spectra of the reaction products to be analyzed. The results are

| | Frequencies employed, cm.$^{-1}$ | N,N-Dimethylcyclohexylamine hydrochloride, mole, % | Trimethylamine hydrochloride, mole % |
|---|---|---|---|
| Run 3 (3 hr.) | 993, 1005 | 93.8 | 6.2 |
| | 900, 993 | 93.2 | 6.8 |
| Run 4 (36 min.) (expanded scale) | 993.7, 1003.8 | 92.9 | 7.1 |
| | Average | 93.3 | 6.7 |

The yields of mixed hydrochlorides amounted to 98 and 105% of theoretical.

(B) ***trans*-4-*t*-Butylcyclohexyltrimethylammonium Chloride (*trans*-II).**—The reaction, carried out at 75° for 150 min., gave an infrared spectrum (10% chloroform solution) which showed no detectable amount of starting material. The absorption intensity at 993.7 cm.$^{-1}$ (expanded scale) showed that no more than 2% (by weight) of trimethylamine hydrochloride could be present. Comparison of the spectrum with that of the product from a reaction of *trans*-4-*t*-butylcyclohexyltrimethylammonium iodide isolated in such a way that all trimethylamine should have been removed by aqueous extraction and evaporation indicated that the percentage of trimethylamine hydrochloride was 0. The weight of hydrochloride isolated corresponded to 100.2% of the theoretical amount of *trans*-4-*t*-butyl-N,N-dimethylcyclohexylamine hydrochloride. For the characterization of the tertiary amine formed, another run was made in a large scale (fourfold), carried out under a nitrogen atmosphere, using a reflux condenser. The tertiary amine was isolated as before, and purified by freeing the amine, and reforming the hydrochloride. *trans*-4-*t*-Butyl-N,N-dimethylcyclohexylamine (*trans*-IV) hydrochloride was isolated in 90% yield, and its infrared spectrum was identical to that of the *trans*-IV hydrochloride prepared above.

(C) ***cis*-4-*t*-Butylcyclohexyltrimethylammonium Chloride (*cis*-II).**—Since the presence of starting material in the product would interfere with the method of analysis, it was first shown by examination of the 890 cm.$^{-1}$ region of the infrared spectrum (where the starting material has strong absorption) that there was less than 2% of the quaternary chloride (*cis*-II) in the product. Since there was a decision as to the choice of the base-line to be made, each calculation was made twice, once using each of two extreme base-lines. The results were again calculated employing pairs of simultaneous equations at two frequencies (993.7 and 1375 cm.$^{-1}$), the data for the 993.7 band being obtained from an expanded scale spectrum of that region. The values used were the average of those presented here.

| | 4-*t*-Butyl-N,N-dimethylcyclohexylamine hydrochloride, % | Trimethylamine hydrochloride, % |
|---|---|---|
| Run 10 | 8.8 | 91.2 |
| (180 min.) | 10.4 | 89.6 |
| Run 12 | 9.0 | 91.0 |
| (150 min.) | 10.4 | 89.6 |

*The weight of hydrochloride isolated from run 12* corresponds to 97.4% of that calculated for a mixture of the composition indicated by the data above.

To characterize the tertiary amine and olefin formed, another run was made in a larger scale (fourfold), carried out as in the case of the *trans*-quaternary ammonium salt. The olefin fraction was extracted with methylene chloride, and after evaporation of the solvent, vacuum transfer and drying with magnesium sulfate, 41% of the olefin was isolated, $n^{25}\mathrm{D}$ 1.4565 (reported[14] for 4-*t*-butylcyclohexene $n^{20}\mathrm{D}$ 1.4583). There was good agreement of the spectrum of this olefin with that of 4-*t*-butylcyclohexene obtained with a Baird instrument.[38] *cis*-4-*t*-Butyl-N,N-dimethylcyclohexylamine (*cis*-IV) was isolated in 3.5% yield by a procedure identical to that employed in the case of *trans*-amine. The infrared spectrum of this sample was identical with that of the *cis*-IV prepared above.

**Attempted Reaction of Cyclohexyltrimethylammonium Chloride (III) with Aqueous Potassium Hydroxide.**—When 156 mg. (0.882 mmole) of III was heated for 3.5 hr. with 5.00 ml. of 0.97 *N* potassium hydroxide at 75°, extraction from chloroform gave 151 mg. (97%) of hygroscopic residue with an infrared spectrum essentially identical with that of the starting material. When a similar reaction was carried out by treating 159 mg. of III with 1.00 ml. of 4.54 *N* potassium hydroxide in a sealed tube in a steam-bath for 16 hr. the residue from chloroform of 177 mg. (111%) had an infrared spectrum which contained all the bands of the starting material and, in addition, broad absorption in the ranges of 3040–3500 and 1035–1200 cm.$^{-1}$.

**Dissociation Constants of *cis*- and *trans*-I Hydrochlorides.**—The apparent dissociation constants, determined in 66% dimethylformamide–34% water, did not differ sufficiently to provide a method of conformational analysis. The $pK_a$ of *cis*-4-*t*-butylcyclohexylamine hydrochloride was 10.27 and that for *trans*-4-*t*-butylcyclohexylamine hydrochloride 10.35.[39]

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[38] This spectrum was provided for Prof. E. Eliel by Prof. S. Winstein to both of whom we are indebted for its use.

[39] We are indebted to Dr. H. Boaz, Eli Lilly and Co., Indianapolis, Ind., for these determinations. The reported relative error is ±0.05.

URBANA, ILL.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

# The Stereochemical Course of the Raney Nickel-catalyzed Cleavage of 2-Arylethanols[1,2]

BY WILLIAM A. BONNER AND THOMAS W. GREENLEE

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The stereochemical course of the Raney nickel-catalyzed C1–C2 cleavage of optically active (−)-2-methyl-2-phenyl-1-butanol (B) to 2-phenylbutane has been investigated, with the observation that B yielded (+)-2-phenylbutane ((+)-F) of 68–70% optical purity. Comparative optical rotatory data are presented which strongly suggest that the conversion of B to (+)-F proceeded with predominant *inversion* of configuration. These conclusions are in accord with a mechanism involving concerted SN2 attack by surface-adsorbed hydrogen at the C2 of those 2-arylethanols undergoing Raney nickel-catalyzed C1–C2 fission. (−)-2-Phenylbutane (F) has been found to undergo slow racemization when heated with Raney nickel in refluxing ethanol. Duplication of such experiments using deuterated Raney nickel in deuterioethanol led to the exchange of 1–8 D atoms/molecule in the F substrate. Racemization and exchange rate data are presented which argue that the H–D exchange at C2 in F is a stereospecific process occurring with *retention* of configuration at a rate up to 30 times as great as the racemization rate of F.

In a previous communication we have reported the Raney nickel-catalyzed cleavage of 2-aryl-

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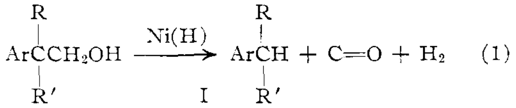
[1] This constitutes Communication XII in the series "The Stereochemistry of Raney Nickel Action." For XI see THIS JOURNAL, **81**, 2122 (1959).

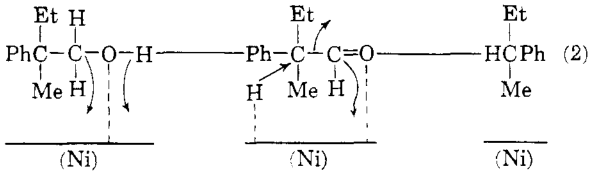
[2] This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

ethanols[3] (I) under conditions of reductive desulfuration. More recently we have studied this reaction radiochemically from the viewpoint of



$$\mathrm{Ar\underset{R'}{\overset{R}{C}}CH_2OH \underset{I}{\xrightarrow{Ni(H)}} Ar\underset{R'}{\overset{R}{C}}H + C{=}O + H_2} \quad (1)$$

identifying the single carbon cleavage by-product, with the findings[4] that this by-product consists of carbon monoxide strongly adsorbed to the catalyst surface and that the stoichiometry of the cleavage reaction may be expressed by equation 1. A mechanism similar to equation 2 has been proposed[3,4] to explain the products, stoichiometry and certain other aspects of such catalytic cleavage



reactions. This mechanism, involving a concerted attack by surface adsorbed hydrogen, might predict that such cleavage reactions should proceed with inversion of configuration and substantial retention of optical activity. In order to test this prediction we have now subjected optically active (−)-2-methyl-2-phenyl-1-butanol (B) the simplest 2-arylethanol which might undergo cleavage to an optically active hydrocarbon product (2-phenylbutane), to the experimental environment producing such cleavage.

2-Methyl-2-phenylbutanoic acid was resolved with quinine, affording the levorotatory enantiomer (A) having $[\alpha]^{25}\mathrm{D}$ −25.6° ($c$ 0.3, $C_6H_6$), in agreement with the value given by Wallis and Bowman.[5] The (−)-2-methyl-2-phenylbutanoic acid was reduced with lithium aluminum hydride yielding (−)-2-methyl-2-phenyl-1-butanol (B) having $[\alpha]^{25}\mathrm{D}$ −5.95° (neat), slightly lower than the literature value[5] of $[\alpha]\mathrm{D}$ −4.90°. When B and Raney nickel were heated in refluxing ethanol for 45 minutes the resulting (+)-2-phenylbutane ((+)-F), purified with the aid of vapor–liquid partition chromatography, had $[\alpha]^{25}\mathrm{D}$ + 9.72° (neat). Optically pure (+)-2-phenylbutane is reported[6] as having $[\alpha]\mathrm{D}$ ±27.3° (neat). Thus the above (+)-F cleavage product was obtained in a state of 67.8% optical purity (*i.e.*, 67.8% (+)-F and 32.2% F).

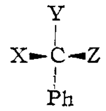
Since it has been shown[7–9] that optically active compounds containing hydrogen on an asymmetric center adjacent to activating groups are slowly racemized by the action of Raney nickel in refluxing ethanol, it appeared probable that the intrinsic optical purity of the above (+)-2-phenylbutane cleavage product was actually higher than the 67.8% lower limit. To test this possibility, a sample of (+)-2-phenylbutane was subjected to the action of a sample of Raney nickel catalyst from the same batch in refluxing ethanol, and found to racemize at a first-order rate of 0.157 hr.$^{-1}$. Using this rate constant to calculate a correction factor, the upper limit of "intrinsic" optical purity for the above (+)-2-phenylbutane cleavage product was estimated to be 70%.

The question as to whether the Raney nickel-catalyzed cleavage of (−)-2-methyl-2-phenyl-1-butanol (B) to (+)-2-phenylbutane ((+)-F) occurred with predominant inversion or retention of configuration can be answered with considerable certainty on the basis of rotatory and chemical data available in the literature.

Table I summarizes the specific rotations of various compounds related to (−)-2-methyl-2-phenyl-1-butanol (B), while Table II shows the percentage decreases in specific rotation engendered by a number of actual or hypothetical group transformations between the several compounds listed in Table I. (Essentially similar percentage decreases obtain if molecular rotations are employed). As described above, we have prepared (−)-2-methyl-2-phenyl-1-butanol (B) by the lithium aluminum hydride reduction of (−)-2-methyl-2-phenylbutanoic acid (A). Similarly (−)-2-phenylbutanoic acid (D) afforded a (−)-2-phenyl-1-butanol (E) whose benzenesulfonate yielded essentially optically pure (−)-2-phenylbutane (F) on lithium aluminum hydride reduction. Since such reductions do not affect the asymmetric center[10,11] it is obvious that establishment of the stereochemical relationship between A and D would provide an answer to the question of the presence or absence of Walden inversion during the catalytic conversion of B into (+)-2-phenylbutane ((+)-F). Let us next consider the cases of (−)-atrolactic

TABLE I

SPECIFIC ROTATIONS OF COMPOUNDS CONFIGURATIONALLY RELATED TO (−)-2-PHENYLBUTANE, F



| Number | X | Y | Z | $[\alpha]\mathrm{D}$,° | Solvent |
|---|---|---|---|---|---|
| A | Me | COOH | Et | −25.6 | $C_6H_6$[a] |
| B | Me | $CH_2OH$ | Et | − 5.95 | Neat[a] |
| D | H | COOH | Et | −87.3 | Neat[a,b] |
| E | H | $CH_2OH$ | Et | −19.45 | Neat[a,b] |
| F | H | Me | Et | −27.3 | Neat[c] |
| G | Me | COOH | OH | −37.7 | EtOH[d] |
| H | Me | $CH_2OH$ | OH | − 8.94 | $Et_2O$[e] |
| J | H | COOH | OH | −154.9 | EtOH[f] |
| K | H | $CH_2OH$ | OH | −40.6 | EtOH[g] |

[a] From present work. [b] Rotation of enantiomer actually measured. [c] Ref. 6. [d] Ref. 7. [e] Ref. 12e. [f] A. E. Dunstan and F. B. Thole, *J. Chem. Soc.*, **97**, 1253 (1910). [g] M. J. Kubitscheck, unpublished research, Stanford University.

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[3] J. A. Zderic, W. A. Bonner and T. W. Greenlee, THIS JOURNAL, **79**, 1696 (1957).

[4] W. A. Bonner and T. W. Greenlee, *ibid.*, **81**, 2122 (1959).

[5] E. S. Wallis and P. I. Bowman, *J. Org. Chem.*, **1**, 383 (1936).

[6] P. W. B. Harrison, J. Kenyon and J. R. Sheperd, *J. Chem. Soc.*, 658 (1926).

[7] W. A. Bonner, J. A. Zderic and G. A. Casaletto, THIS JOURNAL, **74**, 5086 (1952).

[8] W. A. Bonner and J. A. Zderic, *ibid.*, **78**, 3218 (1956).

[9] W. A. Bonner and J. A. Zderic, *ibid.*, **78**, 4369 (1956).

[10] P. Karrer and co-workers, *Helv. Chim. Acta*, **31**, 1617 (1948); **34**, 2202 (1951); **36**, 122 (1953).

[11] M. B. Watson and G. W. Youngson, *J. Chem. Soc.*, 2145 (1954).

TABLE II

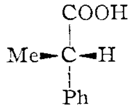
PERCENTAGE DECREASE IN SPECIFIC ROTATION DURING TRANSFORMATIONS BETWEEN CERTAIN COMPOUNDS IN TABLE I

| Transformation(s) | Compounds | Specific rotation decrease, % |
|---|---|---|
| COOH → $CH_2OH$ | A → B | 76.8[a] |
| | D → E | 77.7 |
| | G → H | 76.3 |
| | J → K | 73.8 |
| H → Me | D → A | 70.7 |
| | E → B | 69.4 |
| | J → G | 75.7 |
| | K → H | 78.0 |
| OH → Et | G → A | 32.1 |
| | H → B | 33.4 |
| | J → D | 43.7 |
| | K → E | 52.1 |
| H → Me; Et → OH | D → G | 56.8 |
| | E → H | 54.1 |
| COOH → $CH_2OH$; OH → Et | G → B | 84.2 |
| | J → E | 87.4 |
| COOH → $CH_2OH$; H → Me | D → B | 93.2 |
| | J → H | 94.2 |
| COOH → $CH_2OH$; Et → OH | A → H | 65.1 |
| | D → K | 53.5 |

[a] Calculated by ([α]D of A − [α]D of B)/([α]D of A); others calculated in a similar fashion.

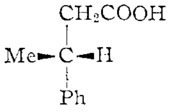
acid (G) and (−)-mandelic acid (J), both known[12] to be of the D-configuration as indicated. Reduction of these configurationally related acids G and J with lithium aluminum hydride afforded the corresponding diols H and K, having the specific rotations listed in Table I. In the four stereochemically definitive conversions of COOH → $CH_2OH$ in Table II, namely A → B, D → E, G → N and J → K, not only are the trends in optical rotation similar, but *the rotational percentage decrease involved in each case is almost invariant* (76.2 ± 1.2%). Furthermore, the remaining hypothetical conversions (Table II) involving interchange of one or more groups among the compounds listed in Table I each involve rotational percentage decreases which are not only qualitatively parallel but also frequently quantitatively similar. These regularities in the optical rotatory relationships among and between the members of the stereochemically uncorrelated compounds (A,B *vs.* D,E,F) in Table I and those assigned to the D-series (G,H,J and K) argue strongly to us for overall configurational identity among the compounds listed in Table I. This conclusion finds additional support in the fact that D(−)-mandelic acid (J) appears to be configurationally related to (−)-2-phenylbutanoic acid (D), (−)-2-phenyl-1-butanol (E) and (−)-2-phenylbutane (F) by application of Marker's rule,[13] an argument again based on optical rotatory data. Extending the above Freudenberg displacement rule[12a] analogies further, we may also examine the optical rotatory changes in the conversion COOH→$CONH_2$. Conversion of the configurationally related D(−)-mandelic and D(−)-atrolactic acids, J and G, to their corresponding amides involves rotational changes to more positive values in each case ([α]D −59.2° (EtOH) and +12.6° (EtOH), respectively, for D(−)-mandelamide[14] and D(+)-atrolactamide[14]). Similarly the conversions of (−)-2-methyl-2-phenylbutanoic and (−)-2-phenylbutanoic acids, A and D, to their amides (of [α]D −14.90° ($C_6H_6$)[5] and −19.9° (75% EtOH),[28] respectively) involve qualitatively similar rotational changes to more positive values, arguing again for the indicated configurational similarities of A, D, G and J.

There are additionally several lines of chemical evidence which bear on the configurational relationships of the compounds in Table I and which support convincingly the configurational assignments argued above on optical bases: (1) Kenyon and co-workers[15] have converted (+)-2-butanol into (−)-2-phenylbutane by treatment of (+)-2-butyl tosylate with phenylmagnesium bromide, a reaction involving Walden inversion. (−)-2-Butanol and (−)-2-phenylbutane (F) have been related[16] to D(+)-glyceraldehyde, as has also mandelic acid (J) by way of D(−)-lactic acid.[17] These relationships argue for the configurational assignments of D(−)-2-phenylbutane (F) and D(−)-mandelic acid (J) summarized in Table I. (2) D-(−)-Atrolactic acid (G) has been configurationally related to D(+)-2-phenylpropanoic acid ((+)-I),[18–20] which has in turn been converted into D-(−)-3-phenylbutanoic acid ((−)-II) by a series of reactions not involving the asymmetric center.[21]



$$\begin{array}{c} COOH \\ | \\ Me\!\rightarrow\!C\!\leftarrow\!H \\ | \\ Ph \end{array}$$

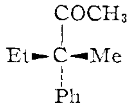
(+)-I



$$\begin{array}{c} CH_2COOH \\ | \\ Me\!\rightarrow\!C\!\leftarrow\!H \\ | \\ Ph \end{array}$$

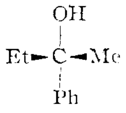
(−)-II

Conversion of (−)-II into optically pure D(−)-2-phenylbutane (F) has been accomplished[22] *via* the primary alcohol and bromide derived from (−)-II, thus correlating the configurations of D(−)-atrolactic acid (G) with D(−)-2-phenylbutane (F). (3) Lastly, (+)-2-methyl-2-phenylbutanoic acid ((+)-A) has been converted[23] to the corresponding ketone ((+)-III). Subjection of (+)-III to the Baeyer–Villiger rearrangement, a reaction known[24]



$$\begin{array}{c} COCH_3 \\ | \\ Et\!\rightarrow\!C\!\leftarrow\!Me \\ | \\ Ph \end{array}$$

(+)-III



$$\begin{array}{c} OH \\ | \\ Et\!\rightarrow\!C\!\leftarrow\!Me \\ | \\ Ph \end{array}$$

(−)-IV

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[12] (a) K. Freudenberg, J. Todd and R. Seidler, *Ann.*, **501**, 199 (1933); (b) K. Freudenberg and H. Biller, *ibid.*, **510**, 230 (1934); (c) W. Kuhn and H. Biller, *Z. physik. Chem.*, **29B**, 1 (1935); (d) V. Prelog and co-workers, *Helv. Chim. Acta*, **36**, 308, 320, 325, 1178 (1953); *cf.* also, (e) E. L. Eliel and J. P. Freeman, THIS JOURNAL, **74**, 923 (1952); (f) K. Mislow and M. Heffler, *ibid.*, **74**, 3668 (1952).

[13] R. E. Marker, *ibid.*, **58**, 976 (1936).

[14] A. McKenzie and I. S. Smith, *J. Chem. Soc.*, **121**, 1348 (1922).

[15] J. Kenyon, H. Phillips and V. P. Pittman, *ibid.*, 1080 (1935).

[16] *Cf.* D. J. Cram, THIS JOURNAL, **74**, 2150 (1952).

[17] K. Mislow, *ibid.*, **73**, 3954 (1951).

[18] W. A. Bonner, J. A. Zderic and G. A. Casaletto, *ibid.*, **74**, 5088 (1952).

[19] E. L. Eliel and J. P. Freeman, *ibid.*, **74**, 926 (1952).

[20] K. Mislow and M. Heffler, *ibid.*, **74**, 3668 (1952).

[21] P. A. Levene, R. E. Marker and A. Rothen, *J. Biol. Chem.*, **100** 595 (1953).

[22] D. J. Cram, THIS JOURNAL, **74**, 2138 (1952).

[23] D. J. Cram and J. Allinger, *ibid.*, **76**, 4516 (1954).

[24] (a) R. B. Turner, *ibid.*, **72**, 878 (1950); (b) K. Mislow and J. Brenner, *ibid.*, **75**, 2318 (1953).

TABLE III

RACEMIZATION AND H–D EXCHANGE OF (+)-2-PHENYLBUTANE (MOL. WT. 134) WITH DEUTERATED RANEY NICKEL IN DEUTERIOETHANOL

| No. | Reacn. time, hr. | $[\alpha]^{25}D$ (neat) | Racemization, % | $k_{rac.}$, hr.$^{-1}$ [a] | Percentage of sample with mass number |  |  |  |  |  |  |  |  | Av. excess D atoms/molecule | Av. resid. H atoms/molecule | $k_{exch.}$, hr.$^{-1}$ (total) [b] | $k_{exch.}$, hr.$^{-1}$ (mass 134) [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  | 134 | 135 | 136 | 137 | 138 | 139 | 140 | 141 | 142 |  |  |  |  |
| 1 | 0 | +26.6° | 0.0 | (0.035)[e] | 100.0[d] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.00 | 14.00 | (0.084)[e] | (1.05)[e] |
| 2 | 4 | +23.9 | 10.2 | .0268 | 4.8 | 15.3 | 24.3 | 25.0 | 17.4 | 8.7 | 3.3 | 1.0 | .3 | 2.95 | 11.05 | .0592 | 0.759 |
| 3 | 6 | +23.0 | 13.5 | .0243 | 3.1 | 12.0 | 22.4 | 25.8 | 19.7 | 10.6 | 4.4 | 1.5 | .5 | 3.07 | 10.93 | .0413 | .579 |
| 4 | 8 | +22.8 | 14.3 | .0193 | 2.7 | 11.0 | 21.8 | 26.1 | 20.3 | 11.4 | 4.8 | 1.5 | .4 | 3.14 | 10.86 | .0318 | .452 |

[a] Calculated by the first-order relation $k_{rac} = (2.3/t) \log (26.6/[\alpha]_t)$. [b] Calculated by the first-order relation $k_{exch} = (2.3/t) \log (14.00/H_t)$. [c] Calculated by the first-order relation $k_{exch} = (2.3/t) \log (100\%/\%\ \text{mass}\ 134_t)$. [d] Natural D abundance ignored; mass number entries corrected for natural $C^{13}$. [e] Obtained by extrapolation of the specific rate *vs.* time plot to $t_0$.

to proceed with configurational retention, followed by lithium aluminum hydride reduction of the resulting acetate, led[23] to (−)-2-phenyl-2-butanol ((−)-IV). Dehydroxylation of (−)-IV with Raney nickel, proceeding with predominant configurational retention,[18] produced[23] (−)-2-phenylbutane of 42% optical purity. The configurations indicated in Table I for (−)-2-methyl-2-phenylbutanoic acid (A) and (−)-2-phenylbutane (F) are in accord with this series of stereochemical observations.

Taken in total, the several optical and chemical correlations outlined above make, we believe, an impressively convincing argument for the configurational relationships of compounds A, B D, E and F in Table I. The presently reported catalytic cleavage of (−)-2-methyl-2-phenyl-1-butanol (B) into (+)-2-phenylbutane ((+)-F) may thus with considerable certainty be concluded to proceed with predominant *inversion* of configuration.

Finally, we have attempted to gain further stereochemical information regarding the previously referred to Raney nickel-catalyzed racemization of 2-phenylbutane by repetition of such experiments with a deuterium tracer. Optically pure (−)-2-phenylbutane was subjected to the action of deuterated Raney nickel[25] in refluxing deuterioethanol,[25] from which reaction mixture aliquots were removed at various time intervals and processed for product, whose optical rotations were then measured and whose deuterium contents were assayed mass spectrometrically. The results of these experiments are summarized in Table III.

As seen in Table III the pseudo first-order rate constant for the racemization of (−)-2-phenylbutane with the sample of deuterated Raney nickel employed was about 0.035 hr.$^{-1}$. This racemization rate was duplicated with a non-deuterated sample of Raney nickel from the same batch. Table III also indicates that more than one, in fact up to a minimum of eight, deuterium atoms can transfer from the Raney nickel catalyst surface to the 2-phenylbutane substrate under the conditions employed, results which are qualitatively in accord with those observed previously for H–D exchanges involving phenylacetamide[25,26] and 2-phenylpropanoamide.[9] The introduction of as many as eight D atoms into a small fraction of the sample strongly suggests that considerable H–D exchange has occurred not only in the aromatic nucleus of the (−)-2-phenylbutane, as previously noted,[26] but also in the β-carbons[9] and possibly the γ-carbon of the aliphatic side chain as well. We have, however, no experimental evidence as to the distribution of deuterium in the samples in question.

It is of some interest to attempt a rough quantitative comparison between the rate of racemization and the rate of H–D exchange in our (−)-2-phenylbutane sample. From the array of mass spectrometric data in Table III it is possible to calculate the pseudo first-order rate constant for total H–D exchange at each time of sampling. Extrapolation of these values to $t_0$ gives an "intrinsic" total H–D exchange rate of 0.084 hr.$^{-1}$ for the (−)-2-phenylbutane sample, a number roughly 2.4 times as great as the extrapolated racemization rate. On the other hand, if one similarly calculates the rate constant at each time for the disappearance of mass 134 from the sample, *i.e.*, the rate at which the *first* hydrogen exchanges, the value obtained by extrapolation to $t_0$ proves to be 1.05 hr.$^{-1}$. It thus appears that the first hydrogen in the molecule exchanges about 12.5 times as fast as the over-all rate of H–D exchange. One would conclude, therefore, that one particular H atom in (−)-2-phenylbutane exchanges much more readily than do random H-atoms, and it is reasonable to assign this role to the α-H on the assymmetric center at C2. If one makes this assumption, then the rate of H–D exchange at the stereochemically pertinent C2 position is at a maximum 30-fold greater than the rate of racemization at this position. While this figure represents a theoretical upper limit to the $k_{exch-\alpha}/k_{rac}$ ratio, it is quite obvious that the exchange reaction at the asymmetric center is a remarkably stereospecific process occurring with predominant *retention* of configuration, a conclusion according with that previously reached in our H–D exchange and racemization studies with (+)-2-phenylpropanoamide.[9]

The above extrapolations of the first-order exchange and racemization rate constants to $t_0$ clearly show a linear decrease in each rate constant with time. Furthermore, the extrapolated value for each rate constant at $t_0$ drops to a value about 40–50% as great after the 8-hour reaction period. Clearly some irreversible change occurs at the catalyst surface as the reaction proceeds, progressively diminishing its power to engender racemi-

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(25) W. A. Bonner, THIS JOURNAL, **76**, 6350 (1954).

(26) W. A. Bonner, *ibid.*, **79**, 2469 (1957).

zation and H–D exchange to roughly comparable extents. The reason for this progressive deterioration of the catalyst as the reaction proceeds is presently unknown, but the phenomenon may be reasonably assumed due to interaction of the catalyst with the deuterioethanol solvent. Such an interaction would lead to the covering of a progressively increasing fraction of the catalyst surface with carbon monoxide[4] and would thus presumably slowly poison the catalyst.

## Experimental

**2-Methyl-2-phenylbutanoic Acid.**—2-Phenylpropanaldoxime was prepared from 2-phenylpropanal (200 g.) and hydroxylamine hydrochloride (250 g.) in aqueous (400 ml.) pyridine (800 ml.) after the procedure of Newman and Clossen.[27] The crude oxime was subjected to distillation and the fraction (121.3 g.) of b.p. 103–118° (15 mm.) was employed in the following dehydration. The oxime and acetic anhydride (500 ml.) were refluxed under a fractionating column whose jacket temperature was maintained in the range 120–135°, such that acetic acid distilled as produced. After three hours only acetic anhydride distilled over, whereupon the remaining reagent was stripped, last traces *in vacuo*. The residue was distilled and the desired 2-phenylpropanonitrile (82.5 g.) was collected in the range 65–150° (20–25 mm.). Sodium amide (30.0 g.) and anhydrous toluene (300 ml.) were placed in a one-liter flask equipped with dropping funnel, reflux condenser and mechanical stirrer. One ml. of the above nitrile was added and the reaction was initiated by warming, whereupon the remaining nitrile was added dropwise with stirring at a rate sufficient to maintain gentle reflux. When nitrile addition was complete, stirring was continued for 30 minutes, after which ethyl bromide (75.5 g.) was added dropwise with stirring during a one-hour period. After an additional hour of stirring, water (100 ml.) was gradually added, and the toluene layer was separated and stripped of solvent through a Vigreux column. The residue was distilled and the 2-methyl-2-phenylbutanonitrile (70 g.) was collected in the range of 126° (24 mm.). The latter was added to a hot solution of potassium hydroxide (37 g.) in methanol (250 ml.). Water was added to incipient turbidity and the mixture was heated under reflux for a period of 11 days, with occasional addition of methanol as turbidity became noticeable. Water (300 ml.) was added to the mixture and air was bubbled through with warming to remove methanol. On cooling, the phases were separated and the aqueous phase was extracted twice with ether (discard), then acidified. The precipitated product was recovered by extraction into ether. Solvent removal from the extract yielded 33.7 g. of tan 2-methyl-2-phenylbutanoic acid, m.p. 54–56°, which was used directly in the resolution below. The pure acid is reported[5] to have m.p. 57–58°.

**(−)-2-Methyl-2-phenylbutanoic Acid.**—The above racemic acid (33.7 g.) was resolved by recrystallization of the quinine (68 g.) salt from dilute ethanol after the procedure of Wallis and Bowman.[5] During the sixth recrystallization three crops were obtained. The first two, totaling 10.1 g. and having $[\alpha]^{25}\mathrm{D}$ −112.4, −112.1° (*c* 3, EtOH), were suspended in water and treated with hydrochloric acid. The resolved acid was extracted into ether and the extracts were dried, decolorized and stripped of solvent to yield 3.14 g. of large, white crystals, m.p. 87–89°, $[\alpha]^{25}\mathrm{D}$ −25.6° (*c* 3, $C_6H_6$); Wallis and Bowman report[5] $[\alpha]^{25}\mathrm{D}$ −23.28° ($C_6H_6$) for this acid.

*Anal.* Calcd. for $C_{11}H_{14}O_{12}$: C, 74.13; H, 7.92. Found: C, 74.02, 74.15; H, 8.12, 8.33.

**(−)-2-Methyl-2-phenyl-1-butanol.**—The above (−)-2-methyl-2-phenylbutanoic acid (3.14 g.) was reduced with lithium aluminum hydride (1.1 g.) in anhydrous ether suspension in the usual manner. Customary processing and solvent removal yielded an oil which distilled at 80–95° (1 mm.). The distillate weighed 2.40 g. and had $d_{26}$ 0.992, $[\alpha]^{25}\mathrm{D}$ −5.95° (neat). Wallis and Bowman report[5] $[\alpha]^{25}\mathrm{D}$ −4.90° (neat) for this substance.

**Raney Nickel Cleavage of (−)-2-Methyl-2-phenyl-1-butanol.**—The above levorotatory alcohol (2.40 g.), Raney nickel slurry (*ca.* 8 g.) and absolute ethanol (25 ml.) were heated under reflux for 45 minutes, whereupon the catalyst was filtered and rinsed with ethanol. The ethanol was stripped under a small fractionating column and the residue was poured into water, which was then extracted five times with pentane. The pentane extracts were passed through a column of alumina to remove small amounts of starting material and other hydroxylic components, and the pentane was carefully stripped from the effluent through a Vigreux column. The residue was distilled in a semi-micro still and the product collected in the b.p. range 150–180°. A known weight of the distillate was diluted with a known weight of stock *rac*-2-phenylbutane to give a sufficient quantity for accurate optical rotation measurements, a procedure which gave a value $[\alpha]^{25}\mathrm{D}$ +9.72° (neat) for the undiluted (+)-2-phenylbutane product. A correction for the racemization of the 2-phenylbutane cleavage product under the reaction conditions employed (*vide infra*) raised the above value to $[\alpha]^{25}\mathrm{D}$ +10.94° (neat) as the approximate intrinsic optical rotation of the cleavage product. In earlier control experiments starting with *rac*-2-methyl-2-phenyl-1-butanol it was found by vapor–liquid partition chromatographic examination that the *rac*-2-phenylbutane product was chemically homogeneous. Such samples had infrared spectra identical with that of an authentic sample.

**(+)-2-Phenylbutanoic Acid.**—2-Phenylbutanoic acid (110 g.) was resolved by repeated crystallization of its cinchonidine (200 g.) salt from 70% ethanol after the procedure of Levene and Marker.[28] After three recrystallizations the cinchonidine salt (115 g.) was decomposed by suspension in dilute hydrochloric acid and the resolved acid was recovered by ether extraction. Solvent removal left crude (+)-2-phenylbutanoic acid which was purified by vacuum distillation, b.p. 115–130° (1–2 mm.), $[\alpha]^{25}\mathrm{D}$ +87.3° (neat). Levene and Marker quote[28] $[\alpha]^{25}\mathrm{D}$ +84.4° (neat) for this product.

**(+)-2-Phenyl-1-butanol** was prepared by lithium aluminum hydride reduction, in the usual manner, of the above (+)-2-phenylbutanoic acid. The crude product was distilled at 120–135° (21 mm.) to give a 93% yield of product having $[\alpha]^{25}\mathrm{D}$ +19.45° (neat). Levene and co-workers report[29] $[\alpha]^{25}\mathrm{D}$ + 18.9° (neat) for (+)-2-phenyl-1-butanol.

**(+)-2-Phenylbutane.**—The above (+)-2-phenyl-1-butanol (29.3 g.) and anhydrous pyridine (60 ml.) were mixed and chilled in ice, after which benzenesulfonyl chloride (35 g.) was added with cooling and stirring over a period of several hours. The mixture was kept at 0° for an additional hour, allowed to stand at 25° overnight and then added to water (1000 ml.). The product was extracted into ether and the extract was washed well with water and dried, then stripped of solvent at aspirator pressures. The crude benzenesulfonate ester (58.6 g.) was held at 50° (1 mm.) for several hours to remove residual solvent, then reduced directly using lithium aluminum hydride (7.6 g.) in anhydrous ether under conventional conditions. The final ether extract was washed well with dilute sodium hydroxide solution, then dried, filtered and stripped of solvent through a small Vigreux column. The residual (+)-2-phenylbutane was distilled giving 19.2 g. of product having b.p. 165–175° and $[\alpha]^{25}\mathrm{D}$ +26.6° (neat). Kenyon and co-workers report[6] $[\alpha]^{25}\mathrm{D}$ −27.3° for the enantiomeric (−)-2-phenylbutane.

**Racemization of (+)-2-Phenylbutane by Raney Nickel.**—In order to correct the specific rotation of the (+)-2-phenylbutane, $[\alpha]^{25}\mathrm{D}$ +9.72°, obtained in the above cleavage reaction for racemization after its formation, the following experiment was performed. A sample (1 g.) of partially racemic (+)-2-phenylbutane having $[\alpha]^{25}\mathrm{D}$ +1.30° (neat) and Raney nickel (3 g.) (from the same batch as the above cleavage reaction) were heated in refluxing absolute ethanol (15 ml.) for 6.25 hours. The 2-phenylbutane was recovered in the usual manner and showed $[\alpha]^{25}\mathrm{D}$ +0.488° (neat). Assuming constant catalyst activity and a first-order rate of racemization (*vide infra*) the specific rate constant for racemization was calculated as $k = (2.3/6.25) \times \log(1.30/0.488) = 0.157$ hr.$^{-1}$. Using this rate constant the rotation of the above (+)-2-phenylbutane, $[\alpha]^{25}\mathrm{D}$ +9.72°, was corrected for such racemization during the 0.75-hour reaction period by the relation $0.157 = (2.3/0.75) \times \log([\alpha]_0/9.72)$, whence $[\alpha]_0 = 10.94°$. This figure, arguing for

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(27) M. S. Newman and R. D. Clossen, THIS JOURNAL, **66**, 1554 (1944).

(28) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **100**, 685 (1933).

(29) P. A. Levene, L. A. Mikeska and K. Passoth, *ibid.*, **88**, 27 (1930).

70% "intrinsic" optical purity of the (+)-2-phenylbutane produced in the above cleavage, is based on the obviously invalid assumption that all of the product of this optical purity was produced instantaneously, after which it racemized during the 0.75-hour reaction period. The optical purity of the (+)-2-phenylbutane actually isolated was 67.8%. The correct "intrinsic" optical purity of the cleavage product must lie between these two extremes. As indicated below, Raney nickel of different batches appeared to vary markedly in its ability to racemize (+)-2-phenylbutane.

**The H–D Exchange of (+)-2-Phenylbutane with Deuterated Raney Nickel.**—Hoping to note a simple relationship between the rate of racemization of (+)-2-phenylbutane and H–D exchange of the latter with deuterated Raney nickel catalyst, we have performed the following experiments. Deuterioethanol[15] (83 ml.), deuterated Raney nickel[15] (*ca.* 30 g.) and the above (+)-2-phenylbutane, $[\alpha]^{25}_{D}$ +26.6° (10 ml.) were heated in a flask equipped with a magnetic stirrer and reflux condenser ($CaCl_2$). Stirring under reflux was continued for 8 hours and aliquots of the reaction mixture (including catalyst) were removed at 2-hour intervals. The (+)-2-phenylbutane in each aliquot was recovered in the usual way by dilution with water and extraction with pentane. Pure product from each sample was collected from the vapor–liquid partition chromatographic column, then measured for both its optical rotation and mass spectrometrically determined deuterium content. These data are recorded in Table III, where it is seen that the racemization process follows a first-order rate expression reasonably well. A parallel experiment was performed in which absolute ethanol (83 ml.), ordinary Raney nickel (*ca.* 30 g.) (from the same batch from which the deuterated catalyst was prepared) and the same (+)-2-phenylbutane (10 ml.) were allowed to react and sampled in a similar fashion. The optical rotation of the product recovered from each aliquot was almost identical to that of the product from the corresponding aliquot in the first experiment, providing independent confirmation of the rate data in Table III. It is noteworthy that the batch of catalyst used in these experiments gave racemization rates considerably lower than those obtained using the batch of catalyst employed in the earlier racemization experiments above. This emphasizes the non-uniformity of Raney nickel catalyst samples with respect to racemization ability.

STANFORD, CALIF.

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION, RESEARCH DEPARTMENT, U. S. NAVAL ORDNANCE TEST STATION]

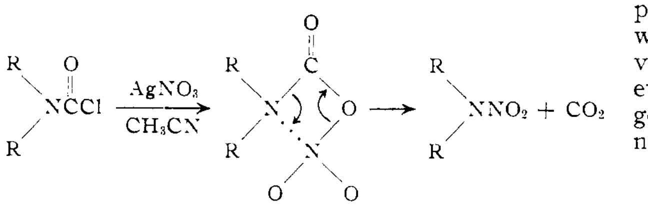
# The Reaction of Alkyl Chloroformates with Silver Nitrate.[1a,b] Evidence for Stereoselective Intramolecular Formation of Nitrate Esters

BY ROBERT BOSCHAN

RECEIVED MAY 20, 1958

A novel method has been discovered for the preparation of nitrate esters from alkyl chloroformates by treatment with silver nitrate under very mild conditions. By this method, a stereoselective synthesis of a nitrate ester is achieved in which the bond on the carbon atom adjacent to the nitrate ester group remains essentially intact. Hence, it is possible to prepare nitrate esters of compounds in which there is concern regarding oxidation or acid sensitivity in conventional methods of nitration involving nitric acid or mixed nitric and sulfuric acids. Hexyl chloroformate has been prepared from the corresponding $O^{18}$ enriched alcohol, and this ester has been converted to nitrate ester, leaving the C–O bond predominantly uncleaved.

Recent work by Norris,[2] in which a carbamyl chloride I is converted to a nitramine III, presumably *via* an unstable intermediate such as II,



I II III

suggested the study of the analogous reactions of alkyl chloroformates reported here. Of the various methods of preparation of nitrate esters,[3] the only method which does not involve rupture of the bond on the carbon atom adjacent to the nitrate ester group is the rather vigorous treatment of alcohols with nitric acid or with mixed nitric and sulfuric acids. The synthesis of nitrate esters from the corresponding chloroformates should be very useful in cases where the alcohols are sensitive to treatment with strong acids or oxidizing agents, or where a nitrate ester of known stereochemistry is desired.

In general, the method of synthesis consists of the treatment of the alkyl chloroformate (usually prepared by reaction of the corresponding alcohol with phosgene) with silver nitrate in an inert solvent. A heterogeneous reaction can be run in ether, benzene or carbon tetrachloride, or a homogeneous reaction can be carried out with acetonitrile as solvent.

The over-all stoichiometry appears to be

$$ROCOCl + AgNO_3 \longrightarrow RONO_2 + CO_2 + AgCl$$

Several nitrate esters, including amyl, hexyl bornyl, cetyl and cholesteryl nitrates, have been prepared by this method. The cholesteryl ester, previously unreported in the literature, was prepared in better than 90% yield from the corresponding chloroformate. The saponification of this ester to give cholesterol indicated that its conversion to the nitrate probably proceeded with retention of configuration.

Attempted elucidation of the mechanism of this conversion involved three approaches: (1) $O^{18}$ labeled chloroformate ester was converted to nitrate ester. (2) The stereochemistry of the nitrate ester resulting from an optically active chloroformate ester was studied. (3) The kinetics of the reaction were examined. Each of these studies will be discussed separately.

**(1) Labeled Oxygen Studies.**—With the intent

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(1) Portions of this paper were presented at (a) the 130th Meeting of the American Chemical Society in Atlantic City, N. J., September 16–21, 1956, p. 10-O of abstracts; and (b) at the 132nd Meeting of the American Chemical Society in New York, N. Y., September 8–13, 1957, p. 74P of abstracts.

(2) W. P. Norris, THIS JOURNAL, **81**, 3346 (1959).

(3) R. Boschan, R. T. Merrow and R. W. Van Dolah, *Chem. Revs.*, **55**, 485 (1955).