The Total Synthesis of Optically Active Veatchine

All the published[1] syntheses in the diterpene alkaloid series, including our own work, involved the total synthesis of a *racemic* intermediate, the correlation of this material with an *optically active* degradation product of the same structure and finally the conversion of this *optically active* relais compound to the *optically active* alkaloid. Thus, in the strictest sense, this synthetic work represents neither the synthesis of the natural form of the alkaloid nor the synthesis of its racemate. Since we have recently developed a very efficient method[2] for the preparation of the intermediates I and II, we have decided to complete the total synthesis of the optically active form of veatchine IV in order to give at least to this first representative of the diterpene alkaloids a fully classical treatment.

The synthetic racemic compound I[2] was reduced with sodium borohydride to one epimer of the corresponding alcohol. This amorphous material was heated in xylene with succinic anhydride and pyridine and yielded the racemic form of the half-ester III (mp 188 °). Compound III was treated with 1 equivalent of brucine and crystallization from methanol gave one of the 2 diastereoisomeric brucine salts, mp 136 °. Decomposition of this salt yielded 1 enantiomer of compound III, mp 181 °. Saponification of this material gave the corresponding optically active alcohol. This compound was crystalline and melted at 240 °. Finally, Jones' oxidation of the alcohol yielded 1 enantiomer of compound I (mp 138 °). This material was indistinguishable by IR, mass spectrometry, and by thin-layer chromatography in several systems from the previously reported synthetic racemate[1,2] (mp 218 °) and also from the 'natural' degradation product (vide infra) of the same structure. Also the melting points of the 'natural' degradation product and of the synthetic compound were identical. The 2 materials, however, gave a strong melting point elevation and showed mirror image-like optical rotatory dispersion curves. It was thus clear that the synthetic material corresponded to the mirror image of the natural compound and in view of the absolute configuration established[3] for the natural material must be represented by the mirror image of formula I. The amorphous mother liquor of the crystalline brucine salt was decomposed and the liberated hemiester III crystallized to the melting point of 181 °. Saponification yielded an alcohol, mp 240 °, and Jones' oxidation of this compound gave the ketone I, mp 138 °. This material gave no melting point elevation or depression with the 'natural' compound of the same structure. The 2 materials were furthermore indistinguishable by IR and mass spectrometry, and by thin-layer chromatography in several systems. The optical rotatory dispersion curves of the 'natural' and synthetic compounds (recorded through the courtesy of Professor W. A. Ayer, University of Alberta) were superimposable.

The preparation of the 'natural' ketone I was accomplished as follows. Compound II (mp 161–163 °) prepared according to Djerassi[3] was ketalized in benzene with ethylene glycol and *p*-toluenesulfonic acid to the ketal VI (mp 179 °). This material was then converted to the mesyl ketal V (mp 199 °) by reduction with lithium in ammonia in the presence of alcohol followed by mesylation. Deketalization in aqueous acetic acid yielded the desired compound I (mp 138 °) which was identical with the previously described synthetic materials[2] by IR, mass spectrometry, and thin-layer chromatography. The reverse process, i.e. the conversion of I to II, was accomplished in exactly the same manner (substituting acetylation for mesylation) and the compounds V, VI and II thus prepared were identical with those mentioned above by thin-layer chromatography, IR, mass spectrometry and mixed melting point.

Since we have already described[4] the conversion of Djerassi's compound II to garryine and veatchine, the total synthesis of the natural optically active form of these alkaloids is complete[5].

Zusammenfassung. Die erste Totalsynthese des Garrya-Alkaloids Veatchin, das heisst des natürlichen optischen Isomeren, wird beschrieben.

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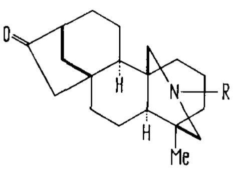
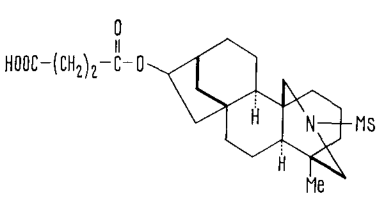
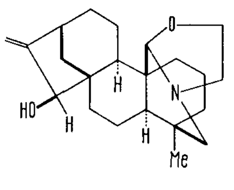


I (R=Ms)

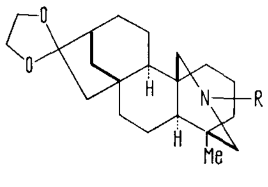
II (R=$-\underset{\underset{O}{\|}}{C}-CH_3$)



III



IV



V (R=Ms)

VI (R=$-\underset{\underset{O}{\|}}{C}-CH_3$)

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[1] W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi and Y. Hayase, J. Am. chem. Soc. *85*, 2342 (1963). – W. Nagata, M. Narisada, T. Wakabayasi and T. Sugasawa, J. Am. chem. Soc. *86*, 929 (1964). – S. Masamune, J. Am. chem. Soc. *86*, 291 (1964). – Z. Valenta, K. Wiesner and C. M. Wong, Tetrahedron Letters (*1964*), 2437. – R. W. Guthrie, Z. Valenta and K. Wiesner, Tetrahedron Letters (*1966*) 4645.

[2] K. Wiesner, S. Uyeo, A. Philipp and Z. Valenta, Tetrahedron Letters (*1968*), 6279.

[3] H. Vorbrueggen and C. Djerassi, J. Am. chem. Soc. *84*, 2990 (1962).

[4] R. W. Guthrie, W. A. Henry, H. Immer, C. M. Wong, Z. Valenta and K. Wiesner, Coll. Czech. chem. Commun. *31*, 602 (1966).

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