Tetrahedron Letters No.16, pp. 1059-1065, 1965. Pergamon Press Ltd.
Printed in Great Britain.

FORMATION OF AZIRIDINES BY LITHIUM ALUMINUM HYDRIDE REDUCTION OF KETOXIMES*[1]

Keizo Kitahonoki, Katsumi Kotera, Yoriko Matsukawa, Sadao Miyazaki
Tetsuo Okada, Hiromi Takahashi, and Yoshihiro Takano

Shionogi Research Laboratory, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka, Japan

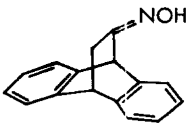
(Received 24 February 1965)

The reduction of ketoximes with lithium aluminum hydride (LAH) usually gives the corresponding primary amine (1). It has been also reported that the reduction of certain aryl ketoximes (2) and strained alicyclic oximes (3) yields the rearranged secondary amine together with the primary amine.

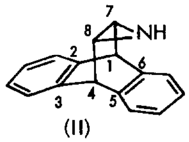
We have now found that the reductions of a series of benzylketoximes and benzobicyclo(2.2.2)octenone oximes by LAH in tetrahydrofuran afford the corresponding aziridine derivatives as main products.

When dibenzobicyclo(2.2.2)octadienone oxime (I) (4) was treated with an excess of LAH in refluxing tetrahydrofuran for 5 hours, the aziridine (II), m.p. 143-145°, $C_{16}H_{13}N$ (MW calcd., 219.3; found (Rast), 231), was obtained in 27% yield. Elution chromatography on alumina easily isolated the aziridine (II) from the accompanied by-products, anthracene (26% yield), the 7-aminodibenzobicyclo(2.2.2)octadiene (4) (0.6% yield) and a small amount of other several unidentified basic compounds.

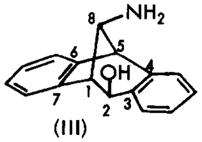
[*1] Satisfactory analyses were obtained for all compounds described. NMR spectra were taken with a Varian A-60 spectrometer in $CDCl_3$ with tetramethyl silane as internal standard.



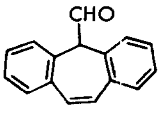
(I)



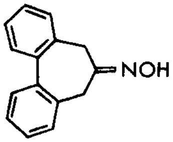
(II)



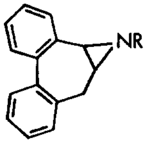
(III)



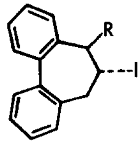
(IV)



(V)



(VI)a: R=H
b: $R=CONHC_6H_5$



(VII)a: R=NCO
b: $R=NHCO_2C_2H_5$

The structure of the aziridine (II) was based on the spectral data (IR $\nu_{max}^{CHCl_3}$ 3276 cm^{-1} (NH), no C=N band around 1660 cm^{-1}; NMR, only four groups of peaks, 5.55τ (C_1-, C_4-H; A_2X_2 type), 7.42τ (C_7-, C_8-H; A_2X_2 type, broad), 9.53τ (1 NH, broad singlet), around 2.87τ (8 aromatic protons, multiplets)), and established by the following chemical transformations. An N-acetyl derivative, m.p. 193-195°, was obtained on its treatment with acetic anhydride and pyridine. The hydrogenation of II over palladium on carbon in methanol gave the primary amine. Heating a solution of II in N-sulfuric acid cleaved the aziridine ring to give the rearranged amino-alcohol (III), m.p. 182-183°, and the unsaturated aldehyde (IV), m.p. 113-114°, in 67% and 13% yield, respectively. The structure and stereochemistry of III were deduced from the spectral data, and confirmed by mixture melting point and comparison of infrared and NMR spectra with an authentic sample of syn-8-amino-exo-2-hydroxy-dibenzo(3.2.1)octadiene, reported by Cristol et al. (5). The aldehyde (IV) (IR ν_{max}^{Nujol} 1722 cm^{-1} (CHO), UV $\lambda_{max}^{95\%\ EtOH}$ 291 mμ (ε 14,230)) is considered to be identical with the product formed by rearrangement of the epoxide (II, >O instead of >NH) (6).

The reduction of the oxime (V) (7) in the same manner also afforded the aziridine

(VIa), oil, in 70% yield (as the crystalline phenylcarbamoyl derivative (VIb), m.p. 152-153°, obtained on the treatment with phenylisocyanate) and 6-amino-1,2:3,4-dibenzocycloheptadiene (8) in 7% yield. The structure of VIa was assigned by the infrared spectrum ($\nu_{max}^{CHCl_3}$ 3326 cm^{-1} (>NH)), by its catalytic reduction to the above primary amine, and also by cleavage of the aziridine ring with various acids.*[2] The structure of VIa was supported by identification with a sample independently prepared by the method of Drefahl and Ponsold (9) from 1,2:3,4-dibenzocycloheptatriene (8) through the iodo-isocyanate (VIIa), m.p. 121-122°, and the iodo-urethane (VIIb), m.p. 163-164° (dec.).

Thus, we have investigated the applicability of this reaction for some benzylketone oximes, such as benzylmethylketone, dibenzylketone, desoxybenzoin, and β-tetralone, and also for ketoximes in bridged ring system, such as benzobicyclo(2.2.2)octenone (10) and bicyclo(2.2.2)octanone. Reductions of all of these oximes produced the corresponding aziridines,*[3] VIII (11), IX, X (12), XI (13), XII, XIII, and XIV (>NH instead of >NCONH C_6H_5), although the yields varied depending on the sort of the oximes used. The results are summarized in Table I.

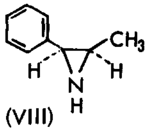
In contrast with the result of Rerick et al. (2d) that the reduction of dibenzylketoxime with LAH afforded the primary amine almost quantitatively, our results showed that the reduction of the oxime in tetrahydrofuran gave the cis-aziridine (IX) in good yield. This contrast might be due to the difference of the experimental conditions. It is important to recognize that the cis-aziridines, VIII, IX*[4] and X, were produced

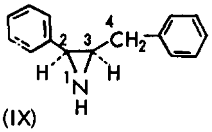
---

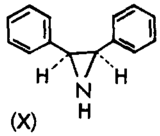
*[2] The cleavage of the aziridine ring of VIa will be reported elsewhere.

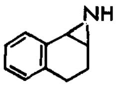
*[3] The structure proof and the identification of these aziridines will be reported later.

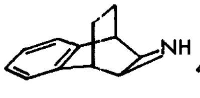
*[4] The cis configuration of VIII and IX was assigned chiefly by the NMR data. The C_2-H of VIII appears at 6.99τ as a doublet ($J_{2,3}$=6.5 c.p.s.) and that of the phenylcarbamoyl derivative of IX at 6.06τ as a doublet ($J_{2,3}$=6.0 c.p.s.). These values of coupling constants show that VIII and IX are cis-aziridines. Cf. A. Hassner and C. Heathcock, Tetrahedron Letters, No. 19, 1125 (1964).

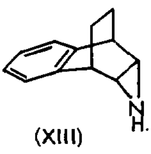

(VIII)

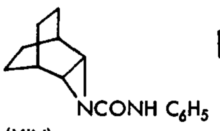

(IX)


(X)


(XI)


(XII)


(XIII)


(XIV)

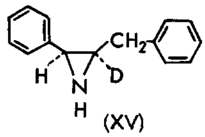

(XV)

TABLE I

Formation of Aziridines by LAH Reduction of Ketoximes [a]

Parent ketone of oximes	Aziridine Structure	m.p., °C	Yield, % [b]	Phenylcarbamoyl derivative m.p., °C
Benzylmethylketone	VIII	41-43	34	92-94
Dibenzylketone	IX	42-43	73	123-125
Desoxybenzoin	X	83-84 (12)	25	163-164
β-Tetralone	XI	52-53.5 (13)	40	157-158
1,2:3,4-Dibenzocycloheptadien-6-one	VIa	oil	70	152-153
Dibenzobicyclo-(2.2.2)octadienone	II	143-145	27	-
Benzobicyclo(2.2.2)-octenone	XII XIII	88.5-89.5 108-110	46 4.3	-
Bicyclo(2.2.2)-octanone	-	-	2.8	XIV 152-153

a. Reductions were carried out at a mole ratio of LAH to oximes of 2-6: 1 in refluxing tetrahydrofuran for 2-5 hours.

b. The theoretical yield of the isolated aziridines to the oximes.

stereoselectively by the present reaction.*5

The reduction of benzobicyclo(2.2.2)octenone oxime yielded mainly the exo-

---

*5 The tosylate, acetate and methylether of dibenzylketoxime were also reduced to IX, although in somewhat smaller yields.

aziridine (XII) and a small amount of the endo-aziridine (XIII). Bicyclo(2.2.2)-octanone oxime, not having a fused benzene ring gave a poor yield of the aziridine, which was characterized as its phenylcarbamoyl derivative (XIV).*6

The yields of the aziridines were much dependent on the kind of solvent used for the reduction. For example, when ether was used as a solvent instead of tetrahydrofuran, the aziridine formation was reduced or not recognized at all.

Treatment of dibenzylketoxime with lithium aluminum deuteride afforded cis-2-phenyl-3-benzyl-3-deutero-ethylenimine (XV), m.p. 43-44° (phenylcarbamoyl derivative, m.p. 128-129°), in 75% yield. The location of deuterium introduced in XV is determined by the comparison of the NMR spectra of IX and XV. The spectrum of IX showed peaks at about 6.68τ (C_2-H, poor doublet as the X part of an A_2BX system) and about 7.52τ (C_3-H and two C_4-H, multiplet as the A_2B part of the same A_2BX system). On the other hand, the spectrum of XV showed the signals of C_2-H and two C_4-H at 6.72 (singlet) and 7.54τ (singlet) in relative peak areas of C_2-H: C_4-H: NH=1 : 2 : 1. These data clearly indicate the absence of a proton at C_3 in XV and hence the introduction of deuterium at that position. The existence of a C-D streching band at 2228 cm^{-1} in the infrared of XV gave additional evidence of the structure.

Since it has been known (14) that the double bond of azirine is usually reduced with lithium aluminum hydride without ring cleavage, the above label experiment and the stereoselective formation of aziridines strongly suggest the presence of an azirine intermediate in the reaction.

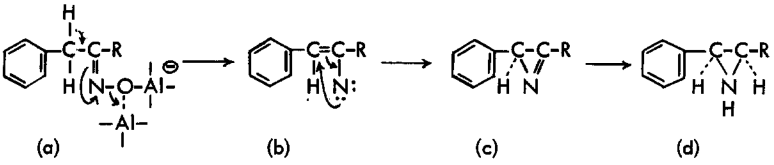
Although at the present time we have not carried out a detailed mechanistic study on this reaction, it seems to us that the general mode of the present reaction may

---

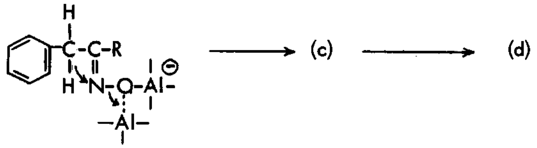
*6 Other methods for the synthesis of aziridines fused to the bicyclo(2.2.2)octane system, hitherto unreported, may be tedious.

be classified as similar to the Grignard reaction of ketoximes (15) or the Neber and the related rearrangements (16). Therefore, either one of the two mechanism pictured below seems to be most reasonable for our results so far obtained.

i)



ii)



i) Concerted elimination of a proton at the benzylic position and the $-\mathrm{O}-\mathrm{Al}\overset{\ominus}{\lesseqgtr}$ group from (a) might be facilitated by the uncharged aluminum species (17), giving the azirine intermediate (c) (15b, 16, 18) through the unsaturated nitrene (b). This azirine (c) is reduced to the cis-aziridine (d) by the attack of hydride mainly from the opposite side of the bulky phenyl group. ii) Concerted γ-elimination accompanied with the direct formation of (c) without nitrene formation would be another possible course. The formation of the aziridines of the benzobicyclo(2.2.2)octene systems in fair yields may be attributed to a probable benzylic character*[7] of the methylene group adjacent to the carbonyl.

The reduction of the ketoximes dèscribed here may provide an useful method for the synthesis of some kinds of aziridine derivatives. Further studies on this reaction and its mechanism are in progress.

---

*[7] Recently, homobenzylic conjugation on the 7-position of benzonorbornene was demonstrated by H. Tanida et al. in the acetolysis reaction of the anti-7-brosylate. Even though the mechanisms of both reactions are quite different, the assumption of the similar character would not be unreasonable because of the related geometrical situation. Refer to H. Tanida, T. Tsuji and H. Ishitobi, J.Am.Chem.Soc., **86**, 4904 (1964).

Acknowledgements. We wish to thank Dr. K. Takeda and Prof. E. Ochiai for their encouragement, and Dr. W. Nagata and Dr. H. Tanida for valuable discussions. Thanks are also due to Dr. K. Tori for interpreting the NMR spectra.

REFERENCES

1. N.G.Gaylord, Reduction with Complex Metal Hydrides, p. 751. Interscience Publishers, Inc., New York, 1956.
2. (a) E.Larsson, Svensk. Kem. Tidskr., 61, 242 (1949); (b) D.R.Smith, M. Marienthal, and J.Tipton, J. Org. Chem., 17, 294 (1952); (c) R.E.Lyle and H. J.Troscianiec, ibid., 20, 1757 (1955); (d) M.N.Rerick, C.H.Trottier, R.A. Daignault, and J.D.DeFoe, Tetrahedron Letters, No. 10, 629 (1963); (e) A.E. Petrarca and E.M.Emery, ibid., No. 10, 635 (1963).
3. F.Lautenschlaeger and G.F.Wright, Can. J. Chem., 41, 863 (1963).
4. S.Wawzonek and J.V.Hallum, J.Org. Chem., 18, 288 (1953).
5. S.J.Cristol, J.R.Mohrig, F.P.Parungo, D.E.Plorde, and K.Schwarzenbach, J. Am. Chem. Soc., 85, 2675 (1963). We thank Prof. Cristol for the kind supply of a sample of the amino-alkohol (V) and its NMR data.
6. S.J.Cristol and R.K.Bly, J. Am. Chem. Soc., 82, 6155 (1960).
7. J.Kenner and E.F.Turner, J. Chem. Soc., 99, 2101 (1911).
8. J.W.Cook, G.T.Dickson, and J.D.Loudon, J. Chem. Soc., 746 (1947).
9. G.Drefahl and K.Ponsold, Chem. Ber., 93, 519 (1960).
10. K.Kitahonoki and Y. Takano, Tetrahedron Letters, No. 24, 1597 (1963).
11. S.J.Brois, J. Org. Chem., 27, 3532 (1962).
12. (a) A.Darapsky and H.Spannagel, J. Prakt. Chem., (2), 92, 295 (1915); (b) A. Weissberger and H.Bach, Ber., 64B, 1095 (1931); (c) M.J.Hatch and D.J. Cram, J. Am. Chem. Soc., 75, 38 (1953).
13. A.Hassner and C.Heathcock, Tetrahedron, 20, 1037 (1964).
14. D.J.Cram and M.J.Hatch, J. Am. Chem. Soc., 75, 33 (1953).
15. (a) K.N.Campbell, B.K.Campbell, L.G.Hess, and I.J.Schaffner, J. Org. Chem., 9, 184 (1944) and earlier papers; (b) S.Eguchi and Y.Ishii, Bull. Chem. Soc. Japan, 36, 1434 (1964).
16. C.O'Brien, Chem. Rev., 64, 81-89 (1964) and references cited therein.
17. D.M.S.Wheeler and J.W.Huffman, Experientia, 16, 516 (1960).
18. H.O.House and W.F.Berkowitz, J. Org. Chem., 28, 307, 2271 (1963).