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NON-STEREOSELECTIVITY IN REDUCTIVE ALKYLATION OF $\Delta^{1,9}$-2-OCTALONES

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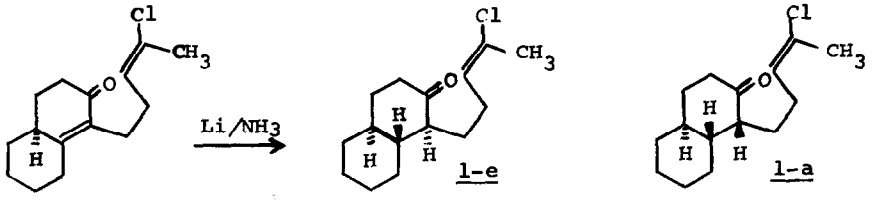
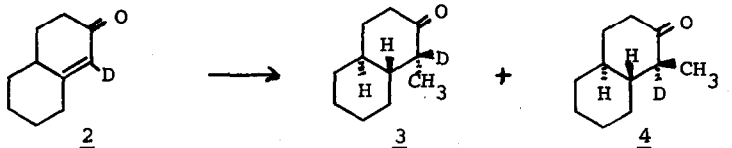
Stereoselective reductive methylation of polycyclic enones of the 1-alkyl-$\Delta^{1,9}$-2-octalone variety has been used advantageously by Stork et al in total syntheses of steroids[1] and the triterpene lupeol[2]. Matthews[3] has also examined the steric course of reductive alkylation of such octalones, with and without a C_{10} substituent, and concluded that the latter controlled the direction of attack by the alkyl halide upon the lithium enolate. In connection with our studies of new approaches for steroid ring D annelation, we required trans-2-decalones bearing chloropentenyl side chains both axially and equatorially oriented at C_1 (1-a and 1-e) in high epimeric purity, thus ruling out inadvertent epimerization in their preparation, especially 1-a.



We have already prepared pure 1-e as a model for 20-keto steroid synthesis[4], as shown above. However, we also observed that attempted preparation of 1-a by reductive alkylation was not stereoselective, and troublesome in other ways as well. Because of intimations that such alkylations should proceed via axial attack[3,5] and the danger that epimerization would equilibrate the kinetic product mixture, we felt it a matter of substantial importance to unambiguously establish the steric course of reductive alkylation of a properly deuterated $\Delta^{1,9}$-2-octalone. Retention of the label after normal work-up would show that isomerization of the initial product(s) had not occurred.

Deuteration of $\Delta^{1,9}$-2-octalone (2), using sodium carbonate in D_2O-dioxane, afforded material whose nmr spectrum was devoid of vinyl proton absorption at 5.62δ, and whose mass spectrum showed ca. 97% d_3 to d_6 species.* Lithium-ammonia reduction[6], followed by reaction with excess methyl iodide in tetrahydrofuran and careful work-up gave both 1-methyl-trans-2-decalones, as indicated by two methyl singlets (broadened by deuterium coupling) in the nmr at 0.92 and 1.03δ. Integration and assignment of these signals with the aid of authentic undeuterated 1-methyl-trans-2-decalone[6] showed the presence of axial C_1-methyl epimer 3 and the equatorial epimer 4 in an approximately 40:60 ratio, which was substantiated by vpc analysis (eleven foot SE-30 column at 180°, 60 cc/min He flow).



2 3 4

The product mixture was then equilibrated with methanolic potassium hydroxide, whereby of the two C_1-epimers only 4 remained (40% yield), as confirmed by vpc and the nmr spectrum, which now displayed one methyl doublet (J = 7Hz) at 0.92δ. The formation of comparable amounts of 3 and 4 clearly implies that simple octalones (e.g. 2) cannot be expected to alkylate stereoselectively[7,8] if indeed the occasional problem of ensuring site selectively has been averted.

Finally, it is in order to compare the stereoselective, axial methylation of the enolates generated from 1-alkyl-$\Delta^{1,9}$-2-octalones[9] with our results. A unifying explanation is provided by noting that 1,2-allyl strain[10] in such enolates (⟷ in structures below) is reduced in the alkylation transition state when rehybridization at C_1 expands the relevant C_1-alkyl-C_9-methylene dihedral angle (R moves downward in A).

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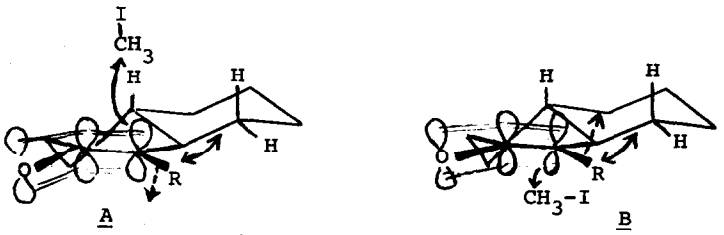
* In the text and in formulas 2-4, only the important C_1-deuterium is shown and discussed.



In formulation B, bottomside electrophilic attack enhances allyl strain by compressing the same dihedral angle. A similar interpretation was offered by Stork in discussion[11] of his lupeol synthesis[2]. In the present case[12] (2→3+4) when R=H the 1,2-allyl strain is of less importance and the two alkylation transition states are more equivalent energetically, at least with respect to this factor.

Whatever the most accurate explanation[13] of the observed experimental findings, we regard it essential that chemists be aware of the special structural requirements for stereoselective alkylation in polycyclic enolates[1-3]; thus the role of 1-alkyl groups should be recognized as well as that of angular C_{10}-substituents.

References and footnotes:

1. G. Stork and J. E. McMurry, J. Amer. Chem. Soc., 89, 5464 (1967).

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5. H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Inc., New York, N. Y., 1965, p. 197.

6. G. Stork, P. Rosen, N. Goldman, R. V. Coombs and J. Tsuji, J. Amer. Chem. Soc., 87, 275 (1965).

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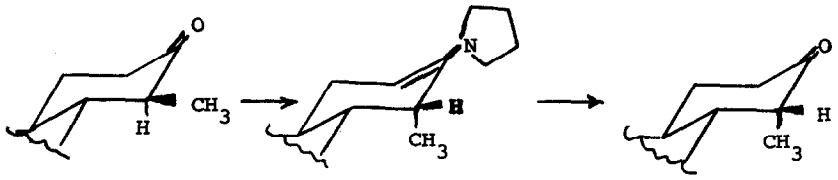
8. Even indirect equilibration[10] of 1-alkyl-2-decalones (via pyrrolidine enamine formation followed by mild hydrolysis) did not show promise for alle-



viating this problem. Thus when the pyrrolidine enamine of 4 was fully formed, nmr revealed the presence of a roughly 1:1 mixture of two epimeric enamines (doublets with J=6.5 Hz at 0.88 and 0.996), rather than the hoped for prevalence of the precursor to 3.

9. This mode of electrophilic attack also occurs in the ketonization of the lithium enolate resulting from lithium reduction of 1-alkyl-$\Delta^{1,9}$-2-octalones (cf. Prep. of 1-e).

10. F. Johnson, Chem. Revs. 68, 375 (1968).

11. G. Stork, Proceedings of 23rd International Congress of Pure and Applied Chemistry, Boston, Massachusetts, July, 1971, Vol. 2, p. 193.

12. Although the excess deuterium incorporated at carbons 3, 8 and 10 in 2 could conceivably produce a steric deuterium isotope effect upon the ratio of 3 to 4 we regard such a factor as quite insignificant and in no way relevant to our qualitative conclusions.

13. The role of such torsional strain in accounting for the steric course of electrophilic additions such as epoxidation and hydroboration to substituted cyclohexenes has also been considered, cf. D. J. Pasto and F. M. Klein, J. Org. Chem., 33, 1468 (1968) and references cited therein.

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