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STEREOCHEMICAL STUDIES IN THE TRISNORLUPANE SERIES—II*

THE STEREOSELECTIVITY OF REDUCTION OF A CYCLOPENTANONE BY COMPLEX METAL HYDRIDES

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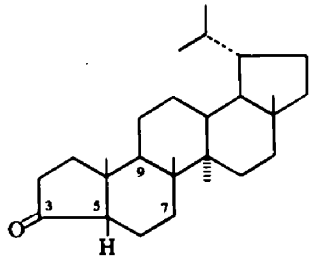
Abstract—The stereoselectivity of the reduction of 4,23,24-trisnor-(5βH)-5(4 → 3)-abeolupan-3-one (I) by complex metal hydrides, under a variety of conditions, is reported. This stereoselectivity is discussed in terms of theories relating to the similar reduction of cyclohexanones.

THE stereoselectivity of reduction of cyclohexanones by complex metal hydrides has been studied extensively[1] but little recent effort has been made to evaluate the similar reduction of non-bridged cyclopentanones. Arguments based on steric interactions alone[1,2] have been invoked to explain the reductions of cyclohexanones which were previously rationalised in terms of additional thermodynamic stability considerations.[3]



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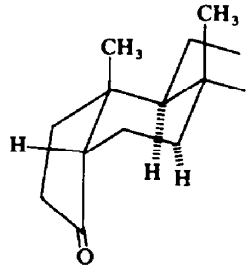

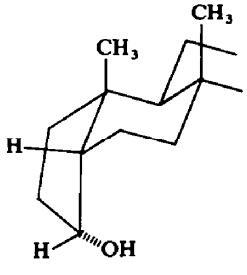

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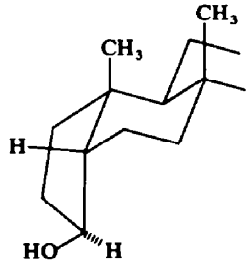

III

* Part I is Ref. 4. Part II was completed in the Department of Organic Chemistry, University of Western Australia, Nedlands, W.A.

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The ketone I [4,23,24-trisnor-(5βH)-5(4 → 3)abeolupan-3-one[4]] is free from the flexibility which can so drastically alter the environment of the carbonyl group in non-bridged cyclohexanones and cause doubt as to the shape of the molecule at the time of reduction.[1] The reduction of the ketone I evaluates the stereoselectivity of reduction of a carbonyl group in a more predictable dissymmetric environment.

Such a project necessarily relies on the ease of separation of the epimeric cyclopentanols formed by the reduction. The ketone I has been shown to afford the alcohols II and III which are separable by chromatography on alumina and which are of established configuration.[5] These configurations were elegantly confirmed by the kinetics of chromic acid oxidation.[6] The validity of the method of separation was confirmed by the separation of a known mixture of pure alcohols II and III (Experimental).

We will base the discussion of the reduction of the ketone (I) principally on steric grounds. Dreiding models reveal that the major hindrances to approach at the carbonyl group are 7α-H and, to a lesser extent, 9α-H. These interactions are intermediate between those found in the chair form of hindered cyclohexanones (e.g. 3,3,5-trimethylcyclohexanone) and the interactions present in the chair form of unhindered cyclohexanones (e.g. 4-t-butylcyclohexanone, cholestan-3-one).

Four variables were used in the reduction of the ketone (I): reducing agent, solvent, temperature and time. The reducing agents were lithium aluminium hydride (LAH), sodium borohydride (SBH) and lithium borohydride (LBH). All reagents were used with diglyme and pyridine as solvents. Ether and tetrahydrofuran (THF) also were used for LAH and LBH reductions and methanol, ethanol and isopropanol also were used for SBH reductions. In all cases, a twenty-fold excess of reducing agent was used and reduction usually exceeded 90%. The axial[5] alcohol (II) usually predominated but its proportion of the reduction product varied between 45% (LBH–pyridine −115°, run 33) and 80% (SBH–methanol −21°, run 19). The results of the reduction are summarized in Table 1.

The proportion of alcohol (II) formed by LAH reduction in THF was independent of time (Runs 2–5). This is in agreement with observations in the cholestane[7] and tropine[8] series and implies irreversibility of the reductive process.

Variation of the reducing agent under fixed conditions causes the % (II) to increase in the order LBH, LAH, SBH; e.g. 58, 61, 69 (diglyme, 21°, runs 30, 10, 22); 59, 61, 66 (diglyme, 100°, runs 31, 11, 23); 45, 58, 66% (pyridine, 115°, runs 33, 14, 24). A smaller but similar variation was found in the reduction of cholestanone.[7] In our series, the difference between reductions by LAH and LBH can be explained by a difference in size between the reducing agents (LAH > LBH) cf. 12. This difference is also pronounced in THF at 21° (LAH, 71%, run 4; LBH, 59%, run 25). Differences in stereoselectivity between LBH and SBH (see above) have been explained in terms of the greater covalent character of LBH which leads to enhancement of product development control.[7] This argument has been criticized[1,2] and we prefer to rationalize the difference in terms of the size of the reducing agent (i.e. SBH > LBH) cf. 12.

Reductions by SBH have been shown to be stereoselectively dependent upon the alcohol used as solvent.[7–9] Thus, SBH in isopropanol, diglyme and pyridine (cf. runs 15, 22, 24) affords results similar to those obtained using LAH in non-polar solvents (e.g. ether, run 8) whereas an enhancement of axial alcohol is observed with SBH in methanol or ethanol as solvent. The same variation is observed with the

TABLE 1.

Run	Hydride	Solvent	Temp	Time	Average %α	Difference between highest and lowest value of %α	Av. yld. alcohols	% Difference between yields of alcohol (II)
1	LAH	THF	−70°	2 hr.	71	1·8	94	2·8
2	LAH	THF	21°	1 min.	70	1·7	85	1·7
3	LAH	THF	21°	5 min.	71	1·0	94	1·4
4	LAH	THF	21°	2 hr.	71	2·4	95	2·3
5	LAH	THF	21°	120 hr.	69	2·0	98	2·9
6	LAH	THF	55°	2 hr.	69	0·7	96	0·7
7	LAH	Ether	−70°	2 hr.	71	1·3	95	1·4
8	LAH	Ether	21°	2 hr.	68	1·2	96	0·3
9	LAH	Ether	35°	2 hr.	69	2·2	96	2·2
10	LAH	Diglyme	21°	2 hr.	61	1·9	98	0·4
11	LAH	Diglyme	100°	2 hr.	61	0·9	99	0·2
12	LAH	Pyridine	−40°	2 hr.	74	2·1	91	0·7
13	LAH	Pyridine	21°	2 hr.	59	1·7	94	1·1
14	LAH*	Pyridine	115°	2 hr.	58	0·8	93	0·4
15	$NaBH_4$	Isopropanol	21°	20 hr.	70	2·1	93	3·8
16	$NaBH_4$*	Isopropanol	21°	20 hr.	71	0·8	94	1·0
17	$NaBH_4$	Isopropanol	82°	5 hr.	69	1·1	95	1·1
18	$NaBH_4$	Ethanol	21°	20 hr.	80	1·5	98	0·3
19	$NaBH_4$	Methanol	21°	20 hr.	80	1·0	97	1·0
20	$NaBH_4$	Methanol	65°	5 hr.	78	1·4	88	5·8
21	$NaBH_4$*	Methanol	65°	5 hr.	78	0·8	92	0·4
22	$NaBH_4$	Diglyme	21°	20 hr.	69	0·9	68	5·0
23	$NaBH_4$	Diglyme	100°	10 hr.	66	0·8	99	0·2
24	$NaBH_4$	Pyridine	115°	5 hr.	66	0·9	98	1·3
25	$LiBH_4$	THF	21°	2 hr.	59	1·1	95	1·6
26	$LiBH_4$*	THF	21°	2 hr.	58	1·2	97	0·4
27	$LiBH_4$	THF	55°	2 hr.	58	2·3	97	2·3
28	$LiBH_4$	Ether	21°	2 hr.	57	0·5	98	0·5
29	$LiBH_4$*	Ether	21°	2 hr.	59	1·1	98	1·1
30	$LiBH_4$	Diglyme	21°	5 hr.	58	1·3	97	0·7
31	$LiBH_4$	Diglyme	100°	2 hr.	59	1·6	98	0·1
32	$LiBH_4$	Pyridine	21°	120 hr.	57	2·9	55	7·0
33	$LiBH_4$	Pyridine	115°	5 hr	45	0·4	95	0·5

* Inverse addition.

ketone (I), the enhancement being ca. 10% (cf. runs 22, 19). We support the implication[9] of solvation forces to account for this effect.

The most significant temperature dependence of the reduction occurs with LAH in pyridine (runs 12, 13, 14; 74–58% II). This change, which is consistent with the results from cholestanone[7] and 3,3,5-trimethylcyclohexanone[10] cannot be explained in terms of significantly different conformers, as is the case with cyclohexanones.[1]

As an alternative to the concept of different spatial arrangements within the transition states leading to the two alcohols,[10] bulky complex formation between LAH and pyridine at −40° could account for the effect. Our reductions using LAH–ether (runs 7–9) and LAH–THF (runs 1–6) did not show the temperature dependence observed with 3,3,5-trimethylcyclohexanone.[10] Unfortunately, the ketone (I) was not reduced by SBH–methanol at −70°. cf. 10.

Reductions of cyclohexanones by LBH–pyridine are faster than reductions by SBH–pyridine.[11] This is found in the present series where no reduction occurred using SBH–pyridine at 21° (even after aqueous work-up cf. 12) whereas LBH under the same conditions (run 32) afforded 55% reduction. We support the view[11] that this reflects the reactivities of the ion pairs of the reducing agents in pyridine. 3,3,5-Trimethylcyclohexanone is reduced at a slow but measurable rate, by LBH–pyridine at 24°, to give predominantly the equatorial alcohol[12] (91%). Under similar conditions (run 32) the ketone (I) affords a significantly large proportion of the equatorial alcohol (III; 43%). This result is a function of the reducing agent rather than of the solvent (compare runs 25–32).

The reduction of the ketone (I) by LAH in pyridine proceeded by direct addition at −40° (run 12) and 21° (run 13). In pyridine under reflux, reduction did not exceed 6%. This is consistent with the finding that aged solutions of LAH–pyridine react through the selective reducing agent lithium (N-dihydropyridyl)-aluminate.[13] Inverse addition of LAH, at 115° (run 14), allowed normal reduction to proceed.

The reduction of 4,23,24-trisnor-(5βH)-5(4 → 3)-abeolupan-3-one by complex metal hydrides confirms that: (a) the proportion of the thermodynamically more stable alcohol increases in the series SBH < LAH < LBH; (b) the effective size of the reducing species from SBH is greater in methanol and ethanol and leads to a diminution of the proportion of the more stable alcohol; (c) the temperature dependence of reductions by LAH–pyridine cannot always be explained in terms of conformations of the ring system; (d) with pyridine as solvent, LBH reductions are faster than SBH reductions and LAH reductions do not proceed *via* direct addition at elevated temperatures.

EXPERIMENTAL

The ketone (I)[4] had m.p. 172–173°. Neutral alumina (Woelm. Act. II) was used for chromatography. LAH and SBH were from B.D.H., England. L.B.H. was from L. Light and Co., England. Ether was distilled from P_2O_5 and stored over Na. THF was successively distilled from KOH and LAH and stored over Na. Pyridine was distilled from P_2O_5. Diglyme was successively distilled at reduced press from KOH and LAH. Isopropanol, EtOH and MeOH were purified by the methods of Vogel.[14] Light petroleum had b.p. 56–60°.

Reduction by direct addition. For reductions at room temp, the hydride (1·3 mmole) was added to the solvent (40 ml) in a 3-necked flask fitted with stirrer and drying tube. The ketone (100 mg; 0·26 mmole) was added and the mixture was stirred for the appropriate time. The reaction was terminated by the cautious addition of water followed by 2N HCl. Extraction through ether (2 × 25 ml) gave the product which was adsorbed from light petroleum–benzene (4:1) on alumina (10 g). Elution with light petroleum–benzene (4:1) afforded unchanged ketone. Elution with light petroleum–benzene (1:1) gave II and with benzene the equatorial III. With pyridine as solvent, 2N HCl was used only after extraction through ether.

For reductions at elevated temps the hydride in the solvent was maintained at the appropriariate temperature during and following the addition of the ketone.

Reductions at −70° and −40° were performed in CO_2–acetone and $CaCl_2$–ice baths respectively.

Reduction by inverse addition. The same procedure was used except that the order of addition of hydride and ketone was reversed.

Separation of artificial mixture. The alcohols II (69·1 mg) and III[5] (29·5 mg) were dissolved in light petroleum–benzene (1 : 1) and separated by chromatography (see above) to give a recovery of 69·0 mg and 29·1 mg respectively.

Tabulation of results. The combined weights of alcohols produced were corrected to the nearest mg. These weights are expressed as % total product (av. yld. alcohols). This value was then normalized to 100 and the normalized % axial alcohol (II) appears as Av. %α. Each run was performed in duplicate and the % difference for the alcohol (II) obtained is recorded.

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