

moved under reduced pressure, and the crude product analyzed by infrared and v.p.c.

The procedure using 2 equiv. of bromine was essentially the same except that after 20 min. irradiation the ampoule was opened and the excess bromine neutralized by addition of the carbon tetrachloride solution to aqueous sodium sulfite.

Experiments employing 0.4, 0.7, 0.75, and 2.0 equiv. of bromine all proceeded readily to give crude products with infrared spectra which were composites of the spectra of I and II. Two small unassigned peaks at 12.31 and 14.43 μ were observed in each case. None of the spectra revealed absorptions characteristic of the diequatorial dibromide III. Analysis by v.p.c. indicated the same relative areas for the diaxial and diequatorial isomers in the chromatograms of each product from the above experiments. That the diequatorial dibromide likely resulted from thermal isomerization in the injection block is suggested by the following evidence. Analysis of a product by v.p.c. with the injection block at 156° indicated II:III = 93:7; with the same sample and the injection block at 218°, II:III = 82:18.

One bromination was run without the use of solvent. *cis*-4-Bromo-*t*-butylcyclohexane (7.0 g., 0.032 mole) and bromine (2.5 g., 0.016 mole) were placed in a small flask equipped with a reflux condenser and magnetic stirring bar. The system was swept out with helium and maintained under positive helium pressure. The flask was immersed in a water bath (10–44°) and the stirred solution was irradiated with a 50-watt frosted bulb until the reaction mixture became colorless (1 hr.). Potassium carbonate was added. Infrared analysis of the product (8.8% in carbon disulfide, 0.33-mm. liquid cells) indicated 52 \pm 3% *cis*-4-bromo-*t*-butylcyclohexane (I) and 45 \pm 5% *trans*-3-*cis*-4-dibromo-*t*-butylcyclohexane (II). Distillation of the product yielded a fraction with b.p. 64° (0.5 mm.), n_D^{25} 1.5229, and an infrared spectrum virtually identical with that of II (infrared contained some absorptions characteristic of I).

trans-4-Bromo-*t*-butylcyclohexane (IV) and *cis*-3-Bromo-*t*-butylcyclohexane (V).—In a manner similar to that used for the photobromination of I, a mixture of IV and V was sealed in an ampoule with bromine (0.8 equiv.) and carbon tetrachloride. Irradiation using a 150-watt frosted bulb was accomplished for about 6 hr. (60–66°) and for about 2 hr. (45–60°). After this length of time, only a light yellow color remained. The hydro-

gen bromide and carbon tetrachloride were removed under reduced pressure and the crude product analyzed by v.p.c. The following peaks were observed: two peaks due to IV and V (retention times = 14–16 min.), two peaks representing 53% of product area (retention times = 11–12 min.), and ten peaks representing 47% of product area (retention times = 27–60 min.).

Competitive Bromination.—A mixture of *cis*-4-bromo-*t*-butylcyclohexane (I) and *trans*-4-bromo-*t*-butylcyclohexane (IV) containing 13% *trans* isomer was prepared from the mixed bromide product (brominative decarboxylation) by dilution with relatively pure *cis* isomer. A weighed sample of this material in CCl₄ and bromine (0.8 equiv.) were placed in a small flask equipped with a condenser and a magnetic stirring bar. The system was swept out with helium and maintained under positive helium pressure. The flask was immersed in a water bath (39–51°) and the stirred solution irradiated for 1 hr. with a 150-watt frosted bulb. The reaction was complete. The hydrogen bromide and the majority of the CCl₄ were removed under reduced pressure and the total weight of the product mixture obtained. A weighed portion of the product was mixed with a known weight of a standard (1,1-diphenylethylene), and v.p.c. analysis accomplished. From the area-weight relationship between the standard and *cis*- and *trans*-bromides, the quantity of each bromide remaining in the product was determined. The ratio of the rate constants for the reaction of each bromide with bromine was then calculated using the expression

$$k_{cis}/k_{trans} = \frac{\log \frac{[cis] \text{ initial}}{[cis] \text{ final}}}{\log \frac{[trans] \text{ initial}}{[trans] \text{ final}}}$$

Acknowledgment.—The support of this research by the Air Force Office of Scientific Research (Contract AF 49(638)457) is gratefully acknowledged. P. D. R. was the recipient of financial support from the Ethyl Corporation Fellowship and the National Science Foundation Cooperative Fellowship program.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.]

Stereochemical Assignments for β -Ketols Formed by Aldol Addition of Three Simple Ketones to *p*-Nitrobenzaldehyde¹

BY MARTIN STILES,^{2a} ROBERT R. WINKLER,^{2b} YU-LAN CHANG, AND LEE TRAYNOR^{2c}

RECEIVED MARCH 14, 1964

The aldol reactions of cyclohexanone and desoxybenzoin with *p*-nitrobenzaldehyde gave both diastereoisomers of the expected ketols VII and VIII. From 2-butanone and *p*-nitrobenzaldehyde the two diastereomeric ketols II derived from reaction at the methylene group were obtained, in addition to the skeletal isomer I resulting from reaction at the methyl group. Stereochemical assignments for *erythro*- and *threo*-II were based upon the reaction scheme in Fig. 1. The stereochemistry of isomer pairs VII and VIII was determined by means of infrared and n.m.r. spectroscopy.

The general features of the aldol reaction are so well understood that it stands as the mechanistic prototype of many reactions in which carbon-carbon bonds are formed. The fundamental studies by Bonhoeffer and Walters³ and Bell⁴ firmly established the two-step enolization-addition mechanism, through kinetic and deuterium exchange experiments with acetaldehyde.

(1) Taken in part from the Ph.D. theses of R. R. Winkler (1961) and L. Traynor (1964) at the University of Michigan.

(2) (a) Fellow of the Alfred P. Sloan Foundation. (b) E. C. Britton Fellow (Dow Chemical Co.) 1959–1960; Sun Oil Co. Fellow 1960–1961. (c) Rohm and Haas Fellow 1962–1964.

(3) K. F. Bonhoeffer and W. D. Walters, *Z. physik. Chem.*, **A181**, 441 (1938).

(4) R. P. Bell, *J. Chem. Soc.*, 1637 (1937); R. P. Bell and M. J. Smith, *ibid.*, 1691 (1958). See also A. Broche and R. Gibert, *Bull. soc. chim. France*, 131 (1955).

The results of a number of related researches which confirm this mechanism have been discussed by Bartlett.⁵

The enolization of aldehydes and ketones has been subjected to unusually detailed scrutiny, which will not be reviewed here.⁶ By contrast, the second step of the

(5) P. D. Bartlett in "Organic Chemistry, an Advanced Treatise," Vol. III, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 102–111.

(6) A recent important paper by H. O. House and K. K. Kramar (*J. Org. Chem.*, **28**, 3362 (1963)) discusses the enolization of unsymmetrical ketones, particularly with regard to the position of attack by base and to the question of *cis-trans* isomerism of enolates. The transition state for enolization has been discussed in considerable detail with respect to both extent of bond breakage⁷ and preferred geometry.^{8,9}

(7) C. G. Swain and A. S. Rosenberg, *J. Am. Chem. Soc.*, **83**, 2154 (1961), and other papers cited there.

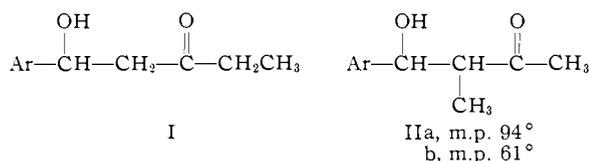
(8) E. J. Corey and R. A. Snee, *ibid.*, **78**, 6269 (1956).

(9) H. E. Zimmerman and H. J. Giallombardo, *ibid.*, **78**, 6259 (1956).

aldol reaction, the addition of an enolate ion to the carbonyl group of the acceptor, cannot be satisfactorily described. We have undertaken to study this aspect of the aldol reaction, with primary emphasis on the preferred geometry of the addition process.

This paper reports stereochemical assignments for three pairs of diastereoisomeric β -ketols, formed by aldol addition of 2-butanone, cyclohexanone, and desoxybenzoin to *p*-nitrobenzaldehyde. A later paper will report the results of other related studies which allow a full discussion of the stereochemistry of the aldol reaction.

Diastereoisomers of 1-*p*-Nitrophenyl-2-methylbutan-1-ol-3-one (II).—From the base-catalyzed reaction of *p*-nitrobenzaldehyde with 2-butanone three β -ketols were obtained,¹⁰ one of which was shown to have the structure I, the other two (m.p. 94 and 61°) being diastereoisomers of the branched structure II. By means of the reactions in Fig. 1 the 94° isomer was converted to the diol diacetate IIIa, whose stereochemistry



Ar = *p*-nitrophenyl throughout this paper

could be deduced as *threo* from the mode of synthesis from *trans*- β -methylstyrene. By the same method the 61° isomer was converted to the *erythro*-diol diacetate IIIb, which could be synthesized from *cis*- β -methylstyrene.

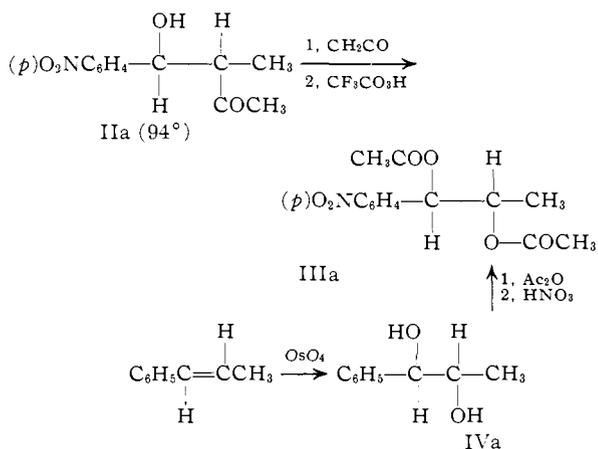


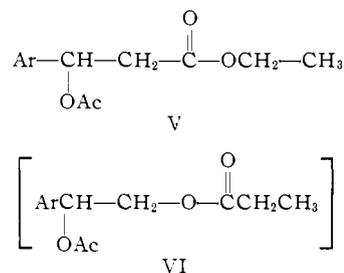
Figure 1.

The Baeyer–Villiger oxidation was selected for the degradation of the ketols because of its known stereochemical integrity.¹¹ The oxidation of the easily obtainable straight-chain isomer I was first studied as a model for the oxidation of IIa and IIb. Attempts to oxidize the model ketol or its acetate with peracetic acid were unsuccessful. In most such attempts there was evidence that an elimination reaction to form the corresponding α,β -unsaturated ketone had occurred. The acetate of I was slowly but cleanly oxidized by peroxytrifluoroacetic acid according to the procedure of Emmons and Lucas.¹² The product was identified as

(10) M. Stiles, D. Wolf, and G. V. Hudson, *J. Am. Chem. Soc.*, **81**, 628 (1959).

(11) For a recent discussion see P. A. S. Smith in "Molecular Rearrangements," Vol. I, P. deMayo, Ed., Academic Press, Inc., New York, N. Y., 1963, pp. 577–589.

ethyl β -acetoxy- β -(*p*-nitrophenyl)propionate (V). There was evidence for no more than a trace of the alternative

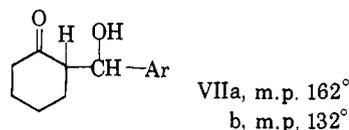


oxidation product VI. Evidently the two electronegative substituents on C-1 of the ketoacetate greatly reduce the migratory tendency of the methylene group at C-2 relative to that at C-4. When the branched ketones IIa and IIb were oxidized under the same conditions, the reactions took the course indicated in Fig. 1. The effect of the electronegative substituents in these cases was obviously insufficient to cause any deviation from the generalization¹¹ that methyl ketones invariably yield acetates.

The *threo*- and *erythro*-diols IVa and IVb were prepared by Svoboda and Sicher¹³ from *trans*- and *cis*- β -methylstyrene, respectively, by permanganate oxidation. Osmium tetroxide was found to give a superior yield of the diols, and both methods were utilized in the present work.

Both synthetic IIIa and that derived from oxidation of IIa exhibited a wide melting range, unchanged upon remelting and unchanged by chromatography and repeated crystallization. The substance is clearly homogeneous chemically, since it was hydrolyzed to the corresponding diol, m.p. 91.5–92°, quantitatively. No explanation can be offered for this curious behavior. The *erythro* isomer IIIb behaved normally. In both the *threo* and *erythro* series the identity of material from oxidation of II and from the synthetic sequence was demonstrated by comparison of samples of diols as well as diacetates.

Diastereoisomers of 2-(α -Hydroxy-*p*-nitrobenzyl)-cyclohexanone (VII).—The aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde has been reported¹⁴ to give a 90% yield of a ketol, m.p. 151°. No mention was made of a second isomer. Under the conditions described,¹⁴ using alkali at room temperature, we obtained a mixture which could be resolved by silica gel chromatography into two diastereoisomers, VIIa, m.p. 161–162°, and VIIb, m.p. 131–132°, in the ratio of 4.4 to 1.0. When the reaction was carried out



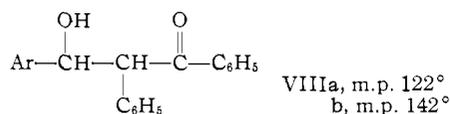
under milder conditions (0.2 *N* NaOH, 0°, 2 hr.) the ratio of VIIa to VIIb was 1.8. Under these milder conditions VIIa and VIIb are not interconverted, and the latter ratio must therefore be determined by relative rates of formation of the two isomers.

(12) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(13) M. Svoboda and J. Sicher, *Collection Czech. Chem. Commun.*, **20**, 1452 (1955).

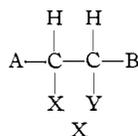
(14) J. D. Billimoria, *J. Chem. Soc.*, 1126 (1955).

Diastereoisomers of α -Phenyl- β -hydroxy- β -(*p*-nitrophenyl)propiophenone (VIII).—The base-catalyzed reaction between equimolar quantities of *p*-nitrobenzaldehyde and desoxybenzoin in aqueous dioxane at 0° gave a 75% yield of a mixture of ketols and 25% recovered starting material. The reaction apparently reaches equilibrium at 75% conversion, since increases in reaction time did not affect the result appreciably. Silica gel chromatography separated the ketol mixture into two stereoisomers, VIIIa, m.p. 120.5–122°, and VIIIb, m.p. 141–142.5°. The ratio VIIIa/VIIIb was approximately 3 under a wide variety of experimental conditions.



Stereochemical Assignments from N.m.r. Spectra.—Attempts to establish the stereochemistry of the two pairs of diastereoisomers derived from cyclohexanone (VIIa and b) and from desoxybenzoin (VIIIa and b) by the method used for IIa and IIb were unsuccessful. Treatment of the acetates with peroxytrifluoroacetic acid led either to recovery of starting materials or to an elimination reaction, forming α,β unsaturated ketones. Furthermore, various approaches based upon stereospecific elimination of acetic acid from the ketol acetates were fruitless. The stereochemical assignments could be made, however, by careful consideration of the infrared and n.m.r. spectra of the compounds.

Several studies¹⁵ have shown that the well known relationship between the dihedral angle of adjacent C–H bonds and the spin–spin coupling constants of the protons¹⁶ can be used to obtain information about the preferred conformations of a pair of diastereoisomers of the type X. In the case of 2,3-dibromobutanes (A = B =



bromine, X = Y = methyl for *meso* and A = Y = bromine, B = X = methyl for *dl*) the magnitude of the coupling between the two tertiary hydrogens (7.9 c.p.s. for *meso* and 3.0 c.p.s. for *dl*) indicated considerable preference for conformations with *trans*-bromine atoms.^{15a,b} In the case of (–)-ephedrine (A = methyl, B = phenyl, X = NHCH₃, Y = OH) and (+)- Ψ -ephedrine (A = OH, B = methyl, X = phenyl, Y = NHCH₃) a similar difference in the coupling constants (8.2 c.p.s. for (+)- Ψ -ephedrine and 4.0 for (–) ephedrine) indicated preference for the conformations which allow intramolecular hydrogen bonding between the hydroxyl and amino groups.^{15c} By examination of the infrared spectra of β -ketols II, VII, and VIII, we have ascertained that these compounds possess intramolecularly hydrogen-bonded structures in dilute chloroform or car-

bon tetrachloride solution. By arguments similar to those used in the previous studies the stereochemical assignments for the β -ketols could be made on the basis of the coupling constants between the tertiary hydrogens.

Solutions of each of the six ketols in carbon tetrachloride in the concentration range 0.002–0.006 *M* exhibited one or more strong peaks in the 3450–3590 cm.^{–1} infrared region, in addition to the sharper free hydroxyl peak at about 3615 cm.^{–1} (Table I). The relative intensities of the bonded and nonbonded peaks did not change appreciably with concentration in this range. In the case of IIa and IIb the concentration was varied 15-fold without altering the pattern. Variation in temperature between 0 and 50° likewise had only minor effect on the relative intensities.

TABLE I

ABSORPTION BANDS OF KETOLS IN THE 3400–3700 CM.^{–1} REGION^a

Compound	Free O–H,		Bonded O–H, cm. ^{–1} ^b	$\Delta\nu$	
	cm. ^{–1}				
IIa (<i>threo</i>)	3613	3585	<i>3498</i>	28	115
IIb (<i>erythro</i>)	3615	3540		75	
VIIa (<i>threo</i>)	3618	3590	<i>3542</i>	38	76
VIIb (<i>erythro</i>)	3618	3575	<i>3555</i>	43	63
VIIIa (<i>threo</i>)	3612	3592	<i>3560</i>	20	52
VIIIb (<i>erythro</i>)	3612	3592	<i>3531</i>	20	81

^a Spectra examined with a Perkin–Elmer Model 21 instrument fitted with CaF₂ optics and calibrated against polystyrene; compounds were dissolved in CCl₄ at concentrations 0.002–0.006 *M*.

^b The stronger of two bonded OH peaks is italicized.

Examination of the carbonyl region confirmed the presence of strong intramolecular hydrogen bonds in the ketols. Table II lists the ketone stretching frequencies for each of the six ketols and the corresponding acetates. The shift of the ketone band 13–24 cm.^{–1} toward higher frequency, which accompanied acetylation of the β -hydroxyl group, is attributable to the breaking of the hydrogen bond. In order to ascertain whether acetylation would alter the ketone frequency in the absence of hydrogen bonds, we examined dilute solutions of the β -ketol IX, prepared by Johnson, *et al.*¹⁷ The ketone stretching frequency of this ketol, which cannot form an intramolecular hydrogen bond, differs by no more than 3 cm.^{–1} from that of the corresponding acetate.

TABLE II

INFRARED SPECTRA OF KETOLS AND KETOACETATES IN THE CARBONYL REGION^a

Compound	—Ketone C=O frequency, cm. ^{–1} —		$\Delta\nu$, cm. ^{–1}
	Ketol	Ketoacetate	
IIa	1706 ^b	1722	16
IIb	1703	1718	15
VIIa	1697	1721	24
VIIb	1699	1715	16
VIIIa	1674	1687	13
VIIIb	1671	1684	13
IX	1716	1719	3

^a Observed with Perkin–Elmer Model 337 instrument; compounds were dissolved in CCl₄ at 0.002–0.006 *M*. ^b The carbonyl group of ketol IIa was much broader than the other bands in this table and this number is less accurate than the others.

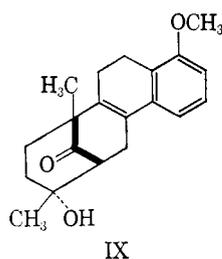
The n.m.r. spectra of diastereoisomers VIIIa and VIIIb (Table III) were exceedingly simple in the high-field region. In addition to the hydroxyl proton reso-

(15) (a) A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, **84**, 743 (1962); (b) F. A. L. Anet, *ibid.*, **84**, 747 (1962); (c) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961).

(16) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **79**, 1005 (1957); M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(17) W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960). We are grateful to Professor Johnson for making this compound available to us.

nance there were two nearly symmetrical doublets characteristic of an AB system in which the difference in chemical shift is large compared to the coupling con-



stant. Isomers IIa and IIb also exhibited a simple doublet due to the proton (H_a) of the $-CH-O-$ group. The signal arising from the other tertiary hydrogen (H_b) in these ketols was more complex, since there was further splitting by the methyl substituent. Measurement of the H_b -methyl splitting from the methyl doublet and the H_a - H_b splitting from the H_a doublet allowed a satisfactory interpretation of the H_b signal, based upon the simple splitting rules. With ketols VIIa and VIIb the H_a signal was also a well resolved doublet, with position and splitting closely resembling that in the other two ketols. The H_b signal was obscured by the cyclohexane methylene protons in these two cases.

TABLE III

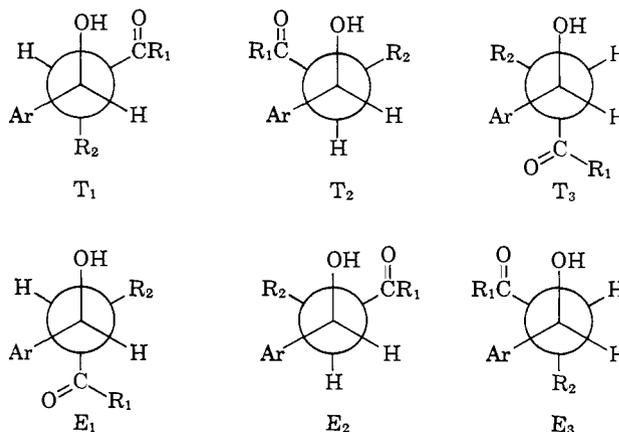
N.M.R. SIGNALS OF METHINE PROTONS IN KETOLS^a

Compound	H_a	H_b	J_{ab}	ΔJ^b
IIa (<i>threo</i>)	293	177 ^c	8.0	1.5
Acetate	358	190 ^d	9.5	
IIb (<i>erythro</i>)	317	172 ^d	3.0	4.0
Acetate	376	182 ^c	7.0	
VIIa (<i>threo</i>)	295	^e	8.0	0.0
Acetate	374	^e	8.0	
VIIb (<i>erythro</i>)	331	^e	2.5	3.5
Acetate	379	^e	6.0	
VIIIa (<i>threo</i>)	332	285	9.0	1.5
Acetate	398	305	10.5	
VIIIb (<i>erythro</i>)	337	284	4.5	5.0
Acetate	404	305	9.5	

^a Chemical shifts in c.p.s. relative to tetramethylsilane as internal standard, measured with Varian A-60 instrument ($CDCl_3$ solution). H_a is the proton on the carbinol carbon, H_b is adjacent to the ketone group. ^b $\Delta J = J_{ab}(\text{acetate}) - J_{ab}(\text{ketol})$. ^c Five-line multiplet. ^d Eight-line multiplet. ^e Signal not sufficiently resolved from methylene signals.

The coupling constant between the tertiary hydrogens is twice as great for VIIIa as for VIIIb, and the difference largely disappears when the ketols are converted to the corresponding acetates. The magnitude of the splitting suggests that the acetates exist predominantly in conformations having $H-C-C-H$ dihedral angles close to the maximum 180° ,^{15,16} and that free ketol VIIIa has an average dihedral angle nearly as large. Isomer VIIIb clearly prefers a conformation with a smaller dihedral angle, and this isomer is assigned the *erythro* structure, in which both conformations (E_2 and E_3) capable of permitting intramolecular hydrogen bonds impose a *gauche* rather than a *trans* relationship between the tertiary hydrogens. The coupling constant increases by 5.0 c.p.s. when the *erythro*-ketol is acetylated, compared to only 1.5 c.p.s. for the *threo* isomer, which suggests that the latter ketol exists predominantly as T_1 .

Extension of these arguments to ketols II and VII predicts the correct stereochemistry for IIa and IIb



II, $R_1 = R_2 = CH_3$
 VII, $R_1 + R_2 = -(CH_2)_4-$
 VIII, $R_1 = R_2 = C_6H_5$

and leads to the conclusion that VIIa is *threo* and VIIb is *erythro*.

Experimental

Acetates of Ketols I and II.—A small drop of sulfuric acid was suspended in 50 ml. of chloroform and 0.420 g. (1.88 mmoles) of 1-(*p*-nitrophenyl)pentan-1-ol-3-one (I)¹⁰ was dissolved in this mixture. Ketene was bubbled into the mixture at a moderately rapid rate for 45 min. The chloroform solution was then washed with water and with 10% sodium bicarbonate before drying over sodium sulfate. The pale yellow oil resulting from removal of solvent was crystallized from benzene-petroleum ether (30–60°) to yield 0.410 g. (82%), m.p. 40–45°. Two further recrystallizations provided the analytical sample, m.p. 45.5–46.5°. After standing for several weeks this sample melted at 70–71°, and all subsequent preparations exhibited the higher melting point.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.67; H, 5.66; N, 5.29.

The two stereoisomers of 1-*p*-nitrophenyl-2-methylbutan-1-ol-3-one (II)¹⁰ were acetylated in the same manner as ketol I. From the *threo* isomer IIa, m.p. 94–95°, the acetate was obtained in 50% yield, m.p. 61.5–62.5°. An additional 10% of impure material, m.p. 53–56°, was obtained.

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.99; H, 5.78; N, 5.29.

From the *erythro* isomer IIb, m.p. 61–62°, the acetate was obtained in 73% yield, m.p. 72.5–73.5°.

Anal. Found: C, 59.15; H, 5.74; N, 5.43.

Oxidation of the Acetate of Ketol I.—The conditions for the preparation and use of peroxytrifluoroacetic acid were essentially those described by Emmons and Lucas.¹² The peroxy acid was prepared from 5.9 mmoles (0.16 ml.) of Becco "90%" hydrogen peroxide and 0.94 ml. (6.8 mmoles) of Matheson trifluoroacetic anhydride in 8 ml. of purified methylene chloride. This solution was then added dropwise to a well stirred and ice-cooled suspension of 6.5 g. of powdered, oven-dried disodium hydrogen phosphate in 12 ml. of purified methylene chloride, containing 1.0 g. (3.8 mmoles) of the ketoacetate. The resulting reaction mixture was stirred at room temperature and aliquots were withdrawn periodically for the iodometric titration of peroxide.¹⁸ After 18 hr. excess peroxy acid was destroyed by addition of potassium iodide, followed by sodium thiosulfate, and additional water was added to dissolve the buffer. The organic layer was separated and combined with a further methylene chloride extraction, and the whole was washed with 10% sodium carbonate and dried over a mixture of sodium and magnesium sulfates. Removal of solvent left a pale oil from which 0.30 g. (30%) of starting material was recovered by crystallization. Chromatography of the residual oil on silica gel, using benzene as eluent, furnished 0.44 g. (41%) of ethyl β -acetoxy- β -(*p*-nitrophenyl)propionate (V), m.p. 53–53.7°.

(18) D. Swern, "Organic Reactions," Vol. 7, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 392.

Anal. Calcd. for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.47; H, 5.40; N, 4.97.

It was later found that the reaction proceeded to completion when the ratio of trifluoroacetic anhydride to hydrogen peroxide was twice that described above. Under these conditions the crude product (97%) had an infrared spectrum which indicated no contamination by unreacted keto ester. In the reactions described below the higher ratio was used.

The diester V (63 mg.) was refluxed for 2 hr. with a dilute solution of potassium hydroxide in methanol. Addition of water and extraction with ether gave only 2 mg. of a neutral unidentified material. Acidification of the alkaline solution furnished 49 mg. of a pale yellow crystalline acid, m.p. 125–200°, whose spectrum suggested it was a mixture of β -hydroxy acid and α,β -unsaturated acid. The acid mixture was refluxed overnight with a mixture of acetic anhydride–triethylamine.¹⁹ The resulting dark solution was acidified with hydrochloric acid, diluted with water, and extracted with ether. The ether solution was extracted with 5% sodium carbonate, and the acid product recovered by acidification of the carbonate solution and extraction with ether. Removal of solvent from the dried ether solution furnished 29 mg. (68%) of yellow orange crystals, m.p. 260° dec. Recrystallization from alcohol gave tan crystals of *p*-nitrocinnamic acid, m.p. 284° (darkened at 220°).

Oxidation of the Acetate of Ketol IIa.—Oxidation of the acetate of ketol IIa was carried out as described in the preceding paragraph. There was obtained, in addition to 8% unreacted acetoxy ketone, an 83% yield of *threo*-1-*p*-nitrophenyl-1,2-propanediol diacetate (IIIa), m.p. 115–125°. The melting behavior and infrared spectrum of this material were unchanged by chromatography on silica gel and repeated crystallization.

Anal. Calcd. for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.75; H, 5.27; N, 4.89.

The *threo*-diol diacetate (157 mg.) obtained above was refluxed for 2 hr. with methanolic KOH. Evaporation of methanol and extraction with ether furnished 110 mg. (100%) of neutral diol which melted at 91.5–92° after recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 55.02; H, 5.72; N, 7.19.

Oxidation of the Acetate of Ketol IIb.—Oxidation of the acetate of ketol IIb with peroxytrifluoroacetic acid was carried out as described above. In addition to 32% recovered acetoxy ketone and 9% of the corresponding α,β -unsaturated ketone, there was obtained 41% of *erythro*-1-*p*-nitrophenyl-1,2-propanediol diacetate (IIb), m.p. 62.5–63.5°.

Anal. Calcd. for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.79; H, 5.21; N, 5.06.

Hydrolysis of the *erythro*-diol diacetate, as described for the *threo* isomer, furnished a 91% yield of the diol, m.p. 79.5–80.5°.

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.90; H, 5.61; N, 6.99.

1-Phenylpropyne.—Phenylacetylene was methylated as described previously.²⁰ A 50% yield of product was obtained, b.p. 78–80° (19 mm.), n_D^{25} 1.5629 (reported²⁰ b.p. 113° (84 mm.), n_D^{25} 1.5650).

***cis*- β -Methylstyrene.**—1-Phenylpropyne (55.7 g., 0.480 mole) in 100 ml. of anhydrous ether was hydrogenated at 3–4 atm. in the presence of 5 g. of Lindlar catalyst²¹ and 2 g. of quinoline. One equivalent of hydrogen was consumed within 2 hr. at room temperature, after which the reaction appeared to stop. After filtration of the catalyst and removal of solvent, the product was distilled through a bubble-cap column, utilizing a trace of picric acid in the still pot as polymerization inhibitor. The bulk of the material (42.9 g.) was collected at 60.5–63° (19 mm.); the fore-run and residue weighed 4.6 and 4.9 g., respectively. The 42.9-g. sample was then fractionated through a spinning band column with the results shown in Table IV.

Each fraction was submitted to gas chromatographic analysis, using 30% silicone oil on firebrick, with a column temperature of 180°. The percentage composition of each fraction is given above. The infrared spectrum of fraction 5, as well as its refractive index (n_D^{25} 1.5407) and ultraviolet spectrum (λ_{max} 290 (ϵ 117) and 240 μ (ϵ 1.37×10^4) in 95% ethanol) agree

with reported values.²² The yield of *cis*- β -methylstyrene corresponds to 58%.

TABLE IV

Fraction	Wt., g.	B.p. (48 mm.), °C.	Composition ^a (v.p.c.), %		
			A	B	C
1	4.50	76–77.5	70	30	0
2	4.13	77.5–79.5	31	69	0
3	3.93	79.5–80.5	24	76	0
4	10.82	80.5–82.5	4	96	0
5	13.66	82.5–83	Trace	99	Trace
6	2.85	83–85	0	63	37

^a A = *n*-propylbenzene, B = *cis*- β -methylstyrene, C = *trans*- β -methylstyrene.

1-Phenylpropanol, b.p. 108.5–109.5° (18 mm.), was prepared in 90% yield by the reduction of propiophenone with sodium borohydride in dry methanol.

***trans*- β -Methylstyrene.**—The procedure for the dehydration of 1-phenylpropanol was adapted from that of Overberger.²³ A mixture of 20 g. of potassium bisulfate (B. and A. “fused powder”) and 10 mg. of picric acid was heated to 220° in a flask fitted with a dropping funnel and a bubble-cap distillation column. The pressure in the system was lowered to 100 mm. and 100 g. of the carbinol, containing 10 mg. of picric acid, was added through the dropping funnel at a rate such that the olefin and carbinol were fairly effectively separated by the column. After addition of the carbinol was complete, the pressure was lowered to 20 mm. until distillation stopped. The crude olefin which distilled during the reaction was redistilled through the same column (10 mg. of picric acid in still pot) to yield 44 g., b.p. 70.5–72° (20 mm.). This material was redistilled through a spinning band column. Five fractions were collected and examined by gas chromatography as described in the preparation of *cis*- β -methylstyrene. The first fraction, b.p. 87–88.5° (48 mm.), weighed 3.98 g. and contained 35% *cis*- and 65% *trans*-olefin. The second weighed 7.47 g., b.p. 88.5–90°, and was 10% *cis* and 90% *trans*. The third fraction, 5.81 g., b.p. 90–90.5°, n_D^{25} 1.5476, contained no more than a trace of *cis*-olefin. The fourth and fifth fractions were pure *trans*-olefin, 21.41 g., b.p. 90.5–91.5° (48 mm.), n_D^{25} 1.5478–1.5480. The ultraviolet spectrum of the fifth fraction in ethanol (λ_{max} 250, 284, and 293 μ ; ϵ 17,300, 1120, and 768, respectively) agreed with that reported previously.²² The total yield of *trans*-olefin was 40%.

***erythro*-1-Phenyl-1,2-propanediol (IVb).**—*cis*- β -Methylstyrene (0.920 g., 7.8 mmoles) was treated with 2.0 g. (7.88 mmoles) of osmium tetroxide in 30 ml. of dry pyridine at room temperature for 24 hr. The resulting solution of osmate ester was decomposed with sodium bisulfite as described by Baran.²⁴ The crude diol, 1.18 g., was recrystallized twice from petroleum ether (30–60°) to give 0.51 g. (43%) of colorless *erythro*-diol-IVb, m.p. 91–92.5° (reported¹³ 91–92°).

The same diol was prepared by oxidation of the *cis*-olefin with potassium permanganate at –40° in aqueous ethanol containing magnesium sulfate, as described previously.¹³ The yield of crude diol was 25%, and of recrystallized material, m.p. 87–89°, 16%.

***threo*-1-Phenyl-1,2-propanediol (IVa).**—From 0.92 g. of *trans*- β -methylstyrene and 2.0 g. of osmium tetroxide, by the same procedure described above, 1.07 g. (90%) of the *threo*-diol, m.p. 52–54° (reported¹³ 54–55°), was obtained. Oxidation of 5.2 g. of the same olefin with permanganate¹³ led to 2.3 g. (34%) of the same diol, m.p. 51–53.5°.

***erythro*-1-(*p*-Nitrophenyl)-1,2-diacetoxypropane (IIIb).**—Two grams (10 mmoles) of diol IVb was acetylated with acetic anhydride in pyridine by a conventional procedure.²⁵ The product (2.97 g.) had an infrared spectrum indicative of a diester, but did not crystallize. A portion (2.29 g.) of the crude diacetate was dissolved in 15 ml. of acetic anhydride containing one drop of sulfuric acid, and 3.1 ml. of fuming nitric acid was added dropwise while maintaining the reaction temperature at 15°. After

(22) R. Y. Mixer, R. F. Heck, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, **75**, 4094 (1953).

(23) C. G. Overberger and J. H. Saunders, “Organic Syntheses,” Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 204.

(24) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).

(25) R. L. Shriner and R. C. Fuson, “The Systematic Identification of Organic Compounds,” 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 165.

(19) H. E. Zimmerman and L. Abramjian, *J. Am. Chem. Soc.*, **81**, 2086 (1959).

(20) K. N. Campbell and M. J. O'Connor, *ibid.*, **61**, 2897 (1939).

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

2 hr. at 15–20° the mixture was diluted with water and extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, dried, and concentrated to 2.65 g. of light yellow oil. Repeated efforts to crystallize this material from a variety of solvents or to purify it by silica gel chromatography were unsuccessful. A crop of crystalline material (0.230 g.) was finally obtained by refrigeration of the oil for several weeks. After recrystallization from benzene–petroleum ether (30–60°), it melted at 58–60.5°, and at 59–61.5° when mixed with a sample of IIb prepared by oxidation of IIB. The two samples exhibited identical infrared spectra. No more crystalline material was obtained from the nitration reaction. The residual oil probably contained both starting material and product resulting from *ortho* nitration.

Hydrolysis of the synthetic diacetate IIb yielded a sample of the diol, m.p. 77–78.5°, mixture m.p. with the sample described previously, 77.5–79.5°. The two samples had the same infrared spectrum.

threo-1-(*p*-Nitrophenyl)-1,2-diacetoxypropane (IIIa).—A 1.86-g. (9.4 mmoles) sample of the *threo*-diol IVa was acetylated and nitrated in one step by treatment with 13 ml. of acetic anhydride and 1 drop of sulfuric acid at room temperature for 0.5 hr., followed by dropwise addition of 3.1 ml. of fuming nitric acid at 15°. After stirring for 2 hr. at room temperature, the mixture was poured onto ice and extracted with ether. The ether solution was washed with aqueous sodium bicarbonate, dried, and evaporated to leave 1.86 g. of yellow oil. The oil deposited 0.70 g. of colorless crystals from benzene–petroleum ether (30–60°). Recrystallization furnished 0.51 g. (28%) of the diacetate IIIa, m.p. 115–126°, whose infrared spectrum compared exactly with the sample of IIIa obtained by oxidation of IIa. The residual oil from the nitration did not yield more crystalline product, although its infrared spectrum was very similar to that of IIIa. It is assumed that it is largely the *ortho* nitro compound.

Hydrolysis of the synthetic diacetate IIIa, as described previously, furnished a sample of the diol, m.p. 87–89°, mixture m.p. with the previous sample of this compound 88–91°. The two infrared spectra were identical.

Condensation of *p*-Nitrobenzaldehyde with Cyclohexanone.—The aldehyde (3.02 g., 0.020 mole) was dissolved in 50 ml. of cyclohexanone cooled in an ice bath, and 3.0 ml. of 0.2 *N* aqueous sodium hydroxide was added. The heterogeneous mixture was stirred at 0° for 2 hr., after which 50 ml. of water and 50 ml. of ether were added, and the layers were separated. The aqueous layer was extracted with two 50-ml. portions of chloroform, and the combined organic extract was dried over MgSO₄. The solvents and unreacted cyclohexanone were removed under reduced pressure and the residue was chromatographed on silica gel deactivated with 25% water, using benzene containing 2–5% petroleum ether (30–60%) as eluent. After elution of a small amount of *p*-nitrobenzaldehyde, there was obtained a series of crystalline fractions. The early fractions were pure *erythro*-2-(α -hydroxy-*p*-nitrobenzyl)cyclohexanone (VIIb), m.p. 131–132°.

Anal. Calcd. for C₁₇H₁₅NO₃: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.70; H, 6.16; N, 5.67.

The late fractions consisted of the *threo* isomer VIIa, m.p. 161–162°.

Anal. Calcd. for C₁₃H₁₃NO₃: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.80; H, 6.08; N, 5.64.

By fractional crystallization from benzene–petroleum ether and chromatography of the mother liquors there was obtained a total of 1.48 g. (30%) of pure *erythro* isomer and 2.68 g. (54%) of pure *threo* isomer in addition to 0.30 g. (6%) of a mixture of the two, contained in intermediate fractions.

When the reaction was carried out at room temperature as described by Billimoria¹⁴ the total yield of ketols was 67%, and the ratio VIIa/VIIb was approximately 4.4. The milder conditions described above did not lead to appreciable interconversion of VIIb and VIIa (less than 5%), but the room temperature reaction led to extensive equilibration.

Acetate of Ketol VIIb.—In 40 ml. of chloroform containing 1 drop of sulfuric acid, 0.394 g. (1.6 mmoles) of ketol VIIb was dissolved and treated with ketene at 0° for 1 hr. The chloroform solution was then shaken with 50 ml. of dilute sodium bicarbonate, washed with water and with saturated sodium chloride, and dried over magnesium sulfate. After removal of solvent, the oil was chromatographed on 40 g. of silica gel. In the fractions eluted with benzene containing 4% ether there was obtained 0.219 g. (50%) of crystalline material, m.p. 75–

78°. Recrystallization from benzene–petroleum ether (30–60°) furnished the analytical sample, m.p. 78–79.5°.

Anal. Calcd. for C₁₃H₁₇NO₅: C, 61.84; H, 5.88. Found: C, 61.79; H, 6.02.

When this ketol was acetylated with acetic anhydride by the method described in the following paragraph, 29% of starting ketol was recovered and the acetate (38%) melted at 69–70°.

Acetate of Ketol VIIa.—One gram (4.0 mmoles) of ketol VIIa was heated at 80° in 15 ml. of acetic anhydride for 42 hr. Excess anhydride and acetic acid were removed under reduced pressure and the residue was chromatographed on silica gel as described for VIIb acetate. There was obtained 0.89 g. (76%) of VIIa acetate, m.p. 137–138°.

Anal. Calcd. for C₁₅H₁₇NO₅: C, 61.84; H, 5.88. Found: C, 61.96; H, 5.86.

Reaction of *p*-Nitrobenzaldehyde with Desoxybenzoin.—Desoxybenzoin (Eastman Organic Chemicals) was purified by washing an ether solution of same with 1% sodium hydroxide, followed by distilled water until the washings were neutral. Drying over magnesium sulfate and removal of solvent was followed by two recrystallizations from methanol to give colorless, odorless crystals, m.p. 57–58°. *p*-Nitrobenzaldehyde was purified by dissolving in a mixture of ether and benzene, washing with 2% sodium carbonate, with water until neutral, and drying over sodium sulfate. Removal of solvent and recrystallization twice from 50% ethanol gave light yellow needles, m.p. 105–106°.

Purified²⁶ dioxane (15 ml.), freshly distilled from sodium, was diluted with 3.0 ml. of water and the solution was degassed with nitrogen for 30 min. Desoxybenzoin (0.98 g., 5.0 mmoles) and 0.75 g. (5.0 mmoles) of *p*-nitrobenzaldehyde were dissolved in the degassed solution, cooled to 0°, and treated with 0.05 ml. of 0.2 *N* sodium hydroxide. After 45 min. at 0° the reaction mixture was poured into 150 ml. of ice–water containing slightly more hydrochloric acid than was needed to neutralize the alkali. The mixture was extracted with 300 ml. of ether in three portions. The ether extract was washed with six 50-ml. portions of ice–water, and then with 75 ml. of saturated salt solution, and dried over magnesium sulfate. The residue (1.77 g.) after removal of solvent was a light oil which slowly solidified. Chromatography on 80 g. of silica gel (Davison grade 923, 100–200 mesh) in benzene yielded, in the first liter of eluate, 0.44 g. of a mixture of unreacted ketone and aldehyde. Subsequent elution with 5% ether in benzene furnished 1.30 g. (75%) of a mixture of hydroxy ketones VIIa and VIIb, as an oil which solidified slowly.

The mixture of VIIa and VIIb was chromatographed on 150 g. of silica gel containing 10% water, using 5% petroleum ether (30–60°) in benzene as eluent. Isomer VIIb appeared first as a series of crystalline fractions (0.28 g.), followed by 0.048 g. of a mixture of isomers, followed by 0.93 g. of isomer VIIa. Recrystallization of the pure fractions from ethanol yielded 0.23 g. of colorless hydroxy ketone VIIb, m.p. 141–142°, and 0.68 g. of VIIa, m.p. 121–122°.

Anal. Calcd. for C₂₁H₁₇NO₄: C, 72.61; H, 4.93; N, 4.03. Found (VIIa): C, 72.55; H, 4.82; N, 4.02; (VIIb): C, 72.52; H, 4.84; N, 4.12.

By further crystallization of the intermediate fractions and the mother liquors, it was estimated that the ratio of VIIa to VIIb in the total product was 3.0.

Acetates of Ketols VIIa and VIIb.—A solution of 116 mg. (0.33 mmole) of ketol VIIb in 4 ml. of chloroform containing a microdrop of sulfuric acid was treated at 0° for 10 min. with ketene (flow rate 1.6 mmoles/min.). The chloroform solution was taken up in 75 ml. of ether and washed successively with two 10-ml. portions of 2% sodium bicarbonate, two 10-ml. portions of water, and 10 ml. of saturated sodium chloride. Drying over magnesium sulfate and removal of solvent left yellow crystals, m.p. 160–163°. Recrystallization from 50% benzene–petroleum ether (30–60°) furnished 70 mg. (54%) of colorless crystals of **ketol VIIb acetate**, m.p. 165.5–166.5°.

From 100 mg. (0.29 mmole) of ketol VIIa by the same method (ketene treatment only 4 min.) there was obtained 110 mg. of colorless crystals, m.p. 170–173°, recrystallization of which from 50% benzene–petroleum ether (30–60°) furnished 85 mg. (71%) of **ketol VIIa acetate**, m.p. 175–176°.

Anal. Calcd. for C₂₃H₁₉NO₅: C, 70.94; H, 4.92; N, 3.60. Found (VIIb acetate): C, 71.03; H, 4.83; N, 3.57; (VIIa acetate): C, 70.92; H, 4.95; N, 3.55.

(26) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1957, p. 285.