(0.238 mol) of S-2,6-diisopropylphenyl dimethylthiocarbamate in 1000 ml of formic acid. The solution was stirred with a magnetic stirrer as 365 ml of 30% hydrogen peroxide was added dropwise. The mixture was stirred overnight. Formic acid was removed under vacuum using a rotary evaporator. The 2,6-diisopropylbenzenesulfonic acid was taken up in water, and the pH was adjusted to 9 using 1 *N* NaOH solution. The water was removed by evaporating on a steam bath. The pH was checked periodically during the evaporation and was maintained at 9 by adding 1 *N* NaOH solution. Sodium 2,6-diisopropylbenzenesulfonate was recrystallized several times by being dissolved in water and precipitated by saturating the solution with NaCl at the boiling point. The white crystalline product was dried in an 80° vacuum oven. A yield of 36.3 g (0.137 mol, 57.7%) of product was obtained.

The Acid-Catalyzed Nitramine Rearrangement. V. The Effect of Isotopic Replacement of Aromatic Ring Hydrogens[1-3]

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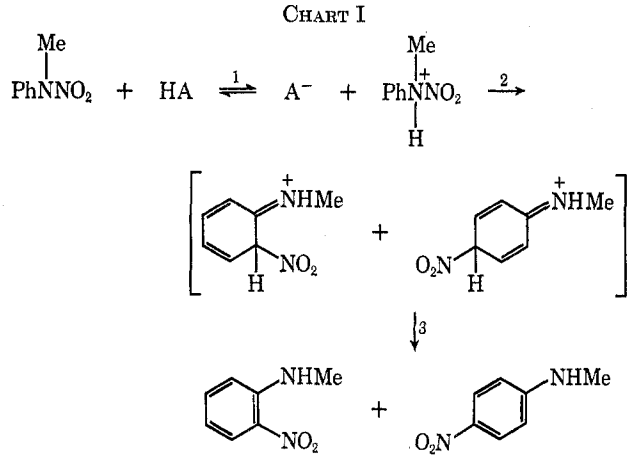
The detection of specific acid catalysis for the aromatic nitramine rearrangement[1b] showed that the rate-determining process in this reaction followed the protonation step. The observed substituent effects[1c] suggested that the breaking of the amine–nitro group bond (Chart I, step 2) was rate limiting. To substantiate this latter assignment, it was desirable to rule out proton loss (step 3) as being significant in rate or product determination. This was accomplished by examining the reactivity of nitramines in which the aromatic hydrogens were replaced by deuterium or tritium atoms.

CHART I



Rates and product distributions were determined for N-nitro-N-methylaniline and N-nitro-N-methylaniline-2,6-d_2 and for N-nitro-N-methyl-*p*-toluidine and N-nitro-N-methyl-*p*-toluidine-2-*t*. The results are listed in Table I. It is obvious that deuterium or tritium substitution at the migration terminus did not affect either the rate of rearrangement or the distribution of products.

TABLE I

EFFECT OF ISOTOPIC REPLACEMENT OF AROMATIC-RING HYDROGENS ON THE AROMATIC NITRAMINE REARRANGEMENT

Compd	10^3k, sec^{-1}	*ortho*,[c] %	*para*,[d] %
N-Nitro-N-methylaniline[a]	1.63 ± 0.04	47.9 ± 1.4	29.3 ± 0.1
N-Nitro-N-methylaniline-2,6-d_2[a]	1.66 ± 0.07	47.8 ± 1.0	29.9 ± 0.5
		% 2-H[e]	% 2-t[f]
N-Nitro-N-methyl-*p*-toluidine[b]	2.65 ± 0.03	100	...
N-Nitro-N-methyl-*p*-toluidine-2-*t*[b]	2.69 ± 0.03	48 ± 2	52 ± 2

[a] Rearrangement was carried out at 40.0° in 0.511 *M* aqueous $HClO_4$ containing 0.500 *M* $NaClO_4$. [b] Rearrangement was carried out at 20.0° in 0.204 *M* aqueous $HClO_4$ containing 0.807 *M* $NaClO_4$. [c] Per cent of 2-nitro-N-methylaniline in the product. [d] Per cent of 4-nitro-N-methylaniline in the product. [e] Per cent of 2-nitro-N-methyl-*p*-toluidine in the nitrated product. [f] Per cent of 2-nitro-N-methyl-*p*-toluidine-2-*t*-in the nitrated product.

These results demonstrate that proton loss (step 3) is not involved in determining the rate of the overall reaction and that, in fact, proton loss must be a relatively fast, facile, low activation energy step in comparison with other changes that occur in the forward progress of the reaction. The first of these points is proved by the finding that the rate of appearance of product was not at all affected by isotopic substitution. If the activation energy of step 3 was of significant magnitude, then the pentadienimine cation intermediate should accumulate and the rate of product formation should be determined by its decomposition. Since its breakdown depends on the scission of a carbon–hydrogen bond, the process should be slowed if a C–D bond replaces the original C–H bond, and the rate of production of nitroanilines from normal and deuterated nitramines should have been different. This result also supports the finding of specific acid catalysis in the nitramine rearrangement, since rate-limiting proton loss (step 3) would have led to general acid catalysis.

It has been suggested that an *ortho* pentadienimine cation intermediate intervenes between the protonated nitramine and the *para* pentadienimine cation[4,5] (Chart II). If the rearrangement follows such a pathway and step 2 is rate determining, then no rate effect of isotopic substitution would be observed. However, if step 4 was reversible or similar in rate to step 5, deuteration of the 2,6 positions of N-nitro-N-methylaniline should lead to a higher proportion of *p*-nitro-N-methylaniline in the product, since C–D bonds are hard to break and step 5 would be retarded. Alter-

(1) Previous papers in this series: (a) W. N. White, D. Lazdins, and H. S. White, *J. Amer. Chem. Soc.*, **86**, 1517 (1964); (b) W. N. White, C. Hathaway, and D. Huston, *J. Org. Chem.*, **35**, 737 (1970); (c) W. N. White and J. R. Klink, *J. Org. Chem.*, **35**, 965 (1970).

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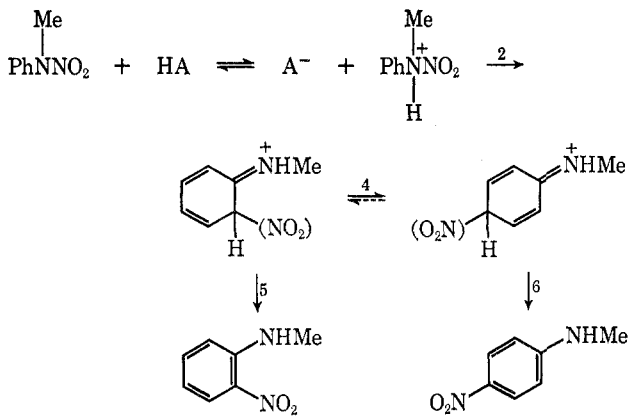
CHART II



natively, if step 4 was much faster than step 5, no *o*-nitro-N-methylaniline would be formed at all or, if step 5 was more rapid than step 4, no *p*-nitro-N-methylaniline would be produced. None of these possibilities is realized experimentally—N-nitro-N-methylaniline and its 2,6-dideuterio derivative rearrange at the same rate to give an identical product consisting of both *o*- and *p*-nitro-N-methylaniline. Thus the mechanism of Chart II is incorrect—both *o*- and *p*-nitro-N-methylaniline must be formed from an intermediate whose partition is not determined by the ease of hydrogen loss. The latter process must occur readily and have a low activation energy.

Negligible isotope effects are expected for reactions with very low activation energies in which the transition state resembles the initial state. Thus step 5 might not be subject to an isotope effect if its activation energy was sufficiently small. However, if significant amounts of *para* isomer are to be formed by the Chart II mechanism, then step 4 would have to have a rate and an activation energy similar to those of step 5. A very low activation energy for an isomerization such as step 4 is quite improbable. Thus the lack of an isotope effect must be attributed to the inadequacy of the mechanism of Chart II.

A similar conclusion can be derived from the behavior of N-nitro-N-methyl-*p*-toluidine and its 2-tritiated derivative. Hydrogen loss from the tritiated position would be slowed so that the nitro group migration to the 4 position would be relatively favored in the mechanism of Chart II. From that point the nitro group may move back unselectively to either of the *ortho* positions or be lost from the molecule. The results would be the same in either case—the N-methyl-2-nitro-4-toluidine formed would contain more tritium than anticipated for statistical replacement of the hydrogens in the *ortho* positions. Since the mechanism of Chart II leads to a conclusion contrary to the observed results, the mechanism must be in error.

These results show that aromatic ring proton loss in the acid-catalyzed nitramine rearrangement is a fast, low activation energy, kinetically insignificant process. This proves that any σ-bonded intermediates formed from the aromatic nitramine rapidly lose protons to reform the benzenoid system. Thus such intermediates cannot intervene as "stepping stones" to other intermediates of the same type, as has been proposed in several mechanisms for the aromatic nitramine rearrangement.[4,5]

Experimental Section

p-**Iodoaniline-2,6-d_2.**—A well-stirred mixture of 7.08 g of aniline-2,4,6-d_3,[6] 70 ml of water, and 9.64 g of sodium bicarbonate was treated with 16.38 g of iodine (in 1-g portions) over a period of 45 min. The temperature was kept at 10° during the addition. The mixture was then stirred at room temperature for 25 min. The aqueous layer was decanted off and the residue was washed several times with water by decantation. The remaining solid was extracted four times with 100-ml portions of boiling petroleum ether (bp 30–60°). Concentration of these extracts afforded 8.8 g (35%) of light tan crystals, mp 60.0–60.5° (lit.[7] mp 60°). A small sample for analysis was purified by sublimation and recrystallized from petroleum ether.

Aniline-2,6-d_2.—To a solution of 7.00 g of *p*-iodoaniline-2,6-d_2 in 10 ml of dry ether was added 175 ml of 0.50 *N* *n*-butyllithium in ether. After 5 min, the solution was cooled in an ice bath and a solution of 35 ml of concentrated hydrochloric acid in 35 ml of water was added as rapidly as possible. The resulting mixture was concentrated to 20 ml, made basic with 10% sodium hydroxide, and extracted with ether. The combined extracts were dried over potassium carbonate and the ether was distilled off through a helices-packed column using a water bath at 50–55°. The residual material was distilled to yield 1.48 g (21%) of aniline-2,6-d_2 as a clear, colorless liquid, bp 100° (25 mm) [lit.[8] bp 119.4° (100 mm)].

N-Nitro-N-methylaniline-2,6-d_2.—This compound was prepared by alkaline nitration[9] of aniline-2,6-d_2.

p-**Toluidine-2-*t*.**—A solution of 2.68 g of *p*-toluidine hydrochloride in 3 ml of tritiated water was heated at 85° for 24 hr. The water was then evaporated. The residual solid was dissolved in 5 ml of ordinary water and the resulting solution was freeze dried. This treatment with ordinary water was repeated four times. The free amine was precipitated from a filtered aqueous solution by addition of 5% sodium hydroxide solution. The solid was collected by filtration, washed with water, and dried. There was obtained 1.66 g (83%) of crude *p*-toluidine-2-*t*, mp 34–35° (lit.[10] mp 42.8°). This material was combined with 3.25 g of normal *p*-toluidine and the mixture was crystallized from petroleum ether to give 4.7 g of colorless plates, mp 42.5–43.5°.

The 2,6-dibromo derivative was prepared by bromination of the amine in acetic acid. It was crystallized from petroleum ether as white plates, mp 78–79° (lit.[11] mp 79°).

N-Nitro-N-methyl-*p*-toluidine-2-*t*.—This substance was obtained by alkaline nitration[9] of *p*-toluidine-2-*t*.

Rearrangement of N-Nitro-N-methyl-*p*-toluidine-2-*t*.—In a typical reaction, 100.0 ml of 1.022 *M* perchloric acid, 110.30 g (0.900 mol) of sodium perchlorate, and 5.0 g of sulfamic acid were placed in a 1-l. volumetric flask. Sufficient water was added to bring the volume to *ca.* 980 ml. The flask was then thermostatted for 45 min at 20° and a solution of 125.1 mg of N-nitro-N-methyl-*p*-toluidine-2-*t* in 10.0 ml of dioxane was added. The contents were mixed and the volume was brought to 1 l. by addition of water. The mixture was kept at 20° for 90 min.

After adjustment of the pH of the mixture to *ca.* 8.5 with sodium hydroxide, it was extracted four times with 100-ml portions of ether. The extracts were evaporated and the residue was dissolved in 3 ml of carbon tetrachloride and chromatographed on a 26 × 170 cm neutral alumina (activity grade II) column using 1:1 diethyl ether–petroleum ether as eluent. The product was eluted by *ca.* 200 ml of the developer. The solvent was evaporated and the residue was recrystallized twice from petroleum ether to yield 92 mg of red-orange N-methyl-2-nitro-4-toluidine-6-*t*, mp 82–83° (lit.[12] mp 84–85°).

The acetyl derivative of this amine was used in the radioactivity assays. It was prepared by warming the amine with acetic anhydride and a trace of sulfuric acid. The product, thrice recrystallized from petroleum ether, melted at 64.0–64.5° (lit.[13] mp 64°).

Deuterium Analysis.—*p*-Iodoaniline-2,6-d_2, aniline-2,6-d_2, and

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N-nitro-N-methylaniline-2,6-d_2 were assayed for their deuterium content by the falling-drop method.[14] The sample was burned to water by vaporizing it into a stream of oxygen which carried the vapors first over the decomposition product of silver permanganate (at 550°) and then over the decomposition product of potassium permanganate. The condensed water was diluted quantitatively with ordinary water so that the final sample contained *ca.* 0.4 at. % deuterium. The drop time in isobutyl benzoate was measured and compared with the drop times for standard D_2O–H_2O mixtures to obtain the atom per cent deuterium in the sample. The standard deviation of the measurement was *ca.* ±0.8%. Three determinations were made on each sample.

The isotopic purity of the various samples follows: *p*-iodoaniline-2,6-d_2, 1.82 D atoms; aniline-2,6-d_2, 1.83 D atoms; and N-nitro-N-methylaniline-2,6-d_2, 1.80 D atoms. These results were verified through independent analyses by a commercial laboratory.[15]

Radioactivity Assays.—*p*-Toluidine-2-*t*, 2,6-dibromo-4-toluidine (prepared from the *p*-toluidine-2-*t*), N-nitro-N-methyl-*p*-toluidine-2-*t*, and the rearrangement product, N-methyl-2-nitro-4-toluidine-6-*t*, were assayed for tritium content by liquid scintillation counting. The scintillator solution contained PPO and POPOP dissolved in an ethanol (23%)–toluene (77%) mixture. Carefully weighed samples of the tritiated compounds were dissolved in aliquots of the scintillator solution and the resulting sample solutions were counted.

To correct for differential quenching effects of the various compounds assayed, 1 ml of a solution of ethanol-*t* in toluene was added to each sample after counting and also to a blank containing only scintillator solution. The samples were then recounted. By comparing the increases in activity of the samples to that of the blank, the extent of quenching could be estimated and the actual sample counts could be corrected for this phenomenon.

Relative activities were calculated from the counts per minute per millimole using the average activity of N-nitro-N-methyl-*p*-toluidine as a standard of comparison. The average relative activities follow: *p*-toluidine-2-*t*, 1.03 ± 0.03; 2,6-dibromo-4-toluidine, 0.00 ± 0.00; N-nitro-N-methyl-*p*-toluidine, 1.00 ± 0.02; and N-methyl-2-nitro-4-acetotoluide-6-*t*, 0.52 ± 0.02.

Rates of Rearrangement of Aromatic Nitramines.—The methods described in previous papers[1b,c] in this series were utilized to determine the kinetic constants for the acid-catalyzed rearrangements of N-nitro-N-methylaniline, N-nitro-N-methylaniline-2,6-d_2, N-nitro-N-methyl-*p*-toluidine, and N-nitro-N-methyl-*p*-toluidine-2-*t*.

Spectrophotometric Analysis of Rearrangement Products.—The percentages of *o*- and *p*-nitro-N-methylaniline obtained from N-nitro-N-methylaniline and from N-nitro-N-methylaniline-2,6-d_2 were determined as described previously.[1a] The quoted results (Table I) are the average of two determinations.

Registry No.—N-Nitro-N-methylaniline, 7119-93-9; N-nitro-N-methylaniline-2,6-d_2, 23998-84-7; N-nitro-N-methyl-*p*-toluidine, 23042-30-0; N-nitro-N-methyl-*p*-toluidine-2-*t*, 23998-86-9.

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Absolute Configuration of 1-Methylalkylamines

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During a study of structure–taste relationships of substituted isoasparagines,[1,2] we were surprised to observe a reversal of configurational requirements for sweetness. Thus, in compounds where R_1 was methyl or methoxycarbonyl and R_2 was cyclohexyl or an aromatic ring, only the LL isomer was sweet. However, in the case of R_1 = methyl and R_2 = *n*-butyl or isobutyl the sweet isomer was LD. It seemed highly unlikely that in a biochemical reaction involving complexing between an optically active substrate and an enzyme site conformational specificity could be reversed by a change from cyclohexyl to *n*-butyl when the structural alteration was insulated from the asymmetric carbon by a methylene group. We were led, therefore, to reexamine the absolute configurations previously assigned to 1-methylhexylamine and 1,4-dimethylpentylamine.[3]

$$H_2NCH(CH_2CO_2H)CONHCH(R_1)CH_2R_2$$

For the sake of consistency with the literature, the designations L and D will be retained. It must be understood that for 1-methylalkylamines the assumption is implicit that the methyl group represents the carboxyl group of the corresponding amino acid and the alkyl group represents the amino acid side chain. This is true whether or not the amino acid so described exists in nature or not. The Cahn–Ingold–Prelog[4] system involves a different assumption, namely, agreement on the sequence rules. For amino acids L = *S*, but for the derived 1-methylalkylamines L = *R* which might introduce an element of confusion. However, for some of the compounds to be described the Cahn–Ingold–Prelog designation allows the argument to be followed with greater facility. Both systems will therefore be used in the present work.

L-Leucine has been related to 1,3-dimethylbutylamine having a positive rotation in methanol.[5] This amine is the closest analog to higher 1-methylalkylamines that can be derived from a naturally occurring amino acid. Resolution of 1,3-dimethylbutylamine, 1-methylhexylamine, and 1,4-dimethylpentylamine was achieved by fractional crystallization of the L-(+)-tartrates.[6] The bases were regenerated and distilled and rotations measured both neat and in methanol. The neat rotations were all negative; 1,3-dimethylbutylamine had a positive rotation in methanol while 1-methylhexylamine and 1,4-dimethylpentylamine had negative rotations in methanol. Treatment of resolved 1,3-dimethylbutylamine with *p*-toluenesulfonyl chloride in pyridine gave an amide identical with that obtained from L-leucine.

As further evidence for absolute configuration of the seven-carbon amines, partial resolution[7,8] of 2-phenylbutyric acid was carried out. The absolute configuration of this acid is *S*-(+).[7] If an excess of an optically inactive acid is caused to react with an optically active amine and the transition state is similar to the final product, then the resulting mixture of diastereoisomeric amides will contain an excess of the amide representing the least hindered transition state. The product can be analyzed easily by isolating unreacted

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