	VII	54-54.5	C ₁₀ H ₁₁ O ₄ N ₂ Cl	46.43	46.45	4.29	4.25
L-(+)-2- <i>s</i> -Butyl-4,6-dinitrochlorobenzene	L-VII	48-49	+18.7 ^d	C ₁₀ H ₁₁ O ₄ N ₂ Cl	...	46.57	..	4.43
D-(-)-2- <i>s</i> -Butyl-4,6-dinitrochlorobenzene	D-VII	49-50	-16.45 ^{d,e}	C ₁₀ H ₁₁ O ₄ N ₂ Cl	...	46.30	..	4.34
L-2- <i>s</i> -Butyl-4,6-dinitro- <i>N</i> -(<i>L</i> - α -phenylethyl)-aniline	L,L-VIII	37-38 ^f	+111.2 ^d	C ₁₈ H ₂₁ O ₄ N ₃	62.95	63.30	6.17	6.24
D-2- <i>s</i> -Butyl-4,6-dinitro- <i>N</i> -(<i>D</i> - α -phenylethyl)-aniline	D,D-VIII	38-39 ^f	-99.4 ^{d,h}	C ₁₈ H ₂₁ O ₄ N ₃	...	63.04	..	6.19
L-2- <i>s</i> -Butyl-4,6-dinitro- <i>N</i> -(<i>D</i> - α -phenylethyl)-aniline	L,D-VIII	36-37 ^f	+216 ^d	C ₁₈ H ₂₁ O ₄ N ₃	...	62.99	..	6.20
D-2- <i>s</i> -Butyl-4,6-dinitro- <i>N</i> -(<i>L</i> - α -phenylethyl)-aniline	D,L-VIII	40-41 ^{f,g}	-211 ^{d,i}	C ₁₈ H ₂₁ O ₄ N ₃	...	63.25	..	6.35
Racemate of 2- <i>s</i> -butyl-4,6-dinitro- <i>N</i> -(α -phenylethyl)-aniline	D,D-L,L-VIII	94-94.5	C ₁₈ H ₂₁ O ₄ N ₃	...	62.71	..	6.43
DL-2- <i>s</i> -Butylphenoxyacetic acid	109-110	C ₁₂ H ₁₆ O ₄	69.21	69.01	7.75	7.86
DL-2- <i>s</i> -Butyl-4,6-dinitrophenyltosylate	115-116	C ₁₇ H ₁₉ O ₇ N ₂ S	51.77	51.48	4.60	4.55
DL-2- <i>s</i> -Butyl-4,6-dinitroaniline	IX	116-117	C ₁₀ H ₁₂ O ₄ N ₂	50.21	50.00	5.48	5.55
DL- <i>N</i> -(α -Phenylethyl)-2,4-dinitroaniline	X	114-114.5	C ₁₀ H ₁₀ O ₄ N ₂	58.53	58.68	4.56	4.28

^a B.p. 228° (760 mm.), n_D^{25} 1.5200, d_4^{25} 0.9804; [M_R]_D calcd. 46.30, found 46.58. ^b Highest value ever obtained was α_D^{25} +17.7 (*l* 1, neat), 97.5% optically pure based on calcd. value of +18.6° for optically pure material derived from the rotation of L-(+)-2-phenylbutane (see Experimental part). ^c 90% optically pure (from *b*, above). ^d c 6.0 in benzene. ^e 84% optically pure if corresponding L-(+)-derivative is 95% optically pure. ^f M.p. under liquid pentane in sealed tube. ^g Higher m.p. than enantiomer probably due to presence of diastereomer since D-VII was less optically pure than L-VII. ^h 96% pure if impurity is the diastereomer L,D-VIII. ⁱ 98.5% pure if impurity is the diastereomer, D,D-VIII.

differences of the ultraviolet absorption spectra of the actual diastereomers. If the configuration of the asymmetric carbon in I is known relative to D-glyceraldehyde, then from the spectra of the two diastereomers of III, one should be able to make assignments of configuration to compounds of structure II used in the preparation of the diastereomers of III. An experimental test of the above argument has been devised and carried out. The system in which I is 2-*s*-butyl-4,6-dinitrochlorobenzene and II is α -phenylethylamine has been chosen for study.

The Preparation and Configuration of 2-*s*-Butylphenol and Derivatives.—The reaction sequence utilized in the preparation and the determination of the configuration of 2-*s*-butyl-4,6-dinitrochlorobenzene is outlined below. The satu-



rated phenol(V)⁶ was prepared by the catalytic reduction of 2-(α -methylallyl)-phenol,⁶ and the saturated phenol (V) was characterized through its

(5) A variety of physical constants has been reported for this compound prepared by other synthetic routes [see R. R. Read, C. A. Hewitt and N. R. Pike, *THIS JOURNAL*, **54**, 1194 (1932) and I. P. Tsukervanik and Z. N. Nayarova, *J. Gen. Chem.*, (U.S.S.R.), **7**, 623 (1937)].

(6) L. Claisen and E. Tietze, *Ber.*, **59**, 2344 (1926).

phenylurethan. The resolution of V through the *l*-menthoxyacetate failed (no crystalline material was obtained), and V did not react with *d*-camphoric anhydride in pyridine at 100°. Attempts to form crystalline alkaloid salts of the phenoxyacetic acid prepared from V also failed. The *d*- and *l*-camphor-10-sulfonates of V were prepared and in each case about ten crystallizations of the esters from ethanol provided material of constant melting point and rotation. The optically active phenols were recovered from the sulfonate esters both by hydrolysis (potassium hydroxide in ethylene glycol at 150°) and by reductive cleavage with lithium aluminum hydride.⁷ Each procedure gave active phenol (V) of the same optical rotation (see Table I).

The configurations of the two enantiomorphs of V were determined relative to that of 2-phenylbutane as follows. Kenner⁸ reported that the treatment of ethanol solutions of aryl *p*-toluenesulfonates with a suspension of Raney nickel and hydrogen at atmospheric pressure and room temperature resulted in a cleavage of the C-O bond to give ArH. Application of this elegant dehydroxylation technique to the *p*-toluenesulfonate of (+)-2-*s*-butylphenol gave (+)-2-phenylbutane of 94% optical purity.⁹ Since the configuration of (-)-2-phenylbutane has been related to that of D-glyceraldehyde by unequivocal methods,¹⁰ then the L-

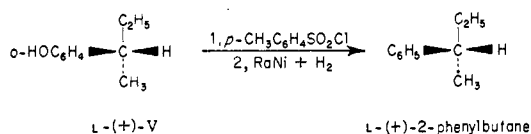
(7) H. Schmidt and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949), report that lithium aluminum hydride cleaves the O-S bond of sulfonate esters when the oxygen is attached to an aromatic ring.

(8) G. W. Kenner, *J. Chem. Soc.*, 3127, S178 (1949).

(9) D. J. Cram, *THIS JOURNAL*, **74**, 2137 (1952), reported α_D^{25} -24.3° (*l* 1 dm. neat) for (-)-2-phenylbutane of proved optical purity.

(10) (a) J. Kenyon, H. Phillips and V. P. Pittman, *J. Chem. Soc.*, 1080 (1935), treated L-(+)-2-butyl *p*-toluenesulfonate with phenylmagnesium bromide to give (-)-2-phenylbutane. That this reaction occurred with inversion of configuration has been demonstrated through a series of interconversions which relate (-)-3-phenyl-1-butene to both (-)-2-phenylbutane and D-glyceraldehyde [(b) D. J. Cram and F. A. Abd Elhafez, *THIS JOURNAL*, **74**, 5843 (1952)].

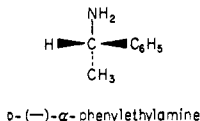
configuration can be assigned to the (+)-isomer and the D- to the (-)-isomer of V.



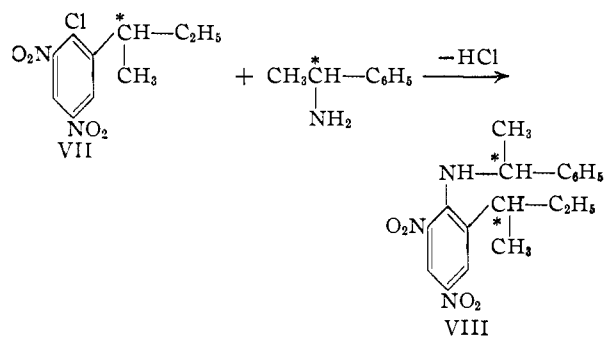
The nitration of D-, L- and D,L-V to give D-, L- and D,L-VI, respectively, proceeded in good yield only when the phenols were first sulfonated and then nitrated. Attempts to resolve D,L-VI through the common alkaloid salts failed. When attempts were made to prepare 2-*s*-butyl-4,6-dinitrochlorobenzene (VII) from the dinitrophenol (VI) and common reagents such as thionyl chloride or phosphorus pentachloride, only polymeric materials were obtained along with much starting material. When heated in diethylaniline with *p*-toluenesulfonyl chloride, *p*-bromobenzenesulfonyl chloride or benzenesulfonyl chloride, the phenol went to VII in 28, 51 and 73% yields, respectively. This remarkable reaction has been applied previously to the conversion of 6-methyl-2,4-dinitrophenol to 6-methyl-2,4-dinitrochlorobenzene¹¹ (see also Borsche, *et al.*¹²).

With the above reaction, D-, L- and D,L-2-(*s*-butyl)-4,6-dinitrochlorobenzene (D-VII, L-VII and VII) were prepared.

Racemic, D(-)- and L(+)-VII were each treated with racemic, D(-)- and L(+)- α -phenylethylamine¹³ to give compounds of structure VIII. When both starting materials were racemic, a mixture of diastereomers was produced, only one of



which was obtained in a crystalline state. When only active starting materials were used, single, ac-



tive diastereomers were obtained as well formed crystals when crystallized from pentane. When allowed to stand in the absence of solvent at room temperature, these crystals slowly crumbled and become oils, the rate of this process being different for the diastereomerically related isomers. All attempts to record melting points failed since the

change from solid to liquid phase occurred at indefinite temperatures. These phenomena were shown to be due to the binding of pentane into the crystal lattices of these compounds in such a way as to give molecular compounds of definite, sharp melting points in the presence of pentane as a second phase in a closed system. The isomer prepared from (-)-amine and (-)-chloride was shown to crystallize with one mole of pentane per three moles of isomer by measuring the loss in weight when the crystalline isomer was heated in vacuum. Fresh crystals of each of the four active isomers of VIII were shown to maintain their geometry at room temperature in the presence of pure pentane vapor at its vapor pressure.

Although freshly prepared solutions of the above crystals did not exhibit mutarotation, the fact that removal of pentane from the crystal lattice results in its destruction suggests that the oils produced are mixtures of easily interconvertible rotational isomers similar to those studied by Adams and co-workers.¹⁴

Racemic 2-*s*-butyl-4,6-dinitroaniline (IX) which was needed as a model compound for the spectral studies was prepared by the treatment of VII with ammonia. Similarly, racemic N-(α -phenylethyl)-2,4-dinitroaniline (X) was prepared from α -phenylethylamine and 2,4-dinitrochlorobenzene. The physical properties and analyses of these and the compounds described above are reported in Table I.

The Relationships between the Ultraviolet Absorption Spectra of the Diastereomeric Substituted Anilines and their Configurations.—An attempt will now be made to decide on the basis of *molecular models* which of the two diastereomers of 2-*s*-butyl-4,6-dinitro-N-(α -phenylethyl)-aniline [(*-*)-D,D-VIII or (+)-L,D-VIII] should exhibit more steric inhibition of resonance. The configurations of (*-*)-D,D-VIII and (+)-L,D-VIII are shown in Chart I, and in these formulations the phenyl, the amino-nitrogen and the asymmetric carbon atoms are all drawn in the same plane. Such a geometry is a condition of full resonance of the pair of electrons on the amino group with the aromatic system.¹⁵ Two conformations involving the two asymmetric carbon atoms have been drawn for each diastereomer in chart I, conformations A and B for (*-*)-D,D-VIII, and C and D for (+)-L,D-VIII. Although 16 other staggered conformations for each diastereomer are theoretically possible, these two least hindered are considered most important.

With respect to judging the relative steric strains in diastereomers (*-*)-D,D-VIII and (+)-L,D-VIII, when conformations A and C are compared all of the steric repulsions of the two isomers are the same except the following: A has a H >-< C₂H₅ and a CH₃ >-< CH₃ repulsion whereas C has a H >-< CH₃ and a CH₃ >-< C₂H₅ repulsion. Therefore

(14) R. Adams and J. R. Gordon, *THIS JOURNAL*, **72**, 2458 (1950), and preceding papers.

(15) Alternative structures in which the α -phenylethyl group is over the nitro group also allow the phenyl, the amino-nitrogen and the two asymmetric carbon atoms to become coplanar. In such structures the internal steric differences between the two diastereomers should largely disappear because of the large distances between the two asymmetric carbon atoms, and therefore these structures may be disregarded since they would make negligible contributions to the differences in the diastereomers.

(11) F. Ullmann and G. Nadai, *Ber.*, **41**, 1870 (1908).

(12) W. Borsche and E. Feske, *ibid.*, **60**, 157 (1927).

(13) A. W. Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 506. The configurations of these substances have been related to D-glyceraldehyde by several different routes (see reference 10b).

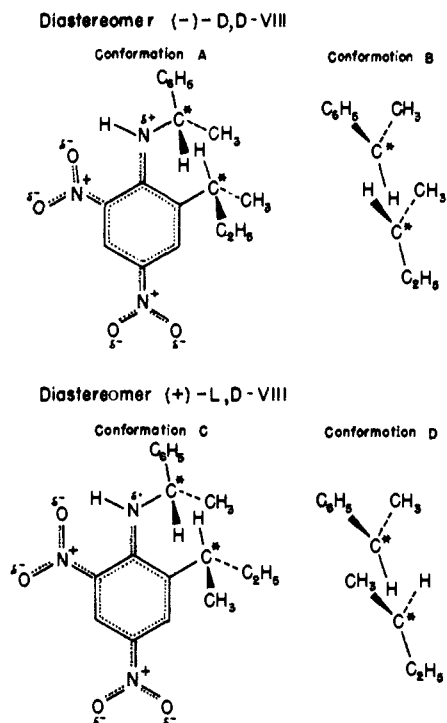


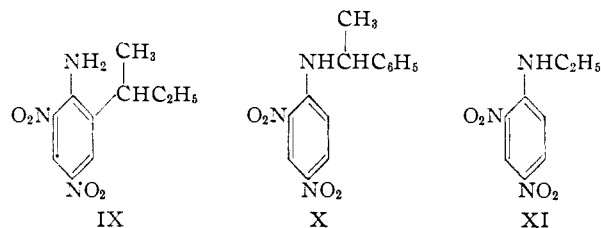
Chart I.—Solid bonds (dark triangular shaped) are in front of the plane, ordinary bonds (—) are in the plane, and dashed bonds (---) are behind the plane of the page. The dotted bonds (....) are used to indicate the hybrid character of the molecules.

conformation A should be more stable than C. Similarly, in conformations B and D all of the steric repulsions are the same for the two isomers except that B has a C₆H₅ >-< H and a CH₃ >-< CH₃ repulsion whereas D has a C₆H₅ >-< CH₃ and a CH₃ >-< H repulsion, and thus B should be more stable than D. Therefore the most favorable conformations of (-)-D,D-VIII would appear to be more sterically compatible than the most favorable conformations of (+)-L,D-VIII, and as a consequence the resonance in (-)-D,D-VIII should be less damped than in (+)-L,D-VIII.

The correlation appears to be established that in two molecules that contain the same type of conjugated system as the one at hand, that molecule in which resonance is subject to the least steric constraint absorbs light (at the wave length of its major absorption band) at higher intensities than the molecule in which resonance is sterically inhibited.^{4b,4d} Usually the wave lengths of the major absorption bands also differ in two such molecules, but although the least inhibited compound in non-nitrogen containing systems usually absorbs at the longer wave lengths, in *p*-nitroanilines no correlation between wave length and steric inhibition of resonance is possible.¹⁶ Thus one would predict that diastereomer (-)-D,D-VIII should have a higher absorbing band than (+)-L,D-VIII in the region of λ 300 to 350 μ .

(16) In nineteen pairs of aromatic nitroanilines taken from ref. 4b, 4d and from the compounds of the present study, in every case the more steric inhibition of resonance, the lower the intensity of the band absorbing at λ_{\max} 300 to 350 μ . In 14 pairs, the major band of the more sterically inhibited substances moved to longer wave lengths, and in five pairs, to shorter wave lengths.

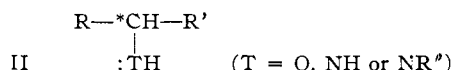
Figures 1 and 2 record the ultraviolet absorption spectra of the two diastereomers [(+)-L,D-VIII and (-)-D,D-VIII] as well as those of the model compounds IX, X and XI. Both methanol and cyclohexane were employed as solvents. The spectra of the two enantiomorphs, (+)-L,D-VIII and (-)-D,L-VIII were shown to be identical as were the spectra of (-)-D,D-VIII, (+)-L,L-VIII and of the racemic compound prepared by mixing equal weights of these two enantiomers.



As predicted on the basis of comparisons of molecular models of the two diastereomers, isomer (-)-D,D-VIII absorbs at higher intensities (ϵ 12,800, λ_{\max} . 336 μ in cyclohexane) than isomer (+)-L,D-VIII (ϵ 11,600, λ_{\max} . 335 μ in cyclohexane). That a considerable amount of steric inhibition of resonance exists in both of these substances is shown by a comparison of their spectra with those of the model compounds. Just as might be expected from their structures, the five compounds arrange themselves in decreasing order of ability to absorb light at about 320 to 340 μ as follows (see Fig. 1): XI > X > IX > (-)-D,D-VIII > (+)-L,D-VIII. Similar relationships exist between the spectra taken in methanol, the usual effect of increasing the λ_{\max} by increasing the polarity of the solvent being observed.

Since those structures drawn for (-)-D,D-VIII and (+)-L,D-VIII in Chart 1 are those which are the most favorable for hydrogen bonding of the amino hydrogen with the *o*-nitro group, the question arises as to whether the spectral differences in the two diastereomers might not be due to the different extents to which hydrogen bonding is possible in the two diastereomers. In the infrared spectra of these compounds and their models (see Experimental part), the wave length of the absorption maximum associated with N-H stretching occurs at the usual place (2.92 to 2.94 μ) and does not differ from compound to compound within experimental error. This fact points to the lack of important hydrogen bonding effects in these molecules.

The above results and arguments point to the conclusion that, at least in principle, the configurations of substances which possess structure II can be related to D-glyceraldehyde through the use of the techniques elaborated above. Before applying the method to molecules of unknown configuration, a number of representative examples of each class



of compound in which the configurations are known before hand should be worked out. The potential value of the technique is considerably diminished by the fact that both enantiomers of the compound

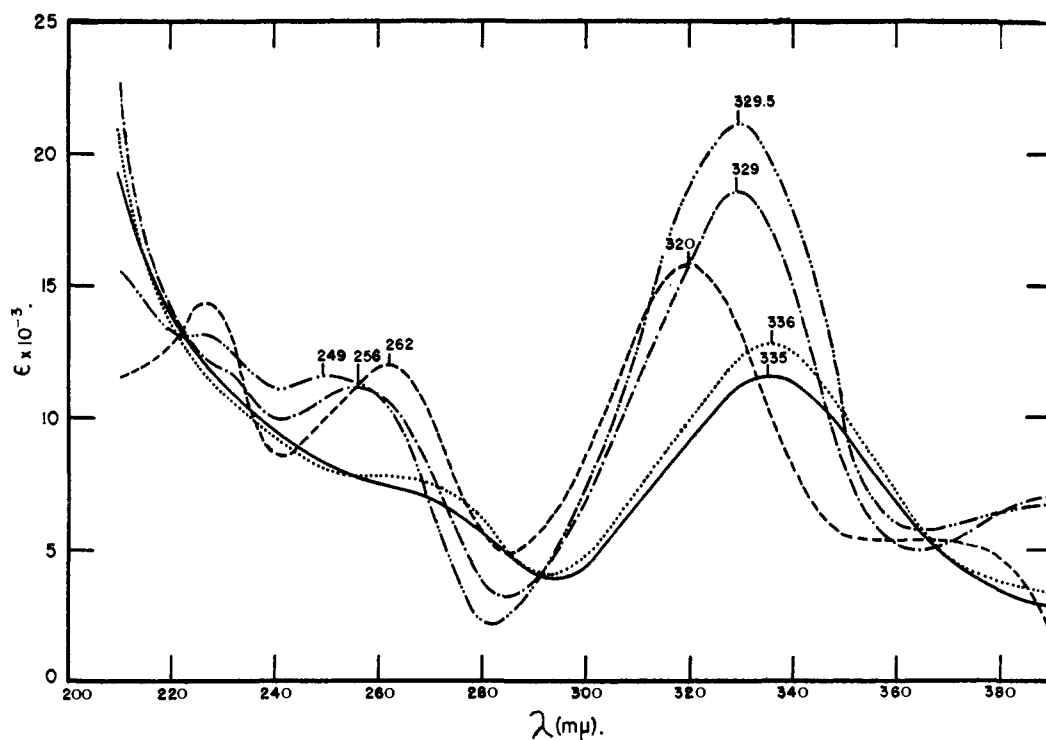


Fig. 1.—Ultraviolet absorption spectra taken in cyclohexane on a Cary (Model 11PMS) Spectrophotometer: curve, (—) *D,D*-VIII; curve —, (+) *L,D*-VIII; curve ---, IX; curve - - -, X; curve - - - - -, XI.

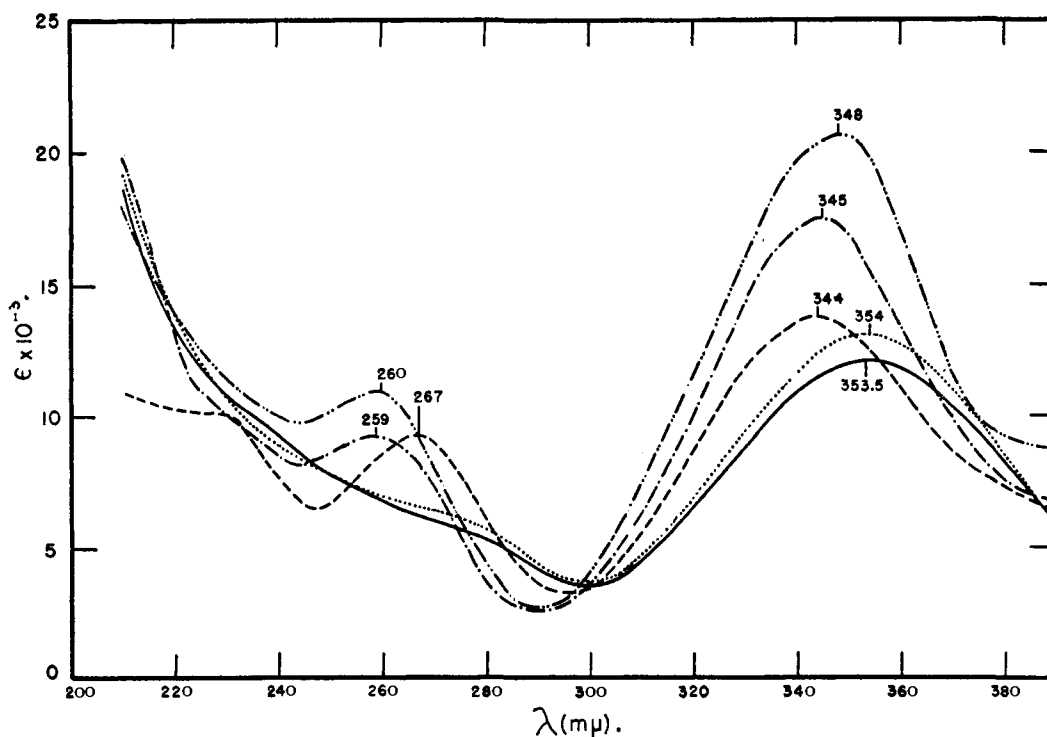


Fig. 2.—Ultraviolet absorption spectra taken in methanol on a Cary (Model 11PMS) Spectrophotometer: curve, (—) *D,D*-VIII; curve —, (+) *L,D*-VIII; curve ---, IX; curve - - -, X; curve - - - - -, XI.

whose configuration is to be determined would have to be available.

Steric Control of Asymmetric Induction in the Formation of the Diastereomerically Related Substituted Anilines.—In paper X of this series¹⁷

(17) D. J. Cram and F. A. Abd Elhafez, *THIS JOURNAL*, **74**, 5828 (1952).

was developed the "Rule of Steric Control of Asymmetric Induction" which allows one to predict on the basis of steric factors alone the configuration of the predominant product formed when a new asymmetric center is created adjacent to an old in certain systems and reactions. It was of interest in the present investigation to see if a correlation could be

made between steric factors and the relative rates of formation of (-)-D,L-VIII and (+)-L,L-VIII from D,L-2-*s*-butyl-4,6-dinitrochlorobenzene (VII) and L-(+)- α -phenylethylamine. By allowing equal molar quantities of VII and the amine to react and determining polarimetrically the ratios of the two diastereomers in the products, it was found that (+)-L,L-VIII must have been formed 1.22 times as fast as (-)-D,L-VIII. This result is the same as would be predicted on the basis of comparisons of molecular models using the same principles applied previously to answering the question of which of the two diastereomers is the most resonance stabilized. The fact that the more resonance stabilized isomer is formed faster [(+)-L,L-VIII or (-)-D,D-VIII] serves to strengthen the frequently drawn analogy¹⁸ between effects in the excited state in light absorption and in the transition state for reactions which are similarly resonance stabilized.

Experimental Part

DL-2-*s*-Butylphenol (V).—The olefin, 2-(α -methylallyl)-phenol¹⁹ (175 g., n_D^{20} 1.5402, and phenylurethan, m.p. 90°) was hydrogenated with 15 g. of Raney nickel in 100 atmospheres of hydrogen for 24 hours at room temperature. The phenol produced was removed from the bomb and flash-distilled to give 157 g. of material (90% yield), b.p. 120–122° (22 mm.), n_D^{20} 1.5196. An analytical sample was prepared by slow distillation of a small amount of material through a sixty-plate center-rod column giving b.p. 226–228° (750 mm.), n_D^{20} 1.5200, d_4^{25} 0.9804 and $[MR]_D$ 46.58 (calcd. 46.30).

The phenylurethan was prepared in the usual way and recrystallized from ligroin (b.p. 85–105°) to give a m.p. of 86°.

DL-2-*s*-Butylphenoxyacetic Acid.—This compound was prepared by the usual procedure and recrystallized from a 3 to 1 ether-pentane mixture, m.p. 109–110°. Attempts to resolve this compound through its brucine and quinine salts failed.

L-(+)-2-*s*-Butylphenol (L-V).—To 500 ml. of dry pyridine was added 226 g. (1.51 moles) of V and 280 g. (1.12 moles) of freshly prepared²⁰ *d*-camphor-10-sulfonyl chloride. The mixture was shaken to effect solution, stoppered and allowed to stand at room temperature for 48 hours. The mixture was then poured onto ice and excess 6 *N* hydrochloric acid, the oil was taken up in ether, washed twice with water, 1 *N* sodium hydroxide and finally again with water. The ether layer was dried and the crude ester was obtained by evaporation of the solvent on the steam-bath, yield 386 g. (95%). Acidification of the sodium hydroxide extract gave unreacted phenol.

The oily ester was dissolved in 500 ml. of absolute ethanol, and the solution was heated to boiling for a few minutes and allowed to stand at 0° for 48 hours. The waxy crystals that separated were recrystallized ten times from absolute ethanol to give 56 g. of *d*-camphor-10-sulfonate (35% yield), melting at 71–72.5°.

D-(-)-2-*s*-Butylphenol (D-V).—Evaporation and hydrolysis (see below) of the combined second, third and fourth filtrates from the recrystallization of the *d*-camphor-10-sulfonate of L-V gave 52 g. of V rich in D-V having α_D^{20} -4.4° (*l*, neat) and n_D^{20} 1.5201. A mixture of *l*-camphor-10-sulfonyl chloride²¹ (39 g. or 0.156 mole), 70 ml. of dry pyridine and 35 g. (0.23 mole) of the V rich in D-V were treated as described for the enantiomer to yield 55 g. of

crude ester (96% yield) which recrystallized easily. After seven recrystallizations this material gave 15.6 g. of pure *l*-camphor-10-sulfonate of D-V, m.p. 70–72°.

Hydrolytic and Reductive Cleavages of the Camphor-10-sulfonates. A. Hydrolysis Procedure.—A mixture of the camphor-10-sulfonate of V, 54 g. of sodium hydroxide and 180 ml. of ethylene glycol was heated at 150° for 16 hours, cooled to 90° and poured into 500 ml. of an ice-water mixture. Concentrated hydrochloric acid (300 ml.) was added slowly with ice to the above solution, and the liberated phenol was extracted with four 500-ml. portions of ether. The combined extracts were dried, and the solvent was removed by distillation through a thirty-plate bubble plate column. The residue was flash distilled to give 20.5 g. (92%) of phenol.

B. Lithium Aluminum Hydride Procedure.—To 4.0 g. of lithium aluminum hydride in 200 ml. of ether was added dropwise with stirring 10.0 g. of the *d*-camphor-10-sulfonate of L-V in 200 ml. of dry ether. After the addition was complete, the mixture was refluxed for 60 hours. The solution was deactivated with methanol followed by water, and finally 6 *N* hydrochloric acid was added. The ether layer was then separated, washed with water, dried and the ether was evaporated. The residue was flash distilled at aspirator pressure, and the distillate was dissolved in pentane and extracted with 6 *N* sodium hydroxide. The aqueous layer was washed with ether, acidified and the phenol was taken up in ether and distilled as before. The distillate (3.2 g.) was distilled through a 60-plate center-rod column giving 1.81 g. (44% theory) of phenol boiling at 226°, n_D^{20} 1.5191, α_D^{20} +17.49°, (*l*, neat).

2-*s*-Butyl-4,6-dinitrophenol (VI).—Compound V (30 g.) was heated with 18 ml. of concentrated sulfuric acid at 100° for 30 minutes, and the resulting solution was added to 50 ml. of water. This sulfonic acid solution was heated on the steam-bath and a solution of 50 ml. of concentrated nitric acid in 25 ml. of water was added dropwise with stirring over a period of 30 minutes. After about half of the nitrating solution had been added, an oil began to separate. After the addition was complete, the mixture was stirred and heated for an additional 30 minutes, cooled, poured into 200 ml. of water, and the oil that separated was taken up in two 100-ml. portions of ether. The ether extract was washed once by 20 ml. of water, dried and the solvent was evaporated. The resulting oil was dissolved in a minimum amount of a 10 to 1 pentane-ether mixture. This solution was placed on a two to one Celite-silicic acid chromatographic column (2 × 40 cm.). The yellow band was eluted by the same pentane-ether solution, and the eluate was evaporated to an oil which was crystallized from pentane at -30° to give 32 g. (65%) of VI melting at 40–41°. The crude nitration product was, in some cases, purified by two recrystallizations of its sodium salt from 6 *N* sodium hydroxide. This method gave yields of only 40%. All attempts to resolve this compound through the common alkaloid salts failed.

Compounds L-VI and D-VI were prepared by the procedure reported above. The starting D-V was 95% optically pure and the product was 84% optically pure due to preferential crystallization of racemic material from pentane.

DL-2-*s*-Butyl-4,6-dinitrophenyltosylate.—A mixture of 5.0 g. of VI, 2.9 g. of potassium carbonate and 4.0 g. of tosyl chloride was stirred and refluxed with 250 ml. of dry acetone for 14 hours. The reaction mixture was poured into 1500 ml. of water, and the organic material was taken up in 500 ml. of ether. The ether layer was washed twice with 500-ml. portions of 1 *N* sodium carbonate solution, dried over potassium carbonate, and the solvent was evaporated. A total of 7.70 g. (94%) of ester melting at 115–116° after one recrystallization from methanol-water was obtained.

DL-2-*s*-Butyl-4,6-dinitrochlorobenzene (VII).—A mixture of 4.6 g. (0.019 mole) of VI, 8.3 g. (0.053 mole) of benzene-sulfonyl chloride and 20 ml. of freshly distilled *N,N*-diethylaniline was sealed in a pressure tube and heated at 100° for 18 hours. The tube was cooled, opened and the dark blue tar was dissolved in 150 ml. of benzene. The benzene solution was washed twice with excess 6 *N* sulfuric acid, twice with water, twice with 10% sodium carbonate solution and was dried over potassium carbonate. No VI was recovered by acidification of the basic extract. The benzene solution was evaporated to an oil under aspirator pressure at room temperature. The residual oil was dissolved in 40 ml. of pentane and put on a 40 × 2 cm. activated alumina column

(18) For instance, see F. A. Matsen, W. W. Robertson and R. L. Chuoke, *Chem. Revs.*, **41**, 279 (1947); L. Doub and J. M. Vandenberg, *This Journal*, **69**, 2722 (1947); and S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, *ibid.*, **74**, 1140 (1952).

(19) Prepared by method of Claisen and Teitz (ref. 6) who report a phenylurethan derivative melting at 90°.

(20) J. Read and R. A. Storey, *J. Chem. Soc.*, 2768 (1930).

(21) This acid was prepared by resolution of *dl*-camphor-10-sulfonic acid as described by H. Burgess and C. S. Gibson [*J. Soc. Chem. Ind.*, **44**, 498T (1925)] and was shown to be of 96% optical purity by comparison with the pure enantiomer.

and was eluted with pentane. The first 300 ml. of eluate was light yellow while a small dark yellow band remained stationary on the column. Evaporation of the eluate gave an oil which was dissolved in 50 ml. of methanol, the solution was heated to boiling, and water was added until the solution became turbid. When cooled, the solution deposited 3.5 g. (73%) of VII as long white needles. Recrystallization of this material gave m.p. 54–54.5°.

Compounds L-VII and D-VII were prepared by the procedure reported above except that L-VI and D-VI were the respective starting phenols.

Relationship of Configuration of L-(+)-2-*s*-Butylphenol (L-V) to L-(+)-2-Phenylbutane.—A mixture of 2.0 g. of (+)-2-*s*-butylphenol having $\alpha^{25D} + 17.55^\circ$ (*l* 1, neat) was heated with 3.0 g. of tosyl chloride and 5 ml. of dry pyridine at 100° for three hours, cooled and poured into 100 ml. of water. The oil was taken up in 50 ml. of ether, the solution was washed three times with 6 *N* sulfuric acid, water, 1 *N* sodium hydroxide, three times with water, dried, and the solvent was evaporated under reduced pressure to give 3.0 g. of an odorless oil. This oily tosylate was dissolved in 75 ml. by pure methanol and placed in a gas washing bottle with 5 g. of freshly prepared Raney nickel. Hydrogen was slowly passed through the system for 16 hours at room temperature. Another 5 g. of Raney nickel was added and hydrogen was passed in for another 16 hours. The methanol solution was then filtered free of catalyst, the catalyst was washed with 75 ml. of methanol, and the combined filtrates were added to 500 ml. of water. The oil was extracted with three 150-ml. portions of pure pentane. The combined extracts were dried and concentrated to about 25 ml. by distillation of the solvent through a bubble-plate column. The concentrated pentane solution was then put on an 18 × 2 cm. alumina column and the product was eluted with 100 ml. of pure pentane. The eluate was concentrated to about 10 ml. by distillation of solvent through a bubble plate column, and the resulting oil was twice flash distilled at 30 mm. pressure to give 160 mg. of 2-phenylbutane, $n^{25D} 1.4875$. A 15.0% (by weight) solution of this distillate in *dl*-2-phenylbutane gave $\alpha^{25D} + 1.71$ (*l* 1/2). This value gives a calculated $\alpha^{25D} + 22.8^\circ$ (*l* 1, neat) for the 2-phenylbutane obtained in this experiment, or an optical purity of 94% for the L-V used, assuming no catalytic racemization.

General Procedure for the Preparation of All Stereoisomers of VIII.—A mixture of 0.50 g. of VII (or isomers) and 2.0 ml. of α -phenylethylamine was sealed in an ampoule and heated at 100° for two hours. The ampoule was then cooled, opened and the contents removed with 15 ml. of boiling chloroform. The chloroform solution was washed with 1 *N* hydrochloric acid, water and dried over potassium carbonate. The chloroform was evaporated, the residual oil was dissolved in 30 ml. of pentane, and the solution was put on a 25 × 2 cm. alumina column. The column was washed with 750 ml. of pentane to remove unreacted VII followed by one liter of 1 to 3 chloroform-pentane mixture which removed the single yellow band. The yellow eluate was evaporated to an oil which was dissolved in 20 ml. of warm pentane and cooled to zero to give crystalline VIII. Recrystallization of this material from pentane gave beautifully crystalline product. The yields were difficult to determine because of the pentane of crystallization, but in each case amounted to 75 ± 10%.

L-2-*s*-Butyl-4,6-dinitro-N-(L- α -phenylethyl)-aniline (L,L-VIII).—Pure L-VII and L-(+)- α -phenylethylamine ($\alpha^{25D} + 38.32^\circ$, *l* 1, neat) was subjected to the general procedure described above to give (+)-L,L-VIII as massive rhombic crystalline clusters from pentane. This material gave a melting point range of 15–35° in an open capillary tube. When sealed in a capillary tube under liquid pentane a melting point of 37–38° was obtained. A small sample was prepared for analysis, spectra and rotation as follows. The unstable crystalline material was washed twice with pentane cooled to –70°, and was heated as an oil at 60° and 0.1 mm. pressure until constant weight was obtained.

D-2-*s*-Butyl-4,6-dinitro-N-(D- α -phenylethyl)-aniline (D,D-VIII).—This compound was prepared from D-VII of 88% optical purity and D-(–)- α -phenylethylamine ($\alpha^{25D} - 38.06^\circ$, *l* 1, neat) by the above procedure. The (–)-D,D-VIII obtained crystallized in the same rhombic form as its enantiomer and gave an open tube melting point of 15–35°.

A melting point taken under pentane in a sealed tube amounted to 38–39°. A pure sample was prepared for analysis, spectra and rotation by the method described for (+)-L,L-VIII: 4.8 mg. of crystalline (–)-D,D-VIII lost 2.8 mg. of pentane on heating and pumping to constant weight. This corresponds to 0.35 mole of pentane per mole of amine in the crystalline state. It was observed that L,L-VIII and D,D-VIII changed from the crystalline to the liquid state on standing in the atmosphere at a much greater rate than did L,D-VIII and D,L-VIII. Since all four stereoisomers maintained their crystalline integrity indefinitely when allowed to stand over pure pentane at its vapor pressure (room temperature), the presence of pentane in the crystal lattice is demonstrated.

L-2-*s*-Butyl-4,6-dinitro-N-(D- α -phenylethyl)-aniline (L,D-VIII).—Chloride L-VII was treated with D-(–)- α -phenylethylamine ($\alpha^{25D} - 38.06^\circ$, *l* 1, neat) as described above to give (+)-L,D-VIII as star-like needle clusters from pentane. An open tube melting point of 25–50° was observed while a melting point of 36–37° was observed under pentane in a sealed tube. The material was purified for analysis, spectrum and rotation as described above. The yield was comparable to those obtained in the preparation of the other diastereomers.

D-2-*s*-Butyl-4,6-dinitro-N-(L- α -phenylethyl)-aniline (D,L-VIII).—Compound D-VII of 88% optical purity was treated with L-(+)- α -phenylethylamine ($\alpha^{25D} + 38.32^\circ$, *l* 1, neat) to give (–)-D,L-VIII with the same crystalline form and open tube melting point as its enantiomer, [(+)-L,D-VIII]. A melting point of 40–41° was obtained under pentane in a sealed tube, and the yield was comparable to those obtained above. The material was purified for analysis, spectrum and rotation as described above.

Preparation of Both Racemates of VIII.—When racemic VII and racemic α -phenylethylamine were subjected to the general procedure described above for the preparation of VIII, a crystalline racemate was obtained which contained no pentane and melted sharply at 94–95°. Evaporation of the mother liquor from which this racemate crystallized gave an oil which would not crystallize. The solid racemate gave an ultraviolet absorption spectrum identical with that of L,L-VIII and D,D-VIII. Accordingly, 20 mg. each of L,L-VIII and D,D-VIII (as oils) were dissolved in 5 ml. of warm pentane and cooled slowly to give a racemate melting at 94.5–95.0° which gave a mixed melting point of 94–95° with the racemate obtained from completely racemic starting materials. Similar treatment of L,D-VIII and D,L-VIII gave an oil which would not crystallize.

The Determination of the Relative Rates of Formation of the Diastereomers of VIII.—A mixture of 166 mg. (0.64×10^{-3} mole) of racemic VII and 75 mg. (0.62×10^{-3} mole) of L-(+)- α -phenylethylamine ($\alpha^{25D} + 38.32^\circ$, *l* 1, neat) was dissolved in 3 ml. of dry benzene and heated at 100° for 40 hours in a sealed ampoule. The ampoule was cooled, opened and the contents put in 15 ml. of pentane. The pentane solution was washed with 1 *N* hydrochloric acid, water, dried and put on a 2 × 15 cm. alumina column. The column was eluted with 300 ml. of pentane which was discarded, and then with 75 ml. of a 1 to 1 pentane-chloroform mixture which removed the yellow band. Evaporation of the eluate to constant weight on the steam-bath with a compressed air jet gave 86 mg. (81%) of an oily mixture of (+)-L,L-VIII and (–)-D,L-VIII, which after heating in vacuum gave $[\alpha]^{25D} - 37.2^\circ$ (*c* 8.60 in benzene). This rotation gives a calculated ratio of L,L-VIII to D,L-VIII of 1.22 and a difference in free energy of activation of approximately 150 cal. per mole.

***dl*-2-*s*-Butyl-4,6-dinitroaniline (IX).**—This compound was prepared by heating 1.70 g. (0.0066 mole) of racemic VII and 0.60 g. of ammonium acetate in a slow stream of dry ammonia at 180° for eight hours. The mixture was then cooled and dissolved in 15 ml. of chloroform, the solution was washed with water, dried over potassium carbonate, and the solvent was evaporated. The residual oil was dissolved in a small volume of benzene and put on a 2 × 25 cm. alumina column. The column was eluted by benzene, the first colorless eluate being discarded. The colored eluate (*ca.* 800 ml.) was evaporated at aspirator pressure to give an oil which was crystallized from benzene-pentane to give 320 mg. (20%) of IX melting at 116–117°.

D,L-N-(α -Phenylethyl)-2,4-dinitroaniline (X).—A mixture of 10.0 g. (0.05 mole) of 2,4-dinitrochlorobenzene and 12.0 g. (0.10 mole) of *dl*- α -phenylethylamine was heated in a sealed tube at 100° for four hours. The tube was cooled, opened

and the contents were dissolved in 200 ml. of boiling ethanol. The ethanol solution was poured into 500 ml. of water, cooled and the oily solid that separated was collected. This material (dry) was mixed with 100 ml. of ether to produce crystals; the mixture was cooled to -10° , filtered and the product was recrystallized from ethanol to give 10.7 g. (75%) of X melting at $114-114.5^{\circ}$.

N-Ethyl-2,4-dinitroaniline (XI).—This compound was prepared by a method previously described,²³ m.p. $114-115^{\circ}$ after two recrystallizations from ethanol-water.

Infrared Absorption Spectra.—The infrared spectra of compounds (–)-D,D-VIII and (–)-D,L-VIII were examined

(23) P. van Romburgh, *Rec. trav. chim.*, **R2**, 104 (1883), reports a m.p. of $113-114^{\circ}$.

at wave lengths between 2 and 4μ in 5 and 6% carbon tetrachloride solutions, respectively, using a 0.3-mm. rock salt cell and a NaCl prism. Model compounds IX, X and XI were similarly examined in 3% solutions in a 1-mm. rock salt cell. A Beckman (model IR2T) spectrophotometer was used in all cases. The H-N stretching frequencies (symmetrical peaks) were found to occur as follows: (–)-D,D-VIII, at 2.93μ ; (–)-D,L-VIII at 2.93μ ; IX, at 2.81μ and 2.92μ ; X at 2.94μ ; and XI at 2.93μ .

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LOS ANGELES, CALIF.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

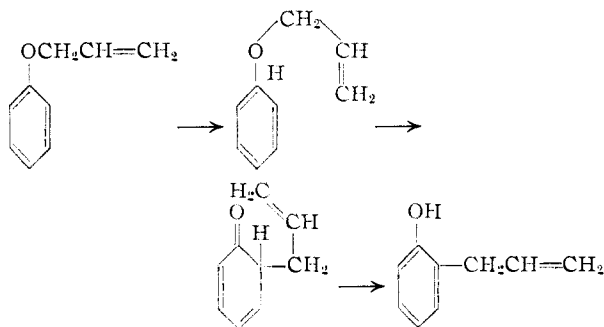
The Claisen Rearrangement of Phenyl Allyl Ethers, Labeled with Carbon-14

By J. P. RYAN¹ AND P. R. O'CONNOR

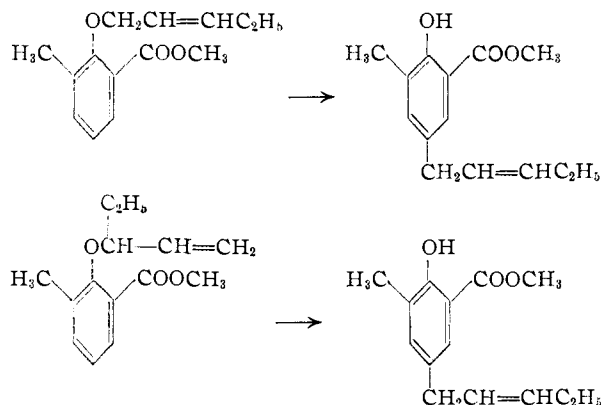
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The Claisen rearrangement of 3-phenoxy-1-propene-1- C^{14} and 3-(2,6-dimethylphenoxy)-1-propene-1- C^{14} has been investigated. The ortho rearrangement proceeds with inversion of the allyl group; the para rearrangement proceeds with no inversion of the allyl group. Possible mechanisms are discussed. It is shown that a four-membered oxygen ring is not an intermediate in a displacement reaction that is part of the synthetic route.

The thermal rearrangement of phenyl allyl ethers to allyl phenols has been the subject of many investigations.² In most cases the allyl group migrates to the ortho position of the benzene ring, when one of these is available, or to the para position when both ortho positions are substituted. Migration to the meta position has apparently not been observed. The rate of rearrangement obeys a first-order kinetic equation and evidence³ points strongly to an intramolecular mechanism for the ortho rearrangement. This information is incorporated in the following reactions for the mechanism of the ortho rearrangement.⁴



The argument for the mechanism of the para rearrangement is less clear. Although a first-order kinetic equation is followed, the para rearrangement has not been shown to be exclusively intramolecular in character.⁵ Moreover, only one example has been examined in which the α - and γ -isomers of a



substituted ether have been employed.^{6,7} This would indicate that, in the course of the rearrangement, the migrating allyl group is free enough to resonate so that only one product results, the one of lower energy. At the present time the two mechanisms that are given most consideration are the two-cycle mechanism advanced by Hurd and Pollack⁸ and the π -complex mechanism of Dewar.⁹

In the two-cycle mechanism the migration of the allyl group to an ortho position with inversion is proposed, to form an unstable compound which rapidly stabilizes by migration of the allyl group to the para position, again with inversion. Such a reaction path incorporating two intermediate quasi six-membered rings seems possible when molecular models are constructed.

In the π -complex mechanism the interaction of the allyl group with the π -electron cloud of the benzene ring is proposed, with migration of the allyl

(1) From the Ph.D. Thesis of J. P. Ryan, 1952.

(2) D. S. Tarbell, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 1.

(3) C. D. Hurd and L. Schmerling, *THIS JOURNAL*, **59**, 107 (1937).

(4) Cf. W. M. Lauer and W. F. Filbert, *ibid.*, **58**, 1388 (1936), for examples of the abnormal rearrangement involving the β -carbon of the allyl group.

(5) See, however, E. R. Alexander and R. W. Klumber, *ibid.*, **73**, 4304 (1951).

(6) O. Mumm and J. Diedericksen, *Ber.*, **72**, 1523 (1939).

(7) O. Mumm, H. Homhardt and J. Diedericksen, *ibid.*, **72**, 102 (1939).

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

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