The Stereochemistry of Nucleophilic Substitution Reactions at Tertiary Carbon. I. Solvolysis of 2-Phenyl-2-butyl *p*-Nitrobenzoate and Hydrogen Phthalate

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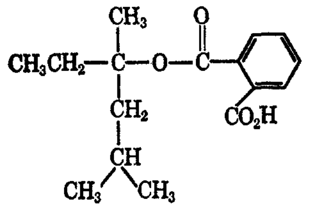
The reaction of hydrogen 2-phenyl-2-butyl phthalate and 2-phenyl-2-butyl *p*-nitrobenzoate with nucleophilic reagents was studied with respect to the stereochemistry of displacement. The relative proportion of inversion over racemization was found to increase as the nucleophile was changed from acetic acid to methanol to azide ion. The greater dependence of stereochemical path on nucleophile rather than on dielectric constant is considered to be inconsistent with a process involving preliminary formation of a tertiary carbonium ion. The stereochemical results provide clear evidence that asymmetric ion pairs or their equivalent are important intermediates in these reactions of the 2-phenyl-2-butyl system.

Considering the wealth of information relating to the mechanism of nucleophilic substitution reactions harvested from the classic studies of secondary carbinyl systems by Hughes and Ingold, *et al.*,[2] and of primary carbinyl systems by Streitwieser,[3] it is surprising that more attention has not been focused on reactions at a tertiary carbon atom. It is in these reactions that intermediates most closely resembling carbonium ions should be formed; yet our conception of the nature and fate of these intermediates derives, to a large extent, from extrapolation of observations made at primary and secondary carbon where the degree of cationic character developed is often negligible.[4,5]

The studies that have been reported suggest a greater variety of solvation states available in reactions involving tertiary carbinyl esters than in reactions involving primary or secondary carbinyl esters. Methanolysis of hydrogen 2,4-dimethyl-4-hexyl phthalate (1) proceeds with 54% inversion of configuration,[6] and that of hydrogen 2-phenyl 2-butyl phthalate (2) with 8–13% inversion,[7] while ethanolysis of the triarylcarbinyl compound (3) occurs with predominant retention of configuration.[8]



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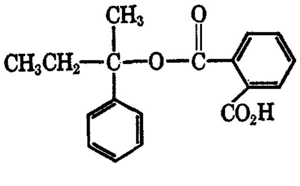

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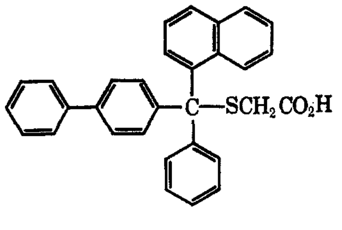

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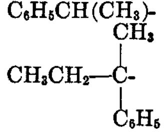
Similar trends toward retention of configuration with increasing stability of the incipient cation are found in deamination reactions of optically active amines in acetic acid (Table I).

TABLE I
STEREOCHEMICAL COURSE OF DEAMINATION REACTIONS IN ACETIC ACID

Amine	Stereochemistry[a]
$CH_3CH_2CH_2CH_2D$-	69% inversion[b]
$CH_3CH_2CH(CH_3)$-	28% inversion[c]
$C_6H_5CH(CH_3)$-	10% retention[d]
 $CH_3CH_2\text{—}C(CH_3)(C_6H_5)$-	24% retention[e,f]

[a] Throughout this paper stereochemical results will be reported as per cent inversion or retention with the difference from 100% understood to be racemization. [b] A. Streitwieser, Jr., and W. D. Schaffer, *J. Am. Chem. Soc.*, **79**, 2888 (1957). [c] K. B. Wiberg, Dissertation, Columbia University, July 1950. [d] R. Huisgen and C. Ruchardt, *Ann.*, **601**, 21 (1956). [e] E. H. White and J. E. Stuber, *J. Am. Chem. Soc.*, **85**, 2168 (1963). [f] F. A. Carey, Ph.D. Thesis, The Pennsylvania State University, 1963.

In this and succeeding papers are reported the results of our studies on nucleophilic substitution reactions in the optically active 2-phenyl-2-butyl system. This was the system of choice because of its ready availability,[7] the surety with which the configurational relationships of many of its derivatives are known (Table II), and because the cation to be formed is both tertiary and benzylic thereby ensuring solvolytic reactivity of the classical unimolecular type.

All of the R*OZ compounds in Table II have been related directly by simple reactions not involving the asymmetric center and are therefore of comparable optical purity. (−)-R*NH_2 results from a Curtius reaction on (+)-2-phenyl-2-methylbutanoic acid,[9,10] and the latter has been related to (−)-R*OH.[11]

Results

Acetolysis.—Both the hydrogen phthalate and *p*-nitrobenzoate esters of optically active 2-phenyl-2-butanol reacted smoothly at 24.5° with acetic acid containing potassium acetate to give mixtures of 2-phenyl-

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[1] Department of Chemistry, University of California, Davis, Calif.

[2] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter VII.

[3] A. Streitwieser, Jr., *J. Am. Chem. Soc.*, **77**, 1117 (1955); **78**, 5597 (1956); **79**, 379 (1957).

[4] A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

[5] N. C. Deno in "Progress in Physical Organic Chemistry," Vol. 2, S. G. Cohen, A. Streitwieser, and R. W. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., 1964.

[6] W. E. Doering and H. H. Zeiss, *J. Am. Chem. Soc.*, **73**, 2391 (1951); **75**, 4733 (1953).

[7] H. H. Zeiss, *ibid.*, **75**, 3154 (1953).

[8] B. L. Murr, *ibid.*, **85**, 2866 (1963).

[9] See Table I, footnote *e*.

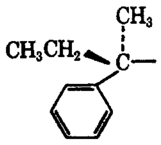
[10] See Table I, footnote *f*.

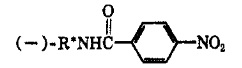
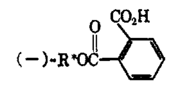
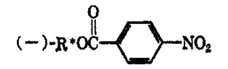
[11] See Table II, footnote *d*.

TABLE II

CONFIGURATIONAL RELATIONSHIPS IN THE 2-PHENYL-2-BUTYL SYSTEM

R* =



Compound	Maximum rotation
(+)-R*OCH_3	$[\alpha]^{25}_D$ +41.6° (1 dm, neat)[a]
(+)-R*OH	$[\alpha]^{27}_D$ +17.6° (1 dm, neat)[b]
(+)-R*NH_2	$[\alpha]^{24}_D$ +16.4° (1 dm, neat)[c]
(+)-R*OAc	$[\alpha]^{25}_D$ +1.6° (1 dm, neat)[d]
	$[\alpha]^{24}_D$ −32.7° (c 2, chloroform)
	$[\alpha]^{25}_D$ −46.2° (c 2, ethanol)[b]
	$[\alpha]^{25}_D$ −58.2° (c 2, chlorolorm)

[a] D. J. Cram, C. A. Kingsbury, and A. Langemann, *J. Am. Chem. Soc.*, **81**, 5786 (1959). [b] Reference 7. [c] See Table I, footnote *f*. [d] D. J. Cram and J. Allinger, *J. Am. Chem. Soc.*, **76**, 4518 (1954).

2-butyl acetate, 2-phenyl-1-butene, *cis*-2-phenyl-2-butene, and *trans*-2-phenyl-2-butene. Since the maximum rotation of even optically pure 2-phenyl-2-butyl acetate is so small (1.6°), the product from acetolysis of the hydrogen phthalate was treated with lithium aluminum hydride to cleave the acetate fraction to 2-phenyl-2-butanol and the rotation of the alcohol was measured to determine the stereochemical course. Dextrorotatory hydrogen phthalate ester (81.3% optically pure) afforded dextrorotatory 2-phenyl-2-butanol (4.1% optically pure) indicating a stereochemical course of 5.0% inversion of configuration.

Acetolysis of (−)-2-phenyl-2-butyl *p*-nitrobenzoate of initial rotation −47.2° gave, after separation into its components, 2-phenyl-2-butyl acetate, unconverted 2-phenyl-2-butyl *p*-nitrobenzoate, and isomeric 2-phenylbutenes. The recovered starting material was found to be partially racemized, having a rotation of −32 ± 4°. The acetate fraction, after flash distillation, was converted to alcohol with lithium aluminum hydride and treated with *p*-nitrobenzoyl chloride in pyridine to give 2-phenyl-2-butyl *p*-nitrobenzoate having a rotation of +2.5 ± 1.0°. That the over-all stereochemical course is one of inversion is clear, the extent being 5.2 ± 2.0%.

Methanolysis.—Use of the vastly more nucleophilic solvent methanol afforded significantly more inverted products than those from acetolysis. In all cases high yields of 2-methoxy-2-phenylbutane were obtained, sometimes accompanied by mixtures of 2-phenylbutenes.

Reaction of hydrogen 2-phenyl-2-butyl phthalate with pure methanol at 23° gave 2-methoxy-2-phenylbutane as the sole product, the rotation of the ether indicating it was formed with 38% inversion of configuration. At 50° it was formed with 28% inversion and at 65° with 13% inversion. Only at 65° were detectable amounts of olefins formed and even in this case elimination occurred only to the extent of 5%.

The *p*-nitrobenzoate ester was less reactive than the hydrogen phthalate by a factor *ca.* 4 at 65°, while the solvolysis product was both less pure (72% 2-methoxy-2-phenyl-butane and 28% 2-phenylbutenes) and less optically pure (7.5% inversion). This figure, however, can be taken only as an index of the minimum stereospecificity of the reaction since, as in the case of acetolysis, starting material is racemized under the reaction conditions. In a control experiment, the metholysis was halted after about 50% reaction and the rotation of the recovered 2-phenyl-2-butyl-*p*-nitrobenzoate was found to have decreased from −47.2 to −36.3°.

The methanolysis of hydrogen 2-phenyl-2-butyl phthalate was also studied in mixed solvents; dilution of the methanol with dioxane or dimethylformamide resulted in an increase in the proportion of elimination and a decrease in the stereospecificity. Where use of pure methanol at 50° gave cleanly 28% inverted 2-methoxy-2-phenylbutane, use of 80 mole % methanol and 20 mole % dioxane as solvent yielded 87% 2-methoxy-2-phenylbutane (14% inverted) and 13% olefins. In a solution of 60 mole % methanol and 40 mole % dioxane the stereospecificity was one of 16% inversion of configuration and the product mixture was composed of 93% 2-methoxy-2-phenylbutane and 7% 2-phenylbutenes. A solution containing 45 mole % methanol and 55 mole % dimethylformamide afforded a mixture of 23% olefins and 77% 2-methoxy-2-phenylbutane which was 8% inverted.

Reaction with Azide.—In order to further study the effect of nucleophile on displacement reactions involving hydrogen 2-phenyl-2-butyl phthalate the ester was allowed to react with sodium azide in 70% aqueous ethanol at 50° for 5 days. The product, a mixture of 2-phenyl-2-butyl azide, 2-ethoxy-2-phenylbutane, and isomeric 2-phenylbutenes, was treated with lithium aluminum hydride to convert the azide fraction to 2-phenyl-2-butylamine which was separated from the other components of the mixture by extraction with dilute hydrochloric acid. Regeneration of the amine from its hydrochloride and measurement of its rotation revealed that formation of 2-phenyl-2-butyl azide from the hydrogen phthalate proceeded with 55.9 ± 1.2% inversion of configuration.

High inversion was also observed when a solution of hydrogen 2-phenyl-2-butyl phthalate in methanol saturated with sodium azide was refluxed 5 days. The solvolysis was slower than in the absence of sodium azide, probably reflecting partial conversion of the free carboxylic acid group of the ester to carboxylate ion. A mixture of olefins, 2-methoxy-2-phenylbutane, and 2-phenyl-2-butyl azide was obtained, the methyl ether being formed with 24.9% inversion and the azide with 61.5 ± 3.6% inversion of configuration.

Similarly, strong nucleophilic participation was found when 2-phenyl-2-butyl *p*-nitrobenzoate was refluxed with methanolic sodium azide. The azide fraction, after reduction with lithium aluminum hydride and conversion of the amine to the corresponding *p*-nitrobenzamide, was found to be formed with 55.9 ± 1.0% inversion of configuration. Moreover, it was found that recovered starting material had not been racemized under these conditions in contrast to the extensive racemization observed in the absence of sodium azide, and that the 2-methoxy-2-phenylbutane fraction was formed with 14% inversion of configuration compared to the 7.5% inversion observed initially.

Discussion

For convenience in discussion a summary of the above results is provided in Table III.

TABLE III

STEREOCHEMISTY OF THE 2-PHENYL-2-BUTYL SYSTEM

Reacn no.	Reactant, R*X	Reagent	Reacn temp, °C	Product, stereochemistry[a]
1	$R^*O_2CC_6H_4(CO_2H)$-*o*	AcOH, AcOK	23	R*OAc, 5.0 ± 0.4% inv
2	$R^*O_2CC_6H_4(NO_2)$-*p*	AcOH, AcOK	23	R*OAc, 5.2 ± 2% inv
3	$R^*O_2CC_6H_4(CO_2H)$-*o*	MeOH	23	R*OMe, 38% inv
4	$R^*O_2CC_6H_4(CO_2H)$-*o*	MeOH	50	R*OMe, 28% inv
5	$R^*O_2CC_6H_4(CO_2H)$-*o*	MeOH	65	R*OMe, 13% inv[b]
6	$R^*O_2CC_6H_4(CO_2H)$-*o*	80% M[c]–20% D[d]	50	R*OMe, 14% inv
7	$R^*O_2CC_6H_4(CO_2H)$-*o*	60% M–40% D	50	R*OMe, 16% inv
8	$R^*O_2CC_6H_4(CO_2H)$-*o*	45% M–55% DMF[e]	50	R*OMe, 8% inv
9	$R^*O_2CC_6H_4(CO_2H)$-*o*	70% E[f]–30% H_2O, NaN_3	50	R^*N_3, 55.9 ± 1.2% inv
10	$R^*O_2CC_6H_4(CO_2H)$-*o*	MeOH, NaN_3	65	R^*N_3, 61.5 ± 3.6% inv R*OMe, 24.9 ± 0.1% inv
11	$R^*O_2CC_6H_4(NO_2)$-*p*	MeOH, NaN_3	65	R^*N_3, 55.9 ± 1% inv R*OMe, 14.3 ± 0.1% inv

[a] Stereochemical results are reported as per cent inversion with the difference from 100% understood to be racemization. [b] Racemization of R*OMe by boiling methanol in the presence of equimolar phthalic acid was reported in ref 7 and would correspond to 3–5% racemization of optically active product for reaction carried out at 65°. Indeed, all of the results in the above table probably represent *minimum* stereospecificity. [c] M = methanol. [d] D = dioxane. [e] DMF = dimethylformamide. [f] E = ethanol.

Perhaps the most significant results of the present work are given by reactions 9, 10, and 11 in Table III, in which R^*N_3 of optical purity 56–61% is formed with inversion of configuration.

In reaction 9 the yield of R^*N_3 isolated as R^*NH_2 was 17%. A reasonable guess is that R^*N_3 may actually have been formed in 30 ± 10% yield, and this, coupled with a 21:1 mole ratio of solvent molecules to moles of sodium azide, indicates that azide ion competes effectively with solvent for the 2-phenyl-2-butyl cation. It has been shown that formation of RN_3 from RX proceeds without involvement of azide ion in the rate-determining step and that azide ion competes effectively with reactive solvent molecules for cases in which R = benzhydryl,[12] R = triphenylmethyl,[13] R = *t*-butyl,[14] and R = 2-octyl.[15] The last is true for reaction of 2-octyl mesylate in 25 vol. % aqueous dioxane to give alcohol and 31% yield of RN_3. These studies, plus our observation that the formation of 2-phenyl-2-butyl azide from the chloride in 80% ethanol does not involve azide ion in the rate-determining step,[16] make it exceedingly reasonable to postulate that reactions 9, 10, and 11 in Table II involve formation of R^*N_3 from a reactive intermediate whose formation from reactant is rate determining. This intermediate contains a significantly stretched R* · · · · OZ system, in which R* has substantial positive charge, but OZ may be formally neutral or negatively charged. In some of the reactions (1, 3, 4, 5, 6, 7, and 8) the leaving group is probably phthalic acid. In reactions 9 and 10, owing to the presence of NaN_3, the leaving group may be hydrogen phthalate. In reactions 2 and 11 the leaving group may be *p*-nitrobenzoate or *p*-nitrobenzoic acid. Thus, it would be incorrect to designate the reactive intermediate as an ion pair for all of the reactions in Table III. Formation of optically active azide may reasonably be postulated to proceed as shown in sequence 1. Of course, the striking aspect of eq 1 is

$$R^*X \xrightarrow[\text{determining}]{\text{rate}} \underset{\substack{\text{ion pair,}\\ \text{or the}\\ \text{equivalent}}}{R^*\cdots\cdot OZ} \xrightarrow[\text{fast}]{N_3^-} \underset{\text{inverted}}{N_3R^*} \qquad (1)$$

that it is able to compete so effectively with solvent-induced racemization (see below) with a system that is both tertiary and benzylic. Part of the answer must lie in the fact that the azide ion is a highly polarizable linear spike, which makes it a very effective nucleophile.

Formation of optically active 2-methoxy-2-phenylbutane with 38% inversion of configuration (reaction 3 of Table III) demonstrates that invertive attack by a methanol molecule on the intermediate is quite competitive with formation of a symmetrically solvated (racemic) cation in methanol at 23°. In connection

$$R^*\cdots\cdot OZ \xrightarrow[\text{fast}]{\text{MeOH}} \text{Me}\underset{H}{\overset{+}{O}}R^* \xrightarrow{\text{fast}} \underset{\text{inverted}}{\text{MeOR}^*} \qquad (2)$$

with the postulate of ion pairs or their equivalent as reactive intermediates in eq 2, the role of ion pairs in the elimination reactions of *t*-BuX in solvents such as AcOH and EtOH has been reported.[17] The olefin to substitution product ratio was found not to be independent of leaving group.

Comparison of reactions 4 and 6 shows that, although dioxane is an "inert" solvent, it intervenes in the methanolysis of R*X and significantly decreases the net inversion of configuration.

Consideration of the dielectric constants of methanol (31.2) and dioxane (2.21), and of the *Y* values of methanol (−1.090) and 90% dioxane–10% water (−2.030),[18] makes it clear that *the ionizing power of the solvent-reactant is decreased by addition of dioxane, and yet racemization is increased.* Although decreased inversion and increased racemization with admixture of dioxane to a methanol solvent–reagent have been observed before in the methanolysis of hydrogen 2,4-dimethylhexyl-4-phthalate[19] and 2-octyl mesylate,[20] it is of considerable interest that the same is true for the 2-phenyl-2-butyl system (comparing reactions 4 and 6) which should be much more sensitive to the ionizing power of the solvent because of the greater stability of its cation.

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[12] M. G. Church, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 966 (1940); M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taheer, *ibid.*, 971 (1940); L. C. Bateman, E. D. Hughes, and C. K. Ingold, *ibid.*, 974 (1940).

[13] C. G. Swain, C. R. Scott, and K. H. Lohmann, *J. Am. Chem. Soc.*, **75**, 136 (1953).

[14] L. C. Bateman, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 960 (1940).

[15] H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.*, **87**, 292 (1965).

[16] This study is part of a general study on PhEtMeC*Cl by L. H. Sommer and F. A. Carey, to be published.

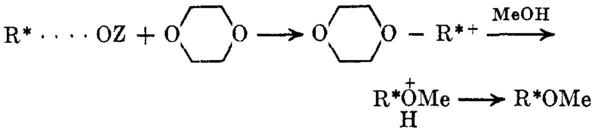
[17] M. Cocivera and S. Winstein, *J. Am. Chem. Soc.*, **85**, 1702 (1963).

[18] A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956).

[19] Reference 4, pp 83–86.

[20] H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.*, **87**, 287 (1965).

For the 2,4-dimethylhexyl-4 phthalate, methanolysis in pure methanol gives 60% inversion and this decreases continuously with added dioxane until ~15% inversion is found for 25 mole % methanol. The leveling off of racemization in going from 20 mole % dioxane to 40 mole % dioxane (reaction 7) for the 2-phenyl-2-butyl system may reflect its greater susceptibility toward racemization by solvents of high ionizing power. This factor would operate in opposition to the role of dioxane in promoting racemization by intervention as an "inert" solvent. The nature of that intervention has recently been postulated to involve formation of an oxonium ion with inversion, followed by displacement of the dioxane by methanol in a second invertive step, thus providing formation of R*OMe with double inversion, or *net retention of configuration*. For the present work this concept is applied in sequence 3.



(3)

Formation of symmetrical intermediates such as **4** provides another possible path for racemization induced by nucleophilic "inert" solvents such as dioxane.[19]

$$D \cdots\cdots R^* \cdots\cdots D \quad (4)$$

Perhaps the major significance of the above results lies in the clear demonstration that ion pairs or their equivalent are important intermediates even in the case of the 2-phenyl-2-butyl system in solvents of good ionizing power such as methanol. The stereochemical results, predominant *retention* of configuration for nitrous acid deamination of R^*NH_2 in acetic acid, and predominant *inversion* of configuration in the reactions in Table III, comprise evidence that these intermediates are asymmetric and can undergo reactions which are stereoselective.

Experimental Section

Melting points are corrected and analyses of new compounds performed by the microanalytical group at Penn State. Infrared spectra were taken using a Beckman IR-5A spectrophotometer, optical rotations were measured on an O. C. Rudolph precision polarimeter, and analyses of product mixtures were performed by vpc carried out using an Aerograph A-90-P gas chromatograph equipped with a 10 ft × 0.25 in. 20% Ucon Polar on Chromosorb column. Relative areas were calculated by tracing the chromatogram, cutting out and weighing the peaks.

(+)- and (−)-Hydrogen 2-Phenyl-2-butyl Phthalate.—2-Phenyl-2-butanol was converted to its hydrogen phthalate and resolved by the method of Zeiss.[7]

(−)-2-Phenyl-2-butyl *p*-Nitrobenzoate.—To a solution of 8.0 g (53.4 mmoles) of (+)-2-phenyl-2-butanol, $[\alpha]^{23}\mathrm{D}$ +14.34° (1 dm, neat), in 50 ml of anhydrous pyridine was added 10.4 g (57.1 mmoles) of freshly recrystallized *p*-nitrobenzoyl chloride. After 3 days at 25° the solution was poured into iced dilute hydrochloric acid and extracted with three 50-ml portions of ether. The combined ether extracts were washed with water and three 30-ml portions of 10% potassium carbonate solution. After drying over anhydrous sodium sulfate and evaporation, 10.1 g (63%) of the desired ester was obtained which after recrystallization from heptane had $[\alpha]^{25}\mathrm{D}$ −47.2° (*c* 2, chloroform), mp 73–83°.

Racemic ester prepared in similar manner melted at 98–99° and exhibited an infrared spectrum identical with optically active material: strong bands at 5.78 (C=O), 6.50 and 7.40 (NO_2), and 7.80 and 9.0 μ (CO).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.74; N, 4.68. Found: C, 68.33; H, 5.66; N, 4.61.

Evidence of maintenance of stereochemical integrity is shown by saponification of the *p*-nitrobenzoate with methanolic potassium carbonate.

A solution of 2.99 g (10 mmoles) of (−)-2-phenyl-2-butyl *p*-nitrobenzoate, $[\alpha]^{25}\mathrm{D}$ −44.3°, in 100 ml of methanol was refluxed with 2.76 g (20 mmoles) of potassium carbonate for 13 hr, then poured into 300 ml of water and extracted with four 50-ml portions of pentane. The combined organic extracts were washed with 30 ml of 10% potassium carbonate solution and dried over sodium sulfate. The solution was evaporated and the residue was chromatographed on 40 g of alumina to give 0.91 g (61%) of 2-phenyl 2 butanol having, after flash distillation at 100° (1 mm), $[\alpha]^{25}\mathrm{D}$ +6.61° (0.5 dm, neat), corresponding to 92% retention of configuration and optical activity.

Acetolysis of Hydrogen 2-Phenyl-2-butyl Phthalate.—To 100 ml of acetic acid, 0.95 *M* in potassium acetate, was added 3.84 g (12.9 mmoles) of hydrogen 2-phenyl-2-butyl phthalate, $[\alpha]^{25}\mathrm{D}$ +37.5°, and the solution was allowed to stand at 24.5° for 17 days. The solution was poured into 300 ml of water and extracted with four 50-ml portions of pentane which were combined and washed with two 30-ml portions of water, three 30-ml portions of 20% potassium carbonate solution, and again with 30 ml of water. After drying over sodium sulfate the solution was concentrated by distilling the pentane through a short column and percolated through 40 g of alumina. Washing the column with pentane removed 0.28 g of a olefin mixture (51% *cis*-2-phenyl-2-butene, 48% 2-phenyl-1-butene, and 1% *trans*-2-phenyl-2-butene), while elution with 250 ml of 3:1 pentane–ether afforded 1.22 g (50%) of 2-phenyl-2-butyl acetate identified by the superimposition of its infrared spectrum with that of authentic material.[11]

The acetate was cleaved with lithium aluminum hydride in 35 ml of ether and the excess reagent was decomposed carefully with water. The solution was decanted from the coagulated salts which were then washed with a small portion of ether. Combination of the ether solutions, washing with cold 2 *N* hydrochloric acid, water, and potassium carbonate solution, followed by drying over potassium carbonate and evaporation gave 0.67 g (70%) of 2-phenyl-2-butanol. After flash distillation at 100° (2 mm) the rotation of the alcohol was $[\alpha]^{25}\mathrm{D}$ +0.307 ± 0.023° (0.5 dm, neat). When the optical purity of the starting material (81%) is considered, the stereochemical course is 5.0 ± 0.4% inversion.

Acetolysis of 2-Phenyl-2-butyl *p*-Nitrobenzoate.—To a glass-stoppered flask containing 100 ml of acetic acid, 0.95 *M* in potassium acetate, was added 3.88 g (13.0 mmoles) of (−)-2-phenyl-2-butyl *p*-nitrobenzoate, $[\alpha]^{25}\mathrm{D}$ −47.2°, and the solution was allowed to stand at 24.5° for 66 days. The product was isolated by pouring the reaction mixture into 300 ml of water and extracting with four 50-ml portions of pentane. The pentane layers were combined and washed twice with 30 ml of water, three 30-ml portions of 20% potassium carbonate solution, and again with 30 ml of water, and dried over sodium sulfate. The solution was concentrated to a volume of 40 ml by distilling the pentane through a short column and then chromatographed on 100 g of alumina. Eluting the column with 200 ml of pentane removed 0.50 g of isomeric 2-phenylbutenes. The next fraction, eluted with 400 ml of 3:1 pentane–ether weighed 1.01 g and consisted predominantly of 2-phenyl-2-butyl acetate with 2-phenyl-2-butyl *p*-nitrobenzoate as an impurity as evidenced from its infrared spectrum. Washing the column with ether removed 0.026 g of 2-phenyl-2-butyl *p*-nitrobenzoate. This recovered ester was considerably racemized, having $[\alpha]^{25}\mathrm{D}$ −32 ± 4° (*c* 0.26, chloroform).

The middle fraction was flash distilled at 100° (2 mm) to give acetate free of *p*-nitrobenzoate. The distillate (0.6 g) was added to a stirred suspension of 0.4 g lithium aluminum hydride in 25 ml of anhydrous ether and after stirring overnight hydrolyzed by the cautious addition of water to the reaction mixture. The ether solution was decanted, the precipitated salts were washed with ether, and the combined solutions were washed with 10 ml of water and dried over potassium carbonate.

The ether was removed leaving 0.21 g of 2-phenyl-2-butanol which was taken up in 4 ml of dry pyridine and 0.3 g of recrystallized *p*-nitrobenzoyl chloride added. After 6 days at 25° the solution was poured into iced dilute hydrochloric acid and extracted with 10 ml, then 5 ml of chloroform. After washing and drying, the chloroform solution was passed through 10 g of alumina and the column was washed with 150 ml of 2:1 pentane–ether to afford 0.19 g of the desired ester. The identity of the product was confirmed by its infrared spectrum; its rotation as measured in a 2.5-dm tube was $[\alpha]^{25}_{\mathrm{D}}$ +2.5 ± 1.0° (*c* 2, chloroform).

Methanolysis of Hydrogen 2-Phenyl-2-butyl Phthalate at 65°.—A solution of 4.0 g (13.3 mmoles) of hydrogen 2-phenyl-2-butyl phthalate, $[\alpha]^{25}_{\mathrm{D}}$ +42.4°, in 100 g of anhydrous methanol was refluxed 12 hr, poured into 300 ml of water, and extracted with four 50-ml portions of pentane. The combined extracts were washed with 30 ml of water, three 30 ml portions of 20% potassium carbonate solution, and 30-ml of water. After drying (sodium sulfate) the pentane was distilled through a short column to leave 1.89 g (85%) of 2-methoxy-2-phenylbutane containing 5% isomeric 2-phenylbutenes. The rotation of the neat liquid, $[\alpha]^{26}_{\mathrm{D}}$ +4.79° (1 dm, neat), when corrected for product purity and optical purity of the starting material, indicates a stereochemical course of 13.2% inversion of configuration.

Methanolysis of Hydrogen 2-Phenyl-2-butyl Phthalate at 50°.—Under conditions identical with those above except for the temperature being maintained at 50° for 24 hr a yield of 1.89 g (85%) of 2-methoxy-2-phenylbutane was obtained. The rotation of the product was $[\alpha]^{26}_{\mathrm{D}}$ +10.53° (1 dm, neat) requiring 27.6% inversion of configuration.

Methanolysis of Hydrogen 2-Phenyl-2-butyl Phthalate at 23°.—The optically active half-ester (3.65 g, 12.2 mmoles, $[\alpha]^{25}_{\mathrm{D}}$ +42.4°), was dissolved in 100 g of methanol and permitted to react at 23° for 22 days. Working up the reaction mixture as above afforded 1.12 g (57%) of pure 2-methoxy-2-phenylbutane, $[\alpha]^{25}_{\mathrm{D}}$ +14.56° (1 dm, neat). This corresponds to a stereochemical course of 38.1% inversion of configuration.

Methanolysis in 80 Mole % Methanol–20 Mole % Dioxane.—To a solution containing 59.3 g (1.85 moles) of methanol and 40.7 g (0.46 mole) of dioxane was added 4.0 g (13.3 mmoles) of hydrogen 2-ph nyl-2-butyl phthalate, $[\alpha]^{25}_{\mathrm{D}}$ +42.4°, and the solution was heated at 50° for 142 hr. The reaction mixture was worked up in the usual manner to yield 1.69 g (77%) of product. Infrared spectroscopy showed only 2-methoxy-2-phenylbutane and isomeric 2-phenylbutenes to be present, in amounts determined by vapor phase chromatography to be 87 and 13%, respectively. Correction of the rotation of the crude product, $[\alpha]^{25}_{\mathrm{D}}$ +4.76° (1 dm, neat), for product purity and optical purity of the starting material (92%) gave a value of 14% inversion accompanied by 86% racemization.

Methanolysis in 60 Mole % Methanol–40 mole % Dioxane.—The solvolysis solution was prepared by mixing 36.6 g (1.14 moles) of purified anhydrous methanol with 63.6 g (0.72 mole) of purified dioxane and adding 4.0 g (13.3 mmoles) of hydrogen 2-phenyl-2-butyl phthalate, $[\alpha]^{25}_{\mathrm{D}}$ +42.4°. After reacting at 50° for 185 hr the solution was worked up as before to give 1.80 g (82%) of material, $[\alpha]^{25}_{\mathrm{D}}$ +5.66° (1 dm, neat), and found to contain 93% 2-methoxy-2-phenylbutane and 7% isomeric 2-phenylbutenes by vapor phase chromatography. Correction for starting material optical purity and product purity gives a stereochemical course of 16% inversion.

Methanolysis in 45 Mole % Methanol–55 Mole % Dimethylformamide.—A solution of 3.87 g (13.0 mmoles) of hydrogen 2-phenyl-2-butyl phthalate, $[\alpha]^{25}_{\mathrm{D}}$ +42.4° in 23.8 g (0.74 mole) of methanol and 66.5 g (0.91 mole) of dimethylformamide was allowed to stand at 49.3° for 31 days, then worked up in the usual manner to yield 0.92 g (45%) of product identified as a mixture of 2-methoxy-2-phenylbutane and olefins by its infrared spectrum and found by vapor phase chromatography to have a composition of 23% olefins and 77% methyl ether. The rotation of the crude material was $[\alpha]^{25}_{\mathrm{D}}$ +2.37° (1 dm, neat) and indicates a stereochemical course of 8% inversion of configuration when corrected for product purity and optical purity of starting material.

Methanolysis of 2-Phenyl-2-butyl *p*-Nitrobenzoate.—To 100 ml of methanol was added 3.32 g (11.0 mmoles) of 2-phenyl-2-butyl *p*-nitrobenzoate, $[\alpha]^{25}_{\mathrm{D}}$ −44.3°, and the solution was refluxed for 76 hr, then poured into 150 ml of water and extracted with four 30-ml portions of pentane. The extracts were washed with three 30-ml portions of 20% potassium carbonate solution and dried over sodium sulfate. After concentration of the solution by distilling the pentane through a short column the product was chromatographed on 40 g of alumina. Elution with 300 ml of pentane afforded 0.67 g of material analyzed by vapor phase chromatography to contain 72% 2-methoxy-2-phenylbutane and 28% isomeric 2-phenylbutenes. This material had $[\alpha]^{25}_{\mathrm{D}}$ −0.843 ± 0.033° (0.5 dm, neat). Correcting for the optical purity on the starting material (75.5%) and the product purity a stereochemical course of 7.5% inversion obtains.

Recovery of 2-Phenyl-2-butyl *p*-Nitrobenzoate from an Interrupted Methanolysis.—In another experiment 0.68 g of the *p*-nitrobenzoate, $[\alpha]^{25}_{\mathrm{D}}$ −47.2°, was refluxed in 30 ml of methanol for 17 hr, poured into 60 ml of water, and extracted with 30 ml of ether. The ether layer was separated, washed with water, dried over sodium sulfate, and evaporated. The residue was chromatographed on 25 g of alumina. After eluting with 100 ml of pentane the column was washed with 100 ml of 3:1 pentane–ether to give 0.33 g of 2-phenyl-2-butyl *p*-nitrobenzoate, $[\alpha]^{25}_{\mathrm{D}}$ −36.3° (*c* 3, chloroform). An independent experiment showed the *p*-nitrobenzoate to be optically stable to chromatography.

(+)-2-Phenyl-2-butylamine.—(−)-2-Methyl-2-phenylbutanoic acid, $[\alpha]^{25}_{\mathrm{D}}$ −28.4° (*c* 2.0, benzene, 95% optically pure),[21] was converted to (+)-2-phenyl-2-butylamine, $[\alpha]^{24}_{\mathrm{D}}$ +15.43° (1 dm, neat), *via* the Curtius reaction.[22]

(−)-N-2-Phenyl-2-butyl *p*-Nitrobenzamide.—To 40 ml of 5% potassium hydroxide solution and 10 ml of chloroform was added 1.0 g (6.71 mmoles) of (+)-2-phenyl-2-butylamine, $[\alpha]^{24}_{\mathrm{D}}$ +15.43° (1 dm, neat), and 2.0 g (10.8 mmoles) of *p*-nitrobenzoyl chloride, and the reaction mixture was allowed to stand overnight. The layers were separated and the aqueous layer was extracted with 10 ml of chloroform. The organic extracts were washed with two 5-ml portions of water, two 5-ml portions of 2 *N* hydrochloric acid, and 5 ml of water, and dried over potassium carbonate.

The solution was concentrated and 15 ml of heptane was added to precipitate the *p*-nitrobenzamide as an oil which soon crystallized. The product was filtered and washed with heptane to give 1.65 g (83%) of N-2-phenyl-2-butyl *p*-nitrobenzamide, mp 121–122°, $[\alpha]^{24}_{\mathrm{D}}$ −30.8° (*c* 2.8, chloroform). Since the 2-phenyl-2-butylamine used was 95% optically pure the maximum rotation of optically pure *p*-nitrobenzamide is −32.7°.

Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 67.96; H, 6.34; N, 9.20.

Reaction of Hydrogen 2-Phenyl-2-butyl Phthalate with Sodium Azide in Aqueous Ethanol.—To a solution prepared by dissolving 19.5 g (0.3 mole) of sodium azide in 140 ml of ethanol and 60 ml of water was added 7.71 g (25.9 mmoles) of hydrogen 2-phenyl-2-butyl phthalate, $[\alpha]^{25}_{\mathrm{D}}$ −29.0°, and the solution was held at 50° for 5 days. The solution was poured into 500 ml of ice water and extracted with four 100-ml portions of pentane, and the pentane layers were combined and washed with three 30-ml portions of water and three 40-ml portions of 20% potassium carbonate solution and dried over sodium sulfate.

The solution was concentrated to 30 ml by distilling the pentane through a short column and chromatographed on 120 g of alumina. A 300-ml pentane wash eluted 2.24 g of material identified by its infrared spectrum as a mixture of 2-phenyl-2-butyl azide, 2-ethoxy-2-phenylbutane, and 2-phenylbutenes. Elution with 200 ml of 4:1 pentane–ether removed 0.34 g of a mixture of products relatively richer in the ether and poorer in azide.

The first fraction containing the azide was dissolved in 15 ml of anhydrous ether and added to a stirred slurry of 1.0 g of lithium aluminum hydride in 30 ml of ether. After stirring overnight the excess reagent was carefully decomposed with water and the ether solution was decanted. The precipitated salts were washed with another 20 ml of ether and the combined ether solutions were extracted with two 20-ml portions of 3 *N* hydrochloric acid to remove the amine from the other components. The acidic solution was neutralized with solid potassium hydroxide and extracted with two 20-ml portions of pentane and the pentane layers were washed with 10 ml of water and dried over sodium sulfate. Evaporation of the pentane afforded 0.65 g of 2-phenyl-2-butylamine identified by comparison of its infrared spectrum with that of authentic material. The optical activity of the amine, $[\alpha]^{25}_{\mathrm{D}}$ −2.876 ± 0.059° (0.5 dm, neat), indicates an optical purity of 35.1% from 62.8% pure starting material and requires a stereochemical course of 55.9 ± 1.2% inversion of configuration.

Reaction of Hydrogen 2-Phenyl-2-butyl Phthalate with Methanolic Sodium Azide.—A solution containing 4.67 g (15.6 mmoles) of hydrogen 2-phenyl-2-butyl phthalate, $[\alpha]^{25}_{\mathrm{D}}$ +38.8°, in 100 g of methanol containing 6.5 g (0.1 mole) of sodium azide was refluxed for 5 days. The solution was poured into 300 ml of water, extracted with pentane, washed, and dried as above.

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[21] D. J. Cram and J. D. Knight, *J. Am. Chem. Soc.*, **74**, 5835 (1952).

[22] D. J. Cram, C. A. Kingsbury, and A. Langemann, *ibid.*, **81**, 5785 (1959).

After concentration to a volume of 40 ml the solution was chromatographed on a column of 100 g of alumina prepared in pentane. Washing the column with 200 ml of pentane eluted 1.7 g of material identified by its infrared spectrum as a mixture of 2-methoxy-2-phenylbutane (COC, 9.3 μ and OCH_3, 3.60 μ), 2-phenyl-2-butyl azide (N=N=N, 4.80 μ), and olefins. A blend of 95% pentane–5% ether (200 ml) eluted 0.47 g of 2-methoxy-2-phenylbutane uncontaminated with azide and containing 8% 2-phenylbutenes (vpc). The rotation, $[\alpha]^{25}\text{D}$ $+4.005 \pm 0.022°$ (0.5 dm, neat), of this material when corrected for product purity and optical purity of starting material gives a stereochemical course of 24.9 ± 0.1% inversion of configuration in the formation of the methyl ether.

The first chromatographic fraction was dissolved in 15 ml of anhydrous ether and added dropwise to 0.75 g of lithium aluminum hydride in 20 ml of ether, and the solution was stirred overnight and worked up in the usual manner. The residue after evaporation of the ether was dissolved in 10 ml of chloroform and 2.0 g of *p*-nitrobenzoyl chloride was added along with 40 ml of 5% potassium hydroxide solution and the mixture was shaken for several minutes and allowed to stand for 1 hr. The layers were separated and the aqueous layer was extracted with 5 ml of chloroform. The organic layers were combined, washed with water, and dried over sodium sulfate. The solution was concentrated and chromatographed on 15 g of alumina. After removing the methyl ether and olefins by eluting with pentane the *p*-nitrobenzamide (102 mg) was washed from the column with 30% ether–70% pentane and identified by comparison of its infrared spectrum with authentic material. The optical activity of the product, $[\alpha]^{25}\text{D}$ $-16.8 \pm 1.0°$ requires a stereochemical course of 61.5 ± 3.6% inversion of configuration.

Reaction of 2-Phenyl-2-butyl *p*-Nitrobenzoate with Methanolic Sodium Azide.—(−)-2-Phenyl-2-butyl *p*-nitrobenzoate (5.0 g, 16.8 mmoles), $[\alpha]^{25}\text{D}$ $-48.3°$, was dissolved in 100 g of methanol containing 6.5 g (0.1 mmole) of sodium azide, and the solution was refluxed 3 days, then poured into 300 ml of water and extracted with four 50-ml portions of pentane. The pentane extracts were combined and washed with three 15-ml portions of water and 30 ml of 10% potassium carbonate solution. After drying (sodium sulfate), the solution was concentrated to 40 ml and chromatographed on a column of 100 g of alumina prepared in pentane. Elution with 200 ml of pentane removed 0.84 g of material identified by its infrared spectrum as a mixture of 2-phenyl-2-butyl azide, 2-methoxy-2-phenylbutane, and 2-phenylbutenes. Two hundred milliliters of 5% ether in pentane eluted a second fraction weighing 1.07 g, free of azide and containing 95% 2-methoxy-2-phenylbutane and 5% 2-phenylbutenes by vpc. The rotation of this fraction was $[\alpha]^{25}\text{D}$ $-4.89 \pm 0.03°$ (1 dm, neat) and indicates a stereochemical course of 14.3 ± 0.1% inversion of configuration in formation of the methyl ether.

Washing the column with 150 ml of 2:1 pentane–ether eluted 0.052 g of unsolvolyzed starting material having $[\alpha]^{25}\text{D}$ $-44.5 \pm 2.5°$ (*c* 0.5, chloroform).

The first chromatographic fraction containing the azide was dissolved in 15 ml of anhydrous ether and added dropwise to a stirred slurry of 0.75 g of lithium aluminum hydride in 20 ml of ether to convert the azide to 2-phenyl-2-butylamine. After stirring overnight, the excess reagent was decomposed with water and the ether layer was decanted from the inorganic salts which were then washed with a small portion of ether. The ether solutions were combined, washed with 10 ml of water, and dried over potassium carbonate. The ether was distilled through a short column to leave 0.57 g of liquid exhibiting no peaks due to azide. In order to separate the amine from the olefins and methyl ether the product was dissolved in 5 ml of chloroform and shaken with 1 g of *p*-nitrobenzoyl chloride and 20 ml of 5% potassium hydroxide solution. After standing for 1.5 hr the chloroform layer was removed and the aqueous layer was washed with another 5-ml portion of chloroform. The combined chloroform extracts were washed with two 30-ml portions of water and dried over anhydrous sodium sulfate.

The solution was concentrated to a small volume and 15 ml of heptane was added to precipitate the 2-phenyl-2-butyl *p*-nitrobenzamide. This derivative was identified by its infrared spectrum and weighed 0.21 g, having $[\alpha]^{25}\text{D}$ $+15.6 \pm 0.3°$ (*c* 2, chloroform). The material is 46.4% optically pure and shows a stereochemical course of 55.9 ± 1.0% inversion of configuration in the formation of 2-phenyl-2-butyl azide.

Registry No.—(+)-R^*OCH_3, 1007-66-5; (+)-R^*OH, 1006-06-0; (+)-R^*NH_2, 10181-67-6; (+)-R^*OAc, 10181-68-7; (−)-$R^*NHC(O)C_6H_4NO_2$, 10181-69-8; (−)-$R^*OC(O)C_6H_4CO_2H$, 10181-70-1; (−)-$R^*OC(O)C_6H_4NO_2$, 5011-60-9; (+)-hydrogen 2-phenyl-2-butyl phthalate, 1038-30-8.

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