INVESTIGATION OF NEOASCORBIGEN

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The synthesis of N-methoxyascorbigen (neoascorbigen) - a natural substance from plants of the Cruciferae family - and also N-ethoxyascorbigen is described. In an acidic media under drastic conditions N-alkoxyascorbigens undergo transformations with the release of ascorbic acid and the formation of oligomers of 1-alkoxy-3-methyleneindolenine or with opening of the lactone ring, decarboxylation, and dehydration and the formation of 2-hydroxy-3-(1-alkoxy-3-indolyl)-4-hydroxymethylcyclopent-2-enone. Amides of neoascorbigen, 3-O-methylglycoside of N-ethoxyascorbigen, and the product of the reduction of N-ethoxyascorbigen by sodium borohydride were obtained for the first time.

Keywords: 2-hydroxy-3-(1-alkoxy-3-indolyl)-4-hydroxymethylcyclopent-2-enones, neoascorbigen, N-ethoxyascorbigen.

The properties of ascorbigen - 2-C-(3-indolylmethyl)-α-L-xylo-3-hexulofuranosono-1,4-lactone (1) formed in plants of the Cruciferae family from 3-hydroxymethylindole (the product from disintegration of the alkaloid glucobrassicin) and L-ascorbic acid (2) [1-3] - have been studied fairly well. In an acidic medium it releases ascorbic acid and forms the products from oligomerization of 3-methyleneindolenine [4], of which the most important is 5H,11H-indolo[3,2-b]carbazole - a powerful activator of cytochrome-dependent oxidase P4301A1 and a modulator of cancerogenase [5, 6].

In addition to glucobrassicin, plants of the Cruciferae family include a series of other indole alkaloids (glucosinolates) [7, 8]. They include neoglucobrassicin (N-methoxyglucobrassicin) - a source of neoascorbigen (N-methoxyascorbigen 3a). The chemical and biochemical characteristics of the latter have not been investigated before, and its biological significance has not been determined.

The aim of the present work was to synthesize neoascorbigen 3a and its homolog N-ethoxyascorbigen 3b and to study the chemical properties of these compounds. The key compound in the synthesis of alkoxyascorbigens 3a,b is 1-hydroxyindole (4). We used the two most convenient methods for its preparation, i.e., the condensation of o-nitrotoluene with dimethylformamide dimethyl acetal followed by the reduction of the dimethylaminovinyl derivative 5 with zinc in an aqueous solution of NH₄Cl [9, 10] or the oxidation of indoline with hydrogen peroxide in the presence of Na₂WO₄ [11].

I-Hydroxyindole 4 is an unstable compound, and it was therefore used in the O-alkylation reaction without purification. During synthesis by the first method the total yield of 1-methoxyindole 6a was 31% (calculated on o-nitrotoluene), and in the second method it was 44% while the yield of 1-ethoxyindole 6b was 41% (calculated on indoline).

1-Alkoxynoloe 6a,b were converted into the corresponding 3-formyl derivatives 7a,b, which were then reduced with sodium borohydride in ethanol to 1-alkoxy-3-hydroxymethylindoles 8a,b. The latter were immediately brought into condensation with L-ascorbic acid 2. As a result the required products 3a,b were obtained with yields of 70 and 65% (calculated on the respective 1-alkoxy-3-formylindole 7). The synthesis of N-alkoxascorbigenes by this method has been described before [12]. However, we showed that apart from these compounds the reaction mixture contained a resinous mixture of side compounds, from which by preparative TLC 1'-methoxy-2'-(1''-methoxy-3''-indolylmethyl)ascorbigen (9a) or its 1'-ethoxy analog (9b) were isolated with yields of 4.2 and 2.5%. Dit 1-methoxy-3-indolylmethane (10a) or its 1-ethoxy analog (10b) were also isolated with yields of about 8.3 and 9.0%. In methanol solution of HCl N-ethoxyascorbigen 3b forms 3-OMe glycoside 11 with a yield of 55%. By the action of sodium borohydride the hemiketal group in compound 3b at position 3 is reduced, and lactone of [2-C-(1'-ethoxy-3'-indolyl)methyl]-L-gulonic acid (12) is formed with a yield of 60%. The structure of the latter was established by PMR using the Overhauser effect: since the intensity of the signals of 2-OH, 5-H, 5-OH, and 6-OH is reduced if the signal of the 3-H proton is suppressed while the intensity of the CH group signal is unchanged, it can be concluded that the 3-H proton and the 2-OH group are in the relative cis position, i.e., compound 12 has the R-configuration at the C5 atom and is a derivative of L-gulonic acid.

N-Methoxyascorbigen 3a reacts with primary amines with opening of the lactone ring and the formation of benzylamide 13a (yield 60%) or butylamide 13b (55%) of 2-C-(3-indolymethyl-1-methoxy)-α-L-xylo-3-hexulofuranosonic acid.