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Reaction of (indol-3-yl)ethanediol with L-ascorbic acid

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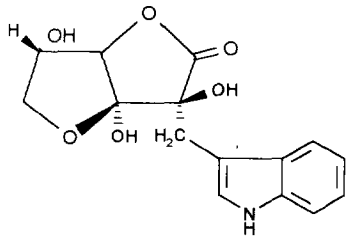
Abstract. Interaction of (indol-3-yl)ethane-1,2-diol with L-ascorbic acid under mild conditions yielded a mixture of products of the L-ascorbic acid 2-C alkylation with the substituted skatyl cation stabilized by the 3-CO hemiketal formation with the participation of the $HOCH_2$ moiety of (indol-3-yl)ethane-1,2-diol. Under the action of ethanolic HCl, tricyclic ketals were formed. The stereochemical configuration of the compounds was determined by NMR methods.

The recent interest to ascorbigen, 2-C-(indol-3-yl)methyl-α-L-xylo-3-hexulofuranosonic acid γ-lactone **1**, which forms in cabbage from 3-hydroxymethylindole and L-ascorbic acid **2**, is connected with the demonstrated anticarcinogenic properties of a diet rich in cabbage or other vegetables of the cruciferous family[1]. The interaction of polyfunctional indolecarbinols with **2** has not been investigated though some of these compounds [e.g. (indol-3-yl)glycerol phosphate which is a precursor of tryptophane biosynthesis[2]] are of great biological importance.



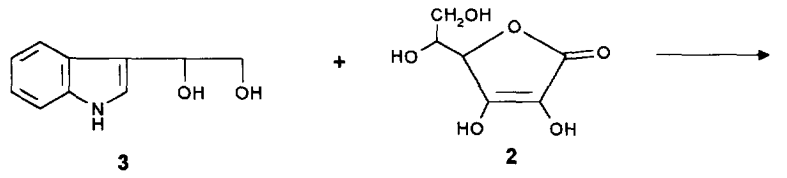
1

(Indol-3-yl)ethanediol **3**[3] and **2** in aqueous ethanol at room temperature give a mixture of compounds **4, 5,** and **6.** Preparative TLC of the mixture[4] led to a single **4**[5] and a mixture of **5** and **6**[6]. Attempts to separate **5** and **6** were unsuccessful: the individual compounds **5** or **6**, isolated after TLC, appeared to be mixtures of these compounds, thus suggesting **5** and **6** to be in equilibrium.

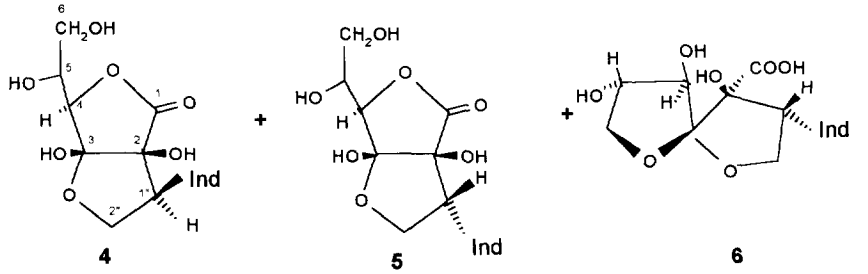
The structure elucidation of the compounds **4, 5,** and **6** was based on the ^1H and ^{13}C NMR data (Tables 1, 2). Signal assignments were accomplished as follows: 1''-H proton was identified by irradiation of 2'-H proton (long-range $^4J_{H,H}$ was present) and then 2''-H_a and 2''-H_b were determined through COSY connectivity; signals in the indole part were assigned as described before[7]. In the ascorbic acid moiety, 6-CH_2 protons were defined from APT and HETCOR experiments; DFCOSY permitted identification of the 5-H and 4-H signals. The $J_{4,5}$ values, which are above 2 Hz, close chemical shifts of the 6-H_a and 6-H_b protons and similar $J_{5,6a}$ and $J_{5,6b}$ values in NMR spectra of **4** and **5** show that the CH_2OH group of the ascorbic acid moiety does not participate in the hemiketal formation as it would if **4** or **5** had the ascorbigen-like skeleton. As in ^{13}C NMR spectra of **1, 4** and **5** chemical shifts of 3-C atoms are similar, **4** and **5** should be hemiketals. It demonstrates that in **4** and **5** 2-C-substituted L-ascorbic acid is stabilized by the hemiketal formation with the participation of the CH_2OH group neighboring to the skatyl carbon atom (1''). These compounds represent a new type of L-ascorbic acid derivatives.

The NMR spectra of compound **6** show that the lactone ring is opened and the 4-C-OH group is unsubstituted whereas a full ketal structure is present. It suggests that **6** is a product of hydrolysis of compound **5** accompanied by the cyclic ketal formation.

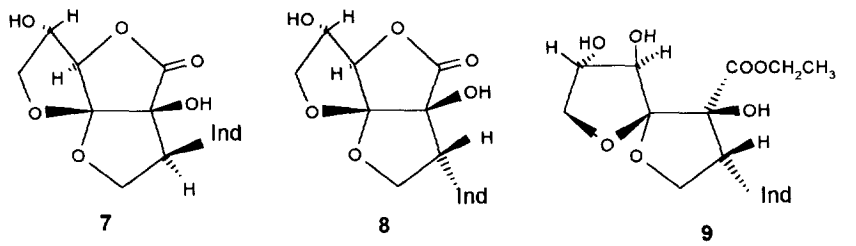
The mixture of **4, 5** and **6** was transformed into a mixture of ketal derivatives **7, 8** and **9** by the incubation in 2% ethanolic HCl solution at room temperature. Similarly, **4** gave individual **7**[8], and the mixture of **5** and **6** gave a mixture of **8** and **9.** Compounds **8** and **9** were separated by TLC[9-11].



3 **2**



4 **5** **6**



7 **8** **9**

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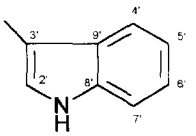

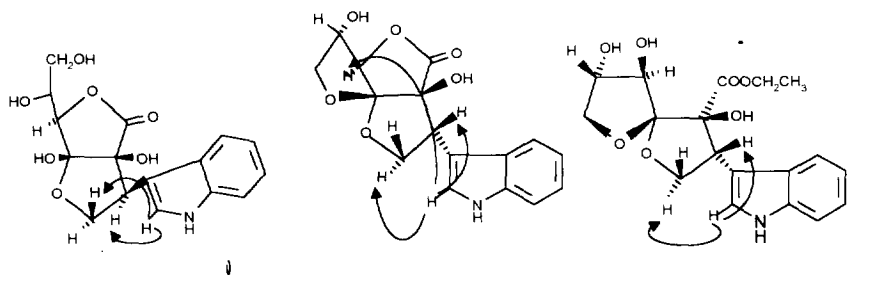

4 **8** **9**

NOE effects

Table 1. ^{1}H NMR spectra of compounds **1** and **4-9** in CD_3OD[12]

	Chemical shifts (coupling constants, Hz)											
	Ascorbic acid moiety				Indole moiety*					-CH-CH_2O		
Com-pound	4-H ($J_{4,5}$)	5-H ($J_{5,6a}$)	6-H_a ($J_{6a,6b}$)	6-H_b ($J_{5,6b}$)	2'-H ($J_{1'',2'}$)	4'-H	5'-H	6'-H	7'-H	1''-H ($J_{1'',2''b}$)	2''-H_a ($J_{1'',2''a}$)	2''-H_b ($J_{2''a,2''b}$)
1	3.76	4.20	3.99	4.12	7.20	7.62	6.97	7.03	7.31	3.23	-	-
	(0.7)	(3.3)	(9.7)	(5.7)						3.40		
4	4.66	4.07	3.70	3.64	7.30	7.77	7.02	7.10	7.35	4.11	4.40	4.31
	(2.5)	(6.7)	(11.0)	(6.7)	(0.6)					(7.8)	(10.0)	(8.5)
5	4.59	4.04	3.64	3.59	7.17	7.75	7.00	7.09	7.33	4.15	4.49	4.16
	(2.3)	(6.9)	(11.0)	(6.6)	(0.7)					(7.8)	(10.0)	
6	4.45	4.14	4.09	3.60	7.24	7.63	7.03	7.11	7.36	4.48	4.76	4.43
	(4.4)	(5.9)	(9.0)	(4.7)	(0.5)					(4.5)	(7.4)	(8.2)
7	4.61	4.31	4.10	3.96	7,32	7,58	7,01	7.10	7.36	4.15	4.45	4.35
	(2.2)	(3.7)	10.0)	(4.9)	(0.5)					(7.4)	(11.3)	(8.0)
8	4.52	4.19	4.06	4.01	7.31	7.68	7.02	7.12	7.34	3.94	4.71	4.36
	(2.2)	(3.6)	(10)	(4.9)	(0.8)					(3.1)	(5.6)	(8.8)
9**	4.42	4.29	4.10	3.52	7.08	7.76	6.99	7.08	7.30	4.27	4.70	4.42
	(7.2)	(7.3)	(8.7)	(6.9)	(1.0)					(8.5)	(11.5)	(7.3)

* In all the compounds investigated the coupling constants of the indole ring protons were the following: $J_{4',5'}$= 8.0, $J_{4',6'}$= 1.0, $J_{4',7'}$= 1.0; $J_{5',6'}$=7.1; $J_{5',7'}$=1.0; $J_{6',7'}$=8.1 Hz.

** Signals of the $OCOOC_2H_5$ group are present at 4.07 and 1.12 ppm.

Table 2. ^{13}C NMR spectra of compounds **1** and **4-9** in CD_3OD

Com-	Ascorbic acid moiety						-CH-CH_2O-	
pound	1-C	2-C	3-C	4-C	5-C	6-C	1"-C	2"-C
1	178.74	80.92	108.68	88.32	75.51	75.51	31.32	-
4	178.74	80.76	108.70	84.91	71.13	63.06	46.00	73.31
5	178.61	80.62	111.74	84.74	71.13	62.95	47.21	71.24
6	176.27	83.53	110.30	78.27	77.06	71.87	40.13	73.76
7	175.89	85.85	119.88	90.42	75.19	75.00	46.98	75.00
8	174.85	85.85	118.69	89.80	75.35	74.80	42.48	75.48
9*	172.72	86.88	115.51	78.89	75.35	71.75	46.53	71.52
	Indole ring							
	2'-C	3'-C	4'-C	5'-C	6'-C	7'-C	8'-C	9'-C
1	126.59	107.50	119.99	119.73	122.25	112.04	125.15	135.74
4	125.72	108.60	120.34	119.88	122.46	112.13	137.96	129.26
5	124.89	108.09	119.72	120.43	122.56	112.36	138.13	129.05
6	123.59	105.44	120.02	120.44	122.45	112.08	137.35	128.59
7	125.48	112.20	119.94	119.89	122.49	112.20	137.79	129.08
8	123.46	111.51	120.20	120.01	122.82	112.19	137.90	128.33
9*	123.10	109.83	120.77	119.76	122.53	112.61	137.79	129.23

*Signals of OC_2H_5 group were observed at 62.60 and 14.21 ppm.

The $J_{4,5}$, $J_{5,6a}$ and $J_{5,6b}$ values and chemical shifts of the 3-C and 6-C atoms in ^{13}C NMR spectra of **7** and **8** show the presence of a second furanose cycle formed with the participation of the ascorbic acid's 6-CH_2OH

group. ^1H NMR and ^{13}C NMR spectra of **9** demonstrate the presence of the $COOC_2H_5$ group and the unsubstituted 4-OH group.

To determine the configuration at the skatyl atom 1'', NOE difference experiments were performed for compounds **4** and **8** under saturation of the 2'-H indole proton signal. An increase in the intensity of the 4-H (9%), 2''-H_b (1%) and 1''-H (2%) signals was observed for compound **8**, while in compound **4** irradiation of the 2'-H proton only led to an increase in the 2''-H_a (4%) and 1''-H (2%) signals intensity. It demonstrates that in compound **8** and, therefore, **5** the indole moiety is in the *endo* position (1''-S configuration) whereas in compound **4** and, therefore, **7** it is in the *exo* position (1''-R configuration). Opening of the lactone ring in compound **9** enables a less rigid conformation for this compound, 4-H and 2'-H protons being more distant than in **8**. This was confirmed by irradiation of the 2'-H signal, which only led to an increase in intensity of the 1''-H (2%) and 2''-H_b (0.5%) signals (but not of 4-H). Easy equilibration of **5** and **6** suggests the 1''-S configuration of **6** and, therefore, **9**. The instability of **5** can be due to the sterical hindrance displayed by the indole ring in the *endo* position.

REFERENCES AND NOTES

1. Preobrazhenskaya, M. N., Bukhman, V. M., Korolev, A. M., Efimov, S. A. *Pharmacology and Therapeutics.* **1994**, *60*, 301.
2. Spande T.F. *Hydroxyindoles, Indole Alcohols and Indolethiols.* in *Indoles* . Part III. Houlihan, N.J.; Ed.; John Wiley & Sons: New York-Toronto, **1970,** p. 170.
3. Preobrazhenskaya, M. N., Zhirnova, K. G.,.Kostyuchenko, N. P., Suvorov, N.N. *Zhurn. Org. Khim.* **1972,** *8*, 994.
4. For preparative and analytical TLC plates, covered with silica gel F_{254} (Merck) were used in a $CHCl_3$-MeOH 7:1 mixture. **4**: R_f 0.19; **5+6** R_f 0.23. Separation yielded 38% of **4** and 25% of **5+6**. HPLC: 6.38 (**4**), 7.77 and 9.68 min (**5+6**) (Spectra-Physics SP-800 instrument, Partisil ODS column, acetonitrile - 0.05M NaH_2PO_4 (pH 3.35), gradient from 13 to 60% of acetonitrile, 25 min.
5. Compound **4**. Anal. Calcd for $C_{16}H_{17}NO_7$: C 57.31; H 5.11; N 4.17. Found C 57.23; H 5.23; N 4.06. IR: 1790 cm^{-1}. $[\alpha]^{20}_D$ -14.6 (*c* 1, EtOH).
6. Mixture **5+6**. Anal. Calcd for $C_{16}H_{17}NO_7$: C 57.31; H 5.11; N 4.17. Found C 57.53; H 5.23; N 4.40. IR: 1790, 1620 cm^{-1}.
7. Lazhko, E. I., Korolev, A. M., Preobrazhenskaya, M. N. *Khim. Geterocycl. Soedin.* **1993,** 352.
8. Compound **7.** IR: 1790 cm^{-1}. $[\alpha]^{20}_D$ +7.2 (*c* 1, EtOH). EI-Ms [m/z(relative intensity, %)]: 317 (8) $[M]^+$, 170 (51) $[M - C_2H_7O]^+$, 143 (23) [Indolyl-CH-CH_2]$^+$, 130 (100) $[C_9H_8N]^+$. R_f 0.65 in a $CHCl_3$ - MeOH 4:1 mixture.
9. Compound **8.** IR: 1790 cm^{-1}. $[\alpha]^{20}_D$ +35.7 (*c* 1, EtOH). EI-Ms [m/z(relative intensity, %)]: 317 (5) $[M]^+$, 171 (5) $[M-C_2H_6O]^+$, 170 (42) $[M-C_2H_7O]^+$, 143 (27) [Indolyl-CH-CH_2]$^+$, 130 (100) $[C_9H_8N]^+$. R_f 0.60 in a $CHCl_3$ - MeOH 4:1 mixture.
10. Compound **9.** IR: 1720, 1770 cm^{-1}. $[\alpha]^{20}_D$ +34.4 (*c* 1, EtOH). EI-Ms [m/z(relative intensity, %)]: 363 (31) $[M]^+$, 143 (100) [Indolyl-CH-CH_2]$^+$, 130 (70) $[C_9H_8N]^+$. R_f 0.70 in a $CHCl_3$ - MeOH 4:1 mixture.
11. Optical rotations were measured on a Perkin-Elmer 241 instrument, IR (in KBr pellets) on a SP-1100 spectrometer (Pye Unicam), EI-mass-spectra were obtained on an SSQ 710 Finnegan instrument at 70 eV.
12. All NMR data were obtained with a Varian VXR-400 instrument operated at 400 MHz for ^1H and at 100.6 MHz for ^{13}C, chemical shifts are given in ppm relative to the signal of the solvent (CD_3OD) used (δ 3.32, 49.00 ppm).

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