pyridine. The mixture was boiled 2 hours, then 78 ml. of ethanol was added and the boiling was continued another 90 minutes. The mixture was quenched with water and the reisolated solid was shown to be only partially converted to oxime, so it was boiled for 16 hours with 80 ml. of pyridine, 80 ml. of ethanol and 11 g. of hydroxylamine hydrochloride, at which time 11 g. more of hydroxylamine hydrochloride was added and the heating was continued an additional 3 hours. The mixture was poured into water and the collected, crude solid had a melting point of 175°. Upon three crystallizations from chloroform–hexane, the melting point of the material became constant at 181°. The oxime XII had a radioactivity content of 8.519 ± 0.004 mc./mole. Five grams of XII was treated in ether with an excess of lithium aluminum hydride, and the mixture was stirred at room temperature for 4 days. The reduction mixture was treated with water until a grainy precipitate was obtained, and the ether was decanted, dried, and treated with anhydrous HCl to yield 2.5 g. of the amine hydrochloride XIII. A portion of XIII was made basic and converted to the amide XIV, m.p. 208°, 8.504 ± 0.02 mc./mole. To 1.19 g. of XIII in 120 ml. of water and 10 ml. of *N* HCl was added 2.25 g. of sodium nitrite. From the reaction mixture was isolated 801 mg. of crude product which upon treatment with Norite in hexane and subsequent crystallization produced 582 mg. of pure white carbinol XV, m.p. 87°, 8.532 ± 0.013 mc./mole. To 297 mg. of XV in 5 ml. of acetic acid was added 350 mg. of CrO_3 in 2 ml. of water. The mixture was left 1 hour at room temperature, warmed on a steam-bath 2–3 minutes, then poured into water. The solid ketone XVI, 275 mg., was collected on a filter and washed with water. It had a melting point of 138°. After one crystallization from ethanol, the material was assayed for radioactivity, 8.486 ± 0.06 mc./mole. After oxidation to benzophenone, the 2,4-dinitrophenylhydrazone XVII was shown to have a molar radioactivity of 2.365 ± 0.03 mc./mole.

The infrared spectrum of ketone XI showed a strong absorption at 8.1 μ and a medium absorption at 11.1 μ, characteristic for deuterium substitution alpha to a carbonyl group, and no adsorption at 8.4 μ, characteristic for the corresponding ketone devoid of deuterium. From the infrared spectrum of ketone XVI it could be calculated that the benzhydryl position contained 45% deuterium and 55% hydrogen.[36] Nuclear magnetic resonance spectroscopy[37] showed that ketone XI possessed only deuterium in the benzhydryl position, whereas the oxime XII and the amide XIV contained 57% and 63%, respectively, of the original deuterium in this same position. Carbinol XV contained 45% of the original deuterium in the benzhydryl position, 15% deuterium at the no. 1 carbon position, and 40% of the molecules contained no deuterium. Ketone XVI contained 49% of the original deuterium in the benzhydryl position. Thus the n.m.r., infrared and carbon-14 data are all in very close agreement. The n.m.r. data indicate that during the oximation about 40% loss of deuterium occurred, but that the lithium aluminum hydride reduction caused no deuterium loss. The oximation was therefore repeated under milder conditions, in which 1 g. of ketone XI, 1 g. of hydroxylamine hydrochloride, 2.7 ml. of pyridine and 7 ml. of ethanol were heated under reflux for 4.5 hours, during which time (after 3.5 hours) another gram of hydroxylamine hydrochloride was added. The isolated oxime XII (0.64 g., m.p. 182°) was treated as before, except that lithium aluminum hydride reduction was carried out for 2 hours in refluxing isopropyl ether. The infrared spectrum of ketone XVI from this second experiment showed that 74% of the original deuterium had remained in the molecule, very close to the percentage expected (72.2%) from the carbon-14 data of the first experiment.

(36) Performed by Mr. A. Tsiomis.

(37) Applications Laboratory, Instrument Division, Varian Associates, Palo Alto, Calif.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF OAK RIDGE NATIONAL LABORATORY, OAK RIDGE, TENN.]

Molecular Rearrangements. XVIII. The Deamination of *erythro*- and *threo*-1-Amino-1-phenyl-2-*p*-tolyl-2-propanol[1]

BY BEN M. BENJAMIN AND CLAIR J. COLLINS

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The deaminations of optically active *erythro*- and *threo*-1-amino-1-phenyl-2-*p*-tolyl-2-propanol (III) have been studied. Whereas the *erythro* isomer yields *p*-methylbenzhydryl methyl ketone (IV) in which inversion predominates over retention in the ratio of 74:26, the *threo* isomer produces IV in which the ratio of inversion to retention is 43:57. These data clearly establish the open carbonium character of the intermediates. The absence of α-phenyl-4′-methylpropiophenone (V) in either deamination product rules out methyl migration during both reactions.

Introduction

In the preceding paper[2] were reported the radiochemical and stereochemical consequences of the deaminations of D- and L-*erythro*-1-amino-1,2-diphenyl-2-propanol (I), labeled in the 1-phenyl group with carbon-14. The results of this investigation, together with the mechanistic interpretation, are given in Fig. 1. Since these data revealed[2] that the deaminations involved an average of 73.5% phenyl migration with inversion of configuration and 26.5% phenyl migration with retention of configuration, we did not invoke bridged ions[3] or neighboring group participation[4] in our rationalization of the mechanism of the reaction. Our conclusion rested on the assumption that topside attack of migrating phenyl through ions B or D to the extent of 26.5% (Fig. 1) must of necessity require complete cleavage of the carbon–nitrogen bond, which in turn demands that an open carbonium ion must be formed. Although it has been implied[5] that rearrangement accompanied by stereospecificity is synonymous with bridged or "nonclassical" ionic intermediates, such cannot be the case in the deamination of *erythro*-I, for one of the properties of neighboring group participation leading to bridged ions is its well-demonstrated[4] ability to enhance the rate considerably over the rate of the same reaction, were it to proceed solely through open carbonium ions. Since, in the deamination of I, the portion of the reaction which, stoichiometrically at least, could conceivably go through ini-

(1) This paper is based upon work performed at Oak Ridge National Laboratory, which is operated for the Atomic Energy Commission by Union Carbide Corporation. Portions of this research were presented at the Eighth Conference on Reaction Mechanisms, Princeton, N. J., September 8, 1960, and at the Conference on Use of Isotopes in Research and Industry, Copenhagen, Denmark, Sept. 15, 1960.

(2) B. M. Benjamin, P. Wilder and C. J. Collins, *J. Am. Chem. Soc.*, **83**, 3654 (1961).

(3) D. J. Cram, *ibid.*, **71**, 3863 (1949).

(4) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957).

(5) See however, A. Streitwieser, Jr., and C. E. Coverdale, *ibid.*, **81**, 4277 (1959).

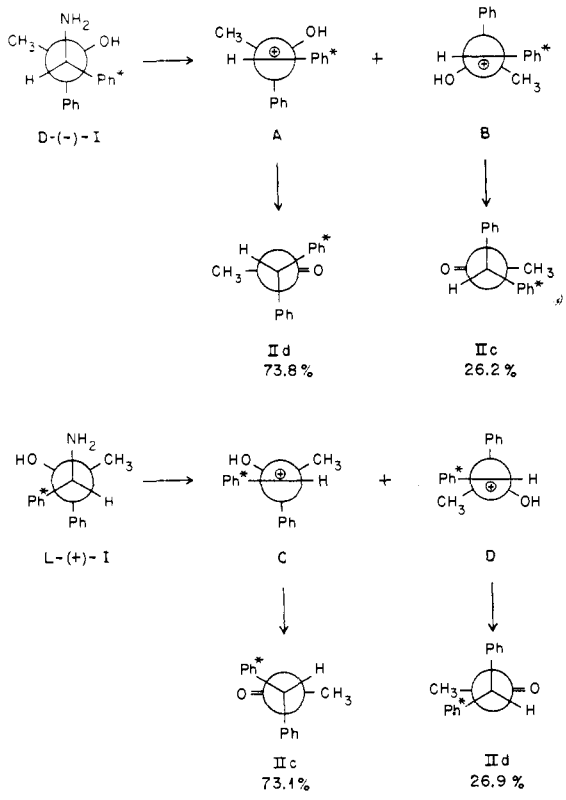


Fig. 1.

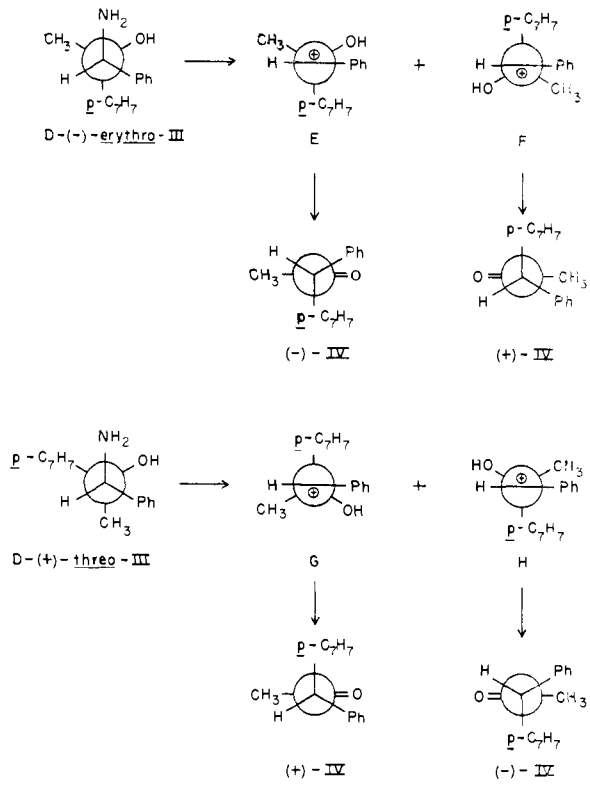


Fig. 2.

tially formed bridged ions does not even compete in rate with the open carbonium ion intermediates (by a ratio of 47:53),[2] it seems quite unnecessary to postulate that such bridged ions are important intermediates.

We believe that data of the foregoing type are of great significance in clarifying the nature of the intermediates in such deamination reactions, particularly in view of the confusion which currently exists[6] on this subject. We therefore prepared, resolved and subjected to deamination *threo*- and *erythro*-1-amino-1-phenyl-2-*p*-tolyl-2-propanol-2-C^{14} (III) (Fig. 2). Our purpose in studying the rearrangements of the foregoing compounds was twofold: (1) we anticipated that the deamination–rearrangement of *erythro*-III should follow the same course as for *erythro*-I, that is, the *p*-tolyl group should migrate with the same ratio of inversion to retention as was exhibited by the 2-phenyl group of *erythro-I*,[7] thus providing an independent check on the data[2] of Fig. 1; and (2) whereas *erythro*-III, on deamination, should provide the open carbonium ion E (Fig. 2) which can undergo *p*-tolyl migration with *inversion* through a *trans* transition state, *threo*-III should yield the open carbonium ion G which will lead to *retention* through a *trans* transition state. Thus *threo*-III should, upon deamination, provide a larger fraction of product of retained configuration than does the *erythro* isomer.

Methods and Results

Racemic *threo*-1-amino-1-phenyl-2-*p*-tolyl-2-propanol (III) was prepared by the addition of *p*-tolylmagnesium bromide to racemic 1-amino-1-phenyl-2-propanone. The *erythro* isomer of III was prepared by the addition of methylmagnesium iodide to α-amino-α-phenyl-4′-methylacetophenone. Both labeled and unlabeled samples of the *erythro* and *threo* isomers were synthesized. The racemic mixtures were resolved through their salts with (+)-tartaric, (+)-10-camphorsulfonic or (+)-camphoric acids. The configurations of *threo*- and *erythro*-III were related through the series of reactions shown in Fig. 3, the (+)-*threo* isomer and (−)-*erythro* isomer both possessing the D-configuration about the no. 1 carbon atom. In order to simplify Fig. 3, we have shown all interconversions in the D-configurations, although in actual fact L-(+)-phenylglycine was, in our experiments, converted to L-(+)-1-amino-1-phenyl-2-methylpropanol-2.

The two enantiomers of *erythro*-III were subjected to the same conditions of deamination previously[2] employed for the rearrangements of D- and L-*erythro*-I (Fig. 1); that is, the hydrochlorides were dissolved in an acetic acid–water mixture [25:75 by volume] and solid sodium nitrite was gradually

(6) J. D. Roberts and C. M. Regan, *J. Am. Chem. Soc.*, **75**, 2069 (1953), and J. D. Roberts and M. Halmann, *ibid.*, **75**, 5759 (1953), favor bridged-ion intermediates for the deamination of propyl-1-C^{14}-amine and of β-arylethyl-1-C^{14}-amines. R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver and J. D. Roberts, *ibid.*, **81**, 4390 (1959), favor non-classical ions in the deamination of cyclopropylcarbinylamine, and speak of "the considerable doubt which exists as to the exact nature of the carbonium ion formed by loss of nitrogen from the diazonium ion," and E. Renk and J. D. Roberts, *ibid.*, **83**, 879 (1961), refer to the "hot carbonium ion imbroglio."

(7) The *p*-tolyl group has been shown to have the same effective bulk as phenyl in certain stereoselective reactions [J. H. Stocker, P. Sidisunthorn, B. M. Benjamin and C. J. Collins, *ibid.*, **82**, 2913 (1960)]. Further, the *p*-tolyl/phenyl migration ratio in several deamination reactions is nearly unity [B. M. Benjamin and C. J. Collins, *ibid.*, **78**, 4952 (1956)].

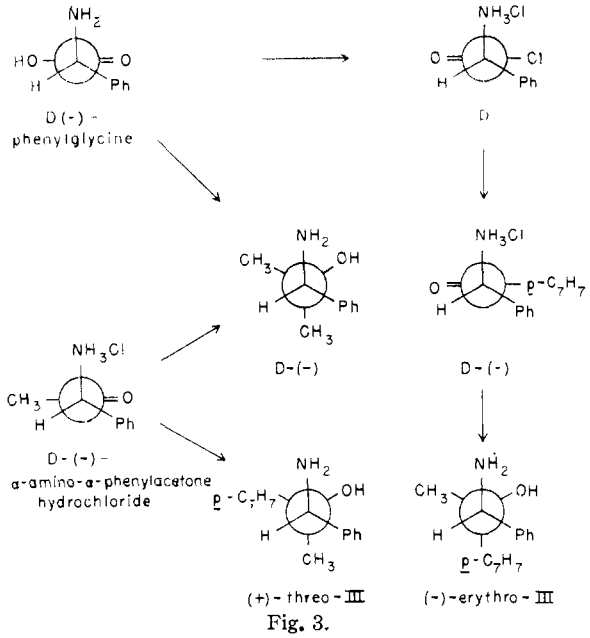


Fig. 3.

added. The temperature of reaction was 24–27°. The isotope-dilution method was used to determine the yields of (+)- and (−)-*p*-methylbenzhydryl methyl ketone (IV). The experiments were performed both with labeled and with unlabeled reactants in order to rule out the possibility of error owing to spurious radioactivity. The racemic diluents (labeled and unlabeled ketone IV) were distilled five times prior to use in the dilution experiments, only the center cuts being saved; the purity of the diluents was established through vapor phase chromatography of a sample of racemic IV which had been treated in an identical manner. The yields of (+)- and (−)-IV upon deamination of *erythro*-III were calculated by the method of Berson,[8] and the results are given in Table I (experiments 1–4). We were not successful in preparing (+)- or (−)-IV in optically pure form. It can be calculated from the data of Table I, and from the rotations of the ketonic fractions obtained upon deamination of *erythro*-III, however, that $[\alpha^{25}]_{IV} = \pm 58°$. The non-ketonic fraction, probably a mixture of glycols, which was held back on a column of alumina comprised 18–20% of total product.

Next the D-(+)-enantiomer of *threo*-III was subjected to the conditions of deamination, and the fractions of (+)- and (−)-IV produced were once again determined by the isotope-dilution method. The results are shown in experiments 5 and 6 of Table I. Determinations of the optical rotations of the ketone fractions produced reveal that the sign of rotation is positive ($[\alpha]^{25}$ +6.0°); this corresponds to a ratio of (+)-IV: (−)-IV of *56:44*, in very good agreement with the results given in experiments 5 and 6, Table I (see however, footnote *d*, Table I). As with the *erythro* isomer, there was a fraction which did not pass through a column of alumina in benzene, but which could be washed off with ethanol and which comprised 18–20% of total product.

(8) J. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4084 (1959).

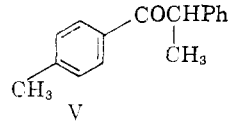
TABLE I

YIELDS OF (+)- AND (−)-IV BY ISOTOPE DILUTION UPON DEAMINATION OF OPTICALLY ACTIVE *erythro*-III AND *threo*-III

Expt.	Reactant	Total[a] ketone, %	Relative yield of enantiomer, % (+)-IV	(−)-IV
(1)[b]	(+)-*erythro*-III (−)-Hydrochloride	78.9	70.4	29.6
(2)[b]	(+)-*erythro*-III (−)-Hydrochloride	78.1	76.5	23.5
	Average:		73.5 ± 3	26.5 ± 3
(3)[c]	(−)-*erythro*-III (+)-Hydrochloride	79.0	25.5	74.5
(4)[c]	(−)-*erythro*-III (+)-Hydrochloride	..	24.4	75.6
	Average:		25.0 ± 0.5	75.0 ± 0.5
(5)[c]	(+)-*threo*-III (+)-Hydrochloride	82.3	57.4[d]	42.6[d]
(6)[c]	(+)-*threo*-III (+)-Hydrochloride	84.5	59.5[d]	41.5[d]
	Average:		58	42

[a] Upon chromatography with alumina, the non-ketonic fraction always amounted to 18–20% of total product. [b] Reactants radioactive. [c] Diluents radioactive. [d] The sensitivity of the method decreases as the ratio of enantiomers approaches unity; thus the error inherent in the radioactivity assays alone would prevent us from distinguishing an enantiomeric ratio of 56:44 from 50:50. The agreement in experiments 5 and 6 with each other and with the enantiomeric ratio of 56:44 calculated from the optical activity of the ketone fractions is therefore fortuitous.

Finally, the products of deamination of *erythro*-III and *threo*-III were analyzed with a vapor-phase chromatograph in order to determine whether the *p*-methylbenzhydryl methyl ketone (IV) produced had been contaminated with α-phenyl-4′-methylpropiophenone (V). The presence or absence of V

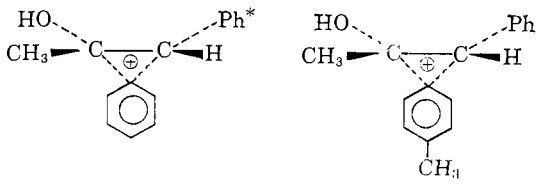


V

in the deamination products should establish whether or not either reactant had undergone methyl migration. Mixtures of authentic IV and V were subjected to vapor-phase chromatography, and it was established that ketone V could be detected in a single pass through the column in a mixture containing 1% V and 99% IV. The deamination products from *erythro*-III and *threo*-III, however, were both devoid of ketone V, thus establishing that neither reactant exhibits a measurable fraction of methyl migration.

Discussion

A comparison of the results listed in Table I for the deamination of *erythro*-1-amino-1-phenyl-2-*p*-tolyl-2-propanol (experiments 1–4) with the data previously reported[2] (Fig. 1) for the deamination of phenyl-labeled *erythro*-1-amino-1,2-diphenyl-2-propanol (I) reveals that D- and L-*erythro*-I and D- and L-*erythro*-III all suffer deamination under identical reaction conditions to yield ketones which have been formed with experimentally identical fractions of retention and inversion (see eq. 1–4 of Fig. 4). These results offer still further confirmation of the open carbonium ion character of the intermediates, for if the bridged ions M and N



M N

were involved, the well-known[9] ability of the *p*-tolyl group to enhance reaction rate through participation should of necessity require a larger fraction of N in the rearrangement of *erythro*-III than of M in the rearrangement of *erythro*-I. The data of Table I and Fig. 4, however, demonstrate identical fractions of inversion for both reactions, thus implying that M and N intervene in neither.

In eq. 5 of Fig. 4 is given the result for the deamination of D-*threo*-III with 43% inversion and 57% retention of configuration. If we compare eq. 5 with eq. 1–4, we see that the fraction of product formed with retention of configuration in the deamination of *threo*-III is significantly greater than that formed in the deaminations of *erythro*-I and *erythro*-III. This phenomenon was predicted (see Introduction), and can be ascribed to the fact that migration of *p*-tolyl with retention in the *threo* isomer follows a path requiring a lower activation energy than does migration of *p*-tolyl with retention in the *erythro* isomer. Thus ion G (Fig. 2) allows migration of *p*-tolyl with retention through a *trans* transition state, whereas migration from ion F with retention (*erythro* series) requires eclipsing of phenyl and methyl in the *cis* transition state.

Experimental

***erythro*-1-Amino-1-phenyl-2-*p*-tolyl-2-propanol (*erythro*-III).**—The monoxime of 4-methylbenzil (42.2 g.), prepared from 4-methyldesoxybenzoin by the method of Taylor,[10] was dissolved in 120 ml. of ethanol and treated with 160 g. of stannous chloride dihydrate dissolved in 200 ml. of concentrated hydrochloric acid. The solution was heated on the steam-bath for 1.5 hours and allowed to stand at room temperature overnight. Most of the alcohol was evaporated from the solution with an air jet. The reaction mixture was cooled on an ice-bath and 10% sodium hydroxide was added slowly until all the tin salts were dissolved. Ice was added occasionally to keep the solution cold. The free 4-methyl-aminodesoxybenzoin[11] was removed by extracting the solution several times with ether, about 1.5 liters.

Dry hydrogen chloride was passed into the ether solution until precipitation was complete. The aminoketone hydrochloride, 23.5 g. (51% yield), was collected on a filter and dried in vacuum. The yield was not improved in several runs. The dry powdered aminoketone hydrochloride (42.5 g.) was added slowly to a Grignard reagent prepared from one mole of methyl iodide and one mole of magnesium. The reaction mixture was heated to reflux for 2 hours and then it was hydrolyzed with saturated ammonium chloride solution. The ether layer was separated and the ether was evaporated. After two crystallizations from hexane, the amino-alcohol, 26 g. (67% yield), had a melting point of 101°.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.52; H, 7.99.

A sample of the aminoalcohol was dissolved in a small amount of ethanol and 6 *M* hydrochloric acid was added. The precipitated aminoalcohol hydrochloride was crystallized from alcohol. It did not melt but sublimed above 300°.

(9) J. G. Burr, Jr., *J. Am. Chem. Soc.*, **75**, 5008 (1953); **77**, 6721 (1955); *Chemistry & Industry*, 850 (1954).

(10) W. J. Taylor, *J. Chem. Soc.*, 2026 (1931).

(11) A. McKenzie and A. D. Wood, *Ber.*, **71B**, 358 (1938).

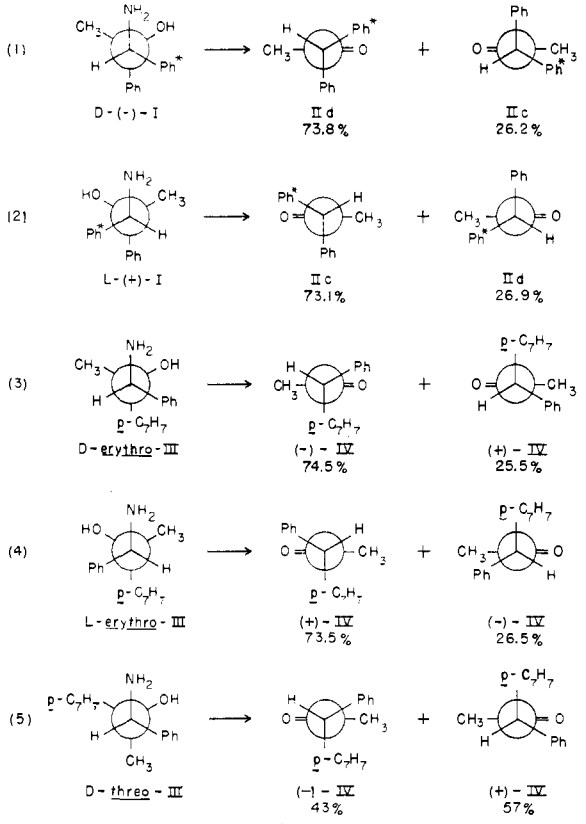


Fig. 4.

Anal. Calcd. for $C_{16}H_{20}NOCl$: C, 69.17; H, 7.26. Found: C, 69.28; H, 7.21.

Resolution of *erythro*-III.—To a solution of 26 g. of the racemic aminoalcohol in 100 ml. of ethanol was added 30 g. of *d*-tartaric acid in 100 ml. of water. Crystallization was complete after 2 hours; $[\alpha]^{24}D$ 2.9° (water). A second and third crystallization of the aminoalcohol *d*-tartaric acid salt did not change the rotation significantly; $[\alpha]^{24}D$ 2.1° (water), m.p. 227°.

Anal. Calcd. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44. Found: C, 61.39; H, 6.55.

The free (+)-aminoalcohol was recovered from the above *d*-tartaric acid salt by treating an aqueous solution of it with dilute sodium hydroxide. It was crystallized twice from hexane and had a melting point of 76°, $[\alpha]^{24}D$ 15.3° (ethanol).

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.82; H, 8.03.

An alcohol solution of the (+)-aminoalcohol was treated with dilute hydrochloric acid. The precipitated salt was crystallized from alcohol twice. It did not melt but sublimed above 300°; $[\alpha]^{24}D$ −45.5° (ethanol).

Anal. Calcd. for $C_{16}H_{20}NOCl$: C, 69.17; H, 7.25. Found: C, 69.67; H, 7.24.

The mother liquor from the *d*-tartrate salt of the aminoalcohol was treated with dilute base and the aminoalcohol recovered from this, 19 g., was treated with 16 g. of *d*-camphoric acid in 100 ml. of 50% ethanol. The crystals which separated were recrystallized twice from dilute alcohol; m.p. 98° dec., $[\alpha]^{24}D$ +12.2° (ethanol).

Anal. Calcd. for $C_{26}H_{35}NO_5 \cdot 1/2H_2O$: C, 69.30; H, 8.05. Found: C, 69.48; H, 8.54.

The *d*-camphoric acid salt was treated with dilute sodium hydroxide and the free (−)-aminoalcohol was obtained; m.p. 76°, $[\alpha]^{24}D$ −15.5° (ethanol).

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 8.94. Found: C, 79.80; H, 7.98.

The (+)-aminoalcohol hydrochloride prepared from the free (−)-aminoalcohol sublimed above 300°; $[\alpha]^{24}D$ 45.7° (ethanol).

Anal. Calcd. for $C_{16}H_{20}NOCl$: C, 69.17; H, 7.25. Found: C, 69.15; H, 7.36.

erythro-1-Amino-1-phenyl-2-*p*-tolyl-2-propanol-2-C^{14}.—Carboxyl-labeled phenylacetic acid was converted to carbonyl-labeled 4-methyldesoxybenzoin by the Friedel-Crafts reaction with toluene. The reaction sequence then was the same as for the preparation and resolution of the non-radioactive aminoalcohol. Starting with 61 g. of carbonyl-labeled 4-methylbenzoin, there was obtained 3 g. of resolved radioactive aminoalcohol hydrochloride, $[\alpha]^{24}D$ −45.0° (ethanol), 7.667 ± 0.023 mc./mole. Subsequent recovery of material from the mother liquors produced a second sample weighing 4.5 g., $[\alpha]^{24}D$ −43.5°, 7.562 ± 0.012 mc./mole.

The (−)-α-Amino-α-phenyl-4′-methylacetophenone.—Phenylglycine was resolved by the method of Ingersoll.[12] Phosphorus pentachloride, 51 g., was mixed with a suspension of 34 g. of phenylglycine hydrochloride, $[\alpha]$ −144° (water), in 500 ml. of acetyl chloride. The mixture was stirred for 3 hours and then the solid was collected on a filter, washed with hexane, and dried in a vacuum desiccator. The α-aminophenylacetyl chloride hydrochloride, 28 g., thus formed was added slowly to a mixture of 110 g. of anhydrous aluminum chloride in 310 ml. of toluene while the reaction mixture was cooled by an ice-salt-bath. The mixture then was heated to 50–60° for an hour, after which time ice and concentrated hydrochloric acid were carefully added. A crystalline material remained in the aqueous phase. It was collected on a filter and washed with ether. The crude aminoketone hydrochloride was crystallized from water; $[\alpha]^{25}D$ −187° (*c* 1, water), m.p. 261°. More product was recovered from the mother liquor; $[\alpha]^{25}D$ −188°.

Anal. Calcd. for $C_{15}H_{16}ClNO$: C, 68.88; H, 6.16. Found: C, 68.79; H, 6.16.

(+)-*erythro*-III was synthesized by the procedure analogous to that described for racemic *erythro*-III except that optically active α-amino-α-phenyl-4′-methylacetophenone was used. The aminoalcohol III was isolated and converted to the hydrochloride salt which was crystallized from ethanol–water; $[\alpha]^{25}D$ 45.1° (*c* 1, ethanol).

1-Phenyl-1-*p*-tolylpropanone (IV).—Two methods were used to synthesize this ketone. The procedure found in the literature,[13] starting with phenylacetone, gave a product which had an infrared spectrum identical with that of the ketone obtained by the second method which was nitrous acid rearrangement of the aminoalcohol *erythro*-III. Similar derivatives of the ketone obtained by both methods had the same melting points and mixed melting points. The material used in isotope-dilution studies was obtained by treating the aminoalcohol with nitrous acid in a manner similar to that described in the following section. The crude ketone product was placed on a column of Fisher alumina which was eluted with 50% benzene in hexane. The solvents were evaporated and the ketone was distilled five times, b.p. 114–115° at 0.15 mm. A solution of 1.5 g. of the above ketone in 10 ml. of pyridine and 10 ml. of alcohol was treated with 1.5 g. of hydroxylamine hydrochloride. The mixture was boiled for 2 hours and then the oxime was isolated and crystallized four times from alcohol; m.p. 155°. The oxime, prepared from an optically active sample of ketone, $[\alpha]D$ 27°, did not have a detectable rotation.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.34; H, 7.16. Found: C, 80.15; H, 7.11.

The thiosemicarbazone of ketone IV was prepared by boiling for 2 hours a mixture of 0.93 g. of thiosemicarbazide and 2.3 g. of ketone in 40 ml. of 75% alcohol containing 2 ml. of acetic acid and 3 ml. of pyridine. Crystals separated from the solution when it had been left undisturbed at room temperature for 18 hours. They were recrystallized five times from alcohol; m.p. 160°. Optically active ketone, $[\alpha]D$ 27°, was converted into its thiosemicarbazone. The crude derivative was triturated with hexane and its rotation was determined; $[\alpha]$ 13° (ethanol). Five crystallizations of the material resulted in isolation of racemic thiosemicarbazone, m.p. 160°.

Anal. Calcd. for $C_{17}H_{19}N_3$: C, 68.65; H, 6.44. Found: C, 68.61; H, 6.44.

(12) A. W. Ingersoll, *J. Am. Chem. Soc.*, **47**, 1168 (1925).

(13) E. M. Schultz, U. S. Patent 2,703,329 (Mar. 1, 1955).

1-Phenyl-1-*p*-tolylpropanone-2-C^{14}.—A sample of pure racemic radioactive IV was prepared from radioactive aminoalcohol in exactly the same way as the non-radioactive material. A gram of this material was converted to thiosemicarbazone and assayed for carbon-14 content; 7.560 ± 0.002 mc./mole.

threo-1-Amino-1-phenyl-2-*p*-tolyl-2-propanol (*threo*-III).—Phenylacetone, 36.7 g., was dissolved in 250 ml. of ether. Hydrogen chloride gas was added below the surface of the solution at the rate of 3 bubbles per second. Isoamyl nitrite, 26.0 g., was then added dropwise over a period of a half-hour. Hydrogen chloride was passed through the solution for another hour. The ether solution then was washed thoroughly with ice-water to remove hydrochloric acid. Isonitrosophenylacetone was recovered by washing the ether solution four times with 75-ml. portions of 10% sodium hydroxide. The combined alkaline extracts were made neutral with hydrochloric acid and the precipitated isonitrosophenylacetone[14] was purified by crystallization from alcohol; m.p. 165°. The oxime was dissolved in 100 ml. of alcohol containing 15 ml. of concentrated hydrochloric acid; 10% palladium-on-carbon catalyst, 3.5 g., was added and the compound was hydrogenated at atmospheric pressure. The reaction was interrupted when 5 liters of hydrogen was consumed and the catalyst was removed by filtration of the hot mixture. Colorless crystals of 1-amino-1-phenylacetone hydrochloride (12 g.)[15] separated when the filtrate was cooled, m.p. 190° dec. The dry powdered aminoketone hydrochloride was added to the Grignard reagent prepared from 115 ml. of *p*-bromotoluene and 24 g. of magnesium in 600 ml. of ether. The mixture was stirred and heated for 1 hour. The complex was decomposed with ammonium chloride solution and racemic *threo*-III was recovered from the ether layer and crystallized from hexane; m.p. 94°.

Resolution of α-Amino-α-phenylacetone.—A solution of 15.2 g. of the racemic aminoketone hydrochloride in 100 ml. of water was mixed with 23.3 g. of (+)-10-camphorsulfonic acid. The solution was made homogeneous by stirring. Within a few minutes a precipitate began to form. Precipitation was complete after a half-hour and the crystals were collected on a filter and dried; $[\alpha]^{25}D$ −153° (*c* 0.5, ethanol). The filtrate was concentrated and more of the latter compound was collected; $[\alpha]^{24}D$ −149° (*c* 0.5, ethanol). The filtrate from this crop was set aside and marked A. The two crops of crystals were combined and crystallized twice from alcohol; yield 6.5 g., $[\alpha]^{24}D$ −159° (*c* 0.5, alcohol).

Anal. Calcd. for $C_{19}H_{27}NO_4S$: C, 59.84; H, 7.13. Found: C, 60.06; H, 7.19.

The (+)-camphorsulfonic acid salt (6.5 g., 0.017 mole) was dissolved in ethanol and an aqueous solution of 4.5 g. (0.098 mole) of barium chloride was added. All of the solvent was evaporated on the steam-bath in a current of air. The solid residue was triturated several times with hot alcohol. The combined alcohol solutions were concentrated and cooled. Crystals of pure (−)-α-amino-α-phenylacetone hydrochloride separated, $[\alpha]^{25}D$ −359° (*c* 0.5, ethanol). It was crystallized from ethanol; $[\alpha]^{25}D$ −360° (*c* 0.5, ethanol), m.p. 202° dec. (capillary).

Anal. Calcd. for $C_9H_{12}ClNO$: C, 58.22; H, 6.52. Found: C, 58.48; H, 6.49.

The filtrate marked A, described above, was left undistributed for 24 hours during which time needle-shaped crystals had formed in it. These were collected on a filter and washed with cold ethanol. They were found to be pure resolved (+)-α-amino-α-phenylacetone hydrochloride, $[\alpha]^{25}D$ +360° (*c* 0.5, ethanol), m.p. 203° dec. Rotation of the compound was not changed by further crystallization.

Anal. Calcd. for $C_9H_{12}ClNO$: C, 58.22; H, 6.52. Found: C, 58.28; H, 6.55.

Resolution of *threo*-III.—A solution of 22 g. of racemic *threo*-III in 50 ml. of ethanol was mixed with 15 g. of (+)-tartaric acid in 50 ml. of water. The solid salt which separated was collected on a filter and fractionally crystallized from ethanol–water mixture. There remained a small quantity of salt after five cycles of crystallization; $[\alpha]^{25}D$ 9.7° (*c* 1, water).

(14) A. Kolb, *Ann.*, **291**, 280 (1896).

(15) S. Gabriel, *Ber.*, **41**, 1151 (1908).

Anal. Calcd. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44. Found: C, 60.72; H, 6.44.

The tartaric acid salt was dissolved in water and treated with dilute sodium hydroxide and the liberated aminoalcohol was crystallized from hexane; $[\alpha]^{25}D$ −64.5° (*c* 1, ethanol), m.p. 110°.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94. Found: C, 79.74; H, 7.95.

The aminoalcohol was dissolved in ethanol and treated with 6 molal hydrochloric acid. The hydrochloride salt which separated was crystallized twice from water; $[\alpha]^{25}D$ −50° (ethanol).

A portion of the filtrate from the tartaric acid salt was treated with dilute sodium hydroxide. The free aminoalcohol which was recovered was fractionally crystallized from hexane. A small amount of partially resolved amine was recovered, $[\alpha]^{25}D$ 58°, m.p. 109–110°.

(+)-*threo*-III.—Powdered solid (−)-α-amino-α-phenylacetone, 16 g., [α] −359°, was added in small portions to the Grignard reagent from 14 g. of magnesium and 100 g. of *p*-bromotoluene. The reaction mixture was worked up in the same way as described in a previous section for racemic *threo*-III. The free aminoalcohol was converted to the hydrochloride salt, yield 10 g., $[\alpha]^{25}D$ 50.3° (ethanol), m.p. 257–258° (capillary).

Anal. Calcd. for $C_{16}H_{20}ClNO$: C, 69.17; H, 7.25. Found: C, 68.69; H, 7.24.

A small sample of the aminoalcohol hydrochloride was dissolved in water and the solution was treated with sodium hydroxide. The free aminoalcohol III which separated was crystallized from hexane; $[\alpha]^{25}D$ 64.0° (ethanol), m.p. 110°.

Anal. Calcd. for $C_{16}H_{11}NO$: C, 79.63; H, 7.94. Found: C, 80.28; H, 7.81.

The (−)-1-Amino-1-phenyl-2-methyl-2-propanol.—The ethyl ester of phenylglycine hydrochloride was prepared from phenylglycine hydrochloride, [α] −144°, as described by McKenzie and Wills.[16] The ester (4.6 g., 0.021 mole) was treated with the Grignard reagent from 0.21 mole of methyl bromide and 0.21 mole of magnesium. The reaction mixture was worked up in the usual way and 2 g. of free aminoalcohol was recovered and crystallized from hexane; [α] −11.2° (*c* 1, ethanol), m.p. 53–53.5°. The (−)-aminoalcohol was also prepared by the action of methyl Grignard reagent on (−)-α-amino-α-phenylacetone; $[\alpha]^{25}D$ −8.1; m.p. and mixed m.p. with the sample prepared from (−)-phenylglycine 52–53.5°.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.72; H, 9.08.

A solution of the aminoalcohol in ether was treated with dry hydrogen chloride. The ether was evaporated and the residual amine hydrochloride was crystallized from benzene containing a little ethanol; $[\alpha]^{25}D$ −10.4° (*c* 1, ethanol), m.p. 209–210° (capillary).

The aminoalcohol hydrochloride prepared from (−)-α-amino-α-phenylacetone had the same rotation and melting point.

Anal. Calcd. for $C_9H_{16}ClNO$: C, 59.55; H, 8.00. Found: C, 59.74; H, 7.86.

Reaction of *erythro*-(+)- of -(−)-III and (+)-*threo*-III with sodium nitrite.—The following description is typical of the method used for the rearrangement of *erythro*-III and the analysis of the product by isotope-dilution technique. A sample of the hydrochloride salt of *erythro*-III, $[\alpha]^{24}D$ −45.0°, 7.667 ± 0.023 mc./mole, weighing 2.4296 g., was dissolved in 100 ml. of 25% acetic acid solution. To this was added, over a 5-minute period, a solution of 1.3 g. of sodium nitrite in 10 ml. of water. The solution was allowed to stir (magnetic bar) for 2 hours at room temperature. At the end of this time the mixture was diluted with water and the oily product was recovered by three ether extractions. The ether extracts were washed first with water, then with dilute sodium bicarbonate solution and again with water. The ether was evaporated and 2.017 g. of an oily material remained, $[\alpha]^{24}D$ 24.7° (ethanol). All of the product was transferred to a 100-ml. volumetric flask, the solution diluted to the mark with ethanol and divided into two 50-ml. aliquots. To aliquot 1 was added 1.0041 g. of pure non-radioactive 1-phenyl-1-*p*-tolylpropanone (IV) and to aliquot 2 was added 1.0095 g. of IV. The solvent was evaporated from aliquot 1 and the ketone material was placed on a 8″ × 1″ column of Fisher alumina and the column was eluted with 25% benzene in hexane. The ketone recovered from the eluent was completely racemic. This was converted to the thiosemicarbazone derivative which was crystallized three times and assayed for carbon-14 content; 3.339 ± 0.016 mc./mole. The ketone in aliquot 2 was converted directly to its thiosemicarbazone derivative which was crystallized five times. The portion of the derivative recovered in this way was not optically active, m.p. 160°. It was assayed for carbon-14 content; 3.200 ± 0.0014 mc./mole. From the above data it can be calculated that the total yield of ketone IV, racemic and (+), is 1.5494 g., 78.9%, the yield of (+)-IV is 1.079 g. or 70.4% of the total and the yield of (−)-IV is 0.4715 g. or 29.6% of the total.

In a second run 4.2872 g. of aminoalcohol hydrochloride, $[\alpha]^{25}D$ −43.5° (alcohol), 7.562 mc./mole, in 200 ml. of 25% acetic acid was treated with 4 g. of sodium nitrite in 20 ml. of water. The product, $[\alpha]^{25}D$ 25°, was dissolved in 250 ml. of alcohol in a volumetric flask and this solution was divided into three aliquots; no. 1, 50 ml., and no. 2 and 3, 100 ml. each. To aliquot 1 was added 1.0046 g. of non-radioactive ketone IV. The mixture was made homogeneous and the optically active ketone was caused to become racemic by treating the solution with 10 drops of 10% sodium hydroxide and warming. The ketone was then converted to the thiosemicarbazone and crystallized four times; m.p. 160°, 2.648 ± 0.014 mc./mole. The total yield of ketone in aliquot 1 was 0.5413 g., 78.1%. To aliquot 2 was added 1.0136 g. of IV. The ketone was converted directly to the thiosemicarbazone and crystallized five times; m.p. 160°, 3.610 ± 0.008 mc./mole. From these data the yield of (+)-IV was found to be 76.5% and the yield of (−)-IV was 23.5% of the total.

In a third run 4.3101 g. of non-radioactive aminoalcohol hydrochloride, $[\alpha]^{25}D$ 45.7°, was deaminated with 4 g. of sodium nitrite as described above. The product, $[\alpha]^{25}D$ −23°, was dissolved in 200 ml. of alcohol in a volumetric flask and divided into three aliquots: no. 1, 50 ml.; no. 2, 50 ml., and no. 3, 100 ml. To aliquot 1 was added 0.7104 g. of ketone IV, 7.560 ± 0.002 mc./mole, and the solvent was evaporated; the ketone was passed through a column of Fisher alumina and recovered as described above. It was completely racemic. Its thiosemicarbazone derivative was prepared; 3.843 ± 0.010 mc./mole. The total yield of (+)- and (−)-IV in aliquot 1 of run 3 was, therefore, 0.8701 g. or 79% of the theoretical yield. To aliquot 2 was added 1.0082 g. of IV, 7.560 mc./mole. The thiosemicarbazone of the ketone was prepared as described above and assayed for carbon-14; 4.681 ± 0.020 mc./mole. The yield of (−)-IV was then 74.5% of the total ketone present and the yield of (+)-IV was 25.5%. To aliquot 3 was added 1.0151 g. of IV, 7.560 mc./mole. As before, the thiosemicarbazone was recovered and assayed; 3.524 ± 0.004 mc./mole. The yield of (−)-ketone IV in aliquot 3 was, therefore, 75.6% of the total ketone and the yield of (+)-IV was 24.4%.

(+)-*threo*-III, [α] 50.3°, 2.573 g., was treated with sodium nitrite and the product, [α] 12° (ethanol), was worked up in exactly the same way as described for the *erythro* isomer. The product was divided into two equal aliquots. To one aliquot was added 0.9079 g. of 1-phenyl-1-*p*-tolylacetone (IV), 7.7373 ± 0.027 mc./mole. The ketone was racemized on a column of alumina and then converted to the thiosemicarbazone which was crystallized three times and assayed for carbon-14 content; 3.796 ± 0.013 mc./mole. Thus the total yield of this ketone was 0.8555 g. (82.3%). A small amount of hydroxylic material, 0.235 g., [α] 9.6°, was recovered from the alumina column by eluting it with 5% methanol in ether. To the second aliquot was added 0.9977 g. of IV. It was converted to the thiosemicarbazone and the racemic portion of this derivative was isolated and assayed for carbon-14; 3.992 ± 0.022 mc./mole. The yield of (+)-IV was 0.4901 g. (57.4% of the ketonic fraction). In a second run the yield of ketone IV was 84.5% and the yield of (+) IV was 59.5% of the total ketone fraction.

In a separate experiment, 1.1155 g. of (+)-*threo*-III hydrochloride was treated with sodium nitrite in acetic acid. The product had $[\alpha]^{25}D$ 10.9°. A drop of 10% sodium hydroxide was added to the polarimeter tube and

(16) A. McKenzie and G. O. Wills, *J. Chem. Soc.*, **127**, 283 (1925).

the solution was made homogeneous. The ketone was racemized and the gross material now had $[\alpha]^{25}D$ 4.9°. Since the average yield of ketone is 83.4%, the ketonic part of the product had $[\alpha]^{25}D$ 7.2°. A portion of the product was passed through a column of Fisher alumina. The hydroxylic material recovered from the column had $[\alpha]^{25}D$ 14.5°.

The deamination products of both *erythro*- and *threo*-III were analyzed by gas–liquid chromatography.[17] The chromatogram of the ketonic fraction indicated the presence of only one substance. It was found that 1% of *p*-tolyl α-methylbenzyl ketone in the presence of IV could be detected. Therefore, no methyl migration takes place.

(17) A Burrell Kromo-Tog model K-1, fitted with a 1/4-inch column backed with Apiezon supported on Kromat-F-13, was used.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, IND.]

Steric Hindrance as a Factor in the Alkylation of Ambident Anions: The Alkylation of Potassium 2,6-Di-*t*-butylphenoxide[1,2]

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The reactions of potassium 2,6-di-*t*-butylphenoxide provide a particularly clear demonstration of the importance which steric effects may assume in the alkylation of ambident anions: methyl iodide gives an 88% yield of ether and 6% carbon alkylation; ethyl iodide gives an 11% yield of ether and 66% carbon alkylation; isopropyl iodide gives exclusively carbon alkylation.

In an earlier paper it was emphasized that steric hindrance is one of the prime factors in considering the alternate reaction paths available to an ambident anion.[4] The present study, which employs the 2,6-di-*t*-butylphenoxide ion, a well defined and relatively inflexible structure, provides a demonstration that under the proper auspices steric hindrance is an overriding factor. As can be seen from Table I, on treatment with a set of alkyl halides of increasing steric requirement an unmistakable shift from oxygen to carbon alkylation occurs.[4a]

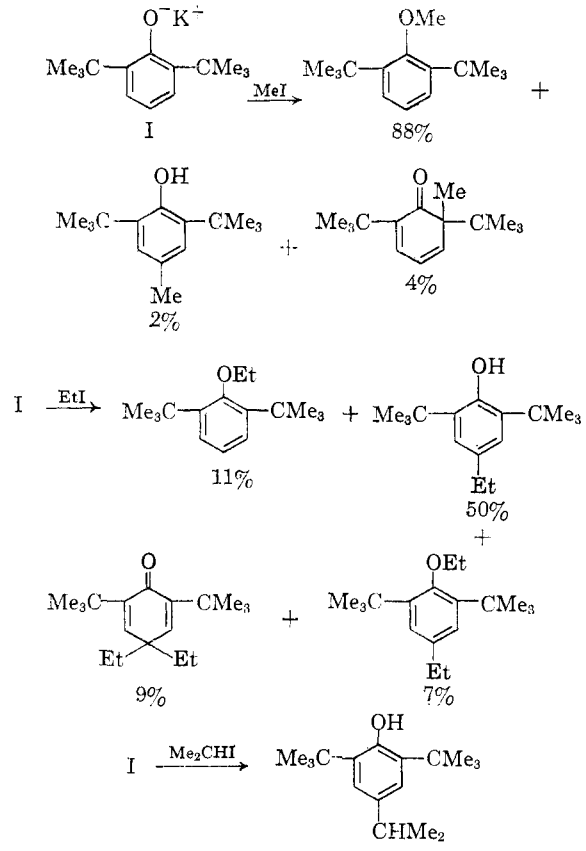
TABLE I

ALKYLATION OF POTASSIUM 2,6-DI-*t*-BUTYLPHENOXIDE

Alkyl iodide	O-Alkylation, %	C-Alkylation, %
Methyl	88	6
Ethyl	11	66[a]
Isopropyl[b]	0	100

[a] This is a conservative figure almost certainly too low by at least 8% (*cf.* Experimental). [b] Here only 28% of the alkyl halide undergoes substitution; elimination of hydrogen iodide accounts for the remainder.

The detailed accounting of products is of some interest in its own right and is summarized in the following equations; structure proofs are discussed in the Experimental section.



In a study which antedated ours, Coffield, Filbey, Ecke and Kolka[5] called attention to significant differences in behavior in the reactions of 2,6-diisopropylphenol and 2,6-di-*t*-butylphenol. Of particular interest is the difference observed on treating the sodium salts of these phenols with benzoyl chloride; the diisopropylphenoxide gives a 65% yield of 2,6-diisopropylphenyl benzoate whereas with the di-*t*-butylphenoxide none of the corresponding ester is isolated; instead the product is 2,6-di-*t*-butyl-4-benzoylphenol (24% yield). Also of interest is the observation of Cohen[6] that the methyl ethers (II) can be prepared in 58–65% yields by treatment of the sodium salts of the corresponding phenols with methyl iodide.

The importance of steric hindrance in controlling the course of ambident anion alkylations has been recognized for several other types of anions. Thus,

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(2) Paper III in the series, "The Chemistry of Ambident Anions."

(3) XR Fellow of the Purdue Research Foundation 1958–1960.

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

(4a) As anticipated, the reaction of methyl, ethyl or isopropyl iodide with potassium phenoxide under the identical conditions employed with potassium 2,6-di-*t*-butylphenoxide gives, in each instance, 75–85% yields of the pure ether and no carbon alkylation product could be isolated. We are indebted to Mr. Richard Derby of this Laboratory for these experiments.

(5) T. H. Coffield, A. H. Filbey, G. G. Ecke and A. J. Kolka, *ibid.*, **79**, 5019 (1957).

(6) L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957).