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

Studies in Stereochemistry. XXVIII. Reactivity Differences between Diastereomers in the Wagner–Meerwein Rearrangement[1]

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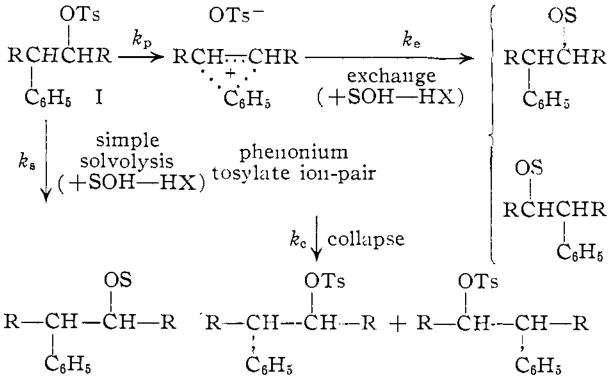
The rates of formolysis and acetolysis of the diastereomers of 3-phenyl-2-butyl tosylate, 4-phenyl-3-hexyl tosylate and of 2,5-dimethyl-4-phenyl-3-hexyl brosylate have been measured. The $k_{\text{erythro}}/k_{\text{threo}}$(titrimetric) values for acetolysis are 1.2, 1.8 and 6.4, respectively, and 1.2, 2.6 and 8.2 for formolysis, respectively. That these ratios do not change much in the two solvents suggests that in each system, the division of phenonium tosylate (or brosylate) ion-pairs between collapse and exchange reactions with solvent is quantitatively similar for the *threo* and *erythro* diastereomers. The values of the ratios, k_α/k_t (polarimetric and titrimetric rate constants), decrease in value for the *threo* isomers in passing from the less to the more sterically hindered systems. As the bulk of the eclipsed groups increases, the ratio of exchange (with solvent) to collapse of these symmetrical *cis*-phenonium tosylate (or brosylate) ion-pairs increases. The products of solvolysis of 2,5-dimethyl-4-phenyl-3-hexyl brosylate have been examined in detail. Olefin or the products of hydrogen migration (mostly from the 2-position) dominate over those resulting from phenyl migration. Only traces of products of simple solvolysis were found. The yields of these various products indicate that the diastereomeric rate factor of 8.2 for the formolysis in this system is due not to differences in rate for the part of the reaction leading to phenonium ion, but to differences in rate for the part leading to olefin, and the products of hydrogen migration. These results suggest that in this system the differences in rate for solvolysis for the *threo* and *erythro* isomers reflect more the differences in energy of the diastereomeric starting states rather than differences in eclipsing effects for the diastereomeric transition states.

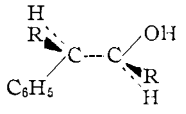
Previous studies of the Wagner–Meerwein rearrangement in systems represented by I have uncovered marked differences in behavior of I with R = CH_3[2] and R = C_2H_5.[3] Although the mechanism for solvolysis for both systems can be encompassed by the formulation, the ratios k_p/k_s and k_c/k_e vary enough to affect the balance of products. The rates of solvolysis (k_t is the titrimetric rate constant) and of change of optical activity (k_α is the polarimetric rate constant) have been reported for *threo*-I with R = CH_3 in both formic and acetic acids,[4] and k_t was reported for *erythro*-I with R = CH_3 in acetic acid.[4a] The rates k_t and k_α also were obtained in acetic acid for *threo*-I with R = C_2H_5, and k_α (but not k_t) was also determined in formic acid.



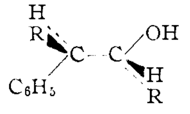
This paper is concerned with reactivity differences between diastereomers of I with R = CH_3, C_2H_5 and $CH(CH_3)_2$. The new kinetic data on particularly the *erythro* isomers of the first two systems coupled with product and kinetic data on the third system allow an evaluation of conformational and eclipsing effects in a series of homologous compounds of increasing steric constraints. All three of these systems possess symmetry properties which allow a maximum amount of information to be extracted concerning the role that phenonium ions play in the Wagner–Meerwein rearrangement.

Kinetics of Solvolyses

The kinetics of acetolysis and formolysis were followed utilizing methods previously described,[4b,4c] and in all cases were found to be cleanly first order. All four stereomers of 3-phenyl-2-butanol (II),[2] 4-phenyl-3-hexanol (III)[5] and 2,5-dimethyl-4-phenyl-3-hexanol (IV)[6] have been previously prepared in an optically pure state, and the absolute configurations of II and III have been completely assigned. As a result of the present work, all of the *relative* configurations of all four isomers of IV can be definitely assigned. None of the *absolute* configurations of the isomers of IV are known, and therefore a *completely arbitrary* assignment is made for convenience (see formulation).



L-*threo*
(+)-II, R = CH_3
(+)-III, R = C_2H_5
(+)-IV, R = $(CH_3)_2CH$



L-*erythro*
(+)-II, R = CH_3
(+)-III, R = C_2H_5
(+)-IV, R = $(CH_3)_2CH$

Table I reports the rate constants needed for comparison of the three systems and of the two diastereomers within each system. The rates were not all run under completely identical conditions. For instance, runs 1–6 were conducted in the absence of a salt for neutralization of the acid liberated, whereas runs 7–21 were made in the presence of such a salt. Enough data were obtained on system II[4a,4b] to indicate that the rate ratios reported in this paper were only slightly sensitive to the presence of salt. In the formolysis of systems III and IV, about 20% by volume of chloroform had

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(1) This work was sponsored by the Office of Ordnance Research, U. S. Army.

(2) (a) D. J. Cram, THIS JOURNAL, **71**, 3863 (1949); (b) **74**, 2129 (1952); (c) **74**, 2137 (1952).

(3) D. J. Cram and F. A. Abd Elhafez, *ibid.*, **75**, 3189 (1953).

(4) (a) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber and J. Corse, *ibid.*, **74**, 1114 (1952); (b) S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2164 (1952); (c) S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).

(5) D. J. Cram, F. A. Abd Elhafez and H. Weingartner, *ibid.*, **75**, 2293 (1953).

(6) D. J. Cram, F A. Abd Elhafez and H. LeRoy Nyquist, *ibid.*, **76**, 22 (1954).

TABLE I

RATE CONSTANTS FOR SOLVOLYSES OF SULFONATE ESTERS OF DIASTEREOMERS OF ALCOHOLS II, III AND IV

Run	Compound	Solvent	Concn. ester, mole/l.	Salt added	Concn. salt, mole/l.	Proc.	T, °C.	Rotations α° Init.	Final	k, sec.$^{-1}$
1[a]	*threo*-II-Ts	AcOH	0.030	....	....	Tit.	74.71	....	....	$(4.95 \pm 0.17) \times 10^{-5}$
2[b]	*threo*-II-Ts	AcOH	.116	NaOAc	0.0957	Tit.	74.91	....	....	$(6.72 \pm .16) \times 10^{-5}$
3[b]	*threo*-II-Ts	AcOH	.116	NaOAc	0.0957	Pol.[c]	74.91	0.53	−0.01	$(3.33 \pm .10) \times 10^{-4}$
4[a]	*erythro*-II-Ts	AcOH	.032	....	....	Tit.	74.72	....	....	$(5.77 \pm .26) \times 10^{-5}$
5[b]	*threo*-II-Ts	HCOOH	.070	....	....	Tit.	24.98	....	....	$(2.28 \pm .03) \times 10^{-4}$
6[b]	*threo*-II-Ts	HCOOH	.116	....	....	Pol.[c]	25.12	3.92	−0.04	$(2.65 \pm .12) \times 10^{-4}$
7	*erythro*-II-Ts	HCOOH	.096	NaOOCH	0.119	Tit.	25.00	....	....	$(2.80 \pm .02) \times 10^{-4}$
8	*erythro*-II-Ts	HCOOH	.098	NaOOCH	.119	Pol.[c]	25.00	−2.53	−1.60	$(2.49 \pm .18) \times 10^{-4}$
9[d]	*threo*-III-Ts	AcOH	.0882	KOAc	.105	Tit.	74.64	....	....	$(1.68 \pm .03) \times 10^{-4}$
10[d]	*threo*-III-Ts	AcOH	.0882	KOAc	.105	Pol.[c]	74.64	−1.47	−0.06	$(5.48 \pm .19) \times 10^{-4}$
11[d]	*threo*-III-Ts	AcOH	.0900	KOAc	.120	Tit.[e]	50.08	....	....	$(1.01 \pm .02) \times 10^{-5}$
12	*erythro*-III-Ts	AcOH	.030	KOAc	.035	Tit.	50.00	....	....	$(1.80 \pm .01) \times 10^{-5}$
13	*threo*-III-Ts	HCOOH[f]	.091	NaOOCH	.123	Tit.	25.00	....	....	$(2.90 \pm .03) \times 10^{-4}$
14[d]	*threo*-III-Ts	HCOOH[f]	.103	NaOOCH	.130	Pol.[c]	25.2	−1.44	0.06	$(3.90 \pm .10) \times 10^{-4}$
15	*erythro*-III-Ts	HCOOH[f]	.030	NaOOCH	.034	Tit.	25.00	....	....	$(7.65 \pm .09) \times 10^{-4}$
16	*threo*-IV-Bs	AcOH	.079	KOAc	.105	Tit.	49.74	....	....	$(4.97 \pm .09) \times 10^{-5}$
17	*threo*-IV-Bs	AcOH	.079	KOAc	.109	Pol.[c]	49.74	−4.64	+0.84	$(6.05 \pm .05) \times 10^{-5}$
18	*erythro*-IV-Bs	AcOH	.079	KOAc	.105	Tit.	49.74	....	....	$(3.18 \pm .03) \times 10^{-4}$
19	*erythro*-IV-Bs	AcOH	.079	KOAc	.109	Pol.[c]	49.74	−0.83	+1.65	$(3.28 \pm .07) \times 10^{-4}$
20	*threo*-IV-Bs	HCOOH[g]	.035	NaOOCH	.041	Tit.	25.00	....	....	$(3.10 \pm .01) \times 10^{-4}$
21	*erythro*-IV-Bs	HCOOH[g]	.034	NaOOCH	.041	Tit.	25.00	....	....	$(2.53 \pm .01) \times 10^{-3}$

to be added to make the system homogeneous. The solvent was always the same for any two rates appearing as a ratio in this paper.

The polarimetric and titrimetric rates for *erythro*-II tosylate formolysis are almost the same (runs 7 and 8) and serve as a check on the method. Unfortunately the polarimetric rate of acetolysis could not be determined because some of the optically active products resulting initially underwent reaction at a rate comparable to that at which the solvolytic reaction occurred (see Discussion). An analysis of the meaning of these kinetic data depends upon a knowledge of the reaction products, a subject taken up in the next section.

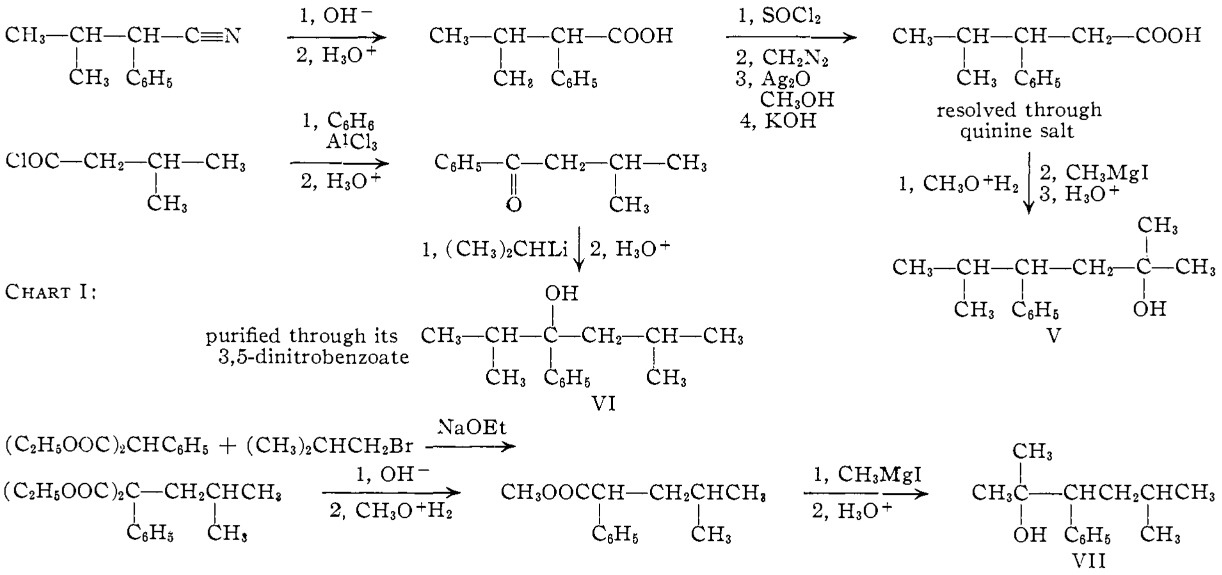
CHART I:

Products of Solvolysis in the 2,5-Dimethyl-4-phenyl-3-hexyl System.—The products of formolysis and acetolysis of the tosylates of the 3-phenyl-2-butyl and 4-phenyl-3-hexyl systems have been previously reported.[2,3] The pattern of products obtained by the solvolyses of 2,5-dimethyl-4-phenyl-3-hexyl brosylate[7] (IV-Bs) is somewhat different from that found for the two simpler homologs. These products (alcohols V and VII) as well as the potential product VI were all prepared by conventional means since their detection in the alcohol mixtures from the hydrolysis of the solvolysis mixtures demanded a knowledge of their individual physical properties. Alcohol V was prepared in an essentially optically pure form since the analytical scheme necessitated a knowledge of its rotation. Alcohol VI was only prepared as its racemate. The third alcohol (product of two 1,2-H shifts) was also synthesized (see formulas) as a racemate.

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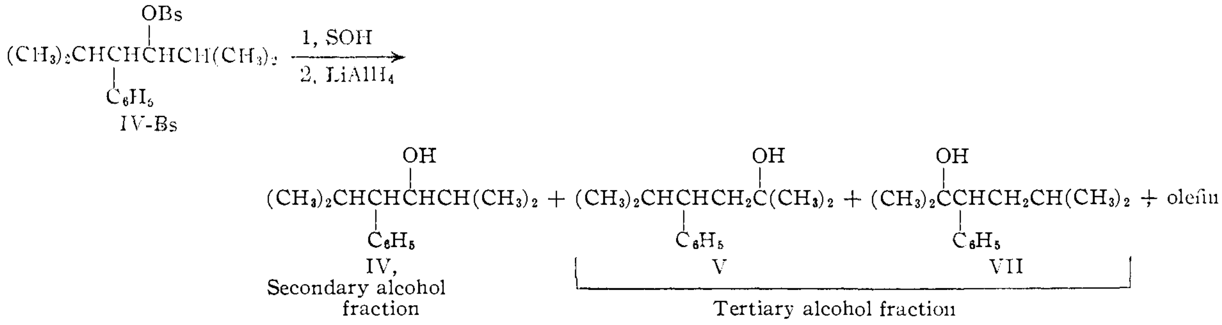
[7] The tosylates of this system, although less reactive kinetically, are much harder to obtain in a pure state than the brosylates.

TABLE II

PRODUCTS OF ACETOLYSIS AND FORMOLYSIS OF BROSYLATE ESTERS OF IV



$$\underset{\text{IV-Bs}}{(CH_3)_2CHCH\underset{C_6H_5}{|}\overset{OBs}{\overset{|}{C}}HCH(CH_3)_2} \xrightarrow[2,\ LiAlH_4]{1,\ SOH} \underset{\text{IV}}{(CH_3)_2CH\underset{C_6H_5}{\underset{|}{C}}H\overset{OH}{\overset{|}{C}}HCH(CH_3)_2} + \underset{\text{V}}{(CH_3)_2CH\underset{C_6H_5}{\underset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}(CH_3)_2} + \underset{\text{VII}}{(CH_3)_2\underset{C_6H_5}{\underset{|}{C}}\overset{OH}{\overset{|}{C}}HCH_2CH(CH_3)_2} + \text{olefin}$$

Products	(+)-*threo*-IV-Bs AcOH (run 1)	(+)-*erythro*-IV-Bs AcOH (run 2)	(−)-*threo*-IV-Bs HCOOH (run 3)	(−)-*erythro*-IV-Bs HCOOH (run 4)
	Starting materials			
Sec. alc. fraction				
Yield, %	28	3.8	15.3	6.9
$[\alpha]^{25}D$	+0.12°[b]	+16.4°[a] (+20.7°)[b]	−0.28°[c]	−16.6[b]
Composition (fraction = 100%)	97% *threo*-IV, racemic 3% *erythro*-IV	95% (+)-*erythro*-IV 5% *threo*-IV	95–100% *threo*-IV, racemic 0–5% *erythro*-IV	95–100% (−)-*erythro*-IV 0–5% *threo*-IV
Tert. alc. fraction				
Yield, %	12	19	32	60
$\alpha^{25}D$ (l = 1 dm., neat)	−1.03°	−1.75°	+0.67°	+1.20°
$n^{25}D$	1.5022	1.5029	1.5022	1.5022
Composition	Partially racemic V + VII	Optically pure V + trace VII	Partially racemic V + VII	Optically pure V + VII
Olefin fraction				
Yield, %	53	70	43	14
$n^{25}D$	1.4992	1.4994	1.5011	1.5007
$\alpha^{25}D$ (l = 1 dm., neat)	−43.0°	−72.1°	+54.8°	+92.7°
ϵ (232 mμ)[d]	1594	474	1788	524

[a] (c, 2.4, $CHCl_3$). [b] After recrystallization (c 2, $CHCl_3$). [c] l = 1 dm., neat. [d] Cyclohexane as solvent.

The brosylates of all four of the optically pure isomers of IV[6] were prepared. The sulfonate esters of the (+)-*threo*- and (+)-*erythro*-alcohols (these isomers differ only in configuration at the carbon carrying the oxygen) were acetolyzed at 50° for 8 titrimetric half-lives. The brosylates of the (−)-*threo*- and (−)-*erythro*-alcohols were formolyzed at 25° for 5 titrimetric half-lives. The olefin–ester products were converted to olefin–alcohol mixtures with lithium aluminum hydride. This mixture was split into an alcohol and olefin component by chromatography. The alcohol fraction was then itself split by careful chromatography into a secondary and tertiary alcohol component, each of which was then examined in detail. Table II records the important data. Control experiments established that the separations were almost quantitative and that the olefins and tertiary formates interconverted somewhat in the formolyses. That tertiary and secondary acetates can be reduced with lithium aluminum hydride without producing olefin has been established previously.[2c]

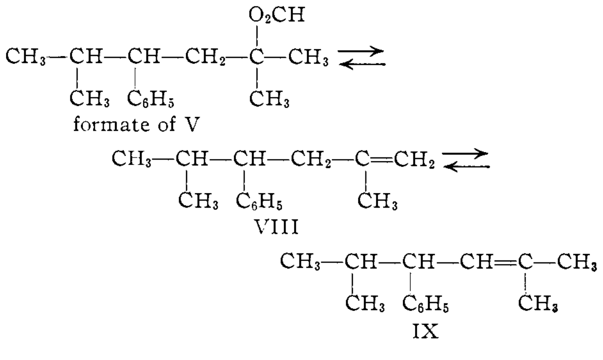
Secondary Alcohols Obtained from Solvolyses.—Infrared analysis[6] of the alcohol fraction obtained in the two acetolysis runs established that from *threo*-brosylate (run 1), the final secondary alcohol product was about 97% *threo*-IV and 3% *erythro*-IV. From *erythro*-brosylate (run 2), the final secondary alcohol product was about 95% *erythro*-VI and 5% *threo*-IV. The rotations of the secondary alcohols obtained in these two runs indicate that the *threo*-alcohol obtained from *threo*-brosylate (run 1) is essentially racemic, whereas the *erythro*-alcohol obtained from *erythro*-brosylate (run 2) is essentially optically pure. Although the infrared analysis was not performed on the alcohols from the formolysis, the similarity of the magnitudes of rotation in runs 1 and 3 and in runs 2 and 4 indicate the results to be similar. In runs 2 and 4 mixed melting point comparisons of the *erythro*-alcohol obtained with authentic material further established the above contentions. In runs 1, 3 and 4, *p*-nitrobenzoates of the secondary alcohols were prepared, and mixed melting point and rotational comparisons between these compounds and the appropriate authentic materials also supported these conclusions (see Experimental). Insufficient material was obtained in run 2 to permit this derivative to be prepared.

Tertiary Alcohols Obtained from Solvolyses.—The infrared spectra of tertiary alcohols, V, VI and VII were not sufficiently different to permit an infrared analysis to be made of the tertiary alcohols from the solvolyses. The infrared spectra of the tertiary alcohols from the solvolyses were almost identical to that of alcohol V. Indeed, the rotation of the alcohol from run 2 (acetolysis of *erythro*-isomer) compares well with that obtained synthetically ($\alpha^{25}D$ −1.75°, l = 1 dm., neat *vs.* $\alpha^{25}D$ +1.81°, l = 1 dm., neat, respectively). This fact suggests this product to consist largely of optically pure V. Unfortunately insufficient material was available from this run to permit formation of a solid derivative. The alcohol from run 4 (formolysis of *erythro*-isomer) was converted to its 3,5-dinitrobenzoate derivative, which upon crystallization and recrystallization gave almost optically pure derivative of V as shown by comparison with an authentic sample. From the filtrates was obtained ester which appeared to be a mixture of ester of V and some other ester, probably of VII. The alcohol from run 1 (acetolysis of *threo* isomer) gave 3,5-dinitrobenzoate ester of partially racemized V and possibly some other ester. The alcohol from run 3 (formolysis of *threo* isomer) gave 3,5-dinitrobenzoate ester of partially racemized V. From the filtrates was isolated the 3,5-dinitrobenzoate ester of racemic VII, as shown by comparison with an authentic sample. The above evidence suggests that optically pure V is produced in both acetolysis and formolysis runs of the *erythro* derivative but that somewhat racemized V was produced from the *threo* derivative. Alcohol VII was demonstrated to arise in the formolysis of *threo* material, and its presence was likely in the formolysis of *erythro* and possible in the acetolysis of the *threo*-brosylate.

Attempts to form the 3,5-dinitrobenzoate of VI failed. The absence of liquid residues from the formation of this derivative of the tertiary alcohols from the solvolysis points to the absence of VI in these mixtures. Even had the formate of VI formed in the formolyses, it probably would have gone to olefin since even the acetate of V slowly went to olefin in formic acid.

Olefins Obtained from Solvolyses.—During attempts to measure k_α for the formolysis of either *threo*-IV-Bs or *erythro*-IV-Bs, it became clear that two reactions were occurring in series with one another, each of which changed the rotation of the solution. The first and faster of these was the ionization of the brosylate, and the second was a reshuffling of certain of the initially formed (kinetically controlled) products. This result contrasts with that observed in the acetolyses where the products, once formed, persisted (see Experimental). To establish what secondary reactions were occurring in the formolyses, the following experiments were conducted.

Unfortunately the formate of V could not be prepared in a pure state. The acetate of active V was prepared and was found to give mixtures of olefins VIII and IX in formic acid under the conditions of the formolyses. Since formate is a better leaving group than acetate, it seems probable that the formate of V can interconvert with olefins VIII and IX under conditions of the formolysis.



formate of V

VIII

IX

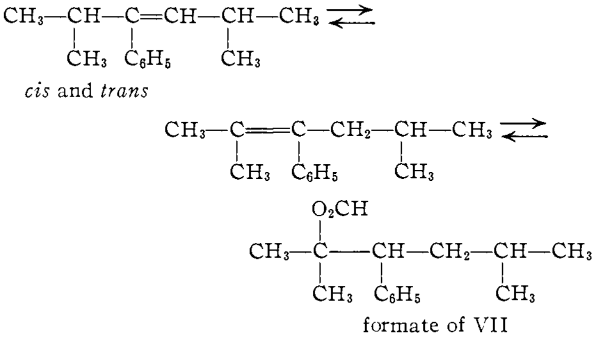
$$\underset{CH_3}{CH_3{-}\underset{|}{C}H}{-}\underset{C_6H_5}{\underset{|}{C}H}{-}CH_2{-}\overset{O_2CH}{\underset{CH_3}{C}}{-}CH_3 \rightleftarrows$$

$$CH_3{-}\underset{CH_3}{CH}{-}\underset{C_6H_5}{CH}{-}CH_2{-}\underset{CH_3}{C}{=}CH_2 \rightleftarrows$$

$$CH_3{-}\underset{CH_3}{CH}{-}\underset{C_6H_5}{CH}{-}CH{=}\underset{CH_3}{C}{-}CH_3$$

That olefins VIII and IX can equilibrate with one another and with the formate of V under the conditions of the formolysis is suggested by the following experiment. The two olefin mixtures from acetolysis runs 1 and 2 were dissolved in the formolysis solutions and allowed to stand at 25° for the lifetime of a run. The rotations increased markedly, and an ester band appeared in the infrared of the material isolated from this treatment.

Conjugated olefins were also produced during the solvolyses as shown by the ϵ's of the olefinic fraction at λ 232 mμ (see Table II). The total ultraviolet spectrum of these fractions showed no λ_{max} but only a general increase in absorption from 260 to 220 mμ. The same was true for the product obtained by treating IV-Bs with sodium ethoxide.[6] The absence of a maximum in this styrene region (230–250 mμ) undoubtedly is due to steric inhibition of resonance of the conjugated olefins. During the above equilibration of olefins in the formic acid solvolysis solutions, the ϵ's of the mixture at λ 232 mμ increased by about one-third. This result suggests that in formic acid the three conjugated olefins equilibrate with one another and that the increase of ϵ is associated with an accumulation of the more thermodynamically stable isomer, the isomer with the least degree of steric inhibition of resonance and the highest ϵ. When the equilibrating solutions were allowed to stand for a much longer time, both the rotations and the ϵ's stopped changing. This result demonstrates that the conjugated and unconjugated systems of olefins are not interconverting at any appreciable rate. Although not demonstrated, the formates of VII and possibly of VI also probably are involved in the equilibration of the conjugated olefins. These results are in harmony with those obtained with the simpler and more studied 2-phenylbutene system of olefins.[8] Attempts to reduce these olefins to 2,5-dimethyl-3-phenylhexane failed.



cis and *trans*

formate of VII

$$CH_3{-}\underset{CH_3}{CH}{-}\underset{C_6H_5}{C}{=}CH{-}\underset{CH_3}{CH}{-}CH_3 \rightleftarrows$$

$$CH_3{-}\underset{CH_3}{C}{=}\underset{C_6H_5}{C}{-}CH_2{-}\underset{CH_3}{CH}{-}CH_3 \rightleftarrows$$

$$CH_3{-}\overset{O_2CH}{\underset{CH_3}{C}}{-}\underset{C_6H_5}{CH}{-}CH_2{-}\underset{CH_3}{CH}{-}CH_3$$

Discussion

Phenonium Ions as Intermediates in the Production of Secondary Acetate and Formate in Systems such as I.—The character of the secondary acetates and formates obtained from the solvolyses of the optically active diastereomers of 2,5-dimethyl-4-phenyl-3-hexyl brosylate indicate that in this reaction a bridged phenylcarbonium ion (a phenonium ion) intervenes as the chief intermediate leading to secondary ester. With one diastereomer, essentially completely racemized ester of the *same* diastereomeric configuration was obtained. With the other diastereomer the product possessed the same configuration as the reactant. Clearly the first diastereomer possesses the *threo* and the second the *erythro* configuration.

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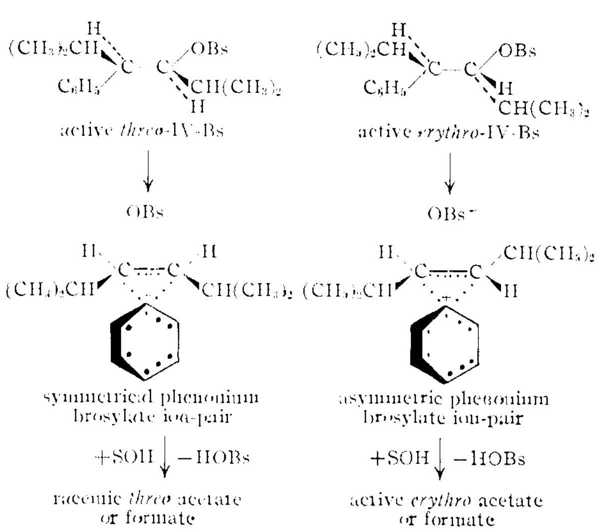
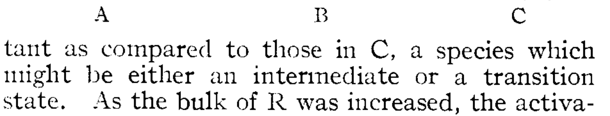
(8) D. J. Cram, This Journal, **74**, 2137 (1952).



The relative absence of products of the *erythro* configuration from *threo* starting material and *threo* products from *erythro* starting materials indicates that in this rather hindered system, simple solvolysis is much slower than solvolysis involving phenyl participation in ionization. Clearly an internally compensated bridged ion (phenonium ion) intervened in the *threo* and an asymmetric bridged ion in the *erythro* system. This kind of product pattern resembles more that observed in the 3-phenyl-2-butyl than that of the 4-phenyl-3-hexyl system. In the former, *simple* acetolysis accounted for about 4–5% of the secondary acetates, and with the *threo* isomer inversion predominated over retention. In the 4-phenyl-3-hexyl system, *simple* acetolysis of the *threo* isomer accounted for about 15% of the secondary acetates, and retention predominated over inversion by a factor of about 5. In the 2,5-dimethyl-4-phenyl-3-hexyl system, *simple* acetolysis gave rise to about 3% of the secondary acetates, inversion being comparable to retention. Thus the most and least-hindered systems resemble each other more with regard to the amounts and direction of simple substitution than they resemble the intermediate system.

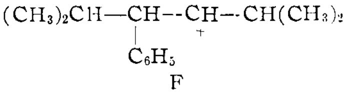
Two alternative hypotheses were offered for the marked predominance of retention over inversion in simple solvolysis in the *threo*-4-phenyl-3-hexyl system.[3] (1) A dynamic equilibrium between two unsymmetrical phenonium ions (A and B) might be substituted for the single symmetrical phenonium ion (C). In A and B the R groups were somewhat staggered and eclipsing effects were unimportant as compared to those in C, a species which might be either an intermediate or a transition state. As the bulk of R was increased, the activation energy for A → B would increase, and the competing simple solvolysis occurring with over-all retention at C_α would consume more of A. (2) Steric control of asymmetric induction by the substituents of the benzyl carbon atom might provide a larger amount of *threo* than *erythro* product in the simple solvolysis reaction involving an open carbonium ion.



The results of the solvolysis of the more hindered 2,5-dimethyl-4-phenyl-3-hexyl system make explanation (1) untenable, and are not inconsistent with (2). Since isopropyl is bulkier than ethyl, eclipsing effects in C should become more important. On the basis of (1), simple substitution with retention would become more prominent. The results are in the opposite direction. On the basis of (2), the ratio of *threo* to *erythro* product should vary with the steric situation at the benzyl carbon, and as phenyl and R approach each other in bulk, the degree of asymmetric induction might decrease.

No evidence now exists which either suggests or demands the substitution of a dynamic equilibrium between unsymmetrical bridged carbonium ions for a single symmetrical bridged carbonium ion in systems where C_α and C_β carry the same substituents. Bridged ions such as C can provide a simpler and therefore better explanation of the facts until new evidence intrudes.

The Involvement of C_β–H in Production of Rearranged Tertiary Acetate and Formate in the 2,5-Dimethyl-4-phenyl-3-hexyl System.—A number of internal consistencies appear in the data of Table II which provide clues as to the mechanisms of olefin and tertiary ester formation. In runs 1 and 2 (acetolyses) where the products were kinetically controlled, the values of the ratios formulated are independent within experimental error of the configurations of the starting material. These data strongly imply that the tertiary ester and olefin had common intermediates, these intermediates being the same for each diastereomeric starting material.[9] The open secondary carbonium ion (F) could not have been the intermediate since the



$$(CH_3)_2CH—\underset{C_6H_5}{\underset{|}{CH}}—\overset{+}{CH}—CH(CH_3)_2$$

F

ε's of the olefin fraction from runs 1 and 2 differ by a factor of 4 (Table II), being higher for the *threo* starting material. More probably the brosylates gave open tertiary carbonium ions (G and H) by hydrogen participation in ionization, and these partitioned between acetate and olefin. The facts that both tertiary alcohols and olefins obtained from *threo* starting materials are optically active indicate that symmetrical phenonium ion was not

CHART II

	α of olefin / α of tert. alcohol	Yield of olefin / Yield of tert. alcohol
threo acetolysis (run 1)	42	4.4
erythro acetolysis (run 2)	41	3.7
threo formolysis (run 3)	82	1.3
erythro formolysis (run 4)	77	0.23

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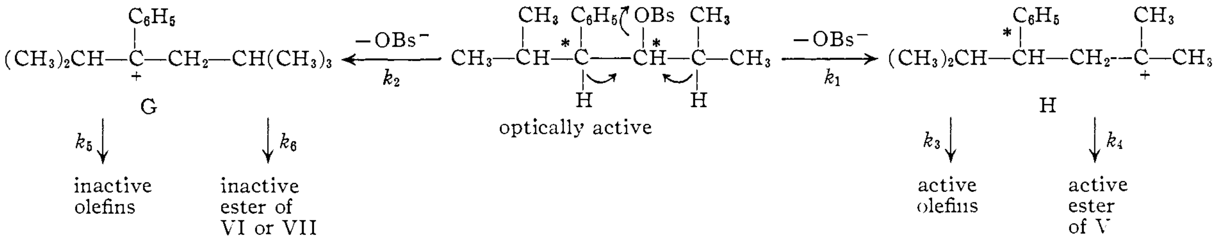
(9) A second condition for the equality of the ratios involving rotations is that the contributions of the active components to the rotation of the mixture are either proportional to their concentrations, or that deviations from proportionality are governed by the same factor in passing from mixtures obtained from run 1 to those of run 2. In the case of solutions of active 3-phenyl-1-butene in mixtures of *cis*- and *trans*-2-phenyl-2-butene and 2-phenyl-1-butene, the rotations were linear with concentrations of the active component.[8] See Experimental for the rotation of a synthetic mixture of tertiary alcohols.



an important precursor in the production of these materials.

The rotation of the tertiary alcohol obtained in run 2 (*erythro*-acetolysis) was 97% that of optically pure V, so apparently $k_1 >> k_2$ with this diastereomer in this solvent. In run 1 (*threo*-acetolysis) the rotation was only about 60% that of optically pure V. With this isomer the starting brosylate ester racemizes at a rate which would make about 20% of alcohol V and of the active olefins racemic. Clearly in this run both the partially inactive tertiary alcohol and olefin fractions are diluted by about the same factor with optically inactive materials arising from the benzylcarbonium ion, G. The higher ϵ of the olefin (Table II) from run 1 also supports this thesis. Thus for the acetolysis of *threo*-brosylate, $k_1 \sim k_2$ and $k_5/(k_5 + k_6) \sim k_3/(k_3 + k_4)$ (this latter relationship is required by the constancy of the ratios of runs 1 and 2 in Chart II).

The results of the formolysis runs are complicated by the fact that the tertiary alcohol and olefin fractions once formed can interconvert to some extent. Runs 3 and 4 were allowed to go for 5 titrimetric half-lives, but since the *erythro* isomer solvolyzed 8 times as fast as the *threo*, the products once formed from the *threo*-brosylate (run 3) had a much longer period in which to approach equilibrium than did those from the *erythro*-brosylate (run 4). This fact accounts for the large differences in the yield ratios of Chart II for runs 3 and 4. That the rotation ratios are rather close for runs 3 and 4 suggests either that the two optically active olefins (VIII and IX) are produced in about the same ratio in a kinetically as a thermodynamically controlled process, or that both reaction times were long enough to allow these two olefins (not the tertiary formate) to equilibrate. The equilibration experiments conducted in formic acid on the olefin fractions from the acetolyses indicate that equilibration of VIII and IX is incomplete in the time of run 4. Thus the former interpretation appears to apply.

Perhaps the most striking internal consistency in the rotation data from the four runs is the constancy of the ratios of rotations of olefins obtained in runs 4 and 2 on the one hand and 3 and 1 on the other. The yields of these olefins varied by as much as a factor of 5, the rotations by as much as a factor of 2, and the starting materials in the formolyses and acetolyses were enantiomerically related.

threo-solvolyses

$$\frac{(\text{run } 3)\ \alpha \text{ olefin formolysis}}{(\text{run } 1)\ \alpha \text{ olefin acetolysis}} = 1.27$$

erythro-solvolyses

$$\frac{(\text{run } 4)\ \alpha \text{ olefin formolysis}}{(\text{run } 2)\ \alpha \text{ olefin acetolysis}} = 1.29$$

This similarity in ratios again emphasizes that the olefins are produced from the same intermediates (open carbonium ions) even though the starting materials are diastereomeric. Further, the fraction of olefinic product having arisen from racemized as compared to active brosylate ester in the *threo*-solvolysis must be about the same for the two solvents. Since the amount in the acetolysis (run 1) was about 20%, the amount in formolysis must have been approximately the same.

Differences in Reactivity between Diastereomers in the Wagner–Meerwein Rearrangement.—The kinetic and yield data for the three systems (II, III and IV) when put together allow an analysis of reactivity differences between diastereomers to be examined as a function of the steric constraints of each system. Two general comparisons will be made. Partial rate factors for the various processes can be calculated in all three *threo* systems, and certain ratios compared with one another. The partial rate factors of the two diastereomers of each system will be compared with one another.

Chart III defines the partial rate factors and the configurational relationships involved, and Table III records the ratios of the partial rate factors of interest. Equations 2 and 3, coupled with the appropriate yield data,[3] were employed in converting the measured titrimetric (k_t) and polarimetric (k_α) rate constants into these ratios (ref. 3 provides sample calculations).

$$k_\alpha = k_0 + k_s + k_{1'} \quad (2)$$

$$k_t = k_0 + k_s + k_{1'}[k_e/(k_e + k_c)] \quad (3)$$

As the system becomes progressively more hindered, in acetic acid the value of $k_e/(k_c + k_e)$ passes from 0.12 for system II to 0.58 for system IV. In other words, ion-pair collapse becomes less favored. By contrast, in formic acid a slight trend in the opposite direction is evident, and in the most hindered system the values are rather close together. This pattern of results indicates that the exchange of an anion of an ion-pair with a solvent molecule is subject to a number of effects, some of which oppose one another.[10]

Of the other ratios of rates of Table III, the most interesting trend is that of $C_{\beta'}$–H (see part structure J) to become more involved in the solvolysis and for C_β–C_6H_5 to become less involved in passing from the least to the most ramified system (II to IV). This trend at least partially reflects the fact that $C_{\beta'}$–H can best participate in ionization at C_α

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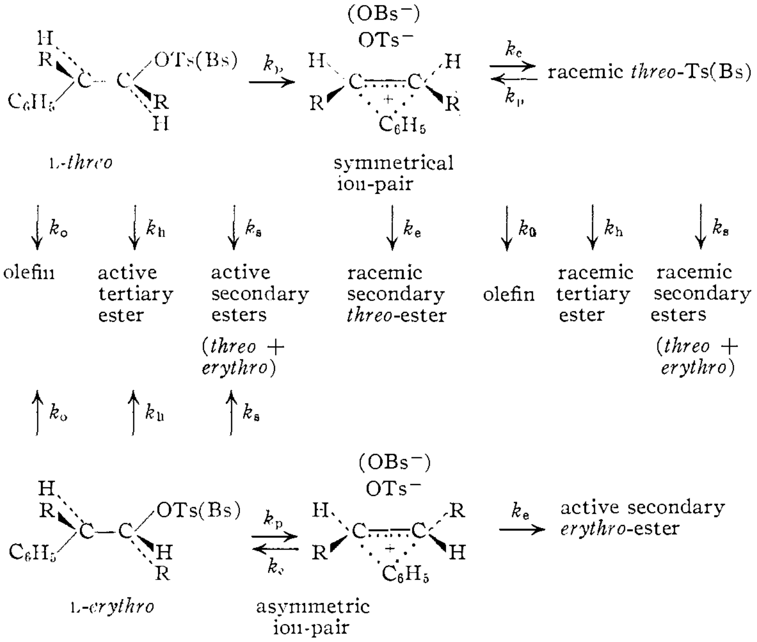
[10] Chloroform was present in the solvent in the formolysis of systems III and IV, so comparisons of these runs with those of II suffer somewhat. However, the dramatic changes in this ratio occur in passing from system III to IV, and about the same concentration of chloroform was present in both runs.

CHART III



when $C_{\beta'}$ is a tertiary carbon and least when $C_{\beta'}$ is methyl.

TABLE III

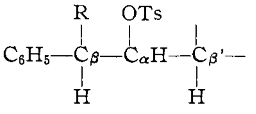
RATE RATIOS OF REACTIONS THAT OCCUR DURING SOLVOLYSIS OF THE *threo*-TOSYLATES OF 3-PHENYL-2-BUTANOL (II) AND 4-PHENYL-3-HEXANOL (III) AND OF THE *threo*-BROSYLATE OF 2,5-DIMETHYL-4-PHENYL-3-HEXANOL (IV)

Run	System	T, °C.	Solvent	$\frac{k_e}{k_c + k_e}$	$\frac{k_p}{k_\alpha{}^a}$	$\frac{k_h + k_o}{k_\alpha{}^a}$	$\frac{k_s}{k_\alpha{}^a}$
2 + 3	II	75	AcOH	0.12	0.91	0.08	0.01
5 + 6[b]	II	25	HCOOH	.83	.82	.18	.0
9 + 10	III	75	AcOH	.16	.83	.13	.04
13 + 14[c]	III	25	HCOOH[d]	.71	.87	.09	.04
16 + 17	IV	50	AcOH	.58	.42	.57	.01
20	IV	25	HCOOH[e]	~ .5[f]	~ .3[g]	~ .7[g]	~ .0[g]

[a] $k_\alpha = k_p + k_h + k_o + k_s$. [b] Temperature difference of 0.14° between runs 5 and 6, k_α being the higher. [c] Temperature difference of 0.20° between runs 13 and 14, k_α being the higher. [d] Actually a 3.33/1 mixture by volume of $HCOOH-CHCl_3$. [e] Actually a 2.86/1 mixture by volume of $HCOOH-CHCl_3$. [f] This ratio was calculated assuming that the same fractions of products were produced *via* racemized brosylate in formolysis and acetolysis, an assumption supported by the rotations of the olefins. [g] Calculations based on same assumptions as in (*f*).

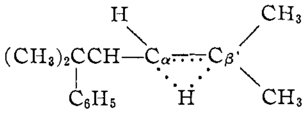
Table IV compares the kinetics of the two diastereomers of each system in terms of the partial rate factors k_p (phenyl participation in ionization) and $k_h + k_o$ (a rough measure of hydrogen participation). The virtue of comparing reactivity differences between diastereomers lies in the fact that any differences must derive fundamentally from geometry. Unfortunately k_p cannot be calculated directly for the *erythro* runs, since the ratio $k_e/(k_c + k_e)$ cannot be determined. The best that can be done, therefore, is to calculate k_p (*erythro*) by assuming that the values of $k_e/(k_e + k_c)$ do not vary much between the diastereomers. This assumption is supported by the fact that although the values of k_α/k_t (Table IV) vary by factors of 4 and 2.5 in passing from acetic to formic acids (for systems II and III), the values of k_t (*erythro*)/k_t (*threo*) vary by factors of only 1 and 1.4 for the respective systems. Furthermore, when the values of $k_e/(k_e + k_c)$ are greater than 0.5, k_p becomes rather insensitive to the value of this ratio. Fortunately ($k_h + k_o$) *erythro* can be calculated directly.

Quite reasonably, the values of k_t (*erythro*)/k_t (*threo*) depart more and more from unity as the system involved becomes more sterically constrained. The ratios of k_p (*erythro*)/k_p (*threo*) show about the same departure from unity in II and III as the ratios of k_t's, whereas the ($k_h + k_o$) (*erythro*)/($k_h + k_o$) (*threo*) ratios are close to unity. In the much more hindered system, IV, the value of k_p (*erythro*)/k_p (*threo*) is about unity, and the ($k_h + k_o$) (*erythro*)/($k_h + k_o$) (*threo*) ratio becomes about 9. On the basis of simple conformational *analysis*,[11] the *threo* isomers of systems II, III and IV are the more stable.[12] A comparison of the eclipsing effects[13] in each diastereomeric pair indicates that neighboring phenyl or hydrogen participation in ionization (from C_β) is more sterically feasible for the *erythro* than for the *threo* isomer (see Table IV). So both the starting states as well as the transition states for neighboring group participation would tend to favor k_p *erythro*/k_p *threo* > 1, and also to favor ($k_h + k_o$) *erythro*/($k_h + k_o$) *threo* > 1 as long as $k_h + k_o$ measures mostly hydrogen involvement from the carbon carrying phenyl (C_β–H). This latter condition applies only to systems II and III. The maximum value for



$$C_6H_5-\overset{R}{\underset{H}{C_\beta}}-\overset{OTs}{C_\alpha}H-\overset{|}{\underset{H}{C_{\beta'}}}-$$

J



K

these ratios in these two systems is 2.8, a fact which indicates both that eclipsing effects are small and that the differences in energy between the starting states are small. In IV, the ratio of k_p's remains near unity, but ($k_h + k_o$) *erythro*/($k_h + k_o$) *threo* amounts to about 9. In this more hindered system, $k_h + k_o$ measures mostly involvement of $C_{\beta'}$–H. Since $C_{\beta'}$ carries two methyls, eclipsing effects in the transition state K should be about the

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[11] (a) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **75**, 339 (1953); (b) D. J. Cram and F. D. Greene, *ibid.*, **75**, 6005 (1953). D. H. R. Barton and R. C. Cookson [*Quarterly Reviews*, **10**, 48 (1956)] have also recognized these principles and quote as an example the work of R. P. Linstead and M. Whalley [*J. Chem. Soc.*, 3722 (1954)] on the relative stability of *meso*- and DL-2,3-disubstituted succinic acids. In this and similar systems as well as those such as the stilbene dibromides [*e.g.*, R. E. Buckles, W. E. Steinmetz and N. G. Wheeler, THIS JOURNAL, **72**, 2496 (1950)], dipole–dipole interactions may play a much more important role than simple steric effects. In these types of systems, the electronic and steric effects happen to reinforce one another. The only tests of the purely steric principles (of which the authors are aware) are those quoted in ref. 11a and 11b.

[12] In the analysis of IV, phenyl is selected as being effectively more bulky than isopropyl, a choice supported by the direction of asymmetric induction in the preparation of the system (ref. 6).

[13] See D. Y. Curtin [*Record Chem. Progress*, **15**, 111 (1954)] for a general discussion.

same for the two diastereomers. Therefore, the factor of 9 is mainly attributable to differences in energy of the two diastereomeric starting states. The proximity of k_p (*erythro*)/k_p (*threo*) to unity therefore implies that the geometries of the transition states for phenyl participation resemble those of the starting states, and that phenyl provides only a small driving force for ionization in this particular system. The relative absence of eclipsing effects in IV recalls the data obtained in a study of the E_2 reaction in the 1,2-diphenyl-1-propyl-X system. The ratio k_{E_2} (*threo*)/k_{E_2} (*erythro*) in this system could be varied from ~ 1 to 57, depending on the strength of the base, the character of the solvent and of the leaving group.[14] In system IV and probably in II and III as well, the transition states for phenyl migration still leave the substituents on C_α and C_β well staggered, and the three-membered ring only slightly formed.

TABLE IV

RATE COMPARISONS FOR SOLVOLYSIS OF DIASTEREOMERIC ESTERS OF II, III AND IV

				Groups eclipsed in bridges							
				threo		*erythro*					
Run	System	Solvent	T, °C.	C_6H_5-bridge	H-bridge[b]	C_6H_5-bridge	H-bridge[b]	*threo* $\frac{k_\alpha{}^a}{k_t}$	$\frac{k_t\ (erythro)}{k_t\ (threo)}$	$\frac{k_p\ (erythro)}{k_p\ (threo)}$	$\frac{(k_h + k_0)\ (erythro)}{(k_h + k_0)\ (threo)}$
1 + 4	II	AcOH	75	CH_3>—<CH_3	C_6H_5>—<CH_3	CH_3>—<H	C_6H_5>—<H	4.6	1.2	1.5	0.7
5 + 7	II	HCOOH	25	C_6H_5>—<H	CH_3>—<H	H>—<CH_3	CH_3>—<CH_3	1.2	1.2	1.2	1.2
11 + 12	III	AcOH	50	C_2H_5>—<C_2H_5	C_6H_5>—<C_2H_5	C_2H_5>—<H	C_6H_5>—<H	3.2	1.8	2.7[c]	1.3[c]
13 + 15	III	HCOOH	25	C_6H_5>—<H	C_2H_5>—<H	H>—<C_2H_5	C_2H_5>—<C_2H_5	1.3	2.6	2.8	1.1
16 + 18	IV	AcOH	50	$(CH_3)_2CH$>—<$(CH_3)_2CH$	C_6H_5>—<$(CH_3)_2CH$	$(CH_3)_2CH$>—<H	C_6H_5>—<H	1.2	6.4	0.9	8.8
20 + 21	IV	HCOOH	25	C_6H_5>—<H	$(CH_3)_2CH$>—<H	H>—<$(CH_3)_2CH$	$(CH_3)_2CH$>—<$(CH_3)_2CH$	..[d]	8.2	..[d]	9.0

[a] The run numbers obviously had to be different for this calculation—data are in Table I. [b] The bridges referred to here are those involving (either as transition states or intermediates) the hydrogen on the C_β carrying the phenyl. [c] The yield data were obtained at 75° and the rates at 50°. It was assumed that the yields in the two diastereomers varied in the same way over the 25° range of temperature. [d] k_α could not be obtained in formic acid.

Experimental

Preparation of the Brosylates of the Stereoisomers of 2,5-Dimethyl-4-phenyl-3-hexanol (IV).—The ordinary methods of preparation of either tosylates or brosylates in this system failed. The following procedure was found applicable to the preparation of all four stereomers. The starting four alcohols were reported previously in an optically pure state, as well as in their two racemic forms.[6] To 25 ml. of benzene (distilled from potassium) were added 1.23 g. (1.42 ml.) of sodium-potassium alloy and 2.58 g. of (–)-*threo*-IV. The mixture was stirred under dry, pure nitrogen at 25° for one hour and at reflux for 4 hours. Control experiments indicated this to be the minimum time for formation of the alcoholate. The reaction mixture was cooled to 0°, the remaining alloy removed (under nitrogen), and a solution of 3.26 g. of pure *p*-bromobenzenesulfonyl chloride in 15 ml. of dry benzene was added rapidly. The resulting mixture was permitted to warm to 15° during the first hour and then stirred at 25° for an additional hour. A few drops of solution gave a neutral test with phenolphthalein solution. The reaction mixture was washed with water, dried (sodium carbonate), treated with a few drops of pyridine and evaporated at 25° under diminished pressure. The resulting oil was crystallized at –20° from an equal volume of pentane (containing a few drops of pyridine). The liquor was decanted quickly, and the crystals were dissolved at 25° in a minimum amount of ether containing a few drops of pyridine and recrystallized by cooling to –20°. After two recrystallizations, the sulfonate ester was obtained (by decantation), dried under vacuum, wt. 3.70 g. (70% yield), m.p. indeterminate because of decomposition.

Anal. Calcd. for $C_{20}H_{25}O_3SBr$: C, 56.46; H, 5.90. Found: C, 56.64; H, 6.12.

The other three stereomers were prepared in from 50–70% yields, and showed similar instability, which prevented the determination of any meaningful m.p.'s or rotations. The ester of (+)-*threo*-IV was not successfully analyzed because of its instability. The analyses of (+)-*erythro*-IV and (–)-*erythro*-IV, respectively, are as follows.

Anal. Calcd. for $C_{20}H_{25}O_3SBr$: C, 56.46; H, 5.90. Found: C, 56.54, 56.33; H, 5.88, 5.79.

Preparation of the Acetates of the Stereomers of 2,5-Dimethyl-4-phenyl-3-hexanol (IV).—In the hope that the acetates of the four stereomers of IV would have rotations that would aid in the analysis of unknown mixtures of stereomers, these esters were prepared by the usual pyridine method in yields of 85–93%. Isomer (+)-*threo*-IV gave $n^{25}D$ 1.4868, $\alpha^{25}D$ +104.3° (l = 1 dm., neat).

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.59; H, 9.72.

Isomer (–)-*threo*-IV gave $n^{25}D$ 1.4868, $\alpha^{25}D$ –104.4° (l = 1 dm., neat). *Anal.* Found: C, 77.31; H, 9.47.

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[14] D. J. Cram, F. D. Greene and C. H. Depuy, THIS JOURNAL, **78**, 790 (1956).

Isomer (+)-*erythro*-IV gave m.p. 45–46°, $\alpha^{25}\text{D}$ +85.7° (l = 1 dm., neat). *Anal.* Found: C, 77.15; H, 9.52.

Isomer (−)-*erythro*-IV gave m.p. 45–46°, $\alpha^{25}\text{D}$ −85.7° (l = 1 dm., neat). *Anal.* Found: C, 77.58; H, 9.64.

Kinetics of Solvolysis of the Brosylates of the Stereomers of IV.—The acetolysis solutions were prepared from C.P. acetic acid, anhydrous potassium carbonate and sufficient acetic anhydride to consume the water produced and leave a 1% excess. The ampoule technique was employed in both the titrimetric and polarimetric runs. The titration reagents and procedures have been reported previously.[4b] The polarimetric readings were taken in a thermostated 2-dm. tube at 25°. In all cases from 8 to 12 points were taken, and the reactions followed to 85–95% completion. A fixed infinity reading was obtained in the polarimetric runs.

The formic acid used in formolysis was purified as before[4c] (100.01% by titration with Karl Fischer reagent), and the requisite amounts of anhydrous sodium formate and of ethanol-free anhydrous chloroform were added. The amount of chloroform needed was determined by trial experiments, homogeneity throughout the run being the criterion. The titrimetric runs were followed by withdrawing 5-ml. aliquots of solution from the reaction and quenching this in 50 ml. of purified dioxane, and titrating this solution with standardized perchloric acid–dioxane solution (method of Winstein and Heck).[15] The indicator was bromcresol green and the light yellow end-point was always compared to a standardized end-point obtained by mixing equivalents of standard solutions together. Fifteen points were taken per run, and the reactions were followed to about 90% completion. The polarimetric formolyses were carried out in a 4-dm. thermostated polarimeter tube, fifteen points, a fixed infinity reading being taken.

4-Methyl-3-phenylpentanoic Acid.—Hydrolysis of 40 g. of 3-methyl-2-phenylbutyronitrile[6] with 56 g. of potassium hydroxide in 300 ml. of diethylene glycol (105° for 72 hours) gave 36 g. (81% yield) of 3-methyl-2-phenylbutanoic acid (recrystallized from pentane), m.p. 60.5–62.5° (reported[16] 62–63°). A solution of 20 g. of this acid in 16 g. of thionyl chloride was allowed to stand for 10 hours at 25°. The excess thionyl chloride was removed under reduced pressure, and the remaining liquid residue was distilled at 125° (13 mm.) to give 21.6 g. (98% yield) of acid chloride, $n^{25}\text{D}$ 1.5050. A solution of 20.4 g. of diazomethane in 500 ml. of dichloromethane was prepared from 50 g. of N-nitrosomethylurea.[17] To 400 ml. of this solution at 0° was added dropwise a solution of 20.6 g. of the above acid chloride in 50 ml. of dichloromethane (75 minutes). The resulting mixture was allowed to warm to 25°, the excess solvent was removed at 30 mm., and the bath temperature was raised to 35°. The remaining liquid residue was cooled, dissolved in 150 ml. of methanol, and 0.7 g. of powdered silver oxide was added. The resulting exothermic reaction was permitted to continue with occasional cooling until the reaction had subsided, when more oxide was added, and the mixture was refluxed for one hour. The mixture was cooled, filtered, evaporated (30 mm.), and the oil was distilled at 105–110° (pot temperature) at 2 mm. to give 19.3 g. (89% yield) of crude ester. Hydrolysis of the substance with 20 g. of potassium hydroxide in 150 ml. of diethylene glycol at 130° for 38 hours gave acid, which was recrystallized three times from pentane to give 12.8 g. (63% yield) of 4-methyl-3-phenylpentanoic acid, m.p. 48–49°. This acid has been reported previously as an oil.[18]

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39; neut. equiv., 192. Found: C, 75.26; H, 8.37; neut. equiv., 192.

The anilide was prepared in the usual way, m.p. 114.5–116° (ethyl acetate).

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.80; H, 7.92.

The above acid was also prepared by the following inferior sequence. The brosylate of 3-methyl-2-phenyl-1-butanol[6] was treated with potassium cyanide, and the resulting nitrile was hydrolyzed to acid, m.p. 48.5–49.5°, undepressed by admixture with an authentic sample.

This acid was resolved through its quinine salt as follows. A solution of 35.7 g. of acid and 52.7 g. of quinine was dissolved in a minimum amount of ethanol and held at 0°. The resulting solid was recrystallized 13 times (ethanol), the salt was converted to the acid to give m.p. 44–45°, $[\alpha]^{25}\text{D}$ +33.99° (c 3.3, $CHCl_3$). The acid was again converted to its quinine salt which was recrystallized three more times from methanol, and the resulting salt was again converted to the acid. This acid (recrystallized from pentane) gave wt. 0.0839 g., m.p. 44–45°, $[\alpha]^{33}\text{D}$ +34.4° (c 3.3, $CHCl_3$). Extensive recycling of the second crops gave more optically pure material of identical physical properties, enough to provide 0.88 g. of optically pure acid.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.21; H, 8.59.

2,5-Dimethyl-4-phenyl-2-hexanol (V).—A solution of 4.92 g. of 4-methyl-3-phenylpentanoic acid (racemic) in 26 ml. of absolute methanol containing 1.3 ml. of concd. sulfuric acid was refluxed for 10 hours. The ester was isolated in the usual way and distilled at a pot temperature of 118° (4.6 mm.) to give 4.91 g. (93% yield), $n^{25}\text{D}$ 1.4932.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.64; H, 8.85.

To a solution of methylmagnesium iodide prepared from 42.7 g. of methyl iodide and 8.0 g. of magnesium turnings, was added a solution of 3.0 g. of methyl 4-methyl-3-phenylpentanoate in 50 ml. of ether. The reaction mixture was stirred for 10 hours and then refluxed vigorously for one hour before decomposing the reaction mixture with 200 ml. of ice-cold saturated ammonium chloride solution. The phases were separated, and the aqueous phase was acidified with sulfuric acid and then extracted with ether. The ether extract was washed, dried, evaporated, and the remaining oil was absorbed on 200 g. of basic alumina of activity I.[19] After elution of the column with pentane had produced no residue, the product was eluted with 50% methanol in ether. The eluent was evaporated, and the liquid residue was dissolved in pentane, washed with water and dried. The pentane was evaporated, and the liquid residue was distilled at 100° pot temperature (1.4 mm.) to yield 2.76 g. (92% yield) of 2,5-dimethyl-4-phenyl-2-hexanol (V), $n^{25}\text{D}$ 1.5021.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.58; H, 10.60.

The 3,5-dinitrobenzoate of V was prepared from 0.10 g. of V, 0.3 ml. of reagent pyridine and 0.12 g. of freshly prepared 3,5-dinitrobenzoyl chloride at 90° (2 hours). The product was isolated in the usual way and recrystallized twice from ether–pentane to give 0.15 g. (77% yield) of light yellow needles, m.p. 89.5–90.5°.

Anal. Calcd. for $C_{21}H_{24}O_6N_2$: C, 62.99; H, 6.04. Found: C, 63.06; H, 6.13.

Hydrolysis of the above derivative in a mixture of 0.05 g. of potassium hydroxide in one ml. of water and 4 ml. of ethanol at 95° for 8 hours gave back the original alcohol V in almost quantitative yield.

The acetate of V proved difficult to prepare, the following method giving the best result. A mixture of 0.109 g. of V, 0.5 ml. of pure acetic anhydride and 0.4 ml. of pure pyridine was held at 50° for 12 days. The product was isolated in the usual way, absorbed on a column of 50 g. of neutral alumina of activity I[19] made up in pure pentane. The product was eluted with 350 ml. of 12% ether in pure pentane, the solvent first was evaporated at 30 mm., and then at 1 mm. The acetate was not distilled due to the possibility of slight decomposition but was analyzed directly, $n^{25}\text{D}$ 1.4864.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.28; H, 9.80.

Attempts to form the formate of V gave a mixture of olefin and formate.

Utilizing the above procedure, optically pure 4-methyl-3-phenylpentanoic acid (0.875 g.) was converted to its methyl ester (0.870 g.), $n^{25}\text{D}$ 1.4931, $\alpha^{25}\text{D}$ +33.47 (l = 1 dm., neat).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.64; H, 8.84.

The above ester (0.87 g.) was divided into two portions, the first being converted to alcohol V (see above) to give after distillation at 118° (pot temperature) and 2 mm. 0.54

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g. of alcohol, n^{25}_{D} 1.5019, α^{25}_{D} +2.02 (l = 1 dm., neat). The other portion was subjected to the same procedure but the chromatographic step was omitted, 0.23 g. of V being obtained, n^{25}_{D} 1.5022, α^{25}_{D} +2.68° (l = 1 dm., neat). The variation in rotation of these two preparations suggested contamination with small amounts of the highly rotating olefins derived from this tertiary alcohol. Therefore the combined alcohol portions were converted to the solid 3,5-dinitrobenzoate derivative (see above), which after a charcoal treatment and two recrystallizations from absolute ethanol gave 0.226 g. of ester, m.p. 89.5–90.5°, decomposition point 160–161° (dependent on heating rate), $[\alpha]^{25}_{\text{D}}$ +15.01° (c 3.3, $CHCl_3$), m.m.p. with same derivative of racemic V, 80.5–82°.

Anal. Calcd. for $C_{21}H_{24}O_6N_2$: C, 62.99; H, 6.04. Found: C, 62.78; H, 6.07.

A second independent preparation of active alcohol V gave α^{25}_{D} +2.79° (l = 1 dm., neat), and its 3,5-dinitrobenzoate gave $[\alpha]^{25}_{\text{D}}$ +15.48° (c 3.3, $CHCl_3$). A total of 0.509 g. of this derivative of active V was hydrolyzed (see above) to give V as an oil which was submitted to chromatography on 50 g. of neutral alumina made up in pentane. A trace of olefin was eluted with pure pentane and alcohol was eluted with pure ether to give after distillation (90–95°, pot temperature, 0.9 mm.) 0.17 g. of optically pure V, α^{26}_{D} +1.83° (l = 1 dm., neat). Another independent preparation gave α^{26}_{D} +1.79° (l = 1 dm., neat).

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.22; H, 10.71.

2,5-Dimethyl-3-phenyl-3-hexanol (VI).—To a solution of 0.254 mole of isopropyllithium in 15.8 ml. of pentane[6] was added dropwise a solution of 25 g. of isovalerophenone in 75 ml. of pentane. The mixture was stirred for 10 hours, treated with ice-water, and the product isolated in the usual way. Distillation of the alcohol gave 20.6 g. (65% yield) of VI, b.p. 97–101° (3 mm.), n^{25}_{D} 1.5029–1.5016. This material (3.64 g.) was treated with a suspension of 0.9 g. of lithium aluminum hydride in ether, and worked up in the usual way. The resulting oil was treated with 4.0 g. of phthalic anhydride and 3 ml. of pure pyridine at 105° for 46 hours. The resulting solution was shaken with ether and dilute, cold hydrochloric acid, and the ether layer was washed with water, extracted with sodium bicarbonate solution and again with water. This operation removed the secondary alcohol present which had come from unreacted ketone. The ether layer was dried, evaporated, taken up in pure pentane and chromatographed on 200 g. of neutral alumina of activity I[19] in pure pentane. Elution of the column with pure pentane gave 0.43 g. of olefin (distilled at 90–95° pot temperature at 6 mm.), n^{25}_{D} 1.4981, λ_{232} (arbitrary), ϵ 4,805. Elution of the column with 9 liters of 32% ether in pure pentane gave alcohol VI which was distilled at pot temperature of 115–117° (4 mm.) to give 1.94 g. of V, n^{25}_{D} 1.5018.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.41; H, 10.57.

Repeated attempts to form a 3,5-dinitrobenzoate of this compound failed to yield any solid derivative.

4-Methyl-2-phenylpentanoic Acid.—To 100 ml. of absolute ethanol was added 5.1 g. of sodium, and the resulting solution was cooled to 50°. Diethyl phenylmalonate[20] (47.2 g.) was added (40 minutes), the mixture was maintained at 50°, and 30.4 g. of isobutyl bromide was added (90 minutes). The solution (pH 10) was brought to reflux, and within 10 minutes solid separated. After 19 hours of reflux the reaction mixture approached pH 7, and the excess ethanol was evaporated. The remaining material was diluted with water, extracted with ether, and the extract was washed, dried and evaporated. The resulting oil was distilled (10 mm.): 1st fraction, b.p. 101–105°, wt. 24.7 g., n^{25}_{D} 1.4921; 2nd fraction, b.p. 130–150°, wt. 6.28 g., n^{25}_{D} 1.4848 (diethyl phenylmalonate, b.p. 156–158° at 9.3 mm., n^{25}_{D} 1.4896); 3rd fraction, b.p. 165–167°, wt. 4.29 g., n^{25}_{D} 1.4861. Hydrolysis of the first fraction gave phenylacetic acid. The third fraction was hydrolyzed with 60 ml. of an aqueous 40% potassium hydroxide solution (20 hours), and the resulting acid was recrystallized once from ether–pentane to give 1.63 g. of 4-methyl-2-phenylpentanoic acid, m.p. 75.5–76.5° (reported[21] 78–79°).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.06; H, 8.47.

2,5-Dimethyl-3-phenyl-2-hexanol (VII).—A solution of 1.63 g. of 4-methyl-2-phenylpentanoic acid and 0.5 ml. of concd. sulfuric acid in 15 ml. of methanol was refluxed for 10 hours, and the resulting solution was worked up as usual. The resulting liquid was distilled at a pot temperature of 110–115° (2.5 mm.) to give 1.70 g. (97% yield) of 4-methyl-2-phenylpentanoate, n^{25}_{D} 1.4882.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.87; H, 8.74.

This ester (1.70 g.) was treated with methylmagnesium iodide (5 g. of magnesium and 29.6 g. of methyl iodide) in the usual way to give VII, wt. 1.53 g. (90% yield), distilling at a pot temperature of 118–122° (3 mm.), n^{25}_{D} 1.5009. A portion (0.8 g.) of this alcohol was chromatographed on 250 g. of neutral alumina of activity I[19] in pentane, and the column was eluted with 8 liters of 32% ether in pentane. The solution containing the alcohol fraction was washed with sodium sulfite solution to remove ether peroxides, and the alcohol was distilled at 122–126° (pot temperature), wt. 0.56 g., n^{25}_{D} 1.5009.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.27; H, 10.64.

A small portion of this alcohol was converted to the 3,5-dinitrobenzoate derivative, m.p. 133.5–134.5°, dec. 170.5–171.5° (depending on rate of heating somewhat), m.m.p. with the same derivative of 2,5-dimethyl-4-phenyl-2-hexanol 81–102°.

Anal. Calcd. for $C_{21}H_{24}O_6N_2$: C, 62.99; H, 6.04. Found: C, 63.10; H, 6.15.

The acetate of VII was prepared in 57% yield by the same method utilized in the preparation and purification of the acetate of V. The ester distilled at 110–115° (pot temperature) and 2 mm., n^{25}_{D} 1.4850.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.14; H, 9.52.

Preparation of Acetolysis Stock Solution.—Glacial acetic acid was distilled (b.p. 115–116°), titrated with standardized Karl Fischer reagent and found to contain 5.46 g. of water per 1400 ml. of acid. A solution of 1400 ml. of this acid, 11.090 g. of anhydrous potassium carbonate (dried for 48 hours at 125°) and 58 ml. of freshly distilled acetic anhydride was refluxed to yield an acetolysis medium, 0.110 molar in potassium acetate and containing 1% excess acetic anhydride (by volume).

Acetolysis of the Brosylate of (+)-*erythro*-2,5-Dimethyl-4-phenyl-3-hexanol (Run 2 of Table II).—This brosylate (5.60 g.) was dissolved in 137 ml. of acetolysis stock solution (0.096 molar in brosylate), and held at 49.97 ± 0.05° for 291 minutes (8 titrimetric half-lives). The solution was then shaken with 1 liter of ice-water and four successive 250-ml. portions of pure pentane. The aqueous layer was then extracted with 150 ml. of pure ether. The organic extracts were combined, washed with water, sodium bicarbonate solution and again with water. The solution was dried, evaporated through a 75-cm. Vigreux column. (All subsequent evaporations of solvent were through this column, and pure, peroxide-free ether and kerosene-free pentane were utilized throughout.) The residual oil was distilled at a pot temperature of 90–115° (2 mm.) to give 2.64 g. of oil and 0.10 g. of pot residue. A solution of the oil in 25 ml. ether was added dropwise to a suspension of 0.624 g. of lithium aluminum hydride in ether. After being stirred for 3.5 hours, the mixture was decomposed with 70 ml. of wet ether and then 50 ml. of ice-water. The product was isolated in the usual way, and the resulting oil was chromatographed on 175 g. of neutral alumina of activity I[19] in pentane. The residues from the pentane eluates were distilled at a pot temperature of 90° (3 mm.) to give 1.74 g. of olefin (see Table II). The residues from the ether eluates were combined with the aid of pentane, and the resulting solution was washed free of peroxides with sodium sulfite solution and water. The pentane layer was dried, evaporated, and the resulting alcohol fraction was distilled at a pot temperature of 102–105° (1.5 mm.) to give 0.57 g. of alcohol. At this point 91% of the starting brosylate ester

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TABLE V

INFRARED DATA CONCERNING ANALYSIS OF ALCOHOLS OBTAINED FROM ACETOLYSIS RUNS 1 AND 2

Sample		Absorbance in infrared[a]					
		1st set of equations			2nd set of equations		
	Slit, mm. →	0.352	0.461	1.05	0.429	0.690	1.20
	wave no., cm.$^{-1}$ →	1149	1010	768	1049	858.4	746.3
threo-IV		0.254	0.232	0.620	1.16	0.012	0.109
erythro-IV		.530	.763	.061	.209	.271	.333
V		1.00	.061	.293	.014	.002	.985
Alcohol run 2		0.819	.219	.226	.052	.031	.800
87%-V, 12% *erythro*-IV, 1% *threo*-IV		.840	.174	.242	.041	.019	.839
Alcohol run 1		.404	.176	.490	.735	.012	.322
28%-V, 1% *erythro*-IV, 71% *threo*-IV		.385	.166	.479	.799	.006	.313

[a] Beckman IR2T infrared spectrophotometer. The readings were taken successively in a 0.03-mm. cell, homogeneous liquid films, NaCl prism.

was accounted for. This mixture was submitted to infrared analysis (see later section).

The alcohol fraction was chromatographed on 171 g. (3 cm. by 35 cm.) of neutral alumina of activity I[19] in pentane, the chromatograph column being wrapped in heavy paper to exclude light. The column was developed with 32% ether in pentane (ether was washed free of peroxides just prior to use and carefully distilled). The results are tabulated (the chromatograph was run continuously for 27 hours). The residues from cuts 1–19 were combined with pentane and dried to give 0.0426 g. of solid material, m.p. 65–68°, $[\alpha]^{25}\text{D}$ +17.3° (*c* 4.3, CHCl$_3$). Recrystallization of the material from pentane gave 0.0243 g., m.p. 68.4–69.2°, $[\alpha]^{25}\text{D}$ +20.7° (*c* 1.7, CHCl$_3$), undepressed by admixture with an authentic sample of optically pure (+)-*erythro*-IV.

Eluent	Vol. of eluent, ml.	Cut	Characteristics
32% ether in pentane	1550	1–10	Blank
	1350	11–19	Crystals
	450	20-22	Blank
	1000	23–28	Droplets
100% ether	500	29–30	Liquid
	800	31	Blank

The liquid residues from cuts 21–31 were dissolved in pentane, the solution was washed with sodium sulfite solution, water, dried and evaporated. Distillation of the oil at a pot temperature of 102–103° (2 mm.) gave 0.47 g. of tertiary alcohol fraction. See Table II for properties. The infrared spectrum of this material proved to be identical to that of 2,5-dimethyl-4-phenyl-2-hexanol and was demonstrated through comparisons of this spectrum with that of a synthetic mixture of V containing 2% of IV to contain less than 2% of this secondary alcohol. Unfortunately this material was lost before a derivative could be prepared.

Acetolysis of the Brosylate of (+)-*threo*-2,5-Dimethyl-4-phenyl-3-hexanol (Run 1 of Table II).—The brosylate ester (6.123 g.) of optically pure alcohol was acetolyzed as in run 2 in 150 ml. of stock solution for 31 hours (8 titrimetric half-lives). The products were isolated as in run 2 to give 3.03 g. of olefin–ester mixture, which gave 1.43 g. of olefin and 1.20 g. of a mixture of secondary and tertiary alcohol (see Table II for physical properties). This mixture was submitted to infrared analysis (see later section). The secondary and tertiary alcohol fractions were separated by chromatography, 1750 ml. of solvent developer coming through the column without any dissolved alcohol in between the secondary and tertiary alcohol fractions. The secondary alcohol fraction amounted to 0.69 g., its infrared spectrum being identical to that of racemic *threo*-IV. This material (0.161 g.) was converted to its *p*-nitrobenzoate derivative,[6] 0.197 g. (71% yield) being obtained after being crystallized once from ethanol, m.p. 115.5–118° (undepressed by admixture with an authentic sample),[6] $[\alpha]^{25}\text{D}$ +0.45° (*c* 3.3, CHCl$_3$). The same derivative of (+)-*threo*-IV has m.p. 145–146°, $[\alpha]^{25}\text{D}$ +105° (*c* 3.3, CHCl$_3$).[6]

Mixed melting points of the following *p*-nitrobenzoates were obtained: (1) 5% derivative of (−)-*threo*-IV +95% racemic derivative, 118.5–123°; (2) 0.5% derivative of (−)-*threo*-IV + 99.5% racemic derivative, 117.5–119.5°; 1% derivative of (+)-*erythro*-IV + 99% racemic derivative of *threo*-IV, m.m.p. 110.5–140°.

The tertiary alcohol fraction amounted to 0.24 g., and its infrared spectrum was almost identical to that of authentic alcohol V. This fraction (0.160 g.) was converted to its 3,5-dinitrobenzoate derivative (see previous section) to give upon crystallization from ethanol 0.1554 g. (50% yield) of orange derivative. This material was crystallized three times from ethanol (charcoal treatment) to give 0.048 g. of derivative, m.p. 82.5–84° (decomposition, 162.5–163.5°), $[\alpha]^{25}\text{D}$ −8.37 (*c* 3.3, CHCl$_3$). The same derivative of optically pure V (m.p. 89.5–90.5°) gave $[\alpha]^{25}\text{D}$ +15.01° (*c* 3.3 CHCl$_3$). The mixed melting point of this derivative of active and racemic V gave 80.5–82°. Fractional crystallization of the filtrates from the above purification gave no material that melted above the melting point of the derivative of optically pure V (89.5–90.5°).

Infrared Analysis of Secondary–Tertiary Alcohol Mixtures from Runs 1 and 2.—The infrared spectra of pure *threo*-IV, *erythro*-IV and V were determined, and the most advantageous wave lengths for analysis selected. The absorbance of the two unknown mixtures at these wave lengths was determined. Two independent sets of three simultaneous equations were solved to give estimates of the three components. Synthetic mixtures of approximately the same composition were prepared and similarly analyzed, and the unknown mixtures were corrected to the known for deviations from Beer's law. Table V records the pertinent data. For run 2, the first set of equations gave 1% *threo*-IV, 17% *erythro*-IV and 83% V, and the second set gave 1% *threo*-IV, 19% *erythro*-IV and 80% V. For run 1, the first set of equations gave 70% of *threo*-IV, 2% of *erythro*-IV and 28% of V, whereas the second set gave 66% of *threo*-IV, 3% of *erythro*-IV and 30% of V. These values compare well with those obtained for the balance of secondary and tertiary alcohol obtained from the chromatograms.

Preparation of Formolysis Stock Solution.—Formic acid was purified by the method of Winstein and Marshall,[4c] and the chloroform was purified immediately before use. A mixture of 105 ml. (1.55 g.) of chloroform in 300 ml. of formic acid was prepared, and the solution made 0.040 *N* in sodium formate with anhydrous, analytical grade reagent.

Formolysis of the Brosylate of (−)-*erythro*-2,5-Dimethyl-4-phenyl-3-hexanol (Run 4 of Table II).—A mixture of 4.78 g. of brosylate in 320 ml. of stock formolysis solution was shaken vigorously until solution was complete, and the resulting solution was held at 25.00 ± 0.01° for 23 minutes (5 titrimetric half-lives). The products were isolated as in run 2 to give 0.295 g. of olefin and 1.552 g. of a mixture of the secondary and tertiary alcohols (81% yield of products at this point). The alcohol mixture was submitted to chromatographic separation to give a secondary and tertiary alcohol fraction with a large blank fraction intervening.

The secondary alcohol fraction came to 0.137 g. of material, m.p. 68.4–69°, m.m.p. with authentic (−)-*erythro*-IV, 69.5–70.5° (see Table II for other properties). A sample of this fraction (0.0795 g.) was converted to its *p*-nitrobenzoate derivative[6] to give 0.0913 g. (67% yield) of material, m.p. 168.5–169.5° (undepressed by admixture with authentic material), $[\alpha]^{26}\text{D}$ −46.1° (*c* 3.3, CHCl$_3$). Authentic material[6] gave m.p. 168.5–170.0°, $[\alpha]^{25}\text{D}$ −47.0° (*c* 3.3, CHCl$_3$).

The tertiary alcohol fraction came to 1.189 g. (see Table II for properties). Its infrared spectrum indicated the presence of less than 2% of *erythro*-IV. A sample (0.203 g.) of this material was converted to its 3,5-dinitrobenzoate (see previous section) to give 0.257 g. (65% yield) of crude orange product, m.p. 87–89°, $[\alpha]^{25}\mathrm{D}$ +12.91° (c 3.3, CHCl$_3$). One recrystallization of this material from ethanol (charcoal) gave 0.145 g. of pure material, m.p. 89.3–90.2°, m.m.p. with an authentic sample, 89.5–90.5°, $[\alpha]^{25}\mathrm{D}$ +14.2° (c 3.3, CHCl$_3$). Fractional crystallization of the filtrates gave crops melting above the melting point of the 3,5-dinitrobenzoate of V, *e.g.*, m.p. 87–104°. This material was probably contaminated ester of VII (m.p. 133.5–134.5°).

Formolysis of Brosylate of (−)-*threo*-2,5-Dimethyl-4-phenyl-3-hexanol (Run 3 of Table II).—A mixture of 5.0 g. of the above ester and 335 ml. of formolysis stock solution was shaken until homogeneous, and the resulting solution (0.035 molar in ester and 0.041 in sodium formate) was held at 25.00 ± 0.01° for 190 minutes (5 titrimetric half-lives). The products were isolated as in run 2 to give 0.960 g. of olefin (see Table II) and 1.141 g. of alcohol fraction (91% yield of products at this point). The alcohol mixture was chromatographically separated into secondary and tertiary alcohol components with a large blank fraction intervening.

The secondary alcohol fraction came to 0.226 g. (see Table II), and possessed an infrared spectrum identical to that of *threo*-IV. Its *p*-nitrobenzoate[6] was prepared from 0.129 g. of alcohol to give 0.158 g. (71% yield), m.p. 119–122° (undepressed by admixture with an authentic sample of derivative of racemic *threo*-IV), $[\alpha]^{25}\mathrm{D}$ −2.13° (c 3.3, CHCl$_3$).

The tertiary alcohol fraction came to 0.536 g., and its infrared spectrum showed the presence of not more than 3% *threo*-IV. This fraction (0.201 g.) was converted to its 3,5-dinitrobenzoate derivative to give 0.270 g. (69% yield) of light orange crystals, m.p. 72–83°, $[\alpha]^{25}\mathrm{D}$ +9.38° (c 3.3, CHCl$_3$). Three recrystallizations of this material from ethanol (charcoal treatment) gave 0.0348 g. of material, m.p. 83–87°, $[\alpha]^{25}\mathrm{D}$ +13.1 (c 3.3, CHCl$_3$). This material was partially racemized derivative of V. Fractional recrystallization of the second crops gave 0.001 g. of the *p*-nitrobenzoate of 2,5-dimethyl-3-phenyl-2-hexanol (VII), m.p. 131.5–132.5°, m.m.p. with authentic material, 132–133.5°.

Controls on the Olefin Products of Acetolysis and Formolysis.—A solution of 0.208 g. of olefin from acetolysis run 1 in 20 ml. of acetolysis stock solution was held at 50° for 31 hours (8 titrimetric half-lives for acetolysis of the brosylate of *threo*-IV) and reisolated (a chromatographic step was included). This treatment changed the rotation of the olefin only slightly, from $\alpha^{25}\mathrm{D}$ −42.91° (l = 1 dm., neat) to −43.94° (l = 1 dm., neat). A similar treatment of the olefin fraction from the formolysis run 3 only changed its rotation from $\alpha^{25}\mathrm{D}$ +54.83° (l = 1 dm., neat) to $\alpha^{25}\mathrm{D}$ +55.43° (l = 1 dm., neat).

A solution of 0.207 g. of olefin from acetolysis run 1 in 60 ml. of formolysis stock solution was held at 25° for 190 minutes (5 titrimetric half-lives for the formolysis of the brosylate of *threo*-IV). The olefin was reisolated, but showed a strong band in the infrared corresponding to formate ester at 1715 cm.$^{-1}$. This material was treated with lithium aluminum hydride, and the product chromatographed to give 0.0027 g. of an alcohol fraction. A similar experiment with the olefin from formolysis run 3 gave similar results.

A solution of 0.207 g. of olefin from acetolysis run 2 in 65 ml. of formolysis stock solution was held at 25° for 190 minutes (5 titrimetric half-lives for the formolysis of the brosylate of *threo*-IV). The product was isolated, treated with lithium aluminum hydride and the olefin fraction isolated by chromatography as before to give 0.16 g. of material. During this treatment the properties of the olefin changed as follows: at the start, $n^{25}\mathrm{D}$ 1.4994, $\alpha^{25}\mathrm{D}$ −72.09° (l = 1 dm., neat), λ_{232} gave ϵ 474 (cyclohexane); at the end, $n^{25}\mathrm{D}$ 1.5016, $\alpha^{25}\mathrm{D}$ −84.49° (l = 1 dm., neat), λ_{232} gave ϵ 595 (cyclohexane). A second experiment was carried out identical to that above except the reaction was permitted to proceed for 14 hours (20 titrimetric half-lives). The recovered olefin fraction gave $n^{25}\mathrm{D}$ 1.5020, $\alpha^{25}\mathrm{D}$ −88.12° (l = 1 dm., neat), λ_{232} gave ϵ 575 (cyclohexane).

A solution of 0.210 g. of olefin from acetolysis run 1 in 70 ml. of formolysis stock solution was held at 50° for 190 minutes. The product was isolated, treated with lithium aluminum hydride, chromatographed, and the olefin fraction was reisolated. During this treatment the properties of the olefin changed as follows: at the start, $n^{25}\mathrm{D}$ 1.4992, $\alpha^{23}\mathrm{D}$ −42.91° (l = 1 dm., neat), λ_{232} gave ϵ 1594 (cyclohexane); at the end, $n^{25}\mathrm{D}$ 1.5007, $\alpha^{27}\mathrm{D}$ −47.24° (l = 1 dm., neat), λ_{232} gave ϵ 2040 (cyclohexane).

Controls on the Stability of the Tertiary Esters Formed in the Solvolyses.—The formate of V could not be prepared, so the more stable acetate of V was used in the control experiment. A solution of 0.201 g. of material was dissolved in 40 ml. of formolysis stock solution and maintained at 25° for 190 minutes. The product was isolated in the usual way, treated with lithium aluminum hydride and chromatographed to give 0.0347 g. of olefin and 0.0749 g. of an alcohol fraction. Clearly the formate of V would have been unstable under the conditions of its formation in the formolyses.

A solution of 0.0346 g. of the acetate of 2,5-dimethyl-3-phenyl-2-hexanol (VII) in 5 ml. of acetolysis stock solution was held at 50° for 31 hours (8 titrimetric half-lives of the acetolysis of brosylate of *threo*-IV). The product was isolated, treated with lithium aluminum hydride, and the alcohol and olefin separated by chromatography. The olefin fraction amounted to 0.0013 g. and the alcohol fraction to 0.0225 g. (69% recovery). This acetate appeared to decompose only slightly under the conditions of its possible formation. The similarities in structure between V and VII indicate the acetate of V should be equally stable under the acetolysis conditions.

A solution of 0.0989 g. of the acetate of VII in 30 ml. of formolysis stock solution was held at 25° for 190 minutes. Work-up of the mixture gave 0.0066 g. of alcohol (37% recovery) and 0.0214 g. of olefin. This experiment indicates that the formate of VII would have been unstable under the conditions of the formolyses, probably equilibrating with the conjugated olefins.

Control on the Dilution Effect of Racemic 2,5-Dimethyl-3-phenyl-2-hexanol (VII) in Optically Pure 2,5-Dimethyl-4-phenyl-2-hexanol (V).—A solution of 0.0392 g. of pure racemic VII in 0.0832 g. of optically pure V ($\alpha^{25}\mathrm{D}$ +1.81°, (l = 1 dm., neat) was prepared and gave $n^{25}\mathrm{D}$ 1.5013, $\alpha^{25.6}\mathrm{D}$ +0.82 ± 0.06° (l = 1 dm , neat). The infrared spectrum of this mixture was essentially identical with that of an authentic sample of V.

Control on the Extent of Resolution During the Fractional Crystallization of the 3,5-Dinitrobenzoate of Partially Active 2,5-Dimethyl-4-phenyl-2-hexanol (V).—Partially optically active 4-methyl-3-phenylpentanoic acid (1.06 g., m.p. 46–47.5°) was esterified to give 1.05 g. of methyl ester, $n^{25}\mathrm{D}$ 1.4931, $\alpha^{25}\mathrm{D}$ −17.77° (l = 1 dm., neat), 53% optically pure. This material gave 0.90 g. of V, $n^{25}\mathrm{D}$ 1.5021, 0.305 g. of which was converted to its 3,5-dinitrobenzoate. This derivative was recrystallized from ethanol. The first crop of 0.33 g., m.p. 81.5–86°, $[\alpha]^{25}\mathrm{D}$ −7.33° (c 3.3, CHCl$_3$), was recrystallized to yield 0.119 g., m.p. 81–87°, $[\alpha]^{26}\mathrm{D}$ −7.25° (c 3.3, CHCl$_3$). A second crop of 0.090 g., m.p. 81–84, $[\alpha]^{24}\mathrm{D}$ −8.58° (c 3.3, CHCl$_3$), was recrystallized to yield 0.0483 g., m.p. 81.5–83.5°, $[\alpha]^{25}\mathrm{D}$ −9.37° (c 3.3, CHCl$_3$). The mother liquor after removal of the second crop gave material, 0.0251 g., $[\alpha]^{26}\mathrm{D}$ −7.97° (c 2.5, CHCl$_3$). The percentage increase in resolution with each crystallization appears to be about +5 ± 12%.

Eluent	Volume of eluent, ml.	Cut	Characteristics
32% ether in pentane	1000	1– 52	Blank
	525	53– 75	Liquid
	1800	76–147	Solid
	75	148–150	Blank
	600	151–153	Blank
100% ether	800	154–155	Liquid
	400	156	Blank

Control on the Chromatographic Separation of 2,5-Dimethyl-4-phenyl-3-hexanol (IV) and 2,5-Dimethyl-4-phenyl-2-hexanol (V).—A mixture of 0.225 g. of (−)-*erythro*-IV, $[\alpha]^{25}\mathrm{D}$ −19.02° (c 3.3, CHCl$_3$) and 0.232 g. of (−)-*threo*-IV, $[\alpha]^{25}\mathrm{D}$ −7.25° (c 5, CHCl$_3$) was melted and well mixed, $[\alpha]^{25}\mathrm{D}$ −12.69° (c 5, CHCl$_3$). A portion (0.3083 g.) of this mixture was diluted with 0.2465 g. of racemic V, and the resulting sample was chromatographed on 166 g. of neutral alumina (3 cm. by 25 cm. column) of activity I[19] made up in pentane. The secondary alcohol was eluted from the column with 32% ether, and the tertiary with 100% ether (the data are summarized below). Cuts 53 through 147 were combined to give 0.23 g. of secondary alcohol, $[\alpha]^{24}\mathrm{D}$ $-12.00°$ (*c* 5, $CHCl_3$). Cuts 154 and 155 were combined to give 0.25 g. of tertiary alcohol, $n^{25}\mathrm{D}$ 1.5026, $[\alpha]^{24}\mathrm{D}$ $-0.21°$ (*c* 5, $CHCl_3$).

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Stereochemistry of the Primary Carbon. VI. The Reaction of Optically Active 1-Aminobutane-1-*d* with Nitrous Acid. Mechanism of the Amine–Nitrous Acid Reaction[1]

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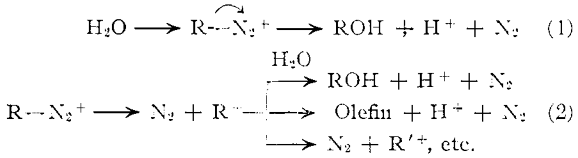
The reaction of *n*-butylamine with sodium nitrite in acetic acid gives a mixture of esters in which the ratio of *n*-butyl acetate to *sec*-butyl acetate is 2:1 and a small amount of alkyl nitrates. The 1-butyl-1-*d*-acetate obtained from optically active 1-aminobutane-1-*d* is 69 ± 7% inverted, 31 ± 7% racemized. A mass spectral investigation of the product from 1-aminobutane-1,1-d_2 shows that 0% ethyl rearrangement occurs. These results in conjunction with other data lead to a complete theory for the product-determining steps of the amine–nitrous acid reaction. The fundamental tenet of this hypothesis is that the alkyldiazonium ion, the last *common* intermediate in the reaction, can undergo a number of competing reactions because of its great instability.

Introduction

Since the first example of Piria[4] and the later extended investigations of Linnemann[5] the reaction of aliphatic primary amines with nitrous acid has been used extensively in preparative and theoretical organic chemistry. In aqueous solution, the reaction generally produces alcohols and olefins, frequently with rearrangement. Although the kinetics of the reaction has been investigated[6] it pertains only to the initial phase of the reaction of the amine with a nitrous acid moiety; the product-determining steps occur later in the reaction sequence and are not amenable to direct kinetic approaches. Analogy to the aromatic series strongly suggests that diazonium ions are intermediates in the reaction.[7] The nature of the reaction products and particularly the similarity of the many rearrangement products to products of typical carbonium ion reactions have led to the interpretation of the product-determining steps of the amine–nitrous acid reaction in terms of solvolytic displacement reactions. The commonly accepted mechanism of the reaction is a competing direct displacement (SN2) on the alkyldiazonium ion by solvent (reaction 1) and a unimolecular fission of the diazonium ion (SN1) to a carbonium ion which subsequently may react with solvent to form product, eliminate a proton to yield olefin or rearrange a hydrogen or a carbon function to a new carbonium ion which ultimately results in products of such rearrangement (reaction 2).[8-11]



$$H_2O \longrightarrow R\text{---}N_2^+ \longrightarrow ROH + H^+ + N_2 \qquad (1)$$

$$R\text{---}N_2^+ \longrightarrow N_2 + R^+ \begin{cases} \xrightarrow{H_2O} ROH + H^+ + N_2 \\ \longrightarrow \text{Olefin} + H^+ + N_2 \\ \longrightarrow N_2 + R'^+, \text{ etc.} \end{cases} \qquad (2)$$

In several cases the experimental observations are in accord with this hypothesis; *e.g.*, the reactions with aqueous nitrous acid of crotylamine, α-methylallylamine, α,α-dimethylallylamine and γ,γ-dimethylallylamine yield, respectively, the same mixtures of isomeric allylic alcohols as the silver ion-catalyzed aqueous solvolyses of the corresponding chlorides[12,13]; cyclopropylcarbinylamine and cyclobutylamine on treatment with aqueous nitrous acid give similar mixtures of cyclobutanol, cyclopropylcarbinol and allylcarbinol.[12] However, in some other examples, this interpretation is clearly not a happy one. *n*-Propyl-, *n*-butyl- and *n*-amylamines, etc., give rather large amounts of secondary carbinol, the product of a rearrangement.[5,b,c,f,14] In solvolytic displacement reactions, rearrangement of *n*-primary to second-

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