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SYNTHESIS OF 2'-DEOXYRIBONUCLEOSIDES OF ALLOPURINOL BY PHASE-TRANSFER GLYCOSYLATION

F. Seela * and H. Steker

Laboratorium für Bioorganische Chemie, Fachbereich 13, Organische Chemie,
Universität Paderborn, Warburger Str. 100, D-4790 Paderborn,
Federal Republic of Germany

ABSTRACT

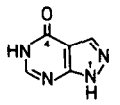
Regioselective glycosylation of 4-methoxy-1H-pyrazolo[3,4-d]pyrimidine (6b) with the halogenose 7 was achieved by employing phase-transfer techniques. The N-1 glycosylation product 3a was formed in preponderance. It was converted into the allopurinol β-D-2'-deoxyribonucleoside 2.

Allopurinol (1) is a progressive inhibitor of xanthine oxidase[1] and is effective in the treatment of gout. β-D-Ribonucleosides of 1 have been prepared[2-5], but the 2'-deoxyribonucleosides are still unknown. During the course of synthetic work it became evident that regiospecific glycosylation at N-1 is difficult to achieve.

Our investigations on pyrrolo[2,3-d]pyrimidine nucleosides have shown that regiospecific N-7 glycosylation with halogenoses can be achieved if phase-transfer techniques were employed[6]. This prompted us to apply this method to pyrazolo[3,4-d]pyrimidines and to undertake the synthesis of the unknown allopurinol-β-D-2'-deoxyribofuranoside 2. As an immediate precursor of the allopurinol system 4-methoxy-1H-pyrazolo[3,4-d]pyrimidine[2] was chosen as the target heterocycle, which was obtained from allopurinol via the 4-chloro compound 6a[7] by nucleophilic displacement of halogen with sodium methoxide. As halogenose the toluoyl-protected sugar 7 was used.

Phase-transfer glycosylation was carried out in a by-phasic mixture of dichloromethane and 50 % aqueous sodium hydroxide. The organic layer contained the halogenose 7, the chromophore 6b, and tetrabutylammonium hydrogen sulfate as phase-transfer catalyst in a ratio of 1 : 10 (catalyst/chromophore). Glycosylation took place after thorough mixing with a vibromixer at room temperature and was complete within one minute. The layers were separated and the content of the organic layer chromatographed on silica gel with dichloromethane-ethyl acetate (9 : 1) as solvent. Three zones were separated and the contents were isolated in 40 % (fast migrating compound), 7 % (slower migrating compound) and 20 % yield (slow migrating compound). As elemental analyses indicated they correspond to the structure of 2'-deoxyribofuranosides of compound 6b. From the ^{13}C NMR spectrum (Me_2SO-d_6) of the slow migrating material N-2 glycosylation was established since its C-3 signal (δ 124.3 ppm) exhibits a strong upfield shift compared to that of the chromophore 6b (δ 131.1) similar to that of the methyl derivative 8 (δ 124.7)[8]. After deprotection with sodium methoxide a crystalline nucleoside (mp 165°C, UV(MeOH): λ_{max} 259 nm) was obtained showing a pseudo triplet at δ 6.36 (H-1') in

the ^{1}H NMR spectrum. This confirmed β-configuration and established structure 5b; therefore the protected precursor had to be 5a. The main glycosylation product (fast migrating zone) was deprotected as described for 5a which resulted in the formation of a crystalline nucleoside (mp 176°C; UV(MeOH): λ_{max} 246 nm). An almost identical UV spectrum as found for 6c and the coupling pattern of C-7a with the anomeric proton (^{13}C NMR) established N-1 glycosylation. The anomeric configuration was β [^{1}H NMR (Me_2SO-d_6): δ 6.67 (H-1', pseudo triplet)]. The data confirmed the structure of the methoxynucleoside 3b; the structure of the protected glycosylation product was therefore 3a. Since the content of the slightly slower migrating zone of glycosylation exhibited a quadruplet for the anomeric proton (δ 6.84) in the ^{1}H NMR spectrum and gave similar UV data after deprotection it was assigned to the α-anomer 4a; correspondingly the structure of the deprotected nucleoside was 4b.



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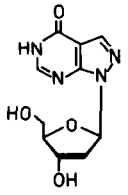

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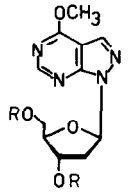
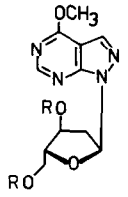
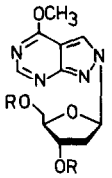


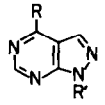
3a: R=Tol
b: R=H



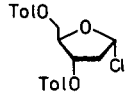
4a: R=Tol
b: R=H



5a: R=Tol
b: R=H



6a: R=Cl, R'=H
b: R=OCH_3, R'=H
c: R=OCH_3, R'=CH_3



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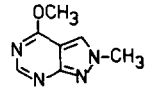

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All efforts to cleave the O-methyl group of 3b under acidic conditions failed but it was noticed recently[8] that nucleophilic displacement of this group with hydroxyl ions occurs easily. By applying 2 N sodium hydroxide to compound 3b the allopurinol 2'-deoxyriboside 2 (mp 203°C) was formed in 80 % yield. The structure was confirmed by NMR spectroscopy. ^{1}H NMR (Me_2SO-d_6): δ 8.14, 8.12(2s,H-3 and H-6), 6.52(qt, H-1'); ^{13}C NMR(Me_2SO-d_6): δ 148.2(C-6), 134.9 (C-4), 87.7(C-4'), 84.0(C-1'). The UV data coincide with those of the N-1 β-D-ribofuranoside of 1[3]. Investigations towards the synthesis of other pyrazolo[3,4-d]pyrimidine 2'-deoxyribonucleosides, employing phase-transfer techniques, are in progress.

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