THE MECHANISM OF THE GARRYFOLINE-CUAUCHICHICINE REARRANGEMENT

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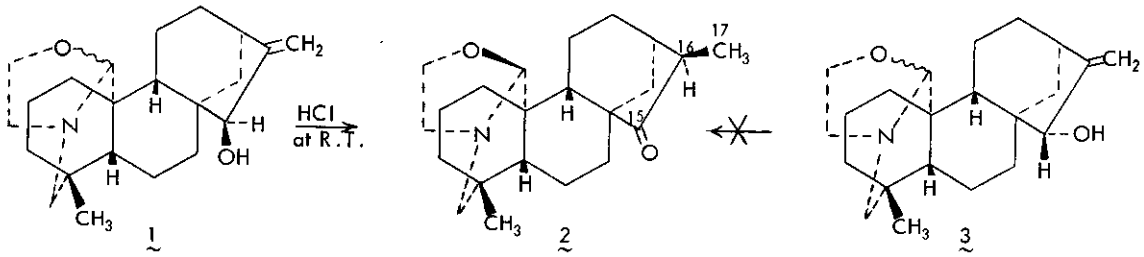
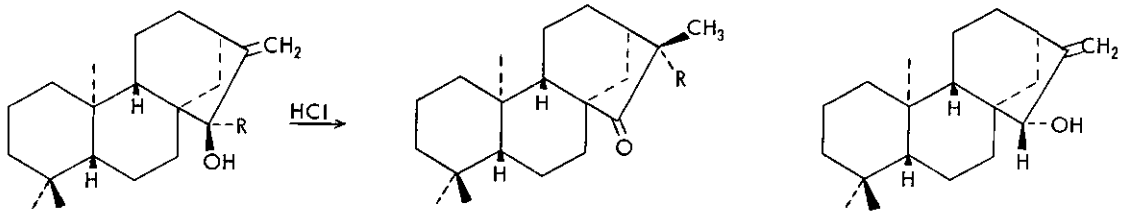
Abstract: — The acid-catalyzed rearrangement of garryfoline to cuauchichicine has been studied by deuterium labeling and ^{13}C NMR spectroscopy to establish its mechanism. Treatment of isogarryfoline with 10% DCl in D_2O yielded a product with a C(16αD) - βCH_2D group, a fact which demonstrates that the rearrangement involves enol formation followed by exo-protonation.

In 1955 the C_{20}-diterpenoid alkaloid, garryfoline (1) was reported to rearrange rapidly to cuauchichicine (2) in dilute mineral acid at room temperature.[1] A similar rearrangement has been observed[2] also in other C_{20}-diterpenoid alkaloids, e.g., atisine, kobusine, napelline, etc. In contrast to the ready rearrangement of garryfoline, the 15-epimeric veatchine (3) is stable even on heating in dilute hydrochloric acid. To explain the extreme ease of acid-catalyzed rearrangement of garryfoline as compared with veatchine, a non-classical structure for the intermediate carbonium ion has been suggested.[3]



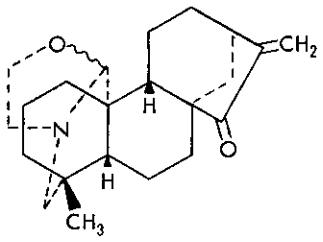


In 1967 Barnes and MacMillan[4] reported the investigation of this rearrangement using the epimeric (-)-kaur-16-en-15-ols as models. They reported that the 15β-ol (4) rearranged rapidly in mineral acid to 16-(-)-kauran-15-one (5) by a 15 —> 16 hydride shift, while the 15α-ol (6) was stable under the same conditions. The English workers proposed a 15 —> 16 hydride shift mechanism on the basis of the rearrangement of [15-D]-(-)-kaur-16-en-15β-ol (7) to 16R - [16-D]-(-)-kauran-15-one (8) in hydrochloric acid. Later they reported[5] that compound

8 exchanges the C(16) deuterium for hydrogen in dilute acid to afford compound 5.

During our recent investigation of the constituents of Garrya ovata var. lindheimeri, we isolated and elucidated the structure of garryfoline and cuauchichicine by ^{13}C NMR spectroscopy and X-ray analysis.[6,7] With the structures of garryfoline (1) and cuauchichicine (2) established with certainty, we decided to investigate the mechanism of this rearrangement by a deuterium incorporation study and ^{13}C NMR spectroscopy.

In order to investigate the reported[4] mechanism of a 15 —> 16 hydride shift for this type of rearrangement, we prepared C(15)-deuterated derivatives of garryfoline. Veatchine (3) was oxidized with Sarett reagent to veatchinone (9), mp. 152-154°, in 60-70% yield. Veatchinone was reduced with $NaBD_4$ in CH_3OD to afford a mixture of the epimeric alcohols 10 and 11. Acetylation of this mixture with acetic anhydride and pyridine yielded a mixture of acetates 12 and 13. These acetates were separated by preparative TLC on alumina using 1% ethanol in hexane. The least polar fraction (amorphous) was assigned the structure of the required β-acetate (12), on the basis of comparison of its ^{13}C NMR spectrum with that of non-deuterated compound 14 (Table 1). As it was observed that the C(15)β-acetyl group is very labile, compound 12 was directly treated with 10% aq. HCl at room temperature for 24 hours in order to effect hydrolysis and rearrangement to the dihydrocuauchichicine derivative. After the usual workup, the product was identified by ^{13}C NMR spectroscopy as a mixture of the ketone 15 and its C(22) hydrolysis product. Hence, the mixture was acetylated using acetic anhydride and pyridine to give compound 15 as the sole product.



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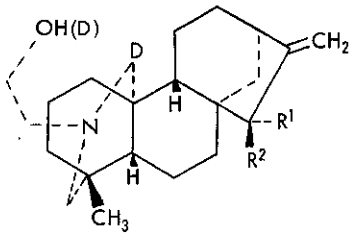
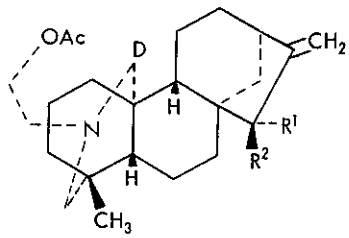


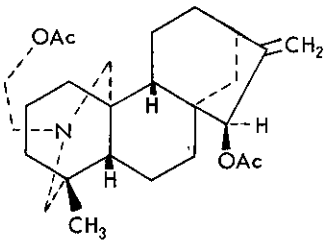
10 $R^1 = D$; $R^2 = OD$

11 $R^1 = OD$; $R^2 = D$



12 $R^1 = D$; $R^2 = OAc$

13 $R^1 = OAc$; $R^2 = D$



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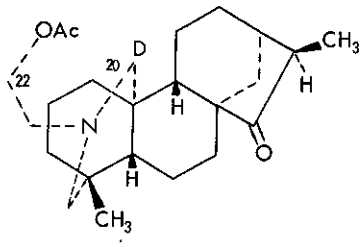

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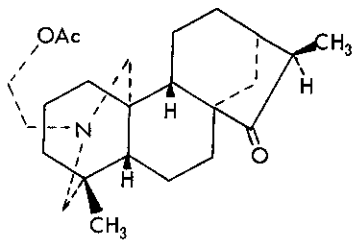

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Comparison of the ^{13}C NMR spectrum of the rearrangement product 15 with that of dihydrocuauchichicine acetate (16) revealed that only the signal of the C(20) carbon at 55.9 ppm was missing in compound 15. Because all other chemical shifts matched those of compound 16, we may conclude that deuterium is not present at C(16) in compound 15 and that the deuterium at C(15) did not shift to C(16) during the rearrangement of 12 to 15. These results demonstrate that this rearrangement does not take place via a 15 —> 16 hydride shift mechanism as claimed for the case of (-)-kaur-16-en-15β-ol (4).

Table 1. ^{13}C Chemical Shifts and Assignments for Veatchine-type Alkaloid Derivatives[a,b]

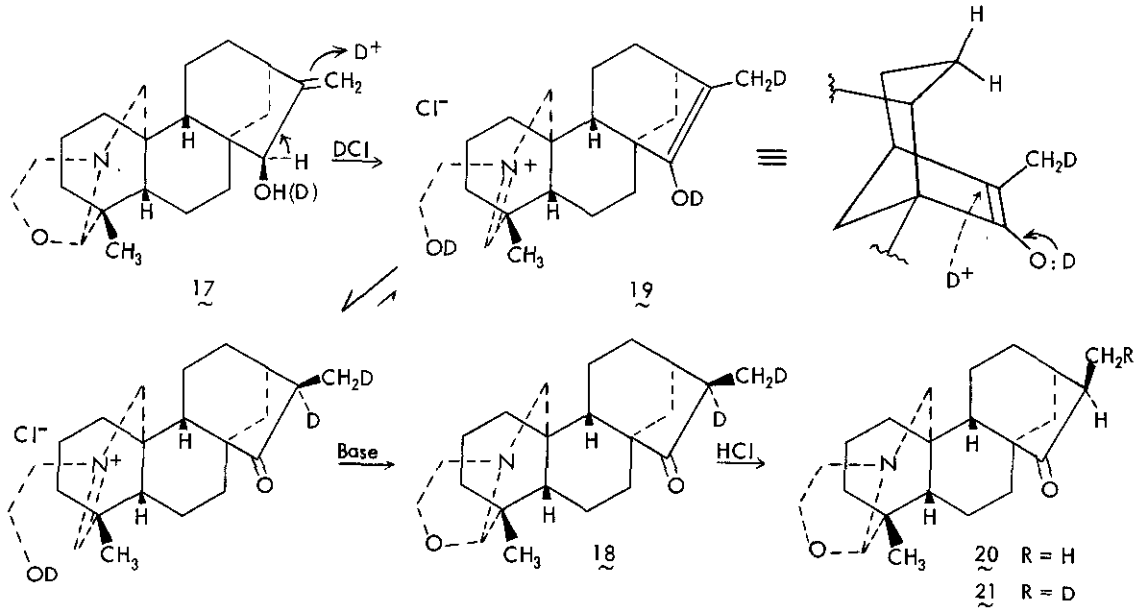
	12	14	15	16	17	18	20
C(1)	41.3[c]	41.3[c]	41.8[c]	41.8[c]	40.7[c]	39.8[c]	39.7[c]
C(2)	19.0	19.0	18.0	18.0	21.3	20.1	20.1
C(3)	40.2[c]	40.2[c]	40.2[c]	40.3[c]	40.5[c]	38.5[c]	38.5[c]
C(4)	33.8	33.8	33.8	33.7	39.9	40.6	40.6
C(5)	49.9	49.9	49.5	49.5	48.7	48.8	48.8
C(6)	17.9	17.9	18.0	18.0	18.2	18.0	18.0
C(7)	33.0	33.0	32.5	32.5	33.0	33.0	33.0
C(8)	45.6	45.7	52.4	52.4	45.5	52.4	52.4
C(9)	44.0	44.0	48.7	48.7	42.8	48.4	48.4
C(10)	39.8	40.0	40.6	40.6	36.1	36.0	35.9
C(11)	22.7	22.7	22.5	22.5	22.4	22.3	22.3
C(12)	37.0	37.0	26.4	26.4	37.2	24.3	24.3
C(13)	41.9	41.8	38.5	38.4	39.7	34.1	34.2
C(14)	37.2	37.2	34.5	34.6	37.6	34.4	34.6
C(15)	-	81.8	225.0	224.9	82.6	224.8	224.7
C(16)	153.7	153.7	48.0	47.9	158.1	-	47.9
C(17)	106.4	106.4	10.1	10.2	105.2	-[d]	10.1
C(18)	26.5	26.5	24.9	24.8	24.5	24.9	24.9
C(19)	60.7	60.8	60.8	60.7	98.6	98.4	98.4
C(20)	-	56.5	-	55.9	51.3	50.6	50.6
C(21)	57.2	57.4	57.4	57.4	54.9	54.9	54.8
C(22)	61.9	61.9	61.8	61.8	58.8	58.9	58.8
C=O	171.6	171.6	171.4	171.4	-	-	-
CH_3	21.0	21.0	21.1	21.0	-	-	-
C=O	171.4	171.4	-	-	-	-	-
CH_3	21.3	21.3	-	-	-	-	-

[a] Chemical shifts in ppm downfield from TMS. Spectra were taken in $CDCl_3$.

[b] Carbon-13 NMR spectra were taken at 15.03 MHz in the Fourier mode using a JEOL FX-60 spectrometer.

[c] These assignments may be interchanged in any vertical column. These assignments are based on Ref. 8.

[d] This signal appears as a weak triplet centered at 10.1 ppm.



To study the rearrangement mechanism further, we treated isogarryfoline (17) with 10% DCl in D_2O at room temperature to give compound 18, mp. 134–136°, in quantitative yield. Comparison of the ^{13}C NMR spectrum of compound 18 with that of isocuauchichicine (20) revealed the presence of deuterium at C(16) and C(17) (Table 1). The mechanism outlined above, involving the enol (19), accounts for incorporation of deuterium at C(16) and C(17) and also explains the C(16αD)-βCH$_2$D stereochemistry observed. During ketonization of the enol (19), transfer of D^+ would be expected to occur from the less-hindered exo side of the molecule to give compound 18 containing the C(16αD)-βCH$_2$D group. This enol —> ketone mechanism was further supported by treatment of compound 18 with HCl. *In dilute HCl no exchange of deuterium by hydrogen in 18 was observed in 24 hours, but* after 96 hours, exchange was observed to give compound 21. These results demonstrate that a 15 —> 16 hydride shift is not involved in the garryine —> cuauchichicine rearrangement. The experiments described support a mechanism involving formation of an enol followed by exo-protonation of the enol.

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Received, 12th October, 1979