

ON THE HOFMANN DEGRADATION OF HETISINE

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IN an earlier Review article on the Aconite-Garrya alkaloids¹ we briefly discussed hetisine, $C_{20}H_{27}O_3N$, the alkaloid isolated from Aconitum heterophyllum. We pointed out that the precise structure of hetisine is unknown, but that it merits a brief discussion since it represents a new structural type among the aconitum alkaloids. Based on the early investigations of Jacobs² as well as on our own limited findings, we made the assumption that the alkaloid possesses an F-dihydroatisine skeleton³ with an additional carbon-carbon bond and an

¹ K. Wiesner and Z. Valenta, Fortschr. Chem. Org. Naturstoffe 16, 26 (1958).

² W. A. Jacobs and C. F. Huebner, J. Biol. Chem. 170, 189 (1947).

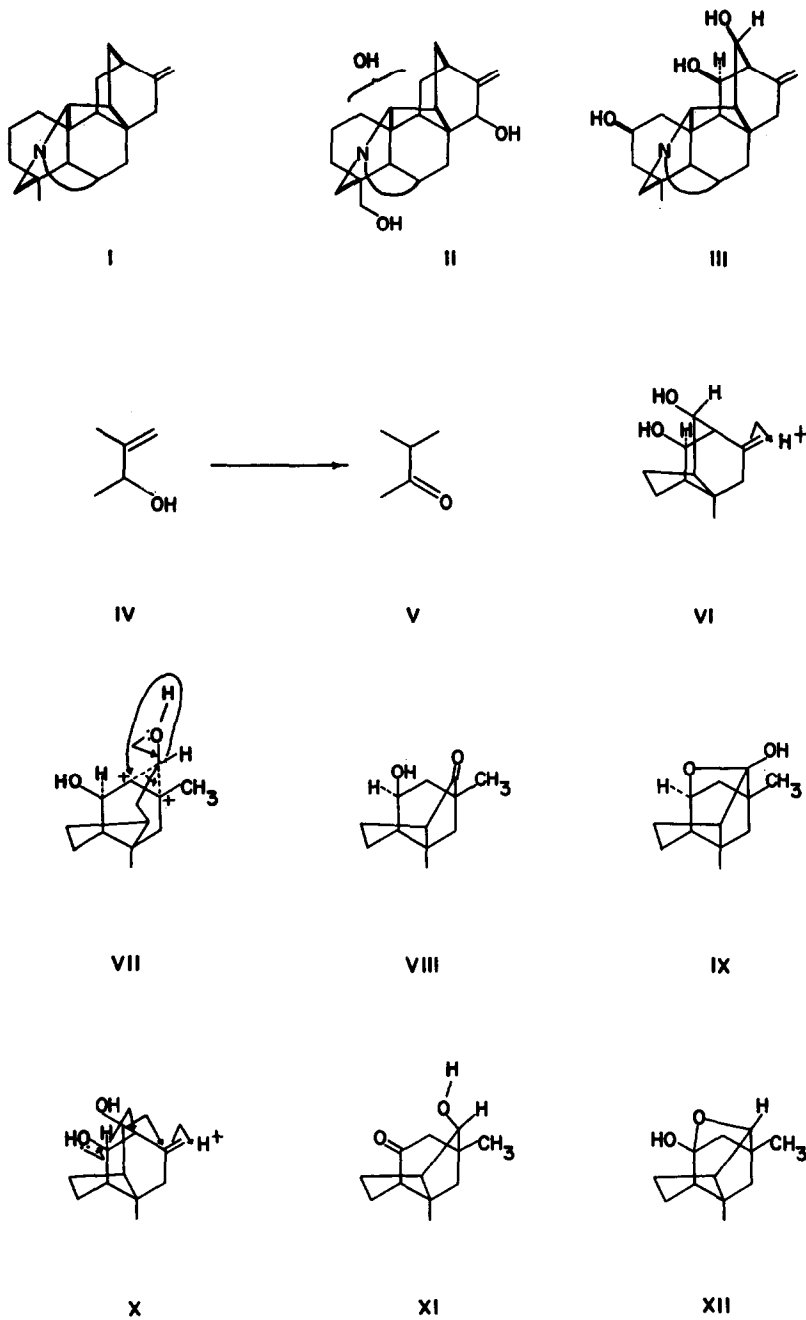
³ K. Wiesner, J. R. Armstrong, M. F. Bartlett and J. A. Edwards, Chemistry and Industry p. 132 (1954).

additional carbon-nitrogen bond instead of the F-dihydro-
atisine N-alkyl side-chain. As one of the best representa-
tions of such a possibility we considered the skeleton
I.* We then gave a very tentative (and incorrect)
example of the possible distribution of the hydroxyls
of hetisine as in II.

Recently, in a beautiful x-ray crystallographic
study, Maria Przybylska⁴ has determined the structure of
hetisine and has shown it to be III. On the basis of
this structure, it is now possible to interpret an un-
usual rearrangement which (besides a faulty Kuhn-Roth
determination) was responsible for our tentative placement

* Recently (S. W. Pelletier, Tetrahedron 14, 76 (1961)) it
has been stated that the interesting work on hypognavinol
by S. Sakai and coworkers (S. Sakai, Chem. Pharm. Bull.
6, 448 (1958)) provides an analogy for this kind of
skeleton. We should like to point out that our tenta-
tive discussion of the hetisine-type alkaloids was com-
pletely independent from the careful studies of the
Japanese school on the alkaloid hypognavine. Our
Review was received by the editor on November 26, 1957.
A copy of the manuscript was simultaneously sent to
Professor E. Ochiai. It was accompanied by a letter
from one of us (K.W.) in which it was suggested, mainly
on biogenetic grounds, that an identical system as in II
(with no primary hydroxyl) is present also in the al-
kaloid hypognavine studied by Professor Ochiai's group.
This communication was acknowledged on December 27, 1957,
by a letter signed by E. Ochiai, T. Okamoto and S. Sakai,
in which it was stated that the Japanese group arrived
at similar, still unpublished, conclusions. The first
structure proposal for hypognavine by Sakai (S. Sakai,
Chem. Pharm. Bull. 6, 448 (1958)) was received by the
Journal on June 4, 1958.

⁴ M. Przybylska, Can. J. Chem. 40, 566 (1962).



of the two hydroxyls and which has represented one of the most puzzling aspects of hetisine chemistry. Jacobs² has described the methiodide of hetisine formed in a sealed tube at 100°C. (m.p. 325°C.) which by a mild Hofmann degradation gave a desmethylhetisine, $C_{21}H_{29}O_3N$ (m.p. 124°C.). This last compound showed the presence of only one double bond (hydrogenation).

We have repeated this work and used quaternization under milder conditions than Jacobs (refluxing methanol). In this manner we have obtained a new isomeric methiodide (m.p. 259°C.; Calculated for $C_{21}H_{30}O_3NI$: C, 53.48; H, 6.42; I, 26.94. Found: C, 53.3; H, 6.3; I, 27.1). Hofmann degradation of the corresponding methoxyhydroxide gave now a normal des-methylhetisine, $C_{21}H_{29}O_3N$ (m.p. 216°C.; Calculated for $C_{21}H_{29}O_3N$: C, 73.42; H, 8.52: Found: C, 73.6; H, 8.5; pK, 7.81.), which possessed an exocyclic double bond and a new double bond, both of which could be hydrogenated. It is thus clear that in Jacobs' work a rearrangement has occurred, but not during the Hofmann degradation as previously assumed.⁵ The non-identity of the two methiodides shows that it was a rearrangement in the course of the vigorous quaternization

⁵ S. W. Pelletier, Tetrahedron 14, 76 (1961).

method used by Jacobs and it is probable that this rearrangement was acid catalyzed. Since according to Jacobs the Hofmann degradation of dihydrohetisine gives a normal product which contains one double bond, the rearrangement in question must have taken place with participation of the original exocyclic double bond of hetisine and involved its disappearance.

Not having had access to Jacobs' methiodide, we have tentatively assumed that it might have been the most commonly encountered rearrangement in the aconite alkaloids¹, i.e., IV→V. This is now clearly ruled out by Przybylska's structure III. It was also ruled out when Solo and Pelletier⁶ showed by I.R. the absence of a carbonyl group in Jacobs' methine and postulated that the carbonyl must be masked as a hemi-ketal. There are now two possible ways to formulate the rearrangement. If it is represented by the structures VI→IX it is necessary to assume an unfavourable stereochemistry of the hydride shift (see arrows in formula VII). Consequently, we prefer the formulation X→XII in which strict antiparallelity of all moving bonds is preserved. Since the dihydroxy [2,2,2]-bicyclo-octane system is completely symmetrical, it is not possible to decide which branch has actually migrated and the rearrangement may be portrayed merely by the partial structures given.

⁶ A. J. Solo and S. W. Pelletier, J. Amer. Chem. Soc. 81, 4439 (1959).