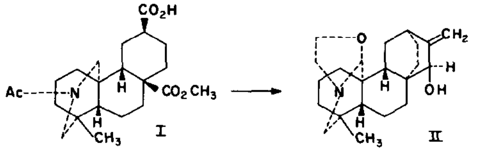
Tetrahedron Letters No. 4, pp. 205-208, 1963. Pergamon Press Ltd.
Printed in Great Britain.

THE DITERPENE ALKALOIDS: A PARTIAL SYNTHESIS OF ATISINE[1]

S. William Pelletier and P. C. Parthasarathy
Department of Chemistry, The University of Georgia
Athens, Georgia, U. S. A.

(Received 5 November 1962)

Recently we reported the interrelation of atisine,[2,3] the major alkaloid of *Aconitum heterophyllum*, and the Garrya alkaloids.[4] A key intermediate in this correlation was the monocarboxylic acid ester, I. In connection with our work on the total synthesis of diterpene alkaloids, we wish to report a successful synthesis of atisine (II) from compound I, involving reconstitution of the bicyclo (2,2,2) octane system with the attached allylic alcohol moiety.



Conversion of the crystalline acid (I), via the acyl chloride, to the corresponding diazoketone, $\nu_{\max}^{\mathrm{nujol}}$ 2092 (N_2), 1724 (CO_2Me), 1639 ($>$C = O), 1623, 1608 cm^{-1} (N Ac), was effected in an overall yield of 80%. Rearrangement of the diazoketone

---

1. This work was presented at the I. U. P. A. C. Second International Symposium on the Chemistry of Natural Products in Prague, August 30, 1962.

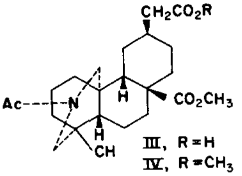
2. K. Wiesner and Z. Valenta, *Progress in the Chemistry of Organic Natural Products*, Vol. XVI, p. 44-53, Springer-Verlag, Vienna (1958).

3a. S. W. Pelletier, *Tetrahedron* **14**, 76-112 (1961).

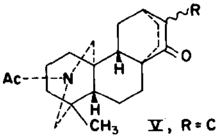
3b. H. Vorbrueggen and C. Djerassi, *J. Amer. Chem. Soc.* **84**, 2990 (1962).

4. S. W. Pelletier, *Ibid.* **82**, 2398 (1960).

using silver benzoate-triethylamine in methanol[5,6] followed by mild alkaline hydrolysis afforded in a yield of 60% the desired homologous acid (III),[7] mp. 270-272°, ν_{max}^{nujol} 1724 (CO_2Me), 1709 (CO_2H), 1608 cm^{-1} (N Ac). Methylation of III with ethereal diazomethane gave the diester (IV) as an oil which sublimed at 160°/0.1 mm. $\nu_{max}^{CHCl_3}$ 1724 (CO_2Me), 1623 cm^{-1} (N Ac). The diester underwent the Dieckmann cyclization with sodium in xylene to afford a resinous mixture of epimeric keto esters (V) in a yield of about 30%, $\nu_{max}^{CHCl_3}$ 1739 (CO_2Me), 1718 ($\rangle C = O$), 1623 cm^{-1} (N Ac). Hydrolysis



III, R = H
IV, R = CH_3



V, R = CO_2CH_3
VI, R = H_2

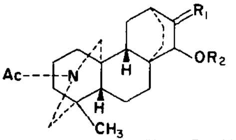
of V followed by sublimation of the resulting β-ketoacids gave the ketone (VI), mp. 170.5 -171°, ν_{max}^{nujol} 1712 ($\rangle C = O$), 1631 (N Ac), 1402 cm^{-1} ($-CH_2CO$) in an overall yield of 50%. The structure of this ketone was confirmed by preparation via another reaction sequence as described below.

The acetate of VII[8] was oxidized with osmium tetroxide-periodate[9,10] to the keto acetate (VIII) in a yield of 75%, mp. 194-195.5°, ν_{max}^{nujol} 1745, 1232 (OAc), 1727 ($\rangle C = O$), 1639, 1634 cm^{-1} (N Ac). Wolff-Kishner reduction of VIII gave a mixture of basic and neutral components. Acetylation of this mixture and subsequent saponification led to a separable mixture of IX, mp. 158.5-160.5, ν_{max}^{nujol} 3378 (OH), 1618 cm^{-1} (N Ac) and

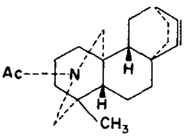
---

5. M. S. Newman and P. F. Beal, J. Amer. Chem. Soc. 72, 5163 (1950).
6. It is interesting to note that the use of silver benzoate-triethylamine as catalyst is the most satisfactory method for effecting a Wolff rearrangement of optically active diazoketones without loss of configuration (K. B. Wiberg and T. W. Hutton, J. Amer. Chem. Soc. 78, 1640 (1956).
7. Satisfactory analytical data were obtained for all new compounds. Melting points are corrected.
8. S. W. Pelletier and W. A. Jacobs, Chemistry and Industry 1116 (1958).
9. R. Pappo, D. S. Allen, R. Lemieux and W. S. Johnson, J. Org. Chem. 21, 478 (1956).
10. Cf. D. Dvornik, and O. E. Edwards, Tetrahedron 14, 56 (1961).

X, mp. 152-153^0, ν_{max}^{nujol} 1639, 1626, (N Ac), 700 cm^{-1} (cis-disubstituted double bond).[11] Mild oxidation of IX with chromium trioxide-pyridine led in good yield (70%) to a ketone which was identical in all respects with VI.



VII , $R_1 = CH_2$; $R_2 = H$
VIII , $R_1 = O$; $R_2 = Ac$
IX , $R_1 = H_2$; $R_2 = H$



X

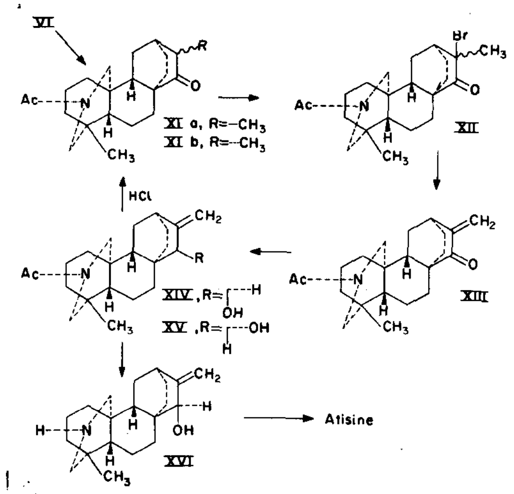
Methylation of VI proceeded smoothly with methyl iodide and sodium hydride in dimethyl sulfoxide to give a mixture of epimeric ketones (XIa and XIb). Subsequent bromination of this mixture in acetic acid and hydrogen bromide gave a mixture of bromoketones (XII) which was dehydrohalogenated to afford the known enone (XIII).[8] In a parallel experiment, the alcohol XIV was isomerized with boiling 10% hydrochloric acid to a mixture of ketones (XIa and XIb) which was separated by crystallization into two sharp melting compounds, mp. 208-208.5^0, ν_{max}^{nujol} 1709 ($\rangle$C = O), 1634 cm^{-1} (N Ac) and mp. 153-156^0, ν_{max}^{nujol} 1709 ($\rangle$C = O), 1631 cm^{-1} (N Ac). Bromination of either ketone (XI) led to a mixture of bromoketones (XII), $\nu_{max}^{CHCl_3}$ 1721 ($\rangle$C = O), 1623 cm^{-1} (NAc), which could be dehydrohalogenated to furnish the enone XIII in 50% overall yield. Previously we had reported reduction of enone XII to the epimeric alcohols (XIV and XV) which can be cleanly separated by chromatography.[8] For the present synthesis, the alcohol with the natural configuration (XIV) (i.e. trans-to the nitrogen bridge) was hydrolysed with potassium hydroxide and a trace of hydrazine in boiling diethylene glycol to afford the secondary amino alcohol (XVI) mp. 151-152.5^0, ν_{max}^{nujol} 3390 (OH), 3175 (NH), 3096, 1642, 897 cm^{-1} ($\rangle$C $=$CH$_2$). This product was identical in every respect with the aminoalcohol derived earlier from the degradation of atisine.[12,13] Since

---

[11] The formation of olefins during the Wolff-Kishner reduction of a-ketols has been noted previously by R. B. Turner, R. Anliker, R. Hebling, J. Meier and H. Huesser, Helv. Chim. Acta, 38, 411 (1955), and by Dvornik and Edwards, Canad. J. Chem. 35, 860 (1957); see also reference 10.

[12] S. W. Pelletier and W. A. Jacobs, J. Amer. Chem. Soc. 78, 4139 (1956).

[13] S. W. Pelletier and W. A. Jacobs, Ibid. 78, 4144 (1956).



this alcohol has already been converted to natural atisine by a five-step sequence,[13] the present work represents a synthesis of atisine from intermediate I.

It should be noted that this synthesis provides direct evidence for the bicyclo (2,2,2) octane system and for the location of the allylic alcohol group in atisine. Work toward a total synthesis of I is underway.

Acknowledgement. This work was supported by Grants GM05807-04 and GM10921-01 from the National Institutes of Health, United States Public Health Service. A portion of this work was carried out in the laboratories of the Rockefeller Institute, New York, New York.