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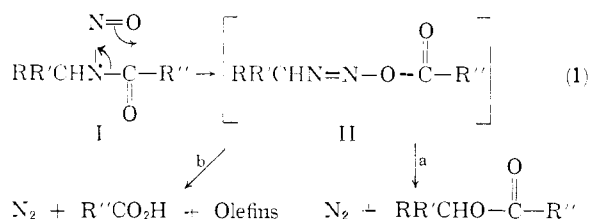
## N-Nitrosoamides. V. N-Nitrosoamides of Secondary Carbinamines; An Example of Intramolecular Inversion of Configuration<sup>1</sup>

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A tracer study of the nitrosoamide reaction has been carried out. N-(1-phenylethyl)-N-nitroso-2-naphthamide labelled in the carbonyl group with oxygen-18 was decomposed in acetic acid to yield nitrogen and 1-phenylethyl 2-naphthoate with 69% of the oxygen-18 still in the carbonyl group. The reaction was purely intramolecular since in acetic acid-O-d, the nitrosoamide yielded *naphthoate* ester containing no deuterium. The optically pure isomer gave (+)-1-phenylethyl 2-naphthoate (81%) (corresponding to retention of configuration) and (-)-1-phenylethyl 2-naphthoate (19%). Both of these esters contained 69% of the oxygen-18 in the carbonyl group, *i.e.*, the enantiomers were formed with the same distribution of O-18. A mechanism is proposed for the nitrosoamide reaction which involves the formation of a diazoester intermediate (RN=N-O<sub>2</sub>CR''), the loss of nitrogen to form an unsolvated carbonium ion and a carboxylate ion, partial rotation of the ions, and C-O bond formation to yield an ester with partial inversion of configuration.

N-Nitrosoamides I of secondary carbinamines decompose readily to yield two sets of reaction products.<sup>2</sup>



It has been shown that diazoesters (II) formed in the rate determining step<sup>3,4</sup> are intermediates in the reaction and that the product carboxylic esters are formed *via* intramolecular paths with predominant retention of configuration.<sup>4</sup> An oxygen-18 study of the ester formation step is the subject of this paper.

### Procedure

N-cyclohexyl and N-(1-phenylethyl)-2-naphthamides (carbonyl O-18) were nitrosated<sup>5</sup> and the product N-nitrosoamides were decomposed under various conditions. The esters obtained (R''CO<sub>2</sub>CHRR') were treated with lithium aluminum hydride and the two alcohols obtained, RR'-CHOH and R''CH<sub>2</sub>OH, were separated and analyzed; tests showed that no mixing of the O-18 occurred during the cleavage reaction. In a number of runs the alcohols were converted into their N-phenylcarbamate derivatives and further purified. The oxygen-18 contents were determined by the method of Doering and Dorfman.<sup>6</sup> The nitrosoamides of secondary carbinamines decompose rapidly at 25° and the oxygen-18 analyses were therefore restricted to the amides, the esters and the alcohols (equation, Table I). In general, the sums of the O-18 contents of the alcohol pairs closely checked the O-18 contents of the esters, and these in turn checked the O-18 contents of the amides, *i.e.*, in effect, an internal control on the analyses was present. In addition, the sample purities were checked by means of infrared spectra, physical constants, and random elementary analyses. We estimate on the basis of the precision observed, the analysis of standard compounds, and the recovery of O-18 (experimental part) that on the average our oxygen-18 results are good to ± 0.02 atom % O-18.

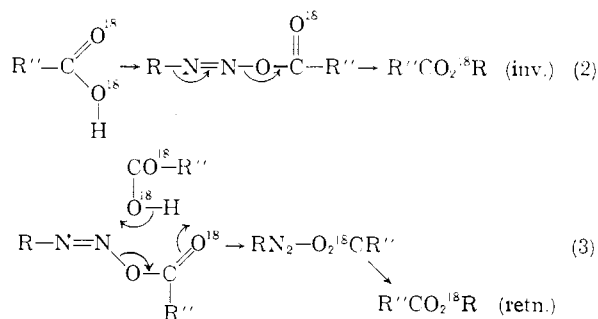
The reaction was also carried out with optically pure N-(1-phenylethyl)-N-nitroso-2-naphthamide (carbonyl O-18). (-)-1-Phenylethylamine and (-)-1-phenylethanol have the

same configuration<sup>7</sup> and since acylation of these compounds yielded (+) N-(1-phenylethyl)-2-naphthamide and (+)-1-phenylethyl 2-naphthoate, respectively, our rotation values and the observation that (+) amide yielded (+) ester (*via* the nitrosoamide) show that the decomposition of the nitrosoamide proceeded with predominant retention of configuration.

### Results

Our data for the decomposition of nitrosoamides labelled in the carbonyl group with O-18 are given in Table I; the last column gives the ester oxygen-18 distribution as a ratio of the oxygen-18 *excess* found in the carbonyl group (as % of the total O-18 *excess*) to that in the ether position. The data show that (1) some equilibration of the oxygen-18 has occurred in all of the runs, (2) most of the oxygen-18 remains in the carbonyl group, (3) the equilibration is almost independent of the alkyl group R (runs 3 and 7) within certain limits and (4) less equilibration occurs in protic solvents. Since it was shown that the labelled ester was stable under the reaction conditions and that no mixing or loss of O-18 occurred during the nitrosation, the O-18 equilibration occurred during the formation of the ester from II.<sup>8</sup> The following discussion will be given, therefore, in terms of reactions of the diazoester II.

There are two reaction paths involving the acid formed by elimination (path b, equation 1) that could, in general, account for the equilibration of the oxygens.



(1) A preliminary account of this work appeared in *THIS JOURNAL*, **80**, 2597 (1958).

(2) Emil H. White, *ibid.*, **77**, 6011 (1955).

(3) R. Huisgen and H. Reimlinger, *Ann.*, **599**, 161 (1956).

(4) Emil H. White, *THIS JOURNAL*, **77**, 6014 (1955).

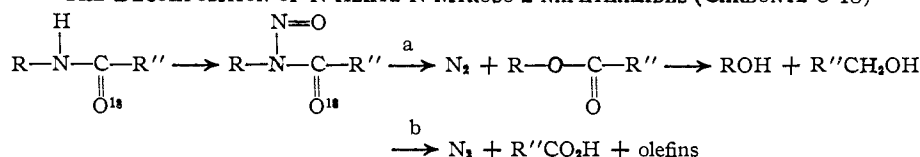
(5) Emil H. White, *ibid.*, **77**, 6008 (1955).

(6) W. Doering and E. Dorfman, *ibid.*, **75**, 5595 (1953).

(7) P. A. Levene, A. Rothen and M. Kuna, *J. Biol. Chem.*, **120**, 777 (1937). (-)-1-Phenylethylamine has been shown to have the same configuration ion as L-(+)-alanine by W. Leithe, *Ber.*, **64**, 2827 (1931).

(8) Mixing of the O-18 cannot of course occur until both oxygens are bonded to the carbon of the carbonyl group. In the rearrangement of I to II, therefore, mixing of the oxygens could not occur until some

TABLE I  
THE DECOMPOSITION OF N-ALKYL-N-NITROSO-2-NAPHTHAMIDES (CARBONYL O-18)



Run	R	Solvent	conc., M	Addend moles/mole nitrosoamide	T, °C.	Yield (%)		Atom % excess O-18 in: <sup>a</sup>				Car- bonyl O-18/ ether O-18 in ester
						Path a CO <sub>2</sub> R	Path b CO <sub>2</sub> H	$\frac{\text{H}}{\text{R}}\text{NCR}''$	$\frac{\text{O}}{\text{R}}\text{OCR}''$	$\frac{\text{R}''}{\text{CH}_2\text{OH}}$	ROH	
1	Cyclohexyl	Pentane	0.025	74 Na <sub>2</sub> CO <sub>3</sub>	20	38	43	1.233	0.644	0.705	0.552	56/44
2	Cyclohexyl	Dioxane	.038	22 Na <sub>2</sub> CO <sub>3</sub>	25	36	39	1.233	.622*	.688*	.532*	57/43
3	Cyclohexyl	Acetic acid	.354	.....	33	32	51	1.233	.611*	.798	.431	65/35
4	dl-Phenylethyl	Dioxane	.041	28 Na <sub>2</sub> CO <sub>3</sub>	50	22	47	1.199	.607*	.642	.550	54/46
5	(-)-1-Phenylethyl	Dioxane	.084	2 CH <sub>2</sub> N <sub>2</sub>	25	15	40 <sup>b</sup>	1.232*	.622	.656	.545	55/45
6	(-)-1-Phenylethyl	Dioxane	.080	2 Formic acid	40	17	63	1.232*	.607	.696*	.514*	58/42
7	(-)-1-Phenylethyl	Acetic acid	.454	.....	28	32	61	1.232*	.592	.842	.372	69/31
8	(-)-1-Phenylethyl	Methanol	.085	5 Acetic acid	28	15	75	1.232*	.615	.784	.439	64/36

<sup>a</sup> To simplify the table, the averages of duplicate O-18 analyses are given. The maximum difference between the values for each pair was 0.006 except for the starred figures where the differences ranged from 0.007 to 0.013. In addition, the amide figure for run 4 is an average of values that differed by 0.030. <sup>b</sup> Found as the methyl ester; analysis showed this to have completely equilibrated oxygens.

Reaction paths of this type are followed by nitrosoamides of 2-butylamine.<sup>4</sup> Nitrosoamides of 1-phenylethylamine, on the other hand, undergo reaction 3 (under favorable circumstances) but not reaction 2.<sup>4,9</sup> In the present case, both reactions have been completely eliminated from runs 3 and 7 because of the swamping effect of the acetic acid used as the solvent, and also from run 5 because of the scavenging effect of the diazomethane. They have been largely eliminated from run 6 (compare results of runs 5 and 6) and run 8. These reactions may account for part of the mixing observed in runs 1 and 2, however, since the sodium carbonate is probably not completely effective in removing the carboxylic acid formed. Experimentally, the amount of this carboxylate exchange was determined through the addition of a known amount of labelled acid to the unlabelled nitrosoamide in a set of duplicate runs; the O-18 content of the esters was thus a measure of the incorporation of external acid under our reaction conditions. The results (Table VI) indicate a negligible "return" for runs 7 and 8 and a maximum "return" of 10% for run 6. Applying this correction to run 6 gives a c/e value of <sup>59</sup>/<sub>41</sub>, only slightly different from that listed.

Another reaction which could account for the mixing of the O-18 is that involving the diazoalkane.<sup>10,11</sup> This path is out of the question for II  $\rightarrow \text{RR}'\text{CN}_2 + \text{R}''\text{CO}_2^{18}\text{H} \rightarrow$

Products of equation 1 (4)

the *naphthoate* ester obtained from runs 3, 5, 7 and 8 for the reasons cited above (the naphthoate stage such as IV is reached. In principle, IV could be formed directly from I, but this would not alter our arguments appreciably. From the nature of the reaction, it is quite unlikely that II returns to I; in a closely related reaction at -75° where such a process would have been detected (run 11), no N-nitroamide was formed.

(9) R. Huisgen and Ch. Rüdhardt, *Ann.*, **601**, 21 (1956).

(10) Emil H. White and Carl A. Aufdermarsh, Jr., *THIS JOURNAL*, **83**, 1174 (1961).

(11) A. Streitwieser, Jr., and W. D. Schaeffer, *ibid.*, **79**, 2893 (1957).

must be a product of an intramolecular reaction because the "return" of naphthoic acid under the conditions used is negligible).

Bimolecular reactions involving the nitrosoamide itself have been ruled out by Huisgen and Rüdhardt who have shown that the stereochemical results are independent of the concentration of nitrosoamide in the system.<sup>9</sup> In view of the nature of the reaction, the steady state concentration of the diazoester II is extremely low, and it is very unlikely that the subsequent decomposition would be bimolecular in II. We conclude therefore, that bimolecular reactions are of no importance for runs 3, 5, 6, 7 and 8 and that the partial mixing of the oxygens observed occurred during a purely intramolecular reaction of the diazoester II.

**Stereochemistry.**—Our results for the decomposition of optically pure N-(1-phenylethyl)-N-nitroso-2-naphthamide (carbonyl O-18) are given in Table II. The configurational results are similar to those found for the corresponding nitrosoacetamides and nitrosobenzamides.<sup>4,9</sup> In all of the cases, a certain amount of "racemization" has occurred. To conclusively rule out the possibility that part of this loss of optical activity was due to an intervention of diazoalkane intermediates or to an exchange of the  $\alpha$ -hydrogen atom in one of the reaction intermediates, the decomposition of N-(1-phenylethyl)-N-nitroso-2-naphthamide was carried out in pure acetic acid-O-d. The 1-phenylethyl 2-naphthoate obtained from this reaction contained essentially no deuterium,<sup>12</sup> and the 1-phenylethyl acetate which was formed contained only a small amount, equivalent to *ca.* 4% incorporation. Therefore certainly for runs 5 and 7 (and with a fair certainty for runs 6 and 8) both the stereochemical changes and the O-18 changes observed occurred in the solvent cage of a single diazoester molecule.

In runs 6, 7 and 9, the 1-phenylethanol obtained from the lithium aluminum hydride cleavage of the

(12) We are indebted to Dr. P. Jordan of the Eidg. Technische Hochschule, Zürich, for these analyses.

TABLE II  
THE DECOMPOSITION OF OPTICALLY PURE N-(1-PHENYLETHYL)-N-NITROSO-2-NAPHTHAMIDE (CARBONYL O-18)

$$\text{R}-\overset{\text{N}=\text{O}}{\text{N}}-\overset{\text{O}^{18}}{\text{C}}-\text{R}' \rightarrow \text{R}-\text{O}-\overset{\text{O}}{\text{C}}-\text{R}' \rightarrow \text{ROH} + \text{R}'\text{CH}_2\text{OH}$$

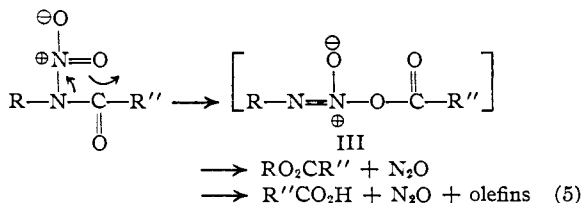
Run (Table I)	% (+) Enantiomer <sup>a</sup> in ester	% (-) Enantiomer <sup>a</sup> in ROH	Total ROH (-ROH + ±ROH)	Atom % excess O-18 (±)ROH <sup>b</sup>	(-)ROH <sup>a</sup>
5	73	75			
6	81	79	0.518	0.543	0.534
			.510	.531	.538
7 <sup>c</sup>	81	81	.375	.379	.378
			.369	.381	.384
8	83				
9 <sup>d</sup>	65	65	.592	.588	
			.590	.588	

<sup>a</sup> These forms correspond to retention of configuration. <sup>b</sup> Analyzed as the N-phenylcarbamates. <sup>c</sup> In addition to the naphthoate, a 17% yield of 1-phenylethyl acetate was obtained containing 56% of the form corresponding to retention of configuration. <sup>d</sup> The nitrosoamide decomposed violently in the solid state in this run. The amide used contained 1.232 atom % excess O-18; the ester formed contained 0.637 atom % excess O-18 and the 2-naphthyl carbinol (R'CH<sub>2</sub>OH), 0.626.

partially racemic naphthoates was treated with phenyl isocyanate (no racemization occurred during the cleavage (Table II) and tests showed that no racemization occurred during the formation of the carbamates). The 1-phenylethyl N-phenylcarbamates were recrystallized to yield pure samples of the levorotatory carbamate (corresponding to retention of configuration) and the DL-carbamate; these were then analyzed for oxygen O-18.

The data (Table II) indicate that (5) about 80% of the ester is formed with retention of configuration, and (6) the 20% of the ester formed with inversion of configuration has the same or very nearly the same O-18 distribution as the 80% formed with retention. For comparison purposes, the oxygen-18 values to be expected for various combinations of inversion, retention, racemization and O-18 equilibration are listed in Table III. Possibility A best accounts for the results. Possibilities F and G indicate the approximate limits of error; we estimate that the ester formed with retention of configuration contained 69 ± ca. 2% of the O-18 excess in the carbonyl group and that the ester formed with inversion contained 69 ± ca. 5% of the O-18 excess in the carbonyl group.

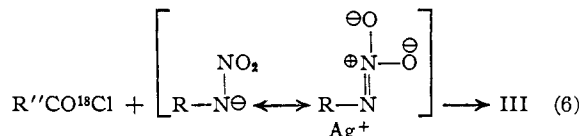
**N-Nitroamides.**—The decomposition of an N-nitroamide was also examined since it has been shown that N-nitroso and N-nitroamides decompose by similar paths.<sup>13</sup>



For our oxygen-18 work, III was prepared *in situ*

(13) Emil H. White and Daniel W. Grisley, *THIS JOURNAL*, **83**, 1191 (1961).

by the reaction of an acid chloride with the salt of a nitroamine.

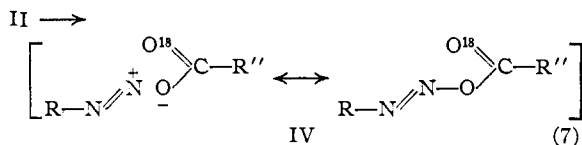


The results are given in Table IV.

These and other data reported earlier<sup>4,13</sup> indicate that (7) the third oxygen atom in III (compared to II) has little effect on the reaction, and (8) the O-18 results in this case are practically independent of the temperature in the range -75 to 25°.

Two other results are pertinent: (9) a bridgehead amine derivative, N-apocamphyl-N-nitroso-1-naphthamide (carbonyl O-18) yielded ester with completely equilibrated oxygens,<sup>14</sup> and (10) an optically pure tertiary carbinamine derivative, N-(2-phenyl-2-butyl)-N-nitrosobenzamide, yielded, in toluene, ester containing 97% of the enantiomer corresponding to retention of configuration.<sup>15</sup>

**Mechanism of the Reaction.**<sup>16</sup>—Two facts in particular, the intramolecular inversion and the O-18 results with the enantiomeric esters, eliminate from consideration completely concerted mechanisms<sup>17</sup> and mechanisms involving solvated, long lived carbonium ions or diazoalkane intermediates.<sup>11</sup> A mechanism related to certain aspects of the nitrous acid-aliphatic amine reaction is, on the other hand, consistent with our results. It is proposed that the first step in the decomposition of the diazoester is the formation of the ion pair IV.



The initial cleavage of the N-O bond is reasonable in view of the facility with which the N-X bond is broken in related aromatic diazonium derivatives, A-N=N-X (X = OH, OR, OAc, CN, etc.).<sup>18</sup> In terms of structures proposed for other ion pairs,<sup>19</sup> the N-O bond in IV (in the solvents used) should have some covalent character and the nitrogen should be bonded to one of the oxygens in particular. An initial cleavage of II into three particles could in principle occur, especially for diazoesters that would yield relatively stable ions; however, the carboxylate ion exchange observed with our compounds and the oxygen-18 results for the apocamphylamine nitrosoamide (complete mixing of the oxygens) can be best accounted for on the basis of a finite lifetime for IV. Furthermore, in the de-

(14) Unpublished work of Carl A. Aufdermarsh, Jr.

(15) Unpublished work of Robert R. Johnson.

(16) A few reactions involving *tert* carbinamines are also presented; it is believed that the mechanisms for the *sec* and *tert* isomers are very nearly the same.

(17) The concerted S<sub>N</sub>i mechanism, e.g. (W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J. Chem. Soc.*, 1207 (1937)). The mechanism for inversion of configuration proposed earlier\* on the basis of the stereochemical results alone is also incorrect.

(18) K. H. Saunders, "The Aromatic Diazo Compounds," 2nd Ed., Longmans, Green and Co., New York, N. Y., 1949.

(19) S. Winstein and G. C. Robinson, *THIS JOURNAL*, **80**, 169 (1958).

TABLE III  
 O-18 VALUES FOR THE REACTION

$$(+)R-N\begin{matrix} H \\ | \\ \text{---} \\ | \\ C \\ || \\ O^{18} \end{matrix}-R'' \quad (1.232 \text{ atom } \% \text{ excess O-18}) \longrightarrow (+ \text{ and } \pm)R-O\begin{matrix} O \\ || \\ \text{---} \\ | \\ C \\ || \\ O \end{matrix}-R'' \longrightarrow R''CH_2OH + (- \text{ and } \pm)ROH \longrightarrow (-)ROH + (\pm)ROH$$

Atom % excess O-18

$$\xrightarrow{\text{Found for run 7}} R''CH_2OH \left[ \begin{matrix} (-)ROH \text{ plus} \\ (\pm)ROH \end{matrix} \right] \begin{matrix} (-)ROH \\ (\pm)ROH \end{matrix}$$

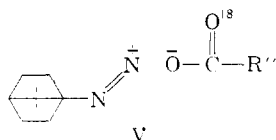
Path for the formation of ester (intramolecular)	Possible O-18 dist. for R-O-C(=O)-R''		Calculated values			
	% in carbonyl position	% in ether position	R''CH <sub>2</sub> OH	(- and ±)ROH	(-)ROH	(±)ROH
(A) 81% retn. 19% inv.	69	31	0.850	0.382	0.382	0.382
(B) 81% retn. 19% inv.	69	31	.806	.426	.382	.499
(C) 81% retn. 19% inv.	80	20	.916	.316	.246	.431
(D) 62% retn. 38% racemization	100	0	.998	.234	.144	.380
(E) 62% retn. 38% racemization	80	20	.845	.387	.334	.475
(F) 81% retn. 19% inv.	71	29	.875	.357	.357	.357
(G) 81% retn. 19% inv.	70	30	.851	.381	.370	.400

 TABLE IV  
 THE REACTION OF 2-NAPHTHYL CHLORIDE-O<sup>18</sup> WITH THE SILVER SALT OF N-NITROCYCLOHEXYLAMINE

Run	Solvent	Temp., °C.	R''COCl	N <sub>2</sub> O	Atom % excess O-18			Carbonyl O-18/ Ether O-18
					R-O-C(=O)-R''	R''CH <sub>2</sub> OH	ROH	
10	CCl <sub>4</sub>	25	1.199 <sup>a</sup>	0	0.609	0.744	0.463	62/38
					.602	.751	.436	
11	CH <sub>2</sub> Cl <sub>2</sub>	-75	1.030 <sup>b</sup>	—	.522	.671	.348	66/34
					.522	.670	.356	

<sup>a</sup> Atom % excess O-18 in N-(1-phenylethyl)-2-naphthamide prepared from this acid chloride. <sup>b</sup> Atom % excess O-18 in the acid from which this acid chloride was made.

composition of diazoesters of primary carbamines<sup>10</sup> and  $\alpha$ -amino acid esters,<sup>2,20</sup> the nitrogens remain bonded to carbon after the N-O bond has been broken (diazoalkanes and the corresponding acids are formed); the nitrogen loss *via* IV is therefore presented as the more general case. Although a short lived diazonium ion could intervene between IV and the ester, it is omitted from the discussion in the absence of any evidence for its existence. Part of the mixing of the O-18 observed is believed to occur at the ion pair stage (IV). The main evidence for this comes from the complete mixing of O-18 observed in the decomposition of the nitrosoamide of apocamphylamine.<sup>14</sup> In this case, the ion

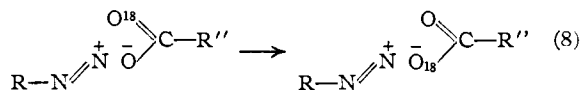


pair V has a relatively long life because of the unfavorable nature of the bridgehead carbonium ion<sup>21</sup> to be formed on the loss of nitrogen. This provides an opportunity for equilibration of the oxygens. If

(20) Unpublished work of Ronald Baumgarten.

(21) W. E. Doering, M. Levitz, A. Sayigh, M. Sprecher and W. P. Whelan, Jr., *THIS JOURNAL*, **75**, 1008 (1953); J. L. Franklin and F. H. Field, *J. Chem. Phys.*, **21**, 550 (1953).

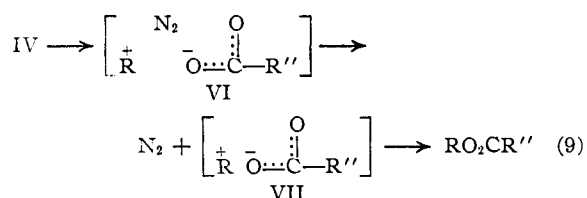
the equilibration were to occur only after the loss of



nitrogen one would have expected a minimum of mixing in the apocamphylamine case.

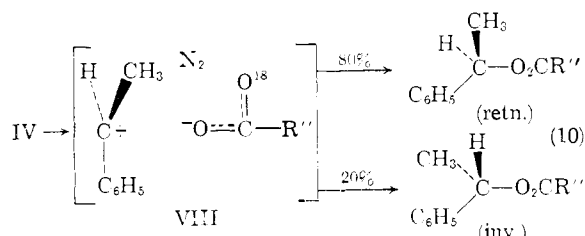
**The Nitrogen-loss Step.**—As far as the ester formation step is concerned, the partial but equivalent oxygen-18 mixing observed for the enantiomeric esters (Table II) requires that the carboxylate ion be free at one stage of the reaction, but since ester formation is in competition with a fast reaction—the rotation of the carboxylate ion (leading to O-18 mixing)—the ion can be free for only a very short period of time. Furthermore, the path leading to retention of configuration and that leading to inversion must be very similar or even identical as far as the carboxylate ion is concerned. For a moderate fraction of the molecules in our reactions, those formed with retention of configuration, the formation of ester from IV can be satisfactorily accounted for on the basis of a dissociation of the diazonium ion followed by a rapid combination of the carbonium ion and the carboxylate ion,<sup>22</sup> presumably *via* the ion pair VII.

(22) The electron deficient nature of the carbon is indicated by the extensive isomerization observed for the nitrosoamide decomposition



The special results (stereochemical and O-18) require additional comment.

It is generally agreed that the loss of nitrogen from an aliphatic diazonium ion is an exothermic process.<sup>23</sup> The transition state should resemble the reactant<sup>24</sup> and since the N-O bond is partially broken in IV, the loss of nitrogen can be considered as essentially a dissociation process involving no specific aid from the carboxylate ion or from the solvent. The high relative yield of naphthoate ester obtained from the run in acetic acid (Table I), the essential independence of the stereochemical results with respect to the solvent,<sup>4,9</sup> and the results in Table II all suggest that the cation in question is not specifically solvated (in the sense of the solvation described by Doering and Zeiss for the carbonium ions in certain solvolytic reactions<sup>25a</sup>). The mechanism for the formation of partially inverted ester from this carbonium ion is given below; while the mechanism is not uniquely defined by the data, it seems a reasonable one to us. It is proposed that in the time interval between the loss of nitrogen from the diazonium ion and the formation of the ester, and probably as a consequence of this loss of nitrogen, some of the carbonium ions rotate sufficiently far so that bond formation with the carboxylate ion can occur on what was the backside of the ion<sup>22b</sup> (at the same time, partial rotation of the carboxylate ion occurs leading to partial mixing of the oxygen-18 (*vide infra*)).



Rotation of the cation about an axis through the center of mass, approximated in this case by the bond from the central carbon to the phenyl group, need not appreciably alter the position of the electron deficient carbon atom with respect to the

in polar solvents. The decomposition of *N*-isobutyl-*N*-nitroso-3,5-dinitrobenzamide in acetic acid yielded a butyl 3,5-dinitrobenzoate fraction containing the *tert*-butyl isomer (40%) and the *sec*-butyl isomer (15%) in addition to isobutyl 3,5-dinitrobenzoate (45%).<sup>2</sup> The non-concerted nature of the reaction is suggested by the O-18 results and by the observation that the decomposition of *N*-nitroso-*N*,*O*-diacetylhydroxylamine (*via*  $\text{CH}_3\text{CON}=\text{N}-\text{O}_2\text{CCH}_3$ ) yielded ketene and

acetic acid in addition to acetic anhydride and nitrous oxide.

(23) (a) R. Huisgen and Ch. Rùchardt, *Ann.*, **601**, 1 (1956); (b) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957).

(24) G. S. Hammond, *THIS JOURNAL*, **77**, 334 (1955).

(25) (a) W. von E. Doering and H. H. Zeiss, *J. Am. Chem. Soc.*, **75**, 4733 (1953). (b) A different type of intramolecular inversion of configuration has been given by Boozer and Lewis (*ibid.*, **75**, 3182 (1953)) for certain chlorosulfite decompositions.

two oxygens, and the subsequent approach of the ions could give *D* and *L* molecules having the same or very nearly the same distribution of O-18. The nonlabelled oxygen atom in IV and VIII is the closer of the two to the carbon undergoing substitution and it seems reasonable to expect that in those cases where the oxygens are not completely equilibrated, the ester will be formed with a major amount of the O-18 still in the carbonyl group. A number of other ion pair reactions involving the carboxylate group (carbonyl O-18) have been shown to proceed with retention of O-18 in the carbonyl group.<sup>26</sup> This mechanism for the decomposition of the diazonium ion pair is related to certain mechanisms which have been proposed for the reaction of nitrous acid with aliphatic amines. Non-solvated carbonium ions<sup>27</sup> have been proposed for this reaction, and also carbonium ions that interact with the solvent<sup>28</sup> or with a group on an adjacent carbon atom<sup>29</sup> at a rate greater than the rate of rotation about a carbon-carbon single bond; it is implied, certainly, that the reactions of these ions are exceedingly fast. The analogous fast step in the intramolecular portion of the nitrosoamide decomposition would be the reaction of the carbonium ion with the carboxylate ion (equation 10); it is quite likely that reactions of this type proceed with little or no activation energy.<sup>30</sup>

Some of the carbonium ions that are formed react with the solvent cage; in run 7, for example, 1-phenylethyl acetate was obtained in addition to the normal naphthoate ester. The acetate contained 56% of the enantiomer corresponding to retention of configuration, and it is considered to be a mixture of 1-phenylethyl acetate formed *via* the diazo acetate (*i.e.*, IX  $\rightarrow$  XI, R' = methyl) and 1-phenylethyl acetate formed by capture of the cation by the solvent (with predominant inversion); little or no acetate is apparently formed by a displacement reaction (equation 2) since in a related study, it has been found that the amount of inversion of configuration is independent of the concentration of added acetic acid or acetate ion.<sup>9</sup>

It might be argued that the inversion of configuration and the O-18 mixing could occur during the lifetime of the ion pair VII. Such reactions might be possible for ion pairs of relatively stable carbonium ions (*e.g.*, R = triphenylmethyl); it is unlikely, however, that reactions other than rapid collapse (to yield the ester and possibly the olefin) are possible for the ion pairs derived from simple alkylamines. For such ion pairs, the R-O bond in VII would be relatively strong with some covalent character<sup>19</sup>; it is not apparent how racemization of the naphthoate ion pair could occur at this stage and why molecules which might have succeeded in inverting their configuration should have the same O-18 distribution as those formed with retention of

(26) D. B. Denney and D. G. Denney, *ibid.*, **79**, 4806 (1957); D. B. Denney and B. Goldstein, *ibid.*, **79**, 4948 (1957); ref. 19. It should be pointed out, however, that the problem of concomitant inversion of configuration was not a factor in these cases.

(27) D. J. Cram and J. E. McCarty, *ibid.*, **79**, 2866 (1957).

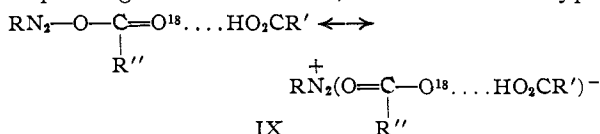
(28) D. Semenov, C. Shih and W. G. Young, *ibid.*, **80**, 5472 (1958).

(29) B. M. Benjamin, H. J. Schaeffer and C. J. Collins, *ibid.*, **79**, 6160 (1957).

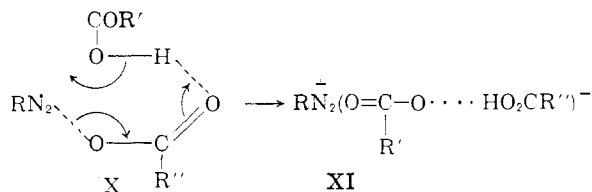
(30) G. N. Lewis, *J. Franklin Inst.*, **226**, 293 (1938); G. B. Kistiakowsky and R. Williams, *J. Chem. Phys.*, **23**, 334 (1955).

configuration. Nor is it apparent on this basis why the observed "racemization" should be so little affected by the solvent or why two R<sup>⊕</sup> groups as different as cyclohexyl and 1-phenylethyl should give almost the same O-18 mixing.

**The Anion and the Loss of Nitrogen.**—Less equilibration of the oxygen-18 is observed in protic solvents (Table II), a result which can be accounted for in terms of hydrogen bonding of the carboxylate ion. In acetic acid, *e.g.*, the reaction should proceed principally *via* forms such as IX and the corresponding solvate of VIII; anions of the type



shown are well known.<sup>31</sup> The hydrogen bonding also provides a reasonable mechanism for the exchanges of the carboxylate group that are often observed.<sup>4,9</sup> In reaction mixtures containing added acid (R'CO<sub>2</sub>H) and IV, esters of both R'CO<sub>2</sub>H and R''CO<sub>2</sub>H are formed and, depending on the reaction conditions, the carboxylate exchange occurs totally or partially on the frontside of the alkyl group R.<sup>32</sup> Significantly, esters of the foreign acid R'CO<sub>2</sub>H are formed only to the extent that R'CO<sub>2</sub>H is a stronger acid than R''CO<sub>2</sub>H. For example, the decomposition of N-(*sec*-butyl)-N-nitroso-3,5-dinitrobenzamide in the presence of benzoic acid gave *sec*-butyl 3,5-dinitrobenzoate but no *sec*-butyl benzoate (*K<sub>a</sub>* for 3,5-dinitrobenzoic acid/*K<sub>a</sub>* for benzoic acid = 27)<sup>33</sup> whereas the reverse procedure, the decomposition of N-(*sec*-butyl)-N-nitrosobenzamide in the presence of 3,5-dinitrobenzoic acid yielded both esters.<sup>4</sup> We conclude that in the latter case the 3,5-dinitrobenzoate ester was formed *via* X → XI (R = *sec*-butyl, R'' = phenyl, R' = 3,5-dinitrophenyl).



**Equilibrium, Stereochemistry and Structure.**—The decomposition of N-(1-phenylethyl)-N-nitrosobenzamide (carbonyl O-18) (Table I) is a reaction in which the various processes leading to O-18 equilibration, "racemization," and ester formation are in close balance. The decomposition in acetic acid, *e.g.*, yielded 32% of the naphthoate ester with *ca.* 20% inversion of configuration and *ca.* 30% mixing of the O-18; a 17% yield of the acetate ester was also obtained. Steric effects can alter this balance as shown by the figures for the decomposition of the nitrosobenzamides of 2-butylamine, 1-phenylethylamine and 2-phenyl-2-butylamine; the product esters contained, respectively, *ca.* 70%,<sup>4</sup> 80% and 97% of the forms cor-

(31) G. M. Barrow and E. A. Yerger, *THIS JOURNAL*, **76**, 5211 (1954); **77**, 4474, 6206 (1955); E. Erlenmeyer, *Ber.*, **42**, 516 (1909).

(32) Ref. 4, run 18 in dioxane illustrates the frontside exchange.

(33) M. E. A. Sirks, *Rec. trav. chim.*, **27**, 207 (1908).

responding to retention of configuration. This trend is attributed to the increase in size of the carbonium ion and the consequent decrease in the rate of rotation of the ion (equation 10).

The ester formation step is not particularly sensitive to electronic effects on the other hand. The nitrosoamides of 1-phenylethylamine and 1-(*p*-methoxyphenyl)ethylamine have been shown to yield esters with the same configurational change (72% *retn.* and 28% *inv.*)<sup>9</sup>; furthermore, we have shown that the nitrosoamides of cyclohexylamine and 1-phenylethylamine decompose with almost the same amount of O-18 mixing (Table I). The mechanism proposed is consistent with this insensitivity to electronic factors. The activation energy for the step in which the carbonium ion is formed is low, and therefore any differences in the activation energies must be small. The fast reactions which follow the formation of the carbonium ion (those leading to inversion of configuration and O-18 equilibration) must therefore be similar for the various nitrosoamides.<sup>34</sup>

**N-Nitroamides.**—The O-18 results (Table IV) indicate that the mechanism presented for the decomposition of the N-nitrosoamides can be extended to the decomposition of the N-nitroamides. The insensitivity of the nitroamide O-18 results with respect to changes in the reaction temperature might be accounted for by a low activation energy for the step involving the loss of nitrous oxide from III; these reaction were heterogeneous, however, and perhaps other factors were responsible.

**NOTE ADDED IN PROOF.**—Run 7 (Tables I and II) has been repeated with N-(1-phenylethyl)-2-naphthamide containing 5.12 atom % *excess* oxygen-18. The product ester (formed with 80% retention of configuration) contained 2.61 atom % *excess* oxygen-18, the carbonyl group of the ester contained 3.64 atom % *excess* oxygen-18, the ether portion of the ester contained 1.82 atom % *excess* oxygen-18, the  $\pm$  1-phenylethanol contained 1.81 atom % *excess* oxygen-18, and the optically pure (–) 1-phenylethanol contained 1.83 atom % *excess* oxygen-18. These results further support the conclusion stated in the text: namely, that the D and L forms of the ester are formed with the same, or very nearly the same, distribution of oxygen-18. We wish to thank Dr. Heinz Kaegi for this experiment.

## Experimental<sup>35</sup>

**Oxygen-18 Analysis.** (a) **Method.**—Samples were analyzed in duplicate by the method of W. Doering and E. Dorfman.<sup>6</sup> The pyrolysis train was modified slightly by the omission of the carbon monoxide scrubber trap (containing 3% bromine in 1:1 carbon tetrachloride–chloroform) which has been found to be unnecessary.<sup>36</sup> The carbon dioxide from each sample was collected in a sample tube immersed in liquid nitrogen. The nitrogen carrier gas was pumped out of the sample tube still immersed in liquid nitrogen and the size of the CO<sub>2</sub> sample was then determined manometrically in a calibrated system. At the beginning and end of each day's analyses, the train blank was collected and its size determined manometrically. The blank was found to be nearly constant on any given day and never exceeded 4% of any CO<sub>2</sub> sample.

(34) This implies that for nitrosoamides of cyclohexylamine, 1-phenylethylamine and related amines, most of the O-18 mixing occurs after the loss of nitrogen from the diazonium ion. The apocamphylamine results given in the text are not covered by this generalization because of the relatively high value of the activation energy for the loss of nitrogen from the bridgehead diazonium ion.<sup>31</sup>

(35) Elementary analyses were by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(36) M. L. Bender and R. D. Ginger, *THIS JOURNAL*, **77**, 348 (1955).

The CO<sub>2</sub> samples and tank CO<sub>2</sub> were examined in a Model 21-401 Mass Spectrometer (Consolidated Engineering Corp., Pasadena, California). The peak heights of mass numbers 44, 45 and 46 were measured by scanning each sample three times. The average ratio of the 46/44 peak heights was determined for each CO<sub>2</sub> sample and for tank CO<sub>2</sub>. Division of 46/44 sample CO<sub>2</sub> by 46/44 tank CO<sub>2</sub> gave  $r = \frac{46/44 \text{ sample CO}_2}{46/44 \text{ tank CO}_2}$ . This ratio ( $r$ ) needs to be corrected for the blank. It was assumed that the blank contained the normal abundance of oxygen-18, *i.e.*,  $\frac{46/44 \text{ blank CO}_2}{46/44 \text{ tank CO}_2} = 1$ . Letting  $R$  equal the desired corrected value, it follows that

$$R = \frac{100r - (\% \text{ blank}) (1)}{(100 - \% \text{ blank})}$$

The atom fraction oxygen-18,  $x$ , was determined by equations a and b which were derived from those of Doering and Dorfman by setting  $R = \frac{46/44 \text{ sample CO}_2}{46/44 \text{ tank CO}_2}$  and rearranging.

$$(a) (0.99592 + 0.00408 R)x = 0.408R - 0.204$$

$$(b) (0.99592 + 0.00408 R)x = 0.8155R - 0.6109$$

Equation a was used for compounds containing one oxygen atom per molecule and for the esters; equation b was used for compounds containing two oxygens, only one of which was labeled (*e.g.*, carbamates labeled in the ether position). The atom % excess oxygen-18 was determined by equation c,

$$(c) \text{atom } \% \text{ excess oxygen-18} = 100x - 0.204$$

0.204 atom % being the normal abundance of oxygen-18.

(b) Errors.—The standard deviation by this method of analysis varies with the percentage of oxygen-18, as shown by the analysis of benzoic acid-O<sup>18</sup> samples containing different amounts of oxygen-18 (each sample was analyzed at least five times).<sup>37</sup>

Atom % excess oxygen-18	Standard deviation
1.352	±0.024
1.017	± .010
0.280	± .012
0.202	± .009

Our duplicate values, in general, fall within these limits (Tables I, II and IV). Another check on our results is the comparison of the total amount of O-18 found in the two alcohols (R'CH<sub>2</sub>OH + ROH) with the amount of O-18 in the starting amide. The results of Table V are quite satisfactory in this respect.

TABLE V  
RECOVERY OF OXYGEN-18

Runs (Tables I, II, IV)	R- $\overset{\text{H}}{\text{N}}-\overset{\text{O}^{18}}{\parallel}-\text{R}'' \rightarrow \text{RO}^{18}\text{H} + \text{R}''\text{CH}_2\text{O}^{18}\text{H}$		Gain or loss
	Amide	Atom % excess O-18 <sup>a</sup> R'CH <sub>2</sub> OH + ROH	
1	1.233	1.257	+0.024
2	1.233	1.220	- .013
3	1.233	1.229	- .004
4	1.199	1.192	- .007
5	1.232	1.201	- .031
6	1.232	1.210	- .022
7	1.232	1.214	- .018
8	1.232	1.223	- .009
9	1.232	1.217	- .015
10	1.199	1.198	- .001
11	1.030	1.023	- .007

\* Averages of duplicate values.

2-Naphthoyl Chloride-O<sup>18</sup>.—2-Naphthoyl chloride (70 g.) was dissolved in a mixture of 50 ml. of water (containing 1.4% H<sub>2</sub>O<sup>18</sup>) (Stuart Oxygen Co.) and 400 ml. of pure dioxane. After refluxing for 47 hr. under nitrogen, the solu-

tion was concentrated to 200 ml. The 2-naphthoic acid-O<sup>18</sup> was collected and washed with water. Further concentration of the mother liquor produced a second crop of acid. The total yield (59.7 g.) was treated with 140 ml. of thionyl chloride and 2 drops of pyridine. The mixture was gently warmed till the evolution of gas ceased. After refluxing for an additional hour, the excess thionyl chloride was removed *in vacuo*. Sublimation of the residue at 0.1 mm. and 100° gave 64.3 g. (96.6% from the acid) of 2-naphthoyl chloride-O<sup>18</sup>, m.p. 51–53°, lit.<sup>38</sup> 51–52°. (+)N-(1-phenylethyl)-2-naphthamide-O<sup>18</sup> prepared from this acid chloride had 1.226 atom % excess oxygen-18.

1-Naphthoyl chloride-O<sup>18</sup> was also prepared by this procedure.

N-Cyclohexyl-2-naphthamide-O<sup>18</sup>.—To an ice cold ether solution of cyclohexylamine (13.9 g., 131 mmoles) in anhydrous ether was added pure 2-naphthoyl chloride-O<sup>18</sup> (10.0 g., 52.4 mmoles). After a few minutes of shaking, the vigorous reaction was over and the amine hydrochloride and most of the amide precipitated. The former was washed out with water leaving the amide suspended in the ether layer. The mixture was filtered to give crude amide and filtrate A. The crude amide was taken up in chloroform, washed with dilute hydrochloric acid, 5% sodium bicarbonate and water. Filtrate A was washed in the same way and combined with the chloroform solution. The mixture was concentrated *in vacuo* to 150 ml. Addition of 100 ml. of hexane caused the amide to precipitate. The amide was recrystallized from this solvent mixture to give, after drying, 10.0 g. of pure amide, m.p. 185.6–187.0°. Concentration of the mother liquor to 50 ml. produced a second crop (1.4 g.), m.p. 185.7–186.6°. Total yield was 11.4 g. (86.0%). A second recrystallization from 1:1 chloroform–hexane produced material melting at 185.8–187.0°.

Anal. Calcd. for C<sub>17</sub>H<sub>19</sub>NO: C, 80.61; H, 7.56; N, 5.53. Found: C, 80.77; H, 7.61; N, 5.42.

The amide contained 1.232, 1.234 atom % excess oxygen-18.

*dl*-N-(1-Phenylethyl)-2-naphthamide-O<sup>18</sup>.—To an ice cold solution of *dl*-1-phenylethylamine (5.72 g., 4.30 mmoles) in chloroform was added a solution of purified 2-naphthoyl chloride-O<sup>18</sup> (4.00 g., 2.09 mmoles) dissolved in chloroform. After 10 minutes at 0°, the solution was washed successively with water (three times), dilute hydrochloric acid, 5% sodium bicarbonate and water. The dried chloroform solution was concentrated *in vacuo* to about 20 ml., and heptane (200 ml.) was added. The amide which separated was dissolved by heating to reflux. A distilling head was attached and the solution was concentrated to 180 ml., at which point the amide began to separate. On cooling 5.18 g. (90.2%) of the amide separated as fluffy white needles. In order to remove traces of heptane, the material was held at 100° (0.1 mm.) for several days, after which it melted at 140–140.8°.

Anal. Calcd. for C<sub>19</sub>H<sub>17</sub>NO: C, 82.89; H, 6.22; N, 5.09. Found: C, 82.57; H, 6.02; N, 5.09.

The pure *dl*-1-phenylethyl-2-naphthamide-O<sup>18</sup> contained 1.184, 1.214 atom % excess oxygen-18.

(-)-1-Phenylethylamine.—The racemic amine was resolved through the *d*-tartrate by the method of Theilacker and Winkler.<sup>39</sup> These authors report that the pure *l*-amine-*d*-tartrate can be obtained in a single step, but it was found that, in the absence of pure seed crystals, two additional recrystallizations from methanol were necessary. The amine was liberated from its tartrate salt by the addition of aqueous alkali and extraction with ether. The dried ether solution was concentrated *in vacuo* and the residual amine distilled. (-)-1-Phenylethylamine, b.p. 72.8° at 12 mm. (lit.,<sup>9</sup> 74° at 15 mm.) was obtained in 25% yield (from the total racemic mixture). It had  $\alpha_{\text{D}}^{25} - 38.11^\circ$  (1 dm., neat), (lit., -38.39°,<sup>9</sup> -38.30°<sup>39</sup>) and was assumed to be optically pure.

(+)-N-(1-Phenylethyl)-2-naphthamide-O<sup>18</sup>.—Optically pure (-)-1-phenylethylamine (45 g., 0.373 mole) was dissolved in 400 ml. of ice cold chloroform which had been purified by washing it twice with sulfuric acid, twice with water and drying it over calcium chloride. An ice cold solution of 2-naphthoyl chloride-O<sup>18</sup> (68 g., 0.356 mole) in

(38) E. B. Hershberg and J. Cason, "Organic Syntheses," Vol. XXI, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 84.

(39) W. Theilacker and H. G. Winkler, *Ber.*, **87**, 690 (1954).

(37) G. S. Dorion, Yale University, unpublished results.



400 ml. of purified chloroform was added slowly with cooling in ice to avoid excessive warming. After shaking for a few minutes, the mixture was shaken briefly with 200 ml. of aqueous sodium hydroxide (1.9 normal). The phases were separated and the chloroform layer was washed with dilute hydrochloric acid and water and then dried. Removal of the chloroform *in vacuo* left fluffy white needles of virtually pure amide (96 g., 98.2%), m.p. 171–172°. It was recrystallized from a mixture of 2500 ml. of 3:2 hexane-chloroform and dried in a vacuum desiccator to give 78 g. of (+)N-(1-phenylethyl)-2-naphthamide-O<sup>18</sup> (1.236, 1.227 atom % excess oxygen-18), m.p. 171.7–172.2°,  $\alpha^{25\text{D}} + 1.592$ ,  $[\alpha]^{25\text{D}} + 48.61^\circ$  ( $c = 3.275$  in CHCl<sub>3</sub>). It was assumed to be optically pure.

After concentration to about 1 liter, the mother liquor produced a second crop (16.5 g.) with m.p. 171.3–171.7° and  $[\alpha]^{25\text{D}} + 47.80^\circ$  ( $c = 3.345$  in CHCl<sub>3</sub>). This material, after recrystallization from fresh hexane-chloroform, gave 11.8 g. of pure amide, m.p. 172.2–173.0°,  $[\alpha]^{25\text{D}} + 48.71^\circ$  ( $c = 3.455$  in CHCl<sub>3</sub>).

**Cyclohexyl 2-Naphthoate.**—A solution of 2-naphthoyl chloride (1.0 g.) and cyclohexanol (0.7 g.) in 10 ml. of pyridine was allowed to stand overnight at 25°. Water (30 ml.) was added and the precipitate was extracted with ether. The ether solution was washed with water and dilute hydrochloric acid, dried with MgSO<sub>4</sub> and concentrated *in vacuo*. The solid residue was recrystallized from pentane at –80° and from 50% aqueous ethanol, then sublimed at 100° and 0.1 mm. to give cyclohexyl 2-naphthoate, m.p. 56.4–57.2°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>18</sub>O<sub>2</sub>: C, 80.28; H, 7.13. Found: C, 80.59; H, 7.31.

**dl-1-Phenylethyl 2-Naphthoate.**—A solution of 2-naphthoyl chloride (0.790 g., 6.47 mmoles) and 1-phenylethanol (1.00 g., 5.24 mmoles) in 20 ml. of pyridine was allowed to stand at 25° for 3 hr. Ether and water were added and the phases were separated after shaking. The ether layer was washed successively with water (twice), dilute hydrochloric acid and 5% sodium bicarbonate. The dried ether solution was concentrated *in vacuo* to give a yellow oil which was dissolved in hexane and filtered to remove a small amount of acid. After removal of hexane, the residual oil was evaporatively distilled at 124° and 0.09 mm. to give 0.884 g. (61.2%) of dl-1-phenylethyl 2-naphthoate as a heavy colorless oil ( $n_{\text{D}}^{40}$  1.6085) which crystallized after three days, m.p. 39–45°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>18</sub>O<sub>2</sub>: C, 82.58; H, 5.84. Found: C, 82.47; H, 5.45.

**(–)1-Phenylethanol.**—The hydrogen phthalate of dl-1-phenylethanol was resolved by crystallization of its brucine salt from acetone and methyl acetate.<sup>40</sup> The (+) hydrogen phthalate was reduced with lithium aluminum hydride to give (–)1-phenylethanol, b.p. 93.8° at 12 mm.,  $n_{\text{D}}^{25} 1.5248$ ,  $\alpha^{25\text{D}} - 2.066^\circ$ ,  $[\alpha]^{25\text{D}} - 45.10^\circ$  ( $c = 4.581$  in methanol),  $\alpha^{25\text{D}} = -43.7^\circ$  (1 dm., neat). Lit.,  $n_{\text{D}}^{25} 1.5244^9$ ,  $[\alpha]^{25\text{D}} - 45.5^\circ$  ( $c = 4.91$  in methanol),<sup>9</sup>  $\alpha^{20\text{D}}$  (neat) = –43.5°,<sup>40</sup> –43.6°.<sup>41</sup> The alcohol was assumed to be optically pure and the rotation value –43.7° was used to calculate the optical purity of the alcohols obtained in runs 5, 6, 7 and 9. (–)1-Phenylethylamine and (–)1-phenylethanol have the same configuration.<sup>7</sup>

**(+)1-Phenylethyl 2-Naphthoate-carbonyl-O<sup>18</sup>.**—2-Naphthoyl chloride-O<sup>18</sup> (2.20 g., 0.011 mole) was added to a solution of optically pure (–)1-phenylethanol (1.50 g., 0.0123 mole) in 20 ml. of pyridine. After standing at 25° for 1 hr. the mixture was warmed at 40° for an additional 2 hr. Water and hexane were added and the phases separated. The organic layer was washed with dilute hydrochloric acid, water and 5% sodium bicarbonate. Removal of hexane *in vacuo* left the crude ester (2.70 g., 89%) as a colorless oil which slowly solidified on standing. This was evaporatively distilled at 0.07 mm. and 140°. The purity of the middle fraction (m.p. 42.2–43.5°) was established by comparison of its infrared spectrum and refractive index ( $n_{\text{D}}^{40}$  1.6078, supercooled) with those of authentic pure dl-1-phenylethyl 2-naphthoate. It analyzed for 1.111, 1.099 atom % excess O-18.

(40) A. J. H. Houssa and J. Kenyon, *J. Chem. Soc.*, 2260 (1930); E. Downer and J. Kenyon, *ibid.*, 1156 (1939).

(41) E. L. Eliel, *This Journal*, 71, 3970 (1949).

The optical rotation,  $\alpha^{25\text{D}} + 3.954^\circ$ ,  $[\alpha]^{25\text{D}} + 118.7^\circ$  ( $c = 3.33$  in 95% ethanol) was used in calculating the percent retention in runs 5, 6, 7, 8 and 9 (Table II).

**2-Naphthylcarbinol.**—An ether solution of 2-naphthoic acid (1.00 g., 5.82 mmoles) was added dropwise with stirring to 40 ml. of ca. 0.8 M lithium aluminum hydride in ether. After stirring overnight the excess hydride was destroyed by dropwise addition of ice water. The precipitate was dissolved by adding 10% sulfuric acid. The ether layer was separated, extracted with 1 N potassium hydroxide, dried and concentrated *in vacuo*. The residue was recrystallized from 50% aqueous ethanol, dried *in vacuo* and sublimed at 80–90° and 0.1 mm. The pure 2-naphthylcarbinol (0.60 g., 65%) melted at 82.2–83.2°; lit.,<sup>42</sup> 80–80.5°.

**N-Cyclohexyl-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup>.**—This compound was freshly prepared for each of runs 1, 2 and 3 by a standard procedure. The following preparation, which was carried out for run 1, is typical. Chloroform was purified by successive washing with sulfuric acid (twice) and water (twice) followed by drying over calcium chloride. A slurry of anhydrous sodium acetate (6.0 g., 73.2 mmoles) in 25 ml. of purified chloroform was cooled to –80° in a three neck flask equipped with mechanical stirrer and flushed with nitrogen. Dinitrogen tetroxide (3.0 ml., 47.2 mmoles) was added, followed by an ice cold solution of 3.50 g. (13.8 mmoles) of N-cyclohexyl-2-naphthamide-O<sup>18</sup> (1.232, 1.234 atom % excess oxygen-18) in 75 ml. of purified chloroform. The –80° bath was replaced with an ice salt bath and the mixture was stirred at –5° for 0.5 hr. It was poured into ice and water and shaken and separated. When the green organic layer was washed with ice cold 5% sodium bicarbonate it became yellow. After drying briefly at 0° over anhydrous magnesium sulfate, it was filtered rapidly. The chloroform was removed by freeze drying. By this procedure the nitrosoamide solution was never allowed to warm above 0°. After removal of the chloroform, the nitrosoamide was obtained as a bright yellow crystalline solid which weighed 3.63 g. (92.8%) and melted with violent decomposition at 61.5°. The infrared spectrum showed the carbonyl (5.87 $\mu$ ) and nitroso (6.67 $\mu$ ) absorptions typical of nitrosoamides<sup>5</sup>; it showed the presence of no more than traces of un-nitrosated amide and decomposition products.

**dl-N-(1-Phenylethyl)-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup> and Optically Active N-(1-Phenylethyl)-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup>.**—These compounds were freshly prepared for each run by the method described for the cyclohexyl analog. Their decomposition points were 66 and 75°, respectively. The purity and identity were established for each run by infrared analysis.

Run 1.—Freshly prepared N-cyclohexyl-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup> (3.63 g., 12.8 mmoles) was dissolved in 500 ml. of pure, dry pentane containing 100 g. of suspended sodium carbonate. The mixture was stirred for 7 hr. at 20°. The pentane solution was decanted from the sodium salts, washed twice with 5% sodium bicarbonate, dried over MgSO<sub>4</sub> and concentrated at reduced pressure. The residual ester was chromatographed on Woelm neutral alumina. The fraction which was eluted with 5% ether-95% hexane was recrystallized twice from pentane by cooling to –80° and rapidly decanting the mother liquor. Sublimation at 100–115° and 0.1 mm. gave 1.23 g. (37.8%) of cyclohexyl 2-naphthoate-O<sup>18</sup> (0.642, 0.646 atom % excess oxygen-18), m.p. 55.2–55.8°. The infrared spectrum was identical with that of analytically pure ester prepared from the alcohol.

Acidification of the sodium salts yielded 0.95 g. (43.2%) of 2-naphthoic acid.

The pure ester (0.560 g., 2.21 mmoles) was dissolved in 20 ml. of anhydrous ether and added dropwise with stirring to 9 ml. of 1.1 molar lithium aluminum hydride in ether. After stirring for 1.5 hr. the mixture was cooled in ice and the excess hydride was destroyed by the cautious addition of 3 ml. of ice water. The two layers were shaken thoroughly and separated. The aqueous layer was extracted three times with ether. The combined ether extracts were dried and concentrated *in vacuo*. The oily residue was evaporatively distilled at 65–70° and 25–35 mm. to yield crude cyclohexanol-O<sup>18</sup> (157 mg., 71.2%). The residue of crude 2-naphthylcarbinol-O<sup>18</sup> was sublimed, recrystallized from ethanol-water and resublimed to give the pure alcohol

(42) E. Bamberger and O. Boekmann, *Ber.*, 20, 1118 (1887).



(246 mg., 68.5%). It melted at 82.0–83.0°, analyzed for 0.703, 0.706 atom % excess oxygen-18, and had an infrared spectrum which was identical with that of pure 2-naphthylcarbinol.

The crude cyclohexanol-O<sup>18</sup> was treated with 167 mg. of phenyl isocyanate, and the mixture was allowed to stand for 2 hr. at room temperature. The solid carbamate which appeared was recrystallized twice from hexane and sublimed at 90–100° and 0.08 mm. to yield cyclohexyl N-phenylcarbamate-ether-O<sup>18</sup> (0.555, 0.549 atom % excess oxygen-18 in the ether position), m.p. 83.8–84.6°; lit.,<sup>43</sup> 82°.

Run 2.—Freshly prepared N-cyclohexyl-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup> (2.70 g., 9.56 mmoles) was dissolved in 250 ml. of purified dioxane<sup>44</sup> containing 22 g. of suspended sodium carbonate. After stirring for 16 hr. at 24–27° the mixture was filtered. Ether was added and the solution was extracted with water to remove the dioxane. The ether solution was dried and the ether removed *in vacuo*. The crude ester was purified by sublimation at 100° and 0.1 mm., four recrystallizations from pentane, and one recrystallization from an ethanol-water mixture. The pure ester (0.88 g., 3.46 mmoles, 36.1%) melted at 55.2–57.2° after drying in a vacuum desiccator and had an infrared spectrum which was identical with that of analytically pure cyclohexyl 2-naphthoate. It contained 0.618, 0.625 atom % excess oxygen-18.

Acidifications of the sodium salts gave 0.64 g., 3.72 mmoles, (39%) of 2-naphthoic acid.

A sample of the ester was cleaved and worked up as described in Run 1. The 2-naphthylcarbinol-O<sup>18</sup> (0.684, 0.692 atom % excess oxygen-18) melted at 82.0–83.5°; its infrared spectrum was identical with that of the pure alcohol. The cyclohexyl N-phenylcarbamate-ether-O<sup>18</sup> (0.525, 0.538 atom % excess oxygen-18 in the ether position) melted at 84.0–85.0°.

Run 3.—Freshly prepared N-cyclohexyl-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup> (3.50 g., 12.4 mmoles) was added to 35 ml. of glacial acetic acid at 30°. The fairly rapid reaction caused the mixture to warm up to 35°. After 15 minutes the nitrosoamide had completely dissolved, and after 2 hr. the color had almost completely disappeared. The mixture was poured into ice water and extracted with pentane. The naphthoic acid which separated was filtered off, and the pentane solution was washed three times with 5% sodium bicarbonate, acidification of which gave a small amount of 2-naphthoic acid. The total yield of acid was 1.08 g. (50.6%). The pentane solution was concentrated *in vacuo* to yield a mixture of cyclohexyl acetate and cyclohexyl-2-naphthoate-O<sup>18</sup>. After chromatography of the mixture, the acetate (0.392 g.) was distilled off at 0.1 mm. and room temperature. The naphthoate residue was sublimed, recrystallized from pentane and resublimed to give 1.08 g. (31.7%) of cyclohexyl 2-naphthoate-O<sup>18</sup> (0.615, 0.606 atom % excess oxygen-18) which melted at 55.3–56.8° and had an infrared spectrum identical to that of the analytically pure ester.

Cleavage of the ester and work up as described in Run 1 gave 2-naphthylcarbinol-O<sup>18</sup> (0.797, 0.799 atom % excess oxygen-18) which melted at 81.8–82.8°. The infrared spectrum was identical with that of an authentic sample. The cyclohexyl N-phenylcarbamate-ether-O<sup>18</sup> (0.432, 0.429 atom % excess oxygen-18 in the ether position) melted at 84.0–84.6°.

Run 4.—Freshly prepared *dl*-N-(1-phenylethyl)-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup> (3.26 g., 10.7 mmoles) was dissolved in 250 ml. of purified dioxane containing 30 g. of suspended sodium carbonate. After vigorous stirring for 1.3 hr. at 48–50° the color had disappeared and the mixture was cooled and filtered to remove the sodium salts. The product was treated as described in Run 2 to yield crude ester contaminated with 2-naphthoic acid and styrene. Extraction with hexane followed by filtration gave 0.21 g. of 2-naphthoic acid. The hexane solution was chromatographed on Woelm neutral alumina. The fraction which was eluted with 5% ether–95% hexane was held at 0.1 mm. to remove traces of styrene. Evaporative distillation at 130° and 0.1 mm. gave 0.657 g. (22.2%) of 1-phenyl-

ethyl 2-naphthoate-O<sup>18</sup> (0.600, 0.613 atom % excess oxygen-18). The infrared spectrum was identical with that of the analytically pure ester. Acidification of the sodium salts gave 0.65 g. of 2-naphthoic acid; the total yield was 0.86 g. (46.8%).

A sample of the ester was cleaved with lithium aluminum hydride as described in Run 1 to give, after purification, 2-naphthylcarbinol-O<sup>18</sup> (0.642, 0.642 atom % excess oxygen-18), m.p. 82.0–83.0°, which had an infrared spectrum identical with that of authentic carbinol. The 1-phenylethanol-O<sup>18</sup> was converted to 1-phenylethyl N-phenylcarbamate-ether-O<sup>18</sup> (0.550, 0.549 atom per cent. excess oxygen-18) which melted at 92.7–93.8°; lit.,<sup>43</sup> 94°. The infrared spectrum was identical with that of an authentic sample of the carbamate.

Run 5.—A solution of diazomethane (70 mmoles) in a mixture of ether (200 ml.) and purified dioxane (200 ml.) was prepared at 0°. To this solution was added 10.2 g. (33.6 mmoles) of optically pure N-(1-phenylethyl)-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup> prepared from the (+) amide. Dissolution was complete after 15 minutes of swirling. The yellow solution was allowed to warm to 25° and the sides of the flask were washed down with 50 ml. of purified dioxane. The mixture was allowed to stand for 5 hr. during which time the color gradually deepened to red-orange and the evolution of nitrogen ceased. At this point, titration showed that the solution contained 26 mmoles of diazomethane.

After a total of 6 hr., the solution was treated cautiously with dilute aqueous hydrochloric acid (vigorous bubbling). On becoming acid the solution changed in color from orange to yellow. After the addition of 200 ml. of dilute hydrochloric acid, the mixture was shaken and the phases separated. The aqueous phase was washed twice with 100 ml. of ether. The combined ether extracts were washed three times with equal volumes of water and twice with 200 ml. of 5% sodium bicarbonate. The ether layer was dried over anhydrous MgSO<sub>4</sub> overnight, filtered and concentrated *in vacuo* leaving ca. 10 ml. of an orange oil which partially crystallized. This material was held under high vacuum for several hours to remove the styrene. The product which remained was taken up in pentane and filtered to remove a small amount of orange solid. The slightly yellow pentane solution was chromatographed on Woelm neutral alumina. The main fraction (5.80 g.), which was eluted with 95:5 pentane–ether, consisted of a mixture of methyl 2-naphthoate-O<sup>18</sup> and 1-phenylethyl-2-naphthoate-O<sup>18</sup>. A comparison of infrared spectra showed that the other fractions, weighing 2.2 g. in all, were of virtually the same composition as the main fraction. The more volatile methyl ester in the 5.80 g. fraction was sublimed from the mixture at 75–80° and 0.1 mm. White crystals of methyl 2-naphthoate-O<sup>18</sup> (2.55 g., 13.7 mmoles, 40% based on the nitrosoamide) collected on the cold finger leaving the crude 1-phenylethyl ester as an almost colorless oil. The methyl ester was recrystallized from 20 ml. of hexane to give white clusters of needles, m.p. 77.6–78.8°; lit.,<sup>45</sup> 73.2° (corr.). It contained 0.619, 0.621 atom % excess oxygen-18.

Cleavage of the methyl 2-naphthoate-O<sup>18</sup> with lithium aluminum hydride gave a 95% yield of 2-naphthylcarbinol-O<sup>18</sup>, m.p. 82–83.5°, containing 0.607, 0.607 atom % excess oxygen-18.

The residual oil from the sublimation was evaporatively distilled at 130–140° and 50μ. The first fraction, 0.060 g., *n*<sub>D</sub><sup>40</sup> 1.6071, was discarded. The second fraction was pure (+)1-phenylethyl 2-naphthoate-O<sup>18</sup> as shown by its refractive index, *n*<sub>D</sub><sup>40</sup> 1.6080, and infrared spectrum. It weighed 1.40 g. (15% yield from the nitrosoamide) and contained 0.621, 0.623 atom % excess oxygen-18. It was 46.6% optically pure as shown by the optical rotation,  $\alpha$ <sub>D</sub><sup>25</sup> + 1.841°, [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 55.4° (*c* = 3.33 in 95% ethanol).

Lithium aluminum hydride reduction and workup as previously described gave a 94% yield of 2-naphthylcarbinol-O<sup>18</sup>, m.p. 82.7–84.2°, containing 0.654, 0.657 atom % excess oxygen-18. Also obtained in 75% yield was (–)1-phenylethanol-O<sup>18</sup>, b.p. 80° at 7.5 mm., *n*<sub>D</sub><sup>25</sup> = 1.5250, containing 0.544, 0.546 atom % excess oxygen-18. The optical rotation in methanol was  $\alpha$ <sub>D</sub><sup>25</sup> – 0.434° (*l* = 0.5), [ $\alpha$ ]<sub>D</sub><sup>25</sup> – 22.6° (*c* = 3.84). Calculated on the basis of the highest reported specific rotation,<sup>9</sup> –45.5°, the optical

(43) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948.

(44) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Massachusetts, 1955, p. 284.

(45) M. S. Newman and H. V. Zahm, *THIS JOURNAL*, **65**, 1100 (1943).

purity is 49.7%, in satisfactory agreement with the value observed for the ester.

Run 6.—Optically pure N-(1-phenylethyl)-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup> was prepared from (+)N-(1-phenylethyl)-2-naphthamide-O<sup>18</sup> by the method previously described. Ten g. (32.8 mmoles) of the nitrosoamide was dissolved in a mixture of 400 ml. of purified dioxane and 2.4 ml. (64.2 mmoles) of formic acid. After 2 hr. at 40° the color had disappeared. The mixture was poured into 1.2 liters of water and extracted with 100 ml. of ether. The aqueous phase was washed twice with ether and the combined ether extracts were washed three times with water and twice with 5% sodium bicarbonate. Acidification of the basic washings gave 3.5 g. (63%) of crystalline 2-naphthoic acid.

The washed ether solution was dried and concentrated *in vacuo* to leave a yellow oil, which was held for a few minutes at 0.1 mm. to remove styrene. It was then chromatographed on 17 g. of Woelm neutral alumina. The fraction which was eluted with 5% ether-95% hexane was evaporatively distilled. The main fraction which came over at 125-140° and 0.09 mm. was 1.52 g. (16.8%) of 1-phenylethyl 2-naphthoate-O<sup>18</sup> (0.606, 0.608 atom % excess oxygen-18),  $n_{40}^{25}D$  1.6132. The optical rotation,  $\alpha_{25}^{24}D + 2.50^\circ$ ,  $[\alpha]_{25}^{24}D + 72.78^\circ$  ( $c = 3.435$  in 95% ethanol) showed it to be 61.0% optically pure.

Anal. Calcd. for C<sub>19</sub>H<sub>16</sub>O<sub>2</sub>: C, 82.59; H, 5.84. Found: C, 82.86; H, 5.90.

The ester was cleaved as described in Run 9 to give 87.5% of pure 2-naphthylcarbinol-O<sup>18</sup> (0.691, 0.701 atom % excess oxygen-18), m.p. 84.0-85.0°. Also obtained, in 63% yield was pure (-)1-phenylethanol-O<sup>18</sup>, (0.518, 0.510 atom % excess oxygen-18), b.p. 73.5° at 6.0 mm.,  $n_{25}^{25}D$  1.5242,  $\alpha_{25}^{25}D$  (neat) -25.50° (58.3% optically pure).

Run 7.—Freshly prepared optically pure N-(1-phenylethyl)-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup> (20.7 g., 68.1 mmoles) from the (+) amide was carefully pulverized and added with stirring to 150 ml. of acetic acid. It did not dissolve immediately but after 2 hr. at 25-30° the mixture became homogeneous. The yellow color disappeared after an additional 2 hr. of stirring at 25-30°. The solution was poured into 300 ml. of ice water and extracted with 150 ml. of hexane. The aqueous phase was diluted with an equal volume of water and washed twice with hexane. The combined hexane extracts were washed twice with water, filtered to remove suspended 2-naphthoic acid (7.1 g., 61%) and washed twice with 5% sodium bicarbonate. The dried hexane solution was concentrated *in vacuo* to leave a yellow oil which was evaporatively distilled after removal of styrene at 0.1 mm. The first fraction (1.5 g.) which came over at 120-130° and 0.090 mm. was 1-phenylethyl acetate,  $n_{25}^{25}D$  1.4946 (lit.,<sup>9</sup>  $n_{25}^{25}D$  1.4941) which had  $\alpha_{25}^{24}D - 0.432^\circ$ ,  $[\alpha]_{25}^{24}D - 16.43^\circ$  ( $c = 2.630$  in benzene). The extrapolated specific rotation for (-)1-phenylethyl acetate, obtained from (-)1-phenylethanol is -130.5°.<sup>9</sup> The product was therefore obtained with 12.6% over-all retention of configuration.

The second evaporative distillation fraction (1.9 g.,  $n_{40}^{25}D$  1.5746) came over at 130-140° and 3 $\mu$  and consisted of a mixture of 1-phenylethyl acetate and 1-phenylethyl 2-naphthoate. It was estimated to contain 80% naphthoate from the refractive index. The third fraction (4.5 g.,  $n_{40}^{25}D$  1.6058), which distilled at 140° and 1-2 $\mu$ , was 1-phenylethyl 2-naphthoate-O<sup>18</sup> as shown by comparison of its refractive index and infrared spectrum with those of authentic samples ( $n_{40}^{25}D$  1.6083). It contained 0.592, 0.592 atom % excess oxygen-18 and was 61.8% optically pure;  $\alpha_{25}^{25}D + 2.55^\circ$ ,  $[\alpha]_{25}^{25}D = 73.7^\circ$ , ( $c = 3.460$  in 95% ethanol).

Cleavage of the ester and purification of the alcohols was performed as described for Run 9. 2-Naphthylcarbinol-O<sup>18</sup> (0.839, 0.845 atom % excess oxygen-18), m.p. 82.0-83.5°, was obtained in 80% yield. (-)1-Phenylethanol-O<sup>18</sup> (0.375, 0.369 atom % excess oxygen-18), b.p. 78° at 6.5 mm.,  $n_{25}^{25}D$  1.5353, which was obtained in 69.5% yield, was 61.8% optically pure ( $\alpha_{25}^{25}D - 27.03^\circ$  (neat)).

Run 8.—Optically pure N-(1-phenylethyl)-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup> (9.00 g., 29.6 mmoles) was added with stirring to a mixture of 350 ml. of dry methanol and 8.5 ml. (148 mmoles) of acetic acid. The nitrosoamide dissolved slowly and rearranged as it went into solution.

After 2 hr. at 25-30° all had dissolved. After an additional hour, the color had disappeared and the reaction mixture was diluted with 3 liters of water and extracted twice with ether. The ether extracts were combined and washed three times with water and 4 times with 5% sodium bicarbonate. The dried ether solution was concentrated *in vacuo* to leave a yellow oil which was chromatographed on Woelm neutral alumina. The material which was eluted with 5% ether-5% hexane was evaporatively distilled. The first fraction (0.102 g.,  $n_{40}^{25}D$  1.6000) was collected at 100-130° and 0.08 mm. and presumably contained traces of acetate ester. The second fraction, which came over at 130° and 0.08 mm., was 1.08 g. (14.5% of 1-phenylethyl 2-naphthoate-O<sup>18</sup> (0.615, 0.614 atom % excess oxygen-18)),  $n_{40}^{25}D$  1.6061. The infrared spectrum was identical with that of the analytically pure *dl*-ester. It was 64.5% optically pure as shown by the optical rotation,  $\alpha_{24}^{24}D$  2.387°,  $[\alpha]_{24}^{24}D + 76.5^\circ$  ( $c = 3.120$  in 95% ethanol).

Acidification of the bicarbonate washings gave 3.8 g. (74.6%) of 2-naphthoic acid.

The ester was cleaved in the manner described to give 2-naphthylcarbinol-O<sup>18</sup> (0.786, 0.781 atom % excess oxygen-18), m.p. 82.3-84.0°, and 1-phenylethanol-O<sup>18</sup> (0.441, 0.437 atom % excess oxygen-18),  $n_{25}^{25}D$  1.5243.

Run 9.—In this run, 40 g. of (+)N-(1-phenylethyl)-2-naphthamide-O<sup>18</sup> was nitrosated by the procedure described. After removal of the chloroform, the nitrosoamide decomposed violently while being scraped from the flask and about 1/3 of the decomposition products were lost through the neck of the flask. The products which remained were extracted with hexane and filtered to yield 4 g. (ca. 16%) of 2-naphthoic acid. The hexane solution was chromatographed, and the ester obtained after removal of solvent and styrene *in vacuo* was evaporatively distilled at 140° and 0.02 mm. to give 5.9 g. (ca. 16%) of 1-phenylethyl 2-naphthoate-O<sup>18</sup> (0.637, 0.637 atom % excess oxygen-18),  $n_{40}^{25}D$  1.5962. The infrared spectrum was virtually identical with that of an authentic sample of the *dl*-ester. It had  $\alpha_{25}^{25}D + 1.161^\circ$ ,  $[\alpha]_{25}^{25}D + 36.03^\circ$  ( $c = 3.222$  in 95% ethanol), and was 30.3% optically pure.

A solution of the ester (5.00 g., 181 mmoles) in 50 ml. of anhydrous ether was added dropwise with stirring to 30 ml. of ca. 2.5 M lithium aluminum hydride in ether. After stirring for 1.5 hr., the mixture was treated with 30 ml. of ice water to destroy the excess hydride. After triturating the mixture for 1.5 hr. the ether was poured off and the aqueous slurry was triturated twice with fresh ether. The combined ether extracts were washed with 25 ml. of 2% sodium hydroxide, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Crude 1-phenylethanol-O<sup>18</sup> was obtained by evaporative distillation of the residual oil at 90-105° and 10 mm. The crude 2-naphthyl carbinol-O<sup>18</sup> (2.50 g., 87.5%) which remained as a solid residue was purified as described in Run 1 to give material melting at 80.5-81.8° and containing 0.623, 0.629 atom % excess oxygen-18.

Distillation of the crude 1-phenylethanol-O<sup>18</sup> (1.93 g., 88.9%) gave the pure alcohol; b.p. 77° at 6.5 mm.,  $n_{25}^{25}D$  1.5250; lit.,<sup>9</sup>  $n_{25}^{25}D = 1.5244$ . The infrared spectrum was identical with that of authentic alcohol. It contained 0.592, 0.590 atom % excess oxygen-18 and was 30.2% optically pure ( $\alpha_{25}^{25}D - 13.24^\circ$  (neat)).

(-)1-Phenylethyl N-Phenylcarbamate.—An equimolar mixture of optically pure (-)1-phenylethanol ( $\alpha_{25}^{25}D - 43.7^\circ$  (neat, 1 dm.)) and phenylisocyanate was allowed to stand at room temperature for several hours and then warmed briefly to 80°. The solid which separated on cooling was recrystallized twice from hexane to give an 80% yield of (-)1-phenylethyl N-phenylcarbamate as heavy well-formed needles, m.p. 100.7-102.0°,  $\alpha_{25}^{25}D - 5.437^\circ$ ,  $[\alpha]_{25}^{25}D - 100.0^\circ$  ( $c = 5.345$  in benzene); lit.<sup>46</sup> m.p. 99°,  $[\alpha]_{16}^{16}D + 101.5^\circ$  (prepared from (+)1-phenylethanol).

A 1.5 g. sample of 1-phenylethanol ( $\alpha_{25}^{25}D - 41.5^\circ$ , neat, 1 dm.) was treated with phenyl isocyanate in a similar manner to yield 2.8 g. of the carbamate. This was treated with an excess lithium aluminum hydride for 24 hr. at 25°. The alcohol was recovered, washed with dilute acid and then base and distilled to yield 1.28 g. of 1-phenylethanol,  $\alpha_{25}^{25}D - 42.1^\circ$ , neat, 1 dm.).

Resolution of L + DL 1-Phenylethyl N-Phenylcarbamate-ether-O<sup>18</sup>.—In each of Runs 6, 7 and 9, the *l* + *dl* 1-phenylethanol-O<sup>18</sup> obtained by reduction of the ester was converted to its N-phenylcarbamate-ether-O<sup>18</sup> derivative,

(46) A. McKENZIE and G. W. CLOUGH, *J. Chem. Soc.*, **103**, 687 (1913).

and this was "resolved" by fractional crystallization from hexane. In a typical resolution (Run 6), 0.230 g. of 58.3% optically pure 1-phenylethanol-O<sup>18</sup> (0.518, 0.510 atom % oxygen-18) and 0.231 g. of phenylisocyanate were mixed and heated for 5 minutes at 90°. After allowing the mixture to stand at room temperature for several hours, the solid carbamate which appeared was dissolved in 10 ml. of boiling hexane and filtered hot to remove traces of sym-diphenylurea. The filtrate was seeded with a crystal of pure (-)-1-Phenylethyl N-phenylcarbamate and allowed to cool to room temperature. The supernatant liquid (mother liquor 1) was rapidly decanted from the well formed needles which had separated. The needles were washed three times with fresh hexane and then recrystallized from 3 ml. of hexane to give 0.122 g. of (-)-1-phenylethyl N-phenylcarbamate ether-O<sup>18</sup> (0.534, 0.538 atom % excess oxygen-18 in ether position), m.p. 101–102°,  $\alpha^{23.5^\circ}\text{D} -5.043^\circ$ ,  $[\alpha]^{23.5^\circ}\text{D} -101.0^\circ$  ( $c = 4.995$  in benzene). Mother liquor 1, on further cooling, deposited fluffy clusters of needles which were recrystallized from 2 ml. of hexane to give 107 mg. of *dl*-1-phenylethyl N-phenylcarbamate-ether-O<sup>18</sup> (0.543, 0.531 atom % excess oxygen-18 in ether position), m.p. 93–94°,  $\alpha^{23.5^\circ}\text{D} -0.016^\circ$ ,  $[\alpha]^{23.5^\circ}\text{D} -0.343^\circ$  ( $c = 4.660$  in benzene).

By the same procedure, the 61.8% optically pure (-)-1-phenylethanol-O<sup>18</sup> (0.375, 0.369 atom % excess oxygen-18) obtained in Run 7 was resolved to give (-)-1-phenylethyl N-phenylcarbamate-ether-O<sup>18</sup> (0.378, 0.384 atom % excess oxygen-18 in ether position), m.p. 100–101°,  $\alpha^{24^\circ}\text{D} -5.34^\circ$ ,  $[\alpha]^{24^\circ}\text{D} -99.9^\circ$  ( $c = 5.345$  in benzene), and *dl*-1-phenylethyl N-phenylcarbamate-ether-O<sup>18</sup> (0.379, 0.381 atom % excess oxygen-18 in ether position), m.p. 92.3–93.3°,  $\alpha^{25^\circ}\text{D} -0.025^\circ$ ,  $[\alpha]^{25^\circ}\text{D} -0.445^\circ$  ( $c = 5.615$  in benzene).

Since the per cent. retention was lower (30%) in Run 9, only the *dl*-1-phenylethyl N-phenylcarbamate-ether-O<sup>18</sup> was obtained after four recrystallizations from hexane. It melted at 92.2–93.2°, had  $\alpha^{24^\circ}\text{D} + 0.030^\circ$ ,  $[\alpha]^{24^\circ}\text{D} + 0.608^\circ$  ( $c = 4.945$  in benzene) and contained 0.588, 0.588 atom % excess oxygen-18.

**Control Experiments.** (A) Denitrosation of N-(1-Hexyl)-N-nitroso-2-naphthamide-carbonyl-O<sup>18</sup>.—The nitrosoamide was prepared as described before<sup>10</sup> by the nitrosation of N-hexyl-2-naphthamide-O<sup>18</sup> containing 1.326, 1.342 atom % excess oxygen-18. A sample (102 mg., 3.58 mmoles) was denitrosated by passing streams of nitrogen and anhydrous hydrogen chloride through its chloroform solution for 30 minutes. After washing with 0.5 N sodium thiosulfate, the solution was concentrated *in vacuo*. The solid residue was recrystallized from ten ml. of hexane to give 77.2 mg. (84.9%) of N-(1-hexyl)-2-naphthamide, m.p. 104.5–105.5°, whose infrared spectrum was identical with that of authentic material. It contained 1.324, 1.339 atom % excess oxygen-18, showing that no loss of label from the carbonyl position had occurred during nitrosation and denitrosation.

**Analysis of Standard Esters.** (B).—1-Hexyl 2-naphthoate-carbonyl-O<sup>18</sup> (1.238, 1.250% excess oxygen-18) was subjected to the same conditions of the reaction and work up as used in Run 2 except that the temperature was held at 50°. After reisolated (87.5% recovery) it was cleaved to 1-hexanol (0.004, 0.002 atom % excess oxygen-18) and 2-naphthyl carbinol-O<sup>18</sup> (1.175, 1.177 atom % excess oxygen-18). Although a small amount (*ca.* 5%) of the label was lost (due probably to exchange with water catalyzed by the acid used after the lithium aluminum hydride reduction), the negligible amount of oxygen-18 found in the hexanol shows that the oxygens of the ester do not equilibrate under the conditions of the reaction and work up.

Run 7 was similarly controlled by using optically pure (+)-1-phenylethyl 2-naphthoate carbonyl-O<sup>18</sup>, (1.111, 1.099 atom % excess oxygen-18). The reisolated pure ester (75.8% recovery) had  $\alpha^{23^\circ}\text{D} + 117.4^\circ$  (95% ethanol). Cleavage produced (-)-1-phenylethanol, (0.00, 0.004 atom % excess oxygen-18),  $n^{25^\circ}\text{D} = 1.5230$  and 2-naphthylcarbinol (1.060, 1.056 atom % excess oxygen-18), m.p. 82–83.2°. The slight loss of label (less than 5%) is attributed to exchange in the naphthylcarbinol; certainly none of the label migrated to the ether position. In fact, if a 5% correction were applied it would slightly increase the ratio, magnifying the unsymmetrical distribution of oxygen-18 in the ester. This correction was not made, however, since in all of the runs in the secondary series,

the loss of label on going from amide to the two alcohols was insignificant and within experimental error (Table V).

(C). **Determination of Intermolecular Reactions with Naphthoic Acid.**—That fraction of the total naphthoate ester which was produced from the free 2-naphthoic acid in solution was determined as follows for Runs 6, 7 and 8 (Table I). Samples of *dl*-N-(1-phenylethyl)-N-nitroso-2-naphthamide (2.20 g., 7.24 mmoles) were decomposed with the same reagents and under the same conditions as those used for Runs 6, 7 and 8, except that 1.63 g. (9.48 mmoles) of 2-naphthoic acid-O<sup>18</sup> (1.026, 1.033 atom % excess oxygen-18) was added in each case. After the reaction was complete, ether and water were added. The mixture was shaken and separated and the ether layer was washed several times with water to remove the water miscible solvent. Aliquots of the aqueous washings were concentrated to give small amounts of 2-naphthoic acid. The bulk of the 2-naphthoic acid was removed from the ether solution by extraction with 5% sodium bicarbonate. The total yield of acid was determined by weighing the combined fractions. The yield of acid produced in the reaction (path b, equation 1) was determined by subtraction of the amount originally added.

The washed ether solution was concentrated *in vacuo* and the residual ester was purified by chromatography and evaporative distillation. The ester was analyzed for oxygen-18. In each case the purity of the ester was established by comparing its infrared spectrum with that of the analytically pure ester. The yields and oxygen-18 data are given in Table VI. The amount of ester which was

TABLE VI

DECOMPOSITION OF 7.24 MMOLES OF N-(1-PHENYLETHYL)-N-NITROSO-2-NAPHTHAMIDE IN THE PRESENCE OF 9.48 MMOLES OF 2-NAPHTHOIC ACID-O<sup>18</sup> (1.026, 1.033 ATOM % EXCESS OXYGEN-18)

Run	Solvent	Conc., M	Acid produced, mmoles	Atom % excess O-18 in ester	% 'Return'
6'	Dioxane <sup>a</sup>	0.08	4.18	0.085 .084	10
7'	Acetic acid	.206	4.30	.017 .011	1.6
8'	Methanol <sup>b</sup>	.085	5.63	.005 .006	0.7

<sup>a</sup> The reaction mixture contained 2 moles of formic acid as in run 6 (Table I). <sup>b</sup> The reaction mixture contained 6 moles of acetic acid as in run 8.

formed from the labelled acid is, respectively, 8.2, 1.4 and 0.4%. However, some of the unlabelled acid produced in the elimination (path b, equation 1) has also "returned" to form the ester. The precise calculation of this value would be difficult. A satisfactory value can be obtained through the approximation that the amount of labelled acid is constant throughout a run (the correction to be applied will be small in any case). The integration of the

$$\text{equation } y = \frac{1.63}{1.63 + ax} \text{ (1.030) from } x = 0 \text{ to } x = 1 \text{ gives}$$

average per cent. excess of O-18 in the acid over the course of the reaction (1.63 = wt. of added acid, 1.030 = atom % excess O-18 in the acid added,  $a$  = wt. of acid formed from the nitrosoamide reaction, and  $x$  = fraction of nitrosoamide decomposed). The value of the integral divided into (100) (atom per cent. excess O-18 in the ester) gives the per cent. of the ester which is formed from free naphthoic acid in solution; these values are given in Table VI. These are maximum values, since the total amount of naphthoic acid present in these runs is far greater than the amount of naphthoic acid produced in the runs of Table I.

The calculations are also based on the assumption that 2-naphthoic acid-O<sup>18</sup> does not exchange its oxygens with unlabelled acid in solution. Exchange of this type would be most likely to occur in Run 7' where acetic acid, as solvent, is present in large excess. The following experiment shows that exchange is unimportant in Run 7' and, by analogy, in Runs 6' and 8'. 2-Naphthoic acid-O<sup>18</sup> (1.026, 1.032 atom % excess oxygen-18) (0.500 g.) was dissolved in 10 ml. of acetic acid and the mixture allowed to stand at 25–30° for 4 hr. (the conditions of Run 7'). The

solution was diluted with 50 ml. of ice water and the 2-naphthoic acid-O<sup>18</sup> which separated was quickly filtered, washed with water and dried in a vacuum desiccator. It contained 1.016, 1.029 atom % excess oxygen-18, showing that the loss of the labelled oxygen from the naphthoic acid was negligible.

**The Decomposition of N-(1-Phenylethyl)-N-nitroso-2-naphthamide in Acetic Acid-O-d.**—Acetic acid-O-d was prepared at 25° in a sealed system by the reaction of deuterium oxide (99.5% pure) with an equimolar amount of acetic anhydride which had been stored over and distilled from calcium oxide. The product was fractionated in the same apparatus and a center cut was used; the infrared spectrum showed no ordinary acetic acid.

To 70 g. (1148 mmoles) of this acid was added freshly prepared and spectroscopically pure (infrared) N-(1-phenylethyl)-N-nitroso-2-naphthamide prepared from 3.0 g. (10.9 mmoles) of the amide, and the mixture was stirred at 26° in an apparatus protected from the atmosphere. The reaction was essentially over after 3 hr. After a total of 11 hr. (10.7 mmoles of N<sub>2</sub> had been evolved), the solution was poured into 500 ml. of H<sub>2</sub>O. The mixture was extracted with pentane-ether (9/1) and the extract washed with dilute NaOH, with H<sub>2</sub>O and then dried. The solvent was removed and the product distilled to give the fractions (pressure and oil-bath temperature listed): (1) 60° at 20 mm. (0.4 g.); (2) 60–100° at 0.05 mm. (0.2 g.); (3) 100–120° at 0.05 mm. (0.05 g.); (4) 120–170° at 0.05 mm. (trace); (5) 170–180° at 0.05 mm. (1 g.); (6) 180° at 0.05 mm. (0.05 g.); a negligible residue remained. The infrared spectrum of (1) showed it to be a mixture of styrene and 1-phenylethyl acetate. The infrared spectrum of fraction 2 was superimposable in detail on that of authentic non-labelled 1-phenylethyl acetate.

*Anal.* Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>: C, 73.14; H, 7.37. Found: C, 73.45; H, 7.84. The analysis for deuterium<sup>12</sup> gave 0.281 ± 0.004 atom % excess deuterium (the calculated value for the ester containing one deuterium atom is 8.33 atom % excess.)

The infrared spectrum of fraction 5 was superimposable in detail on that of authentic non-labelled 1-phenylethyl 2-naphthoate.

*Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>: C, 82.58; H, 5.84. Found: C, 82.57; H, 5.92. The analysis for deuterium<sup>12</sup> gave 0.026 ± 0.002 atom % excess deuterium (the calculated value for the introduction of one deuterium atom is 6.25 atom % excess.)

**Run 10.**—N-Nitrocyclohexylamine, prepared as described by Curry and Mason,<sup>47</sup> was exactly neutralized with a dilute solution of sodium hydroxide. A slight excess of aqueous silver nitrate was added and the precipitate was removed and dried in darkness at 80° and 0.1 mm. A solution of 5.08 g. (26.6 mmoles) of 2-naphthoyl chloride-O<sup>18</sup> (1.199 atom % excess oxygen-18 as shown by analysis of *dl*-N-(1-phenylethyl)-2-naphthamide-O<sup>18</sup> prepared from the acid chloride) in 60 ml. of carbon tetrachloride was added dropwise with stirring to a slurry of this silver salt (7.00 g., 27.9 mmoles) in 75 ml. of carbon tetrachloride at 25°. The nitrous oxide evolved was carried by a stream of nitrogen through a condenser, a Dry Ice trap, and Ascarite drying tube and finally collected in a sample tube cooled in liquid nitrogen. The nitrogen was pumped from the sample tube still cooled in liquid nitrogen, and the nitrous oxide was analyzed in the mass spectrometer. The peak heights for mass numbers 44, 45 and 46 were recorded three times. Tank N<sub>2</sub>O was passed through an ascarite drying tube and collected and analyzed in the same way. The average 46/44 ratio was calculated for sample and tank N<sub>2</sub>O. Since the tank ratio (2.219 × 10<sup>-3</sup>) was slightly greater than the sample ratio (2.118 × 10<sup>-3</sup>), it was concluded that the sample contained no excess oxygen-18.

After 3 hr. of stirring at 25°, the mixture was filtered to remove the bulk of the silver salts. The cloudy filtrate was clarified by washing with 5% sodium thiosulfate. After washing with water and 5% sodium bicarbonate, the carbon tetrachloride solution was dried and concentrated *in vacuo*. The residue, which consisted of 2-naphthoic anhydride, cyclohexyl 2-naphthoate and N-nitrocyclohexylamine, was treated with hexane and filtered to remove the anhydride (1.66 g.). The hexane solution was chromatographed on

Woelm neutral alumina, and the crude ester (2.60 g., 39%) was eluted with 5% ether–95% hexane. The methanol eluate gave 0.5 g. of N-nitrocyclohexylamine, identified by comparing its infrared spectrum with that of authentic material. The crude ester was recrystallized from hexane at –80° to give pure cyclohexyl 2-naphthoate-O<sup>18</sup> (0.609, 0.602 atom % excess oxygen-18), m.p. 55.6–56.8°. The infrared spectrum was identical with that of the analytically pure ester.

Cleavage and workup as described for Run 1 gave 2-naphthylcarbinol-O<sup>18</sup> (0.744, 0.751 atom % excess oxygen-18), m.p. 83.0–84.2°, and cyclohexyl N-phenylcarbamate-ether-O<sup>18</sup> (0.463, 0.436 atom % excess oxygen-18 in the ether position), m.p. 84.1–84.9°.

**Run 11.**—A solution of 6.24 g. (32.7 mmoles) of 2-naphthoyl chloride-O<sup>18</sup> (1.030 atom % excess oxygen-18 as shown by the analysis of the acid used) in 150 ml. of pure methylene chloride at –75° was added to a stirred mixture of 9.00 g. (36.0 mmoles) of silver salt of N-nitrocyclohexylamine and methylene dichloride (60 ml.) at –75°. No reaction occurred until a trace of pyridine was added. Samples were removed by filtration at –80° and their infrared spectra were taken. After a total reaction time of 31 hr., the reaction was complete as shown by the total disappearance of the acid chloride bands in the spectra. The AgCl produced in this run was so finely divided that filtration was futile. Instead, the methylene chloride was clarified by washing twice with 5% sodium thiosulfate. The rest of the isolation and purification procedure was the same as in Run 10. Cyclohexyl 2-naphthoate-O<sup>18</sup> (0.522, 0.522 atom % excess oxygen-18), m.p. 56.0–57.0°, was obtained in 28% yield.

*Anal.* Calcd. for C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>: C, 80.28; H, 7.13. Found: C, 80.04, 80.42; H, 7.12, 6.98.

Cleavage of the ester and work up by the procedure of Run 1 gave 2-naphthylcarbinol-O<sup>18</sup> (0.671, 0.670 atom % excess oxygen-18), m.p. 82.3–83.5°, and cyclohexanol-O<sup>18</sup> which was converted to cyclohexyl-N-phenylcarbamate-ether-O<sup>18</sup> (0.348, 0.356 atom % excess oxygen-18 in the ether position), m.p. 84.0–85.2°.

**The Decomposition of N-(*sec*-Butyl)-N-nitroso-3,5-dinitrobenzamide in the Presence of Benzoic Acid-O-d.**—Benzoyl chloride was stirred with a large excess of D<sub>2</sub>O (99.5%) in an apparatus protected from the atmosphere. When the liquid phase had disappeared, the excess D<sub>2</sub>O was removed by distillation in the same apparatus, and the labelled benzoic acid was sublimed. The infrared spectrum indicated that essentially no C<sub>6</sub>H<sub>5</sub>CO<sub>2</sub>H was present. A solution of this acid (1.37 g., 11.1 mmoles) and N-(*sec*-butyl)-N-nitroso-3,5-dinitrobenzamide (from 1.27 g., 4.75 mmoles of the amide) was prepared in purified dioxane (20 ml.). The reaction was over within 12 hr. The mixture was poured into 500 ml. of H<sub>2</sub>O and the products extracted with ether. The ether phase was washed with H<sub>2</sub>O, dilute K<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O and then dried. The solvent was removed and attempts were made to distill out any *sec*-butyl benzoate that might have been found. Although, under the conditions used (100° and 0.1 mm.) *sec*-butyl benzoate distills readily, and small amounts were isolated from related runs, no benzoate was found. The total product was *sec*-butyl 3,5-dinitrobenzoate containing a small amount of the starting amide. The material was extracted with hot hexane to give 0.30 g. (1.11 mmoles, 23%) of the ester. This was recrystallized from hexane to give pure *sec*-butyl 3,5-dinitrobenzoate, m.p. 73.5–75° (lit. 75°).<sup>48</sup> The infrared spectrum of this ester was compared with the spectrum of pure unlabelled ester, and the spectrum of ester prepared from 2-butanol-2-d (LiAlD<sub>4</sub> and 2-butanone); the latter ester analyzed for 0.7 g. atom deuterium. Although the analyses were not very precise, the infrared comparison indicated that less than 2% of the ester molecules contained deuterium.

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(47) H. M. Curry and J. P. Mason, *THIS JOURNAL*, **73**, 5041 (1951).