

PREPARATION OF SELECTIVELY SIDE-CHAIN DEUTERIATED PYRIDINES  
via PIRYLIIUM SALTS

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SUMMARY

Isotopic exchange of benzylic hydrogens in  $\alpha$ - and  $\gamma$ -alkyl side-chains of pyrylium salts occurs readily by heating in deuterium oxide at normal pressure. As  $\gamma$ -hydrogens exchange faster than  $\alpha$ -hydrogens, one may obtain selective (about 90 % isotopic purity)  $\gamma$ - or  $\alpha$ -deuteration of side-chains by direct or reverse isotope exchange. The deuteriated pyrylium salts are converted by aqueous ammonia into the corresponding pyridines without loss of deuterium. Examples presented are : 2,4,6-tri-( $d_3$ -methyl)-, 2,6-di-( $d_3$ -methyl)-4-methyl-, 2,6-dimethyl-4-( $d_3$ -methyl)-, 2,6,-di-( $d_3$ -methyl)-3,5-dimethyl-, 2,4,6-tri-( $d_3$ -methyl)-3,5-dimethyl-, 2,6-di-( $\alpha$ - $d_2$ -ethyl)-4-( $d_3$ -methyl)-, 2,6-diethyl-4-( $d_3$ -methyl)-, and 2,6-di-( $\alpha$ - $d_2$ -ethyl)-4-methyl-pyrylium perchlorates and -pyridines.

Key Words : Deuterium isotope exchange, Side-chain deuteriated Pyrylium Salts and Pyridines.

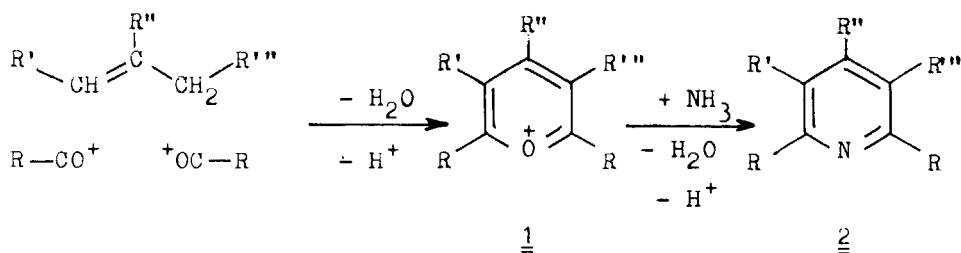
The present paper describes in detail a convenient method for preparing selectively deuteriated alkyl-substituted pyridines possessing  $CD_2$ ,  $CD_2R$  or  $CD_3$  substituents in  $\alpha$ - and/or  $\gamma$ -positions ("benzylic  $\alpha$ - or  $\gamma$ -positions"). Such pyridines were used for evi-

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dencing steric components in the isotope effects observed in the complexation of pyridines with lanthanide shift reagents,<sup>1</sup> and in the quaternization of pyridines with methyl iodide or methyl-d<sub>3</sub> iodide (the Menshutkin reaction).<sup>2</sup> Also, the effects of selective side-chain deuteriations of 2,4,6-trimethylpyridine on the pK<sub>a</sub>,<sup>3</sup> and on electronic absorption spectra<sup>4</sup> were investigated. The initial observations on these deuteriations were made by vibrational spectrometry,<sup>5</sup> but at present the method of choice for controlling the progress of deuteriation and for checking the final isotopic purity is <sup>1</sup>H-NMR spectroscopy.

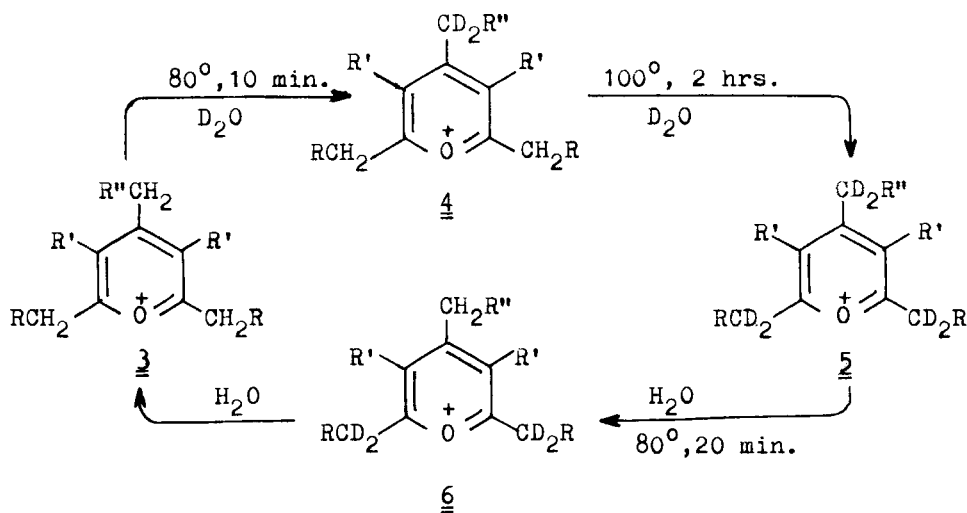
By suitable changes, the method can be adapted for obtaining selectively side-chain tritiated pyridines; progress in this area is expected to be stimulated by recent advances in <sup>3</sup>H-NMR spectroscopy.<sup>6</sup>

Key intermediates for the synthesis and deuteriation of these selectively side-chain deuteriated pyridines are the corresponding pyrylium salts 1 which are readily prepared by diacylation of alkenes,<sup>7</sup> and are converted by ammonia in high yields into pyridines,<sup>8</sup> 2, without loss of deuterium.



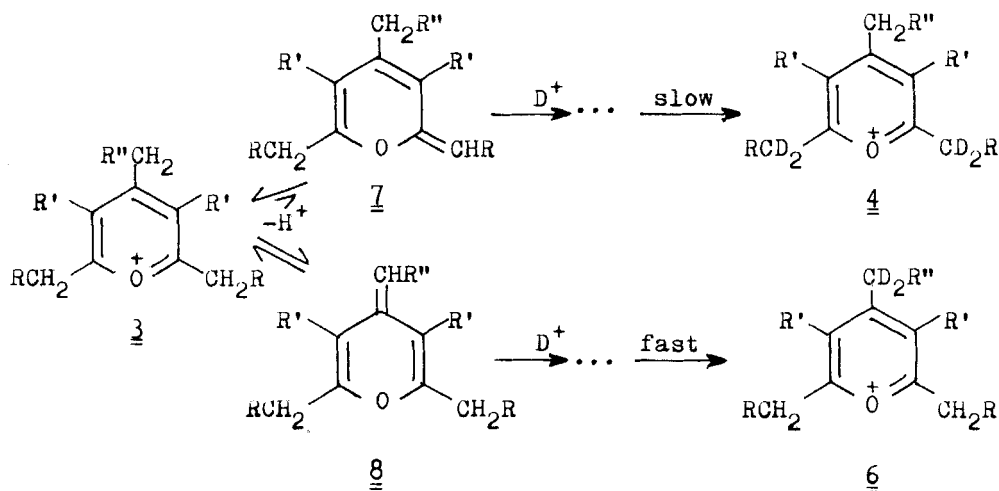
It was reported earlier<sup>9</sup> that pyrylium salts 3 in which R, R' and R'' are hydrogen atoms or alkyl groups undergo rapidly hydrogen exchange in deuterium oxide at benzylic  $\gamma$ -positions, and more slowly at benzylic  $\alpha$ -positions. Therefore, by suitable choice of duration, temperature, pH, and solvent (D<sub>2</sub>O and H<sub>2</sub>O for deuteriation and de-deuteriation, respectively), the selectivity can

encompass not only the distinction between benzylic hydrogens in  $\alpha$  and  $\gamma$  positions which undergo deuteration, and  $\beta$  positions which are not deuteriated, as in 5, but a finer discrimination may be made for deuteration at  $\alpha$  or  $\gamma$  benzylic positions, as in 4 or 6. It should be mentioned that deuteration and de-deuteration rate ratios are usually about 10 : 1 for  $\gamma$ : $\alpha$  positions, leading to isotopic purities of 4 or 6 of about 90 %, whereas the isotopic purity of 5 can reach 99.5 % when working with 99.8 % deuterium oxide. Subsequent reaction with aqueous ammonia at 0 - 10° converts 4, 5, or 6 without loss of deuterium into the corresponding pyridines which do not undergo such selective isotopic exchange reactions in mild conditions.<sup>9,10</sup>

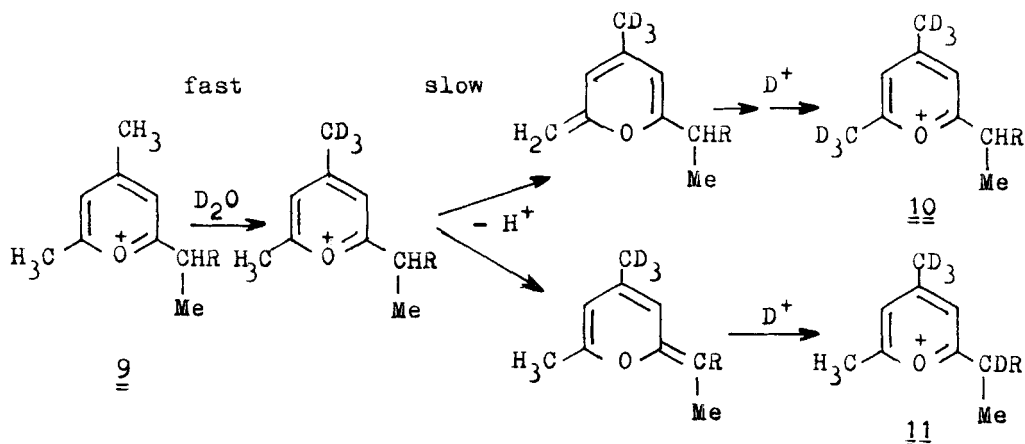


Kinetic studies<sup>11</sup> of the deuteration of pyrylium salts evidenced that the rate increases on increasing the pH of the buffer in the range pH = 0 to 5 (higher pH values destroy pyrylium salts). Arrhenius parameters,<sup>12</sup> the low isotope effect,<sup>12,13</sup> as well as Hammett correlations for 2,6-diaryl-4-methylpyrylium salts<sup>14</sup> agree with a reaction mechanism for deuteration involving anhydrobase (alkylidenepyran) intermediates. Quantum-chemical calculations<sup>15,16</sup> indicate a lower stability of  $\alpha$ -anhydrobases than of the symmetrical  $\gamma$ -anhydrobase (i. e. of 7 than of 8), explaining thereby the rate

differences, i. e. the faster formation of 6 than of 4 by direct isotopic exchange of 3.

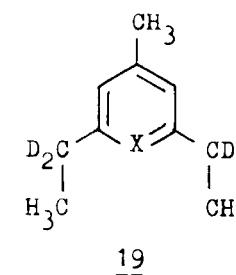
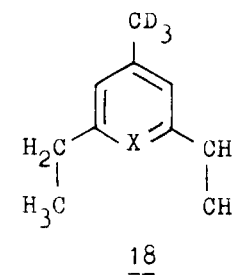
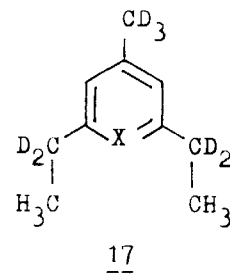
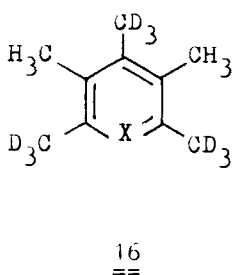
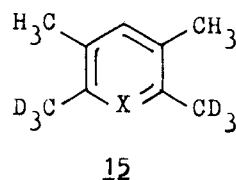
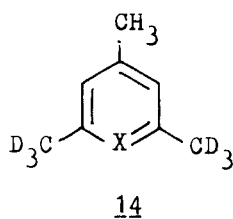
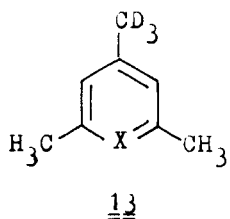
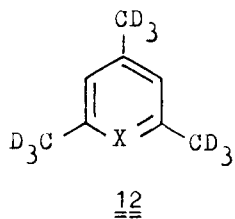


By varying the  $\alpha$ -substituent (Et,<sup>17</sup> iPr<sup>18</sup>) of 2,4-dimethyl-6-Alk-pyrylium (9, R = H or Me) and by comparing intramolecularly the two rates of  $\alpha$ -deuteration, it was found that the isotopic exchange rate for an  $\alpha$ -methyl hydrogen is 2.6 times lower than for an  $\alpha$ -isopropyl or an  $\alpha$ -ethyl benzylic hydrogen; however, owing to the statistical factor (there are three methyl hydrogens, two ethyl hydrogens, and one isopropyl hydrogen in benzylic positions), the rates of formation are approximately equal for 10 and 11.



In the present paper, only a few illustrations of the above

reactions will be presented, starting from 2,4,6-tri-, 2,3,5,6-tetra-, 2,3,4,5,6-penta-methylpyrylium, and 2,6-diethyl-4-methylpyrylium perchlorates which are all obtained readily by diacylation of alkenes or their precursors (alkanols) : the Experimental Part will describe the preparation of side-chain deuteriated pyrylium salts 12 - 19, X = O<sup>+</sup>, and pyridines 12 - 19, X = N.



Other deuteriations of pyrylium salts have been reported, followed in most cases by conversion into the corresponding deuteriated pyridines, namely : 4-ethyl-2,6-dimethyl-,<sup>17</sup> 2-ethyl-4,6-dimethyl-,<sup>17</sup> 2-isopropyl-4,6-dimethyl-,<sup>18</sup> 4-isopropyl-2,6-dimethyl-,<sup>12,13</sup> 4-methyl-2,6-di-t-butyl-,<sup>19</sup> 2,3,4,6-tetramethyl-,<sup>20</sup> 2,4,6-trimethyl-3-phenyl-,<sup>21</sup> 2,3,6-trimethyl-4-phenyl-,<sup>22</sup> 2,6-dimethyl-3,5-nona-methylene-,<sup>23</sup> and 2,6-dimethyl-3,5-heptamethylene-pyrylium and -pyridine.<sup>23</sup>

In addition to uses described above, these side-chain deuteriated heterocycles were employed for unambiguous assignment of nuclear magnetic resonance spectra : <sup>1</sup>H-NMR,<sup>20</sup> and <sup>13</sup>C-NMR spectra.<sup>19</sup>

In all procedures described below, non-buffered deuterium oxide is the deuteriating agent ; in some cases, one may use CH<sub>3</sub>COOD as reported :<sup>10,23-25</sup> it is readily formed by refluxing equimolar

amounts of acetic anhydride and deuterium oxide 99.8 % , but requires longer reaction times at the same temperatures than deuterium oxide as deuteriating solvent for the isotopic exchange.

If deuterium oxide (of lower concentration) is recovered from the filtrates or the distillates as described in the Experimental Part, it may be reused for initial deuteriations ; the final deuteriations should be made with 99.5 - 99.8 % deuterium oxide.

Caution : heating, scratching or knocking dry pyrylium perchlorates may lead to explosions ; heating of perchloric acid in organic solvents, or of aqueous perchloric acid in concentrations higher than 70 % , should be avoided since anhydrous or concentrated perchloric acid explodes readily.

#### EXPERIMENTAL PART

2,4,6-Tri-(d<sub>3</sub>-methyl)-pyridine (12, X = N). 2,4,6-Trimethylpyrylium perchlorate recrystallized from water <sup>26,27</sup> and dried over phosphorus pentoxide in vacuum was heated on the steam bath in the tenfold amount of deuterium oxide with a reflux condenser protected from atmospheric moisture ; initial shaking is necessary till a clear solution results. After two hours, the solution was cooled, the crystals were filtered off, dried, and the operation was renewed twice with fresh portions of deuterium oxide. The <sup>1</sup>H-NMR spectrum in trifluoroacetic acid (which does not differ markedly from that reported in sulfur dioxide <sup>20</sup> or in deuterium oxide <sup>10,11</sup>) finally no longer presents the  $\alpha$ -methyl ( $\delta = 2.90$ ) and the  $\gamma$ -methyl peaks ( $\delta = 2.74$ ), but only the  $\beta$ -hydrogen peak at  $\delta = 7.80$  ppm.

The deuteriated trimethylpyrylium perchlorate (5 g) was introduced into an excess (20 ml) of cold (0°C) aqueous ammonia containing 20 ml of ether. After a few minutes' stirring, the two layers are separated, the ethereal layer is extracted with 20 ml of 10 % hydrochloric acid (when only the collidine is extracted into the lower aqueous layer, leaving any ketonic side-products in the ethereal phase). The aqueous phase is extracted once more with ether,

then it is made alkaline with sodium hydroxide solution, and the separated 2,4,6-tri-(d<sub>3</sub>-methyl)-pyridine is extracted with ether, dried over powdered sodium hydroxide, and distilled under reduced pressure. The yield is 85-90 %, and the <sup>1</sup>H-NMR spectrum (Table 1) indicates that little or no de-deuteriation has occurred during the conversion of pyrylium into pyridine by the action of aqueous ammonia.

Table 1. <sup>1</sup>H-NMR Spectra of Pyridines in CCl<sub>4</sub> ( $\delta$ , ppm) <sup>a</sup>

Position Comp.	$\alpha$	$\beta$	$\gamma$
<u>12</u> - <u>14</u>	/2.37/ s (6H)	6.67 s (2H)	/2.22/ s (3H)
<u>15</u>	/2.33/ s (6H)	2.12 s (6H)	6.98 s (1H)
<u>16</u>	/2.33/ s (6H)	2.11 s (6H)	/2.11/ s (3H)
<u>17</u> - <u>19</u>	/2.36/ q (4H) 1.22 t (6H)	6.67 s (2H)	/2.25/ s (3H)

<sup>a</sup> Peaks whose chemical shifts are written between slashes correspond to side-chain protons which are able to be deuteriated by isotopic exchange of the respective pyrylium salts in D<sub>2</sub>O.

4-(d<sub>3</sub>-Methyl)-2,6-dimethylpyridine (13, X = N). Exactly the same procedure is followed as in the preceding case, but only one deuteriation is effected with the 20-fold amount of 99.8 % deuterium oxide for 10 minutes at 80°C on a preheated water bath with mechanical stirring, and with rapid chilling of the liquid at the end of this period. The subsequent treatment as above leads to a product with practically complete  $\gamma$ -methyl deuteriation and little (8-10 %)  $\alpha$ -methyl deuteriation, as evidenced by the <sup>1</sup>H-NMR spectra of the trimethylpyrylium perchlorate and -pyridine.

2,6-Di-(d<sub>3</sub>-methyl)-4-methylpyridine (14, X = N). The completely deuteriated tri-(d<sub>3</sub>-methyl)-pyrylium perchlorate 12, X = O<sup>+</sup>, is de-deuteriated by heating in the 20-fold amount of distilled water

for 20 minutes at 80°C on a preheated water bath with mechanical stirring, then the same procedure is followed. This single de-deuteriation step yields a product with practically complete de-deuteriation at the  $\beta$ -position, and 8-10 % de-deuteriation at the  $\alpha$ -positions, as shown by  $^1\text{H-NMR}$  spectra of the pyrylium salt and of the pyridine.

2,6-Di-(d<sub>3</sub>-methyl)-3,5-dimethylpyridine (15, X = N). 2-Pentanol was diacetylated with acetic anhydride and perchloric acid, yielding on dilution with a double volume of ethyl ether a black lower layer which contains a mixture of 2,3,5,6-tetramethylpyrylium (about 75 %) and 3-ethyl-2,6-dimethylpyrylium perchlorates (about 25 %), together with perchloric acid.<sup>28</sup> In order to avoid heating this layer during concentrations after deuteriation (because of the danger of explosion), and in order to employ a reasonable amount of D<sub>2</sub>O, the perchlorate anion was replaced by chloride : a concentrated aqueous solution of potassium chloride was added till no more potassium perchlorate precipitated. After filtration on a sintered glass filter, the solution was concentrated under reduced pressure on the hot water bath till no more water was observed to condense in the receiver (usually, during the concentration, one or two filtrations of precipitated KClO<sub>4</sub> are necessary). Then a 15-fold amount of D<sub>2</sub>O was added, and the mixture was heated on the steam bath for three hours with occasional shaking. After evaporation of the D<sub>2</sub>O/H<sub>2</sub>O mixture under reduced pressure, the deuteriation was repeated with fresh portions of D<sub>2</sub>O three times.

The final liquid deuteriated mixture of pyrylium salts was converted directly, by reaction with cold aqueous ammonia as described above, into a mixture of 2,6-di-(d<sub>3</sub>-methyl)-3,5-dimethylpyridine and 3-ethyl-2,6-di-(d<sub>3</sub>-methyl)-pyridine, which was distilled under reduced pressure, and was treated with its double volume of petroleum ether. The former pyridine, 15, X = N, crystallized, was filtered off, and recrystallized from petroleum ether, yielding



colourless or pale yellow crystals with m. p.  $76^{\circ}\text{C}$ , with an isotopic purity of 98 - 99 % (by  $^1\text{H-NMR}$ , according to Table 1).

2,4,6-Tri-( $\text{d}_3$ -methyl)-3,5-dimethylpyridine (16, X = N). 3-Methylhexan-3-ol was diacetylated with acetic anhydride and perchloric acid.<sup>29</sup> Addition of a double volume of diethyl ether caused the separation of a black lower layer containing pentamethylpyrylium (about 70 %) and 4-ethyl-2,3,6-trimethylpyrylium perchlorates (about 30 %) which was converted into chlorides as in the preceding preparation. The deuteriations were carried out as described above, and also the conversion into a mixture of 2,4,6-tri-( $\text{d}_3$ -methyl)-3,5-dimethylpyridine and 4-( $\alpha$ - $\text{d}_2$ -ethyl)-2,6-di-( $\text{d}_3$ -methyl)-3-methylpyridine which was distilled under reduced pressure and left overnight in the presence of atmospheric moisture. As known,<sup>29</sup> pentamethylpyridine and its deuteriated counterpart afford a crystalline hemihydrate. On addition of a small amount of petroleum ether, the hemihydrate of 16, X = N could be filtered off and recrystallized from petroleum ether, yielding colourless crystals with m. p.  $50^{\circ}\text{C}$ . On distillation in vacuum, the product becomes anhydrous, pale yellow liquid, but it is very hygroscopic. According to  $^1\text{H-NMR}$  spectra (Table 1), its isotopic purity is 98 - 99 %.

By suitable modification, following the procedure described for 2,4,6-trimethylpyrylium, it should be possible to obtain selective  $\alpha$ - versus  $\beta$ -deuteriation, and to prepare 4-( $\text{d}_3$ -methyl)-2,3,5,6-tetramethylpyridine by brief deuteriation of pentamethylpyrylium chloride from the reaction mixture, as well as 2,6-di-( $\text{d}_3$ -methyl)-3,4,5-trimethylpyridine by brief de-deuteriation of the totally  $\text{d}_9$ -deuteriated pyrylium chloride ; in both cases, the (de)-deuteriation is followed by conversion into the mixture of pyridines, from which the congeners of pentamethylpyridine are separated as hemihydrate. Because of the isotope effect, the de-deuteriation period for comparable isotope exchange is about twice as long as the deuteriation period.

2,6-Di-( $\alpha$ -d<sub>2</sub>-ethyl)-4-(d<sub>3</sub>-methyl)-pyridine (17, X = N), 2,6-diethyl-4-(d<sub>3</sub>-methyl)-pyridine (18, X = N), and 2,6-di-( $\alpha$ -d<sub>2</sub>-ethyl)-4-methylpyridine (19, X = N) were prepared from 2,6-diethyl-4-methyl-pyrylium perchlorate (obtained from t-amyl chloride, acetyl chloride and aluminium chloride <sup>26,28,30</sup>). The corresponding deuteriated pyrylium congeners were obtained in crystalline state from the non-deuteriated diethylmethylpyrylium perchlorate (m. p. 189°C from water) by : (i) total deuteration for two hours at 100° in D<sub>2</sub>O repeated three times ; (ii) brief deuteration at 80° for ten minutes in D<sub>2</sub>O ; and (iii) brief de-deuteration of the totally d<sub>8</sub>-deuteriated pyrylium perchlorate in H<sub>2</sub>O at 80° for 20 minutes, respectively. The whole procedure is analogous to that described for 2,4,6-trimethylpyrylium and -pyridine analogues. The products were purified by distillation under reduced pressure, and their isotopic purity was checked by <sup>1</sup>H-NMR spectra according to Table 1 : the first pyridine had an isotopic purity of 98-99 %, the other two had isotopic purities of about 90 %.

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Note. The present paper should be considered as Part XIII in the series "Isotopic Exchange of Active Methyl Hydrogens" (the preceding part, XII, is reference 17 quoted above).