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DEUTERATION OF KETONES THROUGH ENAMINES

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Methods for deuterating organic molecules have become increasingly important in recent years because of the existing interest in mechanistic aspects of organic reactions, including deciphering of mass spectral fragmentation patterns. The susceptibility of enamines to electrophilic attack (1) suggested that these compounds might be useful intermediates for the general and stereospecific introduction of deuterium into ketones by selective hydrolysis in deuterated solvents.

Reaction of phosphorus oxychloride with deuterium oxide produced an aqueous solution of deuteriophosphoric acid and deuteriochloric acid which was covered with pentane and cooled to 0°. Addition of a solution of enamine in pentane with stirring resulted in rapid hydrolysis of the enamine, extraction of the ketone into the hydrocarbon phase, and retention of the amine as its salt in the aqueous phase; a ten-fold molar excess of total acid was employed. Utilizing this procedure, pure 2-deuteriocyclohexanone was prepared in high yield from 1-morpholinocyclohexene (1). Deuterolysis of 4-t-butyl-1-morpholinocyclohexene produced 2-β-deuterio-4-t-butylcyclohexanone as would be predicted on stereoelectronic grounds (2);

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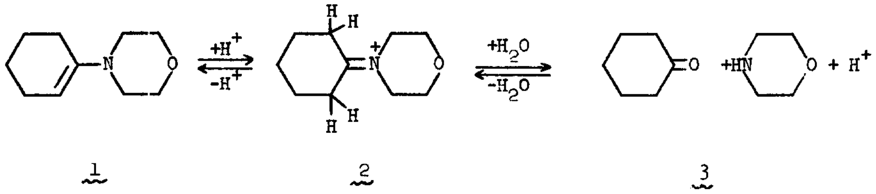
the orientation of deuterium was determined from a study of the n.m.r. spectrum of the ketone (3). This method appears to be general and stereospecific for monodeuterating ketones.

Further reflection on the properties of amines and enamines suggested that the hydrolysis of enamines in weakly acidic solutions might provide a convenient route to ketones in which all of the active hydrogens have been replaced by deuterium. In weakly acidic deuterium oxide, ammonia is known to undergo almost instantaneous exchange of all its hydrogens for solvent deuterium (4). Since in the conjugate acid of an enamine all of the β-hydrogens are equivalent and are vinylogous to protons on nitrogen, rapid exchange of these hydrogens might also be expected. The limiting factor which will determine the degree of exchange will be the relative rates of deprotonation and hydrolysis of the conjugate acid, **2**.



Hydrolysis of partially deuterated **1** (1.24 D/mole) in boiling water (reaction time, one minute) in the absence of catalysts gave **3** (0.85 D/mole); a parallel experiment conducted in deuterium oxide gave **3** (2.86 D/mole). A control experiment showed that exchange of ketone with solvent was negligible under these conditions. In a further experiment, a 50% solution of pyridine in deuterium oxide (containing a trace of hydrolyzed phosphorus oxychloride) was used to hydrolyze **1** (one-half hour at 0°, one minute at 100°). The ketone (**3**) isolated contained 2.11 D/mole; a control experiment using undeuterated **3** in place of **1** resulted in the incorporation of only 0.15 D/mole under identical reaction conditions. These data show that protonation-deprotonation of **1** is rapid and reversible but that hydrolysis of **2** is sufficiently fast to compete with exchange; they furthermore confirm that this technique can be used to prepare randomly labeled polydeuterated ketone in a matter of minutes from an enamine. Although exchange of all of the active hydrogens should be possible, we have not yet found the optimum conditions for hydrolysis to achieve this result.

For the preparation of large quantities of deuterated ketones, utilization of enamines is also particularly economical at the early stages of exchange since more efficient use of deuterium is made than in simple equilibration with deuterium oxide. In addition to forming deuterated ketone on hydrolysis, the N-deuterated amine which is produced can be equilibrated with the ketone. By hydrolyzing **1** with an equivalent of deuterium oxide in benzene, refluxing the solution for several hours, azeotropically removing the water, thereby regenerating deuterated **1**, and repeating this cycle several times, we have synthesized large quantities of 2,2,6,6-tetradeuteriocyclohexanone in high yield using a minimum amount of deuterium oxide. The accompanying table offers a comparison of rates of introduction of deuterium into ketones by this "enamine route" (ε) and by simple exchange (X).

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TABLE

Exchangeable Hydrogens	Exchange Number (ε)[*]					Exchange Number (X)				
	1	2	3	4	5	1	2	3	4	5
1	1.00	----	----	----	----	0.67	0.89	0.96	----	----
2	1.33	1.78	1.93	----	----	1.00	1.50	1.75	----	----
3	1.50	2.25	2.63	2.81	----	1.20	1.92	2.35	2.61	----
4	1.60	2.56	3.14	3.48	3.69	1.33	2.22	2.81	3.20	3.47

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[*] Comparison of introduction of deuterium through the enamine (ε) and by simple exchange of the ketone (X). Calculations are based on the use of molar equivalents of deuterium oxide for both cases and assume that the deuterium content in the enamine corresponds to an equilibrium value; this point was confirmed by experiment.