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HYPOIODITE REACTION OF N-ACETYLJERVINE: THE FORMATIONS OF OXEPANE AND OXETANE RINGS BY HETERO ATOM INSERTION FROM ALKOXYL RADICAL (1)

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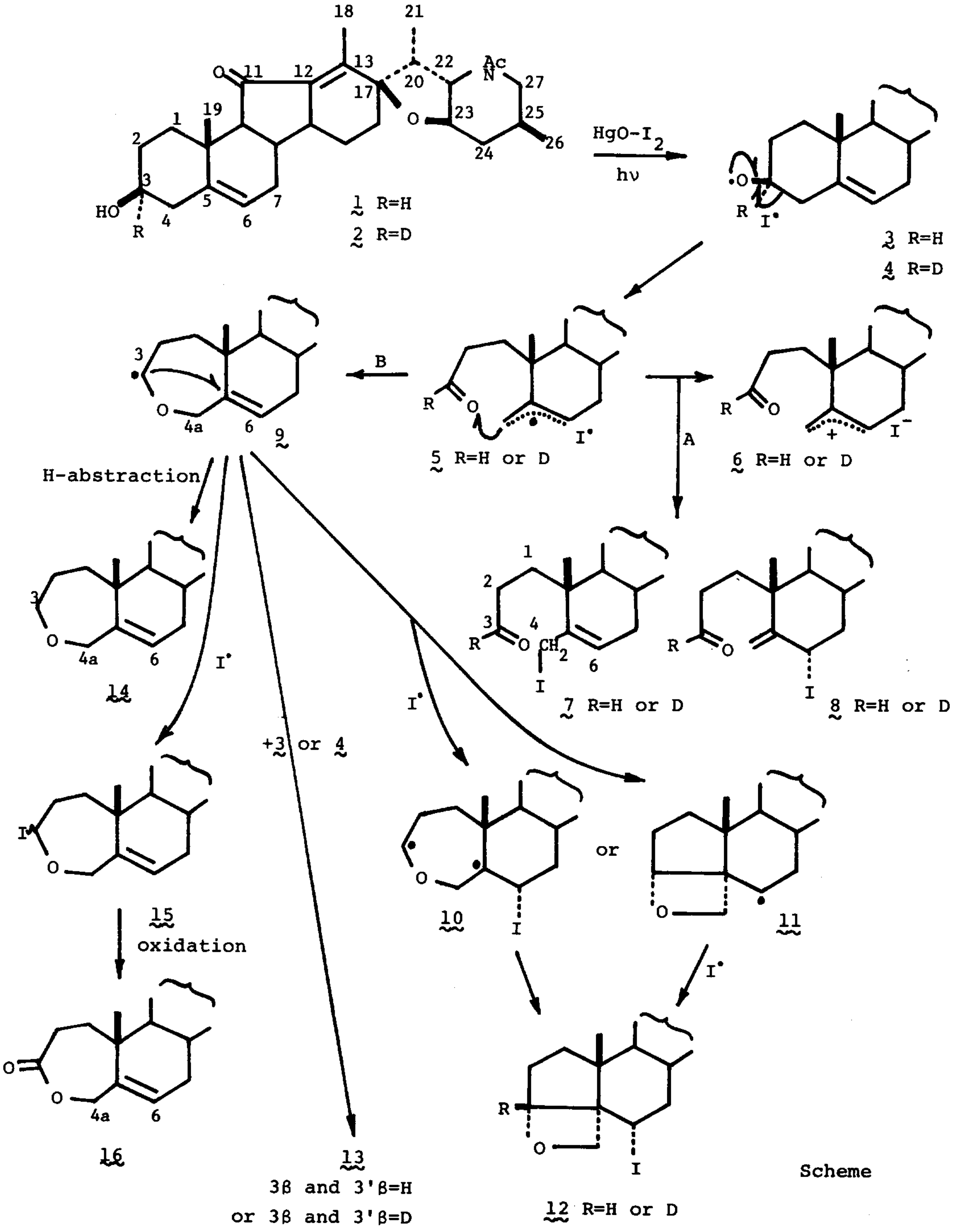
In a preceding paper (1) we clarified the structure of a novel dimeric compound 13, one of the five products formed in the hypoiodite reaction of N-acetyljervine 1. (2) In this paper we discuss the structures of another four products, 7, 12, 14 and 16, obtained in this reaction and the probable sequences of the formation of these products including the dimeric ether 13 discussed in the preceding paper. (3)

As in the case of the dimer 13 (1) it was apparent from the i.r., u.v., and ^{1}H n.m.r. spectra that the C, D, and the heterocyclic rings of all four products were unaltered. (4) The structure of 7, m.p. 159-160°, (5% yield) which contained iodine, was proved to be N-acetyl-4-iodo-11-oxo-3,4-seco-jerv-5,12(13)-dien-3-al on the following ground. (5)

In the i.r. spectrum, except a series of bands due to the N-Ac, α,β-unsaturated carbonyl, no band due to the hydroxyl group was observed. In the n.m.r. spectrum a one-proton singlet at τ1.91, a one-proton doublet at τ4.06 (J=4.5 Hz) and a two-proton triplet at τ5.40 (J=15.0 Hz) were observed and these signals are safely assignable to the C-3 formyl proton, an olefinic proton at the C-6 and the allylic C-4 methylene protons (6) flanked further by an iodine.
The n.m.r. and i.r. spectra of 12, m.p. 218-220° (2% yield), led us to assign N-acetyl-11-oxo-oxidomethylene-3α,5α-A-nor-jerv-5,12(13)-diene as the structure. In the i.r. spectrum, no hydroxyl band was observed. The n.m.r. spectrum showed a broad one-proton singlet at τ4.48 (W_H=3.9 Hz), a one-proton quartet at τ5.55 (J_{AX}^{ap}=4.5, J_{BX}^{ap}=12.3) and a two-proton double doublet of AB system


18
21
13
12
11
O
22
Ac
N
27
20
17
19
25
23
O
1
26
24
2
3
HO
R
4
5
6
7
1 R=H
2 R=D
HgO-I$_2$
hν
·O
R
I·
3 R=H
4 R=D
3
B
O
4a
6
9
R
O
5 R=H or D
I·
A
R
O
+
I$^-$
6 R=H or D
H-abstraction
1
2
3
4
R
O
CH$_2$
I
6
7 R=H or D
R
O
I
8 R=H or D
3
O
4a
6
14
I·
+3 or 4
I·
I
O
15
oxidation
O
10
I
or
O
11
I·
O
O
4a
6
16
13
3β and 3'β=H
or 3β and 3'β=D
R
O
I
12 R=H or D

Scheme

at τ5.84 and τ6.25 (J_{AB}=7.6 Hz). These signals are assignable to the C-3β-H and the C-6β-H attached to the iodine-bearing carbon and isolated methylene protons incorporated in the oxetane ring in a way entirely analogous to the case of oxidomethylene3α,5α-A-nor-cholestane. (7)

We assign N-acetyl-3,11-dioxo-4-oxa-A-homo-jerv-5,12(13)-diene structure for the product 16, m.p. 258-260° (1% yield) (mass, m/e 481, M^+). In the i.r. spectrum of 16 again no OH band was observed, but as well as bands due to the α,β-unsaturated carbonyl (1640 and 1714 cm^{-1}), a new unstrained lactonic carbonyl band (1737 cm^{-1}) was present. In the n.m.r. there were observable typical double doublets attributable to AB system at τ5.84 and τ5.36 (J_{AB}=13.5 Hz) and a one-proton doublet of olefinic proton at τ4.21 (J=3.0 Hz). These protons are assignable to the C-4a methylene protons of the oxepane ring and to the C-6-H.

Finally, the structure of 14 m.p. 165-167°, (<1%) (mass, m/e 453, M^+-14) was clarified as N-acetyl-11-oxo-4-oxa-A-homo-jerv-5,12(13)-diene as follows: in the i.r. spectrum there was no band due to the hydroxyl group. In the n.m.r. spectrum, there was an olefinic one-proton signal at τ4.57 (J=3.0 Hz) and a nine-proton multiplet from τ5.81 to τ7.20. The splitting pattern of the signals of the multiplet was nearly the same as the superimposed signals of the proton signals of C-22-H, C-23-H, C-27-methylene and C-9-H of N-acetyljervine and those of C-3-methylene and C-4a methylene of 4-oxa-A-homo-cholest-5-ene. (7).

The probable sequences of the formations of the five compounds 7, 12, 14, 16 and 13 are summarized in the Scheme. The common intermediate for all five products is considered to be the allyl radical 5. For the formation of oxetane 12 there can be two probable pathways A and B as we previously proposed (7), and on the basis of the same stereoelectronic considerations as two of the present authors suggested (7), the formation of 12 via the Paterno-Büchi reaction of the preformed olefinic aldehyde 8 could be excluded and the formation of 12 via pathway B is more probable. This pathway is considered to involve either successive radical cyclization to form more stable 3α,5α-oxetane (e.g., 5→9→12), or the formation of oxetane via attack of electrophilic oxygen of the excited 5 on the allyl radical moiety. On the other hand, in order to explain the formations of several compounds with oxepane rings, we must assume another radical intermediate, **9**, from which ramification will start to afford **14** by the hydrogen abstraction from the solvent, to give **16** via the formation of jodohydrin **11** followed by oxidation, and to **13** by combination with alkoxyl radical **3**.

We have already assumed the intervention of the intermediate such as **9** in the oxetane formation in the hypoiodite reaction of normal steroids. (6) The formation of several oxepane derivatives such as **13**, **14** and **16** in the present case may support our original proposal, i.e., the formation of oxetanes (e.g., **12**) via successive radical cyclization from the allyl radical (e.g., **5**).

It is rather remarkable that while the products of the hypoiodite reaction in the steroid series were merely 3,4-seco-aldehyde (e.g., **7**) and oxetanes (e.g., **12**), several oxepane derivatives were obtained in the hypoiodite reaction of *C*-nor-*D*-homosteroid.

It would not be wise to attribute this clear variation of products between steroids and *C*-nor-*D*-homosteroids to any single effect. However, a comparison of Dreiding models of assumed intermediates **9** derived from steroids and *C*-nor-*D*-homosteroids indicates that the modification of the C-ring of **9** may introduce a subtle difference in the predominant conformation of the flexible oxepane ring of **9**, and this might be one of the important factors leading to the intermolecular radical addition to lead to the types **13**, **14** and **16** over the intramolecular radical cyclization to oxetanes in the *C*-nor-*D*-homosteroid series.

REFERENCES AND NOTES

(1) Part XXVII of the series "Photoinduced Transformation". Part XXVI, H. Suginome, K. Kato and T. Masamune, preceding paper.
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(3) See for review of hypoiodite reaction. K. Heusler and J. Kalvoda, *Angew. Chem.*, *76*, 518 (1964); J. Kalvoda and K. Heusler, *Synthesis*, 501 (1971).
(4) Details of these spectral data will be published in our full paper. All the spectra in this paper were taken in CDCl$_3$ by 100 MHz instrument.
(5) In this paper, we used "jervane" nomenclature for the C$_{27}$ compounds. Cf., F. C. Chang and R. C. Ebersole, *Tetrahedron Letters*, 3521 (1968).
(6) Nonequivalence of these protons are due to the restriction of rotation of C-4-C-5 bond.
(7) H. Suginome and K. Kato, *Tetrahedron Letters*, 4139 (1973).

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