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From ascorbigens to indolocarbazoles

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Abstract

New methods of L-ascorbic acid derivatization with the use of polyfunctional indole-3-cabinols are described. Reaction of β-hydroxy-*N*-methyltryptamine and L-ascorbic acid gave lactame derivatives; (indol-3-yl)glycolic and L-ascorbic acids produced 2-hydroxy-4-hydroxymethyl-3-(indol-3-yl)-cyclopen-2-enone. Similarly, 4-hydroxy-3-methoxyphenylglycolic and L-ascorbic acids yielded 2-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-4-hydroxymethyl-cyclopen-2-enone. Properties of *N*-methoxyascorbigen (neoascorbigen) were investigated. Alkylation of L-ascorbic acid with polysubstituted pyrrolecarbinols led to pyrrole analogues of ascorbigen. Acidic transformation of 3-formylindole and 1-methyl-3-formylindole led to indolocarbazoles and triindolylmethane derivatives. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Ascorbigen; L-Ascorbic acid; 3-Formylindole; Indolocarbazole; Neoascorbigen; Indolecarbinol; Pyrrolecarbinol

L-Ascorbic acid is easily alkylated in mild conditions (room temperature, water–alcohol solution, pH 4–5) with 3-hydroxymethylindole, with the formation of ascorbigen (2-C-[(indol-3-yl)methyl]-α-L-xylo-3-hexulofuranosono-1,4-lactone (**Asc**), (Scheme 1) [1].

3-Hydroxymethylindole is formed in plants of the cruciferous family from the alkaloid glucobrassicin, and its interaction with L-ascorbic acid in plant tissues proceeds nonenzymatically [2]. For animals and humans **Asc** is a main source of 5*H*,11*H*-indolo[3,2-*b*]-carbazole (**ICZ**), a natural potent Ah receptor agonist. The Ah receptor is a widely occurring ligand-activated transcription factor that mediates the activation of cytochrome 4501A1, P4501A2, glutathione S-transferase, and quinone reductase genes. The binding activity of **ICZ** is only a factor of 3.7×10^{-2} lower than that of the highly toxic environmental contaminant and cancer promoter 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [3–5].

The facile 2-C-alkylation of ascorbic acid prompted us to study the interaction of polyfunctional indole-3-carbinols with ascorbic acid. Indole-3-carbinols, with functional groups in the neighbourhood of carbinol hydroxyl, interact with ascorbic acid with the participation of the functional group. Earlier we investigated the interaction of (indol-3-yl)ethandiol-1,2 with L-ascorbic acid, which yielded a mixture of products of the L-ascorbic acid 2-C alkylation with the substituted skatyl cation stabilized by the 3-CO hemiketal formation with the participation of the CH_2OH moiety of (indol-3-yl)ethandiol-1,2 [6a,b]. The interaction of DL-*N*-methyl-β-hydroxytryptamine with L-ascorbic acid proceeds through the 2-C alkylation of the latter and the intramolecular acylation of the methylamino group, to yield diastereomeric 3-hydroxy-4-(indol-3-yl)-1-methyl-3-(2,3,4-trihydroxybutyryl)-pyrrolid-2-ones (**4a** and **5b**) (Scheme 2), [7]. The 3-C–6-C moiety of ascorbic acid in isomer **4a** represents a cyclic hemiacetal (1′-C–4′-C), whereas in isomer **5b** it exists as an acyclic trihydroxybutyryl residue. Acetylation of compounds **4a** and **5b** with acetic anhydride in pyridine at −16°C afforded **6a** and **6b**, respectively, whose deacetylation (MeONa in

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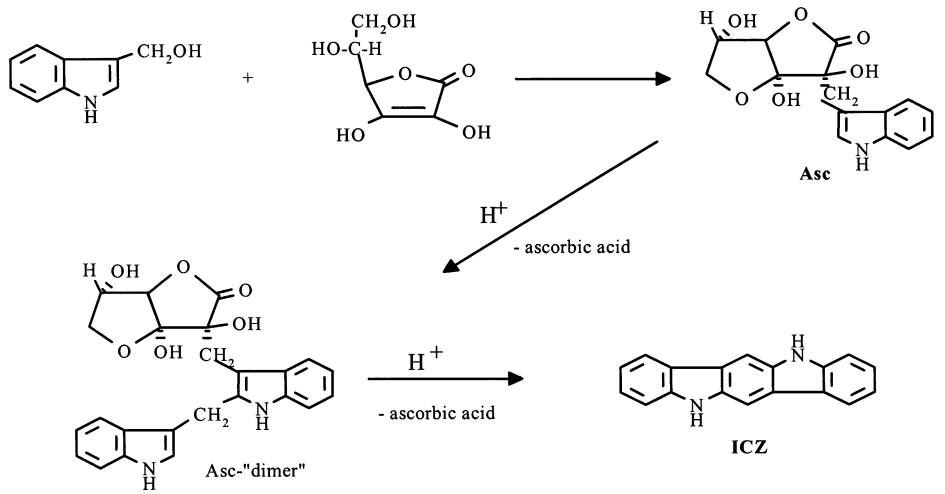
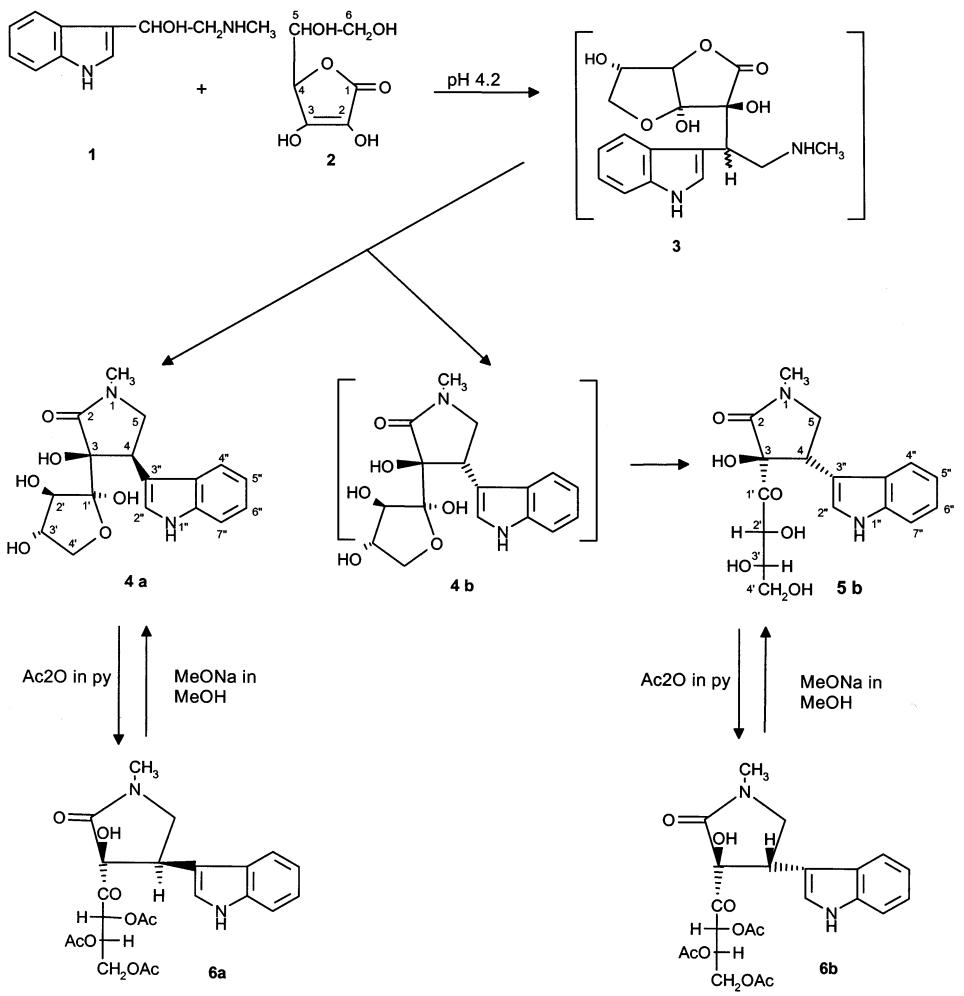


Scheme 1.

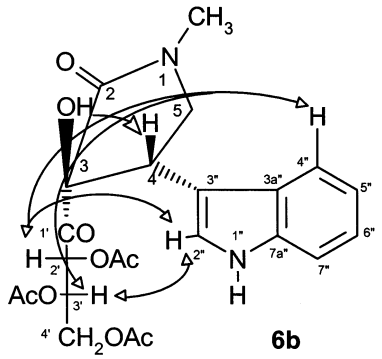
MeOH) gave again individual **4a** and **5b** to show that in the course of the acetylation no racemization occurred.

Among chiral atoms of **4a** and **5b**, there are two (3-C and 4-C of the lactam cycle) whose stereochemistry is not pre-assigned by the stereochemistry of L-ascorbic acid.

The absolute configuration of the 3-C atom is determined by the direction of the electrophilic attack of the

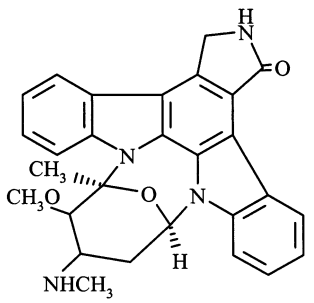


Scheme 2.



⟶ - NOE connectivities

Scheme 3.



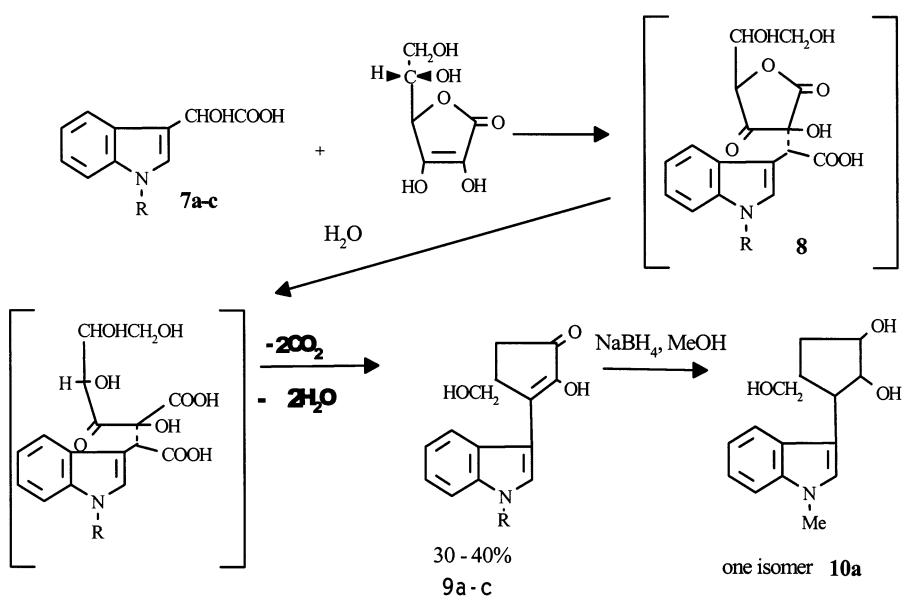
Scheme 4.

substituted skatyl cation at the 2-C atom of the L-ascorbic acid lactone ring [2]. In all the ascorbic acid 2-C-alkylations reported to date, such an attack was directed from the site opposite the CHOH–CH_2OH fragment [8], except for the 2-C methylation of L-ascorbic acid yielding a mixture of 2*S* and 2*R* isomers, which can be explained by the small size of the methyl group [9]. This suggests the *S* configuration at the 3-C of compounds **4a** and **5b**.

The absolute configuration at 4-C of the **4a** and **5b** isomers was determined for their tri-*O*-acetyl derivatives **6a** and **6b**. ^1H and ^{13}C NMR data showed that the frameworks of **6a** and **6b** are the same as that of **5b**. The presence of a sharp signal of the unsubstituted 3-OH group in ^1H NMR spectra of **6a** and **6b** in DMSO-d_6 allowed us to use NOE-difference experiments to determine the disposition of the substituents at 4-C. The selective saturation of the 3-OH proton at 6.73 ppm gave rise to 8% signal enhancement of the 4-H multiplet at 3.87 ppm in **6b**, whereas the saturation of the 3-OH proton in **6a** did not affect the 4-H signal. Based on these data, we assigned the indole residue at 4-C and the carbohydrate moiety at 3-C, a *cis*-arrangement in **6b** and therefore in **5b**, and a *trans*-arrangement in **6a** and therefore in **4a**. This led to the conclusion that the absolute configuration at 4-C is *S* in **5b** and *R* in **4a** (Scheme 3).

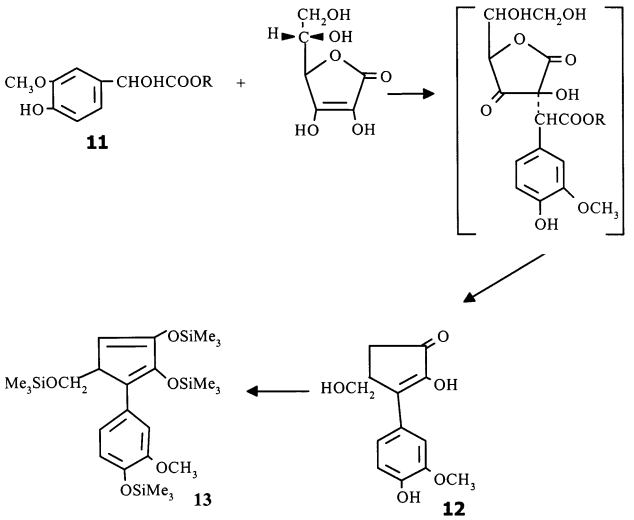
Compounds **4a** and **5b** contain the same indolyl γ-lactame backbone as alkaloid staurosporine (Scheme 4), [10].

The reaction of *N*-alkylindolylglycolic acids (**7**) with L-ascorbic acid in methanol–HCl solution unexpectedly led to 3-(1-alkylindolyl)-2-hydroxy-4-hydroxymethylcyclopent-2-en-ones (**9**, Scheme 5) in 30–40% yields. Bright fluorescence of cyclopentenone derivatives **9** in UV light helped to isolate these compounds by chromatography methods. Formation of the intermediate 2′-carboxyascorbigens (**8**) in this reaction is postulated.



R = methyl (a), allyl (b) or benzyl (c)

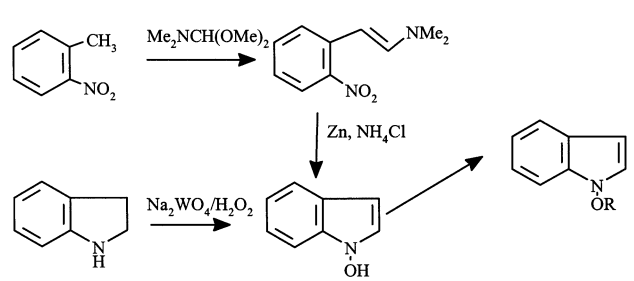
Scheme 5.



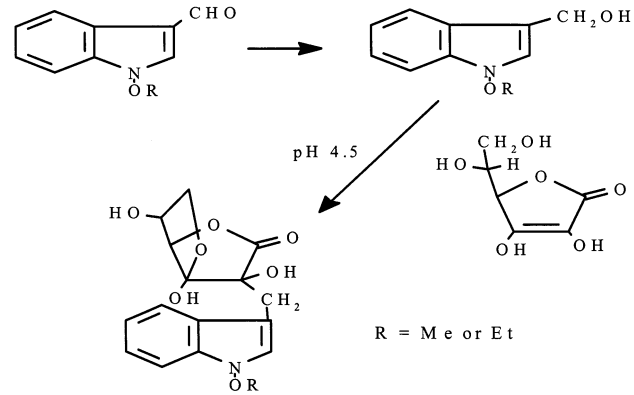
Scheme 6.

A similar reaction proceeds between L-ascorbic acid and vanilomandelic acid (**11**) in MeOH–HCl mixture on heating (Scheme 6), [11]. Vanilomandelic acid is a major metabolite of adrenaline. The structures of cyclopentenone derivatives **9a**–**c** and **12** were confirmed by NMR and HR mass spectrometry (HR-MS) methods and through transformations into reduced (**10**) or per-*O*-silylated (**13**) compounds.

Formation of cyclopentenone derivatives represents an example of a domino reaction, which is a process involving two or more bond-forming transformations (usually C–C bonds) taking place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step. Tandem reaction sequence, cascade reactions, or domino reactions, involve two or more consecutive reactions, each dependent on the formation of a reactive functionality in the preceding step [12,13]. In these reactions C-alkylation of ascorbic acid by the skatyl cation, which takes place in strong acids, is followed by the opening of the lactone ring in ascorbigen-type compounds, decarboxylation, dehydration, aldole-type cyclization of the pentenone cycle, and again decarboxylation, the presence of the carboxyl group in



Scheme 7.



Scheme 8.

the skatyl position facilitating cyclopentenone formation.

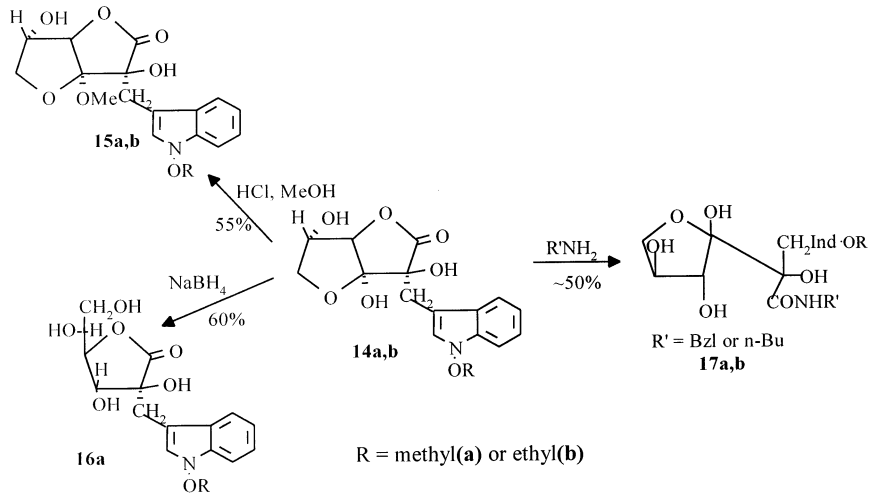
Among alkaloids isolated from plants of the cruciferous family indole glucosinolate alkaloids glucobrassicin and neoglucobrassicin (*N*-methoxyglucobrassicin) predominate; the first is a source of indole-3-carbinol and hence ascorbigen, and the latter is a source of 1-methoxyindole-3-carbinol and hence neoascorbigen (*N*-methoxyascorbigen). The level of neoascorbigen in cruciferous vegetables in most cases is lower than that of **Asc**, though there are vegetables in which the neoglucobrassicin level is higher than that of glucobrassicin [14]. We obtained the data presented in Table 1 by the HPLC method using synthetic neoascorbigen and ascorbigen as standards.

Neoascorbigen and its *N*-alkoxy homologues were prepared from *N*-hydroxyindole, which was obtained by the methods described in (Schemes 7 and 8) and Refs. [15–17], and their properties were compared with the properties of ascorbigen. Similarly to ascorbigen, *N*-methoxy- and *N*-ethoxyascorbigen form *O*-glycosides (**15a**,**b**), amides (**17a**,**b**), or were reduced by $NaBH_4$ to 2-C-[(1-methoxyindol-3-yl)methyl]-L-gulonic acid 1,4-lactone (**16a**) (Scheme 9). Stereochemistry of the 4-C centre of **16a** was confirmed by NOE differential NMR spectroscopy.

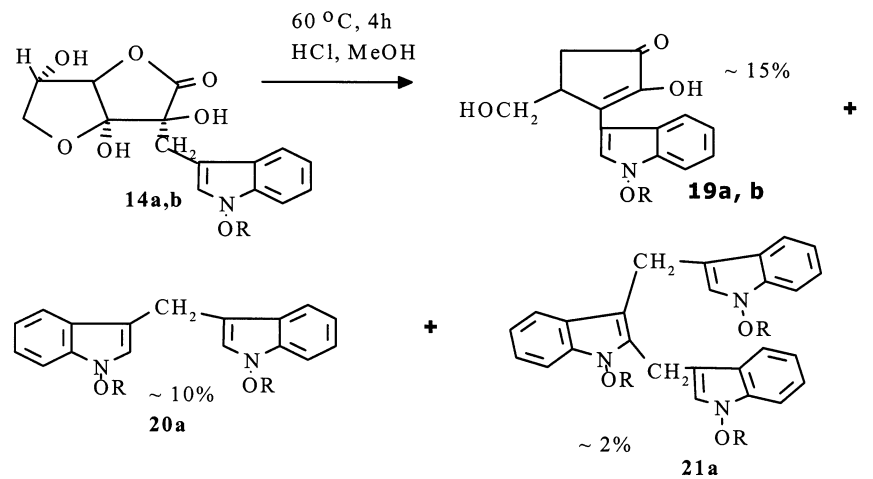
However, neoascorbigen and its ethoxy homologue are more stable in acidic conditions than **Asc** (Table 2). When heated in acidic media they produced 3-(1-alkoxyindolyl)-2-hydroxy-cyclopent-2-en-ones (**19a**,**b**) isolated in ~15% yields. The structures of compounds **19a**,**b** were confirmed by HR-MS and NMR spectroscopy methods. Additionally, small amounts of di(1-alkoxyindol-3-yl)methanes (**20**) and 2,3-di(1-alkoxy-

Table 1
Level of ascorbigen content in cohlrabi cabbage

Ascorbigen	22.30 mg/kg fresh weight
Neoascorbigen	3.50 mg/kg fresh weight



Scheme 9.



Scheme 10.

skatyl)indoles (**21**) were also isolated. The formation of ascorbigen 'dimers' (Table 1), 'trimers' or **ICZ** analogues, which are formed from ascorbigen at 37°C and pH 1 [2], was not observed in this case in mild or drastic acidic conditions (Scheme 10). It suggests that in *N*-alkoxyascorbigen derivatives the nucleophilic attack at the 2-C indole atom is hindered both by sterical hindrance and electronic effects, and the formation of cyclopentenone derivatives occurs even in the absence of carboxyl group.

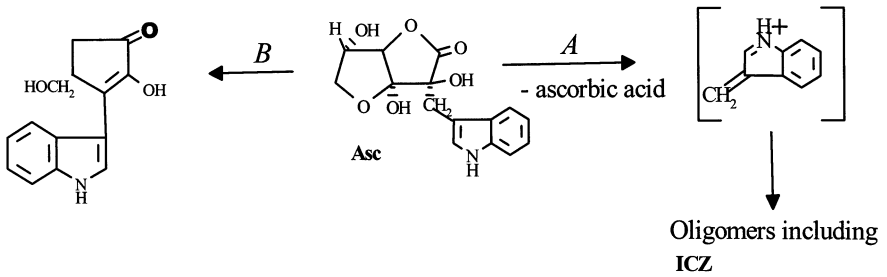
Neoascorbigen and its homologue are more stable in acidic conditions than **Asc**. In contrast with ascorbigen, neoascorbigen cannot be considered as a depot-form of L-ascorbic acid in biological conditions.

In general, ascorbigens in acidic media undergo multiple transformations. In relatively mild conditions (as in gastric juice) natural ascorbigen releases L-ascorbic acid gradually and forms first, ascorbigen 'dimer', skatyl cation being trapped by another molecule of ascorbigen, and then 'trimer' and 5*H*,11*H*-indolo[3,2-*b*]-carbazole (Scheme 11, pathway *A*). Simultaneously, formation of indole-3-carbinol oligomerization products, including **ICZ**, which do not contain ascorbic acid moiety, takes place, especially when the temperature is increased. The molecules of an ascorbigen which have not decomposed with the release of ascorbic acid through pathway *A* decarboxylate and dehydrate with the formation of cyclopentenone derivatives (pathway *B*).

Stability of ascorbigens in acids and decrease of nucleophilicity of the 2-C atom (due to the influence of *N*-substituents) lead to enhancement of cyclopentenone

Table 2
Stability of ascorbigens in acids (pH < 1, 37°C)

Comp.	After 3 h	After 3 days
Ascorbigen (**Ask**)	90%	15%
Neoascorbigen (**14a**)	~98%	85–90%



Scheme 11.

yields. However, we succeeded in the isolation of 3-(indol-3-yl)-2-hydroxy-5-hydroxymethylcyclopent-2-enone after fast reflux of unsubstituted ascorbigen in methanol–conc. HCl mixture in ~2% yield; again bright fluorescence of the compound helped to isolate and purify it by plate chromatography (Scheme 12).

Recent studies demonstrated that some aryl-containing pyrroles have important biological properties. For example, some 1,2-diarylpyrroles are selective inhibitors of cyclooxygenase-2 [18]. Investigating new types of diarylpyrrole derivatives is quite promising.

Pyrrolecarbinols are analogues of 3-indolecarbinols and this suggests that they can interact with ascorbic acid in mild conditions to produce pyrrole analogues of ascorbigen. We investigated derivatives of 1,2-diphenyl-4-acetylpyrrole (**22a**–**c**), obtained as described earlier [19–21], which were used as sources of the corresponding carbinols. Compounds **22a**–**c** were reduced by sodium borhydride in water or aqueous ethanol to the corresponding pyrrolylmethylcarbinols (**23a**–**c**), which were put in the condensation with excess of L-ascorbic acid in 80% aqueous ethanol solution to produce analogues of ascorbigen **24a**–**c** in 73–90% yields (Scheme 13).

As the carbinol group in **23a**–**c** is chiral, the compounds obtained each represented the mixture of two diastereomers, according to ^{1}H NMR spectra in every case, the ratio of diastereomers was approximately 3:2. In EI-MS for **24a**–**c**, the molecular ion peaks were observed. In ^{1}H NMR spectra of **24a**–**c**, all signals of major diastereomers, and in some cases of minor isomers, were identified (Table 3). As in the case of ascorbigen, nucleophilic attack of the carbinol fragment occurs from the side opposite to the ascorbic acid side chain, the 2-C atom in **24a**–**c** has *S*-configuration. Thus, compounds **24a**–**c** are substituted 2-C-[(1-phenyl-2-methyl-5-phenylpyrrol-3-yl)-1(*RS*)-ethyl]-α-L-xylo-3-hexulofuranosono-1,4-lactones.

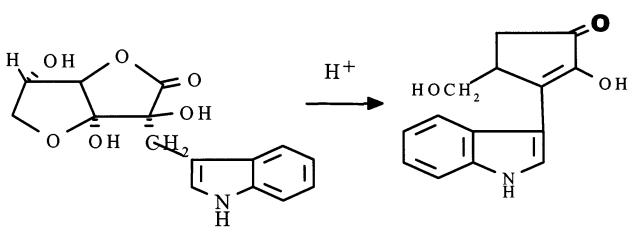
Similarly to ascorbigen [22], pyrrole ascorbigens undergo lactone opening and decarboxylation after stirring with triethylamine in aqueous alcohol solution for several days to give 1-deoxy-1-(pyrrol-3-yl)-L-sorbopyranose (**25**) and -L-tagatose (**26**) derivative mixtures (Scheme 14). The structures of the products obtained were confirmed by EI-MS. When **24a** was incubated with *n*-butylamine, the opening of the lactone ring led to butylamide of 2-C-((1-phenyl-2-methyl-5-phenylpyrrol-3-yl)-1-ethyl)-α-L-xylo-3-hexulo-furanosonic acid (**27**, Scheme 15), whose structure was confirmed by mass spectroscopy.

Thus, 2-C pyrrol derivatives of ascorbic acid are close to indole-containing ascorbigens by their properties and represent new examples of 2-C alkylated ascorbic acid derivatives.

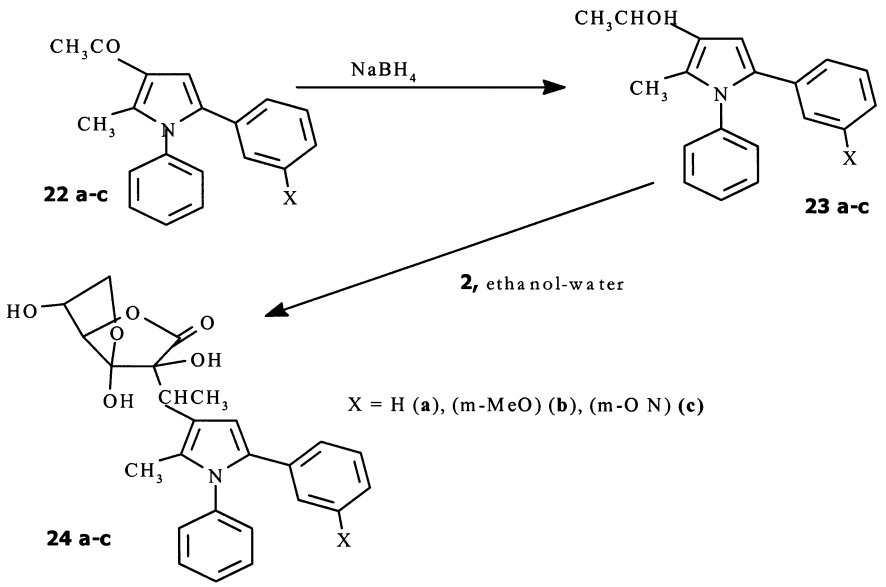
3-Hydroxymethylindole is highly capable of *ipso*-substitution at the C-3 and, in acids, it produces a mixture of indole-derived compounds including diindolylmethane, diskatylindole and indolocarbazole (oligomerization products) [23].

3-Formylindole is also capable of *ipso*-substitution at the C-3, suggesting that this compound can be used in the preparation of indolocarbazoles. In strong acids, 3-formylindole (**28**) forms urorosein (**29**, Scheme 16), [24], which is stable in a methanol solution in the presence of strong acids, e.g. H_2SO_4 or HCOOH (at pH < 1), even after several hours reflux. When dissolved in methanol or glacial acetic acid without addition of strong acids, it produces a mixture of indole-derived compounds (Scheme 17).

The products of the urorosein transformation were isolated by column and plate chromatography and identified using the NMR spectroscopy and mass spectrometry methods. 6-(1*H*-Indol-3-yl)-5*H*,7*H*-indolo[2,3-*b*]-carbazole (**30**) isolated in 43% yield was the major product. A bright orange salt of tri(indol-3-yl)-methylium (**31**), di(indol-3-yl)methane (**33**), colourless tri(indol-3-yl)methane (**34**), and 2,3-diskatylindole (**36**), fluorescent 5*H*,11*H*-indolo[3,2-*b*]carbazole (**37**)



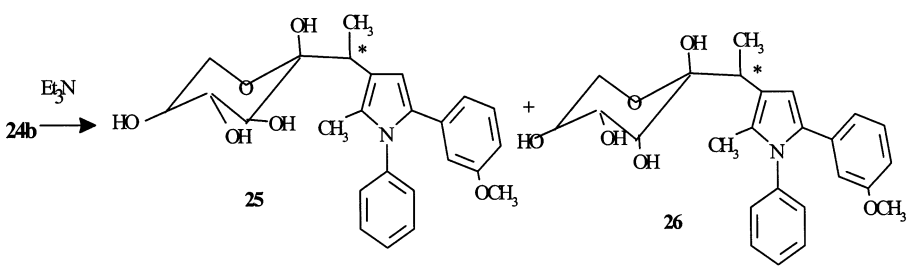
Scheme 12.



Scheme 13.

Table 3
^{1}H NMR spectra of **24 a–c** (carbohydrate moieties of major isomers)

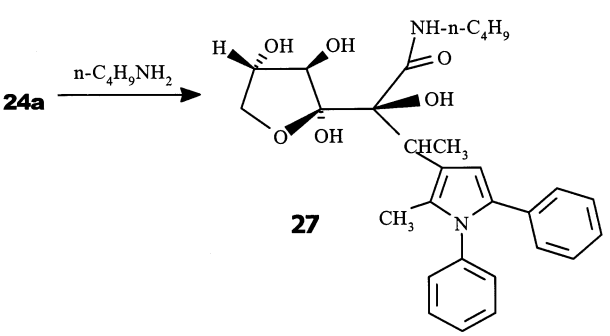
	H-4	H-5	H-6a	H-6e	CH′	CH'_3	Me″	H″
24a	3.70d	4.13ddd	4.18dd	4.00dd	4.49q	1.51d	2.09s	6.34s
*	$J_{4,5} = 0.7$	$J_{5,6a} = 5.8$	$J_{6a,e} = 9.7$	$J_{5,6e} = 3.3$	$J_{CH-CH_3} = 6.2$			
24b	3.77bs	4.15m	4.51dd	4.20dd	3.41q	1.55d	2.09s	6.46s
**					$J_{CH-CH_3} = 7.5$			
24c	3.77bs	4.12m	4.48dd	4.16dd	3.37q	1.53d	2.05s	6.33s
*					$J_{CH-CH_3} = 7.1$			



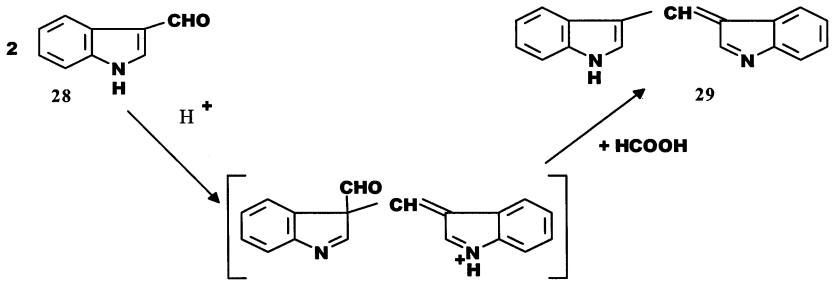
Scheme 14.

and its derivative **38** were obtained in 11, 13, 3, 1, ~2 and 1% yields, respectively. The presence of the unsubstituted indole **35** (8%) was shown by TLC and HPLC methods. The comparison of ^{1}H NMR spectra of all the compounds isolated with the ^{1}H NMR spectrum of the authentic sample of didehydroindolo[3,2-*b*]-carbazole (**32**) [25] showed that the latter is not formed in the reaction of urorosein degradation. The structure of indolyl-indolocarbazole (**30**) was confirmed by NMR methods (Scheme 18).

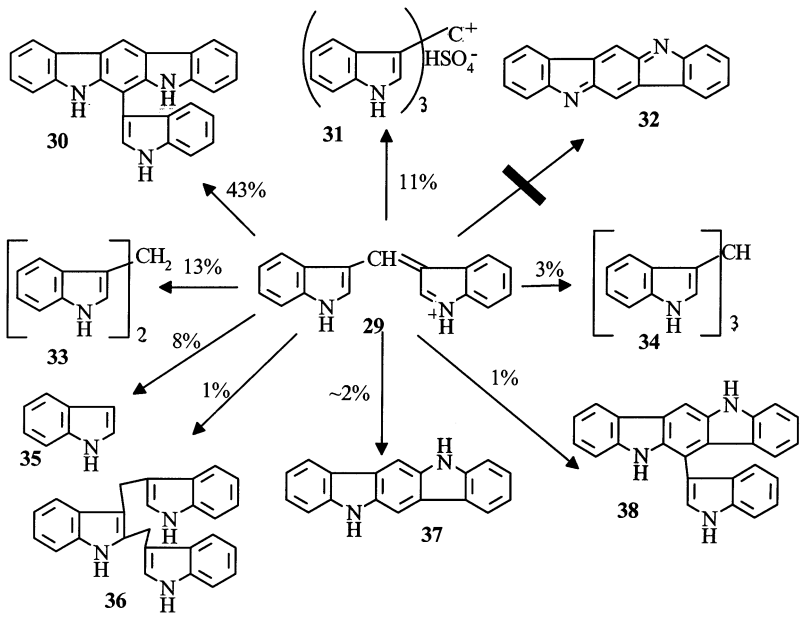
In a similar fashion, 1-methyl-3-formylindole (**39**) was transformed into *N*,*N*′-dimethylurorosein (**40**) by



Scheme 15.



Scheme 16.



Scheme 17.

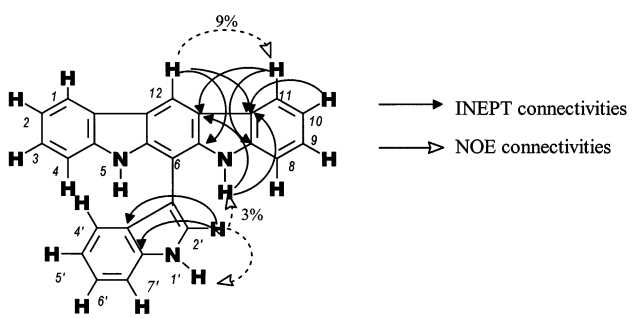
heating in diluted sulfuric acid (Scheme 19). Compound **40** is more stable in solution than **29** and only degrades after heating in a methanol solution at 50–60°C for several hours. The main product of the degradation of **40** is a salt of tri(1-methylindol-3-yl)methylium (**41**, 30% yield). 5*N*,11*N*-Dimethyl-6-(1-methylindol-3-yl)indolo[3,2-*b*]carbazole (**42**) and 5*N*,11*N*-dimethylindolo-[3,2-*b*]carbazole (**43**) were isolated in 26 and 14% yields, respectively.

The structure of **43** was confirmed by comparison with the authentic sample of 5*N*,11*N*-dimethylindolo-[3,2-*b*]carbazole obtained by the method described in Ref. [25]; the structure of **42** was elucidated by NMR (Scheme 20) and HR-MS methods.

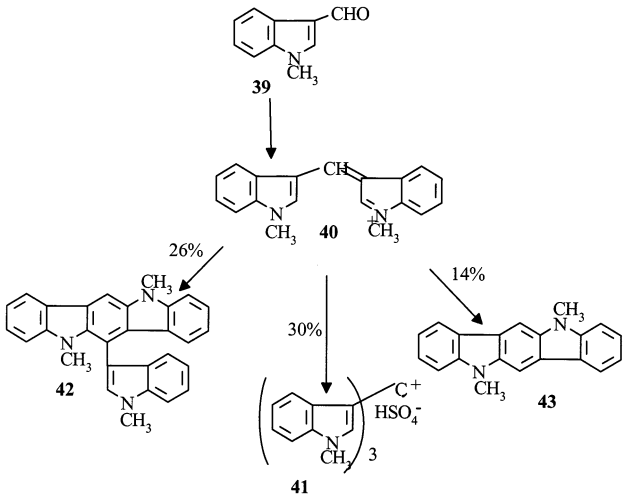
It should be noted that, whereas in the transformations of urorosein a derivative of indolo[2,3-*b*]carbazole (**30**) is formed, only indolo[3,2-*b*]carbazole derivatives **42** and **43** were isolated out of the products of *N*,*N*′-dimethylurorosein transformation.

The mixture of indole derivatives similar to that obtained from urorosein salt **29** by heating in methanolic or acetic acid solutions, was also obtained from 3-formylindoles (**28**) by heating in methanol–conc. sulfuric acid solutions. Urorosein may also form as an intermediate in this reaction, but further transformations in this case proceed through its interactions with 3-formylindole or its degradation products.

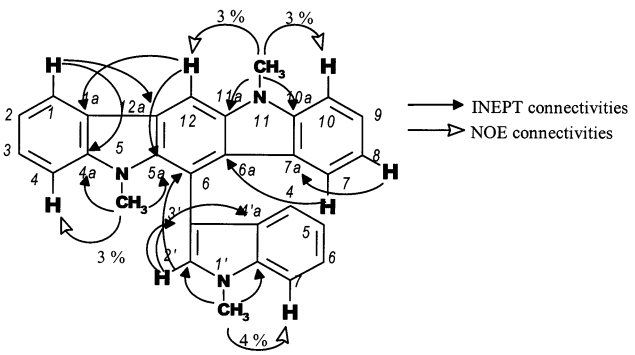
Recently, it was shown that substituted benzaldehydes in the presence of superacids (e.g. CF_3SO_3H) reacted with benzene to give unsubstituted triphenylmethane as the initial intermediate, followed by dispro-



Scheme 18.



Scheme 19.



Scheme 20.

portionation to afford a mixture of diphenylmethane and triphenylmethanol as major final products. This reaction involves transalkylation as a key step (disruption of [aromatic-C]–[formyl-C] bond) [26,27]. Formation of the benzyl cation, which is a source of 1,2-dibenzylbenzene and dihydroanthracene was suggested, as well as of the diphenylmethyl cation and triphenylmethyl cation. Dihydroanthracene after hydride transfer afforded anthracene, diphenyl- and triphenylmethyl cations being acceptors of hydride ions.

For 3-formylindole, which is a derivative of the π-electron-excessive heterocycle, as well as for urorosein, which can be considered as an analogue of the diphenylmethyl cation, the transalkylation proceeds in milder conditions and does not need superacids; in addition, the salt of the trindolylmethylium cation is stable and can be isolated. It is plausible that 5*H*,11*H*-indolo[3,2-*b*]carbazole is formed with the participation of skatyl cation and indole through the intermediate 6,10-dihydro-5*H*,11*H*-indolo[3,2-*b*]carbazole. It is interesting that addition of strong acids stabilises urorosein salt and prevents its recombination, while 3-formylindole undergoes these recombination reactions in strong acids [25,26].

Study on ascorbigens contributes to our understanding of the chemistry and biological role in vivo of L-ascorbic acid and particularly its important 2-C-alkylated derivatives and their relations with the chemistry and biology of indolocarbazoles. Reactions of polyfunctional indolecarbinols and also of pyrrolecarbinols with L-ascorbic acid demonstrate new synthetic approaches based on ascorbic acid derivatization. 3-Formylindoles and uroroseins represent a new and quite available source of indolocarbazole derivatives.

References

[1] R. McDanell, A. McLean, A.B. Hanley, R.K. Heaney, G.R. Fenwick, Chemical and biological properties of indole glucosinolates (glucobrassicins), Food Chem. Toxic. 26 (1988) 59–76.

[2] M. Preobrazhenskaya, V. Bukhman, A. Korolev, S. Efimov, Ascorbigen and other indole derived compounds from Brassica vegetables and their analogues as anticarcinogenic and immunomodulating agents, Pharm. Ther. 60 (1993) 301–313.

[3] P.H. Jellinck, P.G. Forkert, D.S. Riddick, A.B. Okey, J.J. Michnovicz, H.L. Bradlow, Ah receptor binding properties of indole carbinols and induction of hepatic estradiol hydroxylation, Biochem. Pharmacol. 45 (1993) 1129–1136.

[4] L.F. Bjeldanes, J.-Y. Kim, K. Grose, J.C. Bartholomew, Ch.A. Bradfield, Aromatic hydrocarbon responsiveness-receptor agonists generated from indole-3-carbinol in vitro and in vivo: comparison with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, Proc. Natl. Acad. Sci. USA 88 (1991) 9543–9547.

[5] P. Fernandez-Salguero, T. Pineau, D.M. Hilbert, T. McPhail, S.S.T. Lee, S. Kimura, D.W. Nebert, S. Rudikoff, J.M. Ward, F.J. Gonzalez, Immune system impairment and hepatic fibrosis in mice lacking the dioxin-binding Ah receptor, Science 268 (1995) 722–729.

[6] (a) M.N. Preobrazhenskaya, A.M. Korolev, N.I. Isaeva, E.I. Lazhko, L.I. Lomidze, Polyfunctional indole-3-carbinol derivatives: 1-(indol-3-yl)glycerols and related compounds, β-hydroxytryptamines and ascorbigens. Chemistry and biological properties. Farmaco 50 (1995) 369–377. (b) M.N. Preobrazhenskaya, E.I. Lazhko, A.M. Korolev, Reaction of (indol-3-yl)ethanediol with L-ascorbic acid, Tetrahedron Asym. 7 (1996) 641–644.

[7] M.N. Preobrazhenskaya, I.I. Rozhkov, E.I. Lazhko, A.M. Korolev, Interaction of L-ascorbic acid with DL-*N*-methyl-β-hydroxytryptamine, Tetrahedron Lett. 39 (1998) 109–112.

[8] A.M. Korolev, E.I. Lazhko, I.V. Yartseva, I.L. Plykhtyak, L.G. Alexandrova, B.V. Rosynov, M.N. Preobrazhenskaya, The transformation of ascorbigen in acidic media: structure of ascorbigen B, Sov. J. Bioorg. Chem. 17 (1991) 548–555.

[9] A. Poss, R. Belter, Vitamin C in organic synthesis: C-2 methylation, Tetrahedron Asym. 4 (1993) 169–172.

[10] S.W. Yang, G.A. Cordell, Biosynthesis of staurosporine; incorporation of glucose, J. Nat. Prod. 59 (1996) 828–833.

[11] M.N. Preobrazhenskaya, I.I. Rozhkov, E.I. Lazhko, L.N. Yudina, M. Korolev, Reaction of vanilmandelic acid and 4-hydroxybenzyl alcohol derivatives with L-ascorbic acid, Tetrahedron 53 (1997) 6971–6976.

[12] T. Hudlicky, Design constraints in practical syntheses of complex molecules: current status, case studies with carbohydrates and alkaloids and future perspectives, Chem. Rev. 96 (1996) 3–114.

[13] L. Teitze, Domino reaction in organic synthesis, Chem. Rev. 96 (1996) 115–130.

[14] K. Sones, R.K. Heaney, G.R. Fenwick, An estimate of the mean daily intake of glucosinolates from cruciferous vegetables in the UK, J. Sci. Food Agric. 35 (1984) 712–720.
[15] S. Kawasaki, M. Somei, The first total synthesis of 9-omecarbazole-3-carboxaldehyde and methoxybrassinin, Heterocycles 31 (1990) 1605–1608.
[16] M. Somei, K. Ohnishi, Total synthesis of (±) panicalidine B, Chem. Pharm. Bull. 33 (1985) 5147.
[17] V.I. Mukhanov, M.M. Kagansky, A.A. Sorokin, C.G. Antonian, G.V. Tananova, L.I. Mikhailevskaya, A.S. Kinsirski, M.N. Preobrazhenskaya, Synthesis and studying of neoascorbigen and its analogues, Khim. Pharm. Zhur. (in Russian) 28 (1994) 6–10.
[18] I.K. Khanna, R.M. Weier, Y. Yu, P.W. Collins, J.M. Miyashiro, C.M. Koboldt, A.W. Veenhuizen, 1,2-Diarylpyrroles as inhibitors of cyclooxygenase-2, J. Med. Chem. 40 (1997) 1619–1633.
[19] J.S. Aggarwal, A.U. Qureshi, J.N. Ray, Studies in chemotherapy: attempts to find antimalarials. II. Pyrrylindoles, J. Am. Chem. Soc. 54 (1932) 3988–3992.
[20] G. Cirrincione, G. Dattolo, A.M. Almerico, G. Presti, E. Aiello, Polycondensed nitrogen heterocycles. Part 20. Reactivity of diazotized 1-(2-aminophenyl)-pyrroles. Pyrrolo[1,2-*f*]phenanthridines, Heterocycles 24 (1986) 3403–3408.
[21] A.M. Almerico, G. Cirrincione, G. Dattolo, E. Aiello, F. Mingoia, Polycondensed nitrogen heterocycles. Part 25. Aminopyrrolo[1,2-*f*] phenanthridines by decomposition of 2-(3-azidophenyl)-1-arylpyrroles, J. Heterocycl. Chem. 31 (1994) 193–198.
[22] M.N. Preobrazhenskaya, E.I. Lazhko, A.M. Korolev, M.I. Reznikova, I.I. Rozhkov, Transformation of ascorbigen into 1-deoxy-2-(indol-3-yl)-α-L-sorbopyranose and 1-deoxy-2-(indol-3-yl)-α-L-tagatopyranose, Tetrahedron Asym. 7 (1996) 461–466.
[23] K.R. Grose, L.F. Bjeldanes, Oligomerization of indole-3-carbinol in aqueous acid, Chem. Res. Toxic. 5 (1992) 188–193.
[24] W.R. Fearon, W.A. Boggust, Pigments derived from tryptophan: (1) Urorosein, (2) Tryptochrome, Biochem. J. 46 (1950) 62–67.
[25] S. Hűnig, H.-C. Steinmetzer, Kondensierte Stickstoffheterocyclen, Liebigs Ann. Chem. (1976) 1090–1102.
[26] S. Saito, T. Ohwada, K. Shudo, Friedel-Crafts-tape reaction of benzaldehyde with benzene. Diprotonated benzaldehyde as the reactive intermediate, J. Am. Chem. Soc. 117 (1995) 11081–11084.
[27] S. Saito, T. Ohwada, K. Shudo, Superacid-catalyzed reaction of substituted benzaldehydes with benzene, J. Org. Chem. 61 (1996) 8089–8093.