of an authentic sample, and its melting point of 67–68°. *m*-Chlorobiphenyl was identified by its infrared spectrum, in excellent agreement with that of an authentic sample.

Formaldehyde was detected in 45% yield from a reaction run identically with reaction 6. Formaldehyde was isolated by precipitation of its derivative with 1,2,3,4-tetrahydrophthalazine, as described by Schmitz and Ohme.[47] The derivative, 1,2,4,5-bis(*o*-xylylen)hexahydro-*sym*-tetrazine, was recrystallized from chlorobenzene and had mp 278–282° dec (lit.[47] mp 265–270° dec).

Chlorobenzene was isolated from reactions 35 and 36. In these cases, the extent of deuteration was calculated from mass spectrographic data. The normal parent peak was compared with the next higher peak, taking into account a correction factor for the natural abundance of carbon-13.

NOTE ADDED IN PROOF. Recently at the California Institute of Technology, with the cooperation of Dr. Steven Weiner, C. C. W. prepared a solution of 0.002 mole of *o*-chlorobenzene and 0.001 mole of **9** in 20 ml of 2-propanol saturated with sodium 2-propoxide. This solution was irradiated in the cavity of an esr spectrometer. Irradiation stimulated gas evolution and iodide ion was produced, but no esr signal was obtained.

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(47) E. Schmitz and R. Ohme, *Monatsber. Deut. Akad. Wiss. Berlin*, 1, 366 (1959).

The Deamination of Optically Active Neopentylamine-1-*d*

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Abstract: (+)-(*R*)-Neopentylamine-1-*d* (I) underwent deamination in acetic acid to give (−)-(*R*)-2-methyl-1-butene-3-*d* (II) and the corresponding deuterated *t*-amyl acetate which was converted to II of the same optical purity by pyrolysis. The mechanistic implications of the high degree of stereospecificity observed are discussed.

There are few reactions of organic chemistry which have been more extensively examined than the deamination of primary amines, yet basic problems remain unresolved and obvious experiments require attention. We were struck by the fact that in no case had the stereochemistry of migration to primary carbon been investigated in this reaction. Sanderson and Mosher[1] have carried out the deoxidation of optically active neopentyl-1-*d* alcohol and have determined the stereochemistry of methyl migration but have suggested a mechanism different from that usually assumed for deaminations. The stereochemistry of substitution has been investigated in the deamination of *n*-butylamine-1-*d*[2] but no method for determining the stereochemistry of the competing hydrogen migration in such a case has yet been devised.

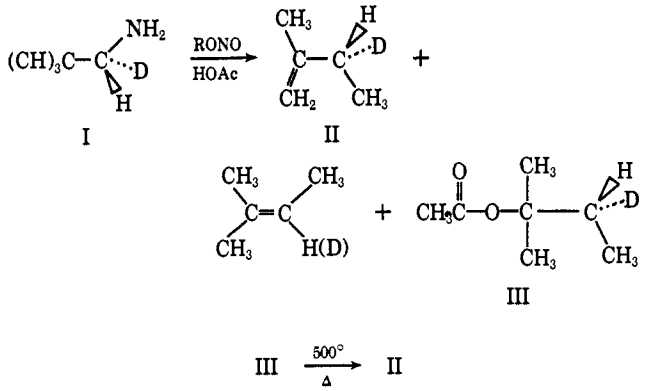
To be sure, many examples of deamination of optically active secondary carbinyl primary amines have been reported[3,4] and these usually show the low stereospecificity expected for relatively free carbonium ions. This would seem to demonstrate that even though product stability is of minimal importance in decomposition of alkyldiazonium salts, its influence is felt to the extent that reactions of primary alkylcarbinyl primary amines are more stereospecific than those of the corresponding secondary carbinylamines. The study of the stereochemistry of the deamination of optically active primary alkylcarbinylamines thus represents an upper limit on the stereospecificity which can be expected in deamination reactions for nonconformational reasons. Migration to give a tertiary carbonium ion should maximize such increases in migration rate as may be derived from the stability of the migration product and one might predict that methyl migration in the deamination of neopentylamine would show close to the maximum stereospecificity possible for loss of nitrogen from a diazonium salt.

Results and Discussion

(+)-(*R*)-Neopentylamine-1-*d* (I) of 93.5%[5] optical purity was treated with *n*-butyl nitrite in acetic acid to give a mixture of (−)-(*R*)-2-methyl-1-butene-3-*d* (II), 2-methyl-2-butene-3-*d* of 58% isotopic purity, (−)-(*R*)-1,1-dimethyl-1-propyl-3-*d* acetate (III), and a trace of neopentyl acetate. The optical rotation observed for II was $\alpha^{3}D$ −0.64 ± 0.05°. Pyrolysis of III at 500° gave II with $\alpha^{3}D$ −0.56 ± 0.03° and $\alpha^{20}D$ −0.52 ± 0.03°. Correction of these values for isotopic and optical impurities in the starting material gives a best value of $\alpha^{20}D$ −0.57° or 85% of the maximum rotation for the enantiomeric form of this compound as determined by Sanderson and Mosher.[1] It should be noted, however, that these authors found $\alpha^{23}D$ +0.61 ± 0.01° in an earlier experiment which is nearly within the experimental error of our value. The deuterium content of the starting amine was 98.5% of one atom of D but had been reduced to 96% in II, which could indicate exchange *via* diazoneopentane in the manner suggested by Friedman[6] and this would be accompanied by some racemization. It seems safe to

(1) W. S. Sanderson and H. S. Mosher, *J. Am. Chem. Soc.*, **88**, 4185 (1966).
(2) A. Streitwieser, Jr., and W. D. Schaeffer, *ibid.*, **79**, 2888 (1957).
(3) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature*, **166**, 179 (1950).
(4) D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, **79**, 2866 (1957).
(5) R. D. Guthrie, W. Meister, and D. J. Cram, *ibid.*, **89**, 5288 (1967).
(6) J. H. Bayless, F. D. Mendicino, and L. Friedman, *ibid.*, **87**, 5790 (1965).

say that methyl migration occurs with at least 85% inversion of configuration at the migration terminus.



Analysis of the 2-methyl-2-butene formed in the deamination for deuterium (see Table I) indicates an isotope effect of $k_H/k_D = 1.5$, which is the same as the value obtained by Silver[7] for deamination of *t*-amyl amine deuterated in the methyl groups. The latter isotope effect was calculated on the basis of olefin ratio. The same calculation in the present example gives a slightly higher value. This could be due to an increased rate of elimination to give the 2-methyl-1-butene but the experimental uncertainties are considerable and the isotope effect based on olefin ratio is very sensitive to experimental error. An isotope effect, $k_H/k_D = 1.5$, can also be calculated from the deuterium content of the 2-methyl-2-butene from pyrolysis of III at 500°. Here again the value is slightly lower than indicated by product analysis and lower than literature values[8,9] determined by product analysis.

Table I. Composition of Methylbutenes from Deamination and Acetate Pyrolysis

Reaction	2-Methyl-1-butene, %	% D in 2-methyl-1-butene	2-Methyl-2-butene, %	% D in 2-methyl-2-butene
Deamination of neopentylamine in acetic acid	43	...	57	...
Deamination of I in acetic acid	51	...	49	58
Pyrolysis of *t*-amyl acetate at 500°	65	...	35	...
Pyrolysis of III at 500°	74	96	26	58

Sanderson and Mosher[1] have suggested a direct mechanism for the formation of II in the deoxideation of neopentyl-1-*d* alcohol, which does not involve the *t*-amyl cation. It would seem unnecessary to invoke such a mechanism in the present case because both substitution and elimination products show the same optical purity. It seems most reasonable to conclude that all of the products of the present reaction with the exception of the small amount of neopentyl acetate arise from the *t*-amyl cation, even though this carbonium ion may differ by reason of solvation, conformation, or energy content from the *t*-amyl cation produced in other ways.[7] The data obtained also mitigate somewhat the value of stereospecificity as a criterion for invoking the direct mechanism.

Too many uncertainties are involved to permit meaningful speculation about the intermediacy of a neopentyl carbonium ion. If the suggested maximum of 15% racemization is in fact the real value, then it would be tempting to regard this as arising from the neopentyl carbonium ion. As Streitwieser found 31% racemization in deamination of *n*-butylamine one could conclude that less carbonium ion was formed in this case or, alternatively, that its reactions were more stereospecific. It is evident that methyl migration is faster than substitution in the deamination of neopentylamine but it is uncertain whether this is due to the rapidity of the migration or the slowness of the substitution. If the same fraction of carbonium ion were formed in this case as in the *n*-butylamine deamination, one would be forced to conclude that rotation about the C_1–C_2 bond is slow enough to allow a significant fraction of methyl migration to occur stereospecifically. It seems most reasonable to us, however, that the methyl migration is concerted with nitrogen loss in at least 85% of the reaction. It would be most interesting to determine the degree of stereospecificity in a migration and substitution occuring competitively but the small amount of neopentyl acetate formed in this reaction made this information economically inaccessible.

Experimental Section

Preparation of Optically Active Neopentylamine-1-*d*. This was prepared according to procedures previously described.[5] The particular sample of neopentylamine hydrochloride used in these experiments was obtained from the hydrolysis of N-(α-methylbenzylidene)neopentylamine-1-*d* having $\alpha^{25}D$ +2.60 ± 0.03° (*l* 0.5 dm, neat) which corresponds to 93% of the maximum rotation for this compound. Analysis of the hydrochloride for deuterium[10] showed 98.5% of one atom of D.

Reagents and Solutions. Acetic acid was purified according to Heidke and Saunders,[11] *n*-butyl nitrite was purchased from Eastman Kodak Company, and *t*-amyl acetate was prepared by a published procedure.[12]

Procedure for Deamination. The hydrochloride was allowed to dissolve in acetic acid, typically about 19 mmoles in 15 ml, and treated with an amount of sodium acetate equivalent to the hydrochloride. The reaction vessel was then sealed with a septum cover and the *n*-butyl nitrite introduced with a calibrated syringe. The gases evolved were passed through a tube containing KOH pellets and into a spiral glass condenser in a liquid nitrogen trap. After the initial vigorous gas evolution had subsided a thin glass tube was introduced through the septum and the mixture blown with nitrogen for 1 hr. The liquid nitrogen trap was designed in such a way as to allow its volatile contents to be forced directly onto a gas chromatograph in 3–4 portions using a 20 ft × 3/8 in. column packed with 27% DC 200 on 45–60 mesh Chromosorb W at 40° and 150 cc/min. (High flow and low temperature gave markedly better resolution than the opposite arrangement.) Peaks were integrated using a disk integrator and the olefins were collected in spiral glass collectors cooled in a liquid nitrogen trap. Some nitrite was observed in this fraction along with a trace of unidentified material which may have been *t*-amyl chloride. Yields were calculated from total weight of volatiles and gas chromatography percentages which were then corrected for isolation efficiencies from control experiments. Normally the gas chromatography traps were not allowed to warm up for weighing but controls on the pyrolysis pro-

(7) M. Silver, *J. Am. Chem. Soc.*, **83**, 3482 (1961).
(8) C. H. DePuy, R. W. King, and D. H. Froemsdorf, *Tetrahedron*, **7**, 123 (1959).
(9) P. S. Skell and W. S. Hall, *J. Am. Chem. Soc.*, **86**, 1557 (1964).
(10) Deuterium analyses were carried out by J. Nemeth, Urbana, Ill., using the combustion and falling-drop method.
(11) R. L. Heidke and W. H. Saunders, *J. Am. Chem. Soc.*, **88**, 5816 (1966).
(12) K. Shishioto, *Repts. Inst. Chem. Research, Kyoto Univ.*, **19**, 98 (1949).

Table II

Compd	mmoles recovd	mmoles cor	Yield, %
Methylbutenes	5.2	5.7	30.5
Nitrite	2.7	2.7	14.5
t-Amyl acetate	6.5	8.8	47.0
t-Amyl alcohol	0.5	0.5	2.5
Neopentyl acetate	0.1	0.1	0.5
Total		17.8	95.0

cedure below showed that the more volatile olefin could be recovered from the part of the procedure involving trapping, gas chromatography, and collection in at least 84% yield.

The acetic acid solution was then poured into a mixture of 30 ml of 35% NaOH solution, 40 ml of pentane, and 100 cc of crushed ice. The pentane layer was separated and the aqueous solution extracted with an additional 20 ml of pentane. The combined pentane layers were dried over anhydrous sodium sulfate and the pentane was boiled off through a 1-ft column packed with glass helices. The residue was subjected to gas chromatographic analysis and separation on the column described above at 105° and 150 cc/min. The alcohols, mainly 1-butanol, and the acetates, mainly *t*-amyl acetate, were separated and these mixtures analyzed further on a 10 ft × 0.25 in. column of 15% polyethylene glycol 400 on 80–100 mesh Chromosorb W at 53° and 200 cc/min. (These conditions avoided the slight pyrolysis of *t*-amyl acetate which occurred at higher temperatures.) In the case of the acetates, this procedure allowed accurate analysis for *n*-butyl acetate and although neopentyl acetate was not completely separated under these conditions, its concentration could be bracketed between 1 and 2% of the total acetate fraction. Controls showed that from reaction mixture to gas chromatographically separated product, *t*-amyl acetate recovery was only 74%, a situation which was not appreciably improved by continuous extraction of the aqueous layer with ether. Typical yield data are summarized in Table II for a reaction carried out on 18.7 mmoles.

An attempt was made to isolate the *t*-amyl alcohol produced in the reaction by preparative gas chromatography of alcohol fractions obtained from several reaction mixtures. A very small amount of *t*-amyl alcohol was obtained which was grossly contaminated with water. The sample showed a small positive rotation which was barely outside of a large experimental error. Even after correction for the aqueous impurity, however, it seemed safe to conclude that the rotation was less than half of that reported by Sanderson and Mosher for an impure sample of the same compound. It is possible that some of our *t*-amyl alcohol arises from secondary reactions.

Procedure for the Pyrolysis of *t*-Amyl Acetate.[13] The pyrolysis was carried out by injecting the acetate fraction obtained above onto a 1-ft Pyrex tube packed with Berl saddles at 500°, and blowing the product through the tube and through the trapping arrangement described above with nitrogen. Gas chromatographic analysis and collection were carried out as described. It was found that 6.5% of the volatile fraction was unpyrolyzed *n*-butyl and neopentyl acetates in the same ratio estimated in the original acetate mixture.

Optical Rotations. The rotations were measured using a Rudolph Model 63 polarimeter. Because only small samples of 2-methyl-1-butene-3-*d* were available, it was necessary to use end-filling polarimeter tubes and keep the samples cold. The only practical way to do this seemed to be carrying out the entire operation in a room kept near 0°. An end plate with a small off-center hole was used to facilitate the refilling required after every few readings.

Deuterium Determination. After performance of such measurements as required above, the purity of the samples were checked by gas chromatography (all samples were of greater than 99% purity) and submitted for combustion and falling-drop analyses.[10] Samples were usually composites from several runs.

(13) W. H. Bailey and W. F. Hale, *J. Am. Chem. Soc.*, 81, 647 (1959).

Nucleic Acids.[1] IV. The Catalytic Reduction of Pyrimidine Nucleosides (Human Liver Deaminase Inhibitors)

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Contribution from Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001. *Received June 19, 1967*

Abstract: The formation of 1-(β-D-ribofurarosyl)-4-aminotetrahydropyrimidin-2(1H)-one [tetrahydrocytidine (III)] and 1-(β-D-ribofuranosyl)tetrahydropyrimidin-2(1H)-one (V) as the major products in the catalytic reduction of cytidine in water over rhodium on alumina is reported. The former compound readily hydrolyzes to give 1-(β-D-ribofuranosyl)-4-hydroxytetrahydropyrimidin-2(1H)-one [tetrahydrouridine (IV)], which is a potent inhibitor of human liver deaminase. The latter compound is also formed by the sodium borohydride reduction of 5,6-dihydrouridine (VI).

The isolation[2] of 5,6-dihydrouridine (VI) as one of the minor nucleosides in tRNA created renewed interest in the chemistry of dihydropyrimidine nucleosides. The earliest synthesis of this type of compound was reported by Levene and LaForge,[3] who prepared 5,6-dihydrouridine (VI) by the reduction of uridine in the presence of colloidal palladium. Subsequent syntheses of dihydropyrimidinenucleosides include catalytic reduction of the parent nucleoside over rhodium on alumina[4] and reduction with sodium in liquid ammonia containing ethanol.[5] More recently Cerutti, *et al.*,[6] reported the sodium borohydride reduction of uridine and uridylic acid in their photoexcited stage to give 5,6-dihydro products.

In the course of work on the synthesis of nucleic

(1) Paper III of this series: H. E. Renis, C. A. Hollowell, and G. E. Underwood, *J. Med. Chem.*, 10, 777 (1967).

(2) J. T. Madison and R. W. Holley, *Biochem. Biophys. Res. Commun.*, 18, 153 (1965); R. W. Holley, G. A. Everett, J. T. Madison, M. Marquisee, S. H. Merrill, J. P. Penswick, and A. Zamir, *Science*, 147, 1462 (1965); G. F. Zachau, D. Dütting, and H. Feldman, *Angew. Chem.*, 77, 1043 (1965).

(3) P. A. Levene and F. B. LaForge, *Chem. Ber.*, 45, 608 (1912).

(4) (a) W. E. Cohn and D. G. Doherty, *J. Am. Chem. Soc.*, 78, 2863 (1956); (b) M. Green and S. S. Cohen, *J. Biol. Chem.*, 225, 397; 228, 601 (1957).

(5) D. C. Burke, *Chem. Ind.* (London), 1393 (1954); *J. Org. Chem.*, 20, 643 (1955).

(6) P. Cerutti, K. Ikeda, and B. Witkop, *J. Am. Chem. Soc.*, 87, 2505 (1965).