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BOROHYDRIDE REDUCTION OF PIRIDINIUM SALTS. IV.
SIMULTANEOUS LOW TEMPERATURE FORMATION OF (2+2) AND (4+2) CYCLOADDUCTS IN THE REDUCTION OF 1-METHYL-4-CYANO-PYRIDINIUM IODIDE

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In a previous paper (1) we reported the formation of the cycloadduct V, in the borohydride reduction of the pyridinium salt I. If the reduction is carried out at -45° in 0.8N methanolic NaOH the insoluble product IV is formed (60% yield), containing only traces of compound V. However, reductions carried out at temperatures increasing from -45° to -20°, give rise to precipitates containing progressively more of V (e.g. at -33°, V/IV = 0.5; at -29°, V/IV = 1). Above -20° only V is present in the precipitate. The I.R. spectrum of IV shows a single nitrile absorption at 2235 cm^{-1}, and a single double-bond absorption at 1635 cm^{-1}.Compound IV is exceedingly labile and, in the solid state, at 15-20° is quickly converted to V. In chloroform solution the conversion becomes progressively greater as the temperature increases from -45° to -20° (e.g. at -25°, the conversion of IV to V is 50%);above -20° the conversion is complete.An exhaustive analysis of IV could not be performed because of its high lability. However, if the compound is rapidly poured into 6N HCl cooled to -45°, the insoluble product VI which is sufficiently stable for characterization is immediately formed. VI has m.p. 207-210° (dec.) and its I.R. spectrum shows a single nitrile and a single double-bond absorption at 2245 and 1645 cm^{-1} respectively. The N.M.R. spectrum (100 MHz in CF_3COOD) shows, <u>inter alia</u>, a proton at δ 9.22 which does not undergo exchange with deuterium. VI can be easily reduced, either catalytically or with $NaBH_4$, to the product VII (*) m.p. 179-181°, the I.R. spectrum of which shows a single nitrile absorption at 2225 cm^{-1} but no double-bond absorption. The molecular weight of VII (244 from mass spectrum) and its elemental analysis, indicate a dimeric structure with respect to the dihydropyridine II, with four extra hydrogens. The N.M.R.spectrum of VII (100 MHz in benzene-d_6) shows signals of aliphatic protons at $\delta 1.83(CH_3)$, 1.3-1.68, 1.89-2.36, and 2.64, with peak area ratios of 3 : 2 : 4 : 1. The N.M.R. data confirm the dimeric nature of VII and indicate that the molecule is symmetrical. The above experimental data and the sequence of reactions leading to the formation of VII are most reasonably accounted for by the head-to-head cyclobutane structure, shown in the chart, or by its head-to-tail isomer. Since VII derives directly along an unambiguous pathway from IV <u>via</u> VI, it must therefore be assumed that IV also has a symmetrical head-to-head (or head-to-tail) cyclobutane structure, the formation of which can be reasonably explained with the (2+2) cycloaddition of two molecules of the dihydropyridine intermediate II. IV must contain two enamine groups since by protonation gives VI, safely characterized as an imonium dication by the chemical shift of the vinylic protons (9.22) and by the reactivity towards $NaBH_4$. It should be noted that, while the head-to-head structure of IV includes a 1,2-divinylcyclobutane system, the head-to-tail structure contains a 1,3-divinylcyclobutane system. The rapid conversion of IV to V, which appears to be an intramolecular rearrangement, seems to exclude the head-to-tail structure, since only 1,2-divinylcyclobutanes are known to undergo facile intramolecular rearrangements (2).

On treatment with conc. H_2SO_4 in glacial CH_3COOH, VI is converted to VIII, to which the structure 5,10-dimethyl-2,13-dioxo-3,5,10,12-tetraazapentacyclo-[9,3,1,$1^{4,14}$,$0^{1,8}$,$0^{7,14}$]-hexadecane has been assigned on the basis of the following data. VIII has m.p. 268-270° (dec.), molecular weight 276 (from mass spectrum), and its I.R. spectrum shows a NH band at 3190 cm^{-1} and carbonyl absorption at 1650 cm^{-1}. The N.M.R. spectrum (see Table), combined with the molecular weight, indicates that VIII also has a symmetrical dimeric structure. Two equivalent methyl groups at $\delta 2.37$ and two protons at $\delta 8.24$ can be immediately identified; the latter exchange with deuterium, and can be attributed to two equivalent -CO-NH groups. The presence of two $\overset{3(12)}{NH}—\overset{4(11)}{CH}—\overset{16(15)}{CH_2}$ sequences is clearly suggested by the coupling constants and by the chemical shift values. A $-\overset{6}{CH_2}-\overset{7}{CH}-\overset{8}{CH}-\overset{9}{CH_2}-$ sequence, forming a symmetrical AA′ BB′ XX′ system, is also suggested by the parameters measured, although their complete analysis was not possible because the signals were partly superimposed. As a whole, the elemental analysis, the low frequency of the carbonyl absorption, and the N.M.R. data clearly show the presence of two δ-lactamic rings, which is only consistent with a pentacyclic structure for VIII. The formation of two δ-lactams is obviously only possible if VII has an <u>anti</u> structure. Molecular models show that only this configuration fulfils the steric requirements for attack of the nitrile on the imonium cation on the same side with respect to

CHART I

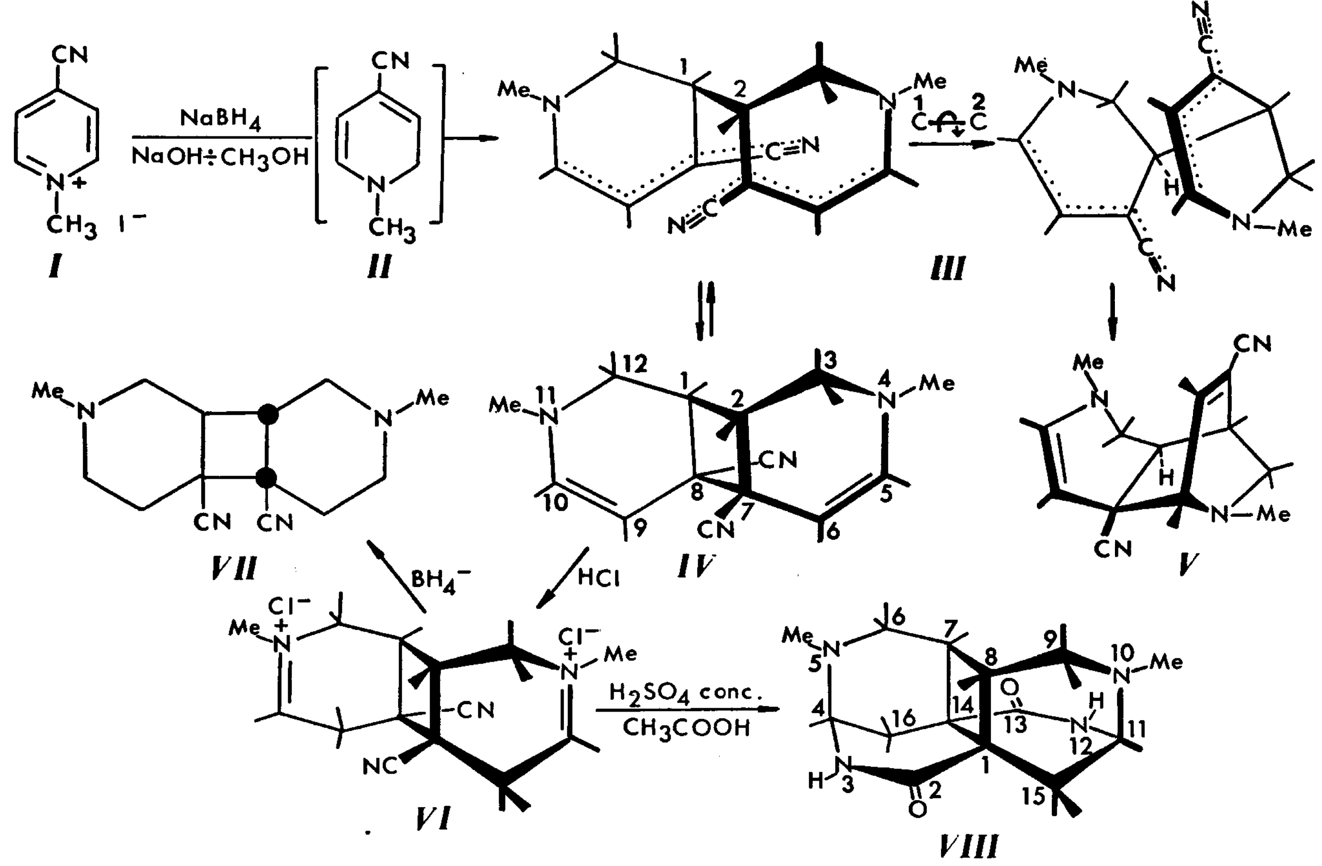

Table: N.M.R. Data for VIII

H	Me	NH	9(6)	8(7)=9′(6′)	11(4)eq	15(16)ax	15(16)eq
δ(ppm)	2.37	8.24	2.77	2.33-2.57	4.03	2.27	1.46
J	11eq,15ax	11eq,15eq	11eq,NH	15ax,15eq	15ax,NH ≅ 15eq,NH	$\|8,9 + 9,9'\|$	
Hz	2.7	3.5	5.0	13.5	0.4	17.5	

the plane of the cyclobutane ring, according to the classic Ritter reaction (3). Consequently, since VII and IV also have an *anti* configuration, the structure *trans*-*cis*-*trans*-7,8-dicyano-4,11-dimethyl-4,11-diazatricyclo$[6.4.0.0^{2,7}]$-dodeca-5,9-diene is assigned to the latter. As already stated, IV is easily converted to V at low temperatures. It can be excluded that this thermal conversion involving a [1,3] sigmatropic shift, proceeds *via* a concerted mechanism, which is hindered by unfavorable constraints imposed by tricyclic structure of IV (4). The conversion of IV to V is likely to fall into the class of rearrangements which involve the formation of a diradical intermediate, as in the case of the *trans*-1,2-divinylcyclobutane and structurally related compounds (2).As illustrated in the chart, the stereochemical course of such a rearrangement clearly shows the compelling relationship between the *anti* configuration of IV and the *endo* stereochemistry of V.

The concerted (2+2) thermal cycloaddition of molecules such as 1,2-dihydropyridine II is forbidden on the grounds of orbital symmetry considerations (4). Moreover, the head-to-head orientation of the cycloadduct appears to exclude ionic mechanism, since the polarisation effects induced by the cyano group on the adjacent double bond in the monomer should rather give a head-to-tail addition (5). Therefore the thermal dimerisation is likely to proceed through a two-step mechanism, involving the formation of the biradical III, stabilised by the resonance of the odd electrons with both the adjacent unsaturated groups (5). Finally, the simultaneous formation of IV and V with a V/IV ratio which increases with the temperature in the range -45° to -20°, and the conversion of IV to V in chloroform solution with a parallel variation of the V:IV ratio in the same temperature range, suggest that IV and V could arise from two branches of a common mechanism via the same biradical intermediate III, IV being the product from kinetic control and V that from thermodynamic control.

References and footnotes

* The conversion of IV to VII is useful in the analysis of the mixture of IV and V, since under conditions where VII is formed from IV, V yields its 5,6-dihydroderivative (1).

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