An Approach to the Synthesis of Cyclopentane Analogues of the Lyxosyl *C*-Nucleosides

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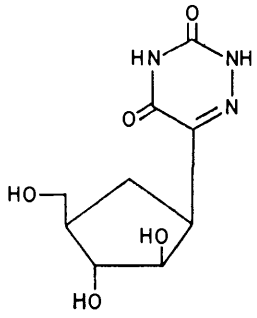
The Diels–Alder adduct of cyclopentadiene and maleic anhydride has been converted into 5-*endo*,6-*endo*-*O*-isopropylidene-3-methoxycarbonylnorborn-2-ene. Cleavage of the double bond in this unsaturated ester affords methyl 2-(2′β,3′β-*O*-isopropylidene-4′β-methoxycarbonylcyclopent-1′β-yl)glyoxalate in which all the substituents are on the same side of the cyclopentane ring. This cyclopentane derivative is a potential synthon for cyclopentane analogues of the lyxosyl *C*-nucleosides, and its transformation into 5-(4′β-hydroxymethyl-2′β,3′β-dihydroxycyclopent-1′β-yl)-6-azauracil has been examined.

As part of a study into the synthesis of *C*-nucleosides and related compounds, Just [1] prepared some carbocyclic analogues (having a cyclopentane rather than a tetrahydrofuran ring system); the uracil analogue (1) is a representative example. The synthesis of (1) was carried out by elaboration of the cyclopentane derivative (2), derived from oxidative cleavage of the norbornene

RESULTS AND DISCUSSION

The Diels–Alder addition of cyclopentadiene to maleic anhydride is well documented and readily affords the *endo*-anhydride adduct (7), which on hydrolysis yields the *endo-cis*-dicarboxylic acid (8).[3] Oxidation of this acid (8) leads to the bis-lactone (9) [4] having potential *endo-cis*-hydroxy-functions at C-5 and C-6 as required in the



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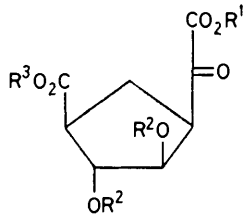

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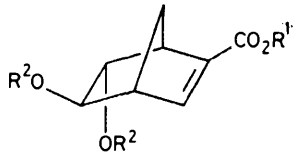

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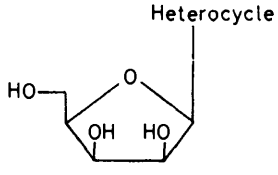

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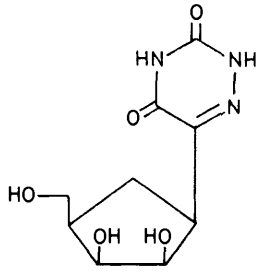

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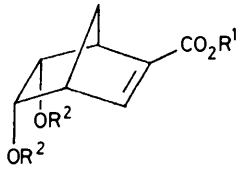

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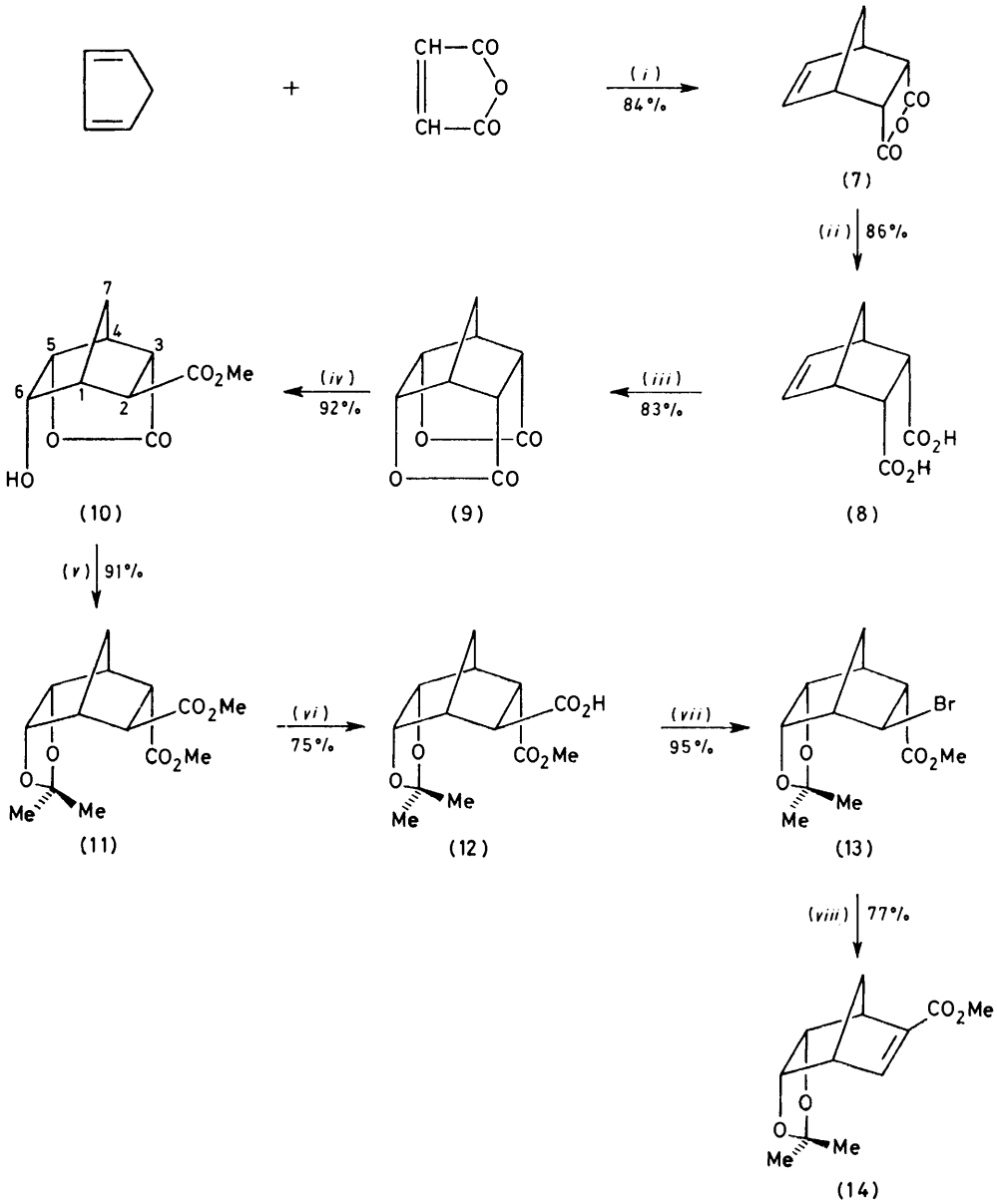
(3). *C*-Nucleosides of type (4) in which the carbohydrate moiety is D-lyxose, having all the groups attached to the furanose ring in the β-configuration, have received little study.[2] As a complement to the work of Just we have investigated the synthesis of the cyclopentane analogue (5), requiring as a precursor synthon the norbornene derivative of type (6) for which the synthetic Scheme 1 was employed.

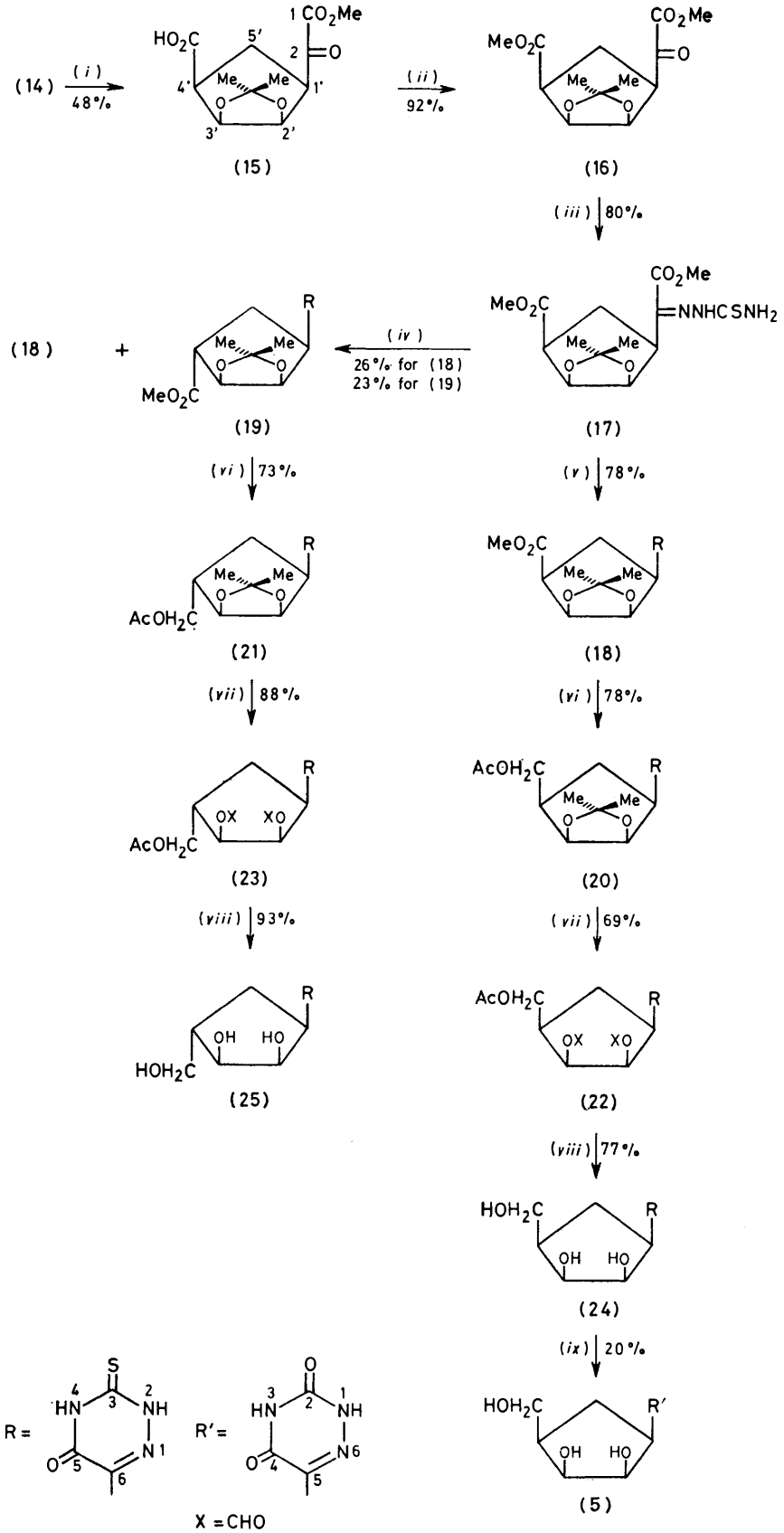
synthon (6). Treatment of the bis-lactone (9) with sodium methoxide in methanol resulted in the opening of the lactone function to give the hydroxy-ester γ-lactone (10). Under the basic conditions of the reaction epimerisation occurs to leave the ester methoxycarbonyl group in the more stable *exo*-position. This is consistent with the known greater thermodynamic stability of the methyl ester of norborn-2-*exo*-ylcarboxylic acid over its

2-*endo*-epimer.[5] Treatment of the hydroxy-ester γ-lactone (10) with 2,2-dimethoxypropane in anhydrous methanol saturated with dry hydrogen chloride resulted in opening of the lactone ring and protection of the resultant *endo-cis*-5,6-diol system to give the *trans*-bis-es er the unsaturated ester (14). Conversion of the ester (14) into the *C*-nucleoside carbocyclic analogues (5), (24), and (25) is outlined in Scheme 2. In this scheme the cyclisation of the thiosemicarbazone (17) on treatment with sodium methoxide to afford the triazinone (18) had to be



SCHEME 1 (*i*) 0 °C, EtOAc; (*ii*) H_2O; (*iii*) $Pb(OAc)_4$–AcOH; (*iv*) NaOMe–MeOH; (*v*) 2,2-Dimethoxypropane–HCl; (*vi*) KOH–t-BuOH; (*vii*) HgO–Br_2; (*viii*) Et_3N–tetrahydrofuran

(11). Selective hydrolysis of the 2-*exo*-methoxycarbonyl function in (11) was achieved by reaction with potassium hydroxide in t-butyl alcohol–water (10 : 1) at room temperature for 17 h, to give the half-ester (12). The Cristol–Firth modification of the Hunsdiecker reaction [6] for the conversion of alkyl carboxylic acids into alkyl halides was applied to the half-ester (12) and afforded the bromide (13). Treatment of (13) with triethylamine resulted in loss of hydrogen bromide giving carried out at room temperature for 0.5 h; at a higher temperature and longer reaction time some epimerisation of the C-4′ methoxycarbonyl group occurred to afford (19). The conversion of the thioxotriazinone (25) into the 6-azauracil (5) could not be accomplished satisfactorily using the procedure of reaction with methyl iodide employed by Just [1] to prepare (1) from its thioxotriazinone analogue. Application of an alternative procedure for such conversions due to Sorm [7] gave a



SCHEME 2 (*i*) $KMnO_4$–$NaIO_4$; (*ii*) CH_2N_2; (*iii*) $H_2NCSNHNH_2$–HCl; (*iv*) NaOMe, 45 °C; (*v*) NaOMe, room temperature; (*vi*) $LiAlH_4$–tetrahydrofuran–Ac_2O–pyridine; (*vii*) HCO_2H; (*viii*) NaOH–MeOH; (*ix*) MeI–H^+

product which, although it could not be satisfactorily purified, had spectral properties appropriate for (5). We believe that the procedures described afford a route to the synthesis of cyclopentane analogues of the lyxosyl *C*-nucleosides that is of general synthetic utility.

The norbornanes (10)—(13) and norbornene (14) were recognised on the basis of their spectral data (see Experimental section) which is consistent with published information [8] relating to norbornanes and norbornenes. The compounds (15)—(25) had appropriate spectral properties based on the n.m.r. spectrum of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone [9] [to distinguish (18) from (19)] and of cyclopentane derivatives.[10]

EXPERIMENTAL

Norborn-5-ene-2-*endo*,3-*endo*-dicarboxylic acid anhydride (7) (84%, m.p. 163—164 °C) and norborn-5-ene-2-*endo*,3-*endo*-dicarboxylic acid (8) (86%, m.p. 178 °C) were prepared by the method of Fieser,[3] and 5-*endo*,6-*endo*-dihydroxynorbornane-2-*endo*,3-*endo*-dicarboxylic acid bis-lactone (9) (83%, m.p. 63 °C) by the method of Fray.[4]

5-endo,6-endo-*Dihydroxy*-2-exo-*methoxycarbonylnorbornane*-3-endo-*carboxylic Acid γ-Lactone* (10).—The bis-lactone (9) (5.40 g, 29.97 mmol) was dissolved with stirring in a solution of sodium methoxide in methanol [prepared from sodium (3.46 g, 0.15 g atom) and anhydrous AnalaR methanol (115 ml)] at room temperature. After 10 min a white precipitate gradually began to appear. The reaction mixture was stirred for 24 h at room temperature, and afterwards neutralised by the gradual addition of Dowex 50W-X8 (H^+) ion-exchange resin (200 g). When the white precipitate had dissolved, the resin was filtered off and washed with methanol (3 × 20 ml). The combined filtrate and washings were evaporated to afford a pale yellow oil which crystallised on standing, and which on recrystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C) afforded 5-endo,6-endo-*dihydroxy*-2-exo-*methoxycarbonylnorbornane*-3-endo-*carboxylic acid γ-lactone* (10) (5.88 g, 27.71 mmol, 92%) as a white crystalline solid, m.p. 75—76 °C (Found: C, 56.45; H, 5.63. $C_{10}H_{12}O_5$ requires C, 56.58; H, 5.70%); $\nu_{max.}$ ($CHCl_3$) 3 530 (OH), 1 770 (lactone C=O), and 1 740 cm^{-1} (ester C=O); δ(90 MHz, $CDCl_3$) 4.50 (t, H-5), 4.0 (q, H-6), 3.65 (s, CO_2Me), 3.47 (br s, OH), 3.15 (m, H-4), 3.04 (m, H-2), 3.01 (m, H-3), 2.72 (m, H-1), 1.62 (dt, H-7-*anti*), and 1.40 (br d, H-7-*syn*); *J*(1,6-*exo*) 4, *J*(1,7-*anti*) 2, *J*(4,5-*exo*) 6, *J*(5-*exo*,6-*exo*) 6, and *J* (7-*anti*,7-*syn*) 12 Hz; *m/e* 192 (M^+), 177 (M^+ — Me), 174 (M^+ — H_2O), and 164 (M^+ — CO).

Dimethyl 5-endo,6-endo-O-*Isopropylidenenorbornane*-2-exo,3-endo-*dicarboxylate* (11).—The hydroxy-lactone (10) (5.78 g, 27.26 mmol) was dissolved in anhydrous 1,4-dioxan (40 ml) under a nitrogen atmosphere, and 2,2-dimethoxypropane (14.17 g, 136.4 mmol) added to the stirred solution together with a saturated solution (1 ml) of hydrogen chloride in methanol. The resultant solution was stirred at room temperature for 20 h, and the solvent then evaporated to afford a pale reddish oil which crystallised on standing, and was recrystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) to give *dimethyl* 5-endo,6-endo-O-*isopropylidenenorbornane*-2-exo,3-endo-*dicarboxylate* (11) (7.05 g, 24.82 mmol, 91%) as white crystals, m.p. 86—87 °C (Found: C, 59.2; H, 7.25. $C_{14}H_{20}O_6$ requires C, 59.14; H, 7.09%); $\nu_{max.}$ ($CHCl_3$) 1 730 cm^{-1} (C=O); δ (90 MHz, $CDCl_3$) 4.44 (t, H-5,6), 3.72 (s, 2-*exo*-CO_2Me), 3.66 (s, 3-*endo*-CO_2Me), 3.54 (dd, H-2-*endo*), 3.23 (q, H-3-*exo*), 2.97 (m, H-4), 2.66 (m, H-1), 1.72 (dt, H-7-*anti*), 1.56 (dq, H-7-*syn*), 1.45 (s, Me), and 1.30 (s, Me); *J*(1,7-*anti*) 2, *J*(1,7-*syn*) 2, *J*(2-*endo*,3-*exo*) 6, *J*(2-*endo*,7-*syn*) 2, *J*(3-*exo*,4) 4, *J*(4,5-*exo*) 5, *J*(4,7-*anti*) 2, *J*(4,7-*syn*) 2, *J*(5-*exo*,6-*exo*) 4, and *J*(7-*anti*,7-*syn*) 11 Hz; *m/e* 284 (M^+), 269 (M^+ — Me), 254 (M^+ — 2Me), and 226 (M^+ — Me_2CO).

5-endo-6-endo-O-*Isopropylidene*-3-endo-*methoxycarbonylnorbornane*-2-exo-*carboxylic Acid* (12).—Potassium hydroxide (1.63 g, 29.11 mmol) was dissolved in t-butyl alcohol–water (10 : 1) (100 ml). To this solution the diester (11) (6.34 g, 22.32 mmol) was added and the mixture stirred at room temperature for 17 h to afford a pale yellow solution. This solution was neutralised with the addition of Dowex 50W-X8 (H^+) ion-exchange resin to pH 3; the resin was removed by filtration, washed with methanol (50 ml), and the combined filtrates and washings evaporated to afford a white solid. This solid was dissolved in chloroform (70 ml) and the solution extracted with 0.5M aqueous sodium hydrogencarbonate (5 × 40 ml). The combined alkaline solution was acidified to pH 3 and extracted again with chloroform (5 × 40 ml); the combined chloroform extracts were washed with water (2 × 40 ml), dried ($MgSO_4$), and the solvent evaporated to afford 5-endo,6-endo-O-*isopropylidene*-3-endo-*methoxycarbonylnorbornane*-2-exo-*carboxylic acid* (12) (4.5 g, 16.67 mmol, 74.7%) as white crystals, m.p. 193—194 °C (Found: C, 57.3; H, 6.75. $C_{13}H_{18}O_6$ requires C, 57.77; H, 6.71%); $\nu_{max.}$ ($CHCl_3$) 3 200 (CO_2H), 1 735 (C=O of CO_2Me), and 1 710 cm^{-1} (C=O of CO_2H); δ(90 MHz, $CDCl_3$) 9.22 (br s, CO_2H), 4.47 (t, H-5-*exo* and H-6-*exo*), 3.68 (s, CO_2Me), 3.58 (br d, H-2-*endo*), 3.23 (q, H-3-*exo*), 2.98 (m, H-4), 2.75 (m, H-1), 1.79 (br d, H-7-*anti*), 1.57 (br d, H-7-*syn*), 1.46 (s, Me), and 1.31 (s, Me); *J*(2-*endo*,3-*exo*) 6, *J*(3-*exo*,4) 4, *J*(4,5-*exo*) 4, *J*(5-*exo*,6-*exo*) 4, and *J*(7-*syn*,7-*anti*) 11 Hz; *m/e* 270 (M^+), 255 (M^+ — Me), and 226 (M^+ — CO_2).

Methyl 2-exo-*Bromo*-5-endo,6-endo-O-*isopropylidenenorbornane*-3-endo-*carboxylate* (13).—The acid (12) (3.20 g, 11.85 mmol) was dissolved in dry carbon tetrachloride (230 ml) and red mercury(II) oxide (2.12 g, 9.79 mmol) added. The resulting stirred suspension was refluxed in the dark under a nitrogen atmosphere for 45 min and then bromine (3.20 g, 20 mmol) was added dropwise during 1.5 h. After addition was complete the mixture was stirred and refluxed for a further 45 min, and then allowed to cool to room temperature during 1 h. The suspension was filtered through a Celite pad to remove the insoluble mercuric salts, and the filtrate washed successively with aqueous sodium hydrogencarbonate solution (0.5M, 2 × 50 ml), 1M sodium thiosulphate (2 × 50 ml), and water (50 ml). It was dried ($MgSO_4$), filtered, and the filtrate evaporated to afford *methyl* 2-exo-*bromo*-5-endo,6-endo-O-*isopropylidenenorbornane*-3-endo-*carboxylate* (13) (3.42 g, 11.21 mmol, 95%) as white crystals, m.p. 73—75 °C (Found: C, 47.55; H, 5.65; Br, 25.75. $C_{12}H_{17}BrO_4$ requires C, 47.23; H, 5.62; Br, 26.18%); $\nu_{max.}$ 1735 cm^{-1} (C=O); δ($CHCl_3$) 4.90 (q, H-2-*endo*), 4.48 (t, H-5-*exo* and H-6-*exo*), 3.70 (s, CO_2Me), 3.18 (q, H-3-*exo*), 2.98 (m, H-4), 2.72 (m, H-1), 2.16 (dt, H-7-*anti*), 1.72 (dq, H-7-*syn*), 1.43 (s, Me), and 1.27 (s, Me); *J*(1,6-*exo*) 4, *J*(2-*endo*,3-*exo*) 6, *J*(2-*endo*,7-*syn*) 3, *J*(3-*exo*, 4) 4, *J*(4,5-*exo*) 4, *J*(5-*exo*,6-*exo*) 4, and *J*(7-*syn*,7-*anti*) 12 Hz; *m/e* 305 (M^+), 290 (M^+ — Me), and 224 (M^+ — HBr).

Methyl 5-endo,6-endo-O-*Isopropylidenenorborn*-2-*ene*-3-*carboxylate* (14).—The bromoester (13) (3.50 g, 11.47

mmol) was dissolved in anhydrous tetrahydrofuran (50 ml), and triethylamine (6.0 g, 59.30 mmol) was added. The solution was then stirred and refluxed for 24 h, during which time a brownish white precipitate gradually formed and the solution darkened. The precipitate was filtered through Celite, washed with tetrahydrofuran (20 ml), and the combined filtrates evaporated to afford a dark brownish oil. Purification by column chromatography (80 g of Silica gel Merck H Type 60, eluant dichloromethane) gave *methyl* 5-endo,6-endo-O-*isopropylidenenorborn*-2-*ene*-3-*carboxylate* (14) (1.98 g, 8.8 mmol, 77%) as a pale yellow oil which solidified on standing, m.p. 37—40 °C (Found: C, 63.95; H, 7.05. $C_{12}H_{16}O_4$ requires C, 64.20; H, 7.19%); $\nu_{max.}$ ($CHCl_3$) 1 730 cm^{-1} (C=O); δ(60 MHz, $CDCl_3$) 7.04 (d, H-2), 4.78 (t, H-5-*exo* and H-6-*exo*), 3.70 (s, CO_2-Me), 3.34 (m, H-4), 3.15 (m, H-1), 1.82 (dt, H-7-*syn*), 1.52 (br d, H-7-*anti*), 1.22 (s, Me), and 1.17 (s, Me); J(1.2) 3, J(5-*exo*,6-*exo*) 3, and J(7-*anti*,7-*syn*) 11 Hz; *m/e* 224 (M^+), 209 (M^+ — Me), 196 (M^+ — CO), and 166 (M^+ — Me_2CO).

Methyl 2-(2′β,3′β-O-*Isopropylidene*-4′β-*methoxycarbonylcyclopent*-1′β-*yl*)*glyoxylate* (16).—A solution of the unsaturated ester (14) (0.395 g, 1.76 mmol) in acetone (20 ml) was added to a well stirred solution of sodium periodate (2.11 g, 9.87 mmol) and potassium permanganate (0.19 g, 1.20 mmol) in water (60 ml).[11] The resultant mixture was stirred at room temperature for 16 h, then filtered through Celite and the filter pad washed with chloroform (20 ml). The combined filtrates were extracted with chloroform (4 × 30 ml), and the extracts washed with water (2 × 30 ml), dried ($MgSO_4$), and the solvent evaporated to afford the crude acid (15) (0.23 g) as a white solid. Methylation with diazomethane gave a pale yellow solid which on purification by column chromatography (25 g of silica gel Merck H Type 60) using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 3) as eluant afforded the *bis-ester* (16) (0.22 g, 0.77 mmol) as a white crystalline solid, m.p. 131—133 °C (Found: C, 54.35; H, 6.3. $C_{13}H_{18}O_7$ requires C, 54.54; H, 6.57%); $\nu_{max.}$ ($CHCl_3$) 1 730 cm^{-1} (C=O); δ(90 MHz, $CDCl_3$) 5.14 (t, H-2′), 4.88 (t, H-3′), 3.89 (s, $COCO_2$-Me), 3.74 (s, CO_2Me), 3.39 (sextet, H-1′), 2.77 (sextet, H-4′), 2.50 (q, H-5′a), 1.89 (dq, H-5′ b), 1.31 (s, Me), and 1.24 (s, H-8); J(1′,2′) 6, J(1′,5′a) 10, J(1′,5′b) 6, J(2′,3′) 6, J(4′,5′a) 10, J(4′,5′b) 6, and J(5′a,5′b) 12 Hz; *m/e* 286 (M^+), 271 (M^+ — Me), 256 (M^+ — 2Me), and 228 (M^+ — Me_2CO).

Methyl 2-(2′β,3′β-O-*Isopropylidene*-4′β-*methoxycarbonylcyclopent*-1′β-*yl*)*glyoxylate Thiosemicarbazone* (17).—A solution of thiosemicarbazide (0.05 g, 0.55 mmol) in water (3 ml) was added to a well stirred solution of the bis-ester (16) (0.12 g, 0.42 mmol) in methanol (4 ml). Concentrated hydrochloric acid (15 drops) was then added and the thiosemicarbazide gradually dissolved. After a few minutes a white precipitate gradually formed and the reaction mixture was stirred at room temperature for a further 3 h. The precipitate was filtered, washed with water (5 ml) and methanol (5 ml), and dried to afford the *thiosemicarbazone* (17) (0.12 g, 0.33 mmol, 80%) as a white crystalline solid, m.p. 207—209 °C on recrystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C) (Found: C, 46.6; H, 5.7; N, 11.6. $C_{14}H_{21}N_3O_6S$ requires C, 46.80; H, 5.89; N, 11.70%); $\nu_{max.}$ ($CHCl_3$) 3 200, 3 300 (NH), and 1 725 cm^{-1} (C=O); δ(90 MHz, $CDCl_3$) 12.24 (br s, NH), 7.37 (br s, NH_2), 6.61 (br s, NH_2), 4.80 (q, H-2′, -3′), 3.90 [s, −C(=N−)-CO_2Me], 3.75 (s, CO_2Me), 3.10 (m, H-1′), 2.80 (m, H-4′), 2.47 (q, H-5′a), 1.88 (sextet, H-5′b), 1.31 (s, Me), and 1.25 (s, Me); J(1′,2′) 6, J(1′,5′b) 6, J(2′,3′) 6, J(3′,4′) 6, J(4′,5′b) 6, and J(5′a,5′b) 12 Hz; *m/e* 359 (M^+), 344 (M^+ — Me), 300 (M^+ — HCNS), and 269 (M^+ — $HNNHSCNH_2$).

6-(2′β,3′β-O-*Isopropylidene*-4′β-*methoxycarbonylcyclopent*-1′β-*yl*)-3-*thioxo*-2,3-*dihydro*-1,2,4-*triazin*-5(4H)-*one* (18) *and* 6-(2′β,3′β-O-*Isopropylidene*-4′α-*methoxycarbonylcyclopent*-1′β-*yl*)-3-*thioxo*-2,3-*dihydro*-1,2,4-*triazin*-5(4H)-*one* (19).—*Method* 1. A solution (14 ml) of 0.8M sodium methoxide in anhydrous methanol was added to a stirred solution of the thiosemicarbazone (17) (1.38 g, 3.8 mmol) in anhydrous methanol (60 ml). On completion of the addition a yellow solution resulted, which was heated at 45 °C for 45 min. The solution was then cooled and neutralised by the addition of Dowex 50W-X8 (H^+) ion-exchange resin to pH 5. The resin was removed by filtration and the solvent evaporated to give a yellow solid (1.02 g). Purification by column chromatography [Silica gel Merck H Type 60 (40 g)] using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant gave the following compounds: the 4′β-*methoxycarbonyltriazinone* (18) (0.323 g, 0.987 mmol) as a white crystalline solid, m.p. 215—218 °C (Found: C, 47.5; H, 5.55; N, 12.45. $C_{13}H_{17}N_3O_5S$ requires C, 47.71; H, 5.19; N, 12.84%); $\nu_{max.}$ ($CHCl_3$) 3 400 (NH) and 1 720 cm^{-1} (C=O); δ(250 MHz, [$^2H_6$]acetone) 5.06 (t, H-2′), 4.96 (t, H-3′), 3.24 (sextet, H-1′), 3.67 (s, CO_2Me), 3.08 (br s, NH), 3.02 (sextet, H-4′), 2.50 (q, H-5′a), 1.84 (sextet, H-5′b), 1.26 (s, Me), and 1.21 (s, Me); J(1′,2′) 5.2, J(1′,5′a) 12.5, J(1′,5′b) 12.5, J(2′,3′) 5.2, J(4′,5′a) 12.5, J(4′,5′b) 12.5, and J(5′a,5′b) 12.5 Hz; $\lambda_{max.}$ (EtOH) 271 nm (log ε 4.29); *m/e* 327 (M^+), 312 (M^+ — Me), 294 (M^+ — SH), and 268 (M^+ — HCNS): the 4′α-*methoxycarbonyltriazinone* (19) (0.286 g, 0.87 mmol) as a white crystalline solid, m.p. 185—188 °C; δ(90 MHz, [$^2H_6$]acetone) 11.2 (br s, NH), 4.98 (quintet, H-2′, -3′), 3.68 (s, CO_2Me), 3.45 (m, H-1′, -4′), 2.80 (q, H-5′a), 2.40 (dq, H-5′b), 1.29 (s, Me), and 1.23 (s, Me); J(1′,2′) 5, J(2′,3′) 5, and J(5′a,5′b) 12 Hz; $\lambda_{max.}$ (EtOH) 271 nm (log ε 4.30); *m/e* 327 (M^+), 312 (M^+ — Me), 294 (M^+ — SH), and 268 (M^+ — HCNS).

Method 2. 0.8M Sodium methoxide in anhydrous methanol (2.5 ml) was added to a stirred solution of the thiosemicarbazone (17) (0.70 g, 1.95 mmol). A yellow solution resulted and stirring was continued at room temperature for 0.5 h, when analysis of an aliquot of the reaction mixture showed that none of the semicarbazone (17) remained. The solution was adjusted to pH 5 by the addition of Dowex 50W-X8 (H^+), the resin filtered off, and the solvent evaporated to afford the 4′β-methoxycarbonyltriazinone (18) (0.50 g, 1.53 mmol) with properties as reported previously.

6-(4′β-*Acetoxymethyl*-2′β,3′β-O-*isopropylidenecyclopent*-1′β-*yl*)-3-*thioxo*-2,3-*dihydro*-1,2,4-*triazin*-5(4H)-*one* (20).—A solution (3 ml) of 0.5M lithium aluminium hydride in tetrahydrofuran was added to a stirred solution of the ester (18) (0.229 g, 0.69 mmol) in anhydrous tetrahydrofuran (20 ml) cooled in an ice-bath under nitrogen. A vigorous reaction immediately occurred and the mixture was stirred for a further 0.5 h at 0 °C, and then for 2 h at room temperature. Ether (30 ml) and tetrahydrofuran (20 ml) were added to the reaction mixture and then a saturated solution of ammonium chloride was added dropwise until a granular precipitate formed. The precipitate was filtered, washed with tetrahydrofuran (20 ml), and the combined filtrate and washings evaporated giving a pale yellow solid. The solid was dissolved in pyridine (10 ml), acetic anhydride (3 ml) added, and the solution stirred at room temperature

for 16 h. Removal of the solvent by evaporation under reduced pressure gave a yellow solid which was purified by column chromatography [silica gel Merck Type 60 (20 g)] using ethyl acetate–light petroleum (b.p. 60—80 °C) (9 : 11) as eluant to afford the *4′β-acetoxymethyl derivative* (20) (0.18 g, 0.53 mmol, 78%) as white crystals, m.p. 202—205 °C (Found: C, 49.25; H, 5.6; N, 11.95. $C_{14}H_{19}N_3O_5S$ requires C, 49.27; H, 5.57; N, 12.32%); $\nu_{max.}$ ($CHCl_3$) 3 400 (NH) and 1 730 cm^{-1} (C=O); δ(90 MHz, [$^2H_6$]acetone) 12.2 (br s, NH), 5.04 (t, H-2′), 4.73 (t, H-3′), 4.20 (d, C*H*$_2$OCOMe), 3.25 (quintet, H-1′), 2.20 (m, H-5′a,4′), 2.01 (s, CH_2OCOMe), 1.80 (m, H-5′b), 1.28 (s, *Me*), and 1.22 (s, Me); *J*(1′,2′) 6, *J*(1′,5′a) 12, *J*(1′,5′b) 6, *J*(2′,3′) 6, *J*(3′,4′) 6, and *J*(4′,6′) 7 Hz; $\lambda_{max.}$ (MeOH) 271 nm (log ε 4.02); *m/e* 341 (M^+), 326 (M^+ — Me), 283 (M^+ — Me_2CO), and 156 ($C_6H_6N_3OS^+$).

6-(4′α-Acetoxymethyl-2′β,3′β-O-isopropylidenecyclopent-1′β-yl)-3-thioxo-2,3-dihydro-1,2,4-triazin-5(4H)-one (21).—A solution (4 ml) of 0.5M lithium aluminium hydride in tetrahydrofuran was added to a stirred solution of the ester (19) (0.23 g, 0.7 mmol) in tetrahydrofuran (20 ml), cooled in an ice-bath under a nitrogen. A vigorous reaction immediately ensued and the mixture was stirred for a further 0.5 h at 0 °C, and 0.75 h at room temperature. Work-up as for (20) gave a yellow solid which was purified by column chromatography [silica gel Merck H Type 60 (20 g)] using ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 3) as eluant to afford the *4′α-acetoxymethyl derivative* (21) (0.175 g, 0.51 mmol) as white crystals, m.p. 165—168 °C (Found: C, 49.05; H, 5.6; N, 11.9. $C_{14}H_{19}N_3O_5S$ requires C, 49.27; H, 5.57; N, 12.32%); $\nu_{max.}$ ($CHCl_3$) 3 400 (NH), 1 730 (C=O), and 1 600 cm^{-1} (C=N); δ(90 MHz, [$^2H_6$]-acetone) 11.2 (br s, NH), 5.05 (t, H-2′), 4.59 (d, H-3′), 4.0 (d, C*H*$_2$OCOMe), 3.36 (quintet, H-1′), 2.50 (m, H-4′,-5′a), 2.04 (s, CH_2OCOMe), 1.80 (m, H-5′b), 1.28 (s, Me), and 1.23 (s, Me); *J*(1′,2′) 5, *J*(1′,5′a) 12, *J*(1′, 5′b) 6, *J*(2′,3′) 5, and *J*(4′,6′) 6 Hz; $\lambda_{max.}$ (MeOH) 271 nm (log ε 4.17); *m/e* 341 (M^+), 326 (M^+ — Me), 283 (M^+ — Me_2CO), and 156 ($C_6H_6N_3OS^+$).

6-(4′β-Acetoxymethyl-2′β,3′β-diformyloxycyclopent-1′β-yl)-3-thioxo-2,3,-dihydro-1,2,4-triazin-5(4H)-one (22).—A mixture of the 4′β-acetoxymethyl derivative (20) (0.25 g, 0.73 mmol) and AnalaR formic acid (15 ml, 98—100%) was stirred at room temperature for 48 h.[12] The solvent was then evaporated from the resultant homogeneous solution to afford as a yellow oil the *bis-formate derivative* (20) (0.18 g, 0.50 mmol); $\nu_{max.}$ ($CHCl_3$) 3 380 (NH), 1 720 (C=O), and 1 600 cm^{-1} (C=N–); δ(60 MHz, [$^2H_6$]-acetone) 8.10 (s, 2 HCO–O), 5.70 (m, H-2′, -3′), 4.20 (d, C*H*$_2$OCOMe), 3.70 (m, H-1′), 2.80 (m, H-5′a), 2.30 (m, H-4′,5′b), and 2.05 (s, CH_2OCOMe); *J*(4′,6′) 7 Hz; $\lambda_{max.}$ (MeOH) 271 nm (log 4.20); *m/e* 357 (M^+), 342 (M^+ — Me), and 311 (M^+ — HCO_2H).

6-(4′α-Acetoxymethyl-2′β,3′β-diformyloxycyclopent-1′β-yl)-3-thioxo-2,3-dihydro-1,2,4-triazin-5(4H)-one (23).—A mixture of the 4′α-acetoxymethyl derivative (21) (93.3 mg, 0.274 mmol) and AnalaR formic acid (10 ml, 98%) was stirred at room temperature for 17 h.[12] The solvent was then evaporated from the resultant homogeneous solution to afford as a white solid the *bis-formate derivative* (23) (85.6 mg, 0.24 mmol); $\nu_{max.}$ ($CHCl_3$) 3 380 (NH), 1 720 (C=O), and 1 600 cm^{-1} (C=N–); δ(60 MHz, [$^2H_6$]acetone) 8.10 (2s, 2HCO.O), 5.70 (t, H-2′), 5.30 (q, H-3′), 4.20 (d, C*H*$_2$OCOMe), 3.8 (m, H-1′), 2.90 (m, H-4′, -5′a, -5′b), and 2.08 (s, CH_2OCOMe); *J*(1′,2′) 4, *J*(2′,3′) 4, *J*(3′,4′) 6, and *J*(4′,6′) 5 Hz; *m/e* 357 (M^+), 342 (M^+ — Me), and 311 (M^+ — HCO_2H).

6-(4′β-Hydroxymethyl-2′β,3′β-dihydroxycyclopent-1′β-yl)-3-thioxo-2,3,-dihydro-1,2,4-triazin-5(4H)-one (24).—Aqueous sodium hydroxide solution (2.5 ml, 1.0M) was added to a stirred solution of the bis-formate derivative (22) (0.18 g, 0.5 mmol) in methanol (13 ml), and stirring was continued at room temperature for 16 h. Dowex 50W-X8 (H^+) was then added to adjust the pH of the solution to 4, the resin was filtered off, washed with methanol (20 ml), and the combined filtrates and washings evaporated to afford a semi-solid product. Purification by column chromatography [silica gel Merck type 60 (15 g)] using methanol–chloroform (1 : 9) as eluant gave the *thioxotriazinone* (24) (0.1 g, 0.37 mmol) as a white crystalline solid, m.p. 210—213 °C (Found: C, 41.95; H, 5.2; N, 16.4. $C_9H_{13}N_3O_4S$ requires C, 41.69; H, 5.02; N, 16.22%); $\nu_{max.}$ (Nujol) 3 400 (NH, OH), 1 680 (C=O) and 1 600 cm^{-1} (C=N–); δ(250 MHz, [$^2H_5$]pyridine) 5.11 (t, H-2′), 4.73 (q, H-3′), 4.27 (d, C*H*$_2$OH), 3.74 (dq, H-1′), 2.95 (sextet, H-5′a), 2.60 (m, H-4′), and 2.10 (sextet, H-5′b); *J*(1′,2′) 5, *J*(1′,5′a) 10, *J*(1′,5′b) 8.8, *J*(2′,3′) 5, *J*(3′,4′) 7.5, *J*(4′,5′a) 10, *J*(4′,5′b) 8.8, *J*(4′,6′) 5, and *J*(5′a,5′b) 15 Hz; $\lambda_{max.}$ (MeOH) 271 nm (log ε 4.06); *m/e* 259 (M^+), 241 (M^+ — H_2O), 223 (M^+ — $2H_2O$), 205 (M^+ — $3H_2O$), and 156 ($C_5H_6N_3OS^+$).

6-(4′α-Hydroxymethyl-2′β,3′β-dihydroxycyclopent-1′β-yl)-3-thioxo-2,3-dihydro-1,2,4-triazin-5(4H)-one (25).—Aqueous sodium hydroxide solution (2 ml, 1.0M) was added to a stirred solution of the bis-formate derivative (23) (80 mg, 0.22 mmol) in methanol (15 ml) and the resultant solution stirred at room temperature for 16 h, then worked up as for (24) to afford the *thioxotriazinone* (25) (58 mg, 0.22 mmol) as a white crystalline solid, m.p. 220—223 °C on recrystallisation from methanol–chloroform (Found: C, 41.9; H, 5.3; N, 16.4. $C_9H_{13}N_3O_5S$ requires C, 41.69; H, 5.02; N, 16.22%); $\nu_{max.}$ (Nujol) 3 400 (NH, OH), 1 680 (C=O), and 1 600 cm^{-1} (C=N–); δ(250 MHz, [$^2H_5$]pyridine) 5.25 (t, H-2′), 4.60 (q, H-3′), 4.24 (dq, C*H*$_2$OH), 3.90 (sextet, H-1′), 3.30 (sextet, H-5′a), 2.95 (dq, H-4′), and 2.15 (dq, H-5′b); *J*(1′,2′) 4.2, *J*(1′,5′a) 10, *J*(1′,5′b) 10, *J*(2′,3′) 4.2, *J*(3′,4′) 8.4, *J*(4′,5′b) 6.7, *J*(4′,6′a) 6, *J*(4′,6′b) 4.2, *J*(5′a,5′b) 14, and *J*(*gem*-CH_2OH) 10 Hz; $\lambda_{max.}$ (MeOH) 271 nm (log ε 4.25); *m/e* 241 (M^+ — H_2O), 223 (M^+ — $2H_2O$), 205 (M^+ — $3H_2O$), and 156 ($C_5H_6N_3OS^+$).

5-(4′β-Hydroxymethyl-2′β,3′β-dihydroxycyclopent-1′β-yl)-6-azauracil (5).—*Method* 1. A mixture of the thioxotriazinone (24) (50.0 mg, 0.193 mmol), water (10 ml), and methyl iodide (0.1 ml) was heated in an oil bath at 50—55 °C for 6 h (*cf.* Sorm [7]). The excess of methyl iodide was then allowed to evaporate at 55 °C and atmospheric pressure by removal of the condenser. The remaining solution was neutralised by the addition of Dowex 1-X8-(OH^-), the resin filtered off, and the filtrate heated at 100 °C with Dowex 50W-X8 (H^+) for 1 h. The resin was filtered off and the water evaporated off to afford a semi-solid residue, column chromatography of which (silica gel Merck Type 60, eluant methanol) gave a pale yellow semi-solid product (11.0 mg); $\lambda_{max.}$ (MeOH) 267 nm (log ε 3.68); *m/e* 215, 155, 145, 127, and 113.

Method 2. A mixture of the thioxotriazinone (24) (50 mg, 0.193 mmol), water (10 ml), and methyl iodide (0.1 ml) was heated in an oil-bath at 50—55 °C for 6 h and then excess of methyl iodide removed as in method 1 above. The remaining solution was heated at 100 °C for 1 h, cooled, and passed down a column (2 × 15 cm) packed with

Dowex 1-X8 (formate) and eluted with water. The solvent was evaporated from the eluant to give a semi-solid product column chromatography of which [silica gel Merck H Type 60 (25 g), eluant ethanol] afforded a pale viscous oil (9.3 mg) containing the 6-*azauracil* (5) which on solution in chloroform–light petroleum (b.p. 60—80 °C) (1 : 1) and evaporation of solvent became a white solid, m.p. 209 °C; $\lambda_{max.}$ (MeOH) 266 nm (log ε 3.70); *m/e* 225 ($M^+ - H_2O$), 224, 207 ($M^+ - 2H_2O$), and 189 ($M^+ - 3H_2O$); δ(250 MHz, [$^2H_5$]pyridine) 5.10 (H-2′), 4.75 (H-3′), 4.25 (CH_2OH), 3.77 (H-1′), 2.95 (H-5′a), 2.62 (H-4′), and 2.08 (H-5′b).

We thank the S.R.C. (R. F. K.) and the Malaysian Government (A. S.) for the award of Research Studentships.

[1/126 *Received*, 28*th January*, 1981]

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