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# SYNTHESIS OF 3-(β-D-RIBOFURANOSYL)-5,7-DIHYDROXY-1H-PYRAZOLO/4,3-d/PYRIMIDINE

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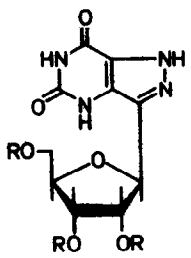
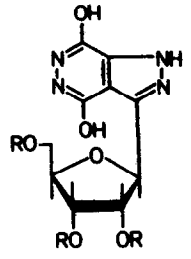
As a part of a study on nucleoside antibiotics we have prepared 3-(β-D-ribofuranosyl)-5,7-dihydroxy-1H-pyrazolo/4,3-d/pyrimidine[1] ("oxoformycin", Ia) which has been hitherto available by biological oxidation of formycin[2]. The synthesis of Ia was accomplished by the procedure described previously[3] in the preparation of 3-hydroxymethyl- and 3-(2-tetrahydrofuryl)-5,7-dihydroxy-1H-pyrazolo/4,3-d/pyrimidine. (A part of the mentioned reaction sequence was applied by Goodman[4] in the synthesis of 3-(2,3-O-isopropylidene-β-DL-erythro-furanosyl)-4,7-dihydroxy-1H-pyrazolo/3,4-d/pyridazine.)



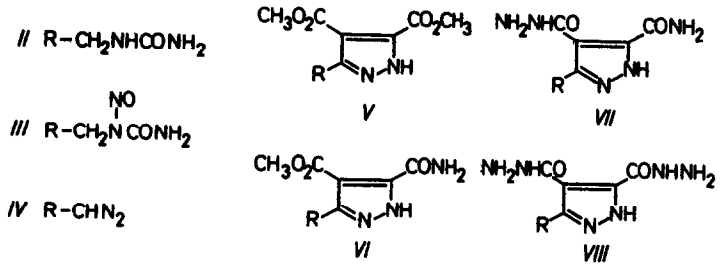
*Ia* R = H ;
*Ib* R = $CH_2C_6H_5$



*IXa* R = H ;
*IXb* R = $CH_2C_6H_5$

3,4,6-Tri-O-benzyl-1-deoxy-1-ureido-2,5-anhydro-D-allitol (II) described earlier[5], was converted into N-nitroso derivative III according to the procedure of Kirmse[6]. $C_{28}H_{31}N_3O_6$; $\lambda$ max in ethanol 213 nm and 236 nm (log $\varepsilon$ 4.17 and 3.66, resp.); ir in carbon tetrachloride: $\nu$ (C=O) 1743 $cm^{-1}$, $\nu$ ($NH_2$) 3530 $cm^{-1}$, 3410 $cm^{-1}$, $\nu$ (N=O) 1500 $cm^{-1}$. The ethereal solution of III was treated with 30% aqueous potassium hydroxide at 0° to give a yellow solution

of diazomethane derivative IV to which, in turn, dimethyl acetylenedicarboxylate was added at 10°. After decolorination of the reaction mixture (within 5 minutes) dimethyl 3-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)-pyrazole-4,5-dicarboxylate (V) was isolated by silica gel chromatography (benzene - ethyl acetate mixture 4 : 1). $C_{33}H_{34}N_2O_8$; $[\alpha]_D^{25}$ +110.4° (c 0.5 in chloroform); $\lambda$ max in ethanol 213 nm (log $\varepsilon$ 4.31); ir in carbon tetrachloride: $\nu$ (C=O) 1746 $cm^{-1}$, 1741 $cm^{-1}$, $\nu$ (NH) 3240 $cm^{-1}$. On treatment of V with methanolic ammonia at 25°, methyl 3-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)-5-carbamoylpyrazole-4-carboxylate (VI) was obtained. (The structure of VI was assigned by analogy with the reported[7] course of ammonolysis of dimethyl pyrazole-4,5-carboxylate.) $C_{32}H_{33}N_3O_7$; $[\alpha]_D^{25}$ +71.3° (c 0.5 in chloroform); $\lambda$ max in ethanol 216 nm and




R = 2,3,5-tri-O-benzyl-β-D-ribofuranosyl

300 nm (log $\varepsilon$ 4.22 and 2.73, resp.); ir in carbon tetrachloride: $\nu$ (C=C) 1693 $cm^{-1}$, 1679 $cm^{-1}$. Hydrazinolysis of the methoxycarbonyl group of VI occurred under reflux in ethanolic solution to yield 3-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)-5-carbamoylpyrazole-4-carboxylic hydrazide (VII). $C_{31}H_{33}N_5O_6$; $[\alpha]_D^{25}$ +178.2° (c 0.5 in chloroform); $\lambda$ max in ethanol 214 nm (log $\varepsilon$ 4.40); ir in carbon tetrachloride: $\nu$ (C=O) 1679 $cm^{-1}$, 1642 $cm^{-1}$. Chromatographical monitoring of the hydrazinolysis of VI revealed that VII reacted subsequently with hydrazine under the formation of 3-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)-pyrazole-4,5-dicarboxylic hydrazide (VIII) which was obtained on the preparative scale in a high yield by treatment of V with hydrazine hydrate in ethanolic solution. $C_{31}H_{34}N_6O_6$; m.p. 158-159.5° from ethanol; $[\alpha]_D^{25}$ +183.4° (c 0.5 in

chloroform); $\lambda$ max in ethanol 214 nm (log $\varepsilon$ 4.39); ir in chloroform : $\nu$(C=O) 1664 $cm^{-1}$, $\nu$ (NH) 3420 $cm^{-1}$. VIII was cyclised into 3-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)-4,7-dihydroxy-1H-pyrazolo/3,4-d/pyridazine (IXb) by treatment with 0.1 M hydrochloric acid in 70% ethanol at 80°. $C_{31}H_{30}N_4O_6$; $[\alpha]_D^{25}$ +173.0° (c 0.5 in chloroform); $\lambda$ max in ethanol 213 nm and 265 nm (log $\varepsilon$ 4.36 and 3.74, resp.); ir in carbon tetrachloride: $\nu$ (C=O) 1652 $cm^{-1}$. After hydrogenolytical removal of benzyl groups over palladium on barium sulphate catalyst, IXb afforded the free C-nucleoside IXa as a crystalline substance (from 50% ethanol) melting at 255-260° (dec.). $C_{10}H_{12}N_4O_6$; $[\alpha]_D^{25}$ +14.4° (c 0.5 in water); $\lambda$ max in 0.1 M HCl 266 nm (log $\varepsilon$ 3.75); $\lambda$ max in 0.05 M NaOH 216 nm and 276 nm (log $\varepsilon$ 4.29 and 3.85, resp.); nmr* in DMSO-$d_6$ with 1% $CH_3CO_2D$, internal tetramethylsilane, $\delta$ in ppm: 5.02 (d, $J_{1',2'}$ 7.0 Hz, $H_{1'}$); 4.28 (q, $J_{2',1'}$ 7.0 Hz, $J_{2',3'}$ 5.5 Hz, $H_{2'}$); 4.04 (q, $J_{3',2'}$ 5.5 Hz, $J_{3',4'}$ 3.5 Hz, $H_{3'}$); 3.88 (q, $J_{4',3'} = J_{4',5'a} = J_{4',5'b}$ 3.5 Hz, $H_{4'}$); 3,63 (q, $J_{5'a,4'}$ 3.5 Hz, $J_{gem.}$ 12.0 Hz, $H_{5'a}$); 3.46 (q, $J_{5'b,4'}$ 3.5 Hz, $J_{gem}$ 12.0 Hz, $H_{5'b}$).

The Curtius degradation of VII as carried out as follows: VII (350 mg) in 10 ml of dimethylformamide was treated at 0° with 1 ml of 2 M HCl and after 5 minutes with 1 ml of 2 M sodium nitrite. After standing at 0° for two hours, the reaction mixture was worked up by diluting with ice water and extracting with ether. Ethereal extracts were concentrated in vacuo at 10°. The residual oil was refluxed in tert. butanol for two hours. Chromatographical purification on silica gel in benzene - ethyl acetate mixture (1 : 1) of the sirupy material obtained after evaporation of tert. butanol, gave 142 mg of a solid fraction which was recrystalized from ethanol to give 94 mg of 3-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)-5,7-dihydroxy-1H-pyrazolo/4,3-d/pyrimidine (Ib). $C_{31}H_{30}N_4O_6$; m.p. 192-193.5° from ethanol; $[\alpha]_D^{25}$ -23.0° (c 0.2 in chloroform); $\lambda$ max in ethanol 288 nm (log $\varepsilon$ 3.76); ir in chloroform: $\nu$ (C=O) 1694 $cm^{-1}$, 1710 $cm^{-1}$, $\nu$ (NH) 3385 $cm^{-1}$, 3430 $cm^{-1}$. The mass spectrum of Ib exhibits a molecular peak at m/e 554 and an intense peak at B+30 (m/e 181) which is characteristic for fragmentation of C-nucleosides[8]. Using the sodium-liquid ammonia procedure[9] for removal of benzyl groups, Ib (46.1 mg) was converted

* Recorded with a Varian HA 100 at 100 MHz.

to 19.0 mg of the free C-nucleoside Ia. $C_{10}H_{12}N_4O_6$; m.p. 284-285° (dec.) from water; (m.p. reported[1] for "oxoformycin" 274°); $\lambda$ max in 0.1 M HCl 288 nm (log $\epsilon$ 3.76), $\lambda$ max in 0.05 NaOH 226 nm, 250 nm, 303 nm (log $\epsilon$ 4.43, 3.81 and 3.72, resp.); ir in KBr pellet is identical with that reported by Umezawa[1] for "oxoformycin".

Compound Ib appears as a versatile intermediate for the synthesis of formycin analogues.

Satisfactory analytical data were obtained for all compounds where the empirical formula is given.

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