in vacuo to give 14-chloro-5α,14β,17βH-cholestane (4; 200 mg, mp 104–106 °C) which exhibited physical and spectroscopic properties identical with those of authentic material.[3]

(b) At −30 °C. The acetates **1d** or **5d** (200 mg) in $CHCl_3$ (0.5 mL) were treated with HCl at −30 °C for 0.5 h. The usual workup afforded a solid which after chromatography on silica gel G–Celite–$AgNO_3$ (1:1:0.3) yielded 3β-(acetyloxy)-5α-cholest-8(14)-ene (**2a**, 35 mg) and 3β-(acetyloxy)-5α-cholest-14-ene (140 mg). Both compounds were identical with authentic samples. The same result was obtained when the reaction was conducted at −60 °C in diethyl ether for 20 min.

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Registry No. **1a**, 2465-00-1; **1d**, 59531-52-1; **2a**, 6562-21-6; **3**, 69224-70-0; **4**, 73465-15-3; **5c**, 73465-16-4; **5c** 4-bromobenzoate ester, 73396-47-1; **5d**, 73465-17-5; **6a**, 55123-81-4; **6b**, 73465-18-6; **6c**, 73465-19-7; **6d**, 73465-20-0; 3β-(acetyloxy)-5α-cholest-14-ene, 40446-06-8.

Hexahydro-4,6-methanocyclopenta[*b*]pyran-2-(3*H*)-one and the Structural Proof for Brendan-4-one

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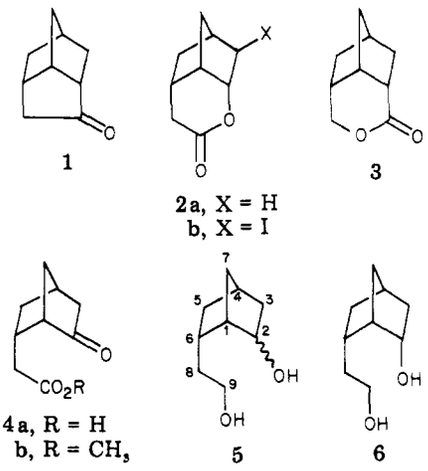
Recently Nickon and his colleagues have provided a synthesis and structural proof for brendan-4-one (**1**).[1] An important stage in the proof of structure is the Baeyer–Villiger oxidation of **1** to afford the two δ-lactones **2a** and **3** (Chart I) as a mixture, which could not be separated. Saponification of this mixture followed by acidification at 0 °C resulted in the regeneration of **3**, with **2a** being converted to the hydroxy acid. Without separation, this mixture of **3** and the hydroxy acid derived from **2a** was treated with diazomethane, oxidized with Brown's reagent and saponified. This resulted in the conversion of **2a** into the keto acid **4a**, which could now be separated from **3** and which on methylation with diazomethane afforded the keto ester **4b**, identical with authentic material. The reduction of **4b** with lithium aluminium hydride produced a crystalline diol given the structure **5**, for which the stereochemistry of the hydroxyl group at C-2 was not known but was thought to be endo as in **6**. Although other reported[1] evidence, such as the Wolff–Kishner reduction of **1** to brendane, supports the structure **1**, the above structural evidence is incomplete in view of (a) the failure to isolate **2a**, a compound which has never previously been prepared or isolated, and (b) an absence of knowledge of the C-2 stereochemistry in **5** which is needed to deduce with absolute certainty the stereochemistry of **1**. The structural proof is additionally unsatisfactory because the 60-MHz spectrum of **5** is reported[1] as δ 4.62–3.58 (m, 6), 2.57–1.66 (m, 6), and 1.45–0.78 (m, 4). Such a spectrum is inconsistent with a structure (**5**) for which only five protons in the region δ 4.62–3.58 corresponding to **CHOH** and **CH_2OH** would be anticipated.

We had available the iodo δ-lactone **2b**[2] and found that it could be smoothly deiodinated to the parent δ-lactone

Chart I



2a by using the tri-*n*-butyltin chloride plus sodium borohydride reagent of Corey and Suggs.[3] Reduction of **2a** with lithium aluminium hydride led to the diol **6** in which the stereochemistry of the hydroxyl group at C-2 is fixed as endo. The melting point of 71–72 °C for **6** compares with that of 73–74.5 °C reported[1] for **5**. The NMR spectral data at 60 MHz reported[1] for **5** are the same as those we now find for **6** with the exception that resonances in the range δ 4.65–3.58 correspond to five and not six protons. At 90 MHz the spectrum (the details of which are recorded in the Experimental Section) has less overlap and greater separation of resonances than that recorded at 60 MHz. Confirmation that the compound **5** prepared by Nickon does in fact have the structure **6** was obtained by converting **2a** into the keto ester **4b** by using the procedures employed by Nickon and then reducing **4b** with lithium aluminium hydride. The product was identical in all respects with **6** prepared by the direct reduction of **2a**, thus proving conclusively that **5** has the structure **6** in which the hydroxyl group at C-2 is endo.

The reduction of the ketonic carbonyl group in **4b** to afford **6** may be compared with the observation of Brown[4] that in the corresponding reduction of norbornan-2-one there is an 8.1:1 preference for exo hydride ion attack leading to the same preference for the production of an *endo*-hydroxyl group. The presence of the *endo*-CH_2CO_2Me group at C-6 in **4b**, which is being simultaneously reduced to CH_2CH_2OH, results in a complete preference for exo hydride ion attack at C-2, leading to the exclusive formation of **6**.

Experimental Section

Hexahydro-4,6-methanocyclopenta[*b*]pyran-2(3*H*)-one (2a). A solution of 7-*exo*-iodohexahydro-4,6-methanocyclopenta[*b*]pyran-2(3*H*)-one (**2b**; 2.78 g, 10 mmol) and tri-*n*-butyltin chloride (0.65 g, 20 mmol) in dry ethanol (200 mL) was prepared under a nitrogen atmosphere. A suspension of sodium borohydride (0.475 g, 12.5 mmol) in ethanol (50 mL) was added and the stirred mixture irradiated by a Philips 300-W ultraviolet lamp. Initially diborane gas was rapidly evolved, but this had largely ceased after 1 h when TLC analysis [30% ethyl acetate, 70% petroleum ether (bp 60–80 °C), Merck silica gel; R_f 0.4 for **2b** and 0.5 for **2a**] of an aliquot of the reaction mixture showed that all the starting material (**2b**) had been consumed to afford a single product. A few drops of acetic acid were then added to the reaction mixture to destroy excess sodium borohydride, and the solvent was evaporated. The residue was dissolved in methylene chloride (100 mL) and the resultant solution washed with saturated aqueous

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sodium bicarbonate (2 × 25 mL) and water (2 × 25 mL) and then dried over magnesium suflate. The solution was filtered, the solvent evaporated, and the crude product purified by column chromatography (40 g of Merck H silica) using 15:85 ethyl acetate–petroleum ether (bp 60–80 °C) as eluent to give lactone **2a** (1.18 g) as a white crystalline solid: mp 65–70 °C; IR ($CHCl_3$) 1737 (s, C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.88 (m, H-2 (exo)), 2.62 (d, CH_2CO_2), 2.50–1.90 (m, 5 H), 1.60–0.90 (m, 4 H).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.82; H, 7.95.

2-(2-*endo*-Hydroxynorborn-6-*endo*-yl)ethanol (6). Lithium aluminium hydride (76 mg, 2.0 mmol) was suspended in tetrahydrofuran (10 mL) at 0 °C, and a solution of the lactone **2a** (100 mg, 0.66 mmol) in tetrahydrofuran (10 mL) was added. The mixture was stirred at 0 °C for 2 h, and stirring was then continued overnight while the temperature was allowed to rise to room temperature. The reaction was then quenched by the addition of methanol (2 mL), water (25 mL) was added, and the mixture was acidified with dilute hydrochloric acid to pH 2. The mixture was extracted with ether (5 × 25 mL), and the combined extracts were dried over $MgSO_4$, filtered, and evaporated to afford a residue which was purified by sublimation at 0.15 mmHg followed by recrystallization from hexane to give the diol **6** as white crystals (60 mg, 0.395 mmol): mp 71–72 °C; IR ($CHCl_3$) 3400 (OH) cm^{-1}; ^1H NMR (60 MHz) δ 4.62–3.58 (m, 5 H), 2.57–1.66 (m, 7 H), 1.45–0.78 (m, 4 H); ^1H NMR (90 MHz) δ 4.27 (pentet, H-2 (exo)), 4.08 (m, 2 OH), 3.73 (m, H-9), 2.42 (m, H-1), 2.16 (m, H-4), 1.98 (m, H-8, H-3 (exo), H-5 (exo)), 1.78 (m, H-6 (exo)), 1.34 (m, H-7), 0.97 (m, H-3 (endo), H-5 (endo)); $J_{1,2(exo)} = 3.5$ Hz, $J_{2(exo),3(exo)} = 9.5$ Hz, $J_{2(exo),3(endo)} = 4.2$ Hz; on addition of D_2O the peak at δ 4.08 disappeared.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.99; H, 10.32.

The identical compound (**6**) could be prepared from **2a** by using the procedure of Nickon[1] to convert it into the keto ester **4b** which was then reduced with lithium aluminium hydride.

Acknowledgment. Support from the Science Research Council and Glaxo Group Research, Ltd., is gratefully acknowledged.

Registry No. 2a, 14734-16-8; **2b**, 26433-43-2; **6**, 73395-76-3.

Synthesis of 5-Amino-9-(β-D-ribofuranosyl)-*v*-triazino[4,5-*b*]-pyrimido[4,5-*d*]pyrrol-4-one and Unusual Ring Opening of This New Ring System with the Vilsmeier-Haack Reagent

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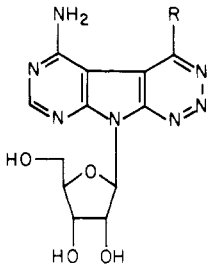
It has been reported[1b] that certain bicyclic nucleosides containing a *v*-triazine ring (e.g., 2-azaadenosine) display some in vivo activity against L-1210 mouse leukemia. In view of this fact, we initiated research designed to synthesize "linear" tricyclic nucleosides in which analogues of 2-azapurine are incorporated into a tricyclic heterocycle. The structure of this type of nucleoside (**1**) can be viewed as resembling adenosine on one side of the molecule and a 2-azapurine nucleoside analogue on the other side. The interesting structural features of **1** should prove to be valuable for studying the relationship that substrate structure has to the interaction of enzymes in purine nucleoside metabolism.



1

The chemical syntheses and reactions of *v*-triazines (1,2,3-triazines) have been the subject of several extensive reviews.[2] The more commonly employed methods for the synthesis of the *v*-triazine ring use intramolecular coupling reactions via a diazotization. In the field of nucleoside chemistry, this type of ring annulation has been employed[3] for the synthesis of 2-azapurine nucleosides from 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside). Therefore, for the synthesis of the desired tricyclic nucleosides we elected to use 6-aminosangivamycin[4] (**2**) as our starting material.

Selective diazotization of the exocyclic amino group at the 6-position of **2** furnished the unique [6,5,6] "linear" tricyclic nucleoside, 5-amino-9-(β-D-ribofuranosyl)-*v*-triazino[4,5-*b*]pyrimido[4,5-*d*]pyrrol-4-one (**3**) (see Scheme I), which not only provided the desired nucleoside but also a derivative of a new ring system. However, our attempts to prepare the 4-chloro analogue of **1** (R = Cl) resulted in the discovery of an interesting ring opening of the *v*-triazino ring. The isolation and identification of the ring-opened product has offered some insight into the mechanism of this interesting ring-opening reaction.

Results and Conclusions

Treatment of 6-aminosangivamycin (**2**) with nitrous acid at ice-bath temperature furnished a moderate yield of a product, after column chromatography, which we assumed to be **3**. Evidence that ring closure had taken place was found in the ^1H NMR spectrum of **3** which displayed a broad 1-proton singlet at δ 15.53 for a lactam (NH) group and only one signal (doublet) that could be assigned to an amino group. The signal for the amino group was split into two 1-proton singlets (δ 7.20 and 7.76), indicating that strong hydrogen bonding may exist between one of the amino protons and the 4-one group. Although the empirical formula for **3** was established by elemental analysis and by the mass spectrum, these data do not establish the direction in which the ring annulation had taken place. If ring closure had occurred between the 4-amino group and the carboxamide group, then a "triangular" tricyclic nucleoside such as **8**, with a seven-membered ring, would have been formed instead of **3**. The possible formation of **8** was excluded by the following: (1) The ring-closed product (**3**) shows a significant bathochromic shift in the ultraviolet spectrum (λ_{max} (MeOH) = 343 nm) in comparison[4] to **2** (λ_{max} (MeOH) = 293 nm). This large bathochromic shift has been found to be characteristic for all the "linear" tricyclic nucleosides derived from bicyclic pyrrolo[2,3-*d*]-

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