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OPTIMIZATION OF THE TENULIN-ISOTENULIN CONVERSION

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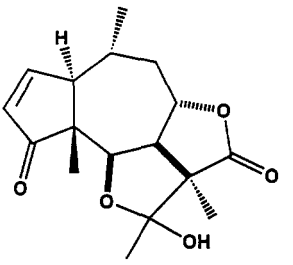
ABSTRACT.—Several literature methods for effecting the retro-aldol conversion of tenulin [**1**] to isotenulin [**2**] have been difficult to reproduce in our laboratory and in those of other workers. We report herein a first systematic study of this reaction where an aqueous reaction solution buffered at neutral pH resulted in a maximal yield of chromatographically pure **2**.

The sesquiterpene lactone tenulin [**1**] has a significant place in the history of natural products chemistry. This bitter principle was first isolated in 1939 by Clark (1) in high yield from a number of *Helenium* species. Subsequent studies on the structure of tenulin (2–5) spanned 35 years and culminated in a 1975 paper by Herz and Sharma (6) that provided confirmation of the final structural detail. The determination of tenulin's structure stands as a very early example of the successful use of ^{1}H-nmr spectroscopy in natural products chemistry (6). More recently, a broad spectrum of biological activity has been revealed for tenulin [**1**] and its analogues: toxicity (7), antitumor (8,9), anti-inflammatory (10,11), antihyperlipidemic (12), genotoxicity (13), antifeedant (14), germination stimulant (15), and HMG CoA reductase inhibition (16). These continuing biological studies indicate that interest in tenulin [**1**] and its derivatives (e.g., isotenulin [**2**]) remains active.

The retro-aldol conversion of **1** into isotenulin [**2**] by aqueous base is a classic reaction characteristic of **1** (1). Numerous methods for effecting this reaction have been described in the literature (1–3) and the inconsistencies of the results have been noted (3). Indeed, in our hands, the literature methods have not been reproducible. For example, on one occasion the method of Clark (1) using boiling tap H_2O was successful as reported. A few days later, using H_2O from the same tap, the reaction failed and starting material was recovered in high yield. Other literature procedures (e.g., aqueous $NaHCO_3$) gave variable yields (26–73%) of material, varying likewise in quality (as measured by tlc). A likely explanation for these results is that the hemiketal ring opening to give **2** and the appearance of side-products are very sensitive to small changes in solution pH (such as might occur among tap H_2O samples from one day to the next). In order to test this notion and to maximize the efficiency and reproducibility of this important step, we carried out a systematic study of the effect of pH on the tenulin-isotenulin reaction.



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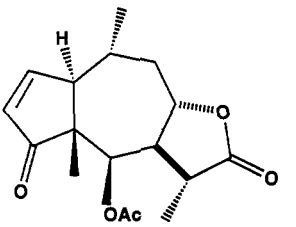

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A standard procedure was defined for the reaction whereby 50 mg of **1** in 3 ml of aqueous KH_2PO_4/NaOH buffer (17) was refluxed for 15 min, followed by

concentration of the cold solution *in vacuo* and precipitation of the isotenulin [**2**] product. These reactions were run at pH values ranging between 6.0 and 8.0 with the results listed below:

pH=6.0: 24% yield, 1:1 tenulin/isotenulin
6.8: 67% yield of pure isotenulin (by tlc)
7.0: 72% yield of pure isotenulin (by tlc)
7.2: 72% yield of isotenulin (higher R_f impurity)
7.3: 48% yield of isotenulin (higher R_f impurity)
8.0: the product was a complex mixture

Foremost, it is clear that the reaction buffered at pH=7.0 gave an optimal result in terms of yield and product purity. The yields of isotenulin [**2**] reported in the literature (1–3) were typically 50–70%. What has happened to the remainder of the mass? For the pH=7.0 run, the aqueous filtrate was extracted with CH_2Cl_2 and the dried organic solution was evaporated. No organic soluble material was recovered. Thus, a major side-reaction of the tenulin-isotenulin conversion is the production of a H_2O-soluble product. It seems likely that lactone hydrolysis occurs under the reaction conditions to give an ionic carboxylate moiety rendering the sesquiterpene H_2O soluble. We also note that at pH=6.0 the conversion to **2** is very sluggish. Moreover, on the basic side (pH=8.0), major side-reactions occur, giving a complex mixture of products. No attempt has been made to identify the above H_2O-soluble products or the pH=8.0 complex mixture. Most importantly, then, the procedure outlined above (pH=7.0) and detailed in the Experimental now represents a simple, reproducible method for the conversion of the sesquiterpene lactone tenulin [**1**] into chromatographically pure isotenulin [**2**] in good yield.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Tenulin [**1**] was isolated from *Helenium amarum* according to a published procedure (18) and was identified by ir, nmr, uv, ord-cd, C,H analysis, and direct comparison with an authentic sample, kindly supplied by Prof. W. Herz.

PREPARATION OF ISOTENULIN [**2**].—A solution of 50 mg of tenulin [**1**] in 3.0 ml of KH_2PO_4/NaOH buffer at pH=7.0 (17) was refluxed for 15 min. The reaction mixture was cooled on an ice bath and concentrated *in vacuo* cold for 5 min. The crystalline product was isolated by vacuum filtration and was air-dried to give 36 mg of isotenulin [**2**]. Isotenulin prepared in this manner gave a single circular spot on tlc (1:1, Me_2CO-hexane).

The same procedure at other pH values between 6.0 and 8.0 gave less satisfactory results (see text).

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