REACTION OF 6-AZAURIDINE WITH THIONYL CHLORIDE IN HEXAMETHYLPHOSPHORAMIDE*

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Received August 10, 1988
Accepted September 12, 1988

Reaction of 6-azauridine (*I*) with a mixture of thionyl chloride and hexamethylphosphoramide afforded 5′-chloro-5′-deoxy-6-azauridine (*II*) and a mixture of *SR*- and *SS*-isomers of 5′-chloro--5′-deoxy-2′,3′-O-sulfinyl-6-azauridine (*IIIa* and *IIIb*) which were separated by column chromatography on silica gel; compounds *IIIa* and *IIIb* also arose in the reaction of compound *II* with diphenyl sulfite. Removal of the cyclic sulfinyl group from the isomeric sulfites *IIIa* and *IIIb* gave compound *II*; reaction of *IIIa* and *IIIb* with imidazole in dimethylformamide afforded the 5′-chloro-5′-deoxy-2,2′-anhydro derivative *IV*.

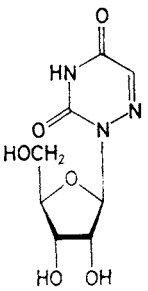
Ribonucleosides react with thionyl halides in hexamethylphosphoramide under formation of 5′-halogeno derivatives[2-4] whereas 2′-deoxyribonucleosides give 3′,5′-dihalogeno derivatives[3]. We have found[1,5-7] that the reaction of ribonucleosides with thionyl chloride in hexamethylphosphoramide or acetonitrile affords, in almost quantitative yield, a mixture of isomeric cyclic 5′-chloro-5′-deoxy-2′,3′-O-sulfinyl derivatives, differing in configuration at the sulfur atom. The *R* : *S*-isomer ratio (with the *S*-isomer predominating) depends on the reacting nucleoside[5-8] and the formed 5′-deoxy-5′-halogeno-2′,3′-sulfinyl derivatives are suitable intermediates in the preparation of nucleoside analogues[1,5-11].

According to the literature[10-13], under milder conditions the reaction of ribonucleosides with thionyl chloride in acetonitrile affords cyclic 2′-3′-O-sulfinyl derivatives that have an intact hydroxyl in the position 5′. These papers do not describe products, differing in configuration on the sulfur atom; however, they mention cyclic 2′,3′-sulfites as suitable precursors of pyrimidine 2,2′-anhydro derivatives (cf. ref.[10]). The reactions with thionyl chloride and sulfuryl chloride have also been compared[4] but only for the case of adenosine.

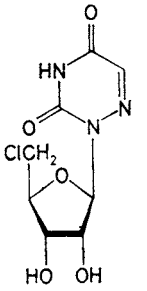
In our previous paper[14] we described the formation of 5′-chloro-5′-deoxy-6-azauridine (*II*) in an 18% yield in the reaction with thionyl chloride in hexamethylphosphoramide. The present communication concerns the identification of two other products of this reaction, the isomeric cyclic 2′,3′-O-sulfinyl derivatives *IIIa* and *IIIb*,

* Published in part in a preliminary communication (ref.[1]).

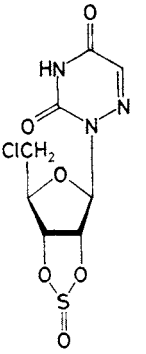
which under the described reaction conditions are formed in the ratio 2 : 3 in a total yield of 50% (refers to the whole fraction of unseparated mixture of isomers). Because of difficult separation, the preparative yields of the pure isomers *IIIa* and *IIIb* were lower. Other, minor, products of this reaction have not been studied. The composition of the reaction mixture and the ratio of the isolated products (particularly the *II*:(*IIIa* + *IIIb*) ratio) depended on the reaction conditions and the work-up method. When the reaction was performed at room temperature and the hexamethylphosphoramide was distilled off only after decomposition of the thionyl chloride and neutralization with aqueous solution of sodium hydrogen carbonate, the known[14] chloro derivative *II* was isolated as the principal product (yield 50%). On the contrary, when after the reaction at room temperature the solvent was rapidly evaporated at 95°C/10 Pa, a mixture of isomeric 2',3'-O-sulfinyl derivatives *IIIa* and *IIIb* was isolated as the main fraction. Prolonged heating (particularly in the presence of a base) led to the known[14] anhydro derivative *IV*. Similarly to the analogous carbonates[14], the cyclic sulfites *IIIa* and *IIIb* were decomposed on silica gel to give the derivative *II*.



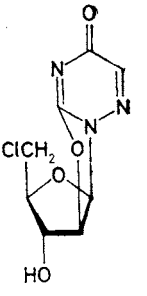
I



II



IIIa, SR
IIIb, SS



IV

The cyclic 2',3'-O-sulfinyl derivatives *IIIa* and *IIIb* were also prepared by reaction of the diol *II* with diphenyl sulfite[15], the *R* : *S*-isomer ratio being analogous to that in the reaction with thionyl chloride.

The cyclic sulfinyl derivatives *IIIa* and *IIIb* were separated by column chromatography on silica gel and the configuration on the sulfur atom was assigned (see[8]). Thus, compound *IIIa* ($[\alpha]_D^{25}$ −101·9°) has the configuration *R* at the sulfur atom and the compound *IIIb* ($[\alpha]_D^{25}$ −41·2°) was assigned the configuration *S*.

The structure of compounds *IIIa* and *IIIb* was confirmed by the characteristic S=O band at 1 215 cm^{-1} in the IR spectrum and by fragments of *m*/*z* 260 and 228, corresponding to loss of chloromethyl and sulfinyl group, respectively, from the

molecular ion. The suggested structures *IIIa* and *IIIb* have also been confirmed by chemical reactions. Thus, for example, on treatment with methanolic sodium methoxide both isomers *IIIa* and *IIIb* were converted into the known[14] 5'-chloro derivative *II* and their reaction with imidazole in dimethylformamide gave the described[14] anhydro derivative *IV* (analogously as in the uridine series).

These reactions of *IIIa* and *IIIb* are analogous to those of the corresponding cyclic 2',3'-O-carbonates[14,16,17]. Similarly to the mentioned carbonates, both sulfites are relatively stable compounds and show no signs of isomerization.

EXPERIMENTAL

Melting points were determined on a Boetius micro melting point apparatus (G.D.R.), optical rotations on a Perkin–Elmer 141 MC polarimeter. UV spectra were recorded on a JASCO ORD/UV-5 instrument IR spectra were taken on a UR-20 (Zeiss, Jena) spectrophotometer; wavenumbers are given in cm^{-1}. ^1H NMR spectra were measured on a Tesla BS-467 (CW mode 60 MHz) instrument, ^{13}C NMR on JEOL FX-60 (FT mode 15 MHz) with tetramethylsilane as internal standard, chemical shifts are given on δ-scale (ppm), coupling constants (J) and band widths (W) in Hz. All parameters were obtained by first-order analysis.Mass spectra were measured on an AEI-901 spectrometer. Preparative chromatography was carried out on columns of silica gel (according to Pitra, 30—60 μm, Service Laboratories of this Institute), thin-layer chromatography (TLC) was performed on silica gel G according to Stahl (Woelm) and on ready-to-use SILUFOL TLC (Kavalier) plates. The systems used are: A ethyl acetate, B ethyl acetate–methanol (10 : 1), C ethyl acetate–benzene (1 : 1). Spots were detected by spraying with sulfuric acid followed by heating, and by UV light (254 nm). Solutions were dried over anhydrous sodium sulfate and taken down on a rotatory evaporator at bath temperature 40—50°C and pressure 2—2·5 kPa. Analytical samples were dried over phosphorus pentoxide at about 25 Pa. Identity of samples prepared by different routes was proven by TLC, comparison of IR spectra and mixture melting point determination.

(*SS*)-5'-Chloro-5'-deoxy-2',3'-O-sulfinyl-6-azauridine (*IIIa*) and
(*SR*)-5'-Chloro-5'-deoxy-2',3'-O-sulfinyl-6-azauridine (*IIIb*)

A) Thionyl chloride (1 ml; 13·7 mmol) and hexamethylphosphoramide (10 ml) were mixed, set aside for 5 min at 20°C, and 6-azauridine (*I*; 980 mg; 4 mmol) was added. After stirring at room temperature for 1 h, the solvent was evaporated at 20°C/10 Pa and then at 95°C/10 Pa. The thick oil was chromatographed on a column of silica gel (150 g) in ethyl acetate. Two principal fractions were obtained: the first (620 mg; 50%) consisted of isomeric chlorosulfinyl derivatives *IIIa* and *IIIb* (about 2 : 3), the second one (190 mg; 18%) contained 5'-deoxy-5'-chloro-6-azauridine (*II*). The first fraction was rechromatographed on a column of silica gel (150 g) in benzene–ethyl acetate (7 : 3), affording 330 mg of chromatographically pure (TLC in A, B and C) less polar compound *IIIb*, 100 mg of an intermediate fraction (*IIIa* + *IIIb*) and 134 mg of pure (TLC in A, B and C) more polar compound *IIIa*.

The more polar isomer was crystallized from benzene–methanol (1 : 1) to give 75 mg (6·1%) of compound *IIIa*, m.p. 145—167°C (decomp.); $[\alpha]_D^{25}$ −101·9° (*c* 0·53; acetone). TLC: R_F 0·94 (A), 0·36 (C). UV spectrum (methanol): λ_{max} 258 nm (log ε 3·79), λ_{min} 222 nm (log ε 3·42). IR spectrum (KBr): 1 215 (S=O), 3 203 (NH), 1 736, 1 714, 1 692 (C=O), 1 602 (C=N).

^{1}H NMR spectrum ($CDCl_3$ and CD_3SOCD_3): 6·51 d, 1 H (H-1′, J(1′, 2′) = 2·0); 5·70 dd, 1 H (H-2′, J(2′, 1′) = 2·0, J(2′, 3′) = 7·5); 5·48 dd, 1 H (H-3′, J(3′, 2′) = 7·5, J(3′, 4′) = 3·6); 4·78 dt, 1 H (H-4′, J(4′, 3′) = 3·6, J(4′, 5′) = J(4′, 5″) = 7·0); 3·72 d, 2 H (2 × H-5′, J(5′, 4′) = 7·0); 7·46 s, 1 H (H-5); 12·45 broad singlet, 1 H (NH). ^{13}C NMR spectrum (CD_3SOCD_3): 157·42 (C-3); 148·77 (C-5); 138·13 (C-6); 92·64 (C-1′); 90·05 (C-2′); 88·92 (C-3′); 87·64 (C-4′); 44·91 (C-5′). Mass spectrum (m/z): 260 (M − CH_2Cl), 228 (M − HSO_3), 218 (M − NCO—SO), 196 (260 − SO_2), 112 (B), 142 (B + 30). For $C_8H_8ClN_3O_6$ (309·7) calculated: 31·03% C, 2·60% H, 11·45% Cl, 13·57% N, 10·35% S; found: 31·40% C, 2·85% H, 11·74% Cl, 13·85% N, 10·52% S.

The less polar isomer was crystallized from ethyl acetate, affording 160 mg (13%) of compound *IIIb*, m.p. 128—150°C (decomp.); $[\alpha]_D^{25}$ −41·2° (*c* 0·41, acetone); TLC: R_F 0·95 (A), 0·42 (C). UV spectrum (methanol): λ_{min} 222 nm (log ε 3·48), λ_{max} 258 nm (log ε 3·83). IR spectrum (KBr): 1 216 (S=O), 3 220 (NH), 1 730 sh, 1 709, 1 692 (C=O), 1 606 (C=N). ^{1}H NMR spectrum ($CDCl_3$ and CD_3SOCD_3): 6·32 d, 1 H (H-1′, J(1′, 2′) = 1·6); 5·85 dd, 1 H (H-2′, J(2′, 1′) = 1·6, J(2′, 3′) = 6·2); 5·61 dd, 1 H (H-3′, J(3′, 2′) = 6·2, J(3′, 4′) = 3·8); 4·39 dt, 1 H, (H-4′, J(4′, 3′) = = 3·8, J(4′, 5′) = J(4′, 5″) = 6·5); 3·73 d, 2 H (2 × H-5′, J(5′, 4′) = 6·5); 7·47 s, 1 H (H-5); 12·45 broad singlet, 1 H (NH). ^{13}C NMR spectrum (CD_3SOCD_3): 157·40 (C-3); 148·69 (C-5); 138·03 (C-6); 90·17 (C-1′); 87·09 (C-2′); 86·47 (C-3′); 86·07 (C-4′); 44·62 (C-5′). Mass spectrum (m/z): 260 (M − CH_2Cl), 228 (M − HSO_3), 218 (M − HNCO—SO), 196 (260 − SO_2), 112 (B), 142 (B + 30). For $C_8H_8ClN_3O_6$ (309·7) calculated: 31·03% C, 2·60% H, 11·45% Cl, 13·57% N, 10·35% S; found: 30·99% C, 2·69% H, 11·53% Cl, 13·51% N, 10·62% S.

B) A mixture of *II* (100 mg; 0·38 mmol), diphenyl sulfite (200 mg, 0·85 mmol) and N,N′-dimethylformamide (2 ml) was stirred at room temperature for 90 min. The reaction mixture, which had the same *IIIa* : *IIIb* ratio (TLC in systems A, B and C) as that described under *A*), was taken down at 40°C/10 Pa and the residue was chromatographed on a silica gel column (100 g) in ethyl acetate–benzene (3 : 7). The obtained fractions were analogous to those described under *A*). Crystallization gave 45 mg (38%) of *IIIb* (from ethyl acetate) and 15 mg (13%) of *IIIa* (from benzene–methanol (1 : 1)). The obtained compounds were identical with those prepared under *A*).

5′-Chloro-5′-deoxy-6-azauridine (*II*)

A) A mixture of *IIIa* (120 mg; 0·39 mmol), methanol (10 ml) and 1M methanolic sodium methoxide (1 ml) was stirred for 20 min, neutralized with Dowex 50WX4 (H^+ form; prewashed with methanol), filtered and the solvent was evaporated. Crystallization from ethyl acetate, afforded 80 mg (78%) of compound *II*, identical with an authentic sample[16]; TLC: R_F 0·58 (A) 0·82 (B) and 0·08 (C).

B) A mixture of *IIIb* (59 mg; 0·2 mmol), methanol (5 ml) and 1M methanolic sodium methoxide (0·5 ml) was stirred at room temperature for 20 min, neutralized with Dowex 50WX4 (H^+ form, prewashed with methanol), filtered and the solvent was evaporated. Crystallization from ethyl acetate furnished 40 mg (76%) of *II*, identical with the product obtained under *A*).

(2*R*)-(2α,3β,3aβ,9aβ)-2,3,3*a*,9*a*-Tetrahydro-3-hydroxy-2-
-chloromethyl-6*H*-furo[2′,3′ : 4,5]oxazolo[3,2-*b*][1,2,4]triazin-6-one (*IV*)

A) A mixture of the sulfinyl derivative *IIIa* (50 mg; 0·22 mmol), N,N-dimethylformamide (1 ml) and imidazole (15 mg; 0·22 mmol) was heated to 150°C for 1 h. Evaporation, chromatography on silica gel (50 g) in ethyl acetate, and crystallization from methanol gave 33 mg (84%) of anhydro derivative *VI*, identical with an authentic sample[16]. TLC: R_F 0·32 (A), 0·50 (B), 0·03 (C).

B) A mixture of the sulfinyl derivative *IIIb* (100 mg; 0·32 mmol), imidazole (30 mg; 0·44 mmol) and N,N'-dimethylformamide (2 ml) was heated to 150°C for 1 h. Evaporation, chromatography on silica gel (50 g) in ethyl acetate, and crystallization from methanol gave 64 mg (81%) of product identical with that obtained under *A*).

The authors are indebted to the Analytical Laboratory of this Institute for the elemental analyses, to Mr P. Formánek for the UV *and* IR *spectral measurements and to Dr P. Fiedler for the interpretation of the* IR *spectra. Their thanks are also due to Dr M. Masojídková for measurement and interpretation of* ^{1}H NMR *spectra, to Dr A. Trka for measurement and interpretation of mass spectra and Mrs Z. Ledvinová for determination of optical rotations. We thank Dr J. Brokeš for the kind gift of diphenyl sulfite.*

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Translated by M. Tichý.