Ring Opening of a 4,9-Dioxa-2-azabicyclo[4.2.1]nonane-3-thione

By **Vinko Škarić,* Marijan Hohnjec,** and **Djurdja Škarić,** Laboratory of Stereochemistry and Natural Products, Institute ' Rugjer Bošković,' 41001 Zagreb, Croatia, Yugoslavia

S-Methyl *N*-(5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranosyl)*N*-(2-methoxycarbonylethyl)thiocarbamate (IV) was formed by the action of methyl iodide on methyl 3-(7,8-isopropylidenedioxy-3-thioxo-4,9-dioxa-2-azabicyclo[4.2.1]nonan-2-yl)propionate (I), and a mixture of the corresponding *N*-(5-chloro-β-D-ribofuranosyl)-carbamoyl chloride (V) and bis-[*N*-(5-chloro-β-D-ribofuranosyl)carbamoyl] disulphide (VI) by treatment of compound (I) with thionyl chloride. Some reactions of the carbamoyl derivatives (V) and (VI) are described.

We have recently reported the synthesis of methyl 3-(7,8-dihydroxy-3-thioxo-4,9-dioxa-, -3-thioxo-4-thia-9-oxa-, and -3-oxo-4-thia-9-oxa-2-azabicyclo[4.2.1]nonan-3-yl)propionates and their 7,8-*O*-isopropylidene derivatives [1,2] (I)—(III). The present paper is concerned with the ring opening of the 3-thioxo-4-oxabicyclononane (I) and the chemistry of the products.

The occurrence of 1,4-addition-type [3] ring opening of compound (I) with methyl iodide was proved by the isolation of the iodo-thiocarbamate (IV). Compound (IV) did not exhibit the u.v. maximum at 265.5 nm characteristic of the 2-azabicyclononane (I), and showed n.m.r. signals at τ 7.68 (SCH_3) and 6.64 and 6.66 (CH_2I) [4] and a new i.r. carbonyl stretching band at 1 658 cm^{-1}.

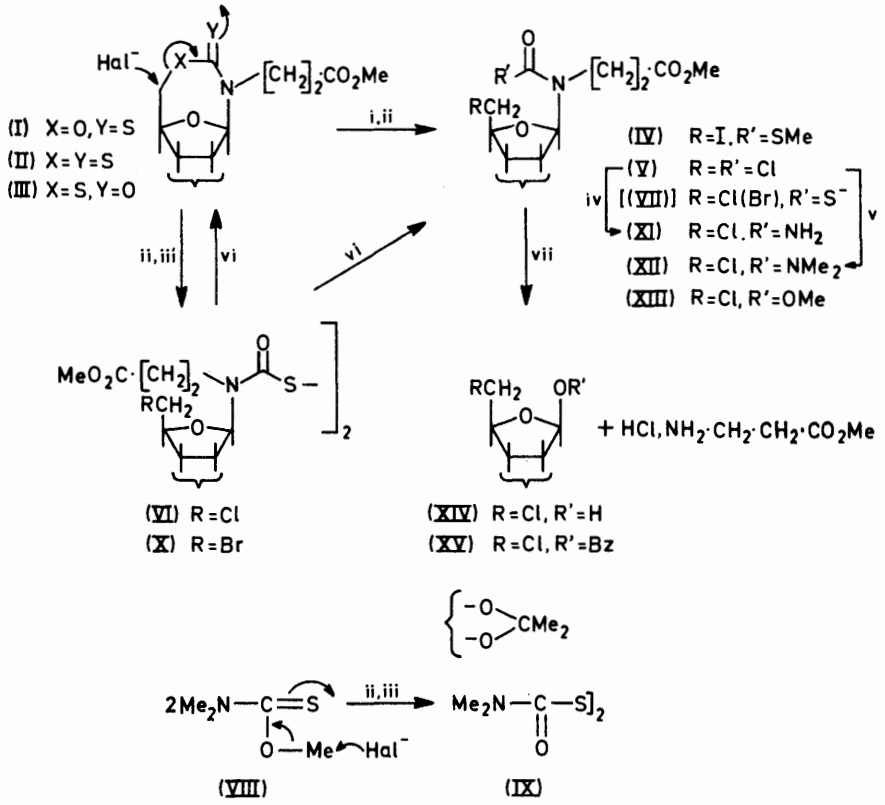
The literature includes various methods for the preparation of deoxyhalogenouridines.[5] We found that 2',3'-*O*-isopropylidene-2,5'-anhydrouridine could be converted into 5'-chloro-5'-deoxy-2',3'-*O*-isopropylideneuridine [6] by reaction with thionyl chloride. Analogously the reaction of compound (I) with thionyl chloride yielded the chlorocarbamoyl chloride (V) (26.7%), but also, to our surprise, the disulphide (VI) (60%). These products and with the possibility of the chloro-thiolcarbamate [(VII)] as a common intermediate, defined the mode of cleavage of compound (I).

The formation of the disulphide (VI) and the earlier reported oxidation of methyl *NN*-dimethylthiocarbamate (VIII) to the disulphide (IX) [7] encouraged us to examine the reaction of compound (I) with bromine. The structure of the resulting disulphide (X) (71%) was consistent with a stepwise ring opening–(or addition–) oxidation mechanism involving the bromo-thiolcarbamate [(VII)] as intermediate. The disulphide (IX) was also obtained by the thionyl chloride route.[7]

[1] V. Skaric and M. Hohnjec, *J.C.S. Chem. Comm.*, 1973, 495.
[2] V. Škarić, M. Hohnjec, and Dj. Škarić, submitted for publication.
[3] T. Mukaiyama, J. Kuwasima, and K. Mizui, *J. Org. Chem.*, 1966, **31**, 32.
[4] V. Škarić, B. Gašpert, and M. Hohnjec, *J. Chem. Soc.* (*C*), 1970, 2444.
[5] J. P. H. Verheyden and J. G. Moffat, *J. Org. Chem.*, 1972, **37**, 2289.
[6] Y. Fijisawa and O. Mitsunoby, *J.C.S. Chem. Comm.*, 1973, 201.
[7] E. C. Cregg, jun., *J. Amer. Chem. Soc.*, 1952, **74**, 3691.

The carbamoyl chloride (V) in anhydrous ammonia or dimethylamine yielded the urea (XI) and its *NN*-dimethyl derivative (XII), respectively.

Treatment of the carbamoyl disulphide (VI) with sodium methoxide in methanol afforded sulphur, the carbamate (XIII), and the bicyclic derivative (III).[1] The recyclisation of the disulphide (VI) to the azabicyclononane (III) indicated a quasi-*cis*-conformation of the ribofuranose 1- and 4-substituents, and this was supported by the chemical shift difference between the isopropylidene methyl resonances, which resembled that



Reagents: i, MeI; ii, $SOCl_2$–C_6H_6; iii, Br_2–CCl_4; iv, NH_3–$O(CH_2{\cdot}CH_2)_2O$; v, Me_2NH–$O(CH_2{\cdot}CH_2)O$; vi, NaOMe–MeOH; vii, H_2O–Me_2CO (1 : 1)

(0.20—0.21 p.p.m.) for compounds (IV)—(VI) and (XI)—(XIII), as earlier reported for β-anomeric nucleosides.[8,9]

Hydrolysis of the carbamoyl chloride (V) gave the thermodynamically more stable 5-chloro-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranose (XIV), and the hydrochloride of β-alanine methyl ester as a by-product. The n.m.r. spectrum of the isolated ribofuranose (XIV), exhibiting an anomeric proton signal at τ 4.51, suggested preferential formation of the β-anomer.[10-12] This assignment was confirmed by conversion into the benzoate (XV), which showed a sharp singlet at τ 3.51 for its anomeric proton.

EXPERIMENTAL

The same techniques and apparatus were used as described previously.[13] In addition, optical rotations were measured for solutions in methylene chloride (*l* 1 dm) unless otherwise stated.

S-Methyl N-(*5-Deoxy-5-iodo-2,3-O-isopropylidene-*β-D-*ribofuranosyl*)-N-(*2-methoxycarbonylethyl*)*thio carbamate* (IV).—A solution of methyl 3-(7,8-isopropylidenedioxy-3-thioxo-4,9-dioxa-2-azabicyclo[4.2.1]nonan-2-yl)propionate (I) (158.5 mg, 0.5 mmol) in methyl iodide (7 ml) was refluxed for 6 h and then evaporated to dryness. The residue dissolved in chloroform was chromatographed on a silica gel (7 g) column. Chloroform–ethanol (99 : 1) eluted analytically pure *product* (180 mg, 79%), R_F 0.36 (t.l.c. in CH_2Cl_2), $[\alpha]_D^{22}$ −33.2° (*c* 1) (Found: C, 36.55; H, 4.7; I, 27.75; N, 2.9; S, 6.9. $C_{14}H_{22}INO_6S$ requires C, 36.6; H, 4.85; I, 27.65; N, 3.05; S, 7.0%), $\nu_{max.}$ 3 030, 2 976, 1 736, and 1 658 cm^{-1}; τ 4.56 (1 H, d, 1-H, $J_{1,2}$ 3.0 Hz), 6.64 (1 H, d, 5-H_a, $J_{5a,4}$ 6.0 Hz), 6.66 (1 H, d, 5-H_b, $J_{5b,4}$ 6.0 Hz), 6.28 (2 H, t, N·CH_2, *J* 7.5 Hz), 6.30 (3 H, s, OCH_3), 7.26 (2 H, t, CH_2·CO, *J* 7.5 Hz), 7.68 (3 H, s, SCH_3), and 8.47 and 8.67 (each 3 H, s, CMe_2).

5'-Deoxy-5'-chloro-2',3'-O-isopropylideneuridine.—A suspension of 2,5'-anhydro-2',3'-O-isopropylideneuridine[14] (66.5 mg, 0.25 mmol) in anhydrous benzene (5 ml) and thionyl chloride (0.4 ml) was stirred for 18 h at room temperature and then evaporated to leave a crystalline residue

[8] J. L. Imbach, J. L. Barascut, B. L. Kam, and C. Tapiero, *Tetrahedron Letters*, 1974, 129.
[9] J. L. Imbach, *Ann. New York Acad. Sci.*, 1975, **255**, 177.
[10] J. Karplus, *J. Amer. Chem. Soc.*, 1963, **85**, 2870.
[11] J. D. Stevens and H. G. Fletcher, jun., *J. Org. Chem.*, 1968, **33**, 1799, and references cited therein.
[12] J. A. Montgomery, *Carbohydrate Res.*, 1974, **33**, 184.
[13] V. Škarić, V. Turjak-Zebić, and Dj. Škarić, *J.C.S. Perkin I*, 1974, 1406.
[14] D. M. Brown, Sir A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 1957, 868.

(45 mg, 60%), R_F 0.6 [t.l.c. in CH_2Cl_2–MeOH (9 : 1)], m.p. 174—178° (from methylene chloride–n-hexane) (lit.,[6] 175.5—176.5°) (Found: C, 47.6; H, 5.25; N, 9.4. Calc. for $C_{12}H_{15}ClN_2O_5$: C, 47.6; H, 5.0; N, 9.25%), $\lambda_{max.}$ 258 nm (log ε 3.01), $\nu_{max.}$ 3 448, 3 195, 2 907, 1 709, 1 672, and 1 623 cm^{-1}.

Treatment of Compound (I) *with Thionyl Chloride.*—To a solution of compound (I) (635 mg, 2 mmol) in anhydrous benzene (24 ml), thionyl chloride (3.2 ml) in benzene (14 ml) was added. The mixture was kept for 4 h at room temperature, then evaporated to dryness, and the residue was chromatographed on a silica gel (25 g) column. Methylene chloride eluted a syrup (190 mg, 26.7%), identified as N-(5-*deoxy*-5-*chloro*-2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-N-(2-*methoxycarbonylethyl*)*carbamoyl chloride* (V), R_F 0.7 [t.l.c. in methylene chloride–ether–ethyl acetate (40 : 2 : 1)], $[\alpha]_D^{22}$ −26.2° (*c* 1) (Found: C, 43.45; H, 5.35; Cl, 19.75; N, 3.9. $C_{13}H_{19}Cl_2NO_6$ requires C, 43.85; H, 5.4; Cl, 19.9; N, 3.95%), $\nu_{max.}$ 3 546, 3 030, 2 994, 1 754, and 1 736 cm^{-1}; τ 4.44br (1 H, s, 1-H), 6.05—6.34 (4 H, m, CH_2Cl and N·CH_2), 6.28 (3 H, s, OCH_3), 7.25 (2 H, t, CH_2·CO, 7.5 Hz), and 8.45 and 8.66 (each 3 H, s, CMe_2). Methylene chloride then eluted an unidentified mixture (86 mg), and a foamy product (422 mg, 60%) identified as *bis*-[N-(5-*chloro*-5-*deoxy*-2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-N-(2-*methoxycarbonylethyl*)*carbamoyl*] *disulphide* (VI), R_F 0.45. Preparative t.l.c. [methylene chloride–ether (1 : 1); acetone as eluant; R_F 0.8] afforded a pure sample, $[\alpha]_D^{19}$ −19.5° (*c* 1), (osmometric in chloroform) 699 (required 705.61) (Found: C, 44.0; H, 5.35; Cl, 9.85; N, 4.0; S, 9.05. $C_{26}H_{38}Cl_2N_2O_{12}S_2$ requires C, 44.25; H, 5.45; Cl, 10.05; N, 3.95; S, 9.1%), $\nu_{max.}$ 1 733, 1 684, and 1 079br cm^{-1}; τ 4.61 (2 H, d, 1-H, $J_{1,2}$ 2.4 Hz), 6.14—6.38 (8 H, m, CH_2Cl and N·CH_2), 6.34 (6 H, s, OCH_3), 7.24 (4 H, t, CH_2·CO, 7.0 Hz), and 8.47 and 8.67 (each 3 H, s, CMe_2).

Bis-[N-(5-*bromo*-5-*deoxy*-2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-N-(2-*methoxycarbonylethyl*)*carbamoyl*] *Disulphide* (X).—A solution of compound (I) (159 mg, 0.5 mmol) in tetrachloromethane (6 ml) was treated with bromine (90 mg) in tetrachloromethane (6 ml). The mixture was refluxed for 30 min, then evaporated, and the residue was chromatographed on a silica gel (10 g) column. Methylene chloride eluted impurities, and methylene chloride–acetone (5 : 1) a foamy *product* (142 mg, 71%) (Found: C, 38.7; H, 4.6; N, 3.5; S, 8.4. $C_{26}H_{38}Br_2N_2O_{12}S_2$ requires C, 39.3; H, 4.8; N, 3.55; S, 8.05%), $\nu_{max.}$ 1 742, 1 692, and 1 082 cm^{-1}.

Bis(*dimethylcarbamoyl*) *Disulphide* (IX).—To a solution of methyl *NN*-dimethylthiocarbamate (VIII) (240 mg, 2.01 mmol) in anhydrous benzene (40 ml), thionyl chloride (2 ml) was added. The mixture was kept for 2 h at room temperature, then evaporated, and the residue was chromatographed on a silica gel (10 g) column. Methylene chloride eluted a crystalline product (100 mg, 48%), m.p. 92—94°, identical (m.p. and i.r. spectra) with that described earlier.[7]

N-(5-*Chloro*-5-*deoxy*-2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-N-(2-*methoxycarbonylethyl*)*urea* (XI).—Into a solution of the carbamoyl chloride (V) (100 mg, 0.28 mmol) in anhydrous dioxan (10 ml), anhydrous ammonia was bubbled for 10 min. Ammonium chloride (14 mg) was filtered off, the mother liquor was evaporated to dryness, and the residue was purified by preparative t.l.c. [in methylene chloride–ether (10 : 1); acetone as eluant; R_F 0.1] to give the urea (XI) (88 mg, 92%), $\nu_{max.}$ 3 497, 3 367, 3 226, 2 959, 1 736, 1 664, and 1 600 cm^{-1}; τ 4.78 (1 H, d, 1-H, $J_{1,2}$ 3.0 Hz), 6.20—6.46 (4 H, m, CH_2Cl and N·CH_2), 6.30 (3 H, s, OCH_3), 7.31 (2 H, t, CH_2·CO, *J* 6.5 Hz), 8.46 and 8.66 (each 3 H, s, CMe_2), and 4.83br (2 H, s, NH_2).

N-(5-*Chloro*-5-*deoxy*-2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-N-(2-*methoxycarbonylethyl*)-N′N′-*dimethyl urea* (XII).—The carbamoyl chloride (V) (100 mg, 0.28 mmol) in anhydrous dioxan (10 ml) was treated with anhydrous dimethylamine by bubbling for 15 min and the product was worked up as described for (XI). The fraction of R_F 0.2 (t.l.c. in CH_2Cl_2) yielded a *syrup* (58 mg, 57%) (Found: C, 48.65; H, 6.8; N, 7.75. $C_{15}H_{25}ClN_2O_6$ requires C, 49.4; H, 6.9; N, 7.7%), τ 4.81 (1 H, d, 1-H, $J_{1,2}$ 2.5 Hz), 6.09—6.67 (4 H, m, CH_2Cl and N·CH_2), 6.34 (3 H, s, OCH_3), 7.40 (2 H, t, CH_2·CO, *J* 7.0 Hz), 8.48 and 8.66 (each 3 H, s, CMe_2), and 7.15 (6 H, s, NMe_2).

Reaction of the Carbamoyl Disulphide (VI) *with Sodium Methoxide.*—The disulphide (VI) (706 mg, 1 mmol) in anhydrous methanol (30 ml) was treated with N-sodium methoxide (4 ml) for 15 min at room temperature. β-Sulphur (44 mg), m.p. 118—120°, separated. The mother liquor was passed through a silica gel (20 g) column; the eluate was evaporated and the residue again chromatographed on a silica gel (50 g) column. Methylene chloride–ether (20 : 1) eluted a syrup identified as *methyl* N-(5-*chloro*-5-*deoxy*-2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-N-(2-*methoxycarbonylethyl*)*carbamate* (XIII) (214 mg, 30.4%), $[\alpha]_D^{22}$ −23.4° (*c* 1) (Found: C, 47.55; H, 6.5; Cl, 10.05; N, 4.25. $C_{14}H_{22}ClNO_7$ requires C, 47.8; H, 6.3; Cl, 10.1; N, 4.0%), $\nu_{max.}$ 2 994, 1 742, and 1 715 cm^{-1}; τ 4.57 (1 H, d, 1-H, $J_{1,2}$ 2.5 Hz), 6.08—6.56 (4 H, m, CH_2Cl and N·CH_2), 6.26 (3 H, s, OCH_3), 6.30 (3 H, s, OCH_3), 7.35 (2 H, t, CH_2·CO, *J* 7.0 Hz), and 8.46 and 8.66 (each 3 H, s, CMe_2).

Methylene chloride–ether (20 : 1) then eluted a mixture (50 mg) and a crystalline product, identified as methyl 3-(7,8-isopropylidenedioxy-3-oxo-4-thia-9-oxa-2-azabicyclo-[4.2.1]nonan-2-yl)propionate[1] (III) (225 mg, 35.5%), m.p. 114—115° (from tetrachloromethane), $[\alpha]_D^{24}$ +26° (*c* 1) (Found: C, 49.3; H, 6.3; N, 4.4; S, 9.9. Calc. for $C_{13}H_{19}NO_6S$: C, 49.2; H, 6.05; N, 4.4; S, 10.1%), $\nu_{max.}$ 1 733, 1 650, and 1 623 cm^{-1}, identical (mixed m.p.[1] and i.r. and n.m.r. spectra) with that obtained previously.[1]

5-*Chloro*-5-*deoxy*-2,3-O-*isopropylidene*-β-D-*ribofuranose* (XIV).—To a solution of the carbamoyl chloride (V) (356 mg, 1 mmol) in acetone (25 ml), water (25 ml) was added. The mixture was refluxed for 1 h and evaporated, and the residue was triturated with methylene chloride to yield the crystalline product (86 mg, 62%), m.p. 105—106°, identical (mixed m.p. and i.r. spectra) with a sample of β-alanine methyl ester hydrochloride. The methylene chloride solution was then chromatographed on a silica gel (15 g) column. Methylene chloride–ether (5 : 1) eluted a foamy *product* (XIV) (200 mg, 96%) which crystallized; m.p. 61—66°, $[\alpha]_D^{24}$ −41° (*c* 1) (Found: C, 45.9; H, 6.25; Cl, 16.8. $C_8H_{13}ClO_4$ requires C, 46.05; H, 6.3; Cl, 17.0%), $\nu_{max.}$ 3 448br, 2 959, 1 070br, and 868 cm^{-1}; τ (with D_2O) 4.51 (1 H, s, 1-H), 5.15 (1 H, d, 2-H, $J_{2,3}$ 6.0 Hz), 5.35 (1 H, d, 3-H, $J_{3,2}$ 6.0 Hz), 5.49—5.77 (1 H, m, 4-H), 6.32—6.46 (2 H, q, CH_2Cl), and 8.51 and 8.66 (each 3 H, s, CMe_2).

1-*O*-*Benzoyl*-5-*chloro*-5-*deoxy*-2,3-O-*isopropylidene*-β-D-*ribofuranoside* (XV).—To a solution of the β-D-ribofuranose (XIV) (20 mg, 0.096 mmol) in anhydrous pyridine (3 ml), benzoyl chloride (0.2 ml) was added. The mixture was

heated for 5 h at 80 °C, then evaporated to dryness, and the residue was purified by preparative t.l.c. [in n-hexane–methylene chloride (2 : 1); methylene chloride as eluant] to give the crystalline *product*, R_F 0.3, m.p. 85—87° (from n-hexane) (21 mg, 70%) (Found: C, 58.5; H, 5.7; Cl, 11.6. $C_{15}H_{17}ClO_5$ requires C, 57.6; H, 5.5; Cl, 11.35%); τ 3.51 (1 H, s, 1-H), 5.10 (1 H, s, 2-H), 5.10 (1 H, s, 3-H), 5.35—5.59 (1 H, q, 4-H), 6.37—6.53 (2 H, t, CH_2Cl), 8.47 and 8.63 (each 3 H, s, CMe_2), and 1.90—2.56 (5 H, m, aromatic).

We thank Mrs. E. Furić for technical assistance.

[6/1292 *Received, 5th July*, 1976]