Tetrahedron Letters No.3, pp. 165-168, 1969. Pergamon Press. Printed in Great Britain.

HALOGENATION OF NUCLEOSIDES BY (HALOMETHYLENE) DIMETHYLENE AMMONIUM HALIDES

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(Received in USA 19 June 1968; received in UK for publication 8 December 1968)

Phosgene, phosphorus oxychloride, phosphorus trichloride and thionyl chloride have been reported (1, 2) to formylate aromatic, heterocyclic and ethylenic compounds when dimethylformamide was used as the solvent. Bosshard (3) has isolated and characterized (chloromethylene) dimethylene ammonium chloride $[(CH_3)_2N{=}CHCl]^+ + Cl^-$ (I) as the product of the reaction of DMF and $COCl_2$. The same compound is also produced by the reaction of $POCl_3$ (2), PCl_3 (4) and $SOCl_2$ (5) with DMF. Adams and Braun (6) have reported that chlorination of aromatic compounds in DMF proceeds through (I).

We have synthesized both (I) and (bromomethylene) dimethylene ammonium bromide (II) and utilized them for the halogenation of nucleosides. By means of these reagents it has been possible to synthesize 5'-deoxy-5'-chloro (bromo)-uridine and 5'-deoxy-5'-chloro(bromo)-2', 3'-0-isopropylideneuridine in excellent yields. The reactions with uridine gave only the 5'-halo compound and no other isomers suggesting that the bulkiness of (I) and (II) results in a specificity for the 5'-hydroxyl position.

A number of 5'-halogenated derivatives of uridine have been reported including 5'-deoxy-5'-iodo-2', 3'-0-isopropylideneuridine (7), 5'-deoxy-5'-iodo-uridine (8) and 5'-deoxy-5'-fluorouridine (9). The 5'-deoxy-5'-iodo compounds have been utilized for the synthesis of cyclonucleosides (8, 10), nucleotides (11), sulfur analogs (11) and 5'-deoxy-nucleosides (12, 13).

(halomethylene) dimethylene ammonium halide (I) and (II) (5)

Equimolar quantities of dry DMF and $SOCl_2$ or $SOBr_2$ were reacted together at 27°

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for 30 min. The reaction mixture was evaporated to dryness in vacuo (40°). The residue was washed thoroughly with dry ether and again dried *in vacuo*. Both compounds (I) and (II) are highly hygroscopic and must be made immediately prior to their use.

5'-deoxy-5'-chloro-2',3'-0-isopropylideneuridine

2',3'-0-Isopropylideneuridine 0.500 g (1.75 mmoles) was reacted with 0.215 g (1.75 mmoles) (I) in 10 ml dry DMF at 80° for 1 1/2 hr. The reaction mixture was then cooled and its contents neutralized with 1 *N* NH_4OH. The solution was evaporated to dryness and 15 ml water was added. The water suspension was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and then dried with Na_2SO_4. After decantation, the solution was evaporated to a volume of 5 ml. The addition of hexane to a point of slight cloudiness resulted in the crystallization of 479 mg (90%) of 5'-deoxy-5'-chloro-2',3'-0-isopropylideneuridine: m.p. 173-177°. The solid was recrystallized from $CHCl_3$-hexane: m.p. 173.5-177.5: Rf (paper) (14)-0.80.

Anal. Calcd for $C_{12}H_{15}ClN_2O_5$: C, 47.60; H, 5.03; Cl, 11.71, N, 9.58

Found: C, 47.55; H, 4.92; Cl, 11.71; N, 9.54

5'-deoxy-5'-bromo-2',3'-0-isopropylideneuridine

The procedure employed was the same as that used for the preparation of the chloro derivative except that 0.369 g (1.75 mmoles) (II) was used. A yield of 551 mg (90%) was obtained: m.p. 179-181°. The solid was recrystallized from $CHCl_3$-hexane: m.p. 179-181°; Rf - 0.84.

Anal. Calcd for $C_{12}H_{15}BrN_2O_5$: C, 41.50; H, 4.32, Br, 23.20; N, 8.07

Found: C, 41.62; H, 4.46; Br, 23.28; N, 8.07

5'-deoxy-5'-chlorouridine

Uridine 2.00 g (8.20 mmoles) was reacted with 1.01 g (8.20 mmoles) (I) in 10 ml dry DMF for 8 hr at 120°. The reaction mixture was cooled and then neutralized by 1 *N* NH_4OH. The solution was evaporated to dryness and the residue was dissolved in 100 ml methanol. Norite A (neutral) 1 g was added and the mixture stirred at 27° for 3 hr. After filtration the filtrate was evaporated to a volume of 10 ml. The solid deposited at this time was removed by filtration. The liquid was chromatographed on 4 8" x 8" PF$_{254}$ silica gel layered (1 mm) glass plates using butanol-saturated with water. The plates showed 1 u.v. absorbing band at Rf 0.65. This band was removed and extracted with methanol. After filtration the filtrate was evaporated to 10 ml. The solution was allowed to stand for 3 d at 10° during which a white precipitate of 5'-deoxy-5'-chlorouridine was deposited. After filtration the filtrate was evaporated to a volume of 5 ml and allowed to stand for 1 d at 10°. An additional yield of product precipitated. The total product weighed 1.73 g (80%); m.p. 167-168°. The solid was recrystallized from acetone; m.p. 170-172°; Rf - 0.42; cis-glycol spray test (15)-positive.

Anal. Calcd for $C_9H_{11}ClN_2O_5$: C, 41.15; H, 4.22; Cl, 13.50; N, 10.67

Found: C, 40.96; H, 3.29; Cl, 13.44; N, 10.75

5'-deoxy-5'-bromouridine

The procedure employed was the same as that used for the preparation of the chloro derivative except that 1.73 g (8.20 mmoles) (II) was used. The total product weighed 1.90 g (75%); m.p. 171-175°. The solid was recrystallized from acetone; m.p. 172-175°; Rf - 0.47; cis-glycol spray test - positive.

Anal. Calcd for $C_9H_{11}BrN_2O_5$: C, 35.20; H, 3.64; Br, 26.03; N, 9.13

Found: C, 35.25; H, 3.60; Br, 26.15; N, 9.13

Acknowledgment

This research was supported by Grant P-303 from the American Cancer Society and Contract PH 43-65-1035 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health. Jay S. Roth is grateful for Career Award RC 63-31 from the National Cancer Institute, National Institutes of Health.

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