STRUCTURE AND CONFIGURATION OF THE ISOIMPERIALINES

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The structure and configuration of imperialine have been established previously [1, 2]. It contains secondary and tertiary hydroxy groups and a carbonyl group. When imperialine was heated in alcoholic alkali, Chu and Loh obtained isoimperialine with mp 226-228° C [3], the UV and IR spectra of which lacked the absorption bands of a carbonyl group. We established that isoimperialine is a mixture of two bases [4]. We obtained these bases, with mp 205-207° C and 221-223° C, by a preparative method. It was erroneously considered that when the isoimperialines were heated in 10% sulfuric acid at 95° C they were converted into imperialine. The mutual transformations of imperialine into the isoimperialines and of the isoimperialines into imperialine led us to erroneous conclusions: inappropriate structural formulas were proposed for the isoimperialines.

In a further investigation of the products of the isomerization of imperialine, it was established that the previously-isolated β-isoimperialine is a pure product while α-isoimperialine was not adequately purified. The pure α-isoimperialine that we have now obtained melts at 239-240° C. In addition, in a repeated study of the action of 10% sulfuric acid on α- and β-isoimperialines it was found that the latter is stable in an acid medium and is not converted into imperialine. The α- and β-isoimperialines are not reduced by sodium in n-butanol or by sodium tetrahydroborate in aqueous methanol.

The mass spectra of the α- and β-isoimperialines have characteristic peaks of ions with m/e: 98; 111; 112 (100%); 154; 155; 156; $(M-57)^+$; $(M-45)^+$; $(M-43)^+$; $(M-19)^+$; $(M-15)^+$; M^+ (431).

The schemes of the fragmentation of α- and β-isoimperialines and imperialine [1] are similar in the main; they differ only by the value of the molecular ion. In the α- and β-isoimperialines the molecular ion has m/e 431, and in imperialine it is 429.

The facts given show that β- and α-isoimperialines lack ketol bonds. In addition, they have made it possible to suggest that β-isoimperialine is identical with dihydroimperialine and α-isoimperialine with isodihydroimperialine.

For a direct comparison of the substances mentioned, dihydroimperialine and isodihydroimperialine were isolated from the products of the reduction of imperialine with metallic sodium in n-butanol. Thus, it has been established that reduction with sodium in butanol forms not only isodihydroimperialine, as described by Chu and Loh [3] and by Boit [5], but also dihydroimperialine. For comparison, dihydroimperialine and isodihydroimperialine were also obtained by the reduction of imperialine with sodium tetrahydroborate in aqueous methanol. In the reduction of imperialine with sodium and n-butanol, the main product was isodihydroimperialine, while in the reduction with sodium borohydrate it was dihydroimperialine.

The results of a direct determination of the melting point of mixtures and of a comparison of IR spectra (Fig. 1) showed the identity of β-isoimperialine and dihydroimperialine, on the one hand, and of α-isoimperialine and isodihydroimperialine, on the other.

No reductions of a carbonyl group with an ethanolic solution of caustic potash have been described in the literature. Apparently, in this reaction the ethanol is the reducing agent and the caustic potash is a catalyst. The most likely reduction mechanism here can be represented in the following way:

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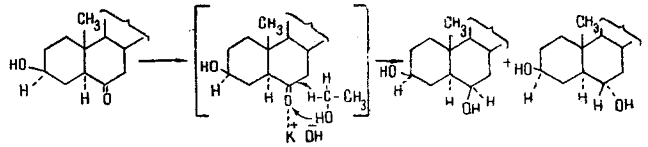


The corresponding configurations of dihydroimperialine and isodihydroimperialine were determined by comparing the NMR spectra of the bases and their acetyl derivatives with the NMR spectra of imperialine and acetylimperialine (Fig. 2).

The NMR spectrum of dihydroimperialine exhibits the following characteristic resonance signals: singlets at 0.93 ppm (3H, 19-CH_3) and 1.0 ppm (3H, 21-CH_3), doublet at 1.01 ppm (3H, 27-CH_3) and (J = 6.5 Hz), two-proton multiplet with a center at 3.56 ppm (2H, H_a-C_3- and $-C_{20}-OH$), and a one-proton multiplet at 3.75 ppm (1H, H_e-C_6-). The NMR spectrum of diacetyldihydroimperialine exhibits singlets at 0.92 ppm (3H, 19-CH_3), 1.01 ppm (3H, 21-CH_3), and 1.95 ppm (3H, $-C_3-COOCH_{3(e)}$, 3H, $-C_6-COOCH_{3(a)}$), a doublet at 1.01 ppm (3H, 27-CH_3), and multiplets at 3.46 ppm (H, $-C_{20}-OH$), 4.65 ppm (H, $H_a-C_6-COOCH_3$), 4.89 ppm (H, $H_e-C_3-COOCH_3$). In the NMR spectrum of isodihydroimperialine there are singlets at 0.72 ppm (3H, 19-CH_3) and 1.0 ppm (3H, 21-CH_3), a doublet at 0.99 ppm (3H, 27-CH_3) (J = 6.5 Hz), and a multiplet with a center at 3.43 ppm (3H, C_3-H_a; C_6-H_e; $C_{20}-OH$), and in the IR spectrum of diacetylisodihydroimperialine there are singlets at 0.79 ppm (3H, 19-CH_3), 1.0 ppm (3H, 21-CH_3), and 1.95 ppm (6H, $C_3-COOCH_{3(e)}$ and $C_6-COOCH_{3(e)}$), a doublet at 0.99 ppm (3H, 27-CH_3), and multiplets at 3.20 ppm (H, $C_{20}-OH$) and 4.60 ppm (2H, $H_a-C_3-COOCH_3$ and $H_a-C_6-COOCH_3$).

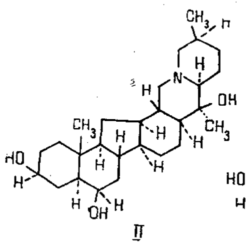
In the NMR spectrum of imperialine there are singlets at 0.67 ppm (3H, 19-CH_3) and 0.99 ppm (3H, 21-CH_3), a doublet at 0.98 ppm (3H, 27-CH_3) (J = 7 Hz), and a multiplet at 3.45 ppm (2H, H_a-C_3 and $C_{20}-OH$), and in the NMR spectrum of acetylimperialine there are singlets at 0.69 ppm (3H, 19-CH_3), 0.99 ppm (3H, 21-CH_3), 1.95 ppm (3H, $C_3OOCH_{3(e)}$), and 3.44 ppm (H, $C_{20}-OH$), a doublet at 1.01 ppm (3H, 27-CH_3), and a multiplet with a center at 4.06 ppm (H, $H_a-C_3-COOCH_3$).

The facts given show that the chemical shift from the 19-methyl proton of imperialine moves downfield by 5 Hz in the formation of isodihydroimperialine. Such a displacement of the signal is characteristic for the protons of a 19-methyl group when an α-oriented hydroxy group is introduced at C_6 of steroid compounds [6]. The proposed configuration for the hdyroxyl is also confirmed by the fact that in diacetylisodihydroimperialine the chemical shift from the C_6 proton is found in a stronger field at 4.60 ppm, like the signals from the axially-oriented protons at C_3 of acetylimperialine and diacetylimperialine. This figure is characteristic of the axially-oriented protons of the steroid alkaloids [7].

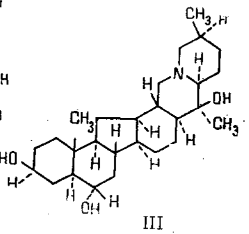
Furthermore, the chemical shifts of the protons of the 19-methyl group of dihydroimperialine are moved downfield by 26 Hz as compared with the signal from the corresponding group of imperialine. The difference in the chemical shifts of their acetyl derivatives is 23 Hz. These results are very close to the values of the shifts found for steroid compounds [6] having axially-oriented hydroxy and acetyl groups at C_6, which is once again confirmed in the NMR spectrum of diacetyldihydroimperialine by a one-proton signal at 4.9 ppm characteristic of an equatorially-oriented proton on a carbon atom connected with an acetyl group [7].

Consequently, in dihydroimperialine the hydroxy group at C_6 has the β-axial orientation, and in isodihydroimperialine it has the α-equatorial orientation.

Thus, the following configurations have been proposed for dihydroimperialine (II) and isodihydroimperialine (III):



II



III

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer (tablets with KBr), the mass spectra on an MKh-1303 instrument, and the NMR spectra on a JNM-4H-100/100 MHz spectrometer (in $CDCl_3$).

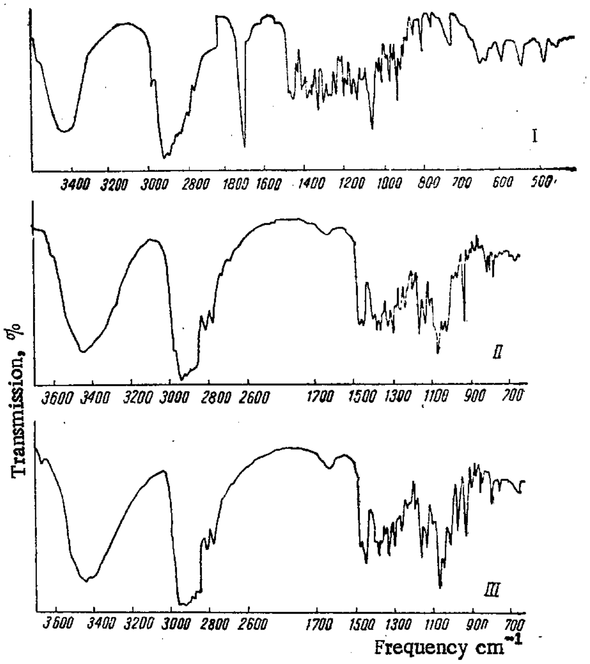


Fig. 1. IR spectra of imperialine (I), dihydroimperialine (II), and isodihydroimperialine (III).

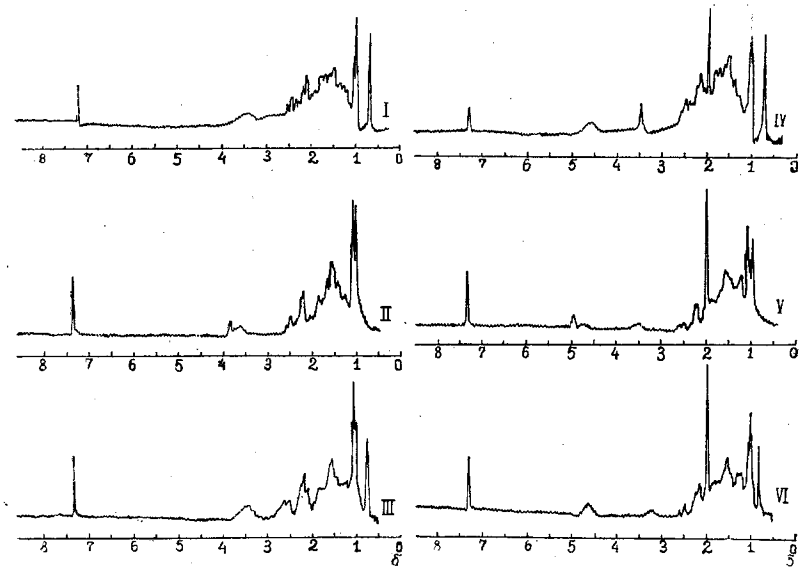


Fig. 2. NMR spectra of imperialine (I), dihydroimperialine (II), isodihydroimperialine (III), acetylimperialine (IV), diacetyldihydroimperialine (V), and diacetylisodihydroimperialine (VI).

A mixture of imperialine (2 g) and caustic potash (20 g) in 40 ml of ethanol was heated in the boiling water bath for 5 h. The reaction product was mixed with 200 ml of water and extracted with chloroform. The chloroform solution was washed with water and evaporated. The residue – a viscous light brown product – was converted into a powder in vacuum, dissolved in a mixture of benzene and chloroform (4 : 1), and chromatographed on Al_2O_3 (l = 2 cm; d = 2.5 cm). The reaction products were eluted with a mixture of benzene and chloroform (4 : 1) and from the moment when isodihydroimperialine appeared in the eluate elution was continued with methanol–chloroform (1 : 4). The eluates were collected in fractions of 10-15 ml and the evaporation residues were chromatographed on a thin layer of Al_2O_3 and $CaSO_4$ (9 : 1) in the ethyl acetate–chloroform–methanol (30 : 20 : 3) [1] system. The eluates contained a mixture of imperialine and dihydroimperialine, pure dihydroimperialine, and a mixture of dihydroimperialine and isodihydroimperialine, and, finally, pure isodihydroimperialine. After the elimination of the solvent, the mixture of dihydroimperialine and isodihydroimperialine obtained from the eluates was reseparated by the above-described chromatographic method. A total of 0.880 g of dihydroimperialine with mp 205-207°C (from acetone), R_f 0.4, and 0.270 g of isodihydroimperialine with mp 239-240°C (from methanol), R_f 0.3 was obtained.

Action of Sulfuric Acid on Dihydroimperialine. A mixture of 0.05 g of dihydroimperialine and 10 ml of 10% sulfuric acid was heated for 2 h. The cold acid solution was made alkaline with sodium carbonate, and the base extracted with chloroform. The solvent was distilled off and the residue was chromatographed on alumina in system (1). Imperialine and dihydroimperialine were used as markers. The reaction product and dihydroimperialine had the same R_f value (0.4). A mixture of the dihydroimperialine isolated from the acid solution after recrystallization from acetone, and of authentic dihydroimperialine gave no depression of the melting point.

Action of Sulfuric Acid on Isodihydroimperialine. The treatment of the isodihydroimperialine, the isolation of the reaction product, and its comparison with authentic isodihydroimperialine were performed under the conditions of the experiment with dihydroimperialine. The isodihydroimperialine was recovered unchanged.

Reduction of Imperialine. A solution of 0.5 g of imperialine in 25 ml of n-butanol was heated at 80° C. With constant stirring by a magnetic stirrer, 0.5 g of metallic sodium was added in small pieces. The reaction product, after cooling, was treated with water and extracted with chloroform. The solvent was distilled off in vacuum, and the residue was redissolved in chloroform and extracted with 0.5% sulfuric acid. The acid solution was made alkaline with sodium carbonate and the base was extracted with chloroform. The residue after the chloroform had been distilled off was dissolved in benzene–chloroform (4 : 1) and passed through Al_2O_3 (l = 2 cm; d = 2.5 cm). The elution of the base was also continued with a mixture of benzene and chloroform (4 : 1) and, after the appearance of an eluate with pure isodihydroimperialine, with methanol–chloroform (1 : 4).

The content of bases in the eluates was monitored by thin-layer chromatography in system (1). The presence of fractions containing a mixture of imperialine and dihydroimperialine, pure dihydroimperialine, a mixture of dihydroimperialine and isodihydroimperialine, and pure isodihydroimperialine was established. The mixtures of bases were repurified by passage through the adsorbent.

The fractions of pure bases yielded 0.03 g of dihydroimperialine with mp 205-207° C (from acetone) and 0.33 g of isodihydroimperialine with mp 239-240° C (from methanol). A mixture of authentic isodihydroimperialine with the isodihydroimperialine obtained from imperialine by heating it with alcoholic alkali gave no depression of the melting point.

Reduction of Imperialine. At room temperature, 0.2 g of sodium tetrahydroborate was added gradually over 3 h to a solution of 0.5 g of imperialine in 50 ml of 10% aqueous methanol. The aqueous methanol was distilled off in vacuum, and the residue was dissolved in chloroform and extracted with 5% sulfuric acid. The acid solution was made alkaline with sodium carbonate and the base was extracted with chloroform. On thin-layer chromatography in system (1), the residue after the distillation of the solvent yielded spots of dihydroimperialine and isodihydroimperialine. The mixture was separated under the conditions described for the products of the reduction of imperialine with sodium and n-butanol.

In this way, 0.42 g of chromatographically pure dihydroimperialine with mp 205-207° C (acetone) and 0.03 g of isodihydroimperialine with mp 239-240° C (from methanol) were isolated.

The dihydroimperialine so obtained was identical with the dihydroimperialine isolated in the reduction of imperialine with alcoholic alkali.

SUMMARY

1. The possibility has been shown of reducing a ketone – imperialine – in alcoholic alkali, and a proposed mechanism of this reaction is given.

2. The configurations of dihydroimperialine and isodihydroimperialine have been established.

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