of **13** (520 mg, 1.32 mmol) in 12 mL of anhydrous THF was cooled to −65 °C and lithium hexamethyldisilazane (1.00 equiv, 1.32 mL of a 1 N solution) was added via cannula. Stirring was continued at −65 °C for 20 min while formaldehyde, generated by the thermal cracking of paraformaldehyde, was bubbled into the solution. The THF solution was allowed to warm to room temperature and was stirred for 15 min. The THF solution was concentrated under reduced pressure and filtered through a silica plug (1:2 ethyl acetate/petroleum ether) to give 136 mg (30% for two steps) of pure **14** as a colorless oil. **14**: IR (neat) 2955, 1738, 1240 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 6.20 (1 H, d, $J$ = 7 Hz), 6.08 (1 H, dd, $J$ = 7, 2.8 Hz), 5.57 (1 H, d, $J$ = 3 Hz), 5.29 (1 H, d, $J$ = 2.8), 4.81 (1 H, d, $J$ = 3 Hz), 3.80 (3 H, s), 3.78 (3 H, s), 2.4–1.8 (4 H, m), 2.05 (3 H, s); $^{13}C$ NMR $\delta$ 171.7, 170.4, 163.7, 147.7, 132.1, 128.2, 102.1, 78.2, 66.4, 52.7, 52.4, 28.4, 24.6, 21.1; mass spectrum, $m/e$ (rel intensity) 298 (0.4), 267 (2.8), 239 (4), 197 (60), 179 (28), 155 (52), 137 (100).

**Methyl 1β-[[1-(Methoxycarbonyl)ethenyl]oxy]-4α-hydroxycyclohex-2-ene-1-carboxylate (15).** To an ice-cold solution of 14 (65 mg, 0.22 mmol) in 1.5 mL of anhydrous methanol was added NaOMe (3 equiv, 35 mg). The temperature of the reaction mixture was maintained at 0 °C for 1 h. The reaction mixture was diluted with 10 mL of saturated $NH_4Cl$ solution and extracted with three 10-mL portions of $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were dried ($MgSO_4$) and evaporated to give a golden oil which was purified by flash chromatography (1:1 ethyl acetate/petroleum ether) to give 38 mg (68%) of pure **15** as a colorless oil. **15**: IR (neat) 3444, 2955, 1735, 1624, 1439, 1168 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 6.13 (1 H, dd, $J$ = 9, 2.8 Hz), 6.08 (1 H, d, $J$ = 9 Hz), 5.57 (1 H, d, $J$ = 3 Hz), 4.70 (1 H, d, $J$ = 3 Hz), 4.27 (1 H,br s), 3.79 (6 H, s), 2.5–1.7 (4 H, m); $^{13}C$ NMR $\delta$ 171.7, 163.5, 147.2, 136.3, 125.8, 101.0, 78.6, 64.5, 52.8, 52.5, 28.5, 28.3; mass spectrum, $m/e$(rel intensity) 257 (0.7), 256 (5.5), 238 (8.0), 224 (39), 165 (95), 155 (100), 137 (80), 91 (70), 59 (68); HRMS calcd for $C_{12}H_{16}O_6$ 256.0947, found 256.0947.

**1β-[(1-Carboxyethenyl)oxy]-4α-hydroxycyclohex-2-ene-1-carboxylic Acid (16) and Disodium Salt 4.** To a stirred solution of **15** (87 mg, 0.29 mmol) in 6 mL of THF/$H_2O$ was added NaOH (4 equiv, 1.17 mL of a 1 N solution). Stirring was continued at 0 °C for 1.5 h. The reaction mixture was acidified with HCl (1.2 mL of a 1 N solution) and immediately loaded onto a Bio-Rex 70 sodium ion exchange column (0.5 x 4 in.). Elution with water (50 mL) and lyophilization of the eluent, followed by trituration with anhydrous ether, gave 110 mg (100%) of **4** as a white solid. The diacid form was obtained as follows: a portion of **4** was dissolved in water. The water was acidified with 1 N HCl to pH 3 and extracted with ethyl acetate. The ethyl acetate layer was dried ($MgSO_4$), filtered, and evaporated to give **16** as a colorless oil. **16** (diacid): $^1H$ NMR (acetone-$d_6$, 300 MHz) $\delta$ 6.18 (1 H, d, $J$ = 11 Hz), 5.95 (1 H, dd, $J$ = 11, 4 Hz), 5.17 (1 H, d, $J$ = 3 Hz), 4.40 (1 H, d, $J$ = 3 Hz), 4.27 (1 H, br s), 2.17 (2 H, m), 1.92 (1 H, m), 1.67 (1 H, m). **4** (disodium salt): $^1H$ NMR ($D_2O$, 300 MHz) $\delta$ 6.20 (1 H, d, $J$ = 10 Hz), 5.96 (1 H, d, $J$ = 10 Hz), 5.18 (1 H, s), 4.42 (1 H, s), 4.28 (1 H, br s), 2.2–1.6 (4 H, m).

**Kinetics of [3,3] Rearrangements of 14, 15, 16, and 4 to 17, 18, and 19.** Samples (2.5 mg) of each compound were dissolved in 700 μL of the respective deuteriated solvents in NMR tubes. The samples were maintained at 30 °C either in the NMR probe or in a separate constant-temperature bath. Periodically, $^1H$ NMR spectra were recorded. $K_{rearr}$ was determined from the slope of the line $\ln [(I_{sm})/(I_{prod} + I_{sm})] = K_{rearr} \times t$, where $I_{sm}$ and $I_{prod}$ represent the integral values of the lowest-field vinyl signal of each species ($\delta$ 6.2 and 6.8, respectively). In all cases, the disappearance of starting material obeyed first- order kinetics to at least 90% completion. Results are given in Table I and Figure 1. **17**: $^1H$ NMR (300 MHz) $\delta$ 6.72 (1 H, s), 4.76 (1 H, m), 3.92 (3 H, s), 3.75 (3 H, s), 3.1–2.9 (3 H, m), 2.6–2.2 (2 H, m), 2.06 (3 H, s), 1.9–1.7 (2 H, m). **18**: $^1H$ NMR (300 MHz) $\delta$ 6.68 (1 H, s), 4.29 (1 H, br s), 3.90 (3 H, s), 3.76 (3 H, s), 3.14 (1 H, dd, $J$ = 16, 7.6 Hz), 2.96 (1 H, dd, $J$ = 16, 8 Hz), 2.85 (1 H, m), 2.5–2.1 (2 H, m), 1.9–1.7 (2 H, m). **19** (disodium salt): $^1H$ NMR (300 MHz) $\delta$ 6.78 (1 H, s), 3.63 (1 H, m), 2.96 ( 1 H, dd, $J$ = 13, 4 Hz), 2.80 (1 H, dd, $J$ = 13, 5.5 Hz), 2.68 (1 H, br s), 2.37 (2 H, m), 1.86 (1 H, m), 1.68 (1 H, m).

**Acknowledgment.** We are grateful to the National Institutes of Health, Grant GM 31958, for financial support.

# Regiospecific Reduction of the 2-Carbonyl Group of the 6-Hydroxypyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-trione System by Selected Metal Hydrides. A Novel Reduction of a Fused Xanthine Nucleus

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*Received August 28, 1987*

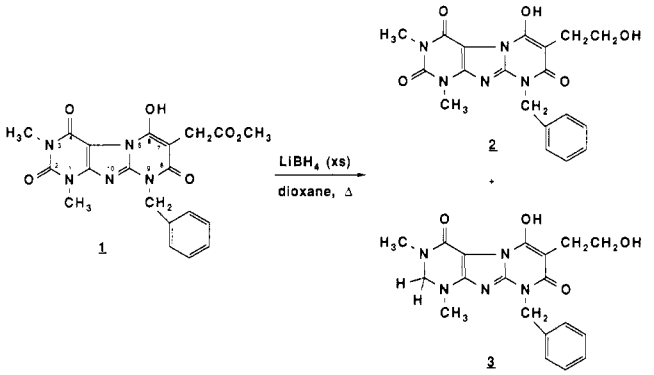
A series of substituted 6-hydroxypyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-triones **1** have been reduced to the corresponding 2,3-dihydro-6-hydroxypyrimido[2,1-*f*]purine-4,8(1*H*,9*H*)-diones **2** by treatment with excess lithium borohydride in refluxing dioxane or sodium bis(2-methoxyethoxy)aluminum hydride in a refluxing dimethoxyethane–toluene mixture. The reduction occurs regiospecifically at the carbonyl group at the 2-position of the tricyclic nucleus, as demonstrated by spectroscopic and X-ray crystallographic data. The only side products observed are chromatographically immobile materials. Other reducing agents such as sodium borohydride, borane–tetrahydrofuran, or lithium aluminum hydride fail to effect this reduction. In order to achieve practical reaction rates with lithium borohydride, the solubilities of the substrates have been enhanced by means of silylation. MNDO calculations of the relative stabilities of postulated reaction intermediates suggest a possible explanation of the observed regiospecificity of the reduction.

During the course of preparation of a series of novel pyrimido[2,1-*f*]-purine-2,4,8(1*H*,3*H*,9*H*)-triones[1] with interesting antiinflammatory activity, the 7-(methoxycarbonyl)methyl compound (**1**; Scheme I) was treated with excess lithium borohydride in dioxane. In addition to the desired 7-hydroxyethyl product **2**, a second alcohol was isolated and identified as the 2-desoxy derivative **3**. This selective reduction to the methylene oxidation state of the urea-like carbonyl group of a fused xanthine nucleus in the

(1) Blythin, D. J.; Kaminski, J. J.; Domalski, M. S.; Spitler, J.; Solomon, D. M.; Conn, D. J.; Wong, S. C.; Verbiar, L. L.; Bober, L. A.; Chiu, P. J. S.; Watnick, A. S.; Siegel, M. I.; Hilbert, J. M.; McPhail, A. T. *J. Med. Chem.* **1986**, *29*, 1099.

0022-3263/88/1953-3265$01.50/0 

**Scheme I**




presence of other nonenolized amide-like carbonyl groups appears to be unprecedented. Where analogous products have been reported, they have been generated from quaternary iminium intermediates[2] or via Raney nickel treatment of a thiocarbonyl-containing derivative.[3] Metal hydride reductions of 1,3-dialkylated uracil have been reported with sodium borohydride (photoreduction at 254 nm in water)[4] and with lithium tri-*sec*-butylborohydride (in tetrahydrofuran).[5] In both cases saturation of the 4,5-double bond was the only reductive process observed.

The literature contains several examples of lithium aluminum hydride reduction of heterocyclic systems including, for example, imidazolidinones,[6] 2(1*H*)-pyrimidines,[6-9] hydantoins,[10-12] and barbiturates.[8,11,12] Most examples employ as solvent ether or tetrahydrofuran at room temperature or reflux for varying periods of time. Milder conditions effect carbonyl reduction, whereas more forcing conditions frequently give rise to reductive ring cleavages. Where selective carbonyl reduction is observed in multicarbonyl compounds,[10-12] the urea carbonyl is generally most resistant to reduction. When ring cleavage occurs,[7,8,10,13] the scission takes place between the urea carbonyl carbon (with attendant reduction thereof) and an adjacent nitrogen. Sodium borohydride reduction of barbituric acid derivatives has been extensively studied by Rautio and co-workers.[14] Again, both carbonyl reduction and ring cleavage have been observed, depending upon reaction conditions, but the sites of ring cleavage are generally not the urea carbon–nitrogen bonds as observed in the lithium aluminum hydride reactions cited. Thus, no direct precedent for the observed reaction appears to have been reported, and in the structurally closest analogous cases known, a distinctly different pattern of reactivity is observed.

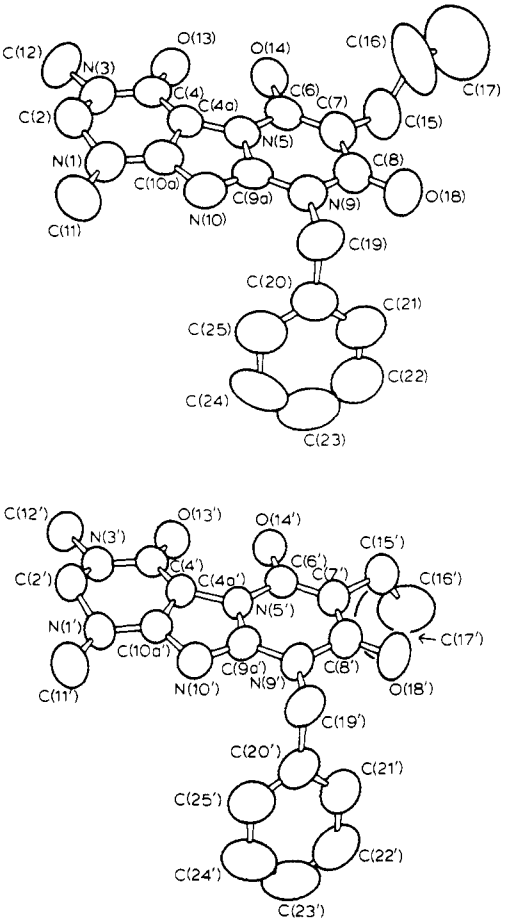



**Figure 1.** Solid-state conformations of the two crystallographically independent molecules of **5c**.

Because of the novelty of the observed reduction as well at its apparent regiospecificity in a nucleus containing three nonenolized carbonyl groups, we set out to examine its synthetic utility for the preparation of the 2,3-dihydro analogues of our original series of interest. This paper describes our findings with respect to the effect of altering various parameters—especially the nature of the reducing agent—on the course of the reaction. In addition to spectroscopic characterization, the X-ray crystal structure of the novel 2,3-dihydropyrimido[2,1-*f*]purine system is presented. Finally, MNDO calculations of the relative stabilities of postulated reaction intermediates have been performed and suggest a possible explanation for the observed regiospecificity of the reduction.

## Results and Discussion

When 9-benzyl-1,3-dimethyl-6-hydroxy-7-[(methoxycarbonyl)methyl]pyrimido[2,1-*f*]purine-2,4,8-(1*H*,3*H*,9*H*)-trione[15] (**1**; Scheme I) was treated with an excess of lithium borohydride in dioxane at 60 °C for 21 h, thin-layer chromatography indicated the presence of two main chromatographically mobile reaction products. Isolation of these products and characterization by NMR ($^1$H and $^{13}$C) and mass spectroscopy showed that the main component was indeed the expected alcohol **2**, obtained in about 35% yield. The mass spectrum and elemental analysis of the second product, a sharp-melting (with decomposition) solid (isolated in 7% yield) homogeneous to TLC, supported a molecular formula corresponding to the

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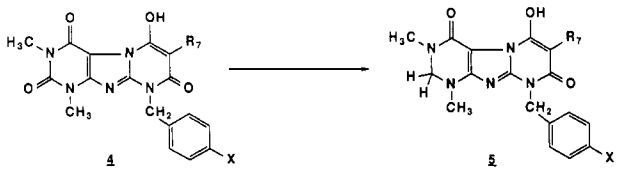
(12) Knabe, J.; Geismar, W.; Urban, C. *Arch. Pharm. (Weinheim, Ger.)* **1969**, *302*, 468.
(13) Lehmann, J.; Kraft, G. *Arch. Pharm. (Weinheim, Ger.)* **1982**, *315*, 967.
(14) For a succinct summary of this work, see: Rautio, M. *Ventron Alembic* **1982**, *27*, 1.
(15) Solomon, D. M.; Conn, D. J.; Wong, S. C.; Kaminski, J. J. *Heterocycles* **1986**, *24*, 2179.

**Scheme II**



| | $R_7$ | X |
|---|---|---|
| **a** | H | H |
| **b** | H | F |
| **c** | $C_3H_7$-*n* | H |
| **d** | $C_3H_7$-*n* | F |
| **e** | $CH_3$ | F |

loss of 14 atomic mass units, which suggested the reduction of a carbonyl group to a methylene. The fragmentation pattern further indicated that the reduction had occurred in the xanthine portion of the molecule: loss of the malonyl portion of the C ring left a major fragment with a mass which was 14 amu lower than the corresponding fragment from product **2**. The $^1H$ NMR spectrum showed a new methylene singlet at $\delta$ 4.45 and a significant upfield shift in the $CH_3$ groups at *both* $N_1$ and $N_3$. The $^{13}C$ NMR spectrum further indicated the presence of one fewer $sp^2$ and one more $sp^3$ carbon than exhibited by product **2**. Collectively, this evidence led us to assign structure **3** to this second product. The correctness of this assignment was eventually substantiated by an X-ray crystal structure determination of analogous reduction product **5c** (Figure 1).

The noteworthiness of the process leading to product **3** derives from the fact that it involves the unprecedented reduction of a xanthine amide carbonyl to the corresponding methylene by a metal hydride. Paradoxically, the specific reagent employed, lithium borohydride, is not ordinarily regarded as an effective agent for amide reduction.[16,17] Furthermore, the reduction was observed to occur regiospecifically in a molecule containing three additional tertiary heterocyclic amide groups, of which the carbonyls of two reside in the keto tautomeric form, as does the carbonyl which undergoes reduction.

The preference of the carbon–oxygen unit at position-6 of the starting pyrimidopurines for the enolic tautomeric form, as shown in Schemes I and II, has been established for both the solution phase (by $^1H$ NMR) and the solid state (by X-ray).[1] The representation of the 6-carbonyl group of the 2,3-dihydro products in the enolic form is similarly supported.

Our interest in the parent pyrimidopurine system derived from its antiinflammatory pharmacologic activity.[1] Thus, the potential ability to produce an analogous series of compounds selectively reduced at the 2-carbonyl position was of significant interest to us and led us to explore some of the parameters of the reductive process. The objective of our investigation was to devise a practical approach to the synthesis of a series of analogues having variable substituents at position-7. To this end, it was ascertained that 7-unsubstituted compounds **5a** and **5b** (Scheme II) could be prepared and were amenable to subsequent alkylation at the 7-position with suitable electrophiles, as has been described for the original 2-oxo series of compounds.[15] Alternatively, as suggested by the first example (Scheme I), 7-substituted-2-oxo substrates could be reduced at position-2 with concommitant reduction of susceptible functional groups present at the 7-(or other)position.

The majority of the observations described below have been made on the specific substrates **4a–d** shown in Scheme II—i.e., with either hydrogen or an *n*-propyl group at the 7-position and an unsubstituted or *p*-fluoro-substituted benzyl group at position-9. Characterization of the resultant reduction products (**5a–d**) is summarized in Table II.

**Substrate Solubility; Effect on Reaction Rate.** The chief practical limitation of lithium borohydride promoted reduction of the pyrimido[2,1-*f*]purinetrione system initially encountered was the excessively long (7 to >14 days) reaction times required to effect substantial reduction. This appeared to be the result of low solubility of the substrates in solvents compatible with the metal hydride reagent. Thus, a number of experimental variations were examined in an effort to enhance solubility. These approaches included comparison of the ethereal solvents tetrahydrofuran, dimethoxyethane, dioxane, and diglyme over temperatures ranging from 60 to 160 °C, examination of the effect of preforming the sodium or lithium enolates of the substrate, addition of lithium-complexing 12-crown-4 to the reduction mixture, and the use of sonication. None of these measures resulted in discernible rate enhancement. We have, however, found that the treatment of the tricyclic substrates with hexamethyldisilazane in chloroform is an effective means of enhancing their solubilities and of thus decreasing reaction times substantially compared with the corresponding nonsilylated substrates. The pyrimidopurines examined could be completely reduced in 1–3 days in refluxing dioxane by using the presilylation technique. Compound **4a** is an exceptional case in that its reduction can be effected in less than 24 h even without prior silylation. The effect of silylation on the yields of the desired reduction products was not carefully assessed but was clearly beneficial in the case of **4a**. (See Experimental Section.) The intermediate trimethylsilyl derivatives have not been characterized but have been used directly as crude oils after evaporation under reduced pressure of solvent and excess reagent. No attempt has been made to isolate silylated reaction products, which would be expected to be cleaved by the aqueous workup employed. It is possible that cleavage of the presumably highly labile enol silane occurs during the course of the reduction.

**Investigation of Other Reducing Agents.** The effect of a variety of reducing agents on the pyrimidopurinetrione nucleus, using **4c** as a representative model, has been examined. Sodium borohydride–ethanol was ineffective in reducing **4c**; only starting material was recovered after prolonged reflux with an excess of sodium borohydride. It should be noted that borohydride was added periodically throughout the reaction period to compensate for deterioration of the reagent. Borane–tetrahydrofuran complex, a generally effective reagent for the reduction of amides,[18] gave no observable product during a 4-h treatment of **4c** at room temperature but yielded a complex array of products when the reaction mixture was refluxed. The mixture probably included some of the desired reduction product **5c**, but its isolation was judged impractical on the basis of TLC analysis. Surprisingly, treatment of presilylated **4c** with excess lithium aluminum hydride in re-

(16) See, e.g.: Walker, E. R. H. *Chem. Soc. Rev.* **1976**, *5*, 23.

(17) However, instances of amide reduction by lithium borohydride have been noted: Davis (Davis, M. *J. Chem. Soc.* **1956**, 3981) reports the reduction of *N,N*-dimethylbenzamide to a mixture of *N,N*-dimethylbenzylamine and benzyl alcohol in refluxing THF. Very recently, lithium borohydride has been shown to be an effective reagent for the reduction of primary and tertiary amides when methanol (4 equiv) is present in refluxing diglyme or THF: Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000.

(18) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.

fluxing dimethoxyethane for 21 h gave only unchanged starting material. Similarly, after 3 days at 90 °C in dioxane with a large excess of lithium aluminum hydride added in several portions during the heating period, there was no evidence of reaction. However, after a total of 6 days at 90 °C, TLC analysis showed a very complex reaction mixture. No definitive evidence for the presence of desired product **5c** could be discerned from the $^1$H NMR or mass spectrum.

Tetrabutylammonium borohydride treatment of pyrimidopurine **4e** produced no evidence of reaction after 2 days in refluxing dioxane, and lithium tri-*sec*-butylborohydride[5] produced a complex mixture of products upon reaction with **4a** in tetrahydrofuran at room temperature. Only one other reagent among the metal hydrides examined effected satisfactory reduction to methylene of the 2-carbonyl group of the tricyclic nucleus: sodium bis(2-methoxyethoxy)aluminum hydride in a refluxing mixture of dimethoxyethane and toluene exhibited a yield and speed of reduction of the underivatized starting compound **4c** comparable to that observed with lithium borohydride only after silylation of the substrate. The generality of the effectiveness of sodium bis(2-methoxyethoxy)aluminum hydride for this reduction has not been demonstrated. Furthermore, the reagent would not be expected to be compatible with fluorinated aryl substrates. Catalytic hydrogenation had no effect on the tricyclic nucleus per se. Prolonged (5–6 days) shaking in a Parr apparatus at 50 psi and 40–60 °C of a solution of **4a** in dimethylformamide with 20% palladium hydroxide on carbon catalyst (with or without HCl) resulted only in apparent cleavage of the 9-*N*-benzyl group. The identification of the crude hydrogenolysis product as the debenzylated derivative is considered tentative in that its polarity and limited solubility inhibited satisfactory purification.

**General Procedure for the Selective Reduction of the 2-Carbonyl Group of the 6-Hydroxypyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-trione System.** On the basis of the observations described above, the following general procedure was devised: the pyrimidopurine to be reduced was first trimethylsilylated by refluxing it in chloroform containing 2 to 4 equiv of hexamethyldisilazane[19] and a catalytic quantity of ammonium sulfate. When all of the substrate had dissolved, solvent and excess reagent were removed under reduced pressure and the residual oil was treated with dioxane. Lithium borohydride (2.5–3 mol per mol of substrate)[20] was added portionwise and the mixture brought to reflux, which was continued until the starting material was consumed as determined by thin-layer chromatography. It should be noted that the reaction mixtures, which may be homogeneous at the outset, invariably formed suspensions as reflux proceeded.

When the reaction was judged complete, excess reagent was quenched by the careful addition of aqueous acid, the bulk of the dioxane was removed under reduced pressure, and the residue was subjected to aqueous workup and chromatographic isolation of the desired product (details in Experimental Section). Although the reactions appeared very clean by TLC and $^1$H NMR[21] analyses, isolated yields did not exceed 45%. The remainder of the material was generally retained on the chromatography column as a very polar residue. None of the possible isomeric reduction products has ever been detected.

**X-ray Crystal Structure Analysis of 5c.** The identity of starting materials **4** as the variously substituted 6-hydroxypyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-triones has been unequivocally established by X-ray analysis.[1] Although rearrangement of the ring system was considered to be unlikely under the conditions of the reactions, and the spectroscopic data (vide supra) were consistent with the location of the new methylene group at the 2-position, compound **5c** was subjected to single-crystal X-ray analysis to verify definitively the site of reduction and the integrity of the ring system. The crystal structure was solved by direct methods. Full-matrix least-squares refinement of atomic parameters[22] converged to $R = 0.065$ ($R_w = 0.095$)[23] over 3543 reflections. The asymmetric crystal unit comprises two crystallographically independent molecules of **5c** separated by normal van der Waals distances. Bond lengths and angles[22] are in accord with expected values. The only major conformational difference between the two forms occurs in the orientation of the *n*-propyl substituent as shown in Figure 1. Thus, the results confirm the assignment made on the basis of spectroscopic evidence. Moreover, in common with the parent series, the enolic form at $C_6$ in the reduced product is again stabilized by a strong intramolecular O–H···O hydrogen bond [$O_{14}$···$O_{13}$ 2.508 (3) Å, $O_{14'}$···$O_{13'}$ 2.517 (6) Å].

**Regarding the Observed Regiospecificity of the Reduction.** Simple inspection of the structure of the tricyclic ring system reveals no apparent stereochemical or electronic basis on which to rationalize the observed regiospecific preference of this reduction for the 2-carbonyl group over those at the 4- or 8-position. The relative lack of importance of steric factors is suggested by the observation that the same specificity for the site of reduction is exhibited by both lithium borohydride and sodium bis(2-methoxyethoxy)aluminum hydride, reagents which clearly differ from one another in their steric demands.

Reversible product formation with the attendant possibility of product interconvertibility was regarded as unlikely in the reduction process under consideration. Nevertheless, calculations of the heats of formation of the observed product **5c** and its respective 4-reduced (**4-iso-5c**) and 8-reduced (**8-iso-5c**) isomers were performed by using MNDO in order to ascertain whether the relative stabilities of the isomeric 2-, 4-, and 8-reduced products might suggest a thermodynamic explanation for the observed specificity in the site of reduction. The results[24] demonstrate that the observed 2-reduced isomer is *less* stable than either the 4- or 8-reduced isomer by 6.5–7 kcal/mol, thus corroborating the assumption of a lack of thermodynamic control of the reaction outcome.

Calculation of the relative stabilities of plausible reaction intermediates did, however, yield some useful insight into the origin of the observed regiospecificity. Table I shows the structures of two sets of postulated reaction intermediates and their calculated heats of formation ($H_f$). Set A derives conceptually from addition of a hydride and coordination of boron with the oxygen at positions-2, -4, and -8, respectively. Set B also derives from addition of a hydride but treats the oxygen at the site of reduction as an anion. In addition, a second anionic charge is localized on the oxygen at position-6. The presence of this latter

(19) Silylation has also been performed in neat hexamethyldisilazane, but for the larger scale preparations, a smaller excess of reagent in chloroform solvent proved to be more economical and convenient.

(20) No effort has been made to ascertain the minimum amount of lithium borohydride required to effect complete reduction.

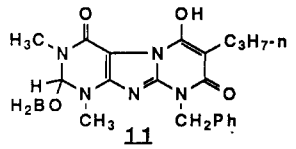
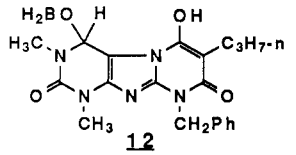
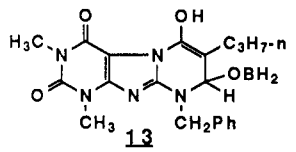
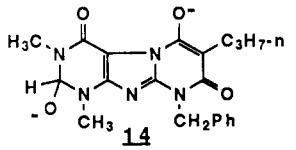
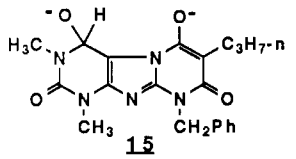
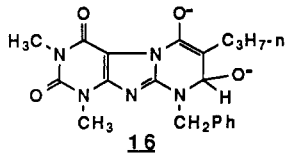
(21) The 2-methylene group exhibits a characteristic singlet at $\delta$ 4.2–4.5 in the $^1$H NMR spectrum ($CDCl_3$) and a peak at 67–68 ppm in the $^{13}$C NMR spectrum ($CDCl_3$; TMS internal standard in both cases).

(22) Supplementary material; see the paragraph at the end of the paper.

(23) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$.

(24) Calculated heats of formation ($H_f$): **5c**, −23.22 kcal/mol; **4-iso-5c**, −30.07 kcal/mol; **8-iso-5c**, −29.76 kcal/mol.

**Table I. Calculated Heats of Formation of Postulated Reaction Intermediates**

| possible intermediate | calcd heat of form ($H_f$), kcal/mol |
|---|---|
| Set A | |
|  11 | −90.52 |
|  12 | −86.79 |
|  13 | −85.88 |
| Set B | |
|  14 | −89.80 |
|  15 | −86.47 |
|  16 | −86.85 |

anion should be considered even when silylating starting materials are utilized, since cleavage of the silyl moiety from this significantly acidic center may occur under the reaction conditions. Comparison of the heats of formation of isomer sets A and B demonstrates that, in both cases, the 2-reduced species is the most stable of the three possible isomeric intermediates. In accordance with Hammond's postulate,[25] the respective transition states leading to these intermediates should resemble the corresponding intermediates in this endothermic process and should thus exhibit the same relative stabilities. Therefore, the 2-reduced intermediates, having the lowest energy transition states, should be the most rapidly formed. If, as is likely, this initial irreversible delivery of hydride constitutes the rate-determining step in the overall reduction process, then these calculations provide a rationalization for the observed regiospecificity via kinetic control of the reduction.

## Experimental Section

**General.** Melting points were determined on a Thomas-Hoover (mp's below 240 °C; corrected) or Electrothermal (mp's above 240 °C; uncorrected) capillary melting point apparatus. $^1$H NMR spectra were recorded on a Varian CFT-20 (79.5 MHz) or EM-390 (90 MHz) spectrometer and are expressed as ppm ($\delta$) from $Me_4Si$ internal standard. The solvents in which the spectra were obtained are specified in the text. IR spectra were obtained on Nujol mulls and were recorded on a Nicolet 10 MX Fourier transform infrared spectrophotometer. EI mass spectra were obtained on a Varian MAT CH5 spectrometer. FAB mass spectra were obtained on a Finnigan MAT 312 double focusing instrument equipped with a saddle field ion source from Ion Tech. Microanalyses were performed by the Physical Analytical Services Department of the Schering Pharmaceutical Research Division, and carbon, hydrogen, and nitrogen results were within ±0.4% of theory except as noted in the text. TLC was performed on plates of silica gel F-254 supplied by E. Merck (Darmstadt) or Analtech. Developed plates were visualized in UV light and/or iodine vapor. Flash chromatography[26] was performed on silica gel supplied by E. Merck (No. 9385) or J.T. Baker (No. 7024). Unless otherwise indicated, all reagents and chemicals were obtained commercially and were used without pretreatment or further purification.

**General Procedure for the Reduction of the 6-Hydroxypyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-trione System.** To a suspension of the pyrimidopurinetrione substrate (**4**) in chloroform (10–20 mL per g of substrate) were added hexamethyldisilazane (2–20 equiv) and a catalytic quantity (30 mg per g of substrate) of ammonium sulfate. The mixture, protected by a drying tube, was refluxed until a clear solution was obtained (generally, 16–20 h), and then solvent and excess reagent were removed under reduced pressure. In some instances, as noted in the specific examples which follow, this silylation step was omitted and substrate **4** was subjected directly to the reduction procedure.

The following reduction step was conducted under a nitrogen atmosphere. The crude silylation product (or untreated substrate **4**) was dissolved (suspended) in 1,4-dioxane (45 mL per g; solvent dried over 4A molecular sieves). To the well-stirred solution (suspension), contained in a water bath at room temperature, was added cautiously and portionwise powdered lithium borohydride 6 mol per mol of substrate). When the addition was complete, the resultant suspension (at this stage both silylated and untreated starting material gave a suspension) was allowed to stir for a few minutes at room temperature before the pot temperature was gradually raised by means of an oil bath to the temperature specified for each of the examples that follow.[27] Severe foaming was observed at this stage, but gradually subsided. Heating was continued, and the progress of the reaction was assessed by partitioning aliquots between chloroform and 1 M HCl. The chloroform extracts were then monitored by TLC (silica; chloroform–methanol–ammonia (75:24:1)) and $^1$H NMR (disappearance of the original *N*-methyl protons) for the consumption of starting material. When the reaction was judged complete (see specific examples below for reaction times), the reaction mixture was cooled to room temperature and was quenched by the *cautious*, dropwise addition of 3 M HCl. Dioxane was then distilled under reduced pressure. The residue was treated with chloroform, and the mixture was stirred for half an hour. Layers were separated, and the aqueous phase (strongly acidic) was extracted twice with chloroform. Combined extracts were dried over anhydrous sodium sulfate, the drying agent was filtered, and the filtrate was evaporated under reduced pressure. The crude reduction product (**5**) thus obtained was then subjected to the appropriate purification technique, as described in the individual examples below.

**Preparation of Sodium Salts.** Two general procedures were followed with the choice depending mainly on the water solubility of the substrate and its corresponding sodium salt. The salts of more soluble compounds were lyophilized directly from a pure aqueous medium (Method A), whereas the salts of less soluble materials were obtained by evaporation under vacuum from an aqueous methanolic solution (method B).

**Method A.** To a stirred suspension of substrate **5** in water (approximately 85 mL per g of substrate) was added an aqueous solution of 1 equiv of sodium hydroxide (300 mL of water per g of sodium hydroxide). The mixture thus prepared was stirred for 5 h at room temperature and the resultant hazy solution filtered. The filtrate was lyophilized, and the residual solid was

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(27) Reflux temperature is generally preferred; however, in some experiments lower temperatures were tried initially in order to evaluate the effectiveness of milder conditions.

**Table II. Substituted 2,3-Dihydro-6-hydroxypyrimido[2,1-*f*]purine-4,8(1*H*,9*H*)-diones**

| compd [formula] | $R_7$ | X | anal. calcd/found C | H | N | (other) | mp, °C (recrystlzn solvent) | chromatography system |
|---|---|---|---|---|---|---|---|---|
| **5a** | H | H | 60.17 | 5.05 | 20.64 | | 176–82 | MeOH–EtOAc–AcOH |
| $[C_{17}H_{17}N_5O_3]$ | | | 60.40 | 4.95 | 20.56 | | (MeOH–EtOAc) | (95:5:0.1) |
| **5b** | H | F | 57.14 | 4.51 | 19.60 | F, 3.23 | 214–32 dec | $CH_2Cl_2$–acetone–AcOH |
| $[C_{17}H_{16}N_5O_3F]$ | | | 57.46 | 4.49 | 19.87 | 3.47 | ($CH_3CN$) | (75:25:0.15) |
| **5c** | $C_3H_7$-*n* | H | 62.98 | 6.08 | 18.36 | | 177–178.5 | EtOAc–hexanes |
| $[C_{20}H_{23}N_5O_3]$ | | | 62.84 | 6.03 | 18.35 | | (EtOAc) | (75:25) |
| **5d** | $C_3H_7$-*n* | F | 55.81 | 5.15 | 16.27 | Na, 5.52 | 215 dec | $CHCl_3$–EtOH–$NH_4OH$ |
| $[C_{20}H_{21}N_5O_3FNa{\cdot}0.5H_2O]$ | | | 55.80 | 5.04 | 16.54 | 5.42 | | (90:2:0.1) |

| yield, % | $^1$H NMR (solvent) | mass spectrum (EI), *m/z* (rel intensity) | IR, $cm^{-1}$ (Nujol) |
|---|---|---|---|
| 43 | ($CDCl_3$): 3.02 (s, 3 H), 3.07 (s, 3 H), 4.48 (s, 2 H), 5.32 (s, 2 H), 5.37 (s, 1 H), 7.15–7.6 (m, 5 H), 15.7 (br s, OH) | 339 (100, $M^+$), 270 (50), 125 (89), 91 (86) | 1658, 1650, 1605, 1565, 1515 |
| 18 | ($CDCl_3$): 2.96 (s, 3 H), 3.05 (s, 3 H), 4.26 (s, 2 H), 5.24 (s, 2 H), 5.35 (s, 1 H), 6.95 (t, 2 H, J ≃ 9 Hz), 7.54 (br dd, 2 H, *J* ≃ 5, 8.5 Hz), 15.73 (br s, OH) | 357 (100, $M^+$), 288 (57), 180 (71), 109 (90) | 1675 (sh), 1650, 1605, 1565, 1530, 1510 |
| 44 | ($CDCl_3$): 0.92 (t, 3 H, *J* ≃ 7 Hz), 1.58 (m, 2 H), 2.46 (t, 2 H, *J* ≃ 7 Hz), 2.99 (s, 3 H), 3.04 (s, 3 H), 4.41 (s, 2 H), 5.29 (s, 2 H), 7.10–7.65 (m, 5 H), 15.25 (br s, 1 H) | 381 (24, $M^+$), 352 (100), 295 (52), 91 (77) | 1670, 1640, 1610, 1560 (br), 1511 |
| 16 | (DMSO-$d_6$): 0.80 (t, 3 H, *J* ≃ 7 Hz), 1.35 (m, 2 H), 2.30 (t, 2 H, *J* ≃ 6.5 Hz), 2.87 (s, 6 H), 4.27 (s, 2 H), 5.10 (s, 2 H), 7.07 (t, 2 H, *J* ≃ 9 Hz), 7.38 (dd, 2 H, *J* ≃ 6, 9 Hz) | 444 (100, $[M + 2Na]^+$) (FAB) | 1640, 1610, 1578, 1530, 1510 |

triturated with ether–hexanes (1:3). The sodium salt (usually a fractional hydrate) was isolated by filtration and generally gave acceptable analytical data without further purification.

**Method B.** A suspension of substrate **5** in water (55 mL per g of substrate) containing 1 equiv of sodium hydroxide was stirred at room temperature for 15 min before being diluted with methanol (50 mL per g of substrate) to produce a clear solution. Water and methanol were removed under reduced pressure, and the residue was triturated with ether (5 mL per). The sodium salt (usually a fractional hydrate) was isolated by filtration and generally required no further purification.

**9-Benzyl-1,3-dimethyl-6-hydroxy-7-(2-hydroxyethyl)pyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-trione (2) and 9-Benzyl-2,3-dihydro-1,3-dimethyl-6-hydroxy-7-(2-hydroxyethyl)pyrimido[2,1-*f*]purine-4,8(1*H*,9*H*)-dione (3).** This was the original experiment in which the reduction of the ring carbonyl group was discovered, the objective having been side-chain reduction to **2**. Hence conditions are not optimized for the preparation of **3**. Longer reaction times at higher temperature would undoubtedly improve the yield of **3** significantly.

The reaction was carried out in accordance with the general procedure without silylation of substrate **1** prior to reduction, which was conducted at 60 °C for 21 h. The two reduction products **2** and **3** did not resolve in the TLC system used to monitor the reaction, and it was incorrectly concluded initially that only a single product had been formed. In this experiment, products **2** and **3** were fortuitously separated during the workup as a result of their apparently different solubilities. However, the reproducibility and efficiency of this procedure are in some doubt. It is therefore recommended that the crude reaction product be column chromatographed in a suitable system based upon our subsequent observation that **2** and **3** can be cleanly resolved on TLC by a solvent system of chloroform–methanol–ammonium hydroxide (80:20:0.1). The fraction enriched in product **3** should be crystallizable from methanol. In the present experiment, recrystallization from methanol of the crude isolate gave title product **3** with mp 193–194 °C dec, exhibiting the following spectroscopic characteristics. $^1$H NMR ($CDCl_3$ plus a drop of DMSO-$d_6$ to clarify solution): 2.76 (t, 2 H, *J* = 6 Hz), 2.98 (s, 3 H), 3.05 (s, 3 H), 3.73 (t, 2 H, *J* = 6 Hz), 4.50 (s, 2 H), 5.31 (s, 2 H), 7.1–7.6 (m, 5 H). MS (EI): *m/z* (relative intensity) 383 (26, $M^+$), 352 (100), 295 (74), 91 (89). IR (Nujol): 1661, 1608, 1582, 1517 $cm^{-1}$. Anal. Calcd for $C_{19}H_{21}N_5O_4$: C, 59.52; H, 5.52; N, 18.27. Found: C, 59.20; H, 5.39; N, 18.21.

Recrystallization of **2** from chloroform gave a white solid with mp 184.0–184.5 dec. $^1$H NMR (DMSO-$d_6$): 2.58 (t, 2 H, *J* ≃ 7 Hz), 3.30 (s, 3 H), ~3.43 (overlapping s [3 H] and t [2 H]), 5.27 (s, 2 H), 7.10–7.47 (m, 5 H). MS (EI): *m/z* (relative intensity) 397 (2, $M^+$), 379 (9), 366 (36), 91 (100). IR (Nujol): 3500, 1704, 1675, 1645, 1613, 1531 $cm^{-1}$. Anal. Calcd for $C_{19}H_{19}N_5O_5$: C, 57.42; H, 4.82; N, 17.63. Found: C, 57.29; H, 4.76; N, 17.47.

**9-Benzyl-2,3-dihydro-1,3-dimethyl-6-hydroxypyrimido-[2,1-*f*]purine-4,8(1*H*,9*H*)-dione (5a), 9-(4-Fluorobenzyl)-2,3-dihydro-1,3-dimethyl-6-hydroxypyrimido[2,1-*f*]purine-4,8(1*H*,9*H*)-dione (5b), 9-Benzyl-2,3-dihydro-1,3-dimethyl-6-hydroxy-7-propylpyrimido[2,1-*f*]purine-4,8(1*H*,9*H*)-dione (5c), and 9-(4-Fluorobenzyl)-2,3-dihydro-1,3-dimethyl-6-hydroxy-7-propylpyrimido[2,1-*f*]purine-4,8(1*H*,9*H*)-dione (5d).** Compounds **5a**, **5b**, **5c**, and **5d** were prepared from the corresponding triones by application of the general reduction procedure. Relevant experimental and physical data are summarized in Table II. All reductions were performed at reflux. The reactions of **4a**, **4b**, and **4c** were complete in 1 to 3 days, whereas **4d** required 17–21 days.

**9-(4-Fluorobenzyl)-2,3-dihydro-1,3-dimethyl-6-hydroxy-7-methylpyrimido[2,1-*f*]purine-4,8(1*H*,9*H*)-dione (5e).** The reduction of substrate **4e** was conducted without presilylation. After 2 days at 80 °C and another 18 h at reflux, $^1$H NMR indicated the presence of a substantial mixture of products including title compound **5e** and unchanged starting material **4e** in a ratio of approximately 5:1. No attempt was made to isolate **5e** from the mixture, but its presence was unequivocally ascertained by the detection of the characteristic singlet for the 2-methylene group at δ 4.45 ($CDCl_3$).

**Treatment of 9-Benzyl-1,3-dimethyl-6-hydroxy-7-propylpyrimido[2,1-*f*]purine-2,4,8(1*H*,3*H*,9*H*)-trione (4c) with Various Metal Hydrides. Sodium Bis(2-methoxyethoxy)-aluminum Hydride.** To a suspension of 500 mg (1.27 mmol) of **4c** in a mixture of 32 mL of dry (3A sieves) dimethoxyethane and 12 mL of dry (3A sieves) toluene, were added cautiously, under a nitrogen atmosphere, three 0.5-mL portions (1.5 mL = 5.1 mmol) of 3.4 M sodium bis(2-methoxyethoxy)aluminum hydride in toluene (Red-Al; Aldrich). The resultant mixture was heated in an oil bath and maintained at reflux for 17 h. The mixture was allowed to cool, another 0.5 mL (1.7 mmol) of 3.4 M Red-Al was added, and reflux was resumed for 5 h. The mixture was cooled, concentrated under reduced pressure, acidified (25 mL of 1.5 M aqueous HCl), and subjected to aqueous workup to obtain 220 mg (46%) of **5c** (characterization: see Table II).

**Sodium Borohydride.** To a stirred suspension of 403 mg (1.02 mmol) of **4c** in 20 mL of anhydrous methanol at room temperature and under a nitrogen atmosphere was added 187 mg (4.94 mmol)

of sodium borohydride. The reaction mixture was stirred at room temperature for 17 h and then at 80 °C for 108 h. Aqueous workup gave back starting material **4c**. No evidence of any reaction product was detected.

**Borane–Tetrahydrofuran Complex.** To a stirred suspension of 500 mg (1.3 mmol) of **4c** in 16 mL of dry tetrahydrofuran, maintained at 1–5 °C, was added 1.3 mL (1.3 mmol) of a 1.0 M solution of borane–tetrahydrofuran in tetrahydrofuran. After 4 h of stirring at room temperature, no reaction products were detected by TLC (chloroform–methanol–ammonium hydroxide [75:24:1]). Addition of another 1.3 mL (1.3 mmol) of 1.0 M $BH_3$–THF and refluxing for 3.5 h similarly failed to effect any detectable reaction. Following the addition of a further 3.9 mL (3.9 mmol) of 1.0 M $BH_3$–THF and another 10 h of reflux, TLC revealed the presence of a multicomponent mixture containing spots corresponding to both starting material **4c** and desired product **5c** in addition to unidentified materials.

**Lithium Aluminum Hydride. (a) In Dimethoxyethane.** Substrate **4c** (500 mg, 1.26 mmol) was silylated by the general procedure. A solution of the silylated substrate in 10 mL of dimethoxyethane (dried over 4A sieves) was treated with 45 mg (1.1 mmol) of lithium aluminum hydride, and the resultant mixture was allowed to reflux under a nitrogen atmosphere for 21 h. An aliquot of the reaction mixture was quenched with 3 M HCl and subjected to aqueous workup. TLC and $^1H$ NMR analyses of the solid thus isolated showed only unchanged starting material.

**(b) In Dioxane.** Substrate **4c** (500 mg, 1.26 mmol) was silylated by the general procedure. A solution of the silylated substrate in 15 mL of dioxane (dried over 4A sieves) was treated with a total of 560 mg (14.8 mmol) of lithium aluminum hydride, which was added in four portions over a period of 6 days, during which time the reaction mixture was maintained at 90 °C. TLC analysis of an aliquot (aqueous workup) showed only unchanged starting material. Another 140 mg (3.65 mmol) of lithium aluminum hydride was added, and heating at 90 °C was continued for another 3 days. Aqueous workup of the reaction mixture gave 240 mg (~50% recovery) of a gum which TLC revealed to be a complex mixture of materials. The complexity of the mixture was further confirmed by $^1H$ NMR ($CDCl_3$) and mass spectra, neither of which contained evidence of the presence of desired product **5c**.

**Calculation of Heats of Formation.** The calculations were carried out on an IBM 3081 Model K computer operating at 15 Mips using the MNDO molecular orbital approximation.[28] The MNDO program was obtained through QCPE,[29] converted to VS FORTRAN 77, and adapted to run on the IBM 3081 computer. The structural input was generated by using the MOPAC/SYBYL[30] interface, and the geometries were found by minimizing the total energy using the standard Davidon–Fletcher–Powell[31] optimization procedure. All geometric variables were allowed to optimize.

**X-ray Crystal Structure Analysis of 5c.** Crystal data: $C_{20}H_{23}N_5O_3$, $M_r$ 381.44, monoclinic, $a$ = 13.559 (3) Å, $b$ = 19.366 (2) Å, $c$ = 20.328 (4) Å, $\beta$ = 132.94 (2)°, $V$ = 3907.6 Å$^3$, $Z$ = 8, $D_{calcd}$ = 1.297 g cm$^{-3}$, $\mu$(Cu K$\alpha$ radiation, $\lambda$ = 1.5418 Å) = 7.0 cm$^{-1}$. Space group $P2_1/c(C_{2h}^5)$ uniquely from the systematic absences: $0k0$ when $k \neq 2n$, $h0l$ when $l \neq 2n$. Sample dimensions: 0.12 × 0.26 × 0.60 mm.

Preliminary unit-cell parameters and space group information were provided by oscillation and Weissenberg photographs. Intensity data ($h,k,\pm l$) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu K$\alpha$ radiation, incident-beam graphite monochromator; $\omega$–$2\theta$ scans, $\theta_{max}$ = 67°). From a total of 7036 independent measurements after averaging equivalent ($0,k,\pm l$) forms, only those 3543 reflections with $I > 3.0\sigma(I)$ were retained for the structure analysis and corrected for the usual Lorentz and polarization effects. Refined unit-cell parameters were derived from the diffractometer setting angles for 25 reflections ($40° < \theta < 49°$) widely separated in reciprocal space.

The crystal structure was solved by direct methods. Nonhydrogen atom coordinates were derived in part from an initial $E$ map and from subsequent $F_o$ Fourier syntheses. Hydrogen atoms, save those on the $CH_2CH_3$ moieties of the $n$-propyl substituents, were all located in difference Fourier syntheses evaluated following several rounds of full-matrix least-squares adjustment of non-hydrogen atom positional and anisotropic thermal parameters. Continuation of the least-squares iterations, with all hydrogen atoms included at their calculated positions, led to convergence at $R$ = 0.065 ($R_w$ = 0.095).[23]

Neutral atom scattering factors used in the structure-factor calculations were taken from ref 32. In the least-squares iterations, $\sum w\Delta^2$ ($w = 1/\sigma^2(|F_o|)$, $\Delta = (|F_o| - |F_c|)$ was minimized. Crystallographic calculations were performed on a PDP11/44 computer by use of the Enraf-Nonius SDP suite of programs incorporating the direct methods program MULTAN11/82.

**Supplementary Material Available:** Tables of fractional atomic coordinates, thermal parameters, bond lengths, bond angles, torsion angles, and displacements of atoms from least-squares planes (13 pages). Ordering information is given on any current masthead page.

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# Asperketals A–F, New Diterpenoids of the Dilophol Class from the Caribbean Gorgonian *Eunicea asperula*

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*Received December 1, 1987*

Six new diterpenoids, asperketals A–F (**1–6**), have been isolated from the Caribbean sea whip *Eunicea asperula*. Compounds **1–5** are ketals and hemiketals possessing 10-membered-ring skeletons analogous to the recently reported marine metabolites dilophol and obscuronatin. Similarly, asperketal **6** is a new diterpenoid ketal related to the *Eunicea*-derived diterpenoid fuscol. The structures of these new compounds were assigned on the basis of chemical and spectral studies and particularly upon spectral analyses involving nuclear Overhauser enhancement difference spectroscopy (NOEDS).

Marine octocorals of the order Gorgonacea, the sea whips and sea fans (phylum Cnidaria), are recognized as a rich source of biologically active and structurally unique secondary metabolites.[1] In the Caribbean Sea, sea whips of

0022-3263/88/1953-3271$01.50/0 