DEUTERATION WITH LINDLAR'S CATALYST: EFFECTS OF VARIOUS POISONS ON ISOTOPIC PURITY

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SUMMARY

The Lindlar-catalysed deuteration of methyl stearolate was studied to determine the effect of various poisons on the rate of reaction and on the isotopic purity of the methyl oleate-9,10-d_2 produced. Poisons containing both exchangable and nonexchangable α protons on the heterocyclic ring [quinoline, quinaldine, γ-collidine, acridine, and pyridine] were used. All poisons yielded methyl oleate-9,10-d_2 having 94-97% isotopic purity. Very little over-reduction of oleate to stearate occurred. Lindlar-catalysed H-D exchange involving the poisons was not significant.

Key Words: Deuteration, Catalyst, Lindlar, Methyl Stearolate

INTRODUCTION

The preparation of deuterated olefins via the Lindlar-catalysed (1) reduction of acetylenic precursors is a convenient and well-documented method (2-5). The isotopic purity of the final deuterated products, however, is reported to vary considerably. Since Lindlar-catalysed H-D exchange involving the α hydrogen of quinoline can occur (6), methyl oleate-9,10-d_2 was prepared by Lindlar reduction of methyl stearolate (MeSo) in the presence of various poisons in order to investigate their effect on isotopic purity. The final product was purified by silver resin chromatography and analysed by mass spectroscopy to determine the amount and distribution of the deuterium isotope incorporation.

*The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

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EXPERIMENTAL

Materials. Methyl stearolate was prepared by the bromination/dehydrobromination of oleic acid (7). The poisons quinoline, pyridine (both MCB Reagents), quinaldine (2-methylquinoline) and γ-collidine (2,4,6-trimethylpyridine) [both Aldrich] were distilled before use. Acridine (9-azaanthracene; Aldrich) was used as received. Lindlar catalyst [palladium (5%) on calcium carbonate (lead poisoned)] was obtained from Aldrich. Hexane (Fisher) was certified ACS and Spectroanalysed. All other reagents were analytical grade or better. All runs were made using the same tank of deuterium gas (98%, Matheson). The same procedure was followed for all runs, and identical samples of catalyst, hexane, methyl stearolate, and poisons were used.

Methods. Hexane (50 ml) was added to a 100-ml round-bottomed flask (heat-dried) equipped with a side arm/septum and magnetic stirrer. An ice bath was used to maintain the initial temperature at 10-12°C. The hexane was degassed twice with house vacuum/argon and three times with house vacuum/deuterium (D_2) gas. The Lindlar catalyst was added, and the reaction vessel was again degassed three times with house vacuum/D_2 gas. The slurry was stirred for 20 min, the appropriate poison was added via syringe (except for acridine), and stirring was continued for 30 more min at 7°C. The methyl stearolate was then added via gas-tight syringe, and the rate and the amount of deuterium gas uptake was measured (8).

After deuterium gas uptake had ceased, the reaction mixture was stirred for 4 more min and then filtered through Celite to remove the catalyst. The reaction mixture was then transferred to a separatory funnel, washed with 3 x 35 ml portions of 5% HCl to remove the catalyst poison, and once more with 35 ml distilled water. The hexane layer was then dried over sodium sulfate [Na_2SO_4 (4 hr)], the Na_2SO_4 was removed by vacuum filtration through a Buchner funnel and the hexane was evaporated on a rotary evaporator.

The residue was analysed by gas chromatography (F&M 810 gas chromatograph; 10' x 1/8" stainless-steel column packed with 20% OV275; 190°C isothermal;

TABLE 1

Lindlar reduction conditions

Run	Poison	Poison (m moles)	Lindlar (mg)	MeSo (m moles)	Initial Rx rate*	GC analyses (%) MeSt	MeOl**	MeSo	Rx. time (min)
1	Quinoline	1.97	151	10.3	8.6	0.0	99.5	0.5	20
2	Quinoline	1.16	150	10.0	3.6	1.0	99.0	0.0	30
3	Quinaldine	18.53	1,000	15.3	---	1.0	98.0	1.0	25
4	Quinaldine	1.97	156	10.2	8.1	0.0	99.5	0.5	21
5	Quinaldine	2.06	152	10.0	3.8	0.0	100	0.0	30
6	Pyridine	2.03	152	10.3	7.7	0.3	99.7	0.0	20
7	Pyridine	1.92	151	19.8	3.3	0.0	100	0.0	35
8	γ-Collidine	2.02	150	10.2	8.6	0.8	98.2	0.0	22
9	Acridine	2.02	155	10.3	1.7	0.0	83.4	16.3	60

* μmoles D_2 gas per mg catalyst per minute at 7°C.

**Contains ~0.5% of the trans isomer. If the reaction is carried out in the absence of poison, greater than 3% of the trans isomer and 2% methyl stearate-d_4 are produced.

FID) to determine the amount of methyl stearate (MeSt) and unreduced methyl stearolate present. See Table 1 for a summary of specific reaction conditions, rates and GC analyses.

The methyl oleate (MeOl) 9,10-d_2 was isolated by silver resin chromatography of 0.5-1.0 g samples on a 3 x 30 cm glass column packed with silver ion saturated XN1010 (Rohm and Haas) sulfonic acid resin (100/120 mesh) (9). The samples were eluted with methanol at a flow rate of 1.8 ml/min. The recovered methyl oleate (>99% pure) was then analysed by mass spectroscopy (MS) (8) to determine the deuterium distribution. (Nuclide 12-906 Mass Spectrometer with 70 eV impact ionization inlet at 200°C). Several samples of methyl oleate-d_2 were reduced to methyl stearate-d_2 using potassium azodicarboxylate (KADC) (10) by the procedure of Hamersma and Snyder (11). The stearate samples were purified by silver resin chromatography and analysed by mass spectroscopy to confirm the accuracy of the oleate-d_2 MS analyses.

RESULTS AND DISCUSSION

As illustrated in Table 2, we found no evidence that Lindlar-catalysed H-D exchange at the α proton of quinoline significantly affected the deuterium content of the final methyl oleate-d_2. Such an effect should have been evident in the comparison of reductions using quinaldine (no α protons), quinoline (one α proton), and pyridine (two α protons). Similar results were found in the comparison of the methyl oleate-d_2 produced by the Lindlar reduction of methyl stearolate using pyridine and γ-collidine. The same may be said for acridine.

TABLE 2

Deuterium distribution of silver resin purified methyl oleates 9,10-d_2 produced in runs 1 thru 9, Table 1

	Number of deuteriums (%)						Average no. of deuteriums
Run #*	0	1	2	3	4	5	per molecule
1	1.0	3.0	94.1	0.3	1.1	0.5	1.99
1+	0.7	3.6	95.1	0.2	0.2	0.2	1.98
2	1.0	2.3	94.8	0.4	1.1	0.4	1.99
3	1.0	2.5	95.3	0.3	0.6	0.3	1.98
4	1.1	1.9	95.8	0.3	0.6	0.3	1.98
5	0.8	3.3	94.8	0.1	0.7	0.3	1.97
5+	0.7	3.5	95.2	0.2	0.1	0.3	1.96
6	1.0	3.4	94.5	0.1	0.7	0.3	1.97
7	1.0	1.7	96.5	0.1	0.7	0.0	1.98
7+	0.4	2.1	97.0	0.1	0.1	0.3	1.98
8	1.0	2.4	94.4	0.7	1.1	0.4	1.99
8+	0.4	2.6	96.4	0.2	0.2	0.2	1.98
9	1.0	1.4	96.5	0.2	0.6	0.3	1.99

* + Denotes KADC reduction of previous run.

The reaction followed typical zero order kinetics. Rate constants were similar for quinoline, quinaldine, γ-collidine and pyridine (see Table 1). All of the poisons should be distilled prior to use. The slower rates indicated for quinoline (run #2), quinaldine (run #5) and pyridine (run #7) were most likely caused by deterioration of the distilled poisons (stored in the freezer

at -20°C for 6 weeks prior to use). Acridine was used as purchased. This may account for the lower reaction rate observed.

Thus, all of the listed poisons with the possible exception of acridine will give similar results when used in a Lindlar reduction. Although little over-reduction was noted for our internal acetylene, these results may not be applicable to terminal acetylenes, which are reported to be more reactive and may tend to over-reduce (5).

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