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The Synthesis of Some Purine Nucleosides from 4,6-Di-*O*-acetyl-3-deoxy-3-(ethoxycarbonylamino)-D-glucal

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The acid catalyzed reaction of 4,6-di-*O*-acetyl-3-deoxy-3-(ethoxycarbonylamino)-D-glucal and 6-chloropurine in nitromethane solution gave 6-chloro-9-(4′,6′-di-*O*-acetyl-2′,3′-dideoxy-3′-ethoxycarbonylamino-α- and β-D-*arabino*hexopyranosyl)purine. These were converted to the corresponding deblocked 6-dimethylaminopurine nucleosides by treatment with ethanolic dimethylamine; acetylation of these gave the respective 4′,6′-di-*O*-acetyl derivatives. The anomeric assignments for the nucleosides were based on their nmr spectral data.

The biological activity of natural products like puromycin and 3′-amino-3′-deoxyadenosine (2) has given rise to great interest in the preparation of synthetic analogues which may be potentially useful as antimetabolites. The fact that some nucleosides containing 2-deoxy-D-*arabino*-hexopyranose have been shown (3) to be powerful inhibitors of a nucleoside phosphorylase from Ascites tumour cells, has also prompted us to synthesize nucleosides containing a 2-deoxy-3-(ethoxycarbonylamino)hexopyranose moiety from the glycal (I) (17).

The acid-catalyzed fusion reaction between fully acetylated sugars and purines, developed by Japanese workers (4-6) and by Robins and co-workers (7-9), is a simple, general procedure for the synthesis of purine nucleosides. By working in organic solvents, the reaction can be carried out under milder conditions (10). Under conditions of acid catalysis 2′-deoxynucleosides can also be prepared from a glycal by using a fusion method (11,12) or by working in ethyl acetate solution (12,13).

The last two procedures can also produce 2′,3′-unsaturated pyranosylpurine nucleosides (11,14) as well as a glycal-type compound (14-16) where the heterocyclic base is attached at the 3-position of the sugar.

In the present work, nitromethane was used as solvent for the reaction between 4,6-di-*O*-acetyl-3-deoxy-3-(ethoxycarbonylamino)-D-glucal (17) (I) and 6-chloropurine. The glycal I and 6-chloropurine in nitromethane with sulfamic acid as catalyst, was heated under nitrogen with

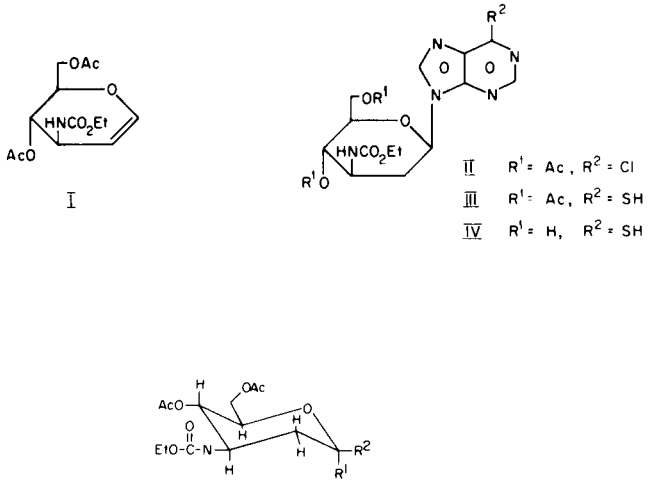
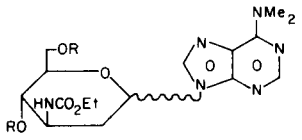


Figure 1 (a) C 1 (β), R^1 = H, R^2 = 6 - chloro - 9 - purinyl
(b) C 1 (α), R^1 = 6 - dimethylamino - 9 - purinyl, R^2 = H



V Base α, R = Ac
VI Base α, R = H
VII Base β, R = H
VIII Base β, R = Ac

continuous agitation to give the corresponding nucleoside as an anomeric mixture in the excellent yield of 48%. Fractional crystallization gave 6-chloro-9-(4′,6′-di-*O*-acetyl-2′,3′-dideoxy-3′-ethoxycarbonylamino-β-D-*arabino*hexopyranosyl)purine (II) and an oil containing both α and β anomers.

That glycosidation had occurred at N-9 was ascertained by comparison of the ultraviolet spectrum of II with the ultraviolet spectra of 6-chloro-9-methylpurine and 6-chloro-7-methylpurine (18), as well as by comparison of the ultraviolet spectra of the two nucleosides VI and VII (prepared from the oil and II, respectively) with the spectra of 6-dimethylamino-9-methylpurine and 6-dimethylamino-7-methylpurine (19).

The β-configuration for II was assigned after inspection of its nmr spectrum. This shows a quartet centered at τ 3.95 with $J_{1',2'ax}$ 11 Hz and $J_{1',2'eq}$ 2.5 Hz for the anomeric proton, from which it is clear that H-1′ must be assigned an axial position. The one-proton triplet at τ 5.00 is due to the resonance of H-4′(H-4′ in an analogues nucleoside (14) resonates at τ 4.82). The coupling constants $J_{4',3'} = J_{4',5'}$ 10 Hz which represent two axial-axial couplings only, support the assignment of the peak and establishes that H-4′ is in an axial position. From these observations as well as from the fact that the carbohydrate moiety has the D-*arabino* configuration (17), it is possible to assign the β-configuration to compound II in which a D C_1 conformation as shown in Figure 1(a) is adopted by the sugar moiety.

The nmr spectrum of the oil, obtained after fractional crystallization of II, shows a broadened doublet at τ 3.68 and a quartet at τ 3.95, indicative of a mixture of α and β anomers (11). When this oil was treated with an ethanolic solution of dimethylamine, crystals of only one anomer, the nucleoside VI, m.p. 207-211°, were deposited. The mother liquor was not further investigated. The nmr spectrum (DMSO-d_6) of VI shows a broadened doublet at τ 3.83 with $J_{1',2'ax}$ 4 Hz and $J_{1',2'eq} < 1$ Hz. Similar treatment of the crystalline nucleoside II gave the 6-dimethylamino nucleoside VII, m.p. 236-240°, in good yield.

Additional proof for the assignment of the anomeric configurations was obtained from the nmr spectra of the nucleosides V and VIII, which were obtained by acetylation of the corresponding nucleosides VI and VII. The anomeric proton of VIII appears as a split doublet at τ 4.09 with $J_{1',2'ax}$ 12 Hz and $J_{1',2'eq}$ 2.5 Hz, whereas H-4′ appears as a triplet at τ 5.07 with $J_{4',3'} = J_{4',5'}$ 10 Hz. From these data it is clear that both H-1′ and H-4′ must be in axial positions.

The nmr spectrum of V shows a broadened doublet at τ 3.80 with $J_{1',2'ax}$ 5 Hz and $J_{1',2'eq} < 1$ Hz; H-1′ must therefore be in an equatorial position. Once again, H-4′ appears as a triplet at τ 5.07, $J_{4',3'} = J_{4',5'}$ 10 Hz. From the preceding evidence, it is possible to assign the α-configuration for V, and thus for VI. The sugar moiety of V also adopts a D C_1 conformation as depicted in Figure 1(b).

The nmr spectra of V and VIII showed that the ethoxycarbonylamino group at C-3′ was not attacked by dimethylamine under the conditions that were used.

Treatment of the nucleoside II with thiourea in ethanol solution gave the thio-nucleoside III in good yield. Without purification, the acetate groups were removed with sodium ethoxide in ethanol to give crystalline 6-thio-9-(2′,3′-dideoxy-3′-ethoxycarbonylamino-β-D-*arabino*hexopyranosyl)purine IV. As only the β-anomers of the nucleosides were required for biological evaluation, the α-anomer of the thionucleoside was not prepared.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Ir spectra were measured with a Perkin-Elmer Model 237 spectrophotometer and uv spectra in ethanol on a Unicam Model S.P. 800 spectrometer. Nmr spectra were recorded on a Varian HA-100 spectrometer. Chemical shifts are given on the τ scale with tetramethylsilane as internal standard for chloroform-*d* solutions, unless otherwise stated. Optical rotations were measured with a Bendix-NPL Automatic Polarimeter Type 143. Mass spectra were determined with an A.E.I. MS-9 spectrometer using the direct insertion technique. Tlc and plc (2 mm plates) were performed on silica gel GF_{254} (Merck), and spots were detected either with uv light at 254 mμ or with iodine vapour. Analyses were done on a Perkin-Elmer 240 Elemental Analyser.

6-Chloro-9-(4′,6′-di-*O*-acetyl-2′,3′-dideoxy-3′-ethoxycarbonylamino-β-D-*arabino*hexopyranosyl)purine (II).

A mixture of the glycal I (15) (301 mg., 1 mmole), 6-chloropurine (231 mg., 1.5 mmoles) and sulfamic acid (48 mg.) in nitromethane (15 ml.) was magnetically stirred and heated under nitrogen in an oil bath at 105° for 2.5 hours. The mixture was evaporated to dryness, extracted with chloroform (100 ml.) and the chloroform solution washed with saturated aqueous sodium bicarbonate (2 x 100 ml.). The solution was dried (sodium sulphate) and evaporated to give an oil which still contained some of the glycal I (tlc on silica, chloroform-methanol 24:1). Purification of the oil by plc with chloroform-methanol 49:1 as eluent gave a foam (220 mg., 48%) which on fractional crystallization from acetone-ether-hexane yielded colourless needles (72 mg., 15.8%) and an oil (106 mg., 23%) from the mother liquor. The crystalline fraction had m.p. 147-149°, M^+ 455, ν max (chloroform) 3420 (NH); 1740, 1720 cm^{-1} (C=O), λ max (ethanol), 263 mμ (ε, 9,350); $[\alpha]_D^{23}$ -22° (c 1.36, chloroform); nmr τ 1.24 singlet (H-8), 1.62 singlet (H-2), 3.95 quartet (H-1′, $J_{1',2'ax}$ 11 Hz, $J_{1',2'eq}$ 2.5 Hz), 4.61 doublet (NH, lost on addition of deuterium oxide/triethylamine), 5.00 triplet (H-4′, $J_{4',3'} = J_{4',5'}$ 10 Hz), 5.54-6.03 multiplet (H-3′, H-5′, H-6′), 5.90 quartet (OCH_2CH_3) 7.14-7.64 multiplet (H-2′eq, H-2′ax), 7.89, 7.97 two singlets (Ac), 8.79 triplet (OCH_2CH_3).

Anal. Calcd. for $C_{18}H_{22}ClN_5O_7$: C, 47.5; H, 4.9; N, 15.4. Found: C, 47.4; H, 4.9; N, 15.4.

6-Dimethylamino-9-(2′,3′-dideoxy-3′-ethoxycarbonylamino-β-D-*arabino*hexopyranosyl)purine (VII).

A solution of II (950 mg.) in 30 ml. ethanolic dimethylamine (33% w/w) was gently refluxed for 5 hours, during which time the product precipitated. The mixture was cooled, filtered and washed with cold ethanol and hexane; yield 570 mg. An additional 59 mg. was recovered from the mother liquor on addition of hexane. Recrystallization from ethanol-hexane gave fine needles, 549 mg. (69%), m.p. 236-240°; m/e 334 (M^+-ethanol); λ max (ethanol), 273 mμ (ε, 17,800); nmr (DMSO-d_6): τ 6.00 quartet (OCH_2CH_3), 8.83 triplet (OCH_2CH_3).

Anal. Calcd. for $C_{16}H_{24}N_6O_5$: C, 50.5; H, 6.4; N, 22.1. Found: C, 50.7; H, 6.5; N, 21.9.

6-Dimethylamino-9-(2′,3′-dideoxy-3′-ethoxycarbonylamino-α-D-*arabino*hexopyranosyl)purine (VI).

As has been described for the preparation of VII, 1.2 g. of the oil, obtained after isolation of II, was refluxed 7 hours in ethanolic dimethylamine solution (35 ml.). The solution was left at ambient temperature for 2 days, during which time a product crystallized from the solution. Recrystallization from ethanol gave pure VI, 450 mg., m.p. 207-211°, M^+ 380, λ max (ethanol) 274 mμ (ε, 17,300), nmr (DMSO-d_6) τ 3.83 broadened doublet (H-1′, $J_{1',2'ax}$ 4 Hz, $J_{1',2'eq} < 1$ Hz), 6.00 quartet (OCH_2CH_3), 8.83 triplet (OCH_2CH_3).

The mother liquor was not further investigated.

Anal. Calcd. for $C_{16}H_{24}N_6O_5$: C, 50.5; H, 6.4; N, 22.1. Found: C, 50.3; H, 6.5; N, 21.7.

6-Dimethylamino-9-(4′,6′-di-*O*-acetyl-2′,3′-dideoxy-3′-ethoxycarbonylamino-α-D-*arabino*hexopyranosyl)purine (V).

A mixture of VI (100 mg.) in pyridine (1 ml.) and acetic anhydride (1 ml.) was magnetically stirred at room temperature for 1.5 hours when tlc showed the reaction to be completed. The mixture was poured into ice-cold water, and extracted with chloroform (3 x 25 ml.). The combined chloroform extracts were successively washed with cold 3% aqueous hydrochloric acid (3 x 20 ml.) water (2 x 10 ml.) and a saturated aqueous sodium bicarbonate solution (10 ml.).

Evaporation of the solvent gave an oil which crystallized on standing. Recrystallization from acetone-hexane gave crystalline V, (45 mg., 36.8%), m.p. 130-132°, $[\alpha]_D^{23}$ +97° (*c* 1.0 chloroform), ν max (chloroform) 3420 (NH), 1740, 1720 (C=O), 1600 cm^{-1} (C=C); nmr τ 1.65 singlet (H-2), 1.91 singlet (H-8), 3.80 broadened doublet (H-1′, $J_{1',2'ax}$ 5 Hz, $J_{1',2'eq} < 1$ Hz), 4.82 doublet (NH, lost on addition of deuterium oxide/triethylamine), 5.04 triplet (H-4′, $J_{4',3'} = J_{4',5'}$ 10 Hz), 5.60-6.08 5-proton multiplet (τ 5.70 quartet, H-6′, $J_{6'_I,6'_{II}}$ 12.5 Hz, $J_{6'_I,5'}$ 5 Hz; τ 5.89 quartet, OCH_2CH_3; τ 6.00, H-$6'_{II}$, $J_{6'_{II},5'}$ 2.5 Hz), 6.28 multiplet (H-5′) 6.50 singlet (NMe_2), 7.70 multiplet (H-2′), 7.96, 7.99 two singlets (Ac), 8.77 triplet (OCH_2CH_3).

Anal. Calcd. for $C_{20}H_{28}N_6O_7$: C, 51.7; H, 6.1; N, 18.1. Found: C, 52.0; H, 6.3; N, 17.7.

6-Dimethylamino-9-(4′,6′-di-*O*-acetyl-2′,3′-dideoxy-3′-ethoxycarbonylamino-β-D-*arabino*hexopyranosyl)purine VIII.

The method as described for the preparation of V was employed to give VIII from VII in 58% yield after recrystallization from acetone-hexane, m.p. 164-165°; $[\alpha]_D^{23}$ -33° (*c* 1.1 chloroform), ν max (chloroform) 3430 (NH), 1740, 1720 (C=O), 1600 cm^{-1} (C=C); nmr τ 1.70 singlet (H-2), 2.14 singlet (H-8); 4.09 quartet (H-1′, $J_{1',2'ax}$ 12 Hz, $J_{1',2'eq}$ 2.5 Hz), 4.94 doublet (NH, lost on addition of deuterium oxide/triethylamine), 5.07 triplet (H-4′, $J_{4',5'} = J_{4',3'}$ 10 Hz), 5.58-6.20 multiplet (H-6′, H-5′, H-3′), 5.94 quartet (OCH_2CH_3), 6.72 singlet (NMe_2), 7.26-7.52 multiplet (H-2′eq), 7.57-7.85 multiplet (H-2′ax), 7.93, 7.99 two singlets (Ac), 8.82 triplet (OCH_2CH_3).

Anal. Calcd. for $C_{20}H_{28}N_6O_7$: C, 51.7; H, 6.1; N, 18.1. Found: C, 52.0; H, 6.2; N, 18.1.

6-Thio-9-(2′,3′-dideoxy-3′-ethoxycarbonylamino-β-D-*arabino*hexopyranosyl)purine (IV).

A solution of II (273 mg. 0.5 mole) and thiourea (81 mg.) in absolute ethanol (7 ml.) was magnetically stirred and refluxed for 1 hour. The product precipitated. The mixture was cooled to room temperature, filtered and washed with absolute ethanol, yielding 202 mg. (75%) of a white solid III, ν max (potassium bromide) 1740, 1720 (C=O), 1600 cm^{-1} (C=C).

To 56 mg. of this solid in absolute ethanol (3 ml.), was added 5 mg. sodium hydride (50% dispersion in mineral oil) and the mixture stirred to give a clear solution. After about 1 hour, the product IV began to separate. Stirring was continued for an additional 30 minutes, the mixture acidified with glacial acetic acid, the precipitate filtered and washed with cold ethanol. Recrystallization from aqueous ethanol gave crystalline IV, 32 mg. (69%), m.p. 197-199°.

Anal. Calcd. for $C_{14}H_{19}N_5O_5S$: C, 45.5; H, 5.2; N, 19.0. Found: C, 45.6; H, 5.2; N, 18.7.

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