[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY, EAST LANSING, MICH., AND THE RESEARCH AND DEVELOPMENT DEPARTMENT, AMERICAN OIL CO., WHITING, IND.]

Carbonium Ion Rearrangements. VI. Mechanism of the Rearrangement of Neopentyl Compounds

BY GERASIMOS J. KARABATSOS,[1a] CHESTER E. ORZECH, JR.,[1b] AND SEYMOUR MEYERSON[1c]

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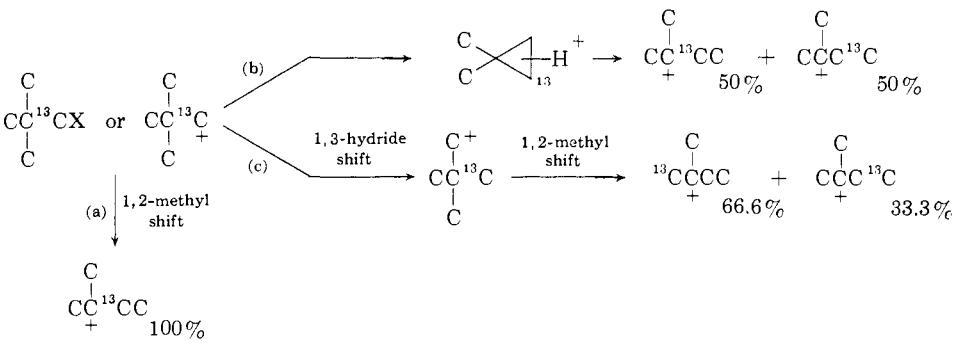
The *t*-amyl alcohols obtained from the deamination of neopentyl-1-^{13}C and neopentyl-1,1-d_2-amines, from the solvolysis of neopentyl-1-^{13}C and neopentyl-1,1-d_2 tosylates, and from the solvolysis of neopentyl-1-^{13}C iodide were analyzed by n.m.r. and mass spectrometry. Also analyzed by n.m.r. was the *t*-amyl chloride obtained from the reaction of neopentyl-1-^{13}C alcohol with triphenyl phosphite and benzyl chloride. The label originally present at C-1 of the neopentyl compounds always ends up at C-3 of the *t*-amyl compounds. The results rule out the intervention of 1,3-hydride shifts, protonated cyclopropanes, or hydrogen-bridged ions during the rearrangement.

The intermediacy of cationated cyclopropanes in gas-phase ionic decompositions in the mass spectrometer is well documented.[2] The suggestion[3] that such species may intervene as intermediates in liquid phase carbonium ion rearrangements, however, has not been substantiated. Conversion of the neopentyl group to the *t*-amyl group by the reaction of neopentyl-1-^{13}C alcohol with hydrogen bromide[4] or by deoxideation of neopentyl-1,1-d_2 alcohol[5] proceeds with no perceptible intervention of protonated cyclopropanes. Nevertheless, the recently reported 1,3-hydride shifts[6,7] and proton exchange between cyclopropane and sulfuric acid[8] might be interpreted in terms of protonated cyclopropanes, either symmetrical (I) or hydrogen bridged (II).

I II

The path of the rearrangement can be elucidated by suitably labeling the neopentyl group and locating the isotope in the *t*-amyl group. Chart I summarizes the isotopic distributions predicted for various paths on the assumption that isotope effects are negligible and that no further scrambling of atoms occurs once the *t*-amyl structure is attained. Path a, 1,2-methyl shift, leads to a *t*-amyl cation labeled solely at C-3; path b, involving a protonated cyclopropane, distributes the label equally between C-3 and C-4; path c, a single 1,3-hydride shift followed by a 1,2-methyl shift, distributes the label between C-1 and C-4 in a 2:1 ratio.

CHART I



Results

The *t*-amyl alcohol obtained from the deamination of neopentyl-1-^{13}C and neopentyl-1,1-d_2-amines, from the solvolysis of neopentyl-1-^{13}C and neopentyl-1,1-d_2 tosylates, and from the solvolysis of neopentyl-1-^{13}C iodide were analyzed by n.m.r. (60 Mc.) and mass spectrometry. The *t*-amyl chloride obtained from the reaction of neopentyl-1-^{13}C alcohol with triphenyl phosphite and benzyl chloride[10] was analyzed by n.m.r.

We have been investigating several systems under diverse experimental conditions in order to assess the effect of structure and mode of carbonium ion formation of the relative importance of 1,2-shifts, 1,3-shifts, and protonated cyclopropanes in carbonium ion rearrangements.[9] We shall discuss in this paper the rearrangement of neopentyl compounds to *t*-amyl compounds.

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(2) (a) P. N. Rylander and S. Meyerson, *J. Am. Chem. Soc.*, **78**, 5799 (1956); (b) S. Meyerson and H. Hart, *ibid.*, **85**, 2358 (1963); (c) H. M. Grubb and S. Meyerson in "The Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press, Inc., New York, N. Y., 1963, p. 453.

(3) (a) P. S. Skell and I. Starer, *J. Am. Chem. Soc.*, **82**, 2971 (1960); (b) M. S. Silver, *ibid.*, **82**, 2971 (1960).

(4) G. J. Karabatsos and J. D. Graham, *ibid.*, **82**, 5250 (1960).

(5) P. S. Skell, I. Starer, and A. P. Krapcho, *ibid.*, **82**, 5257 (1960).

(6) G. J. Karabatsos and C. E. Orzech, Jr., *ibid.*, **84**, 2838 (1962).

(7) P. S. Skell and I. Starer, *ibid.*, **84**, 3962 (1962); P. S. Skell and R. J. Maxwell, *ibid.*, **84**, 3963 (1962).

(8) R. L. Baird and A. Aboderin, *Tetrahedron Letters*, **4**, 235 (1963).

(9) Several recent publications have re-emphasized differences in the behavior of carbonium ions produced under different experimental conditions: (a) E. J. Corey, J. Casanova, Jr., P. A. Vatakencherry, and R. Winter, *J. Am. Chem. Soc.*, **85**, 169 (1963); (b) E. J. Corey and R. L. Dawson, *ibid.*, **85**, 1782 (1963); (c) M. S. Silver, *ibid.*, **83**, 3482 (1961); (d) M. S. Silver, *J. Org. Chem.*, **28**, 1686 (1963).

(10) Neopentyl iodide has been prepared in 75% yield from the reaction of neopentyl alcohol with triphenyl phosphite and methyl iodide [S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953); N. Kornblum and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6653 (1955)] without much rearrangement (the latter authors report 6% *t*-amyl iodide). We prepared neopentyl iodide and neopentyl bromide (triphenyl phosphite and benzyl bromide) by this method with no detectable (n.m.r. analysis) rearrangement. The reaction, however, of neopentyl alcohol with triphenyl phosphite and benzyl chloride led to an approximately 50–50 mixture of neopentyl chloride and *t*-amyl chloride.

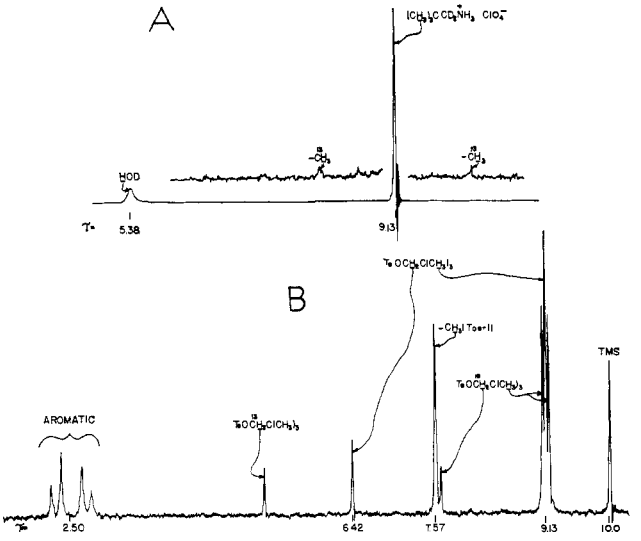


Fig. 1.—A, Proton n.m.r. spectrum of neopentyl-1,1-d_2-ammonium perchlorate in deuterium oxide. B, Proton n.m.r. spectrum of neopentyl-1-^{13}C tosylate in carbon tetrachloride.

N.m.r. Analysis.—Isotopic composition of the ^{13}C-labeled neopentyl compounds was determined by integration of the $-^{12}CH_2-$ and $-^{13}CH_2-$ signals. The values, believed to be accurate to $\pm 4\%$, in terms of per cent labeled molecules are: neopentyl-1-^{13}C-ammonium perchlorate, 31.5%; neopentyl-1-^{13}C tosylate, 55.8%; neopentyl-1-^{13}C iodide, 54.3%; and neopentyl-1-^{13}C chloride, 53.7%. Neopentyl-1,1-d_2-ammonium perchlorate and neopentyl-1,1-d_2 tosylate were estimated to be at least 96% d_2. Figure 1 shows typical spectra.

TABLE I

PARTIAL MASS SPECTRA OF *t*-AMYL ALCOHOLS

	Relative intensity[a]						
Mass	I[b]	II[c]	III[d]	IV[b]	V[e]	VI[f]	VII[g]
53	3.10	2.33	1.62	3.84	2.06	1.09	1.09
54	0.60	1.24	1.82	0.74	2.38	1.83	1.84
55	41.6	29.1	18.4	47.8	22.1	3.19	3.16
56	0.47	11.8	22.4	0.41	26.0	11.1	11.3
57	2.62	2.20	1.68	2.75	1.64	36.0	36.3
58	1.82	2.28	2.45	1.76	2.33	2.13	2.12
59	100.0	100.0	100.0	100.0	100.0	100.0	100.0
60	0.10	0.24	0.20	0.05	0.18	2.27	2.29
61	.12	.09	.08	.17	.13	0.10	0.11
69	.81	.69	.39	1.01	.47	.17	.17
70	3.80	2.65	1.96	5.87	3.04	.43	.41
71	5.46	4.97	4.37	5.62	5.61	2.24	2.25
72	0.20	1.83	3.22	0.14	3.16	3.58	3.63
73	55.6	39.1	24.4	55.3	24.6	5.66	5.62
74	0.07	16.3	31.4	0.05	31.6	2.14	2.14
75	0	0	0	0	0	57.9	57.5
76	0	0	0	0	0	0.79	0.80

[a] Contributions from ions containing heavy isotopes in natural abundance have been removed. [b] Unlabeled. Interpretation of spectra of labeled compounds requires comparison with spectra of the corresponding unlabeled species measured consecutively or nearly so to ensure constant instrument operating characteristics. The spectra shown here were measured in two groups at different times. Hence two spectra, I and IV, are reported for the unlabeled alcohol. Spectrum I was measured at the same time as II and III, IV at the same time as V, VI, and VII. [c] From the deamination of neopentyl-1-^{13}C-amine. [d] From the solvolysis of neopentyl-1-^{13}C tosylate. [e] From the solvolysis of neopentyl-1-^{13}C iodide. [f] From the deamination of neopentyl-1,1-d_2 amine. [g] From the solvolysis of neopentyl-1,1-d_2 tosylate.

The *t*-amyl alcohols isolated from the rearrangement of the d_2-labeled neopentyl compounds showed no protium at C-3 (less than 5%). Those obtained from the ^{13}C-labeled compounds showed no ^{13}C at C-1 or C-4. From integration of the $-^{13}CH_2-$ signals at τ 7.4 *vs.* other signals (OH, $-^{12}CH_2-$) the amount of ^{13}C at C-3 from deamination was estimated to be 30.6%; from tosylate solvolysis, 53.2–57%; and from iodide solvolysis, 53.8%. The *t*-amyl chloride also showed no ^{13}C at C-1 or C-4. Typical spectra[11] are shown in Fig. 2. Apparently, all the labeled atoms—deuterium and ^{13}C—in the *t*-amyl compounds are confined to the C-3 position.

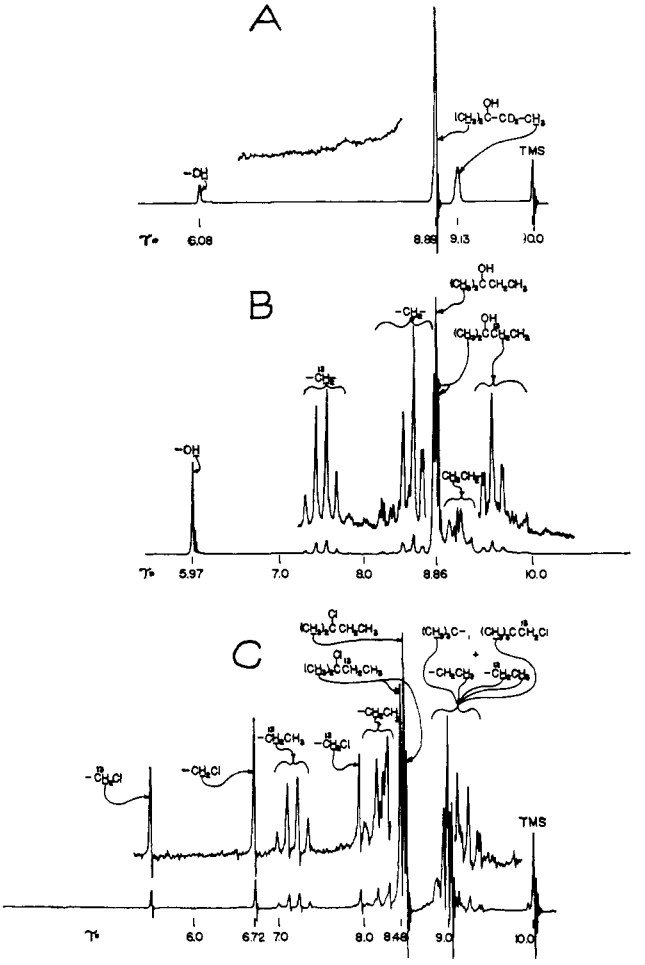


Fig. 2.—A, Proton n.m.r. spectrum in carbon tetrachloride of *t*-amyl alcohol obtained from the deamination of neopentyl-1,1-d_2-ammonium perchlorate. B, Proton n.m.r. spectrum in carbon tetrachloride of *t*-amyl alcohol obtained from the solvolysis of neopentyl-1-^{13}C tosylate. C, Proton n.m.r. spectrum in carbon tetrachloride of neopentyl chloride and *t*-amyl chloride obtained from the reaction of neopentyl-1-^{13}C alcohol with triphenyl phosphite and benzyl chloride.

Mass Spectral Analysis.—Table I shows partial spectra of *t*-amyl alcohols obtained from the rearrangement of labeled neopentyl compounds. Analysis[12] of these spectra gives the following results: retention of ^{13}C label in the $C_5H_{11}^+$ ion, parent-less-hydroxyl, is 30, 55, and 54% for the alcohols obtained from the deamination, solvolysis of tosylate, and solvolysis of iodide, respectively. Retention of ^{13}C label in the $C_4H_9O^+$ ion, parent-less-methyl, is 29.4, 56.3, and 56.2%; in the $C_4H_7^+$ ion, parent-less-methyl-and-water, it is 29, 55, and 54%. Hence no label is at C-1.

(11) It is worth pointing out that the high field $-^{13}CH_2-$ signal close to the $-CH_3$ signal is not, as it should not be, a quartet (A_3B_2X system).

(12) G. J. Karabatsos, F. M. Vane, and S. Meyerson, *J. Am. Chem. Soc.*, **85**, 733 (1963).

TABLE II

PERCENTAGE DISTRIBUTION OF LABEL IN THE *t*-AMYL COMPOUNDS OBTAINED FROM THE REARRANGEMENT OF NEOPENTYL COMPOUNDS

Neopentyl compd.	Reaction	Product	Label in *t*-amyl compd., % C-1	C-2	C-3	C-4
$(CH_3)_3C^{13}CH_2N^+H_3ClO_4^-$	Deamination	*t*-Amyl alcohol	0	0	100	0
$(CH_3)_3CCD_2N^+H_3ClO_4^-$	Deamination	*t*-Amyl alcohol	0	..	100	0
$(CH_3)_3C^{13}CH_2OTs$	Solvolysis	*t*-Amyl alcohol	0	0	100	0
$(CH_3)_3CCD_2OTs$	Solvolysis	*t*-Amyl alcohol	0	..	100	0
$(CH_3)_3C^{13}CH_2I$	Solvolysis	*t*-Amyl alcohol	0	0	100	0
$(CH_3)_3C^{13}CH_2OH$	Reacn. with $(C_6H_5O)_3P$ + $C_6H_5CH_2Cl$	*t*-Amyl chloride			>96[a]	
$(CH_3)_3C^{13}CH_2OH$	Reacn. with HBr	Pentenes + *t*-amyl bromide			>96[b]	
$(CH_3)_3CCD_2OH$	Deoxideation	Pentenes			>96[c]	

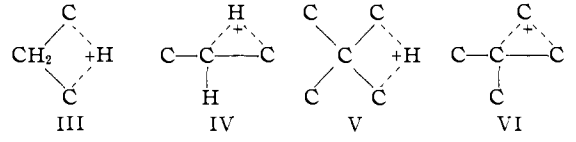
[a] Calculated from the n.m.r. spectrum. [b] Ref. 4. [c] Ref. 5.

^{13}C retention in the $C_3H_7O^+$ ion, parent-less-ethyl, is not more than 0.2, 0.2, and 0.2%. If intensities at masses 74 and 75 in the spectra of the deuterated alcohols are attributed solely to $C_4H_9O^+$-d_1 and -d_2, respectively, and if unlabeled $C_4H_9O^+$ is assumed absent, an estimate can be made of the isotopic distribution of this fragment-ion and, by inference, of the parent molecule: 3.6% d_1 and 96.4% d_2 in both alcohols. Deuterium retention in the $C_3H_7O^+$ ion is essentially zero. All the ^{13}C and deuterium, therefore, is confined to the ethyl groups.

The n.m.r. and mass spectral data are in good agreement, and the combination of the two leads to the conclusion that all label originally at C-1 of the neopentyl compounds ends up at C-3 of the *t*-amyl compounds. Table II summarizes the results.

Discussion

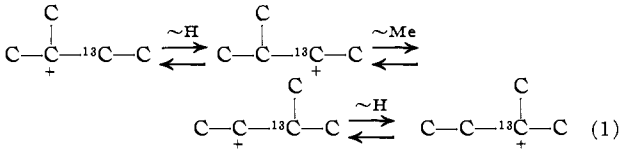
In the liquid phase reactions, regardless of experimental conditions, neopentyl compounds rearrange to *t*-amyl compounds without the intervention of 1,3-hydride shifts, protonated cyclopropanes, or hydrogen-bridged ions. The ability of 1,3-hydride shifts to compete with 1,2-shifts in the *n*-propyl system (III *vs.* IV) but not in the neopentyl system (V *vs.* VI) can be rationalized in terms of formation of a tertiary carbonium ion in VI but only a secondary in IV, and



III IV V VI

in terms of greater release of nonbonded interactions in going from the neopentyl group to VI than from the *n*-propyl to IV.

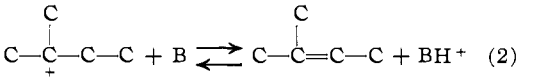
The results exclude the occurrence of 1, a reaction sequence that is significant in the reactions of *t*-amyl



(1)

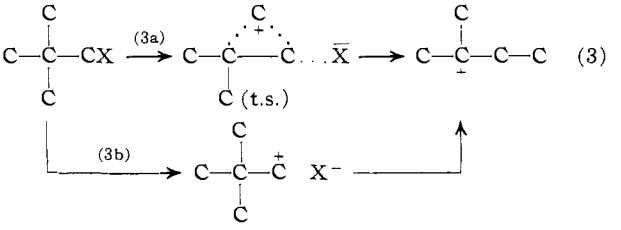
halides with aluminum halides.[12,13] This difference in the behavior of the *t*-amyl cation is reasonable. Under the present experimental conditions the cation is irreversibly captured by nucleophile at rates approaching those of collision reactions. Consequently rearrangement to the secondary carbonium ion, which requires at least 11 kcal./mole of activation energy, cannot compete favorably with nucleophilic capture or with proton elimination. Under the conditions of alkyl halide–Lewis acid reactions, however, competition becomes effective because the carbonium ions are long lived.

Retention of all deuterium in the *t*-amyl products also excludes the reversibility of 2.



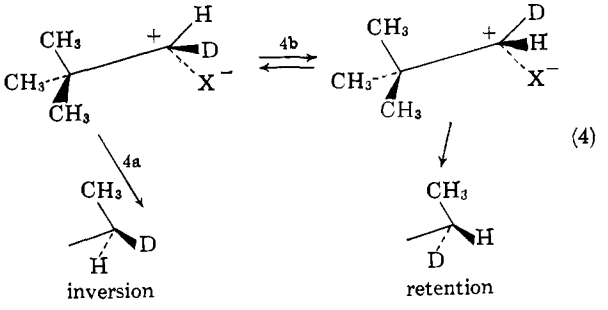
(2)

The methyl shift can proceed either by a synchronous C–X breaking and methyl migration, path 3a, or by a two-step process that involves the intermediacy of the neopentyl cation, path 3b. Mechanisms intermediate between these extremes can also be visualized. The relative merits of 3a and 3b in terms of X have been recently discussed.[9c,14] In most cases the available data bar a choice between the two mechanisms.



(3)

Path 3b apparently intervenes in the reaction of neopentyl iodide with silver nitrate. In this case optically active neopentyl-1-*d* iodide leads to inactive *t*-amyl alcohol.[14] Path 3a has been implicated[14] in the deoxideation of neopentyl alcohol, because optically active (presumably inverted) 2-methyl-1-butene-3-*d* results from optically active neopentyl-1-*d* alcohol. The results, however, are equally compatible with path 3b provided the methyl rearrangement (4a) is faster than or competes favorably with rotation of the –CHD group with respect to X (4b). We suggest that these differences in the behavior of neopentyl cations may



(4)

inversion retention

(13) J. D. Roberts, R. E. McMahon, and J. S. Hine, *J. Am. Chem. Soc.*, **72**, 4237 (1950).

(14) W. A. Sanderson and H. S. Mosher, *ibid.*, **88**, 5033 (1961).

reflect the importance of X in product control rather than a change from a two-step to a concerted mechanism. Vibrationally excited neopentyl cations, *e.g.*, those formed from deamination and deoxidation, may undergo rearrangement faster than rotation about the $-\overset{+}{C}HD$ group with respect to X. Recent publications have focused attention on the importance of counter ion X and solvent in the competition between product formation and conformational changes of carbonium ions.[15]

Experimental

Synthesis of Labeled Compounds.—All compounds were prepared according to well established procedures. Trimethylacetic 1-^{13}C acid was the source of all the ^{13}C-labeled compounds. It was prepared in 91% yield (based on barium carbonate-^{13}C) from the carbonation, at −60°, of *t*-butyllithium with carbon-^{13}C dioxide generated from barium carbonate-^{13}C and 30% aqueous perchloric acid; carbonyl absorptions in the infrared: 5.97 (^{12}C=O), 6.05 μ (^{13}C=O); m.p. 35°. Reduction of the acid with lithium aluminum hydride gave neopentyl-1-^{13}C alcohol, m.p. 52°, in 92.8% yield. The alcohol was converted to the tosylate, m.p. 42–43°, in 92.3% yield by the pyridine method, and to neopentyl-1-^{13}C iodide[10] in 75% yield. Three-hour reflux of the acid with thionyl chloride (1:1.5 mole/mole) and addition of ammonium hydroxide gave the amide, m.p. 156–157°, in 90% yield. The amide was dehydrated to the nitrile with thionyl chloride in 27% yield; infrared absorptions of nitrile: 4.50 (^{11}C=N), 4.60 μ (^{13}C=N). Reduction of the nitrile with lithium aluminum hydride and treatment of the resulting amine with 70% aqueous perchloric acid gave neopentyl-1-^{13}C-ammonium perchlorate, m.p. 168–169°, in 75.6% yield after recrystallization from *n*-heptyl alcohol–*n*-pentane mixtures. The corresponding deuterated compounds were prepared by reduction with lithium aluminum deuteride. All liquid compounds were purified by gas chromatography.

Reactions of the Neopentyl Compounds.—Deamination of neopentylamines[16] gave *t*-amyl alcohol in 52.3% yield. Solvolysis of neopentyl tosylates in 50% aqueous acetic acid[9c] gave *t*-amyl alcohol in 9.5% yield. Solvolysis of neopentyl-1-^{13}C iodide in 14% aqueous silver nitrate[17] gave a 65.8% yield of *t*-amyl alcohol. Each alcohol was purified by gas chromatography.

Isotopic Analysis.—Mass spectra were measured with a Consolidated Model 21-103C mass spectrometer; n.m.r. spectra were determined at 60 Mc. on a Model A-60 spectrometer (Varian Associates, Palo Alto, Calif.), at a temperature of about 38°.

Acknowledgment.—We thank the United States Atomic Energy Commission (Grant AT(11-1)-1189) and the National Science Foundation (G-19243) for financial support of the work performed at Michigan State University.

(15) (a) D. J. Cram and M. R. V. Sahyun, *J. Am. Chem. Soc.*, **85**, 1257 (1963); (b) P. S. Skell and W. L. Hall, *ibid.*, **85**, 2851 (1963).

(16) J. D. Roberts and M. Halmann, *ibid.*, **75**, 5759 (1953).

(17) F. C. Whitmore, E. L. Wittle, and A. H. Popkin, *ibid.*, **61**, 1586 (1939).

[CONTRIBUTION FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY, SHREWSBURY, MASS.]

Chemistry of Conjugate Anions and Enols. IV. The Kinetically Controlled Enolization of α,β-Unsaturated Ketones and the Nature of the Transition State[1,2]

BY SUDARSHAN K. MALHOTRA AND HOWARD J. RINGOLD

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To establish the kinetically favored direction of enolization of α,β-unsaturated ketones the incorporation of deuterium into testosterone has been studied with weak acid, strong acid, and strong base catalysis. Isotope distribution, as determined by a combination of infrared and n.m.r. analysis, both before and after C-1(2) dehydrogenation with *Bacillus sphaericus*, demonstrated that strong acid led to preferential but not exclusive formation of the thermodynamically more stable $\Delta^{3,5}$-enol, while weak acid and strong base strongly favored formation of the $\Delta^{2,4}$-enol and -enolate. Comparison of enolization rates of the isomeric 6-methyltestosterone derivatives showed that with base the 6α-methyl compound formed the $\Delta^{3,5}$-conjugate anion more rapidly, while with strong acid the axial 6β-methyl isomer yielded the $\Delta^{3,5}$-enol fastest. It is concluded that in enolization with weak acid or strong base the transition state resembles the ketone form. The stereochemistry of enol protonation and the relationship of methylenic proton acidity to the transition state is discussed.

Steroidal Δ^4-3-ketones in common with other α,β-unsaturated ketones may undergo enol (enolate) dependent reaction at the α' (C-2) position *via* the homoannular $\Delta^{2,4}$-diene (Fig. 1, A,B) or at the α (C-4) or γ (C-6) positions *via* the $\Delta^{3,5}$-heteroannular diene (Fig. 1, C). While it is abundantly clear from a variety of reactions such as deconjugation,[3] alkylation,[4] enol ether, and enol acetate formation[5] that the thermodynamically more stable enol as well as enolate anion is the heteroannular $\Delta^{3,5}$-diene, the kinetically favored direction of enolization under acid and base catalysis has not been established with any degree of certainty. Wenkert and Jackson[6] found that the treatment of a tricyclic α,β-unsaturated ketone with sodium triphenylmethyl, followed by carbonation, led to essentially equal quantities of the α- and α'-carboxylic acids. This suggested equal rates of formation of the two possible anions assuming that no equilibration occurred during carbonation, which may be a doubtful assumption. Ringold and Turner[7] explained the dichlorodicyanoquinone-mediated C-1(2) dehydrogenation of Δ^4-3-keto steroids in the absence of strong acid as an attack on the kinetically determined $\Delta^{2,4}$-dienol, while Malhotra and Ringold[2] demonstrated in a qualitative manner the preferential formation of the $\Delta^{3,5}$-enol of cholest-4-en-3-one by treatment with deuterium chloride in diglyme.

Steric Course of Testosterone Enolization.—In view of the importance of chemical and enzymatic enolization reactions to the steroid field and in the hopes that such data would serve as a general model for

(1) Supported by grant T-185, American Cancer Society.

(2) Previous paper in this series: S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1538 (1963).

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(4) H. J. Ringold and S. K. Malhotra, *J. Am. Chem. Soc.*, **84**, 3402 (1962).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 310 and 311.

(6) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **81**, 5601 (1959).

(7) H. J. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962).