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1,5-DIAZABICYCLO[4.3.0] NONANE, THE OXIDATION PRODUCT OF SPERMINE

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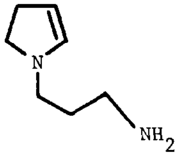
Summary: The structure of the product of the chemical or enzymatic oxidation of spermine was shown to be 1,5-diazabicyclo[4.3.0] nonane (III).

The importance of naturally-occurring polyamines in the regulation of many biological processes[1] has recently stimulated research into their metabolism. It has long been known that the products of the enzymatic[2] and chemical[3] oxidation of spermine (I) are identical, but the structure of the products has never been conclusively established. Thus, oxidation of spermine by air in alkaline solution, using a copper catalyst, had been reported[3] to give 1,3-diaminopropane and a base $C_7H_{14}N_2$, corresponding to the clevage of the molecule next to one of the NH groups (Eq. 1):

$$\underset{(I)}{H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2} + O_2 \longrightarrow C_7H_{14}N_2 + H_2N(CH_2)_3NH_2 + H_2O_2 \qquad (1)$$

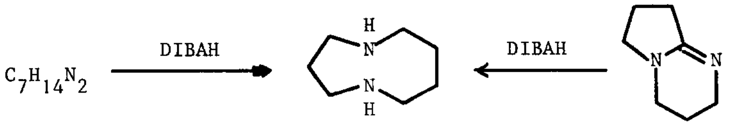
The diamine $C_7H_{14}N_2$ was originally assigned, on the basis of chemical degradation, the structure of a 1-(3-aminopropyl)pyrroline, the location of the double bond being left undefined.[3] Later workers[4] assumed it to be 1-(3-aminopropyl)-2-pyrroline (II).

When the base $C_7H_{14}N_2$ was prepared by oxidation of spermine following the original procedure[3] with minor modifications, it gave ^1H and ^{13}C n.m.r. spectra which were not in accord with structure (II): no evidence could be found for any olefinic protons (^1H n.m.r.) or double-bonded carbon atoms (^{13}C n.m.r.). A possible alternative structure was (III), a bicyclic aminal, which could be formed by intramolecular cyclisation after cleavage of one 1,3-diaminopropane group (Eq. 1).



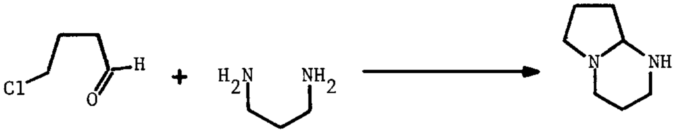
(II)

Reduction of the spermine oxidation product with diisobutylaluminium hydride (DIBAH), a reagent which regioselectively cleaves bicyclic aminals and the related amidines to monocyclic diamines,[5] yielded a product with an identical ^{13}C n.m.r. spectrum to that of 1,5-diazacyclononane prepared by DIBAH cleavage of 1,5-diazabicyclo[4.3.0.]non-5-ene (DBN) (Eq. 2):



(2)

Conclusive proof of this structure was obtained by synthesis of the compound by an unambiguous route (Eq. 3). 4-Chlorobutanal, prepared by pyrydinium chlorochromate oxidation[6] of the corresponding alcohol, was allowed to react with 1,3-diaminopropane in the presence of anhydrous potassium carbonate.[7] The 1,5-diazabicyclo[4.3.0.]nonane obtained was identical in all respects (^1H n.m.r., ^{13}C n.m.r., i.r., g.l.c. and m.s.) with the oxidation product of spermine, proving that the correct structure for the base $C_7H_{14}N_2$ (Eq. 1) is (III) and not, as previously assumed, (II).



(III)

(3)

All the reported chemistry of the oxidation product of spermine which could not be rationalised in terms of structure (II) can now be understood, such as its failure to undergo ozonolysis and its anomalous reaction with nitrous acid.[3] The observation that neither the enzymatic nor the chemical oxidation leads to cleavage of the second (3-aminopropyl) group of spermine, which could not be explained in terms of structure (II), is now readily understood.

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