NUCLEIC ACID COMPONENTS AND THEIR ANALOGUES. CLXI.* SYNTHESIS OF SOME 1-AMINO-1-DEOXY-D-PSICOSE DERIVATIVES

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The acid-catalysed methanolysis of the azido ketone *III* (obtained by reaction of the bromo ketone *IV* with lithium azide in acetone) afforded an anomeric mixture of methyl 1-azido-1-deoxy-D-psicofuranosides from which (after benzoylation) the crystalline β-anomeric benzoate *I* was isolated. The free β-glycoside *V* was obtained from the benzoate *I* by the action of methanolic ammonia. The acetamido derivative *II* was prepared by catalytic reduction of compound *I* in a mixture of ethyl acetate and acetic anhydride. The attempted conversion of glycosides *I* and *II* to the corresponding glycosyl bromides by the action of hydrogen bromide failed. With compound *I*, the azido group was replaced by bromine and the 2,3-furanosene *XII* was obtained as the single product from the glycoside *II*. As determined polarographically, the kinetics of the reaction between the bromo ketone and sodium azide are of the second order.

In the present paper, we wish to report the synthesis of methyl 1-azido-3,4,6-tri-O-benzoyl-1-deoxy-β-D-psicofuranoside (*I*) and methyl 1-acetamido-3,4,6-tri-O-benzoyl-1-deoxy-β-D-psicofuranoside (*II*) along with some experiments concerning the potential application of compounds *I* and *II* in the synthesis of analogues of the nucleosidic antibiotic psicofuranine[1,2].

In the synthesis of glycosides *I* and *II*, 3,4,5,6-tetra-O-acetyl-1-azido-1-deoxy-D-psicose (*III*) was used as the key intermediate because of its assumed accessibility by reaction of 3,4,5,6-tetra-O-acetyl-1-bromo-1-deoxy-D-psicose (*IV*) with sodium azide. As shown by Boyer and Straw[3], the reaction of simple α-halo ketones with sodium azide in aqueous ethanol leads to the corresponding α-azido ketones. In our case, however, the substitution reaction of the bromo ketone *IV* with sodium or lithium azide was very slow and was accompanied by alcoholysis of acetyl groups. The yield of the required azido ketone *III* was therefore unsatisfactory. Moreover, the isolation was rather difficult because of the similar chromatographical mobility of the product *III* and the starting compound *IV*. In order to determine the optimum conditions for the formation of the azido ketone *III* from the bromo ketone *IV*, the time dependence of the substitution was examined by means of polarography which made

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possible to determine the concentration of both the starting compound *IV* and the reaction product *III*.

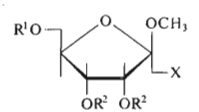
TABLE I

Rate Constant k_2 Values in Reactions of the Bromo Ketone *IV* with Sodium Azide at 25°C

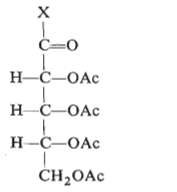
Solvent	Acetone	Acetonitrile	96% Ethanol
k_2, $M^{-1} s^{-1}$	26·2	4·82	0·033

The bromo ketone *IV* is reduced polarographically in the pH range of 1—7 at positive potentials with two electrons. In the strongly acidic as well as in the strongly alkaline pH region, a time-dependent decrease of the polarographic wave may be observed which is due to the hydrolytical removal of the bromide ion. (Also the increase of the bromide ion concentration may be determined polarographically as the anodic wave). The azido ketone *III* affords two two-electron waves in the pH region of 1—7. The acetate buffer solution of pH 4·7 proved suitable as medium for the polarographic analysis of the reaction mixture. The wave of the azido ketone *III* is under these conditions best developed and the limiting currents of compounds *III* and *IV* represent a linear function of concentration. The reaction rate of the bromo ketone *IV* with the acetate ion may be neglected in comparison with the reaction rate of the bromo ketone *IV* with the azide ion.

The kinetics of the reaction of the bromo ketone *IV* with sodium azide have been now shown to be of the second order. A similar conclusion has been arrived at by Sisti and Lowell[4] in kinetics of the reaction between simple α-halo ketones and the azide ion as well as some other nucleophilic agents. The rate constants k_2 (Table I) depend strongly on the solvent; this dependence is in accordance with the "solvent-effect" theory of Parker[5]. The observed k_2 values also correlate with the rate constants of the bimolecular reaction between methyl *p*-toluenesulfonate and lithium bromide in the appropriate solvents[6].



I, $R^1 = R^2 = Bz$, $X = N_3$
II, $R^1 = R^2 = Bz$, $X = NHAc$
V, $R^1 = R^2 = H$, $X = N_3$
VI, $R^1 = H$, $2\,R^2 = C_6H_5B$, $X = N_3$

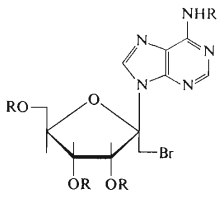


III, $X = CH_2N_3$
IV, $X = CH_2Br$
VII, $X = CH_2NHAc$
VIII, $X = CHN_2$
IX, $X = CH_3$

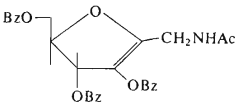
On the basis of the above results, the reaction of the bromo ketone *IV* was performed in acetone as solvent and sodium azide was replaced by lithium azide which is more soluble in acetone. Under these modified reaction conditions, the required azido ketone *III* was obtained in 70–80% yield and was free of the starting bromo ketone *IV*.

The acid-catalysed methanolysis of the azido ketone *III* afforded a mixture of anomeric methyl 1-azido-1-deoxy-D-psicofuranosides which was benzoylated to allow isolation of the crystalline glycoside *I* by column chromatography on silica gel. The attempted isolation of the other anomer in a homogeneous form failed. When treated with methanolic ammonia, the glycoside *I* afforded the chromatographically and electrophoretically homogeneous methyl 1-azido-1-deoxy-β-D-psicofuranoside (*V*) which was characterised as 3,4-O-phenylboronate *VI*. Infrared spectrum of compound *VI* in chloroform exhibits a band of the associated CH_2OH group at 3465 cm^{-1} which is indicative of the β-configuration at the anomeric center[7].

Catalytic reduction of the azido glycoside *I* in a mixture of ethyl acetate and acetic anhydride afforded the required glycoside *II*. An alternative preparation of compound *II* would start from 1-acetamido-3,4,5,6-tetra-O-acetyl-1-deoxy-D-psicose (*VII*) which was obtained by catalytic reduction of the azido ketone *III* in a mixture of ethyl acetate and acetic anhydride. The acid-catalysed methanolysis of compound *VII* affords a mixture of anomeric methyl 1-acetamido-1-deoxy-D-psicofuranosides which, however, is difficult to separate by chromatography. Consequently, the alternative route for the preparation of compound *II* is of no advantage in comparison with the former route. For the synthesis of the intermediate *VII*, also the catalytic hydrogenation of 3,4,5,6-tetra-O-acetyl-1-deoxy-1-diazo-D-psicose (*VIII*) was considered taking into account the paper of Birkofer[8] on the formation of ω-aminoacetophenone acetyl derivative by hydrogenation of ω-diazoacetophenone on a palladium catalyst in a mixture of ethyl acetate and acetic acid, but only the earlier reported[9] 3,4,5,6-tetra-O-acetyl-1-deoxy-D-psicose (*IX*) was obtained as the single product by hydro-



X, R = Bz
XI, R = H



XII

genation of compound *VIII* on a palladium catalyst in ethyl acetate or acetic anhydride.

In connection with the proposed synthesis of psicofuranine analogues carrying an amino group on the carbon atom at position 1', it would be of interest to transform the protected glycosides *I* and *II* into the corresponding glycosyl bromides by the action of hydrogen bromide in acetic acid. In the case of compound *I*, however, this reaction did not appear promising. The alkyl and aryl azides are known[10] to liberate nitrogen or azoimide in strongly acidic media and to afford complex mixtures of products. The instability of the azido group in acidic media was probably the cause of difficulties encountered by Fox and coworkers[11] in the attempted conversion of 1,6-di-O-acetyl-4-azido-2,3-di-O-benzoyl-4-deoxy-α-D-glucopyranose into the corresponding halogenose. Treatment of the glycoside *I* in dichloromethane with hydrogen bromide in acetic acid and the subsequent reaction of the thus-obtained crude glycosyl bromide with the chloromercuri salt of 6-benzamidopurine afforded 9-(3,4,6-tri-O-benzoyl-1-bromo-1-deoxy-β-D-psicofuranosyl)-6-benzamidopurine (*X*) as the single nucleosidic product. By the action of methanolic ammonia on compound *X*, the free 9-(1-bromo-1-deoxy-β-D-psicofuranosyl)adenine (*XI*) was obtained. Consequently, the formation of the glycosyl bromide was accompanied by replacement of the azido group by the bromo atom. To our knowledge, such a reaction of alkyl azides has not been reported so far. It may be assumed by analogy with the paper of Kreher[12] on the decomposition of alkyl azides with aluminium chloride in benzene that the protonated azido group becomes the "leaving group" for the substitution by the bromide ion.

The reaction of the glycoside *II* with hydrogen bromide in dichloromethane was also anomalous. Conditions which were suitable for the preparation of analogous glycosyl bromides from the corresponding protected glycosides[2], led in the case of compound *II* to a 27% recovery of the starting material *II* and to a 37% yield of a crystalline substance which was ascribed the structure of 1-acetamido-3,4,6-tri-O-benzoyl-1-deoxy-D-psico-2,3-furanosene (*XII*) on the basis of elemental analysis and infrared spectrum similar to that of the earlier prepared 2,3,5-tri-O-benzoyl-D-ribo-1,2-furanosene[13].

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). The analytical samples were dried at 25°C/0·01 Torr for 8 h. Infrared spectra were measured on a Zeiss Model UR 10 apparatus. Polarographic measurements were performed on a LP 7 polarograph connected to a recording electron millivoltmeter EZ 7.

Kinetic Measurements

An equimolar mixture of the bromo ketone *IV* and sodium azide (10^{-3}M solutions in the appropriate solvent) were thermostatted at 25·0 ± 0·1°C in the Wobser U 8 apparatus. Samples (0·5 ml) were withdrawn at certain time intervals and polarographically analysed in the Kalousek

vessel with a separated calomel electrode (S.C.E) in 5 ml of an acetate buffer solution of pH 4·7. The time-dependent decrease of the bromo ketone *IV* wave at positive potentials ($E_{1/2} = +0{\cdot}05$ V/s.c.e) and the simultaneous increase of the azido keto *III* wave at the more negative potentials were evaluated from calibration graphs. The rate constants k_2 were determined graphically (accuracy, ±10%).

Methyl 1-Azido-3,4,6-tri-O-benzoyl-1-deoxy-β-D-psicofuranoside (*I*)

A solution of compound *III* (3·73 g; 10 mmol) in 0·1M methanolic hydrogen chloride (150 ml) was kept at room temperature for 15 h and then neutralised with silver carbonate. The insoluble portion was filtered off and washed with three 50 ml portions of methanol. The filtrate and washings were combined and evaporated under diminished pressure. The residue was dissolved in pyridine (20 ml) and the solution was treated under ice-cooling with benzoyl chloride (5 ml). The reaction mixture was kept at room temperature for 2 days, poured onto ice, and extracted with two 50 ml portions of ether. The ethereal extracts were successively washed with 5% aqueous phosphoric acid and saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and evaporated. The residue was chromatographed on a column of silica gel (300 g) in 92 : 8 benzene–ethyl acetate. The corresponding chromatographical fractions were combined, evaporated, and the residue crystallised from ethanol at 0°C for 12 h to afford 1·33 g of the protected glycoside *I*, m.p. 72·5—73·5°C (ethanol); $[\alpha]_D^{25}$ −12·2°C (*c* 0·42, ethyl acetate). For $C_{28}H_{25}N_3O_8$ (531·5) calculated: 63·27% C, 4·74% H, 7·91% N; found: 63·51% C, 4·78% H, 7·64% N. The last chromatographical fractions afforded a sirupous mixture containing the corresponding α-anomer as the predominant component.

Methyl 1-Acetamido-3,4,6-tri-O-benzoyl-1-deoxy-β-D-psicofuranoside (*II*)

Acetic anhydride (1·0 ml) and 5% PdO on barium sulfate (1·5 g) was added to a solution of the protected glycoside *I* (1·64 g; 3 mmol) in ethyl acetate (9·0 ml). A mild stream of hydrogen was then passed through the stirred mixture for 5 h. The catalyst was filtered off and washed with ethyl acetate. The filtrate and washings were combined, evaporated under diminished pressure, the residue coevaporated with two 15 ml portions of toluene, and the final residue chromatographed on a column of silica gel (150 g) in the solvent system benzene–ethyl acetate (3 : 5) to afford 1·50 g (91·5%) of compound *II* in the form of a solid foam; $[\alpha]_D^{25}$ −1·0 (*c* 0·50; ethyl acetate). For $C_{30}H_{29}NO_9$ (547·6) calculated: 65·81% C, 5·34% H, 2·56% N; found: 65·88% C, 5·36% H, 2·54% N.

3,4,5,6-Tetra-O-acetyl-1-azido-1-deoxy-D-psicose (*III*)

A solution of the ketone[9] *IV* (4·11 g; 10 mmol) in acetone (50 ml) was treated dropwise under stirring and external ice-cooling with a solution of lithium azide[14] (0·61 g; 12·5 mmol) in ethanol (15 ml) over 45 min. The reaction mixture was kept at room temperature for 30 min, evaporated under diminished pressure, the residue dissolved in chloroform (50 ml), the solution washed with two 50 ml portions of water, dried over magnesium sulfate, and evaporated. The residue was chromatograghed on a column of silica gel (200 g) in the solvent system benzene–ethyl acetate (7 : 3) to afford 3·26 g (87%) of the chromatographically homogeneous sirupous product *III*, $[\alpha]_D^{25}$ +3·65° (*c* 0·78; ethyl acetate). Infrared spectrum (chloroform): 2115 cm^{-1} (N_3); 1748 cm^{-1} and shoulder at 1765 cm^{-1} (C=O acetate); sh. 1725 and sh. 1707 cm^{-1} (C=O ketone). For $C_{14}H_{19}N_3O_9$ (373·3) calculated: 45·04% C, 5·13% H, 11·26% N; found: 45·42% C, 5·12% H, 11·03% N.

Methyl 1-Azido-1-deoxy-β-D-psicofuranoside (*V*)

A solution of compound *I* (532 mg; 1 mmol) in 15 ml of methanolic ammonia (saturated at 10°C) was kept at room temperature for 3 days, evaporated under diminished pressure, and the residue chromatographed on a column of silica gel (30 g) in the solvent system ethyl acetate–acetone–ethanol–water (5 : 1 : 1 : 1) to afford 185 mg (84%) of the sirupous glycoside *V*, $[\alpha]_D^{25}$ −30·47° (*c* 0·90; water). Periodic acid uptake (pH 6·8, 25°C): 0·90 mol. For $C_7H_{13}N_3O_5$ (219·2) calculated: 38·35% C, 5·98% H, 19·17% N; found: 38·76% C, 6·20% H, 18·66% N.

Methyl 1-Azido-1-deoxy-β-D-psicofuranoside 3,4-O-Phenylboronate (*VI*)

From a mixture of the glycoside *V* (110 mg; 0·5 mmol), phenylboronic acid (52 mg; 0·5 mmol) and benzene (10 ml), the solvent (about 5 ml) was distilled off in the course of 1 h. The remaining benzene was evaporated under diminished pressure and the residue was crystallised from ether–light petroleum (40—60°C) to afford 107 mg of compound *VI*, m.p. 90·5—91·0°C, $[\alpha]_D^{25}$ −113·2° (*c* 0·36; benzene). Infrared spectrum (chloroform): 2110 cm^{-1} (N_3), 3610 cm^{-1} (OH), 3465 cm^{-1} (assoc. OH). For $C_{13}H_{16}BN_3O_5$ (305·1) calculated: 51·18% C, 5·29% H, 13·77% N, 3·55% B; found: 51·50% C, 4·99% H, 13·48% N, 3·20% B.

1-Acetamido-3,4,5,6-tetra-O-acetyl-1-deoxy-D-psicose (*VII*)

To the solution of compound *III* (3·73 g; 10 mmol) in ethyl acetate (15 ml), there was added acetic anhydride (2·5 ml) and 5% PdO on barium sulfate (4·0 g). A mild stream of hydrogen was then passed through the stirred mixture at 25°C for 5 h. The catalyst was filtered off, washed with two 5 ml portions of ethyl acetate, the filtrate and washings combined, evaporated, and the redisue coevaporated with two 15 ml portions of toluene. The final residue was triturated with diisopropyl ether (40 ml), the crystalline portion collected with suction, and recrystallised from diisopropyl ether–ethanol (7 : 1) to afford 2·73 g (70%) of compound *VII*, m.p. 111—112°C, $[\alpha]_D^{25}$ −19·1° (*c* 0·50; ethyl acetate). Infrared spectrum (chloroform): 1514 cm^{-1} (C=O amide II), 1677 cm^{-1} (C=O amide I), 1750 cm^{-1} (C=O acetate), 3425 cm^{-1} (NH). For $C_{16}H_{23}NO_{10}$ (389·4) calculated: 49·36% C, 5·95% H, 3·60% N; found: 49·57% C, 5·97% H, 3·51% N.

3,4,5,6-Tetra-O-acetyl-1-deoxy-D-psicose (*IX*)

To a solution of the diazo ketone[9] *VIII* (537 mg; 1·5 mmol) in acetic anhydride (3·0 ml), there was added acetic acid (0·1 ml) and 5% PdO on barium sulfate catalyst (500 mg). A mild stream of hydrogen was then passed at room temperature through the mixture for 12 h. Chloroform (20 ml) was added, the catalyst filtered off, the filtrate washed with three portions of saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and evaporated under diminished pressure. The residue was coevaporated with toluene (15 ml) and crystallised from ethanol to afford 400 mg (80%) of compound *IX*, m.p. 74—76°C, undepressed on admixture with an authentic specimen[9]. When acetic anhydride was replaced by ethyl acetate (5·0 ml) as solvent, the hydrogenation afforded (under otherwise identical conditions) 315 mg (63%) of compound *IX*, m.p. 74—76°C (ethanol).

9-(3,4,6-Tri-O-benzoyl-1-bromo-1-deoxy-β-D-psicofuranosyl)-6-benzamidopurine (*X*)

A solution of compound *I* (2·66 g; 5 mmol) in dichloromethane (15 ml) was treated at 0°C with a precooled (0°C) 50% solution (15 ml) of hydrogen bromide in acetic acid. The mixture was

kept at 0°C for 30 min and at room temperature for 10 min, diluted with dichloromethane (25 ml), and poured onto ice. The organic layer was washed at 0°C with three 10 ml portions of saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and evaporated under diminished pressure. The residue was dissolved in acetonitrile (20 ml), the solution treated with the chloromercuri salt of 6-benzamidopurine (3·31 g; 7 mmol), the whole mixture stirred at room temperature for 16 h, and diluted with chloroform (100 ml). The solid portion was filtered off and washed with three 10 ml portions of chloroform. The filtrate and washings were combined, evaporated under diminished pressure, and the residue dissolved in chloroform (100 ml). The solution was washed with three 20 ml portions of 10% aqueous potassium iodide and two 20 ml portions of water, dried over magnesium sulfate, evaporated under diminished pressure, and the residue chromatographed on a column of silica gel (100 g) in benzene–ethyl acetate (1 : 1) to afford 620 mg (16%) of compound *X* as a solid foam, $[\alpha]_D^{25}$ −15·8° (*c* 0·35; ethyl acetate). For $C_{39}H_{30}BrN_5O_8$ (776·6) calculated: 60·32% C, 3·89% H, 9·03% N, 10·29% Br; found: 60·16% C, 3·92% H, 9·05% N, 10·78% Br.

9-(1-Bromo-1-deoxy-β-D-psicofuranosyl)adenine (*XI*)

A solution of compound *X* (777 mg; 1 mmol) in 25 ml of methanolic ammonia (saturated at 15°C) was kept at room temperature for 3 days, evaporated under diminished pressure, and the residue chromatographed on a column of silica gel (40 g) in the solvent system ethyl acetate–acetone–ethanol–water (6 : 1 : 1 : 1) to afford 245 mg (68%) of the chromatographically pure compound *XI* in the form of a solid foam. Ultraviolet spectrum (water): λ_{max} 208 and 261 nm (log ε 4·16 and 4·07, resp.). CD spectrum (water): 215 nm (−7600), sh. 227 nm (−1670), 245 nm (+1700), sh. 262 nm (+300). For $C_{11}H_{14}BrN_5O_4$ (360·2) calculated: 36·68% C, 3·92% H, 19·45% N, 22·19% Br; found: 35·23% C, 4·39% H, 18·65% N, 21·29% Br. Even after 20 h of drying at 25°C/0·01 Torr, the specimen contained 5% of water.

1-Acetamido-3,4,6-tri-O-benzoyl-1-deoxy-D-psico-2,3-furanosene (*XII*)

A solution of compound *II* (548 mg; 1 mmol) in dichloromethane (3 ml) was treated at 0°C with a 30% solution (3 ml) of hydrogen bromide in acetic acid. The reaction mixture was kept at 0°C for 30 min and at room temperature for 10 min, diluted with dichloromethane (9 ml), and poured onto ice. The organic layer was washed at 0°C with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and evaporated under diminished pressure. The residue was chromatographed on a column of silica gel in benzene–ethyl acetate (2 : 3) to afford 150 mg (27%) of compound *II* and 190 mg (37%) of compound *XII*, m.p. 116·5–118·0°C (ethanol), $[\alpha]_D^{25}$ −14·4° (*c* 0·50; ethyl acetate). Infrared spectrum (chloroform): 1681 cm^{-1} (C=O amide), 3000 cm^{-1} (NH). For $C_{29}H_{25}NO_8$ (515·5) calculated: 67·57% C, 4·89% H, 2·72% N; found: 67·51% C, 4·89% H, 3·01% N.

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