316. 4-Oxa(thia)-9-oxa-2-azabicyclo[4.2.1]nonane-3-on(thion) Derivatives

by **Vinko Škarić, Marijan Hohnjec** and **Djurdjica Škarić**

Laboratory of Stereochemistry and Natural Products,
Institute 'Rudjer Bošković', 41001 Zagreb, Croatia, Yugoslavia

Deditadet to Professor *R. B. Woodward* on his 60th birthday

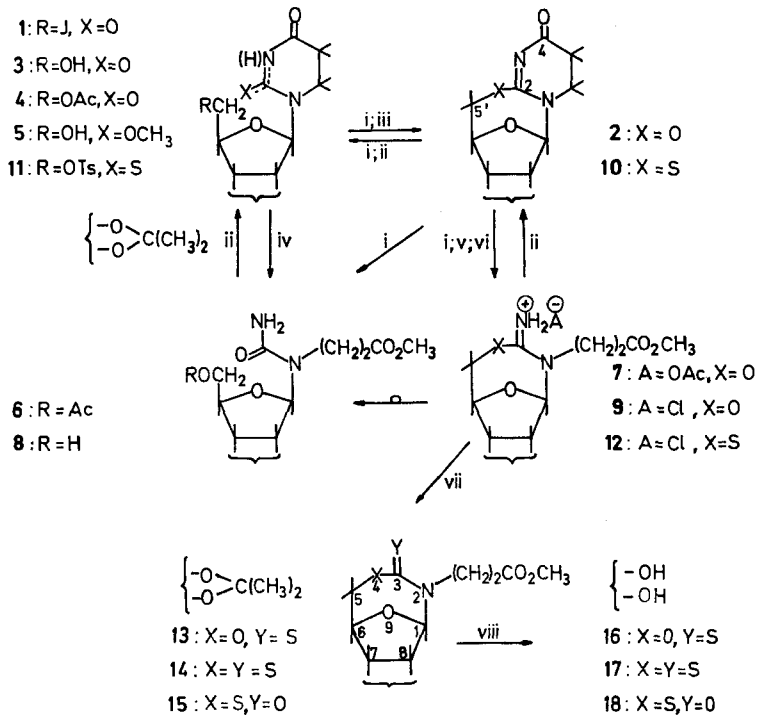
(18. VI. 76)

Summary. The synthesis of **7**,8-dihydroxy-2-(2-methoxycarbonylethyl)-4,9-dioxa-2-azabicyclo[4.2.1]nonane-3-thione (**16**) and of its parents 9-oxa-4-thia-3-thione **17**, and 9-oxa-4-thia-3-one **18** is described. The conversion of 5′-deoxy-5′-iodo-2′,3′-*O*,*O*-isopropylidene-5,6-dihydrouridine (**1**) into the 2-*O*-methyl-5,6-dihydrouridine **5**, the 5′-*O*-acetyl-5,6-dihydrouridine **4**, and into the *N*-(5-*O*-acetyl-2,3-*O*,*O*-isopropylidene-β-D-ribofuranosyl)-*N*-(2-methoxycarbonylethyl)-urea (**6**) invoked 2′,3′-*O*,*O*-isopropylidene-2,5′-anhydro-5,6-dihydrouridine (**2**) as the common intermediate.

In continuation of our studies on the chemistry of anhydrodihydronucleosides [1] we have observed that the conversion of 5′-deoxy-5′-iodo-2′,3′-*O*,*O*-isopropylidene-5,6-dihydrouridine [2] (**1**) into 2′,3′-*O*,*O*-isopropylidene-2,5′-anhydro-5,6-dihydrouridine (**2**) markedly depends upon the reaction time, media, and the concentration of reactants.

Prolonged treatment of 5′-iodo-5,6-dihydrouridine (**1**) with silver acetate in methanol (*path i*) afforded the hydroacetate of 7,8-isopropylidenedioxy-2-(2-methoxycarbonylethyl)-4,9-dioxy-2-azabicyclo[4.2.1]nonane-3-imine (**7**) as the main product. When the reaction was carried out in the presence of an excess of silver acetate 2′,3′-*O*,*O*-isopropylidene-5,6-dihydrouridine (**3**), its 5′-*O*-acetyl- and 2-*O*-methyl-derivatives **4** and **5**, respectively, and *N*-(5-*O*-acetyl-2,3-*O*,*O*-isopropylidene-β-D-ribofuranosyl)-*N*-(2-methoxycarbonylethyl)urea (**6**) were isolated.

The formation of **4**, also made by the hydrogenation of 5′-*O*-acetyl-2′,3′-*O*,*O*-isopropylidene-uridine [3], indicated the nucleophilic attack of the acetate ion at position 5′ of anhydrodihydrouridine **2**, in accordance with the behaviour of pseudourea [4] [5]. An analogous, hitherto unsuccessful ring opening of 2′,3′-*O*,*O*-isopropylidene-2,5′-anhydro-uridine [6] was now observed by the isolation of 5′-*O*-acetyl-2′,3′-*O*,*O*-isopropylidene-uridine in 24% yield. The ease of the formation of 2′,3′-*O*,*O*-isopropylidene-2-*O*-methyl-5,6-dihydrouridine (**5**) from anhydrodihydrouridine **2** (*path ii*) indicated a nucleophilic attack of the methoxide ion at position 2. The transformation of anhydrodihydrouridine **2** into *N*-(5-*O*-acetyl-ribofuranosyl)urea **6** (*path i*) proceeded through the opening of both the dihydrouracil and seven-membered dioxa-aza ring systems by the attacks of the methoxide and acetate ions at position 4 and 5′(5), respectively. The synthesis of urea derivative **6** was easily ac-



i: AgOAc/MeOH; *ii*: NaOMe/MeOH; *iii*: $Et_3N/O(CH_2CH_2)_2O$; *iv*: (a) 0.1N NaOH, (b) CH_2N_2/Et_2O/MeOH, (c) $(CH_3CO)_2O$/py; *v*: HOAc/MeOH; *vi*: HCl/MeOH 3:97; *vii*: H_2S/DMF/Et_2N; *viii*: conc. hydrochloric acid/MeOH 0.06:1

complished by the cleavage of the C(3)-C(4) bond of 2′,3′-*O*,*O*-isopropylidene-5,6-dihydrouridine (**3**) (*path iv*), followed by the esterification, and acetylation [7] of the resulting *N*-(2,3-*O*,*O*-isopropylidene-β-D-ribofuranosyl)-*N*-(2-methoxycarbonylethyl) urea (**8**).

The formation of the hydroacetate **7** under appropriate conditions and its spontaneous transformation into *N*-(5-*O*-acetyl-ribofuranosyl)urea **6** indicated a faster opening of the 5,6-dihydrouracil than of the dioxa-aza ring system. Our search for a more convenient 2-azabicyclo[4.2.1]nonane synthesis showed that anhydrodihydrouridine **2** in methynol/acetic acid (*path v*) also yielded compound **7**. This led us to the more stabile hydrochloride of 7,8-isopropylidenedioxy-2-(2-methoxycarbonylethyl)-4,9-dioxa-2-azabicyclo[4.2.1]nonane-3-imine (**9**) by allowing anhydrodihydrouridine **2** to react with methanol/hydrochloric acid (*path vi*). Similarly, 2′,3′-*O*,*O*-isopropylidene-2,5′-anhydro-2-thio-5,6-dihydrouridine (**10**), prepared from 2′,3′-*O*,*O*-isopropylidene-5′-*O*-tolylsulfonyl-2-thio-5,6-dihydro-uridine (**11**) (*path iii*), generated the hydrochloride of 7,8-isopropylidenedioxy-2-(2-methoxycarbonylethyl)-9-oxa-4-thia-2-azabicyclo[4.2.1]nonane-3-imine (**12**) in 81% yield. It is worth noting that bicyclic hydrochloride **9** recombined (*path ii*) into 2-*O*-methyl-5,6-dihydro-uridine **5**, most probably through anhydrodihydrouridine **2** as an intermediate.

NMR. spectra[a] [b] (Numbering according to formulae **13**–**18**)

Compound	H—C(1)	H—C(8)	H—C(7)	H—C(6)	H_A—C(5)	H_B—C(5)	H_2C—N	OCH_3	H_2C—CO	$(CH_3)_2C$
2	4.97 *s*	4.95 *d* $J_{2',3'} = 5.5$	4.82 *d*	4.57 *s* br.	4.45 *q* $J_{5'A,5'B} = 14.5$	4.09 *q*	4.07 *m* [c])–3.63		2.62 *t* $J_{H2C,H2C} = 7.6$	1.52 *s* 1.37 *s*
10	5.07 *s*	5.13 *d* $J_{2',3'} = 6.0$	4.85 *d*	4.81 *q* $J_{4',5'A} = 2.0$	3.50 *q* $J_{5'A,5'B} = 14.5$	2.72 *q*	4.24 *m* [c])–3.47		2.61 *t* $J_{H2C,H2C} = 7.3$	1.48 *s* 1.35 *s*
7	5.06 *s*	4.83 *d* $J_{8,7} = 6.0$	4.69 *d*	4.42 *s* br.	4.26 *q* $J_{5A,5B} = 15.5$	3.95 *q*	6.11 *t* $J_{H2C,H2C} = 6.5$	3.71 *s*	2.75 *t* $J_{H2C,H2C} = 6.5$	1.47 *s* 1.31 *s*
9 [d])	5.31 *s*	4.97 *d* $J_{8,7} = 5.6$	4.82 *d*	4.69 *ca.*–4.59	4.72 *q* $J_{5A,5B} = 14.0$	4.35 *q*	4.07 (5) [e])–3.79	3.71 *s*	2.83 *t* $J_{H2C,H2C} = 6.2$	1.45 *s* 1.33 *s*
12 [f]	5.51 *s*	5.34 *d* $J_{8,7} = 6.0$	5.04 *d*	4.95 *q* $J_{6,5A} = 2.0$	3.51 *q* $J_{5A,5B} = 14.7$	3.14 *q*	4.35 (5) [e])–3.91	3.72 *s*	2.90 *t* $J_{H2C,H2C} = 6.0$	1.51 *s* 1.38 *s*
13	5.22 *s*	4.85 *d* $J_{8,7} = 5.7$	4.74 *d*	4.54 *d* $J_{6,5B} = 1.0$	4.38 *d* $J_{5A,5B} = 12.5$	3.99 *q*	4.16 *t* $J_{H2C,H2C} = 7.0$	2.75 *s*	2.87 *t* $J_{H2C,H2C} = 7.0$	1.49 *s* 1.33 *s*
14	5.47 *s*	5.04 *d* $J_{8,7} = 5.7$	4.77 *d*	4.79 *q* $J_{6,5A} = 2.0$	3.53 *q* $J_{5A,5B} = 14.5$	2.50 *q*	4.33 *t* $J_{H2C,H2C} = 7.0$	3.69 *s*	2.84 *sext* $J_{H2C,H2C} = 7.0$	1.49 *s* 1.33 *s*
15	5.20 *s*	5.04 *d* $J_{8,7} = 5.5$	4.84 *d*	4.80 *q* $J_{6,5A} = 2.0$	3.44 *q* $J_{5A,5B} = 14.5$	2.54 *q*	3.81 *t* $J_{H2C,H2C} = 6.7$	3.71 *s*	2.65 *t* $J_{H2C,H2C} = 6.7$	1.51 *s* 1.35 *s*
16	5.24 *s*	4.45 *s* br.	4.41 *s* br.	4.30 *ca.*–3.90	4.35 *q* $J_{5A,5B} = 13.0$	3.96 *q*	4.30 *ca.*–3.90	3.69 *s*	3.23 (8) [e])–2.55	
17	5.57 *d* $J_{1,8} = 1.6$	5.00 *q* $J_{8,7} = 7.0$	4.59 (5) [e])–4.17	4.78 *q* $J_{6,5A} = 2.8$	3.55 *q* $J_{5A,5B} = 14.3$	2.55 *q*	4.59 (5) [e])–4.17	3.71 *s*	3.09 (6) [e])–2.81	
18	5.23 *d* $J_{1,8} = 1.5$	4.89 *q* $J_{8,7} = 6.2$	3.33 *d*	4.75 *q* $J_{6,5A} = 2.4$	3.43 *q* $J_{5A,5B} = 14.5$	2.53 *q*	3.92 *m* [c])–3.35	3.69	2.85 (4) [e])–2.59	

[a]) See introduction to exper. part; [b]) Values for doublets *d*, triplets *t*, and quartets *q* refer to multiplet centres; *ca.* refers to estimated positions when resonance is obscured by those of other protons; [c]) Unresolved multiplet *m*; [d]) Solution in CD_3OD; [e]) Figures in parantheses denote the numbers of lines in multiplets; [f]) Solution in deuterium oxide.

The treatment of the cyclic hydrochlorides **9** and **12** with hydrogen sulfide (*path vii*) yielded the 4,9-dioxa- and 9-oxa-4-thia-derivatives **13** and **14**, respectively. The replacement of the sulfur by an oxygen atom at position 3 in compound **14** using thionyl chloride in benzene yielded 9-oxa-4-thia-2-azabicyclo[4.2.1]nonan-3-one (**15**).

The acid hydrolysis of the 2-azabicyclo[4.2.1]nonanes **13**, **14**, and **15** (*path viii*) completed the synthesis affording **16**, **17**, and **18** in very good yields.

The NMR. spectra of anhydronucleosides [8] [9], and of the azabicyclo[4.2.1]-nonanes reported here (see Table) evidenced 2,5'-anhydro and corresponding azabicyclononane structures by characteristic singlets attributed to the anomeric 1'(1) protons, and by two quartets corresponding to the geminal 5'(5) protons. Thus, the anomeric proton of azabicyclo[4.2.1]nonane-3-imines **7**, **9**, **12**,-3-one **15**, and -3-thiones **13**, **14**, and **16** gave rise to a singlet at δ 5.06–5.51 ppm, in good agreement with the prediction from the application of the *Karplus* curve fo the neighboring *trans*-hydrogen atoms in a five-membered ring [10]. However, the anomeric proton of 2',3'-*O*-unprotected 4-thia derivatives **17** and **18** exhibited the doublets (J = 1.6 and 1.8 Hz) in good accordance with that of 2-C-thio-2,5'-anhydrouridine [11]. The spectra of the 4-thia-derivatives **14**, **15**, **17**, and **18** revealed further upfield two quartets characteristic of the geminal protons at C(5) centred at δ 3.43–3.55 ppm (H_A-C(5)) and 2.50–2.55 ppm (H_B-C(5)) ($J_{A,B}$ = 14.0–15.5 Hz) and also a larger separation of these resonances (0.90–1.03 ppm) than the one observed for these resonances in the spectra of 4-oxa-bicyclononanes **13**, and **16** (0.39 ppm). The separation between the two methyl resonances of the 7,8-*O*,*O*-isopropylidene group in the azabicyclononanes **7**, **9**, and **12–15** is 0.12–0.16 ppm.

Experimental Part

General. The same techniques and apparatus were used as described previously [12]. In addition, optical rotations were measured in methylene chloride (l = 1 dm) unless otherwise stated. The NMR. spectra were taken in deuteriochloroform solution using a Model A 60 *Varian* spectrometer. The line positions are given in the δ values, with tetramethylsilane as the internal standard and spin coupling constants J in Hz. The IR. results are given in cm^{-1}, the λ_{max} in the UV. spectra in nm (log ε).

5'-O-Acetyl-2',3'-O,O-isopropylidene uridine. 5'-Deoxy-5'-iodo-2',3'-*O*,*O*-isopropylidene-uridine [3] (10 g, 25.4 mmol) was converted into 2',3'-*O*,*O*-isopropylidene-2,5'-anhydro-uridine which was separated by filtration as described previously [6] (4.2 g, 62%). In addition, the filtrate was evaporated to dryness and chromatographed on a silica gel (30 g) column using acetone/methylene chloride 1:1 as eluant. The product (2 g, 24%) was identical (UV. and IR. spectra) with that obtained from the acetylation of 2',3'-*O*,*O*-isopropylidene-uridine [3].

5'-O-Acetyl-2',3'-O,O-isopropylidene-5,6-dihydrouridine (**4**). A solution of 5-,*O*-acetyl-2',3'-*O*,*O*-isopropylidene-uridine [3] (2 g, 8.85 mmol) in anhydrous methanol (50 ml) containing 5% Rh/C (1 g) was stirred in hydrogen atmosphere under 3.5 atm for 4.5 h. The catalyst was filtered off, and the filtrate evaporated to a foam (100%). Prep. TLC. (ether/ethylacetate 4:1, recovery with methanol) gave **4**, Rf *ca.* 0.4, $[\alpha]^{23} = -32.2°$ (c = 1). – IR.: 3521, 3300, 3012, 1733, 1718, 1701. – NMR.: 5.57 (*d*, J = 2.0, 1H, H—C(1')); 4.98 (*q*, J = 2.0 and 7.0, 1H, H—C(2')); 4.73 (*q*, J = 7.0 and 2.5, 1H, H—C(3')); 3.52 (*t*, J = 6.5, 2H, 2H—C(6)); 2.69 (*t*, J = 6.5, 2H, 2H—C(5)); 2.06 (*s*, 3H, CH_3CO); 1.54 and 1.33 (2*s*, each 3H, $C(CH_3)_2$).

$C_{14}H_{20}N_2O_7$ (328.32) Calc. C 51.21 H 6.14 N 8.53% Found C 51.30 H 6.43 N 8.38%

2',3'-O,O-Isopropylidene-2-O-methyl-5,6-dihydrouridine (**5**). – a) To a solution of 2',3'-*O*,*O*-isopropylidene-2,5'-anhydro-5,6-dihydrouridine [2] (**2**; 134 mg, 0.5 mmol) in anhydrous methanol (80 ml) silver acetate (375 mg, 2.25 mmol) was added. The suspension was heated under reflux

for 15 min, the precipitate filtered off, and the excess of silver ion removed from the filtrate with hydrogen sulfide. The solvent was removed i.V. and prep. TLC. (methylene chloride/acetone 1:1, recovery with methanol) separated the product **5** (112 mg, 75%), Rf 0.25, m.p. 128–130° (acetone/*n*-hexane), $[\alpha]_D^{18} = -42.5°$ ($c = 1.0$). – UV.: 244 (4.05). – IR.: 3472, 3012, 2967, 1661. – NMR.: 3.95 (*s*, 3H, OCH_3); 3.55 (*t*, $J = 7.5$, 2H, 2H—C(6)); 2.56 (*t*, $J = 7.5$, 2H, 2H—C(5)); 1.57 anp 1.35 (*2s*, each 3H, $C(CH_3)_2$).

$C_{13}H_{20}N_2O_6$ (300.31) Calc. C 51.99 H 6.71 N 9.33% Found C 51.71 H 7.01 N 9.18%

b) A solution of **2** (54 mg, 0.2 mmol) in anhydrous methanol (10 ml) was treated with N sodium methoxide in methanol (0.2 ml) and set aside for 30 min at RT. The mixture was evaporated to a residue, from which on prep. TLC. crystalline **5** (100%) was separated, Rf *ca.* 0.25, m.p. 127–129°, identical (IR., UV., and NMR. spectra) with the product obtained in a).

N-(2,3-O,O-Isopropylidene-β-D-ribofuranosyl)-N-(2-methoxycarbonylethyl)urea (**8**). A solution of *2',3'-O,O*-isopropylidene-5,6-dihydrouridine (**3**; 2 g, 7 mmol) in 0.1 N NaOH (200 ml) was set aside for 30 min at RT. and then treated with ion exchange resin (Dowex (H-form), pH 3). The resin was filtered off, and the filtrate evaporated at 30° to a hygroscopic powder (2 g, 94%), Rf 0.12 (ethylacetate). The solution of the thus obtained *N*-(2-carboxylethyl)-*N*-(2,3-*O,O*-isopropylidene-β-D-ribofuranosyl)urea (2 g, 6.6 mmol) in anhydrous methanol (20 ml) was treated with an excess of diazomethane in ether, and then evaporated to dryness. The residue was dissolved in methylene chloride and chromatographed on a silica gel (40 g) column. Ethylacetate/ether 1:1 eluted **8** as a foamy product (1.52 g, 72.5%), $[\alpha]_D^{22} = -15.7°$ ($c = 1$). – IR.: 3448 br., 3030, 2976, 1761, 1667 br., 1600. – NMR.: 5.50 (*s*, 2H, NH_2); 3.72 (*s*, 3H, OCH_3); 3.66 (*t*, $J = 6.5$, 2H, H_2C—N); 2.67 (*t*, $J = 6.5$, 2H, H_2C—CO); 1.55 and 1.35 (*2s*, each 3H, $C(CH_3)_2$).

$C_{13}H_{22}N_2O_7$ (318.32) Calc. C 49.05 H 6.97 N 8.80% Found C 49.03 H 7.20 N 8.91%

A quantitative yield of *2',3'-O,O*-isopropylidene-5,6-dihydrouridine [2] (**3**) was obtained, when ester **8** (20 mg, 0.063 mmol), dissolved in anhydrous methanol (1 ml), was treated with N sodium methoxide in methanol (0.063 ml) for 10 min at RT. and then passed through a silica gel (0.5 g) column.

N-(5-O-Acetyl-2,3-O,O-isopropylidene-β-D-ribofuranosyl)-N-(2-methoxycarbonylethyl)urea (**6**). To a solution of **8** (795 mg, 2.5 mmol) in anhydrous pyridine (6 ml) distilled acetic anhydride (0.9 ml) was added. The mixture was set aside for 4 h at RT., and then evaporated to chromatographycally pure, oily **6** (100%), Rf 0.5 (acetone/methylene chloride 1:1), $[\alpha]_D^{24} = +12.1°$ ($c = 1$). – IR.: 3509, 3413, 3257, 2890, 1736, 1672 br., 1605. – NMR.: 5.33 (*s*, 2H, NH_2); 5.69 (*s*, 3H, OCH_3); 3.62 (*t*, $J = 7.0$, 2H, H_2C—N); 2.66 (*t*, $J = 7.0$, 2H, H_2C—CO); 2.06 (*s*, 3H, CH_3CO); 1.53 and 1.33 (*2s*, each 3H, $C(CH_3)_2$).

$C_{15}H_{24}N_2O_8$ (360.36) Calc. C 49.99 H 6.71 N 7.77% Found C 50.18 H 6.70 N 7.70%

Treatment of 5'-deoxy-5'-iodo-2',3'-O,O-isopropylidene-5,6-dihydrouridine [2] (**1**) *with silver acetate.* To a solution of **1** (3 g, 7.55 mmol) in anhydrous methanol (600 ml) silver acetate (5.5 g, 32.9 mmol) was added, the mixture heated under reflux for 15 min, and worked-up as reported previously [2]. An oil separated which on trituration with acetone yielded *2',3'-O,O*-isopropylidene-2,5'-anhydro-5,6-dihydrouridine (**2**; 345 mg, 17%), m.p. 215–223°, identical (UV. and IR. spectra) with that described earlier [2]. The solution was evaporated to dryness and chromatographed in methylene chloride on a silica gel (70 g) column. Methylene chloride/acetone 5:1 eluted a foam identified as **4** (78 mg, 3.1%). Methylene chloride/acetone 1:1 eluted **6** (337 mg, 12.3%), **3** (336 mg, 15.5%), **5** (211 mg, 8.4%), and **2** (511 mg, 25%).

Hydroacetate of 7,8-isopropylidenedioxy-2-(2-methoxycarbonylethyl)-4,9-dioxa-2-azabicyclo-[4.2.1]nonane-3-imine (**7**). – a) A solution of 5'-iodo-5,6-dihydrouridine (**1**; 5.5 mg, 13.9 mmol) in anhydrous methanol (1.1 l) was treated with silver acetate (10 g, 60 mmol), heated under reflux for 30 min and worked up as already described. The residue was triturated with dioxan (15 ml) and the solvent removed i.V. yielding crystalline **7** (2.5 g, 50%), Rf 0.15 (methylene chloride/acetone 1:1); m.p. 180–185°. – IR.: 3509, 3279, 2994, 1742, 1667, 1560. – NMR.: 6.35 (br.*s*, 2H, NH_2); 2.13 (*s*, 3H, CH_3CO).

b) A solution of **2** (67 mg, 0.25 mmol) in anhydrous methanol (50 ml) was heated under reflux with glacial acetic acid (0.02 ml) for 45 min, evaporated to a residue, and separated by prep. TLC. (methylene chloride/acetone 1:1, recovery with acetone yielding crystalline **7** (26 mg, 44%), m.p. 180–185°, identical (mixed m.p. and IR. spectra) with the product obtained under a).

Hydrochloride of 7,8-isopropylidenedioxy-2-(2-methoxycarbonylethyl)-4,9-dioxa-2-azabicyclo[4.2.1]nonane-3-imine (**9**) – a) To a solution of **2** (54 mg, 0.2 mmol) in anhydrous methanol (20 ml) hydrochloric acid/methanol 3:97 (0.3 ml) was added and kept for 1 h at RT. The solution was concentrated to 1 ml and precipitated with ether at 0°. Crystalline **9** separated (34 mg, 51%), m.p. 136–138° (methanol/ether), $[\alpha]_D^{20} = +122.5°$ ($c = 0.9$, CH_3OH). – IR.: 3450 br., 2965 br., 1736, 1678, 1610.

$C_{13}H_{21}ClN_6O_2$	Calc.	C 46.36	H 6.28	Cl 10.53	N 8.32%
(336.78)	Found	,, 46.36	,, 6.34	,, 10.77	,, 8.21%

b) Hydroacetate **7** (1 g, 2.78 mmol) in anhydrous methanol (5 ml) and hydrochloric acid/anhydrous methanol 3:97 (6 ml) was kept for 5 min at RT. and worked up as described under a). Crystalline **9** (839 mg, 90%), m.p. 132–135°, identical with the product obtained under a), separated.

A 94.5% yield of **5**, m.p. 129–131°, was obtained from hydrochloride **9** (3.57 mmol) in anhydrous methanol (25 ml), treated with N sodium methoxide in methanol (7.3 ml), and worked up as already described.

2′,3′-O,O-Isopropylidene-5′-O-tolylsulfonyl-2-thio-5,6-dihydrouridine (**11**). A solution of 2′,3′-*O*,*O*-isopropylidene-2-thio-5,6-dihydrouridine (400 mg, 1.32 mmol), m.p. 143–145°, reported earlier as a foam [2], in anhydrous pyridine (4 ml) was treated with toluene-*p*-sulfonyl chloride (340 mg, 1.79 mmol) for 16 h at RT. The solvent was removed i.V., the residue taken up in methylene chloride and chromatographed on a silica gel (15 g) column. **11** was eluted with ether (334 mg, 35%), m.p. 144–146° (methylene choride/hexane), $[\alpha]_D^{25} = -36.0°$ ($c = 1$,). – UV.: 233 (4.21), 274.5 (4.13). – IR.: 3430 br., 3250, 2985, 2940, 1727 br., 975, 902, 825. – NMR.: 7.27–7.88 (*m*, 4H, arom.H); 3.43–3.97 (*m*, 2H, 2H—C(6)); 2.66 (*t*, $J = 6.5$, 2H, 2H—C(5)); 2.44 (*s*, 3H, CH_3); 1.57 and 1.32 (2*s*, each 3H, $C(CH_3)_2$).

$C_{19}H_{24}N_2O_7S_2$	Calc.	C 49.99	H 5.30	N 6.14	S 14.04%
(456.52)	Found	,, 50.13	,, 5.38	,, 6.31	,, 13.76%

2′,3′-O,O-Isopropylidene-2,5′-anhydro-2-thio-5,6-dihydrouridine (**10**). To a solution of **11** (300 mg, 0.66 mmol) in anhydrous dioxan (60 ml) triethylamine was added. The mixture was heated under reflux for 75 min, evaporated to dryness, dissolved in methylene chloride, and chromatographed on a silica gel (15 g) column. Methylene chloride/acetone 1:1 (50 ml) eluted an unidentified component (70 mg). The product **10** was eluted with acetone (122 mg, 65%), m.p. 208–210° (methylene chloride/hexane), $[\alpha]_D^{25} = +158°$ ($c = 1$). – UV.: 272.5 (4.09). – IR.: 3430 br., 2975, 1670.

$C_{12}H_{16}N_2O_4S$	Calc.	C 50.69	H 5.67	N 9.85	S 11.27%
(284.33)	Found	,, 50.45	,, 5.95	,, 9.96	,, 11.49%

Hydrochloride of 7,8-isopropylidenedioxy-2-(2-methoxycarbonylethyl)-9-oxa-4-thia-2-azabicyclo[4.2.1]nonane-3-imine (**12**). A 81% yield of **12**, m.p. 187–189° (methanol/ether) was obtained, when **10** (0.176 mmol) was treated with hydrochloric acid/methanol 3:97 for 45 min as described for compound **9**. It showed $[\alpha]_D^{26} = +205°$ ($c = 0.4$, CH_3OH). – UV.: 226 (3.36), 278 sh (2.69). – IR.: 3534, 2994, 1730, 1642, 1570.

$C_{13}H_{21}ClN_2O_5S$	Calc.	C 44.25	H 6.00	Cl 10.05	N 7.94	S 9.08%
(352.84)	Found	,, 44.01	,, 6.18	,, 10.26	,, 8.21	,, 9.21%

7,8-Isopropylidenedioxy-2-(2-methoxycarbonylethyl)-4,9-dioxa-2-azabicyclo[4.2.1]nonane-3-thione (**13**). Into a suspension **9** (50 mg, 0.148 mmol) in anhydrous dimethylformamide (3 ml) and triethylamine (0.15 ml) hydrogen sulfide was bubbled for 1 h and then kept for 30 min at RT. After evaporation the residue (34 mg, 73%) was separated by prep. TLC. (methylene chloride/acetone 20:1, recovery with acetone). Crystalline **13** was obtained, Rf 0.8, m.p. 149–150° (acetone/hexane), $[\alpha]_D^{29} = +56.6°$ ($c = 1$). – UV.: 265.5 (4.22). – IR.: 3040, 2976, 1733. – MS. (*m/e*): 317 (M^+).

$C_{13}H_{19}NO_6S$	Calc.	C 49.20	H 6.03	N 4.41	S 10.10%
(317.35)	Found	,, 49.47	,, 6.18	,, 4.11	,, 10.29%

7,8-Isopropylidenedioxy-2-(2-methoxycarbonylethyl)-9-oxa-4-thia-2-azabicyclo[4.2.1]nonane-3-thione (**14**). A 52% yield of **14** was obtained when **12** (49 mg, 0.14 mmol) was treated with hydrogen sulfide under the above described conditions. Prep. TLC. (methylene chloride/acetone 40:1), Rf 0.5, separated the product as yellow crystals, m.p. 166–167°, $[\alpha]_D^{22} = +79.7°$ ($c = 1.3$). – UV.: 262 (3.82), 293 (4.09). – IR.: 3440 br., 2995, 2940, 1729, 1625 br.

7,8-Isopropylidenedioxy-2-(2-methoxycarbonylethyl)-9-oxa-4-thia-2-azabicyclo[4.2.1]nonane-3-one (**15**). To a solution of **14** (150 mg, 0.45 mmol) in benzene (10 ml) thionyl chloride (0.6 ml) was added and the mixture kept for 20 h at RT. It was then evaporated to dryness. Prep. TLC. (methylene chloride, recovery with acetone), Rf 0.1, afforded crystalline **15** (12 mg, 85%), m.p. 114–115°, $[\alpha]_D^{24} = +26°$ ($c = 1$). – IR.: 3509, 3300, 1736, 1653, 1626,

$C_{13}H_{19}NO_6S$	Calc.	C 49.20	H 6.03	N 4.41	S 10.10%
(317.35)	Found	,, 49.30	,, 6.32	,, 4.41	,, 9.91%

7,8-Dihydroxy-2-(2-methoxycarbonylethyl)-4,9-dioxa-2-azabicyclo[4.2.1]nonane-3-thione (**16**). A solution of **13** (100 mg, 0.315 mmol) in methanol (50 ml) and hydrochloric acid (0.3 ml) was heated under reflux for 5 h and then evaporated to dryness. Prep. TLC. (methylene chloride/methanol 50:3, recovery with methanol separated the starting material (29 mg), Rf 0.7, and crystalline **16** (55 mg, 88%), Rf 0.20, m.p. 92–94° (methanol/ether/hexane), $[\alpha]_D^{22} = +25.8°$ ($c = 0.9$, CH_3OH). – UV.: 265 (4.09). – IR.: 3460 br., 2990, 2922, 1723.

$C_{10}H_{15}NO_6S$	Calc.	C 43.32	H 5.45	N 5.05	S 11.56%
(277.29)	Found	,, 43.04	,, 5.43	,, 5.39	,, 11.42%

7,8-Dihydroxy-2-(2-methoxycarbonylethyl)-9-oxa-4-thia-2-azabicyclo[4.2.1]nonane-3-thione (**17**). A 92% yield of **17** was obtained from a 3 h hydrolysis of **14** (0.168 mmol) under the above mentioned conditions, Rf 0.7 (methylene chloride/methanol 20:1, recovery with methanol, $[\alpha]_D^{24} = +26.6°$ ($c = 0.9$). – UV.: 262 (3.79), 2935 (4.04). – IR.: 3460, 2959, 1733, 1623.

$C_{10}H_{15}NO_5S_2$	Calc.	C 40.94	H 5.15	N 4.78	S 21.86%
(293.35)	Found	,, 40.75	,, 5.38	,, 4.56	,, 22.07%

7,8-Dihydroxy-2-(2-methoxycarbonylethyl)-9-oxa-4-thia-2-azabicyclo[4.2.1]nonane-3-one (**18**). A 83% yield of **18** was obtained from a 3.5 h hydrolysis of **15** (0.5 mmol). It showed Rf 0.7 (methylene chloride/methanol 10:1, recovery with methanol), m.p. 115–116° (methylene chloride/hexane), $[\alpha]_D^{24} = +24.2°$ ($c = 0.6$, CH_3OH). – IR.: 3500, 2950, 1716 br., 1625 br.

$C_{10}H_{15}NO_6S$	Calc.	C 43.32	H 5.45	N 5.05	S 11.56%
(277.29)	Found	,, 43.25	,, 5.43	,, 5.27	,, 11.94%

We thank Mrs. *E. Furić* for technical assistance.

REFERENCES

[1] *V. Škarić & M. Hohnjec*, J. chem. Soc. Chem. Commun. *1973*, 495.
[2] *V. Škarić, B. Gašpert & M. Hohnjec*, J. chem. Soc. (C) *1970*, 2444.
[3] *D. H. Brown, Sir A. Todd & S. Varadarajan*, J. chem. Soc. *1957*, 868.
[4] *E. Debritz*, Angew. Chem. Int. Ed. *5*, 470 (1966).
[5] *S. R. Sandler & W. Karo*, 'Organic Functional Group Preparation', Vol. 12 II, Academic Press, New York–London 1971, p. 166.
[6] *D. H. Brown, Sir A. Todd & S. Varadarajan*, J. chem. Soc. *1956*, 2388.
[7] *T. Naito, M. Hirata, T. Kawakami & M. Sano*, Chem. pharm. Bull. *9*, 703 (1961).
[8] *B. A. Otter, E. A. Falco & J. J. Fox*, J. org. Chemistry *34*, 1390 (1969).
[9] *K. Isovo & T. Azuma*, Chem. pharm. Bull. *20*, 193 (1972).
[10] *R. U. Lemieux & D. R. Lineback*, Ann. Rev. Biochemistry *32*, 155 (1963); *M. Karplus*, J. Amer. chem. Soc. *85*, 2870 (1963).
[11] *S. Shibuya, A. Kininaka & H. Yoshino*, Chem. pharm. Bull. *22*, 719 (1974).
[12] *V. Škarić, B. Gašpert, M. Hohnjec & G. Laćan*, J. chem. Soc. Perkin I, *1974*, 267.