Tetrahedron Letters,Vol.27,No.13,pp 1513-1516,1986 0030-4039/86 $3.00 + .00
Printed in Great Britain

ON THE DECEPTIVE BEHAVIOR OF tri-n-BUTYLTIN HYDRIDE IN THE REDUCTION OF ACETATES OF SOME BROMOHYDRINS. A STEREOSPECIFIC RADICAL REARRANGEMENT

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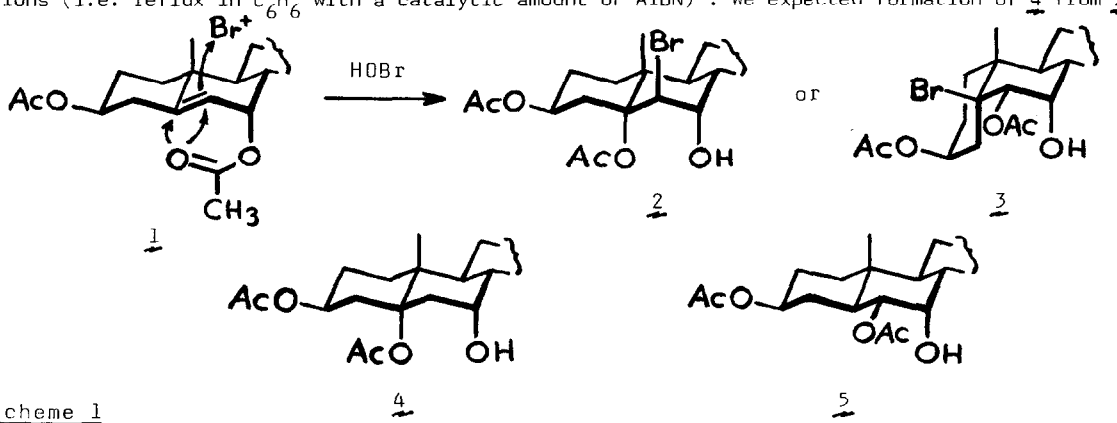
Abstract: Radical hydrogenolysis of the bromohydrin acetate 7 with Bu_3SnH surprisingly leads to the 6α-acetoxy derivative 8 and not to the expected product 6. Structural requirements of this stereospecific rearrangement are discussed. Isotopic labeling demonstrated that the rearrangement proceeds as a 1,2-shift involving the ether oxygen of the acetoxy group (21 → 22) in contrast to an earlier observation.

Reductive removal of halogens by means of Bu_3SnH is an established, mild and reliable method which tolerates various functional groups in the substrate molecule[1]. We have used this radical reduction in a number of instances both for structure elucidation and synthetic purposes and we have always obtained good yields of the expected products[2].

Recently we have studied the reactivity of the diacetoxycholestene 1 towards electrophilic reagents[3]. On HOBr addition 1 afforded a single bromohydrin as the only isolable product (56%) for which two structures (2 or 3) could be suggested (Scheme 1). Though the spectral data[3] (IR, ^{1}H-NMR) together with the mechanistic considerations[3,4] strongly supported structure 2, they still gave no conclusive evidence for the unambiguous assignment[5]. In order to achieve the final proof we attempted to remove the bromine atom by treatment with Bu_3SnH under the standard conditions (i.e. reflux in C_6H_6 with a catalytic amount of AIBN)[1]. We expected formation of 4 from 2



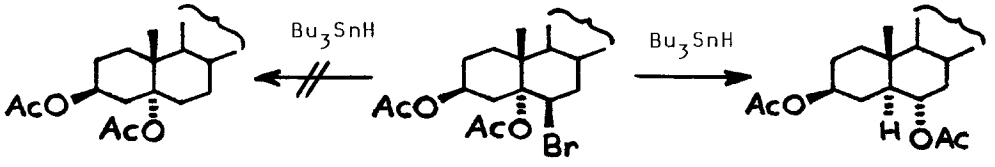
1 2 3

4 5

Scheme 1

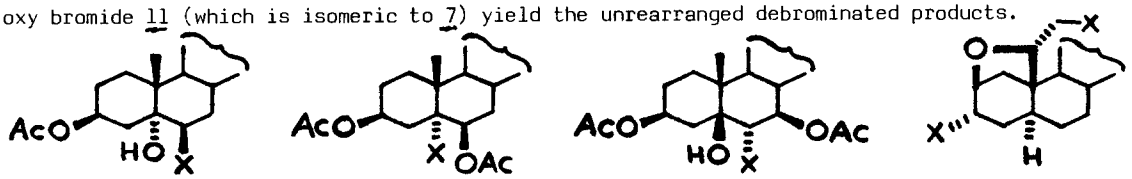
whereas the isomer 3 should give 5. The reaction proceeded smoothly and afforded triol diacetate 5 as the major product (42%) whose structure was deduced from IR and NMR spectra[6,7]. This result seemed to support the less probable structure 3 for the bromohydrin in question. Nevertheless we still did not feel convinced and a suspicion arose that a rearrangement might have occured during the dehalogenation step[8].

To check this assumption we prepared by an unequivocal route the acetoxybromide[9] 7 as a model of 2 and reduced it with Bu_3SnH under the same conditions. The reduction was clean and readily afforded a single product which turned out to be the diacetoxy derivative[10] 8 instead of the expected isomer 6 (Scheme 2). Hence, an unexpected rearrangement must have occurred when both the model 7 and the bromohydrin of unknown structure were treated with Bu_3SnH. Thus we have obtained further evidence in support of formula 2 to the bromohydrin in question[5].



Scheme 2 6 7 8

This type of rearrangement is not unprecedented in the literature[8]. However, only little is known of its structural requirements and more information is therefore desirable. To this end we undertook a brief study of a series of several related bromohydrins and their derivatives (9, 11, 13 and 15; Scheme 3)[11]. None of the tested compounds, however, undergoes the rearrangement and, instead, all of them afford products of simple hydrogenolysis (10, 12, 14 and 16)[12]. Note that both the bromohydrin 9 (whose acetate 7 readily rearranges) and the acetoxy bromide 11 (which is isomeric to 7) yield the unrearranged debrominated products.



9, X = Br 11, X = Br 13, X = Br 15, X = Br
10, X = H 12, X = H 14, X = H 16, X = H

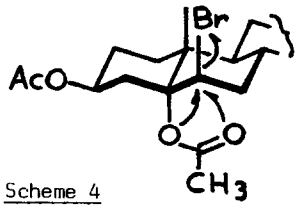
Scheme 3

From these findings it may be concluded that the rearrangement has some specific requirements: (1) Only esters of vicinal bromohydrins can rearrange. (2) The mutual orientation of AcO and Br must be anti-periplanar[13] (i.e. diaxial in cyclohexane ring). (3) The acetoxy group can migrate only from tertiary to secondary carbon[14] (compare 7 and 11).

The driving force for the rearrangement to occur thus appears to comprise two factors: (1) The stereoelectronic effect (alignment of Br and AcO)[13] and (2) the stabilization of the secondary radical at $C_{(6)}$ by migration of AcO to yield the more stable tertiary radical at $C_{(5)}$ which is subsequently quenched to give the product.

The bidentate character of the migrating group raised the question of the relative reactivity of the carbonyl vs. the ether oxygen atoms, i.e. whether the rearrangement proceeds as a 1,2--shift involving the ether oxygen or as a 2,3-shift[8,15] with intervention of the carbonyl oxygen (see Scheme 4).

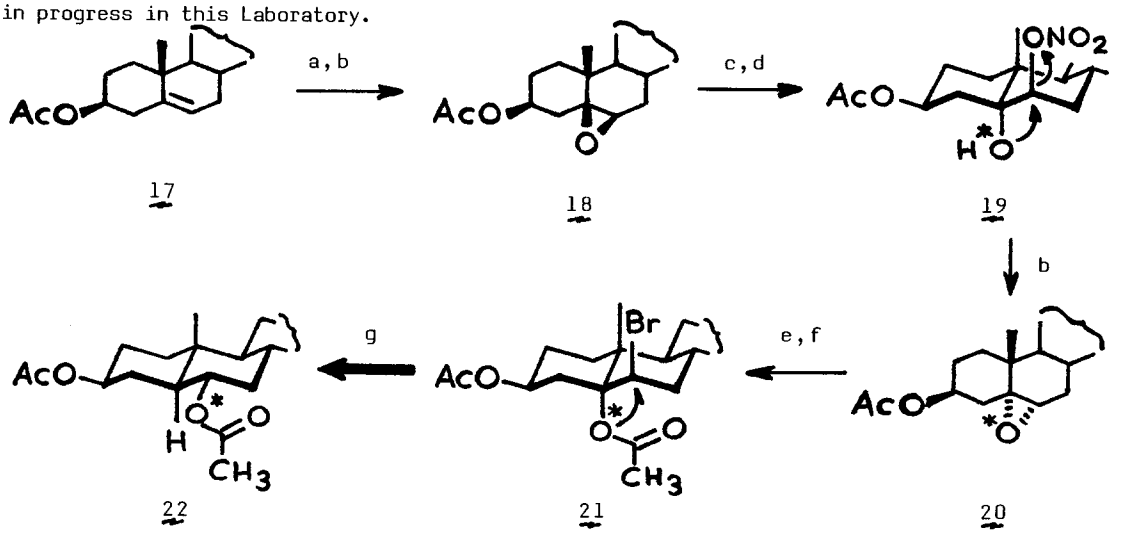
The actual role of the two potential pathways was elucidated by a labeling experiment: The labeled substrate 21 was prepared from cholesteryl acetate (17) in seven steps (Scheme 5)[16]. The label was introduced by acid cleavage of the 5β,6β-epoxide 18 with water enriched in ^{18}O isotope. Resulting diol was converted via the nitrate 19 to the 5α,6α-epoxide 20 whose content of ^{18}O (13.9±0.2%) was established by mass spectral analysis. Fission of the epoxide 20 with HBr followed by acetylation furnished the desired labeled compound 21[17].



Scheme 4

The labeled acetoxy bromide 21 was then reduced with Bu_3SnH and the resulting product 22 analyzed by ^{13}C-NMR spectroscopy[17,18]. The analysis showed that the label remained in the ether oxygen. This qualitative information was supplemented by quantitative determination of the content of ^{18}O by mass spectrometry: The diacetate 22 was hydrolyzed ($LiAlH_4$, Et_2O, 20°C) to the 5α-cholestane-3β,6α-diol whose mass spectrum revealed the presence of 10.7±0.4 % of ^{18}O. Hence, it follows that at least 77% of the label remained in the ether oxygen of the migrating acetoxy group. On this ground we can conclude that the rearrangement proceeds as a 1,2-shift in this case. This is, however, in conflict with the observation of Beckwith and Thomas[15], who found, though in a different substrate, a 2,3-shift of an ester group. This difference is not quite clear to us at present. It may stem from the rigid character of our compound and from strict anti-disposition of both the leaving Br and the migrating AcO group.

Summarizing, we have observed a Bu_3SnH mediated radical rearrangement that occurs when specific structural requirements are met. It may thus mislead the chemist in structure elucidation or in synthetic strategy. On the other hand it might prove synthetically useful, for instance in radical ring closure of olefins where one could plan the rearrangement prior to the cyclization. Further investigation of the features and scope of the reported rearrangement is in progress in this Laboratory.



17 18 19 20 21 22

Scheme 5: a, $CH_3CONHBr$, $HClO_4$, dioxane, H_2O, r.t. 20 min; b, $KHCO_3$, H_2O, dioxane, MeOH, reflux 5 min; c, $HClO_4$ (trace), 20.7% $H_2{}^{18}O$ in H_2O, dioxane, r.t. 1 h; d, 65%-HNO_3, Ac_2O, $CHCl_3$, -20°C, 1 h; e, 48%-HBr, $CHCl_3$, 0°C, 10 min; f, CH_3COCl, $PhNMe_2$, $CHCl_3$, 60°C, 72 h; g, Bu_3SnH, AIBN, C_6H_6, reflux 30 min.

Acknowledgement: Our sincere thanks are due to Sir Derek Barton, Prof. G. Stork and Prof. D. Curran for stimulating discussion.

References and Notes:

1. (a) For review see: Kuivila H.G.: Synthesis 1970, 499. (b) For other methods see: Tureček F., Vereš K., Kočovský P., Pouzar V., Fajkoš J.: J.Org.Chem. 48, 2233 (1983) and references given therein.
2. (a) Kočovský P., Tureček F.: Tetrahedron Lett. 22, 2699 (1981), Collect.Czech.Chem.Commun. 46, 2877 and 2892 (1981). (b) Kočovský P., Starý I., Tureček F., Hanuš V.: Collect.Czech. Chem.Commun. 48, 2994 (1983). (c) Kočovský P.: ibid 48, 3643 (1983). (d) Kočovský P., Drašar P., Pouzar V., Havel M.: ibid 47, 108 (1982).
3. (a) Starý I.: Thesis, Charles University, Prague 1984. (b) Starý I., Zajíček J., Tureček F., Vašíčková S., Kočovský P.: to be published.
4. Kočovský P.: Collect.Czech.Chem.Commun. 48, 3629 (1983).
5. The C-NMR spectrum provided the final evidence in favor of the structure 2 (see ref.[3]).
6. All new compounds gave satisfactory elemental analyses.
7. H-NMR spectrum of 5: 0.65 (3 H, s, 18-H), 0.91 (3 H, s, 19-H), 2.02 and 2.10 (2 x 3H, s, 2 x CH_3COO), 4.67 (1 H, m, ΣJ = 26 Hz, 3α-H), 4.77 (1 H, dd, J = 11.9 and 2.8 Hz, 6β-H), 3.82 (1 H, ΣJ = 6 Hz, 7β-H).
8. Rearrangements of this type have been occasionally reported. For review see: Beckwith A. L.J., Ingold K.U.: Free radical rearrangements, in the book Rearrangements in Ground and Excited States, (P. deMayo, Ed.), Vol. 1, p. 242, Academic Press, New York 1980.
9. Blunt J.W., Fischer A., Hartshorn M.P., Jones F.W., Kirk D.N., Yoong S.W.: Tetrahedron 21, 1567 (1965).
10. Identical with an authentic sample (see: Nussim M., Mazur Y., Sondheimer F.: J.Org.Chem. 29, 1120 (1964).
11. All bromo derivatives are known compounds. For 9 see: Ueno Y.: J.Pharm.Soc.Japan 72, 1622 (1952), for 11 see: Levine S.G., Wall M.E.: J.Amer.Chem.Soc. 81, 2826 (1959), for 13 see ref.[3] and for 15 ref.[2b]
12. All of the reaction products are known compounds. For 10 see: Plattner P.A., Petrzilka T., Lang W.: Helv.Chim.Acta 27, 513 (1944), for 12 see: Plattner P.A., Heusser H., Feuger M.: Hel.Chim.Acta 32, 587 (1949), for 14 see ref.[3] and for 16 ref.[2b]
13. (a) A model with syn-periplanar disposition which should align Br and AcO as well (and which might in principle lead to a syn-rearrangement) remains to be studied. (b) The potential influence of steric compression of 6β-Br by the 10β-Me has not been investigated.
14. Migration from tertiary to primary carbon has also been reported (ref.[8,15]).
15. Beckwith A.L.J., Thomas C.B.: J.Chem.Soc., Perkin Trans. 2, 1973, 861.
16. For an analogous strategy see: Kočovský P., Černý V., Tureček F.: Collect.Czech.Chem. Commun. 44, 234 (1979).
17. 21. C-NMR spectrum: 12.19, 18.68, 18.96, 21.12, 21.29, 22.22, 22.56, 22.80, 23.77, 24.05, 26.39, 28.01, 28.14, 29.61, 31.45, 32.64, 35.49, 35.73, 36.14, 39.50, 39.82, 40.40, 42.73, 45.53, 55.46, 56.20, 56.36, 70.17, 88.92, 88.96, 169.71, 170.31. The presence of two signals of C-5 (at 88.92 and 88.96) is due to the isotope effect of ^{18}O.
    22. C-NMR spectrum: 12.01, 13.25, 18.66, 21.07, 21.28, 21.42, 22.56, 22.81, 23.83, 24.08, 27.13, 28.01, 28.36, 34.10, 35.75, 36.12, 36.57, 36.87, 37.64, 39.48, 39.72, 42.61, 48.48, 53.56, 56.12, 56.19, 72.30, 72.34, 73.13, 170.55, 170.84. Two signals of C-6 (at 72.30 and 72.34) are significant as a proof of the connection of C-6 to ^{18}O.
18. For determination of ^{18}O distribution in ester groups by C-NMR see also: (a) Vederas J.C.: J.Amer.Chem.Soc. 102, 374 (1980) and (b) Kočovský P., Tureček F.: Tetrahedron 39, 3621 (1983).

(Received in UK 7 February 1986)