Synthesis of Marinobufagin and Marinobufotoxin from Telecinobufagin[1]

Venom from the Brazilian toad *Bufo icerticus* Spix was recently shown to contain marinobufotoxin (V)[2]. The corresponding genin marinobufagin (IVa) has been isolated from 5 different toad species and from the Chinese medicinal preparation Ch'an Su[3]. To make both marinobufagin and marinobufotoxin more readily available for medically-oriented studies, we have investigated synthetic approaches to these naturally occurring bufadienolides. We now wish to report a partial synthesis of marinobufagin (IVa) and marinobufotoxin (V) from telocinobufagin (I).

Selective dehydration of telocinobufagin (I) with hydrochloric acid in methanol yielded 14-dehydro telocinobufagin (II, mp 198–200°, 51% yield)[4]. Reaction of olefin II with N-iodosuccinimide in dioxane-water gave iodohydrin IIIa which was converted directly upon treatment (room temperature, 60 min) with pyridine to marinobufagin (IVa, mp 223–225°, 45% yield). The product (IVa) was found identical with an authentic sample isolated from Ch'an Su[3]. The substitution of N-bromoacetamide or N-bromosuccinimide for the N-iodo reagent afforded bromohydrin IIIb and led to 33 and 31% yields, respectively, of marinobufagin.

Reaction of marinobufagin (IVa) with suberic α-anhydride[5] in pyridine (reflux, 6 h) gave suberate ester IVb (92% yield by preparative thin layer chromatography). The corresponding methyl ester derivative IVc (needles from acetone-ether, mp 107–112°) was prepared (diazomethane) and found identical with an authentic specimen isolated[6] from Ch'an Su. The half ester of suberic acid (IVb) was condensed at −10° (in tetrahydrofuran containing triethylamine) with *i*-butyl chloroformate. The cold solution of mixed carbonic anhydride was added to arginine monohydrochloride in methanol-water. Marinobufotoxin (V, mp 176–185°) was isolated in 88% yield by preparative thin layer chromatography and found identical with an authentic sample (mp 174–181°)[7].

While marinobufagin has been converted[8] to telocinobufagin the present study constitutes the first partial synthesis of marinobufagin and of marinobufotoxin. The synthesis of marinobufotoxin also constitutes unequivocal support for the recent structural assignment[2]. Presently we are undertaking a total synthesis of telocinobufagin by way of the plant bufadienolide scillarenin[9].

Zusammenfassung. Telecinobufagin (I) wurde in Marinobufagin (IVa) und in Marinobufotoxin (V) übergeführt. Hauptreaktionsschritte: Umsetzung des Olefins II zum Halohydrin III mit anschliessender Epoxydierung (III → IVa). Das so erhaltene Marinobufagin (IVa) wurde mit Arginin-monohydrochlorid unter Verwendung der MCA-Technik zu Marinobufotoxin (V) kondensiert.

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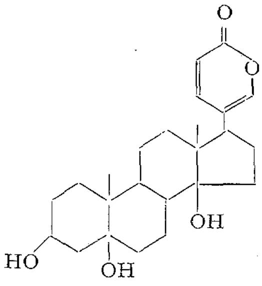
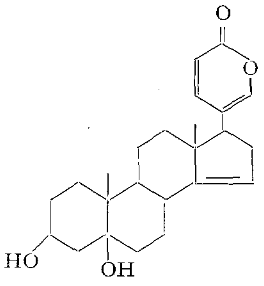
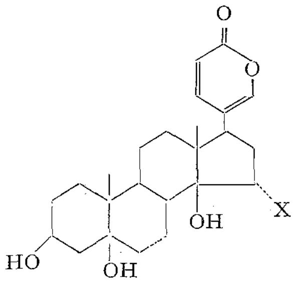
Department of Chemistry, Arizona State University, Tempe (Arizona 85281, USA), 3 January 1972.



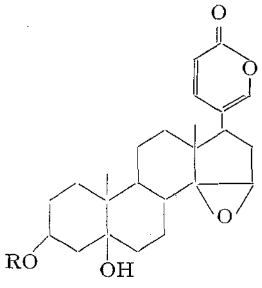
I



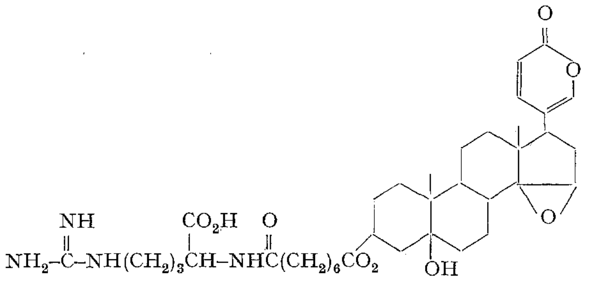
II



IIIa, X = I
b, X = Br



IVa, R = H
b, R = CO(CH$_2$)$_6$CO$_2$H
c, R = CO(CH$_2$)$_6$CO$_2$CH$_3$



V

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[2] H. O. Linde-Tempel, Helv. chim. Acta *53*, 2188 (1970).

[3] See Y. Kamano, H. Yamamoto, K. Hatayama, Y. Tanaka, M. Shinohara and M. Komatsu, Tetrahedron Lett *1968*, 5668.

[4] The structure of each new substance was supported by the results of UV-, IR-, proton magnetic resonance and mass spectral measurements as well as elemental microanalysis.

[5] J. W. Hill and W. H. Carothers, J. Am. chem. Soc. *55*, 5023 (1933).

[6] Y. Kamano, H. Yamamoto, Y. Tanaka and M. Komatsu, the 12th Symposium on the Chemistry of Natural Products of Japan, Sendai, October 8, 1968; Abstracts of Papers, p. 166.

[7] We are indebted to Professor K. Meyer for providing the natural specimen.

[8] M. Bharucha, H. Jäger, K. Meyer, T. Reichstein and O. Schindler, Helv. chim. Acta *42*, 1395 (1959).

[9] The total synthesis of scillarenin has been accomplished by U. Stache, K. Radscheit, W. Fritsch, W. Haede, H. Kohl and H. Ruschig, Justus Liebigs Annln Chem. *750*, 149 (1971).

[10] Author to whom correspondence should be addressed.

[11] Dedicatded to Prof. H. Ruschig on the occasion of his 65th birthday.