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SPECIFIC DEUTERATION β TO A KETO GROUP : REDUCTION OF α β-ETHYLENIC KETONES WITH LITHIUM AND DEUTERATED PROPYLAMINE

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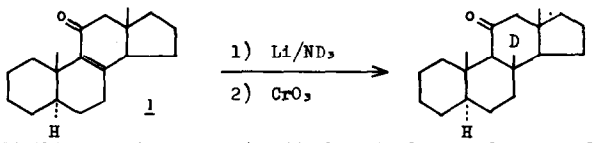
Whereas the introduction of a deuterium atom α to a keto group is a well known process (for a review see ref. 1), this is not the case for the β position. DJERASSI and his co-workers have however described the reduction of the αβ ethylenic ketone 1 by lithium in deuterated liquid ammonia (2).



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We felt this procedure was not entirely satisfactory for several reasons :
- deuterated liquid ammonia is not particularly easy to prepare, to handle, or to store.
- it is difficult to avoid some residual heavy water (used in the preparation of ND_3), so that the Li/ND_3 reduction generally proceeds further to the alcohol. Oxidation is then necessary to obtain the required ketone.

Low molecular weight amines like propylamine (E_{760} = 48°) or isopropylamine (E_{760} = 33°) avoid the aforementioned drawbacks of liquid ammonia.

The action as reducing agent of the combination of amines and lithium had been recognized for aromatic and ethylenic compounds (3) and for thioketals (4). Ethylenic ketones however, had never been submitted to such a treatment.

Scope of the reaction.

For the sake of convenience we first examined the scope of the reaction with undeuterated propylamine.

The reduction of the various conjugated ethylenic ketones so far studied, proceeds much more rapidly in propylamine. This is probably due to the better dissolving power for lithium of the former solvent.

Good yields were obtained with all the conjugated ketones investigated (see table 1)

It will be noted that :

1) The isolated double bonds are not reduced (e. g. carvone 4)
2) As in classical reductions with Li/NH_3 (5), 3-keto Δ^4-steroids yield 5α derivatives.
3) The extension of the reaction to polyfonctional steroids presents certain problems, most probably due to the difficulty of finding a suitable co-solvent for the reduction.

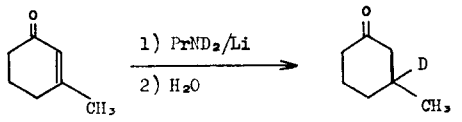
Preparation of deuterated propylamine.

Deuterated propylamine was prepared according to the method of FREJAVILLE and JULLIEN (6). Deuterium is exchanged between propylamine and heavy water (in 30% excess) by a countercurrent process in a thermostated distillation coil.

The isotopic purity of the propylamine thus obtained is better than 98%. *

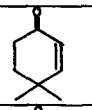
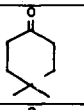
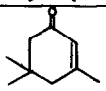
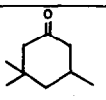
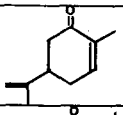
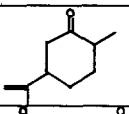
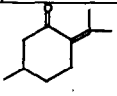
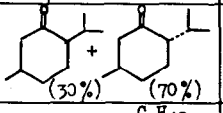
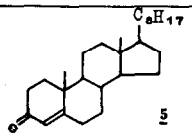
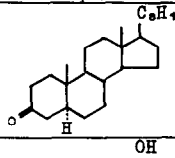
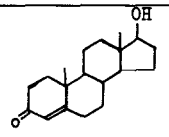
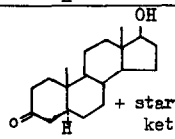
Deuterated Ketones.

The reduction of 3-methylcyclohexenone is a typical example :



* The NMR signal due to the NH_2 protons at 0.88 ppm disappears completely ; nevertheless a broad signal is observed at this position due the CH_2 protons ; this does not allow a more accurate analysis (3). The isotopic purity was also checked by mass and infrared spectroscopy.

TABLE 1

Starting material	Reaction product	Yield*	Experimental conditions
		40 %	3h - 25°C
 **2**		50 %	3h - 25°C
 **3**		50 %	3h - 25°C
 **4**		50 %	3h - 25°C
	 (30 %) (70 %)	55 %	3h - 25°C
 **5**		65 %	6h - Reflux co-solvent : ether
	 + starting ketone	**	72h - Reflux solvent : $PrNH_2$

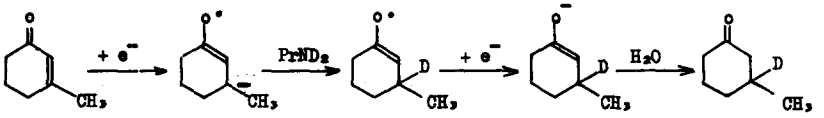
* As pure product isolated by G. C. or recrystallisation.

** In the majority of experiments, a mixture separable only with extreme difficulty, was obtained.

In only one case did the reaction go to completion and the dihydrotestosterone was obtained in 70 % yield.

To a stirred blue solution of 100 mg of lithium in 12 ml of deuterated propylamine, are added at room temperature 500 mg of 3-methylcyclohexenone. After stirring for three hours, 10 ml of H_2O are added. The propylamine is distilled at steam bath temperature and the aqueous layer is extracted with ether. The ether layer is washed with aqueous dilute HCl, dried over calcium chloride and concentrated to 5 ml. The latter extract is refluxed for one hour with 5 ml of 2N methanolic sodium methoxide. After the usual work up, 350 mg of a brown oil are obtained ; after purification by gas chromatography (G.C.) (silicone SE 30 column - 6 metres - 150°C) this yields 200 mg of 3-methyl-3-deuterocyclohexanone. Mass spectrometric analysis affords the following data : isotopic purity : 96% d_1 ; 3% d_0 ; 0.5% d_2 ; 0.5% d_3 (7). The NMR spectrum confirms the location of the deuterium atom ; the methyl group which gave rise to a doublet in the non-deuterated species (δ = 1,02 ppm ; J = 7cps) now gives a narrow triplet (δ = 1,01 ppm ; J_{CH_3CD} = 0,8 cps)(8).

The β-deuterium atom necessarily comes from the amine as the work up with ordinary water does not lower the deuterium isotopic purity. This supports the following mechanism :



where the radical-ion initially formed is sufficiently basic to abstract D^+ from the solvent (see ref. 9).

The following ketones have been reduced in the same way :

- 4,4 dimethylcyclohexenone 2
- isophorone 3
- Δ^4-cholesten-3-one 5

Mass spectrometry reveals that the saturated ketones, after isolation by G.C. but before methanolic MeONa treatment, still contain 15 to 20% of d_2 and d_3 species.

Neither purification by G.C., using hydrogen as carrier gas, nor shaking with an aqueous 5% solution of HCl, is sufficient to remove these extra α-deuterium atoms. Treatment with methanolic MeONa is in all cases necessary in order to obtain an isotopic purity better than 96% .

The good overall yield of the reaction, and the small quantities of deuterated propylamine required, emphasise the synthetic interest of the reduction, which can easily be carried out on the gram scale.

A complete report on this work will be published elsewhere.

Acknowledgments.

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7 - Mass Spectra were recorded on a spectrometer Atlas-Werke CH4.

8 - N.M.R. Spectra were recorded in CCl_4 on a Varian A-60, using $SiMe_4$ as internal reference.

9 - H.O. HOUSE "Modern Synthetic reactions" (Benjamin ed. 1965) p. 61.