

162. *Reaction Kinetics and the Walden Inversion. Part VII.**
The Configurations of some Amino-hydrocarbons.

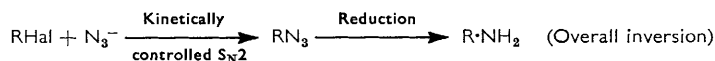
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By application of the stereokinetic rule for S_N2 substitution of azide ions in alkyl halides, and by reducing the azides produced to amines, it is shown that the following pairs of substances have the same sign of rotation when the pair has corresponding configuration: *s*-butyl bromide, *s*-butylamine; 1-methylheptyl bromide, 1-methylheptylamine; 1-phenylethyl chloride, 1-phenylethylamine.

THE work near the turn of the century on the Walden inversion was entirely concerned with interconversions between (1) halides RCl, RBr, (2) oxy-compounds ROH, ROAlk, and (3) amines $R\cdot NH_2$, where R is a parent or substituted hydrocarbon radical.

In the 1930's, the stereokinetic rule for S_N2 substitutions was established;^{1,2} and, by applying it to the bimolecular basic hydrolysis of halides,² the relative configurations of most of the historically more important series of optically active compounds of classes (1) and (2) were connected with their relative signs of rotation, so permitting Walden inversions to be firmly located in reaction routes leading from either of these classes to the other. The next step was to apply the same kind of method to connecting the configurations of the corresponding amino-compounds of class (3) to those of the other classes, so that Walden inversions could be similarly located in processes leading to amines from either of the other classes, or from amines back to either. This was in fact done, mostly in the period 1938—1940, but the work has not yet been reported, though a list of results³ was published in 1950. We now report that part of the work in which R was an unsubstituted hydrocarbon radical, the three series of this type studied being the *s*-butyl, 1-methylheptyl, and 1-phenylethyl series.

In all three series the method has been the same, *viz.*, to conduct a kinetically controlled S_N2 reaction between azide ion and an alkyl halide, which we know will produce inversion of configuration, and then to reduce the alkyl azide produced to the amine, in a reaction which occurs elsewhere than at the asymmetric carbon atom and therefore effects no further configurative change:



Preliminary experiments on the rate of reaction of *s*-butyl bromide with sodium azide having shown that we could conduct this reaction in "80%" ethanol at 50.2°, it was next necessary to discover to what extent the required reaction would in these conditions be

* Part VI, *J.*, 1937, 1252.

¹ Hughes, Juliusberger, Masterman, Topley, and Weiss, *J.*, 1935, 1525; Hughes, Juliusberger, Scott, Topley, and Weiss, *J.*, 1936, 1173; Cowdrey, Hughes, Nevell, and Wilson, *J.*, 1938, 209.

² Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252.

³ Brewster, Hiron, Hughes, Ingold, and Rao, *Nature*, 1950, **166**, 178.

accompanied by (a) solvolysis of the bromide or (b) its racemisation by the bromide ions produced from it. Although it was a formality, it had also to be shown (c) that s-butyl azide is chemically and optically stable under the conditions of its production. The first two points were covered by following the liberation of bromide ion from s-butyl bromide in "80%" ethanol at 50.2° in the absence of sodium azide, and also the change of rotation, not only in these conditions, but also when they were modified by the initial addition of lithium bromide. It was thus found that the reaction of s-butyl bromide with sodium azide in the conditions contemplated would be accompanied by only about 2% of solvolysis of the alkyl bromide, and by less than 1% of racemisation by the bromide ion formed. We considered these disturbances negligible. The third point was checked after the kinetics of the reaction of s-butyl bromide with sodium azide had been studied, by showing that its course, followed polarimetrically, was identical with that followed titrimetrically, and led to a final rotation (of changed sign) that remained constant for a long period after the measured reaction had been completed.

The reaction between s-butyl bromide and sodium azide in "80%" ethanol at 50.2° displayed second-order kinetics, as illustrated in Table 1. This established that an S_N2 reaction is under observation. No salt effect shows in the individual runs, because, of course, the ionic strength remains constant. Runs at different concentrations showed signs of a small negative salt effect at high salt concentrations.

TABLE 1. *Integrated second-order rate constants (\bar{k}_2 in sec.⁻¹ mole⁻¹ l.) in the reaction of s-butyl bromide with sodium azide in "80%" ethanol at 50.2°.*

(Initially, $[C_4H_9Br] = 0.171M$ and $[NaN_3] = 0.207M$. The units of a , b , and x in the formula $\bar{k}_2 = \{2.303/(a-b)t\} \log \{b(a-x)/a(b-x)\}$ are ml. of 0.118N-thiocyanate per 5.00 ml. sample.)

t (min.)	x	$a-x$	$b-x$	$10^4\bar{k}_2$	t (min.)	x	$a-x$	$b-x$	$10^4\bar{k}_2$
0	0	7.20	8.79	—	255	4.07	3.13	4.72	3.9
60	1.42	5.73	7.37	4.0	345	4.47	2.73	4.32	4.0
90	2.10	5.10	6.69	3.7	465	5.11	2.09	3.68	3.7
135	2.90	4.30	5.89	4.0	∞	7.20	0.00	1.59	—
195	3.67	3.53	5.12	4.1					Mean 3.9

The azide formed in these conditions was reduced by hydrogen in the presence of Adams platinum catalyst to s-butylamine. Dextrorotatory s-butyl bromide gave lævorotatory s-butyl azide and s-butylamine; and *vice versa*. It follows that when s-butyl bromide, azide, and amine, and, from previous work, the chloride and alcohol, have like signs of rotation, they have like configurations.

The actual starting point in this series of preparations was s-butyl alcohol, resolved by Pickard and Kenyon's method,⁴ with $[\alpha]_D^{20}$ (max.) 13.9°. Samples, often with only a proportion of this activity, were converted into bromide with hydrogen bromide, and thence through the azide, into the amine, which had 78—80% of the activity calculated as a like proportion of the activity of amine, resolved by Thomé's method through the tartrate,⁵ $[\alpha]_D^{20}$ (max.) 7.44°. However, it seemed likely that some racemisation would accompany conversion of the alcohol into the bromide, and this was checked by hydrolysing a sample of the bromide with concentrated alkali back to the alcohol, which was found to have suffered 18% of racemisation in the double process. We assign this racemisation to the formation of the bromide, and it then follows that there can be no considerable racemisation in any of the other reactions described, and, in particular, none in the substitution by azide ion in s-butyl bromide. Incidentally, we compute from our results that the maximum rotatory power of s-butyl bromide is α_D^{20} 44.3° (l 1 dm.).

The work on 1-methylheptyl bromide pursued a similar course. The same checks on racemisation and solvolysis were made with substantially the same results. The reaction between this bromide and sodium azide in "80%" ethanol at 50.2° displayed second-order kinetics, as illustrated in Table 2, so establishing an S_N2 process. The rate constant

⁴ Pickard and Kenyon, *J.*, 1911, **103**, 1923.

⁵ Thomé, *Ber.*, 1903, **36**, 582.

is smaller than in the *s*-butyl series, and the salt-effect was barely detectable up to 0.3M in salt. The 1-methylheptyl azide was reduced catalytically to the amine.

TABLE 2. *Integrated second-order rate constants (\bar{k}_2 in $\text{sec.}^{-1} \text{mole}^{-1} \text{l.}$) in the reaction of 1-methylheptyl bromide with sodium azide in "80%" ethanol at 50.2°.*

<i>t</i> (min.)	<i>x</i>	<i>a</i> - <i>x</i>	<i>b</i> - <i>x</i>	$10^4 \bar{k}_2$	<i>t</i> (min.)	<i>x</i>	<i>a</i> - <i>x</i>	<i>b</i> - <i>x</i>	$10^4 \bar{k}_2$
0	0	10.45	15.71	—	255	4.30	7.02	11.41	2.56
47	1.12	9.95	14.59	(2.39)	315	4.90	6.15	10.31	2.56
80	1.83	9.33	13.88	2.56	410	5.75	4.70	9.96	2.61
120	2.55	8.62	13.16	2.61					Mean 2.57
180	3.43	7.90	12.28	2.57					

Dextrorotatory 1-methylheptyl bromide gave a levorotatory azide and amine; and *vice versa*. It follows that, when 1-methylheptyl bromide, azide, and amine, and, from previous work, chloride, alcohol, and ethyl ether, have the same sign of rotation, they have corresponding configurations.

The starting point in this series was again the alcohol, resolved by Kenyon's method,⁶ $[\alpha]_D^{17}$ (max.) 9.9°. An estimate of the rotatory power of the bromide has been made⁷ by Gerrard: α_D^{18} 42.6° (*l* 1 dm.). The rotatory power calculated to this figure, of our amine, derived from bromide samples of lower activity, through the azide, was α_D^{20} 8.5° (*l* 1 dm.). Unfortunately the amine has not been directly resolved, and our attempts to resolve it failed, so that we were not able to keep a quantitative account of any racemisation occurring in this case.

The experiments with 1-phenylethyl chloride were complicated by two kinetic disturbances, which were both too large to be neglected, could not be eliminated, and therefore had to be measured and allowed for. In "80%" ethanol at 50.2°, at the concentrations to be used for the conversion of optically active samples of 1-phenylethyl chloride into 1-phenylethyl azide (concentrations chosen to be relatively favourable to that reaction), solvolysis of the chloride occurs at about 40% of the rate of the azide substitution. The solvolysis rate had therefore to be measured, and the material thus made unavailable for the azide substitution allowed for in computations of the rate constants of that reaction. The solvolysis is reciprocally affected by loss of its reactant in the azide substitution. This concurrence of a first-order reaction, which has a positive salt effect, and a second-order reaction, assumed to be without one, each reaction withdrawing the factors of the other, leads to difficult mathematical equations, and was handled numerically, by a reciprocating point-to-point method, in order to isolate the instantaneous (or, really, finite-difference) second-order rate constants of the azide substitution.

The solvolysis products are, of course, optically stable, and their formation makes no difference to the optical activity of concurrently formed 1-phenylethyl azide—except by contributing material to an independent reaction which does destroy optical activity. For both the azide substitution and the solvolysis produce chloride ion; and this racemises, in the known bimolecular way, the 1-phenylethyl chloride waiting to be either azide-substituted or solvolysed. In our conditions the specific rate of attack of chloride ions on 1-phenylethyl chloride is about 80% of the specific rate of attack on it of azide ions. Of course, the concentration of chloride ions starts from zero and rises, while the concentration of azide ions starts at its maximum and falls; and the concentrations of reactants were so arranged that, even at the end of reaction, there were still more azide ions than chloride ion. But even so, the integrated effect of chloride ion in having racemised each element of 1-phenylethyl chloride up to the moment at which azide ion reacted with it, led to a considerable overall loss of optical activity from the total 1-phenylethyl azide produced. This loss had to be calculated, again by a point-to-point numerical method,

⁶ Kenyon, *J.*, 1922, **121**, 2540.

⁷ Gerrard, *J.*, 1946, 741.

and allowed for when computing the optical effect of the azide substitution. The 1-phenylethyl azide, once formed, was optically stable in the conditions of its formation.

The titrimetric first-order rate constant of solvolysis of 1-phenylethyl chloride in "80%" ethanol at 50.2° was initially 1.94×10^{-4} sec.⁻¹. But the reaction had a positive salt effect, and electrolyte was being produced, so that the "instantaneous" rate constant

TABLE 3. Second-order rate constants (k_2 in sec.⁻¹ mole⁻¹ l.) for the reaction of 1-phenylethyl chloride (initially 0.198M) with sodium azide (initially 0.461M) in "80%" ethanol at 50.2°.

<i>t</i> (min.)	Cl ⁻ (%)	10 ⁴ <i>k</i> ₂ (corr.)	<i>t</i> (min.)	Cl ⁻ (%)	10 ⁴ <i>k</i> ₂ (corr.)
2.0	8.5	2.39	18.0	59.2	2.49
5.0	20.3	2.38	28.0	75.2	2.46
8.0	31.4	2.44	43.0	82.9	2.37
12.0	44.6	2.59	58.0	88.4	2.32

rose as reaction progressed. At the salinities employed in the azide substitutions, the appropriate rate constants were close to 2.6×10^{-4} sec.⁻¹. The course of an azide substitution, and, by allowance for solvolysis, the isolation of its individual rate, as expressed in "instantaneous" second-order rate constants, are shown in Table 3.

These results are in agreement with a second-order, and therefore bimolecular, substitution of 1-phenylethyl chloride by azide ion. We assume that the reaction has but little salt effect, but the over-riding need to give the azide substitution as much prominence as possible among the concurrent processes left us too little freedom in the variation of concentrations to permit adequate examination of its salt effect.

The polarimetric first-order rate constant of solvolysis of 1-phenylethyl chloride in "80%" ethanol at 50.2° had the initial value 2.00×10^{-4} sec.⁻¹, nearly the same as the initial titrimetric rate constant. However, the polarimetric constant rose more rapidly as reaction progressed than did the titrimetric constant. This was because the polarimetric effect of solvolysis (which eventually reverses the sign of rotation) became supplemented by that of the chloride-ion substitution which racemises the surviving alkyl chloride. From the initially greater, but less rapidly rising, polarimetric rates observed in the presence of initially added lithium chloride, we evaluated the second-order rate constant of chloride-ion substitution in 1-phenylethyl chloride, as 1.98×10^{-4} sec.⁻¹ mole⁻¹ l. over the range of salinities 0.1—0.3M. As would be expected, the reaction displays no marked salt effect. In calculating this rate constant from the chloride-ion dependence of the polarimetric rate, as well as in using it to compute the racemisation suffered by 1-phenylethyl chloride ahead of its capture by azide ions in the azide substitution, it had, of course, to be remembered that the attack of a halide ion on one alkyl halide molecule racemises two alkyl halide molecules.

The 1-phenylethyl azide produced in the conditions of the kinetic runs described was reduced to 1-phenylethylamine by the catalytic method already mentioned.

Dextrorotatory 1-phenylethyl chloride thus gave levorotatory 1-phenylethyl azide and 1-phenylethylamine. It follows that, when 1-phenylethyl chloride, azide, and amine, and, from previous work, bromide, alcohol, and ethyl ether, have rotations of the same sign, they have like configurations.

The qualitative result that 1-phenylethyl chloride leads in these reactions to 1-phenylethylamine with opposite sign of rotation has already been obtained by Levene *et al.*,⁸ but without kinetic control, and with very extensive, but unaccounted, racemisation.

In the three experiments of which the optical results are in Table 4, the accumulated effect of the racemisation of the 1-phenylethyl chloride on the 1-phenylethyl azide collected after completion of the azide substitution was calculated to have produced 29—30% of racemisation in the alkyl azide. For the rotatory power of 1-phenylethyl chloride, we took

⁸ Levene, Rothen, and Kuna, *J. Biol. Chem.*, 1937, **120**, 277.

Gerrard's ⁷ value, α_D^{16} (max.) 99.6° (*l* 1 dm.), which is supported in the following paper, and also by the results obtained in this one. For the rotatory power of 1-phenylethylamine, we used Holmberg's ⁹ figure, *viz.*, α_D^{19} (max.) = 38.7° (*l* 1 dm.). In the substitution itself, it can be seen from the Table that inversion is complete.

TABLE 4. *Optical effect of conversion of 1-phenylethyl chloride (RCl) into 1-phenylethyl azide under the conditions of the kinetic study of this process, and subsequent conversion of the azide into 1-phenylethylamine (R·NH₂).*

α_D^{20} (<i>l</i> 1 dm.) of RCl used	α_D^{20} (<i>l</i> 1 dm.) of R·NH ₂			
	As obsd.	For RCl α 99.6°	Corr. for Cl ⁻ -racemn.	On R·NH ₂ (max.) α 38.7°
+5.44°	-1.48°	-27.1°	-38.4°	-99.3%
+5.44	-1.48	-27.1	-38.3	-99.1
+11.44	-3.16	-27.5	-39.0	-100.8

We may draw the further conclusion that all the substitutions here described by azide ion in alkyl halides are accurately obeying the stereokinetic S_N2 rule.

EXPERIMENTAL

Preparations.—*s*-Butyl, 1-methylheptyl, and 1-phenylethyl alcohol were resolved by known methods, and inactive and active samples of the first two were converted into bromides with hydrogen bromide, and of the last into chloride by means of thionyl chloride in pentane. (This work was done before Gerrard's method ⁷ appeared.)

For all the kinetic and optical experiments on the reaction of sodium azide with the alkyl halides, the solvent was "80%" ethanol, made by mixing 4 vols. of ethanol with 1 vol. of water. The conditions of these experiments have already been specified.

For the preparation of *s*-butylamine, the *s*-butyl azide was collected from the solution in which it had been formed by pouring the latter into saturated aqueous calcium chloride and extraction with pentane. The pentane solution was dried (CaCl₂), mixed with methanol, and shaken under hydrogen at 10 atm. in the presence of Adams platinum catalyst until absorption of the gas ceased. After the catalyst had been removed, the solution was acidified with hydrochloric acid and evaporated. The residual amine hydrochloride was taken up in water, and the solution was extracted with pentane, concentrated, basified by addition of solid potassium hydroxide, and distilled. The amine, dried over potassium hydroxide, had b. p. $63^\circ/760$ mm. (Found: C, 64.1; H, 14.6. Calc. for C₄H₁₁N: C, 65.7; H, 15.1%). 1-Methylheptylamine was prepared in the same way, except that the pentane solution of azide was concentrated before the methanol and Adams catalyst were added, and that the amine was extracted with ether after final basification of the aqueous solutions of its hydrochloride. It had b. p. $163-165^\circ/760$ mm. (Found: C, 74.3; H, 14.8; N, 10.9. Calc. for C₈H₁₉N: C, 74.3; H, 14.8; N, 10.8%). 1-Phenylethylamine, prepared in the same way, had b. p. $83^\circ/20$ mm. (Found: C, 78.8; H, 9.1; N, 11.9. Calc. for C₈H₁₁N: C, 79.3; H, 9.0; N, 11.7%).

Kinetics.—In all cases, the titrimetric kinetics were followed, either by the liberation of acid as determined by titration with alkali, or by that of halide ion (after removal of the organic material by extraction with ether from an aqueous solution, as was especially necessary in the experiments with 1-phenylethyl chloride) by back-titration with thiocyanate of an excess of added silver nitrate. Samples of this reaction solution were withdrawn by pipettes, the first sample marking the time-zero. Polarimetric kinetics were followed with the aid of tubes with well-lagged jackets, through which water from the thermostat was circulated.

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⁹ Holmberg, *Arkiv Kemi, Min., Geol.*, 1939, **13**, A, 8.