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AZIRIDINE FORMATION BY LITHIUM ALUMINUM HYDRIDE REDUCTION OF KETOXIMES OF BRIDGED RING SYSTEMS[1]

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Abstract—LAH reduction of dibenzobicyclo[2.2.2]octadien-7-one oxime (I) in refluxing THF was found to give an aziridine, dibenzo-3-azatricyclo[3.2.2.0^{2,4}]nonadiene (IIa) in 34% yield, together with 7-amino-dibenzobicyclo[2.2.2]octadiene (III; 3%) and anthracene (IV; 50%). The reduction of benzobicyclo-[2.2.2]octenone oxime (V) also afforded the corresponding aziridines, benzo-3-azatricyclo[3.2.2.0$^{2,4\text{-}exo}$]-nonene (VI; 46%) and benzo-3-azatricyclo [3.2.2.0$^{2,4\text{-}endo}$]nonene (VII; 4%), accompanied with the primary amines, *endo*-form (XIa; 20%) and *exo*-form (Xa; 5%), and a secondary amine, benzo-3-azabicyclo-[3.2.2]nonene (IX; 3%). For structure elucidation of the aziridines, IIa, VI and VII, their syntheses by independent method and cleavage reactions with acids were performed. This new method for aziridine formation was examined on some related ketoximes of bridged ring systems.

THE LAH reduction of ketoximes usually gives the corresponding primary amine.[2] The reduction of certain aryl ketoximes[3] and strained alicyclic oximes[4] yields the rearranged secondary amine together with the primary amine.

In previous communication,[5] we reported that LAH reduction of some ketoximes gives the corresponding aziridines, the yields of which vary depending upon the ketoximes used.*

This paper is concerned with the detailed results obtained by LAH reductions of dibenzobicyclo[2.2.2]octadienone oxime (I), benzobicyclo[2.2.2]octenone oxime (V) and some related ketoximes of bridged ring systems.†

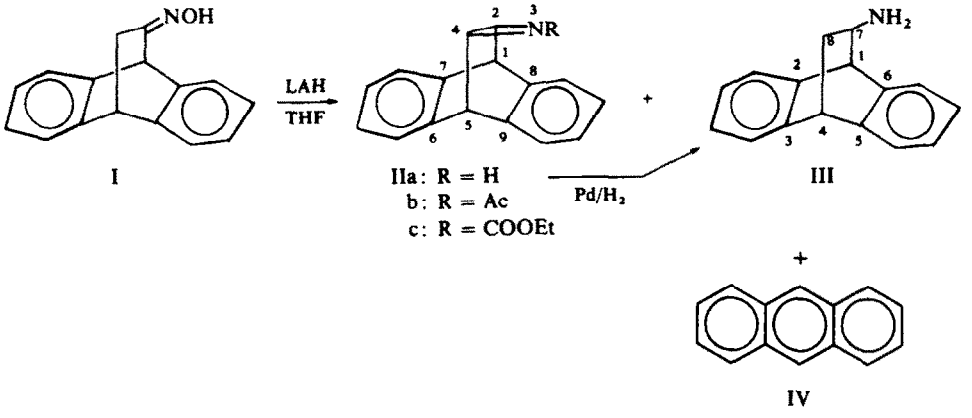
Formation of dibenzo-3-azatricyclo[3.2.2.0^{2,4}]*nonadiene* (IIa) *by* LAH *reduction of the oxime*, I. Treatment of dibenzobicyclo[2.2.2]octadien-7-one oxime (I)[8] with an excess of LAH in refluxing THF for 5 hr gave two basic products, m.p. 143–145° and m.p. 101·5–102·5°, and a neutral product, m.p. 213–216° in 34, 3 and 50% yields, respectively, which were easily separated by elution-chromatography on alumina. The neutral one was readily proved to be anthracene (IV), probably arising from retro-Diels-Alder reaction during the reduction. Minor one of the two bases, m.p. 101·5–102·5° was found to be the expected primary amine in comparison with an authentic 7-amino-dibenzobicyclo[2.2.2]octadiene (III), which was synthesized by reduction of I with metallic sodium and ethanol.[8] Major basic product, m.p. 143–145° was characterized as its N-acetate, m.p. 193–195° and N-carboxylate, m.p. 190–192°. From their spectral data, the structures were deduced to be an aziridine, dibenzo-3-azatricyclo[3.2.2.0^{2,4}]nonadiene, its N-acetate and N-carboxylate, as shown in IIa,

* Waight *et al.* has reported a similar reaction on phenyl vinyl ketoxime.[6]

† In this connection, aziridine formation by LAH reduction of dibenzo[a,c]-cycloheptadien-6-one oxime will be reported by Kotera *et al.*[7]

IIb and IIc, respectively. The IR spectrum of the free base showed at 3276 cm^{-1} the absorption band corresponding to a secondary amine. However, the corresponding absorption was not recognized in the IR spectra of the N-acetate and the N-carbonate. The NMR spectrum of the free base showed peaks at about 7·42 τ (C_2—H and

CHART 1.



C_4—H, poor triplet as the A_2 part of an A_2X_2 system), about 5·55 τ (C_1—H and C_5—H, triplet as the X_2 part of an A_2X_2 system) and at 9·53 τ (>NH, broad singlet). The spectrum of the acetate similarly showed the proton signals of C_2—H and C_4—H at about 6·90 τ and those of C_1—H and C_5—H at about 5·40 τ as the A_2 and X_2 parts of an A_2X_2 system, respectively, but the proton signal due to an >NAc group appeared at 8·17 τ as a singlet instead of the signal attributable to an >NH group.

The free base underwent catalytic hydrogenation in methanol over Pd–C for 6 hr, giving the primary amine III after absorbing one molar equivalent of hydrogen. Accordingly, these results may permit to assign the newly obtained base, and its N-acetate and N-carboxylate as IIa, IIb and IIc, respectively.

Formation of benzo-3-azatricyclo[3.2.2.0$^{2,4\text{-}exo}$]*nonene* (VI) *and benzo-3-azatricyclo*[3.2.2.0$^{2,4\text{-}endo}$]*nonene* (VII) *by* LAH *reduction of* V. With a new method for the synthesis of the aziridine IIa thus found, the LAH reduction of benzobicyclo[2.2.2]-octenone[9] oxime (V) in refluxing THF* was performed. Contrary to the LAH reduction of I, it is expected that the stereoisomers of aziridines and primary amines may exist in a mixture of the reduction products. Actually, repeated elution-chromatography over alumina and/or silica gel gave the stereoisomers of an aziridine, benzo-3-azatricyclo[3.2.2.0^{2,4}]nonene, m.p. 88·5–89·5° and m.p. 108–110°, in 46 and 4%

* The solvent effect on the aziridine formation from these bridged ring ketoximes is remarkable. Instead of THF, glyme, diglyme or 2-methyltetrahydrofuran can be used for the reduction, although quantitative analyses of the products were not accomplished. However, aziridine formation was not recognized at all, when the following solvents were used: tetrahydropyran, ether, di-n-butylether or tetrahydrothiophen.

CHART 2.

V
LAH
THF
VI
VII
VIII
IX
Pd/H2
Xa: R = R' = H
b: R = H, R' = CHO
c: R = H, R' = CH3
d: R = R' = CH3
Xla: R = R' = H
b: R = H, R' = CHO
c: R = H, R' = CH3
d: R = R' = CH3
(i) O3
(ii) H2O2
(iii) Ac2O
XII
XIIIa: R = O
b: R = NH
LAH
IX

yields, respectively, together with a mixture VIII of the isomers of the primary amine Xa and XIa (25%) and benzo-3-azabicyclo[3.2.2]nonene (IX), m.p. 108–110° (4%). The structures and stereochemistry of the aziridine-isomers were also deduced by analytical and spectral data, and by the results of catalytic reduction to the corresponding primary amines. Both of the compounds, m.p. 88·5–89·5° and m.p. 108–110°, corresponded to the same molecular formula $C_{12}H_{13}N$ and showed at 3309 cm^{-1} and 3727 cm^{-1} the respective IR absorption bands corresponding to an $\rangle$NH group and did not exhibit any kind of absorption attributable to a double bond. These results suggest that the compounds may be aziridine derivatives. The results of the NMR study support reasonably this deduction.[10] For example, the proton signals due to $\rangle$NH groups of VI and VII appeared at 9·15 and 10·75 τ, respectively. As to the stereochemistry, catalytic reduction played an important role. Hydrogenation of the compound, m.p. 88·5–89·5° in the presence of palladium-carbon catalyst gave the *exo*-primary amine Xa and that of the compound, m.p. 108–110° afforded the *endo*-primary amine XIa. These results may permit to deduce the stereochemistry as follows: the former is the *exo*-isomer, benzo-3-azatricyclo[$3.2.2.0^{2,4\text{-}exo}$]nonene (VI) and the latter is the *endo*-isomer, benzo-3-azatricyclo[$3.2.2.0^{2,4\text{-}endo}$]nonene (VII). In this case, the stereochemistry of the isomers of the primary amine VIII was established, principally based on the NMR data of the primary amines and their derivatives. Since separation of the isomers of the primary amines, which were obtained by the LAH reduction of V or by the reduction with metallic sodium and ethanol, seemed difficult, the mixture was converted by treatment with ethyl formate into their N-formates, which were subjected to elution-chromatography over alumina. The successful separation of the mixtures afforded pure isomers of N-formates, m.p.

TABLE 1. PROTON CHEMICAL SHIFTS (τ) OF N-SUBSTITUENTS IN PRIMARY AMINES AND THEIR DERIVATIVES (60 Mc, $CDCl_3$)

N-Substituent	*exo*-compound	*endo*-compound
H	8·58 (Xa)	9·08 (XIa)
CHO	1·80 (Xb)	2·15 (XIb)
CH_3	7·53 (Xc)	7·68 (XIc)
$(CH_3)_2$	7·73 (Xd)	7·90 (XId)
H[a]	9·15 (VI)	10·75 (VII)

[a] For comparison, chemical shifts of the proton signals of the secondary amino group in the aziridines, VI and VII.

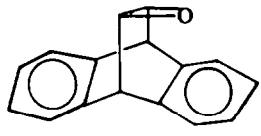
174–175·5° and m.p. 114–115·5°, in 5 and 20% yields in the LAH reduction, and in 22 and 68% yields in the reduction with sodium and ethanol, respectively. Both of the N-formates were transformed into the corresponding free amines, and their N-monomethyl and N,N-dimethyl derivatives. With the primary amines and their derivatives thus obtained, their NMR data were compared to each other in the proton signals of the N-substituents. As shown in Table 1, proton signals of the N-substituents

of the *endo*-compounds shift to higher fields in comparison with those of the *exo*-compounds, probably owing to the shielding effect of the benzene ring.[11]

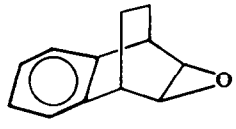
From these findings, it is concluded that the N-formate, m.p. 174–175·5° has *exo*-configuration and the N-formate, m.p. 114·0–115·5° is the *endo*-isomer. Furthermore, the structure of minor product, a secondary amine, which was obtained by LAH reduction of V, was easily established as benzo-3-azabicyclo[3.2.2]nonene (IX) by the independent synthesis from benzobicyclo[2.2.2]octadiene (XII).[9] Oxidation of XII with ozone and subsequent treatment with hydrogen peroxide and with acetic anhydride gave the dicarboxylic anhydride XIIIa, which was converted to the dicarboximide XIIIb by action of ammonia according to the method of Doering and Goldstein.[12] The compound, XIIIb, was reduced with LAH to give the secondary amine IX identical with that obtained by LAH reduction of V. At any rate, in the instance of V, the LAH reduction was also found to give the corresponding aziridines which are composed of the *exo*- and the *endo*-isomers, in a fairly good yield.

Synthesis of the aziridines, IIa, *and* VII *from the corresponding epoxides*, XIV, XV *and* XVII. In order to confirm the deduced structures and stereochemistry of IIa, VI and VII, independent synthesis was undertaken. Synthesis of the aziridino-compounds having a bicyclo[2.2.2]octane ring system has been reported in one instance.[13] Recently, Tanida *et al.*[14] reported that addition of ethyl azidoformate to norbornene, norbornadiene and benzonorbornadiene, having a bicyclo[2.2.1]

CHART 3.

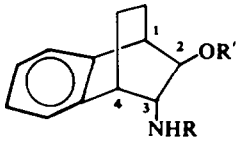


XIV



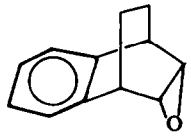
XV

28% NH_4OH



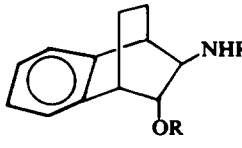
20% MeOH-KOH → VII

XVIa: R = R' = H
b: R = H, R' = COOMe
c: R = Ts, R' = COOMe



XVII

28% NH_4OH



20% MeOH-KOH → VI

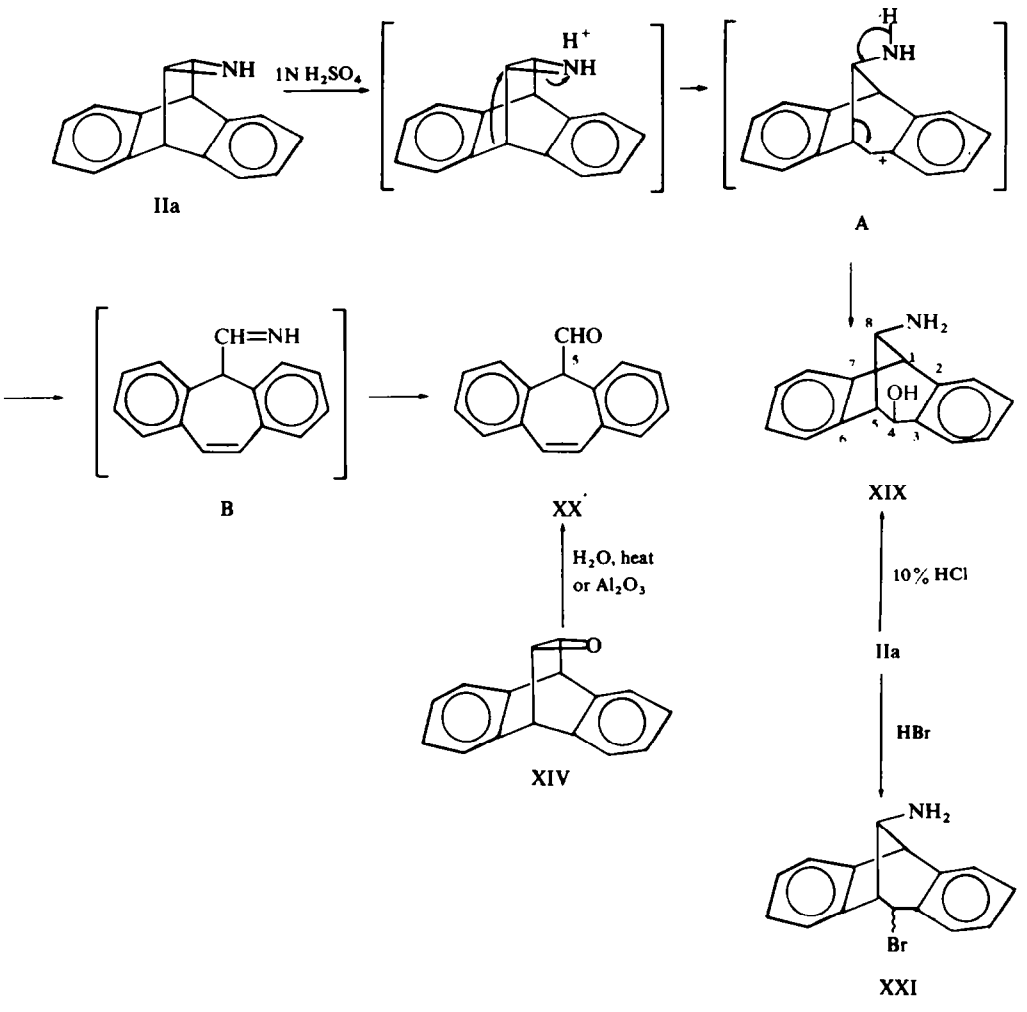
XVIII a: R = R' = H
b: R = H, R' = COOMe
c: R = Ts, R' = COOMe

heptane ring system, led to the corresponding aziridines through the triazole derivatives. However, addition of ethyl azidoformate to dibenzobicyclo[2.2.2]octatriene[15] and benzobicyclo[2.2.2]octadiene (XII) resulted in failure, recovering the starting materials perfectly, probably owing to the difference of ring strains between these two ring systems. Synthesis of the aziridine IIa by addition of iodine-isocyanate according to the method of Drefahl and Ponsold[16] was also attempted. However, all of the addition products was found to be the rearranged compounds having dibenzobicyclo-[3.2.1]octadiene system. The detailed results will be reported elsewhere. Ultimately, ring cleavage reaction with 28% aqueous ammonia[17] on the epoxides XIV, XV and XVII was examined, because such reaction in an alkaline medium does not involve the carbonium ion intermediates, necessary for the rearrangement of the ring system. Actually, the *endo*- and *exo*-aziridines, VII and VI could be synthesized starting from *exo*- and *endo*-epoxides, XV and XVII, with the stereochemistry established.[9,10] Heating of the epoxides, XV and XVII, with 28% aqueous ammonia at 150° in a sealed-tube for 28 hr afforded the corresponding *trans*-amino-alcohols, XVIa, m.p. 165·166·5° and XVIIIa, m.p. 147–148°, in 55 and 73% yields, respectively. The former was transformed by treatment with dimethyl pyrocarbonate into the urethane derivative XVIb, m.p. 114–115°, which gave on tosylation the urethane-tosylate XVIc, m.p. 159–160·5°. The compound XVIc was heated at 80° with 20% methanolic potassium hydroxide, giving the *endo*-aziridine VII in an overall yield of 14% from XV. The latter compound XVIIIa was similarly converted into the corresponding products, the urethane XVIIIb, m.p. 155–156°, the urethane-tosylate XVIIIc, m.p. 166·5–167·5° and then the *exo*-aziridine VI, in an overall yield of 25% from XVII. These results provided unequivocal evidence for the structures and stereochemistry of the aziridines, VI and VII. However, cleavage reaction of the epoxide ring of XVI with ammonia to the corresponding *trans*-aminoalcohol was unsuccessful so far examined, resulting in the formation of several neutral products, which were not further investigated.

Cleavage of the aziridine ring of IIa, VI *and* VII *with acids.* The results obtained from the ring-cleavage reaction with acids support reasonably the assignment of the structures and stereochemistry of the aziridines as IIa, VI and VII, respectively. Heating a solution of IIa in 1N H_2SO_4 in a boiling water-bath for 1 hr cleaved the aziridine ring* to give the rearranged amino-alcohol XIX, m.p. 182–183°, and the unsaturated aldehyde XX, m.p. 110–111·5°, in 67 and 13% yields, respectively. The structure and stereochemistry of XIX were deduced from the spectral data, 3420 cm^{-1} (—OH), 3398, 3332 cm^{-1} (—NH_2), and confirmed by comparison with an authentic sample of *syn*-8-amino-*exo*-4-hydroxy-dibenzobicyclo[3.2.1]octadiene, reported by Cristol *et al.*[18] The aldehyde XX, which showed the IR absorption band at 1722 cm^{-1} (—CHO) and absorption maximum at 291 mμ (ε 14,230) in the UV spectrum, is likely to be identical with the product, 5*H*-dibenzo[b,f]cycloheptatriene-5-carboxy-aldehyde, formed by rearrangement of the epoxide XIV.[19] The probable reaction sequence for the formation of XIX and XX may be analogous to the rearrangements of the epoxide XIV. The carbonium ion intermediate A undergoes nucleophilic attack of OH group at C-4, resulting in the formation of XIX and further rearrangement

* The aziridines IIa, VI and VII are fairly stable toward cold mineral acids and can be recovered mostly unchanged from the acid solution after a short time.

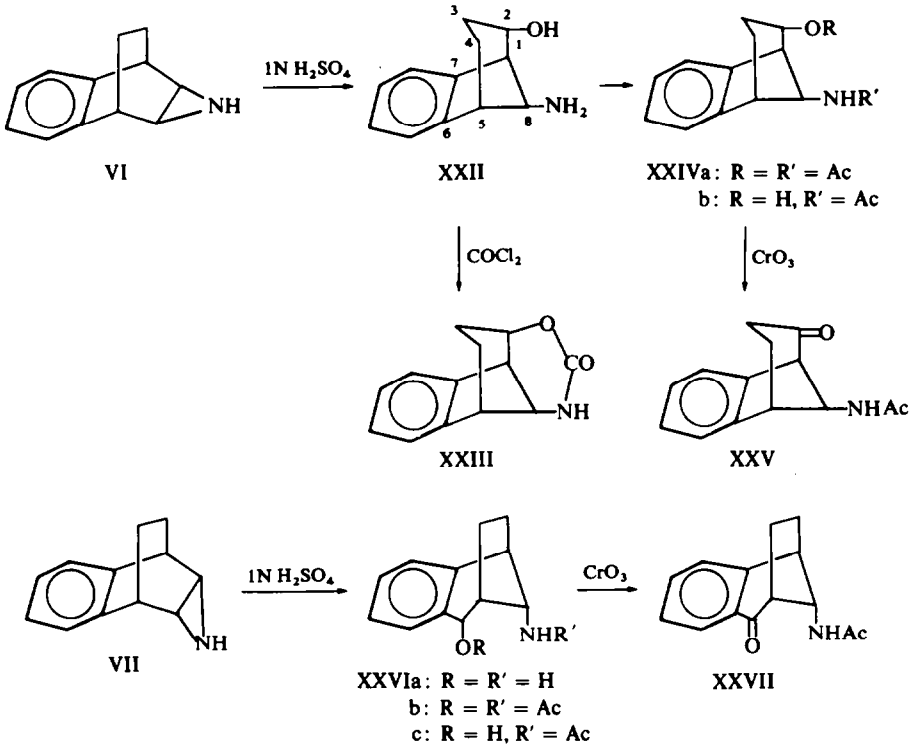
CHART 4.



yielding another intermediate B, which is converted into XX by action of the acid. Heating of IIa with 10% aqueous hydrochloric acid also gave XIX in 75% yield and action of hydrogen bromide in dioxane afforded *syn*-8-amino-ψ-4-bromodibenzobicyclo[3.2.1]octadiene (XXI), m.p. 143–145°.

Heating of the aziridine with 1N H_2SO_4 in a boiling water-bath for 1 hr gave an amino-alcohol, m.p. 127·5–128·5°, which was treated with phosgen affording a carbonate, m.p. 163–164·5°, indicating *cis*-relation between a OH and an NH_2 groups. This shows clearly that the amino-alcohol should have a benzobicyclo-[3.2.1]octene system, because *trans*-amino-alcohol with the retention of the ring system does not provide such a carbonate. Therefore, the structures of the amino-alcohol and its carbonate may be assigned as XXII and XXIII, respectively. The compound XXII, on acetylation, partial hydrolysis of the O-acetate and oxidation with

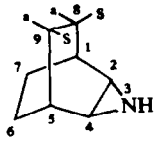
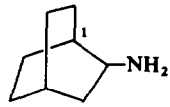
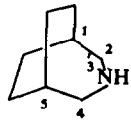
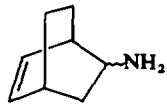
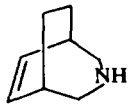
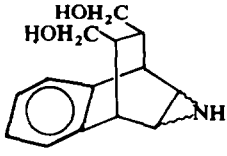
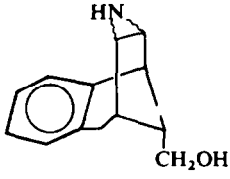
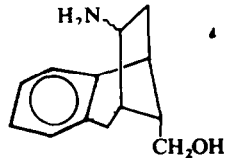
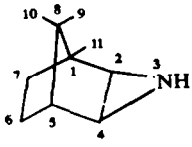
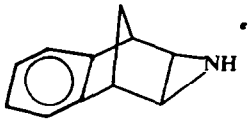
CHART 5.



chromic acid, gave O,N-diacetate XXIVa, m.p. 171·5–172°, N-monoacetate XXIVb, m.p. 166–167·5° and a ketone derivative XXV, m.p. 157·5–159°. The IR spectrum of the ketone exhibited at 1703 cm^{-1} the absorption band due to an isolated 6-membered ketone. These results support the *exo*-configuration of the aziridine ring in VI. Similar working up of the aziridine VII afforded the respective compounds, an amino-alcohol XXVIa, m.p. 126–128°, O,N-diacetate XXVIb, m.p. 100–101·5°, N-monoacetate XXVIc, m.p. 210–211° and an oily conjugated ketone XXVII, characterized as its *p*-nitrophenylhydrazone, m.p. 271·5–273·5°. In contrast with the above ketone XXV, spectral data of the compound XXVII showed the presence of conjugation of its ketonic function with benzene ring, exhibiting 1681 cm^{-1} ($\rangle$CO) and 250, 291 mμ (ε 5440, 1110). These transformations can be reasonably explained only with the *endo*-configuration of the aziridine ring in VII. Strong hydrogen bonding between OH and NH_2 groups observed in the IR spectra of the amino-alcohols, XXII and XXVIa, supports the assigned structures.

Formation of aziridines by LAH *reduction of other bicyclic ketoximes.* With the above-mentioned findings in mind, LAH reduction of the oximes of the ketones, XXVIII–XXXIII, of bridged systems was carried out in refluxing THF. The results are summarized in Table 2. On LAH reduction of the oximes of the bicyclic ketones

TABLE 2. FORMATION OF AZIRIDINES FROM OTHER BICYCLIC KETOXIMES

Parent Ketone	Aziridine Structure	Yield, %	Other products Structure	Yield, %
XXVIII[a]		3		29
				7·4
XXIX[a]	none			16
				6
XXX		14[b]	—	
XXXI	 [c]	51	 [d]	35
XXXII[a]		1	—	
XXXIII	 [e]	3	—	

[a] Reduction products were isolated as phenylcarbamoyl derivatives.

[b] The yield of purely isolated *exo*-isomer, although examination of reduction products on TLC showed that a mixture of aziridines may produce in good yield.

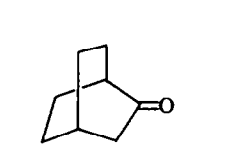
[c] Characterized as diphenylcarbamoyl derivative.

[d] Characterized as acetate.

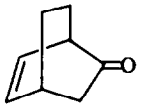
[e] See Ref. 14.

having no aromatic ring, such as bicyclo[2.2.2]octanone (XXVIII), bicyclo[2.2.2]-octenone (XXIX) and camphor (XXXII), the aziridine formation was remarkably reduced or not recognized at all, whereas bicyclic ketoximes bearing an aromatic ring, the oximes of XXX and XXXI gave the corresponding aziridines in fair yields

CHART 6.



XXVIII



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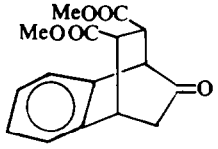

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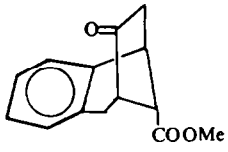
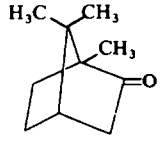
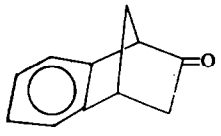


XXXI



XXXII



XXXIII

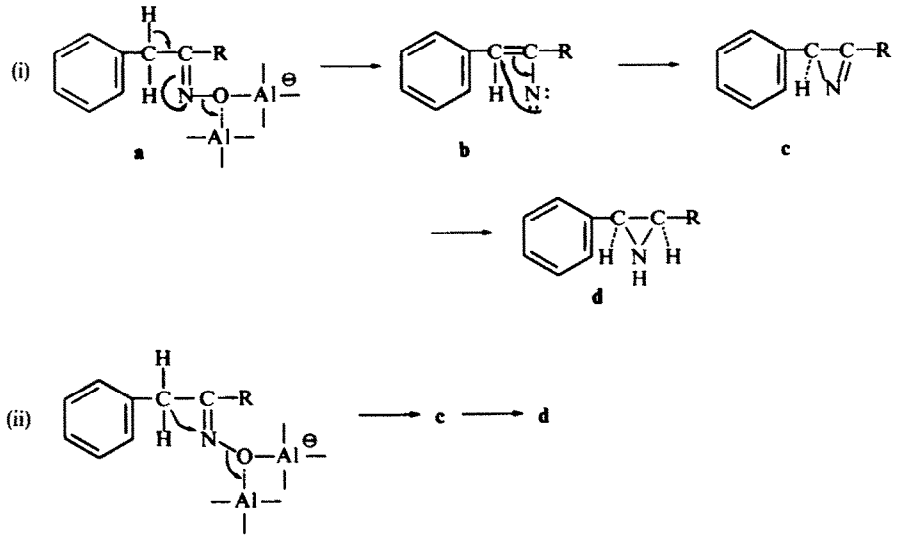
by the reduction. On the other hand, the reduction of the oxime of XXXIII* afforded only a small quantity of the aziridine.* These findings may involve many factors to inspect the reaction mechanism of the mew method for the synthesis of aziridines.

Reaction mechanism and conclusion. At the earlier stage[5] that our group found this new method for the synthesis of aziridines, it seemed to us that the general mode of this reaction may be reminiscent of the Grignard reaction of ketoximes[20] (the Hoch-Campbell synthesis) or the Neber and the related rearrangements.[21] Therefore, based on the discussions for their reaction mechanism, the following two mechanisms (i and ii) were proposed and either one of the two seemed to be most reasonable for our results involving the bicyclic ketoximes described here.[5] Speaking briefly, (i) the formation of the azirine intermediate **c** through the unsaturated nitrene **b**[20b,21,22] and the reduction of **c** to the *cis*-aziridine **d**; (ii) concerted γ-elimination with the inversion of the configuration about the nitrogen atom, like the Beckmann rearrangement, and the direct formation of **c** without nitrene formation. In this connection, the aziridine formation of the benzobicyclo[2.2.2]octene systems in fair yields was considered to be attributable to a probable homobenzylic character[23] of the methylene group adjacent to the carbonyl. Recently, however, further investigation on this reaction has proved that the aziridine formation is effected by the stereochemistry of the oximes used.[24]† As a result, neither of the above two mechanisms could explain

* We thank Dr. H. Tanida for the kind supply of these compounds.

† On LAH reduction of benzobicyclo[3.2.1]octenone oximes, we are now recognizing fruitful findings regarding the stereochemistry of the aziridine formation and homobenzylic character of the methylene group of bridged system.[25]

CHART 7.



reasonably this new finding and then we are now standing at a stage that revised reaction mechanism must be proposed based on a detailed mechanistic study. Endeavour for this purpose is further being continued. In parallel to this, this new method for aziridine formation has been extended to oximes of several types.[26]

EXPERIMENTAL

M.ps were taken by capillary, and are uncorrected. The NMR spectra were determined at 60 Mc with a Varian A-60 spectrometer using TMS as internal standard in $CDCl_3$. The IR spectra were measured using a Koken Model D.S.-301 IR double-monochromatic spectrophotometer and the UV spectra were measured using a Hitachi Model E.P.S.-2 UV spectrometer.

LAH *reduction of dibenzobicyclo*[2.2.2]*octadien-7-one oxime* (I)

Dibenzo-3-azatricyclo[3.2.2.$0^{2,4}$]*nonadiene* (IIa). A soln of I (10·671 g) in THF (70 ml) was dropwise added with stirring at 8° to a suspension of LAH (6·88 g) in THF (130 ml) over a period of 15 min. The mixture was refluxed for 5·5 hr, indicating remarkable color changes, grey—green—dark green—yellowish brown. After cooling, H_2O was added to the reaction mixture to decompose the excess LAH and the resulting inorganic substance was separated by filtration, washed twice with $CHCl_3$, and the filtrate was combined with $CHCl_3$ washings, evaporated to dryness under reduced pressure to leave a residue, which was dissolved in $CHCl_3$ and extracted with 10% HCl aq. The organic layer was washed with H_2O, dried over anhyd K_2CO_3, evaporated to dryness to give a crystalline residue (4·52 g), of which a portion was recrystallized from ether, affording IV, m.p. 213–216°. The yield of crude anthracene was 50·6%. The acidic layer was made alkaline with K_2CO_3, extracted with ether and the ethereal layer was washed with H_2O, dried over anhyd K_2CO_3 and evaporated to give a yellow residue (4·52 g), which was chromatographed on 5% H_2O-containing neutral Woelm Al_2O_3 (130 g). Elution with pet. ether–benzene (19:1–3:7) gave a crystalline residue (3·39 g), which was recrystallized from ether to give 2·7 g (27%) of crude IIa, m.p. 139–141°. A pure sample for analysis had a m.p. of 143–145° as plates on repeated recrystallization from ether: ν_{max}^{Nujol} 3265 cm^{-1} (>NH); NMR, 2·85 τ (8-proton multiplet, aromatic protons), 5·55 τ (2-proton triplet, H_1 and H_5), 7·42 τ (2-proton poor triplet, H_2 and H_4), 9·53 τ (1-proton singlet, >N<u>H</u>). (Found: C, 87·67; H, 5·94; N, 6·31. $C_{16}H_{13}N$ requires: C, 87·64; H, 5·98; N, 6·39%).

Elution with benzene–$CHCl_3$ (1:9–1:1) gave 303 mg (3%) of crude III which was recrystallized from ether to give III (63 mg), m.p. 101–102°, identical with that obtained by reduction of I with sodium metal and EtOH.[8]

Fractions eluted with benzene–$CHCl_3$ (1:1) and $CHCl_3$–MeOH (9:1) gave a residue (566 mg), which was twice recrystallized from MeOH–ether to give XIX (241 mg), m.p. 182–183° as plates. Presumably the compound XIX may be produced by the ring-opening of the aziridine IIa during the treatment of the reaction mixture with 10% HCl aq.

To a soln of IIa (226 mg) in pyridine (3 ml) was added Ac_2O (1 ml) and the mixture was allowed to stand overnight at room temp. Working up left an oily residue, which was dissolved in $CHCl_3$ and washed with 10% HCl aq and with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized 3 times from acetone to yield IIb, m.p. 193–195° as plates: NMR, 5·40 τ (2-proton, triplet, H_1 and H_5) 6·90 τ (2-proton, triplet, H_2 and H_4), 8·17 τ (3-proton, singlet, $NCOCH_3$). (Found: C, 82·82; H, 5·87; N, 5·69. $C_{18}H_{15}ON$ requires: C, 82·73; H, 5·79; N, 5·36%).

A soln of diethyl pyrocarbonate (468 mg) in dry ether (5 ml) was added to a soln of IIa (540 mg) in dry ether (30 ml) and the mixture was allowed to stand at room temp for 4 hr to precipitate a crystalline product (529 mg), which was separated by filtration and recrystallized twice from acetone–ether to give IIc, m.p. 190–192° as needles: ν_{max}^{Nujol} 1713 cm^{-1} (>NCOOC$_2$H$_5$). (Found: C, 78·28; H, 5·91; N, 4·86. $C_{19}H_{17}O_2N$ requires: C, 78·33; H, 5·88; N, 4·81%).

Hydrogenation of IIa *to* III. A soln of IIa (324 mg) in MeOH was shaken in an atmosphere of H_2 in the presence of 15% Pd–C catalyst (800 mg) for 6 hr. After absorbing 1·4 molar equiv of H_2 (45·5 ml), reduction stopped. Working up gave a residue, to which was added a small amount of H_2O, and the mixture was made alkaline with K_2CO_3 and extracted with ether. The ethereal extract was washed with H_2O, dried and evaporated to give an oily residue (274 mg), which showed two spots on TLC. However, the spot of the major product was due to that of III. Recrystallization of the residue from ether gave crude III (60 mg), of which a portion was again recrystallized from ether to give pure III, m.p. 101–103°, which was identical by mixture m.p. and comparison of IR spectra and TLC with an authentic specimen of III.

Preparation of V. A soln of benzobicyclo[2.2.2]octenone[9] (7·53 g) in EtOH (30 ml) was added to 4·5 g of hydroxylamine hydrochloride in pyridine (60 ml). The mixture was refluxed at 150–160° for 8 hr and after cooling evaporated to dryness under reduced press leaving a residue, which was added to 8% HCl aq (50 ml) and extracted with ether. The ethereal layer was washed with H_2O, dried and evaporated to give 8·007 g (97·9%) of crude V, m.p. 142–145°, which on recrystallization from EtOH, gave a pure oxime V, m.p. 149–151° as prisms. (Found: C, 77·21; H, 7·01; N, 7·22. $C_{12}H_{13}ON$ requires: C, 76·97; H, 7·00; N, 7·48%).

ALH *reduction of* V—(A) VI, VII, VIII *and* IX. A soln of V (11·643 g) in THF (180 ml) was added to a suspension of LAH (6·406 g) in THF (200 ml) at 0–3° over a period of 1 hr and the mixture refluxed for 3 hr. Under cooling in ice, excess LAH was decomposed with H_2O and the mixture was extracted with ether. Evaporation of the organic layer dried over anhyd K_2CO_3 left a residue (6·734 g), which was dissolved in ether and extracted with cold 5% HCl aq. The acidic layer was basified carefully under cooling with 10% NaOH aq and extracted with ether. Evaporation of the ether left a basic mixture (5·422 g), which was twice chromatographed over neutral Woelm grade III Al_2O_3. Elution with pet. ether and pet. ether–benzene (9:1) gave 2·69 g (45·9%) of VI and fractions eluted with benzene–pet. ether (1:1) afforded about one gram of a mixture of VII and IX and the eluate with benzene–$CHCl_3$ (20:1)–$CHCl_3$ only yielded 1·46 g (24·6%) of VIII, which was composed of *endo*- and *exo*-isomers.

Recrystallization from pet ether gave pure VI, m.p. 88·5–89·5° as needles. $\nu_{max}^{CCl_4(grating)}$ 3309 cm^{-1} (>NH). (Found: C, 84·44; H, 7·73; N, 8·09. $C_{12}H_{13}N$ requires: C, 84·17; H, 7·65; N, 8·18%).

The above mixture of VII and IX was subjected twice to column-chromatography using Merck SiO_2.

Elution with $CHCl_3$–MeOH (99:1) gave 0·25 g (4·3%) of VII and with $CHCl_3$–MeOH (9:1) afforded 0·19 g (3·2%) of IX. A pure sample of VII, m.p. 108–110°, was obtained as prisms by recrystallization from pet. ether–ether. $\nu_{max}^{CCl_4(grating)}$ 3272 cm^{-1} (>NH). (Found: C, 84·37; H, 7·72; N, 8·25. $C_{12}H_{13}N$ requires: C, 84·17; H, 7·65; N, 8·18%).

Recrystallization from pet. ether gave a pure sample of IX, m.p. 106–108° as plates; ν_{max}^{Nujol} 3275 cm^{-1} (>NH). (Found: C, 83·20; H, 8·80; N, 8·12. $C_{12}H_{15}N$ requires: C, 83·19; H, 8·73; N, 8·09%).

(B) *Separation of the isomers of* VIII. The above-mentioned mixture VIII (1·46 g) and ethyl formate (5 ml) were heated in a sealed tube at 98–106° in an oil-bath for 4 hr. The reaction mixture was chromatographed over neutral Woelm grade III Al_2O_3 to give 1·36 g (20% yield from V) of *endo*-isomer XIb and 0·33 g (5% yield from V) of *exo*-isomer Xb.

The *endo*-isomer was recrystallized from $CHCl_3$ affording a pure sample of XIb, m.p. 114·5–115·5° as rods; ν_{max}^{Nujol} 3250 cm^{-1} (>NH), 1679, 1647 cm^{-1} (NHCHO). (Found: C, 77·75; H, 7·48; N, 7·07. $C_{13}H_{15}ON$ requires: C, 77·58; H, 7·51; N, 6·96%).

Recrystallization of the *exo*-isomer from $CHCl_3$–ether gave prisms of Xb, m.p. 174–175·5°; ν_{max}^{Nujol} 3270 cm^{-1} (>NH), 1659, 1652 cm^{-1} (NHCHO). (Found: C, 77·63; H, 7·46; N, 6·79. $C_{13}H_{15}ON$ requires: C, 77·58; H, 7·51; N, 6·96%).

Reduction of V *with metallic sodium and ethanol*—Xb *and* XIb. To a soln of V (3·23 g) in abs EtOH (160 ml) metallic Na (16 g) was added in portions with stirring at 75–95° in an atmosphere of N_2 over a period of 2 hr and the mixture was heated at 95–105° for 2 hr. Under cooling in ice, 200 ml of H_2O was added and the mixture was extracted with ether. The ethereal extract was treated with 5% HCl aq and the acidic layer was made alkaline with 10% NaOH aq and extracted with ether. The ethereal layer was washed with H_2O, dried over anhyd K_2CO_3 and evaporated leaving 2·73 g (88·8%) of the isomers of the primary amine VIII. A mixture (1·667 g) of the above isomers and ethyl formate (3·5 ml) was heated in a sealed tube at 100° for 4 hr. Evaporation of the reaction mixture left an oily residue (1·987 g), which was twice chromatographed over neutral Woelm grade III Al_2O_3 giving the *endo*-isomer XIb (1·426 g) and the *exo*-isomer Xb (0·455 g).

The exo*-amine* Xa *and its derivatives*, Xc *and* Xd. A mixture of Xb (228 mg) and 10% HCl aq (12 ml) was heated at 95° for 2·5 hr. The mixture was evaporated to dryness under reduced press to leave a crystalline residue (240 mg) which gave by twice recrystallization from EtOH needles of Xa–HCl, m.p. 281–282°. (Found: C, 68·74; H, 7·80; N, 6·93. $C_{12}H_{15}N \cdot HCl$ requires: C, 68·72; H, 7·69; N, 6·68%).

A soln of Xb (229 mg) in THF (10 ml) was added to a suspension of LAH (220 mg) in dry ether (9 ml) at 0– –5° and the mixture was stirred at 37–40° for 16 hr. Working up in the usual manner left 178 mg (87%) of an oily Xc, which was converted to its hydrochloride, m.p. 222·5–224° as needles by recrystallization from EtOH–ether; ν_{max}^{Nujol} 3180 cm^{-1} (>NH). (Found: C, 70·00; H, 8·19; N, 6·41. $C_{13}H_{17}N \cdot HCl$ requires: C, 69·79; H, 8·11; N, 6·26%).

A mixture of Xc (83 mg), formic acid (0·6 ml) and 37% formalin (0·4 ml) was refluxed at 140–150° for 11 hr. Working up in a similar manner to the case of the *endo*-isomer, XId, described later, gave the dimethylamine Xd as an oil (81 mg), which was transformed to its hydrochloride, m.p. 246–247° as needles by recrystallization from MeOH–acetone. (Found: C, 69·50; H, 8·43; N, 6·07. $C_{14}H_{19}N \cdot HCl \cdot \frac{1}{2}H_2O$ requires: C, 69·41; H, 8·53; N, 5·78%).

The endo*-amine* XIa *and its derivatives*, XIc *and* XId. A mixture of XIb (146 mg) and 10% HCl aq (5 ml) was heated at 95° for 2 hr. Evaporation gave quantitatively the hydrochloride (147 mg) of XIa, which gave, by twice recrystallization from EtOH, needles of XIa–HCl, m.p. 228–229°. (Found: C, 68·82; H, 7·80; N, 6·70. $C_{12}H_{15}N \cdot HCl$ requires: C, 68·72; H, 7·69; N, 6·68%).

A soln of XIb (600 mg) in a mixture of THF (6 ml) and dry ether (10 ml) was added to a suspension of LAH (529 mg) in dry ether (10 ml) at 0– –5°, and the mixture was stirred at 26° for 13 hr and at 40° for 3 hr. Working up left 452 mg (81·5%) of a basic residue as an oil, which was dissolved in EtOH and converted to its hydrochloride with 10% HCl aq. Recrystallization from EtOH gave needles of XIc–HCl, m.p. 237–238·5°; ν_{max}^{Nujol} 3208 cm^{-1} (>NH). (Found: C, 70·05; H, 8·23; N, 6·27. $C_{13}H_{17}N \cdot HCl$ requires: C, 69·79; H, 8·11; N, 6·26%).

A mixture of XIc (233 mg), formic acid (0·9 ml) and 37% formalin (0·6 ml) was refluxed at 150° for 12 hr. After evaporation of the mixture, addition of 10% HCl aq (5 ml) to the residue and washing with ether, the acidic layer was basified with 10% NaOH aq and extracted with ether. Evaporation of the ether gave 232 mg (89%) of crude XId, which was converted to its hydrochloride giving needles of XId–HCl (hygroscopic), m.p. 150·5–153°, by recrystallization from MeOH–acetone. (Found: C, 69·40; H, 8·64; N, 5·74. $C_{14}H_{19}N \cdot HCl \cdot \frac{1}{2}H_2O$ requires: C, 69·41; H, 8·53; N, 5·78%).

Catalytic reduction of VI *to* Xa. A soln of VI (330 mg) in EtOH (25 ml) was shaken in an atmosphere of H_2 with 20% Pd–C catalyst (320 mg) for 7 hr. Evaporation of the filtrate gave an oily residue (319 mg), which was chromatographed over neutral Woelm grade II Al_2O_3 to give 78 mg (23·5%) of Xa as an oil, of which the hydrochloride was identical in all respects with an authentic Xa–HCl obtained above.

Catalytic Reduction of VII *to* XIa. A soln of VII (11 mg) in EtOH (4 ml) was hydrogenated with 30% Pd–C catalyst (12 mg) for 30 hr. After the absorption of H_2 (8·15 ml), the catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo* leaving an oily residue (9 mg), TLC of which over SiO_2 or Al_2O_3 using MeOH–$CHCl_3$ (1 : 19) showed the presence of a considerable amount of the starting material VII, but major reduction product was found to be the *endo*-primary amine XIa by comparison with an authentic sample. In contrast to the reduction of VI, VII showed a considerable resistance to the reductive ring-cleavage.

Preparation of XIIIb *from* XII. Two molar equivalents of O_3 was passed into a soln of XII (3·107 g) in AcOEt (60 ml) at −40–−60° over a period of 8·5 hr. Evaporation left a pale yellow residue, to which 30% H_2O_2 (85 ml) was added under cooling in ice. To the mixture was added the soln of $KHCO_3$ (5 g) in H_2O (20 ml) and the mixture was stirred at room temp for 8 hr. After addition of $KHCO_3$ (2 g), the mixture was washed with ether, and then $NaHSO_3$ was added to decompose excess H_2O_2. The mixture was strongly acidified with 4N H_2SO_4 and extracted with ether. Evaporation of the ether left the crude dicarboxylic acid (1·17 g). A mixture of the acid (0·921 g) and Ac_2O (3·6 ml) was heated at 100° for 1·5 hr. Evaporation left a residue (1·002 g), which was dissolved in $CHCl_3$–ether, washed with 5% $KHCO_3$aq and with H_2O, dried over anhyd Na_2CO_3 and evaporated to dryness leaving an oily residue (841 mg). Sublimation of the residue under reduced pressure gave the fraction, b.p. 120–135° (0·02 mm) (386 mg), which gave, by recrystallizations from AcOEt–ether and from CH_2Cl_2–ether, a pure sample of XIIIa, m.p. 109·5–111° (Ref. 12, m.p. 109–111°). (Found: C, 71·27; H, 5·03. Calc. for $C_{12}H_{10}O_3$: C, 71·28; H, 4·99%).

To 28% NH_4OH (14 ml) XIIIa (292 mg) was added and the mixture was heated in a metal-bath, such as the reaction temp was raised up to 200° from 140° over a period of 1 hr, removing the water produced, and up to 300° over 1 hr period and the mixture was retained under heating at 300–310° for 1 hr. After cooling, the residue was dissolved in benzene, filtered and the filtrate was evaporated to dryness leaving a brown residue (213 mg), which was recrystallized from benzene giving plates of XIIIb, m.p. 197–198·5° (Ref. 12, m.p. 206·5–207°). (Found: C, 71·88; H, 5·65. Calc. for $C_{12}H_{11}O_2N$: C, 71·62; H, 5·51%).

LAH *reduction of* XIIIb *to* IX. A soln of XIIIb (82 mg) in THF (15 ml) was added to a suspension of LAH (241 mg) in THF (12 ml) at 0° and the mixture was refluxed for 6 hr. Working up left a basic residue (68 mg), which was chromatographed on Merck SiO_2. Elution with $CHCl_3$–MeOH (50 : 1–20 : 1) afforded a crystalline product (58 mg) which on crystallization from pet ether–ether gave the same IX, m.p. 106–108°, as that obtained by LAH reduction of V.

Synthesis of the endo-*aziridine* VII *from the* exo-*epoxide* XV

A mixture of XV (6 g) and 28% NH_4OH (60 ml) was heated at 150° in a sealed tube for 28 hr. Extraction with $CHCl_3$ gave a crude amino-alcohol (6·5 g), which was chromatographed twice over Woelm grade III SiO_2 to give 144 mg (2·5%) of XV and 3·70 g (56·1%) of XVIa, the latter of which was recrystallized from benzene to give plates of pure XVIa, m.p. 165·5–166·5°; ν_{max}^{Nujol} 3310, 3270, 3180 cm^{-1} (—OH, —NH_2). (Found: C, 76·30; H, 7·92; N, 7·19. $C_{12}H_{15}O\acute{N}$ requires: C, 76·15; H, 7·99; N, 7·40%).

A soln of XVIa (380 mg) and dimethyl pyrocarbonate (343 mg) in $CHCl_3$ (15 ml) was allowed to stand overnight at room temp. Evaporation of the solvent gave quantitative yield of XVIb, which was recrystallized from ether giving needles of XVIb, m.p. 114–115°; ν_{max}^{Nujol} 3268, 1683 cm^{-1} (—NHCOOMe). (Found: C, 67·70; H, 6·96; O, 19·36; N, 5·75. $C_{14}H_{17}O_3N$ requires: C, 67·99; H, 6·93; O, 19·41; N, 5·66%).

To a soln of XVIb (328 mg) in pyridine (3 ml), *p*-toluenesulfonyl chloride (454 mg) was added and the mixture was left at room temp for 70 hr. After addition of cold 2N H_2SO_4 (12 ml) the mixture was extracted with CH_2Cl_2. The extract was washed with 2N H_2SO_4, H_2O and with 5% $NaHCO_3$ aq, dried over anhyd Na_2SO_4 and evaporated to dryness leaving 506 mg (95·1%) of crude XVIc, which gave needles of a pure sample, m.p. 159–160·5°, by recrystallization from CH_2Cl_2–ether; ν_{max}^{Nujol} 3260, 1689 cm^{-1} (NHCOOMe). (Found: C, 63·01; H, 5·73; N, 3·78; O, 19·77. $C_{21}H_{23}O_5NS$ requires: C, 62·82; H, 5·77; N, 3·49; O, 19·93%).

A mixture of XVIc (239 mg) and 20% methanolic KOH (8·5 ml) was refluxed for 2 hr To the mixture H_2O was added and extraction with ether followed by working up in the usual manner left a residue (90·2 mg). Preparative TLC using SiO_2 and MeOH–$CHCl_3$ (1 : 25) gave 29 mg (28·2%) of crude aziridine, which gave prisms of m.p. 106–107° by recrystallization from pet. ether. This was identical with VII in all respects.

Synthesis of the exo-*aziridine* VI *from the* endo-*epoxide* XVII

A mixture of XVII (6 g) and 28% NH_4OH (62 ml) was heated at 150° in a sealed tube for 28 hr. Treatment

of the reaction mixture in a similar manner to the case of XV gave 271 mg (4·5%) of the starting material and 4·85 g (73·6%) of crude amino-alcohol XVIIIa. The latter was recrystallized from benzene affording leaflets of a pure sample, m.p. 147–148°; ν_{max}^{Nujol} 3345, 3305, 3205 cm^{-1} (—OH, —NH_2). (Found: C, 76·10; H, 8·10; N, 7·32. $C_{12}H_{15}ON$ requires: C, 76·15; H, 7·99; N, 7·40%).

A soln of dimethyl pyrocarbonate (708 mg) in $CHCl_3$ (7 ml) was added to a soln of XVIIIa (762 mg) in $CHCl_3$ (20 ml) under cooling in ice and the mixture was left at room temp for 1·5 hr. Working up and recrystallization of the residue from ether–CH_2Cl_2 gave almost quantitative yield of XVIIIb, m.p. 155–156°; ν_{max}^{Nujol} 3301 cm^{-1} (—OH), 3263, 1713, 1662 cm^{-1} (NHCOOMe). (Found: C, 68·14; H, 6·91; N, 5·68; O, 19·03. $C_{14}H_{17}O_3N$ requires: C, 67·99; H, 6·93; N, 5·66; O, 19·41%).

To a soln of XVIIIb (495 mg) in pyridine (3 ml), *p*-toluenesulfonyl chloride (540 mg) was added and the mixture was left overnight at room temp. Working up and recrystallization from CH_2Cl_2–ether gave 779 mg (97·0%) of XVIIIc, m.p. 166·5–167·5° as needles; ν_{max}^{Nujol} 3271, 1710, 1682 cm^{-1} (NHCOOMe). (Found: C, 62·64; H, 5·72; N, 3·39; O, 19·53. $C_{21}H_{23}O_5NS$ requires: C, 62·82; H, 5·77; N, 3·49; O, 19·93%).

A mixture of XVIIIc (402 mg) and 20% methanolic KOH (12 ml) was refluxed for 2 hr. Working up left a residue (156 mg), which was subjected to preparative TLC using SiO_2 and $CHCl_3$–MeOH (50:1) affording 63 mg (36·9%) of crude aziridine, which, on recrystallization from pet. ether, gave needles of VI, m.p. 88–89°. This was the same product as that obtained by LAH reduction of V.

Reaction of IIa *with acids.*

A. *With* 1N H_2SO_4. A suspension of IIa (1·014 g) in 1N H_2SO_4 (20 ml) was heated in a boiling water-bath for 1 hr. The compound IIa was gradually dissolved into the acid soln and, yellow ppt appeared. After cooling, the mixture was extracted with ether and the ethereal layer washed with H_2O, dried over anhyd Na_2SO_4 and evaporated to dryness to give a yellow residue (180 mg), which was recrystallized from ether-n-hexane to yield 135 mg (13%) of XX, m.p. 108–111°; ν_{max}^{Nujol} 1722 cm^{-1} (CHO), λ_{max}^{EtOH} 291 mμ (ε 14,230). (Found: C, 87·00; H, 5·27; O, 7·26. Calc. for $C_{16}H_{12}O$: C, 87·24; H, 5·49; O, 7·26%).

The acidic layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over anhyd K_2CO_3 and evaporated to give a yellow residue (849 mg), which, on recrystallization from MeOH–ether, gave 735 mg (67·1%) of XIX, m.p. 180–182°. A pure sample for analysis had a m.p. of 182–183° as plate.[18] (Found: C, 80·91; H, 6·35; N, 6·07. Calc. for $C_{16}H_{15}ON$: C, 80·98; H, 6·37; N, 5·90%).

B. *With* 10% HCl *aq.* Heating of IIa (117 mg) in 10% HCl aq (3 ml) in boiling water-bath for 1 hr gave a basic product (127 mg), which was recrystallized from MeOH–ether to yield 95 mg (75%) of XIX, m.p. 180–182° as plates.

C. *With dry* HBr. A soln of IIa (208 mg) in dry dioxan was saturated with gaseous HBr and the mixture was refluxed in an oil-bath for 1 hr. Working up gave a basic oily residue (135 mg), which was chromatographed over 5% H_2O-containing neutral Woelm Al_2O_3 (4 g). Elution with pet. ether–benzene (1:1) and benzene gave a residue (43 mg), which, on recrystallization from ether, afforded the bromo-amine XXI (6 mg), m.p. 143–145° as plates. (Found: C, 64·23; H, 4·69; Br, 26·95. $C_{16}H_{14}NBr$ requires: C, 64·01; H, 4·70; Br, 26·62%).

Elution with benzene–$CHCl_3$ (1:1) gave the amino-alcohol XIX (78 mg).

Reaction of VI *with* 1N H_2SO_4

Compounds XXII, XXIII, XXIV *and* XXV. A mixture of VI (1·396 g) and 1N H_2SO_4 (60 ml) was heated at 95–100° for 70 min. After cooling, the mixture was washed with ether, made basic with 10% NaOH aq and extracted with ether and then with $CHCl_3$. The combined extract was washed with H_2O, dried over anhyd K_2CO_3 and evaporated to leave 1·267 g (82·1%) of crude crystalline amino-alcohol, which, on twice recrystallization from ether–pet. ether, gave prisms of XXII, m.p. 126–127·5°; ν_{max}^{Nujol} 3353, 3262, 3206 cm^{-1} (—OH, —NH_2), $\nu_{max}^{CHCl_3}$ 3370, 3264 cm^{-1} (—OH, —NH_2). The measurement of the IR spectrum (grating, 20 mm cell, CCl_4) showed the presence of the hydrogen-bonding: 3385, 3316 cm^{-1} (—NH_2), 3340 cm^{-1} (—OH).[27] (Found: C, 76·07; H, 8·07; N, 7·40. $C_{12}H_{15}ON$ requires: C, 76·15; H, 7·99; N, 7·40%).

To a soln of XXII (79 mg) in pyridine (24 ml) and dry toluene (7·5 ml), 64% phosgen soln in toluene (4 ml) was added below −30° and the mixture was retained at −40–−60° for 3·5 hr, at 0° for 5 days and at 20–25° for 1 day. Under cooling in ice, ice–water (7 g) was added and the mixture was extracted with ether. The ethereal layer was washed with 2N H_2SO_4, 5% $NaHCO_3$ aq and with H_2O, dried over anhyd Na_2SO_4 and evaporated to dryness leaving an oily residue (74 mg), which was chromatographed on Merck SiO_2 (2·1 g). Elution with $CHCl_3$ gave the carbonate XXIII (48 mg) which was purified by recrystallization

from CH_2Cl_2–ether. The prisms of XXIII resolidified around 142–143° and melted again at 163–164·5; ν_{max} 1711 cm^{-1} ($CHCl_3$), 1714 cm^{-1} (CCl_4). (Found: C, 72·49; H, 6·04; N, 6·39. $C_{13}H_{13}O_2N$ requires: C, 72·54; H, 6·09; N, 6·51%).

A mixture of XXII (203 mg), Ac_2O (2 ml) and pyridine (3 ml) was left at room temp for 46 hr. Evaporation left a residue (290 mg), which, on twice recrystallization from $CHCl_3$–CCl_4, gave 245 mg (83·8%) of XXIVa, m.p. 171·5–172°, as prisms; ν_{max}^{Nujol} 3324 (NH), 1734 (OAc), 1662 cm^{-1} (NAc). (Found: C, 70·25; H, 7·15; N, 5·16. $C_{16}H_{19}O_3N$ requires: C, 70·31; H, 7·01; N, 5·13%).

A soln of XXIVa (117 mg) in 1% methanolic KOH (4 ml) was left at room temp for 75 min and H_2O (6 ml) was added to the mixture, which was extracted with ether. The extract was washed with H_2O, dried over anhyd Na_2SO_4 and evaporated to give a crystalline residue (94 mg), which, on twice recrystallization from $CHCl_3$–CCl_4, gave the N-monoacetate XXIVb (60 mg), m.p. 166–167·5°; ν_{max}^{Nujol} 3328, 1647 cm^{-1} (NHAc). (Found: C, 72·52; H, 7·56; N, 6·17. $C_{14}H_{17}O_2N$ requires: C, 72·70; H, 7·41; N, 6·06%).

A soln of XXIVb (103 mg) in pyridine (3 ml) was added under cooling in ice to the complex prepared from CrO_3 (252 mg) and pyridine (2 ml), and the mixture was left at room temp for 36 hr. To the mixture, MeOH (2·6 ml) and H_2O (10 ml) were added. Extraction with ether and evaporation left a crystalline residue (67 mg), which, on recrystallization from $CHCl_3$–CCl_4, gave prisms of XXV (48 mg), m.p. 157·5–159°; ν_{max}^{Nujol} 1703 cm^{-1} (>CO), 3316, 1657 cm^{-1} (NHAc). (Found: C, 72·39; H, 6·64; N, 6·09. $C_{14}H_{15}O_2N \cdot \frac{1}{3}H_2O$ requires: C, 72·20; H, 6·67; N, 6·01%).

Reaction of VII *with* 1N H_2SO_4

Compounds XXVIa, XXVIb, XXVIc *and* XXVII. After heating of VII (117 mg) in 1N H_2SO_4 (6 ml) for 6 hr, the mixture was washed with ether, basified with 10% NaOH aq, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd K_2CO_3 and evaporated to dryness leaving a crystalline residue (117 mg), which, on twice recrystallization from ether, gave 70 mg (60%) of XXVIa, m.p. 126–128° as rods; $\nu_{max}^{CCl_4\,(grating)}$ 3405, 3392, 3330 cm^{-1} (—NH_2, —OH).[27] (Found: C, 75·89; H, 8·11; N, 7·49. $C_{12}H_{15}ON$ requires: C, 76·15; H, 7·99; N, 7·40%).

A soln of XXVIa (139 mg) in pyridine (3 ml) and Ac_2O (2 ml) was allowed to stand overnight at room temp. Working up left an oily residue (194 mg), which was chromatographed on neutral Woelm grade III Al_2O_3 (6 g). Elution with pet. ether–benzene (1 : 1) and benzene gave 156 mg (78%) of XXVIb, which had a m.p. of 101–101·5° as plates by recrystallization from pet. ether–ether; $\nu_{max}^{CHCl_3}$ 3427, 1669 cm^{-1} (NHAc), 1736 cm^{-1} (OAc). (Found: C, 70·21; H, 7·09; N, 5·30. $C_{16}H_{19}O_3N$ requires: C, 70·31; H, 7·01; N, 5·13%).

A soln of XXVIb (84 mg) in 1% methanolic KOH (4·5 ml) was left at room temp for 2 hr. To the mixture, H_2O (6 ml) was added and the mixture was extracted with ether. The extract was washed with 5% HCl aq and with H_2O, dried over anhyd K_2CO_3 and evaporated to dryness leaving a crystalline residue (74 mg), which on recrystallization from $CHCl_3$–CCl_4, gave needles of XXVIc, m.p. 210–211°; ν_{max}^{Nujol} 3367, 3256 cm^{-1} (—OH, —NH), 1643 cm^{-1} (NHAc). (Found: C, 72·62; H, 7·58; N, 5·99. $C_{14}H_{17}O_2N$ requires: C, 72·70; H, 7·41; N, 6·06%).

A soln of XXVIc (18 mg) in pyridine (1 ml) was added under cooling in ice to the complex prepared from CrO_3 (52 mg) and pyridine (0·4 ml), and the mixture was stirred at 0° for 2 hr and left at room temp for 19 hr. To the mixture, H_2O (5 ml) and MeOH (2 ml) were added and the mixture was extracted with ether. The extract was washed with 2N H_2SO_4, 5% $NaHCO_3$ aq and with H_2O, dried and evaporated to dryness leaving an oily XXVII (10 mg). This was not obtained in a crystalline state; $\nu_{max}^{CHCl_3}$ 1681, 1605 cm^{-1} (>CO) λ_{max}^{EtOH} 250, 291 mμ (ε 5440, 1110).

A mixture of XXVII (7 mg) and *p*-nitrophenylhydrazine (7 mg) in EtOH (0·5 ml) and one drop of AcOH was refluxed in a boiling water-bath for 1 hr. Evaporation and crystallization from EtOH–benzene gave rods of *p*-nitrophenylhydrazone, m.p. 271·5–273·5°. (Found: C, 67·90; H, 5·86. $C_{20}H_{20}O_3N \cdot \frac{1}{3}C_6H_6$ requires: C, 67·67; H, 5·86%).

LAH *reduction of the oxime of* XXVIII. A soln of the oxime (1·129 g) in THF (10 ml) was added with stirring at 5–8° to a suspension of LAH (3·045 g) in THF (30 ml) over a period of 20 min and the mixture was refluxed for 3 hr. Working up and separation gave a neutral (91 mg) and a basic residues (820 mg), the latter of which was immediately treated with phenylisocyanate, because of its ease to sublimation. A soln of the basic fraction (420 mg) in dry ether (6 ml) was added at 0° with stirring to a soln of phenylisocyanate (446 mg) in dry ether (1 ml) over a period of 6 min and the mixture was stored overnight in a refrigerator. Filtration left a colorless crystal (628 mg), which was washed with ether and recrystallized

thrice from acetone giving the phenylcarbamoyl derivative (141 mg) of the primary amine, m.p. 217–218° as needles. (Found: C, 73·76; H, 8·42; N, 11·37. Calc. for $C_{15}H_{20}ON_2$: C, 73·73; H, 8·25; N, 11·47%).

Mother liquor of the recrystallization was evaporated and chromatographed over neutral Woelm grade II Al_2O_3 (18 g). The eluate with pet. ether–benzene (1:1) gave, on thrice recrystallization from n-hexane–acetone, the phenylcarbamoyl derivative (15 mg) of 3-azabicyclo[3.2.2]nonane, m.p. 196–198° as needles, which was identical with that obtained by treatment of 3-azabicyclo[3.2.2]nonane with phenylisocyanate. (Found: C, 73·61; H, 8·32; N, 11·32. $C_{15}H_{20}ON_2$ requires: C, 73·73; H, 8·25; N, 11·47%).

Fractions eluted with benzene–$CHCl_3$ (1:1) were subjected to preparative TLC using SiO_2 and $CHCl_3$–MeOH (24:1). Besides the above derivative (60 mg) of the secondary amine, a crude residue (162 mg) was obtained and gave on thrice recrystallization from ether the phenylcarbamoyl derivative (28 mg) of the aziridine, m.p. 152–153° as plates. The structure was deduced from its NMR data; NMR 7·22 τ (2-proton, poor triplet, H_2 and H_4), 7·97 τ (2-proton, multiplet, H_1 and H_5), 8·40 τ (6-proton, multiplet, 2 H_6 and 2 H_7, H_{8s} and H_{9s}); 8·80 τ (2-proton, multiplet, H_{8a} and H_{9a}). (Found: C, 74·24; H, 7·54; N, 11·66. $C_{15}H_{18}ON_2$ requires: C, 74·35; H, 7·49; N, 11·50%).

Furthermore, elution with benzene–$CHCl_3$ (9:1) gave another crop (146 mg) of the phenylcarbamoyl derivative of the primary amine.

LAH *reduction of the oxime of camphor* (XXXII). A soln of the oxime (8·0 g) in THF (100 ml) was added at 12° with stirring to a suspension of LAH (9·1 g) in THF (200 ml) and the mixture was refluxed for 5 hr. Working up separated a neutral fraction (432 mg) as a yellow oil and an oily basic Fraction (6·0 g). From the neutral part, a small amount of the starting oxime was recovered. The basic residue (6·0 g) which involved roughly four basic products on TLC was chromatographed on neutral Woelm grade II Al_2O_3 (180 g). A portion (570 mg) of the eluate with pet. ether was treated with phenylisocyanate and the reaction mixture was chromatographed on Al_2O_3. The elution with pet. ether–benzene (1:1) gave a crude phenylcarbamoyl derivative (160 mg) of the aziridine, which was recrystallized 3 times from ether-n-hexane affording plates of its pure sample (45 mg), m.p. 137–139°; ν_{max}^{Nujol} 1659 cm^{-1} (—NCONH—); NMR 6·82 τ (1-proton, doublet–doublet, H_4), 7·11 τ (1-proton, doublet, H_2), 8·16 τ (1-proton, multiplet, H_5), 8·56 τ (4-proton, multiplet, 2 H_6 and 2 H_7), 8·96 τ (3-proton, singlet, C_9-Me), 9·30 τ (3-proton, singlet, C_{11}-Me), 9·18 τ (3-proton, singlet, C_{10}-Me). (Found: C, 75·43; H, 8·38; N, 10·45. $C_{17}H_{22}ON_2$ requires: C, 75·52; H, 8·20; N, 10·36%).

The other fractions of the first chromatography were used to examine for separation of the basic products, especially of the aziridine produced. Therefore, it is expected that the aziridine may be produced much more than that obtained actually.

LAH *reduction of oxime of* XXIX. A soln of the oxime (836 mg) in THF (10 ml) was added at 5–8° with stirring to a suspension of LAH (2·348 g) in THF (30 ml) and the mixture was refluxed for 4 hr. Working up gave an oily neutral (81 mg) and a basic residue (417 mg) as a yellow oil, the latter of which was treated with phenylisocyanate. The mixture of reaction products (822 mg) was chromatographed on neutral Woelm grade II Al_2O_3 (25 g). Elution with pet. ether–benzene (1:1) and recrystallization of the residue from acetone gave needles of the phenylcarbamoyl derivative of 3-azabicyclo[3.2.2]nonene, m.p. 196–197° in 5·9% yield, the structure of which was determined by identity of its reduction product with 3-azabicyclo-[3.2.2]nonane derivative mentioned above. (Found: C, 74·47; H, 7·61; N, 11·24. $C_{15}H_{18}ON_2$ requires: C, 74·35; H, 7·49; N, 11·56%).

Elution with benzene–$CHCl_3$ (1:1) and $CHCl_3$–MeOH (9:1) gave needles of the phenylcarbamoyl derivative of the primary amine, m.p. 226–227° in 15·8% yield, the configuration of which remained undetermined. (Found: C, 73·96; H, 7·44; N, 11·79. $C_{15}H_{18}ON_2$ requires: C, 74·35; H, 7·49; N, 11·56%).

LAH *reduction of the oxime of* XXX. A soln of the oxime (1·364 g) in THF (20 ml) was added with stirring to a suspension of LAH (1·744 g) in THF (50 ml) over a period of 20 min and the mixture was refluxed for 5 hr. Working up left a residual oil (1·046 g), which showed two spots (R_f-values, 0·63, 0·58) with almost equal intensity on TLC using SiO_2 and $CHCl_3$–MeOH (8:2). These results suggested that reduction products may be composed of almost equal amount of the *exo*- and the *endo*-aziridines. Attempt to separate the isomers or its O,N-triacetate on column-chromatography was unsuccessful. Repeated recrystallization of reduction products from EtOH gave 150 mg (14·4%) of the *exo*-aziridine, m.p. 199–200° as rods, which corresponded to the spot (R_f-value 0·663). (Found: C, 72·72; H, 7·47; N, 6·08. $C_{14}H_{17}O_2N$ requires: C, 72·70; H, 7·41; N, 6·06%).

The stereochemistry of the aziridine was deduced from the spectral data of its O,O-diacetate, m.p. 124–125°; $\nu_{max}^{CCl_4(grating)}$ 3311 cm^{-1} (>NH); NMR 9·15 τ (>NH).

LAH *reduction of the oxime of* XXXI. A soln of the oxime (950 mg), m.p. 154–156°, in THF (50 ml) was added below 2° with stirring to a suspension of LAH (1·447 g) in THF (50 ml) over a period of 10 min and the mixture was refluxed for 3 hr. Working up left a basic residue (869 mg), which was chromatographed on 5% H_2O-containing Woelm SiO_2 (27 g). Elution with $CHCl_3$-MeOH (98:2–95:5) gave 404 mg (51·8%) of a mixture of the isomers (*endo-* and *exo-*) of the aziridines and fractions eluted with $CHCl_3$–MeOH (9:1–1:1) left 274 mg (34·8%) of the isomers of the primary amines. Although examination on TLC indicated clearly that both of the products were composed of the corresponding *endo-* and *exo*-compounds, separation into the respective components was unsuccessful. To a soln of a mixture of the aziridines (79 mg) dry benzene (2 ml), a soln of phenylisocyanate (131 mg) in dry benzene (3 ml) was added under cooling in ice, and the mixture was retained at 0° for 3·5 hr and stirred at room temp for 2 hr. A small amount of H_2O was added to the mixture and the amorphous product (146 mg) was separated by filtration. Elution with $CHCl_3$–MeOH (99:1) on column-chromatography over Woelm grade II SiO_2 (4·3 g) left a crystalline residue (84 mg), which gave on two recrystallization from CH_2Cl_2–EtOH needles (24 mg), m.p. 198–199°. This was the diphenylcarbomoyl derivative of the aziridine but its stereochemistry remained uncertain; ν_{max}^{Nujol} 3265 (NH), 1693, 1658 cm^{-1} ($OCONHC_6H_5$, $NCONHC_6H_5$). (Found: C, 73·42; H, 6·02; O, 11·42; N, 9·11; H_2O, 0·68. $C_{27}H_{25}O_3N_3 \cdot \frac{1}{2}H_2O$ requires: C, 73·18; H, 5·78; O, 11·56; N, 9·48; H_2O, 0·81%).

O,N-Diacetate of the primary amine was obtained as follows: a mixture (78 mg) of the aziridine and the primary amine (product ratio, about 5:3) was acetylated with pyridine (3 ml) and Ac_2O (1 ml) by allowing to stand overnight at room temp. Working up left a residue (92 mg). Two recrystallization from ether gave needles of O,N-diacetate (4·3 mg) of a primary amine. However, the configuration of the N-acetate was not determined yet; ν_{max}^{Nujol} 3245 (NH), 1738 (OAc), 1639 cm^{-1} (NAc). (Found: C, 70·99; H, 7·00. $C_{17}H_{21}O_3N$ requires: C, 71·05; H, 7·37%).

LAH *reduction of the oxime of* XXXIII. A soln of the oxime (441 mg) in THF (6 ml) was added at 8–10° with stirring to a suspension of LAH (866 mg) in THF (15 ml) over a period of 5 min and the mixture was refluxed for 5 hr. Working up left an oily residue (353 mg), which was chromatographed on neutral Woelm grade II Al_2O_3 (10 g). Preparative TLC of the fractions eluted with petroleum ether–benzene (9:1–1) gave a crystalline residue (12 mg), which afforded, on recrystallization from n-hexane, the *exo*-aziridine, m.p. 98–100°, the structure of which was established by comparison with an authentic sample of the *exo*-aziridine.[14]

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REFERENCES

1 Bridged Ring Compound. III. Part II: K. Kitahonoki and A. Matsuura, *Tetrahedron Letters* 2263 (1964).

2 N. G. Gaylord, *Reduction with Complex Metal Hydrides* p. 751. Interscience, New York, N.Y. (1956).

3 [a] E. Larsson, *Svensk. Kem. Tidskr.* **1**, 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* 629 (1963);
[e] A. E. Petrarca and E. M. Emery, *Ibid.* 635 (1963).

4 F. Lautenschlaeger and G. F. Wright, *Canad. J. Chem.* **41**, 863 (1963).

5 K. Kitahonoki, K. Kotera, Y. Matsukawa, S. Miyazaki, T. Okada, H. Takahashi and Y. Takano, *Tetrahedron Letters* 1059 (1965).

6 M. Y. Shandala, M. D. Solomon and E. S. Waight, *J. Chem. Soc.* 892 (1965).

7 K. Kotera, M. Motomura, S. Miyazaki, T. Okada and Y. Matsukawa, *Tetrahedron* **24**, 1727 (1968).

8 S. Wawzonek and J. V. Hallum, *J. Org. Chem.* **18**, 288 (1953).

9 K. Kitahonoki and Y. Takano, *Tetrahedron Letters* 1597 (1963).

10 K. Tori, K. Kitahonoki, Y. Takano, H. Tanida and T. Tsuji, *Ibid.* 869 (1965); K. Tori, K. Aono, K. Kitahonoki, R. Muneyuki, Y. Takano, Y. Tanida and T. Tsuji, *Ibid.* 2921 (1966).

11 Cf. K. Tori, Y. Takano and K. Kitahonoki, *Chem. Ber.* **97**, 2798 (1964).

12 W. von E. Doering and M. J. Goldstein, *Tetrahedron* 53 (1959).

13 A. C. Oehlschlager and L. H. Zalkow, *J. Org. Chem.* **30**, 4205 (1965).

14 H. Tanida, T. Tsuji and T. Irie, *Ibid.* **31**, 3941 (1966).

15 S. J. Cristol and N. L. Hause, *J. Am. Chem. Soc.* **74**, 2193 (1952).

[16] G. Drefahl and K. Ponsold, *Chem. Ber.* **23**, 519 (1960).
[17] Cf. J. Sicher, M. Tichý, F. Šipoš, M. Snoboda and J. Jonaš, *Coll. Czech. Chem. Commun.* **29**, 1561 (1964).
[18] 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-alcohol XIX and its NMR data.
[19] S. J. Cristol and R. K. Bly, *J. Am. Chem. Soc.* **82**, 6155 (1960).
[20] [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).
[21] C. O'Brien, *Chem. Rev.* **64**, 81 (1964) and refs cited therein.
[22] H. O. House and W. F. Berkowitz, *J. Org. Chem.* **28**, 307, 2271 (1963).
[23] Refer to H. Tanida, T. Tsuji and H. Ishitobi, *J. Am. Chem. Soc.* **86**, 4904 (1964).
[24] K. Kotera, T. Okada and S. Miyazaki, *Tetrahedron Letters* 841 (1967).
[25] K. Kitahonoki, A. Matsuura and K. Kotera, *Ibid.* 1651 (1968).
[26] K. Kotera, S. Miyazaki, H. Takahashi, T. Okada and K. Kitahonoki, *Tetrahedron*
[27] Y. Matsui, M. Takasuka and T. Kubota, *Ann. Rept. Shionogi Res. Lab.* **15**, 125 (1965).