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A New Method for the Preparation of 6-Deoxy-6-Halogen Ascorbic Acid Derivatives

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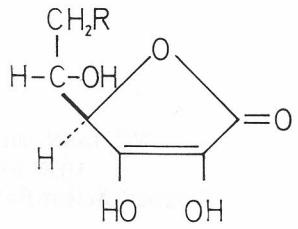
Treatment of ascorbic acid (III) with hydrogen chloride in acetic anhydride or with triphenylphosphine-N-chloro succinimide in dimethylformamide gave 6-deoxy-6-chloro ascorbic acid (Ia). It was found that ascorbic acid with triphenylphosphine — carbontetrahalide (halide = chloride, bromide, and iodide) in pyridine or dimethylformamide gave corresponding 6-deoxy-6-halogen ascorbic acid derivatives.

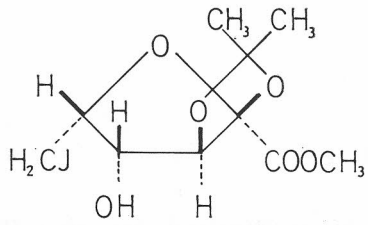
Ascorbic acid (**III**) and its derivatives have shown interesting properties as mediators in the process of heterogeneous catalytic hydrogenation of egzocyclic double bonds. Of special interest were the 6-deoxy-6-halogen derivatives (**I**), particularly the 6-iodo derivative (Ic). Thus, hydrogenation of 11a--chloro-6-demethyl-6-deoxy-6-methylene-5-hydroxytetracycline in the presence of 5% Rh/C and ascorbic acid gave the β-isomer of 6-deoxy-5-hydroxytetracycline, while in the presence of 6-deoxy-6-iodo ascorbic acid a mixture of the α and β-isomers was formed in the ratio of 1 : 1.

Chloro and bromo derivatives of ascorbic acid could be prepared by treating ascorbic acid with the corresponding halogen acid in formic acid[1]. The obtained 6-chloro (bromo)-5-formyloxy intermediates hydrolyzed readily to the corresponding 6-chloro (bromo)-6-deoxy ascorbic acid. The use of acetic acid instead of formic acid as solvent in the case of bromo derivative, gave higher yield on the corresponding 6-bromo derivative[2]. The iodo derivative could not be prepared by this route, and has been prepared via 6-deoxy-6--iodo-2,3-(1-methylethylidene)-**L**-lyxo-2-hexulofuranosonic acid methyl ester (**II**) in several steps, but the yield reported was low (cca 5%)[1]. That was the reason for looking for a more suitable and general method for the preparation of 6-deoxy-6-halogen ascorbic acid.

The substitution of formic by acetic acid as solvent in the preparation of 6-deoxy-6-bromo ascorbic acid stimulated us to use acetic acid also in the reaction of ascorbic acid with hydrogen chloride. Since the solubility of hydrogen chloride is higher in acetic anhydride (cca 700 g/L, at O °C) than in acetic acid (cca 200 g/L, at 0 °C), a saturated solution of hydrogen chloride in acetic anhydride was used in the reaction with ascorbic acid (**III**). After four hours, the 5,6-di-O-acetyl derivative (**IV**) was detected in the reaction. After twenty four hours, the 6-deoxy-6-chloro-5-O-acetyl derivative (**V**) was



I



II

Ia, R = Cl
b, R = Br
c, R = J

formed, which readily hydrolyzed to 6-deoxy-6-chloro ascorbic acid by adding water or by column chromatography on silica gel (Scheme 1).

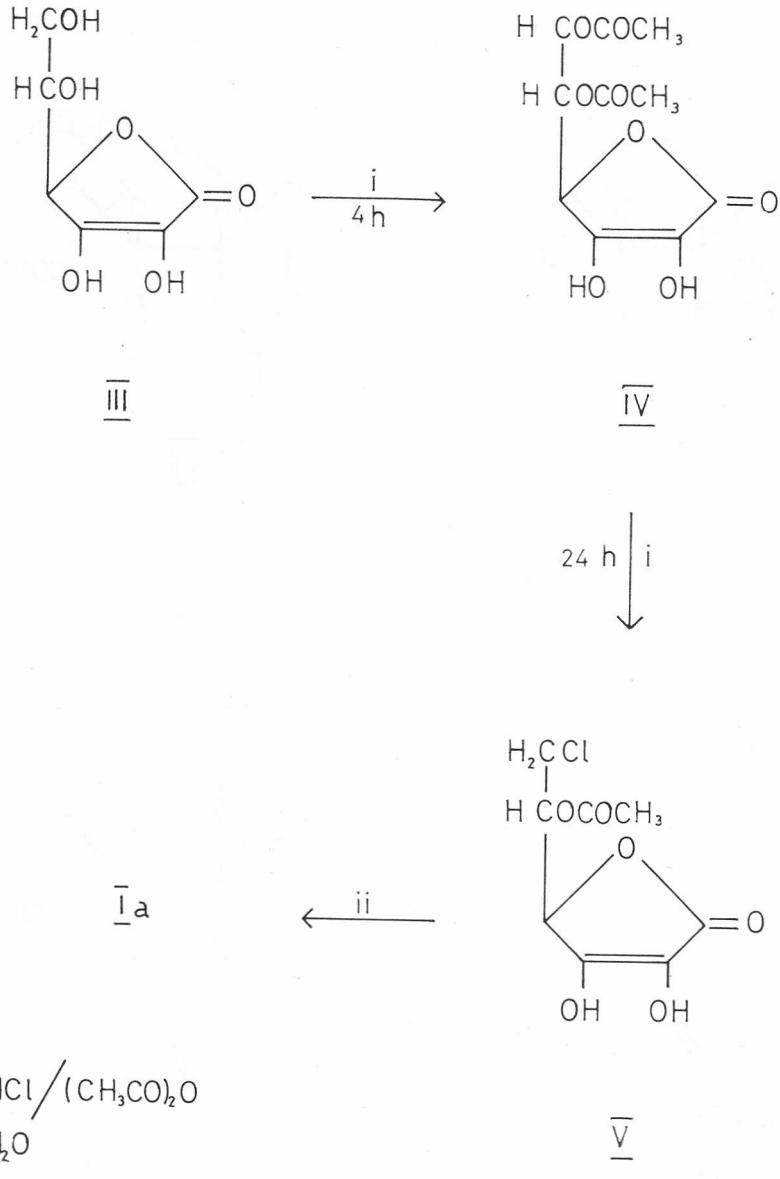
In the preparation of the 6-chloro derivative Hanessian's reagent[3] was also used, reported for the one step substitution of primary hydroxyl groups by halogen. However, the experiments with *N*-chloro-succinimide showed that the reagent is not selective, since (**Ia**) was obtained in a low yield (cca 18%). Application of a similar chlorinating reagent, like chloramine T, did not give better results.

In an attempt to obtain the 6-iodo derivative (**Ic**) in an indirect way i. e. via 6-deoxy-6-iodo-4-(S-methyl)-thiocarbonate (**VIII**), methyl-2,3-O-(1-methyl-ethylidene)-L-lyxo-2-hexulofuranosonic acid (**VI**) was prepared, which with diimidazoylthioketone gave thioketal **VII**. Further addition of methyl iodide gave **VIII**, but selective hydrolysis of **VIII** under basic conditions did not afford II, (Scheme 2).

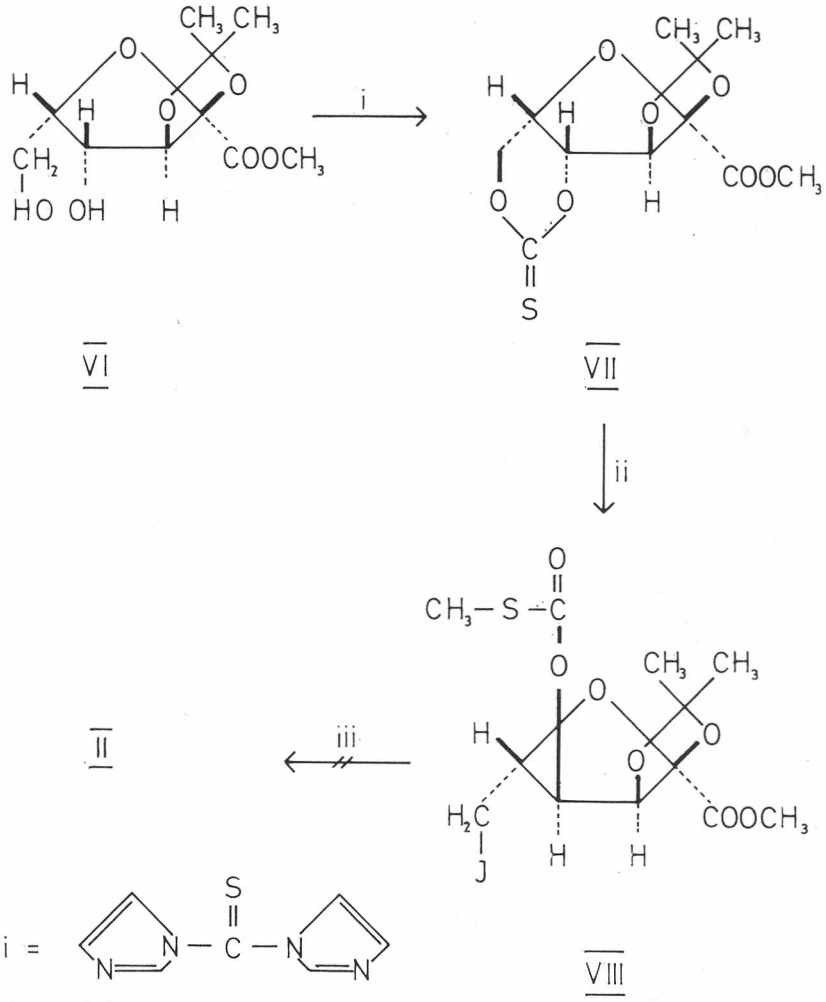
The best result was obtained by triphenylphosphine-carbontetrahalide (halide = chloride, bromide, and iodide), a Downie's type reagent[4]. We found this a general and useful reagent for the one step substitution of the primary hydroxyl group in ascorbic acid. In the preparation of the chloro derivative (**Ia**), we used pyridine as solvent, because it was reported[5] that halogenation of polyhydroxy compounds in this solvent leads to substitution of only the primary hydroxyl group. But in the preparation of the bromo (**Ib**) and iodo (**Ic**) derivatives, dimethylformamide was used with equal efficiency, because in pyridine triphenylphosphine with carbontetrabromide and carbontetra-iodide has formed an insoluble complex $(PH_3PCX_3)^+X^-$, (**X** = bromo, iodo).

The obtained physical data for the prepared 6-deoxy-6-iodo ascorbic acid agree with those recorded in the literature[1] except for the data of optical rotation. The examination of the discrepancy is in progress and will be published in the next publication.

Scheme 1.


H2COH
HCOH
O
=O
OH OH
III
i
4 h
H COCOCH3
H COCOCH3
O
=O
HO OH
IV
24 h i
H2C Cl
H COCOCH3
O
=O
OH OH
V
ii
Ia
= HCl / (CH3CO)2O
= H2O

Scheme 2.


CH3 CH3
O
H
H
O
O
CH2
HO OH
H
COOCH3
i
CH3 CH3
O
H
H
O
O
O
O
C
S
H
COOCH3
VI
VII
ii
O
CH3 – S – C
O
CH3 CH3
O
O
H
O
H2C
J
H
H
COOCH3
VIII
iii
II
i =
S
N
N – C – N
N
N
ii = CH3J
iii = CH3ONa

EXPERIMENTAL

Melting points are uncorrected. The IR spectra were recorded on Perkin-Elmer Infracord Model 257 G. The ^1H NMR spectra were run with a JOEL 90 Q spectrometer in DMSO-d_6 or $CDCl_3$ with TMS as internal standard. Chemical shifts are given in ppm (δ). The ^{13}C NMR spectra were recorded in $CDCl_3$, with TMS as the internal standard, on JOEL SX 90 Q spectrometer. TLC was conducted on original plates (Merck, Kieselgel F_{254}) followed by detection using iodine vapor in solvent systems as follows:

(A) benezene : acetic acid (1 : 1 v/v)

(B) acetone : petroleum ether (40°—70°) (3 : 7 v/v).

Column chromatography was performed on silica gel 0.063—0.200 mm. Optical rotations were measured on a KARL ZEISS POLAMAT A polarimeter at 20 °C.

6-Deoxy-6-chloro Ascorbic Acid (**Ia**)

Procedure using acetic anhydride and hydrogen chloride

The solution of ascorbic acid (2 g, 0.1138 mmol) in acetic anhydride (14 ml) containing hydrogen chloride (6.3 g) was stirred in a sealed tube in an autoclave at 24 °C for 24 hours. The solvent was removed under reduced pressure and coevaporated with water. The oily residue was separated by column chromatography on silica gel (35 g) using solvent system (A). Fractions of 30 ml were collected. The fractions containing the product were evaporated under reduced pressure, coevaporated with ethyl acetate, and the solid residue was recrystallized from nitromethane.

Yield: 1.05 g (58.2%) m. p. 142—143 °C $[\alpha]_D^{20} = 0°$ (c 1.0, H_2O).

Procedure Using Triphenylphosphine-N-Chloro-Succinimide Reagent

To a solution of ascorbic acid (0.44 g, 2.27 mmol), and triphenylphosphine (1.97 g, 7.5 mmol) in dimethylformamide (25 ml), N-chloro-succinimide (1.0 g, 7.5 mmol) was added in three equal portions at intervals of 30 min at 50 °C. The reaction mixture was refluxed for 5 hours, and was then evaporated under reduced pressure at 65 °C. The residue was triturated with water (10 ml), the formed precipitate filtered and washed with water (5 ml). The filtrate was extracted with benzene (10 ml) followed by ethyl acetate (10 × 5 ml). The combined ethyl acetate extracts were washed with water (5 ml), treated with charcoal (0.05 g), filtered and dried. The extracts were concentrated to a small volume (3 ml) and chloroform was added. The mixture was stirred in an ice bath for 2 hours. The precipitate was filtered, washed with chloroform and dried to yield Ia (0.09 g; 18%), identical with that described above.

Procedure Using Triphenylphosphine-Carbontetrachloride Reagent

To a solution of ascorbic acid (1.76 g, 10 mmol), and triphenylphosphine (5.246 g, 20 mmol) in pyridine (10 ml), carbontetrachloride (1.538 g, 10 mmol) was added dropwise at —5 °C. The reaction mixture was stirred at 20 °C for twenty hours, then methanol (10 ml) was added and the mixture was stirred for another hour. The solvents were evaporated under reduced pressure, the residue triturated with a mixture of water (40 ml) and benzene (5 ml). The separated aqueous solution was extracted with benzene (3 × 5 ml), followed by ethyl acetate (10 × 10 ml). The combined ethyl acetate extracts were treated with charcoal (0.2 g), filtered and dried. The ethyl acetate was evaporated under reduced pressure, the residue treated with chloroform, the formed solid product filtered and dried. Recrystallization from nitromethane gave Ia (1.19 g, 61.2%), identical with that described above.

6-Deoxy-6-Bromo Ascorbic Acid (**Ib**)

To a solution of ascorbic acid (1.76 g, 10 mmol), and triphenylphosphine (5.246 g, 20 mmol) in dimethylformamide (30 ml), a solution of carbontetrabromide (3.316 g, 10 mmol) in dimethylformamide (10 ml) was added dropwise at —5 °C. The reaction mixture was stirred at 20 °C for twenty hours. The solvent was evaporated

under reduced pressure and the residue triturated with a mixture of water (60 ml) and benzene (15 ml). The separated aqueous part was additionally extracted with benzene (4 × 15 ml) followed by ethyl acetate (10 × 15 ml). The combined ethyl acetate extracts were treated with charcoal (0.1 g), filtered and dried. The solvent was concentrated under reduced pressure, triturated with chloroform, the formed product filtered and dried. Recrystallization from nitromethane gave Ib (1.09 g, 45.6%); m. p. 176—177 °C; $[\alpha]_D^{20}$ —6.5 (c 1.0, H_2O). Lit.[6] m. p. 175—176 °; $[\alpha]_D^{25}$ —7.3 (c 1.0, H_2O). Lit.[2] m. p. 170—172 °C; $[\alpha]_D^{20}$ —6.3 (c 1.2, H_2O).

6-Deoxy-6-Iodo-Ascorbic Acid (**Ic**)

To a solution of ascorbic acid (1.0567 g, 6 mmol) and triphenylphosphine (3.147 g, 12 mmol) in dimethylformamide (18 ml), a solution of carbontetraiodide (3.12 g, 6 mmol) in dimethylformamide (10 ml) was added dropwise at —5 °C. The reaction mixture was stirred at 20 °C for twenty hours. The solvent was evaporated under reduced pressure and the residue triturated with a mixture of water (60 ml) and benzene (15 ml). The separated aqueous part was additionally extracted with benzene (4 × 15 ml) followed by ethyl acetate (10 × 15 ml). The combined ethyl acetate extracts were treated with charcoal (0.1 g), filtered and dried. The solvent was concentrated under reduced pressure, triturated with chloroform, the formed product filtered and dried. Recrystallization from nitromethane.

Yield 1.01 g (58.8%); m. p. 204—206 °C; $[\alpha]_D^{20}$ — 26 ° (c 1.0, H_2O). Lit.[1] m. p. 203—205 °C; $[\alpha]_D^{20}$ + 10.6 (c 0.5, H_2O).

2,3-O-(1-Methylethylidene)-4,6-thiocarbonyl-L-lyxo-2-hexulofuranosonic Acid Methyl Ester (**VII**)

To a refluxed solution of 2,3-O-(1-methylethylidene)-L-lyxo-2-hexulofuranosonic acid (VI, 0.72 g, 2.9 mmol) in dry tetrahydrofuran (7 ml) under stream of nitrogen, a solution of 1,1-thiocarbonyldiimidazol (0.72 g, 4.03 mmol) in dry tetrahydrofuran (7 ml) was added, and the reaction mixture was refluxed for 45 min. The solvent was evaporated under reduced pressure and the residue dissolved in dichlormethane (15 ml). The solution was washed with 2N HCl, followed by water (2 × 5 ml), and dried. The product was separated by column chromatography on silica gel, using solvent system (B), and recovered from eluted solvent by evaporation and recrystallization from ethyl acetate — petroleum ether.

Yield: 0.25 g (29.7%) m. p. 120—121 °C; TLC (solvent system B), R_f 0.47;

^{13}C NMR spectrum ($CDCl_3$): 165.8 (C_1), 115.2 (C_2), 71.1 (C_3), 86.23 (C_4), 81.9 (C_5), 66.8 (C_6), 53.16 (C_7), 109.8 (C_8), 26.5 and 24.4 (C_9 and C_{10}), 186. (C_{11}).

IR spectrum (KBr): 3500 (s), 1760 (s), 1455 (vs), 1440 (m), 1235 (vs), 1602 (m).

^1H NMR spectrum ($CDCl_3$): 1.44 and 1.58 (d, C—$(CH_3)_2$), 3.85 (s, OCH_3), 4.68 (d, CH_2), 4.9 (m, C_4—H), 5.07 (m, C_3—H and C_5—H).

Anal. $C_{11}H_{14}O_7S$ (290.3) cal'd.: S 11.05%

found: S 10.87%

2,3-O-(1-Methyethylidene)-4-(Methylthio)Carbonyl-6-deoxy-6-iodo-L-ribo-2--hexulofuranosonic Acid Methyl Ester (**VIII**)

The solution of VII (0.72 g, 1.666 mmol) in methyl iodide (25 ml) was refluxed for 18 hours. The superfluous methyl iodide was evaporated under reduced pressure and the residue dissolved in dichlormethane (40 ml). The solution was washed with water (5 × 10 ml) and dried. After evaporation under reduced pressure the product was isolated by column chromatography as described for **VII**.

The product was a colourless oil.

Yield 0.7 g; $[\alpha]_D^{25}$ +42.7° (c 0.107, CH_3OH).

^1H NMR spectrum ($CDCl_3$): 1.38 and 1.56 (s s, C—$(CH_3)_2$), 2.38 (s, S—CH_3), 3.26 (s, CH_2), 3.8 (s, OCH_3), 4.67 (m, C_5—H), 4.95 (s, C_3—H), 5.43 and 5.46 (d, C_4—H).

Anal. $C_{12}H_{17}O_7SJ$ (432,23) cal'd.: S 7.42; J 29.36%

found: S 7.3 J 29.2 %

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The ^{1}H and ^{13}C NMR spectra were recorded by NMR service of the »Rudjer Bošković« Institute.

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SAŽETAK

Priprava derivata askorbinske kiseline

B. Šušković

Askorbinska kiselina daje s trifenilfosfinom i tetrahalougljikom (halo = klor, brom i jod) u piridinu ili dimetilformamidu odgovarajuće 6-deoksi-6-halogen-derivate. 6-deoksi-6-klor-askorbinska kiselina priređena je i reakcijom askorbinske kiseline s klorovodikom u anhidridu octene kiseline ili s trifenilfosfinom i N-klor-sukcinimidom u dimetilformamidu.