PREPARATION AND SOME REACTIONS OF BIS(2',3'-O-CARBONYL--6-AZAURIDINE) 5',5''-CARBONATE

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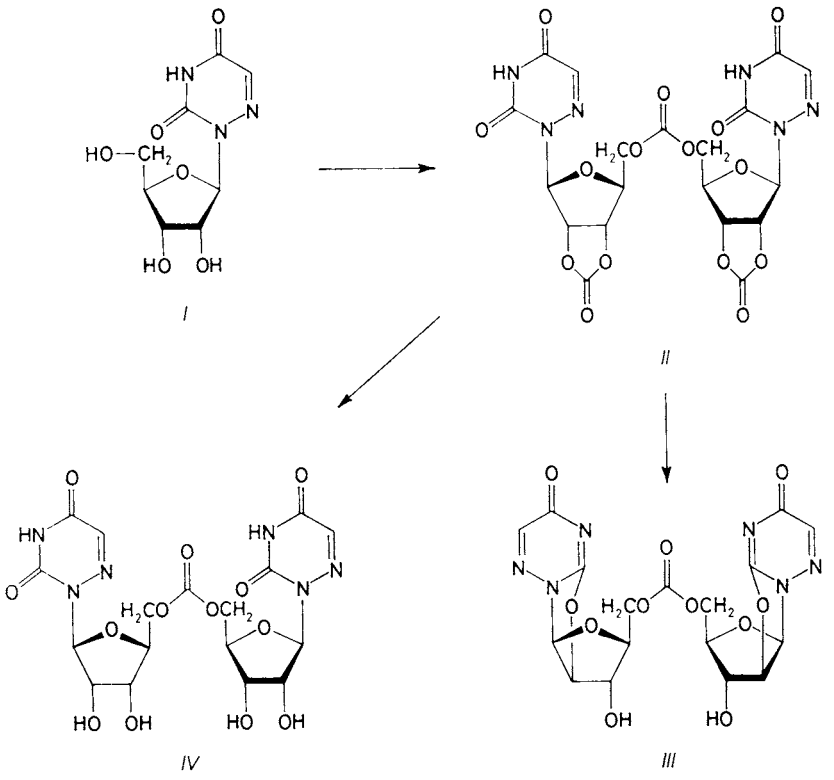
Received October 21st, 1987
Accepted December 15th, 1987

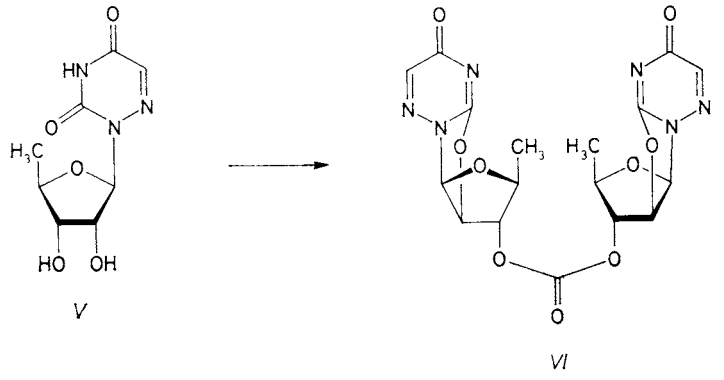
Reaction of 6-azauridine (*I*) with phosgene and hexamethylphosphoramide afforded the title compound *II*. Both its 2',3'-cyclic carbonate groups were selectively deblocked with methanolic sodium methoxide under preservation of the internucleoside carbonate bridge. The carbonate *II* was also converted into the 5',5''-carbonyloxybis(2,2'-anhydro) derivative *III* by heating with imidazole in N,N-dimethylformamide. Several analogues of *II* were prepared by reaction of 1,1'-carbonyldiimidazole with the corresponding nucleosides in N,N-dimethylformamide.

In connection with our previous studies of reaction of pyrimidine nucleosides (with or without a 5'-hydroxy group) with 1,1'-carbonyldiimidazole (CDI) or phosgene[1] we investigated the reaction of nucleosides with phosgene or CDI. Whereas with 5'-substituted nucleosides CDI was clearly the reagent of choice from the viewpoint of experimental procedure as well as yields of the 2',3'-carbonyl derivatives, unsubstituted 6-azauridine (*I*) afforded better yields and purer product with phosgene than with CDI (cf. ref.[1]). Thus, 6-azauridine reacted with phosgene in hexamethylphosphoramide already in 10 to 15 min to give a compound whose TLC mobility corresponded to the cyclic carbonate *VII* whereas after standing at room temperature for about 2 h the reaction mixture contained *VII* and *II* in a 1 : 1 ratio (according to TLC). The compound *II* was obtained as the dominant product irrespective whether the mixture was worked up at the early stage or after longer reaction time the reason being perhaps the elevated temperature during the work-up.

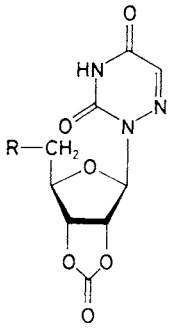
Five-membered cyclic carbonates are characterized in the IR spectrum by a band at 1 810 cm^{-1} (cf. refs[2,3]), similarly to 2',3'-O-carbonyl-6-azauridine (ref.[1]) (carbonate $\tilde{\nu}$(C=O) at 1 820 cm^{-1}). Since the cyclic carbonate group is much more labile to bases than the internucleoside carbonate bridge[2], it was selectively removed by treatment with methanolic methoxide at room temperature; under these conditions the internucleoside carbonate bond was intact even after several hours. Analogously to other carbonates[1,4], the carbonate *II* was treated with imidazole in N,N-dimethylformamide (DMF) at 150°C to give the 5',5''-carbonyldioxybis(2,2'--anhydro) derivative *III* which can serve as an intermediate in syntheses of nucleoside



analogues. This anhydro derivative *III* was also obtained by "one pot" synthesis from CDI and 6-azauridine (*I*). Also here the initial product was 2′,3′-O-carbonyl-6--azauridine (*VII*) which was then converted into the carbonate *II* and further on reaction with base into the anhydro derivative *III*. This pathway was confirmed by TLC monitoring of the reaction and by model reaction of the carbonate *VII* with



CDI leading to the derivative *III* and also by reaction of the carbonate *II* with imidazole as base (vide supra). The lower yields of these reactions with unprotected 6-azauridine (*I*) may be due to formation of minor side-products. Instructive in this respect is the reaction of 5'-deoxy-6-azauridine[5] (*V*) with CDI in DMF which at 150°C afforded the anhydro carbonate *VI* whereas at room temperature yielded 2',3'-O-carbonyl-5'-deoxy-6-azauridine[5] (*VIII*).



VII, R = OH
VIII, R = H

EXPERIMENTAL

Melting points were determined on a Kofler block (Boetius, G.D.R.), specific rotations on an automatic polarimeter Perkin–Elmer 141 MC. UV spectra on a JASCO ORD/UV-5 or SP 8 000 Unicam instruments, λ are given in nm and ε in mol m^{-2}, and IR spectra on a UR 20 (Zeiss, Jena) spectrometer, wavenumbers are given in cm^{-1}. ^1H NMR spectra were measured on a HA 100 instrument, chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. Analytical samples were dried at 30°C/10 Pa. Column chromatography was carried out on silica gel according to Pitra (Service Laboratories of this Institute), particle size 30—60 μm. Solutions were taken down on a rotatory evaporator at about 2 kPa/40°C, unless stated otherwise.

Bis(2',3'-O-carbonyl-6-azauridine) 5',5''-Carbonate (*II*)

A pre-cooled 30% solution of phosgene in toluene (2·5 ml) was added to hexamethylphosphoramide (10 ml, pre-cooled to −10°C). After stirring at room temperature for 5 min, pre-cooled (−10°C) 6-azauridine (*I*; 490 mg; 2 mmol) was added and the foaming mixture was stirred for 30 min at room temperature. The mixture was cooled again to −10°C, another portion (2·5 ml) of pre-cooled 30% solution of phosgene in toluene was added and the mixture was stirred for 5 h without cooling. (If an unsatisfactory conversion was detected by TLC, cf. Table I, another portion (2·5 ml) of the pre-cooled 30% phosgene solution in toluene was added, irrespective of formation of a heterogeneous mixture.) After the end of the reaction the mixture was evaporated at 25°C/20 Pa for 15 min and then the bath temperature was increased to 95°C. The obtained thick sirup was chromatographed on a column of silica gel (150 g) in ethyl acetate to give crude compound *II* (450 mg; 79%) and 2',3'-O-carbonyl-6-azauridine (*VII*) (40 mg; 15%) which, after

crystallization from ethyl acetate (33 mg; 12%), had identical m.p. (148–152°C) and IR spectrum with those of an authentic sample[1]. The crude *II* was crystallized from ethyl acetate, affording 410 mg (62%) of the product, containing one molecule of crystal ethyl acetate; m.p. 185–195°C; $[\alpha]_D^{25}$ −100° (*c* 0·4; acetone). UV spectrum (SP 8 000 UNICAM instrument; in methanol): λ_{min} 221 (log ε 2·99); λ_{max} 260 (log ε 3·31). IR spectrum (KBr): 3 200 (NH bonded azauracil); 1 810 (C=O, carbonate); 1 691 (C=O, azauracil); 1 738, 1 728, 1 708 (C=O); 1 285, 1 264 (C—O—C). ^{1}H NMR spectrum (deuteriochloroform with hexadeuteriodimethyl sulfoxide, tetramethylsilane as internal standard): 12·35 broad s, 2 H (NH); 7·38 s, 2 H (H-5); 6·26 broad d, 2 H (H-1′, J(1′, 2′) = 1); 5·57 dd, 2 H (H-2′, J(2′, 1′) = 1, J(2′, 3′) = 7·5); 5·27 dd, 2 H (H-3′, J(3′, 2′) = 7·5, J(3′, 4′) = 2·5); 4·47 dt, 2 H (H-4′, J(4′, 3′) = 2·5, J(4′, 5′) = 7·0); 3·64 d, 4 H (2 H-5′, J(5′, 4′) = 7·0). For $C_{19}H_{16}N_6O_{15}.C_4H_8O_2$ (656·5) calculated: 42·08% C, 3·69% H, 12·80% N; found: 41·92% C, 3·80% H, 12·38% N.

2,2′-Carbonyldi(oxymethyl)-bis{(2*R*)-(2α,3β,3aβ,9aβ)-2,3,3a,9a-tetrahydro-3-hydroxy-6*H*-furo[2′,3′ : 4,5]oxazolo[3,2-*b*][1,2,4]triazin-6-one} (*III*)

A) A solution of crude *II* (400 mg; 0·7 mmol) and imidazole (95 mg; 1·4 mmol) in DMF (7 ml) was heated to 150°C (bath) for 6 h. After evaporation at 50°C/20 Pa the residue was chromatographed on a column of silica gel (150 g) in ethyl acetate. The main fraction afforded 220 mg (65%) of crude product which was crystallized from methanol; yield 150 mg (41·5%) of *III*, m.p. 140–150°C (decomp.); $[\alpha]_D^{25}$ −46° (*c* 0·4, methanol). UV spectrum (methanol): λ_{min} 214 (log ε 3·15), 238 (log ε 3·02); λ_{max} 223 (log ε 3·21), 255 (log ε 2·13). IR spectrum (KBr): 1 686, 1 656 (C=O azauracil); 1 606, 1 539 (azauracil). IR spectrum (dimethyl sulfoxide): 1 745 sh, 1 682 (C=O); 1 606, 1 540 (azauracil). ^{1}H NMR spectrum (deuteriochloroform with hexadeuteriodimethyl sulfoxide, hexamethyldisiloxane as internal standard, the shifts are corrected for tetramethylsilane as standard: 7·63 s, 2 H (H-5); 6·35 d, 2 H (H-1′, J(1′, 2′) = 5·5); 5·38 dd 2 H (H-2′, J(2′, 1′) = 5·5, J(2′, 3′) = 1·25); 4·45 dd, 2 H (H-3′, J(3′, 2′) = 1·25, J(3′, 4′) = 3)

TABLE I

Thin-layer chromatography. The chromatography was carried out on ready-for-use Silufol^R UV 254 plates (Kavalier, Votice, Czechoslovakia) in a 9 × 18 × 21 cm glass chamber (without internal saturation) with 50 ml of the system. Systems used: S1 ethyl acetate, S2 ethyl acetate–methanol (10 : 1), S3 ethyl acetate–benzene (1 : 1)

Compound	S1	S2	S3
I	0·10	0·40	0·00
II	0·92	>0·9	0·42
III	0·36	0·61	0·03
IV	0·57	0·78	0·05
V	0·43	0·62	0·05
VI	0·26	0·57	0·01
VII[a]	0·55	0·76	0·05
VIII[b]	0·88	>0·9	0·56

[a] Ref.[1]; [b] ref.[4].

4·31 dd, 2 H (H-4′, $J(4', 3') = 3$, $J(4', 5') = 5·5$); 3·59 d, 4 H (2 H-5′, $J(5', 4') = 5·5$). For $C_{17}H_{16}N_6O_{11}.2\,H_2O$ (516·4) calculated: 39·54% C, 3·90% H, 16·27% N; found: 39·50% C, 4·02% H, 16·15% N.

B) Carbonate *VII* (32 mg; 0·1 mmol) in DMF (1·5 ml) was stirred with CDI (33 mg; 0·2 mmol) at room temperature for 6 h. After this time the reaction mixture contained (TLC) exclusively *III*. After evaporation, chromatography and the crystallization the work-up was the same as described ad *A*); yield 20 mg (38%) of *III* of the same quality as the product prepared by the method *A*).

C) A mixture of azauridine (*I*: 123 mg; 0·5 mmol), CDI (195 mg; 1·2 mmol) and DMF (2 ml) was set aside at room temperature for 24 h. The mixture was evaporated in vacuo, chromatographed and worked up as described ad *A*). Three fractions were isolated. The first consisted of carbonate *II* (43 mg; 15%), identical with the above-described compound, the second fraction (6 mg of crude residue) was of the same TLC mobility as the carbonate *VII* and was not further purified. The third fraction was crystallized as described ad *A*) and afforded 85 mg (32%) of *III*, identical with that obtained ad *A*).

Bis(6-azauridine) 5′,5″-Carbonate (*IV*)

A mixture of crude *II* (150 mg/ 0·79 mmol) and 0·1M methanolic sodium methoxide (20 ml) was stirred at room temperature for 30 min and then neutralized with Dowex 50W × 4 (H^+ form, pre-washed with methanol). The solvent was evaporated and the residue chromatographed on a column of silica gel (50 g) in ethyl acetate. The principal fraction was evaporated and crystallized from ethyl acetate to give 170 mg (38%) of *IV*, m.p. 128–134°C, $[\alpha]_D^{25}$ −101° (*c* 0·5; methanol). UV spectrum (methanol): λ_{min} 221 (log ε 2·62), λ_{max} 259 (log ε 3·02). IR spectrum (KBr): 3 475, 3 405, 3 200 (OH, NH); 1 799 sh (C=O, carbonate); 1 708, 1 676 (C=O, azauracil); 1 589 (C=N). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide with deuteriochloroform, hexamethyldisiloxane as internal standard, shifts calculated for tetramethylsilane): 7·46 s, 2 H (H-5); 6·05 d, 2 H (H-1′, $J(1', 2') = 2·5$); 4·35 m, 2 H (H-2′); 3·50–4·70 m, 8 H (H-3′ + H-4′ + 2 H-5′). For $C_{17}H_{20}N_6O_{13}.3\,H_2O$ (570·4) calculated: 35·80% C, 4·59% H, 14·73% N; found: 35·55% C, 4·14% H, 14·73% N.

3,3′-Carbonyldioxybis{(2*R*)-(2α,3β,3aβ,9aβ)-2,3,3a,9a-tetrahydro-2-methyl-6*H*-furo[2′,3′ : 4,5]oxazolo[3,2-*b*][1,2,4]-triazin-6-one} (*VI*)

A solution of 5′-deoxy-6-azauridine[4] (*V*; 100 mg; 0·44 mmol) and CDI (160 mg; 1 mmol) in DMF (4 ml) was heated to 150°C (bath) for 2·5 h. After evaporation the mixture was chromatographed on a silica gel column (40 g) in ethyl acetate. The main fraction afforded 40 mg (41%) of *VI* not melting up to 230°C; $[\alpha]_D^{25}$ −97° (*c* 0·2; methanol). UV spectrum (saturated aqueous solution): λ_{min} 223, 237; λ_{max} 225, 253. IR spectrum (KBr): 3 015, 2 994 (=C—H), 1 756 (C=O, carbonate); 1 693, 1 681 sh (C=O, azauracil); 1 621, 1 548, 1 539 sh (C=N); 1 269, 1 242 (C—O—C). For $C_{17}H_{16}N_6O_9$ (448·4) calculated: 45·54% C, 3·60% H, 18·74% N; found: 45·20% C, 3·60% H, 18·55% N.

The authors thank Mrs Z. Ledvinová for measurement of optical rotations, Mr P. Formánek and Mrs K. Matoušková for IR *and* UV *spectral measurements and Dr P. Fiedler for interpretation of the* IR *spectra. They also are indebted to the staff of the* NMR *Laboratory for measurement and interpretation of the* ^{1}H NMR *spectra and to the staff of the Analytical Laboratory for performing the analyses.*

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Translated by M. Tichý.