

952. *Nucleotides. Part XXXIX.\* 5'-Deoxy-5'-iodo-O<sup>2</sup>:2'-cyclouridine: an X-Ray Crystallographic Study.*

By D. M. BROWN, W. COCHRAN, E. H. MEDLIN,  
and S. VARADARAJAN.

The structure of O<sup>2</sup>:2'-cyclouridine<sup>1</sup> is confirmed by an X-ray crystallographic examination of its 5'-deoxy-5'-iodo-derivative, prepared by the action of methanolic ammonia on 5'-deoxy-5'-iodo-2'-O-toluene-*p*-sulphonyluridine. Iodocyclouridine and O<sup>2</sup>:2'-cyclouridine are related by conversion into 3-β-D-arabofuranosyluracil.

In earlier experiments<sup>1</sup> related to the orientation of the phosphate residue in uridylic acids *a* and *b*, uridine-5' acetate and a uridine-*x*:5' diacetate were converted into monotoluene-*p*-sulphonyl derivatives. On attempted deacetylation with methanolic ammonia both toluene-*p*-sulphonyl derivatives were converted into an anhydrouridine. The product was formulated as a cyclouridine since it was similar to other known cyclonucleosides in its properties,<sup>2,3,4</sup> and structure (II; R = OH) was assigned to it on the grounds of quantitative acid hydrolysis into 3-β-D-arabofuranosyluracil, shown to be identical with

\* Part XXXVIII, *J.*, 1956, 3459.

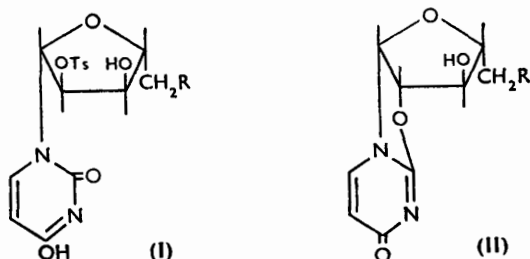
<sup>1</sup> Brown, Todd, and Varadarajan, *J.*, 1956, 2388.

<sup>2</sup> Clark, Todd, and Zussman, *J.*, 1951, 2952.

<sup>3</sup> Michelson and Todd, *J.*, 1955, 816.

<sup>4</sup> Brown, Todd, and Varadarajan, following paper.

the naturally occurring nucleoside spongouridine.<sup>5</sup> The original toluene-*p*-sulphonyl derivatives were therefore formulated as the 2'-isomers.



Confirmation of the position of the new ring in (II; R = OH) was sought by X-ray crystallography. To facilitate this, compounds related to (II; R = OH) carrying heavy

FIG. 1a. Electron density projected on (010). Light atom contours at  $2e\text{\AA}^{-2}$  intervals, with the first contour at  $0.75e\text{\AA}^{-2}$ . Iodine contours are drawn at 10, 20, 40, 60, 80, 90 $e\text{\AA}^{-2}$ .

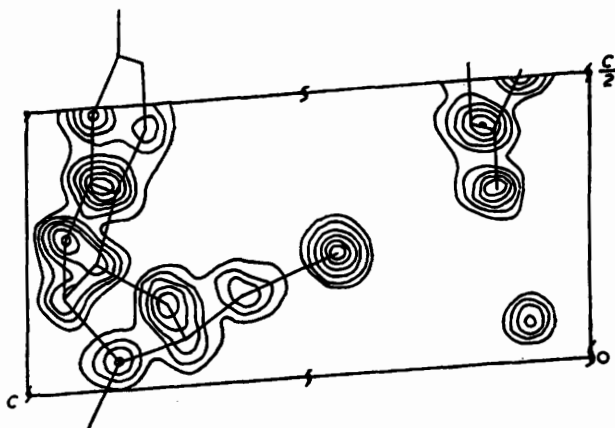
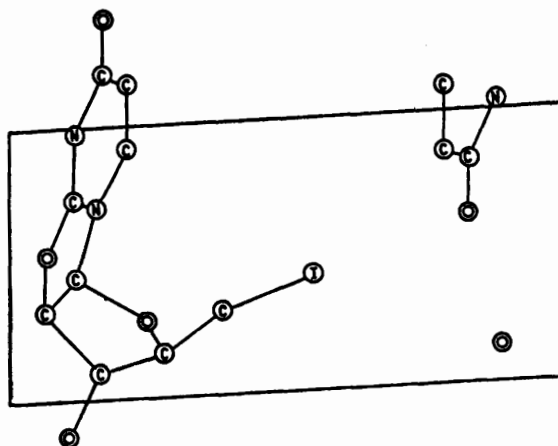


FIG. 1b.



atoms were prepared. 2':3'-*O*-isoPropylideneuridine<sup>6</sup> was converted through the 5'-*O*-toluene-*p*-sulphonyl- and 5'-bromo-5'-deoxy-derivatives into 5'-bromo-5'-deoxy-uridine. This yielded the 2'-toluene-*p*-sulphonyl derivative (I; R = Br) which was

<sup>5</sup> Bergmann and Burke, *J. Org. Chem.*, 1955, **20**, 1501.

<sup>6</sup> Levene and Tipson, *J. Biol. Chem.*, 1934, **106**, 113.

converted into the bromo-compound (II; R = Br) by methanolic ammonia. By a similar series of reactions (II; R = I) was prepared.<sup>4</sup> The bromo- and iodo-*cyclonucleosides* were both closely similar to  $O^2:2'$ -*cyclouridine* (II; R = OH) in their ultraviolet spectra and infrared absorption in the carbonyl region.<sup>1,4</sup> The iodo-compound (II; R = I) was more amenable to crystallographic analysis and its structural relation to (II; R = OH) was established by conversion into spongouridine by acid hydrolysis followed by treatment with aqueous silver acetate and acetic acid.<sup>4</sup>

Direct evidence for structure (II; R = I) is provided by the results of X-ray crystallographic examination. Oscillation and Weissenberg photographs gave the following information about the unit cell:  $a = 9.96$ ,  $b = 5.61$ ,  $c = 10.02$  Å,  $\beta = 93^\circ 0'$ ; space group  $P2_1$ . Fig. 1*a* shows the electron-density projection on (010) with the asymmetric unit superimposed, and Fig. 1*b* the molecular appearance. The reliability index for this projection is 11.5%. The new ring is shown to be formed between  $O^2$  and  $C_{(2)}$  and supporting evidence is given by the deviation of the glycosidic linkage from the direction  $N^3-C_{(6)}$ . In addition, the puckering of the furanose ring brings  $C_{(3)}$  out of the plane on the side opposite to the  $C_{(2)'}-O^2$  bond. The bonds  $C_{(3)'}-O$  and  $C_{(1)'}-N^3$  are in the expected *trans*-relation. It is clear that inversion at  $C_{(2)'}$  to the *arabo*-configuration occurs during formation of the *cyclonucleoside*. It follows from the chemical relation established that the parent *cyclonucleoside*<sup>1</sup> is correctly described as  $O^2:2'$ -*cyclouridine* (II; R = OH).

Generalised projections are being used to establish in greater detail the stereochemistry of (II; R = I) and intermolecular bonds and contacts.

#### EXPERIMENTAL

*5'-Deoxy-5'-iodo-2'-O-toluene-p-sulphonyluridine*.—Toluene-*p*-sulphonyl chloride (0.59 g.; 1.1 mol.) was added to a solution of 5'-deoxy-5'-iodouridine<sup>4</sup> (1.0 g.) in dry pyridine (20 c.c.). After 15 hr. at room temperature the mixture was added to cold water (150 c.c.), and the sticky red product washed with water by decantation. Trituration with ethanol gave the colourless *toluene-p-sulphonyl* derivative as fine needles (0.32 g.) (from ethanol), m. p. 168—169° (Found: C, 37.8; H, 3.4; N, 5.7.  $C_{16}H_{17}O_6N_2IS$  requires C, 37.8; H, 3.9; N, 5.5%). Light absorption in 95% EtOH:  $\lambda_{max}$ , 259, 227 m $\mu$  ( $\epsilon$  9280, 13,900);  $\lambda_{min}$ , 243, 215 m $\mu$  ( $\epsilon$  6430, 11,800).

*5'-Deoxy-5'-iodo- $O^2:2'$ -cyclouridine*.—The toluenesulphonate (0.6 g.) in methanol (300 c.c.) was treated with an equal volume of saturated methanolic ammonia. After 12 hr. solvent was removed, the residue triturated with ethanol (5 c.c.), and undissolved ammonium toluene-*p*-sulphonate filtered off. The filtrate was evaporated and the residue purified by counter-current distribution, the ethyl acetate–water system (20.5 c.c. phase; 100 transfers) being used. The contents of tubes 8—24 were mixed and evaporated to dryness and the crystalline residue was recrystallised from 95% ethanol. *5'-Deoxy-5'-iodo- $O^2:2'$ -cyclouridine* separated in rods (0.1 g.), m. p. 194—195° (decomp.) (Found: C, 33.7; H, 3.2; N, 8.6; I, 36.9.  $C_9H_9O_4N_2I$  requires C, 32.2; H, 2.7; N, 8.3; I, 37.7%). Light absorption in water:  $\lambda_{max}$ , 249, 225 m $\mu$  ( $\epsilon$  8690, 8400);  $\lambda_{min}$ , 235, 210 m $\mu$  ( $\epsilon$  7320, 4890). Infrared absorption bands in the carbonyl region were at 1613 and 1660  $cm^{-1}$ .

*3- $\beta$ -D-Arabofuranosyluracil (Spongouridine)*.—A solution of 5'-deoxy-5'-iodo- $O^2:2'$ -*cyclouridine* (0.25 g.) in 0.1*N*-sulphuric acid (15 c.c.) was heated at 100° for 1 hr., then cooled and passed through a column (10  $\times$  1.5 in.) of Amberlite IR-4B resin (OH form). The column was washed with distilled water (450 c.c.) and percolate and washings were evaporated to dryness under reduced pressure. The residue of 5'-deoxy-5'-iodospongouridine was heated at 100° with silver acetate (1.0 g.) in water (35 c.c.) for 15 min. After filtration through Hyflo Supercel, acetic acid (15 c.c.) was added, and the solution was heated at 100° for a further 15 min. and cooled. Silver ions were removed by hydrogen sulphide and, after being filtered through Supercel, the solution was evaporated. Crystallisation of the residue from dry methanol gave spongouridine (63 mg.) as prisms, m. p. 220—221° alone or in admixture with an authentic specimen.<sup>1</sup>

*5'-Bromo-5'-deoxy-2':3'-O-isopropylideneuridine*.—A solution of 2':3'-*O*-isopropylidene-5'-*O*-toluene-*p*-sulphonyluridine<sup>6</sup> (8.5 g.) and anhydrous lithium bromide (10 g.) in dry acetone (120 c.c.) was heated for 2 hr. at 100° in an autoclave. The solvent was removed, water added to the residue, and the insoluble bromo-compound collected. It formed rectangular rods (6.0 g.), m. p. 184—186°, from ethanol (charcoal) (Found: C, 42.3; H, 4.5; N, 8.4; Br, 23.3.  $C_{12}H_{15}O_5N_2Br$  requires C, 41.5; H, 4.4; N, 8.1; Br, 23.0%).

*5'-Bromo-5'-deoxyuridine*.—The isopropylidene derivative (1.46 g.) was dissolved in anhydrous formic acid (20 c.c.) and after 3 hr. at room temperature the solution was evaporated to dryness. Ethanol (35 c.c.) was added and distilled off under reduced pressure to remove last traces of formic acid. *5'-Bromo-5'-deoxyuridine* separated from ethanol in needles or thin plates (0.83 g.), m. p. 182—184° (Found: C, 35.7; H, 3.9; N, 9.0.  $C_9H_{11}O_5N_2Br$  requires C, 35.2; H, 3.6; N, 9.1%).

*5'-Bromo-5'-deoxy-2'-O-toluene-p-sulphonyluridine*.—*5'-Bromo-5'-deoxyuridine* (3.7 g.) and toluene-*p*-sulphonyl chloride (2.3 g.; 1.1 mol.) were dissolved in dry pyridine (25 c.c.), and the solution was set aside overnight. When this was added to water (250 c.c.) a gum separated. Trituration with methanol gave a solid (2.7 g.) which was then crystallised from methanol. The *2'-O-toluene-p-sulphonyl* derivative formed thick plates, m. p. 162—163° (Found: C, 42.4; H, 3.8; N, 6.1.  $C_{16}H_{17}O_7N_2BrS$  requires C, 41.7; H, 3.7; N, 6.1%).

*5'-Bromo-5'-deoxy-O<sup>2</sup>:2'-cycloauridine*.—*5'-Bromo-5'-deoxy-2'-O-toluene-p-sulphonyluridine* (2.1 g.) was dissolved in half-saturated methanolic ammonia (200 c.c.). After 12 hr. the solution was evaporated to dryness and the residue treated with cold ethanol (10 c.c.). Ammonium toluene-*p*-sulphonate was filtered off and the filtrate was evaporated. The residue was purified by counter-current distribution (20.5 c.c. phase; 100 transfers), the ethyl acetate-water system being used. The contents of tubes 6—16 were pooled and evaporated, and the residue was crystallised from ethanol. *5'-Bromo-5'-deoxy-O<sup>2</sup>:2'-cycloauridine* formed pale yellow stout prisms (0.53 g.), m. p. 185—186° (Found: C, 38.1; H, 3.1; N, 9.7.  $C_9H_9O_4N_2Br$  requires C, 37.4; H, 3.1; N, 9.7%). Light absorption in water:  $\lambda_{max}$ . 247, 225 m $\mu$  ( $\epsilon$  7940, 9450);  $\lambda_{min}$ . 238, 210 m $\mu$  ( $\epsilon$  7500, 6070). Infrared absorption bands in the carbonyl region were at 1613 and 1662 cm.<sup>-1</sup>.

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UNIVERSITY CHEMICAL LABORATORY  
AND CAVENDISH LABORATORY, CAMBRIDGE.

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