Borane Reduction of Uracil Derivatives[1,2]

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Our interest in the synthesis of pyrimidines and, specifically, our need for a suitable synthetic route to 4-hydroxy-5-(hydroxymethyl)-2-thiopyrimidine (**1**) in conjunction with some biochemical studies prompted us to investigate the borane reduction of several uracil derivatives. While the hydroxymethylation of uracil (**2**) to 5-(hydroxymethyl)uracil (**3**) by treatment with paraformaldehyde has been achieved,[5] this reaction failed to provide **1** from 2-thiouracil (**4**) in our hands. West and Barrett[6] have also found and reported that unlike uracil, thiouracil and other pyrimidines with unsubstituted sulfur are much less reactive.

In view of the above results, our strategy was to prepare the hydroxymethylpyrimidine **1** by reduction of the corresponding acid **5**. The acid **5** can be conveniently obtained by condensation of diethyl (ethoxymethylene)-malonate with thiourea[7] followed by alkaline hydrolysis. Because the 5,6 double bond of uracil and uracil derivatives is relatively reactive, particularly toward nucleophiles,[8] the choice of the reagent for selective reduction of the carboxyl function of **5** without affecting the 5,6 double bond is rather limited. It is, however, well established that the reactivity of the carboxylic acid group is greater than an olefinic bond toward borane in tetrahydrofuran[9] (THF). The borane–THF complex, therefore, seemed to be the reagent of choice for the conversion of **5** to the corresponding alcohol **1**. This report deals with the reaction of **5** and some other pyrimidine derivatives with the aforementioned reagent.

Results and Discussion

When the pyrimidine acid **5** (1 mmol) was treated with borane in THF, 5,6-dihydro-2-thiouracil (**11**) was formed in 77% yield with the consumption of 1.5 mmol of borane. Similar treatment of **6** (isoorotic acid) in dimethylformamide (DMF) also resulted in decarboxylation as well as olefin reduction to give dihydrouracil **12** (27%). The formation of **11** and **12** from **5** and **6**, respectively, may be rationalized as follows: The 5,6 double bond of pyrimidine **5** and **6** undergoes hydroboration and the resultant intermediates, resembling β-keto acids, undergo spontaneous decarboxylation to yield dihydropyrimidines **11** and **12**.

For **7** where the SH moiety is free, the 5,6 double bond is reduced by borane, but the 5-carboxyethyl group remains intact, affording **13**. By comparison, when the SH moiety is blocked by a benzyl group **8**, the 5,6 double bond remains intact and the 5-carboxyethyl group is reduced to the corresponding alcohol **10**. This chemistry provides a convenient route for reduction of the ester, while rendering the 5,6 double bond inert to attack by borane. The acid **9** is inert to borane. No reason for the unusual lack of reactivity of the carboxyl group of **9** toward borane can be put forward at present. Uracil or thiouracil could not be reduced by borane.

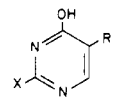
On the basis of the results described above, the essential features for the reduction of the 5,6 double bond of uracil derivatives by borane are that (i) the compounds be in the "ene–one" form and (ii) there must be a sufficiently strong electron-withdrawing group linked at the 5-position of the pyrimidine ring. Unfortunately, 5-fluoro(or chloro-)uracil is not soluble in hot THF or DMF, so their reaction with borane could not be studied; hence, further direct evidence for the second premise could not be adduced. It has been reported recently that for the reduction of uracils by lithium tri-*sec*-butylborohydride (L-Selectride), locking of the uracils in the "ene-one" form is essential.[10] Table I summarizes the reaction conditions and borane reduction products from the different uracil derivatives.

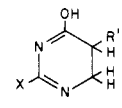
Table I Borane Reduction of Uracil Derivatives

reactant	product	reaction medium	mol of BH_3 per mol of reactant	yield,[a] %
5	**11**	THF	2	77
6	**12**	pyridine	3	27
7	**13**	THF	3	76
8	**10**	THF	2.2	42
9		THF, cold		nr
		THF, hot		degrades
orotic acid		(1) pyridine; (2) Me_2SO; (3) DMF	3	nr
thiouracil		pyridine, hot	3	nr
5-fluoro-uracil		DMF (solubility problem)	2.2	nr
5-iodo-uracil		THF	2	nr
uracil, 5-chlor-ouracil		solubility problem		

[a] nr = no reaction.

Utilizing the borane reduction chemistry, our target compound **1** was readily obtained. Compound **10** was afforded by borane reduction of **8**. Debenzylation of **10** with sodium and liquid ammonia gave **1**.





1, X = SH; R = CH_2OH
2, X = OH; R = H
3, X = OH; R = CH_2OH
4, X = SH; R = H
5, X = SH; R = COOH
6, X = OH; R = COOH
7, X = SH; R = CO_2Et
8, X = $SCH_2C_6H_5$; R = CO_2Et
9, X = $SCH_2C_6H_5$; R = COOH
10, X = $SCH_2C_6H_5$; R = CH_2OH
11, X = SH; R′ = H
12, X = OH; R′ = H
13, X = SH; R′ = CO_2Et

Conclusions

In summary, the results of an investigation on the reduction of uracil derivatives with borane and the synthesis

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(2) Irrespective of the predominant tautomeric structures, the hydroxypyrimidines are presented here in the enol form.

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of 1 have been presented. Although carboxylic acid groups are generally more reactive toward borane than double bonds, decarboxylation and reduction of the 5,6 double bond occurred preferentially in pyrimidines 5 and 6. In contrast, an unusual lack of reactivity toward borane was observed for 9; both the carboxyl and double-bond functionalities were totally inert. The selectivity obtained in the borane reduction of the 5-carboxyethyl group of 8 conveniently provided 10. A separate debenzylation step readily affords 5-(hydroxymethyl)-2-thiouracil (1). Key structural features important for the successful reduction of the 5,6 double bond are the "ene-one" form[10] and an electron-withdrawing group of appropriate strength at the 5-position of the pyrimidine.

Experimental Section

All melting points were determined with a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded with the use of a Varian Associates FT-80 instrument. Chemical shifts are reported on the scale in parts per million downfield from internal tetramethylsilane (Me_4Si), and apparent coupling constants (J) are given in hertz (Hz). Infrared spectra (IR) were obtained with the use of a Perkin-Elmer 257 grating infrared spectrophotometer. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

The tetrahydrofuran was Fisher reagent grade and was freshly distilled from lithium aluminum hydride. Diethyl(ethoxymethylene)malonate, 2-thiouracil, uracil, and the borane–THF were obtained from Aldrich Chemical Company. Isoorotic acid, orotic acid, 5-chlorouracil, 5-fluorouracil, and 5-iodouracil were supplied by Sigma Chemical Company. All other chemicals were reagent grade.

Ethyl 4-Hydroxy-2-mercaptopyrimidine-5-carboxylate (7). The ester 7 was prepared by following a literature procedure:[7] mp 254–256 °C (lit.[5] mp 245 °C); IR (KBr) 3500 (NH), 1745 (ester carbonyl) 1670 (amide carbonyl) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) 1.25 (3 H, t, J = 8, CH_3), 4.16 (2 H, q, J = 8, -CH_2-), 7.95 (1 H, s, H-6).

4-Hydroxy-2-mercaptopyrimidine-5-carboxylic Acid (5). The preceding ester 7 (5 g, 25 mmol) on hydrolysis by refluxing with an aqueous alcoholic KOH solution (2 N, 50 mL) gave the acid 5 (4.30 g, 100%); mp 297 °C dec; in its ^{1}H NMR spectrum only a singlet at 8.00 due to both carboxylic proton and H-6 could be observed; IR (KBr) 3520 (NH), 1700 (acid carbonyl), 1635 and 1580 (amide carbonyl) cm^{-1}. Anal. Calcd for $C_5H_4N_2O_3S$: C, 34.88; H, 2.34; N, 16.27. Found: C, 34.78; H, 2.30; N, 16.12.

Ethyl 4-Hydroxy-2-(benzylthio)pyrimidine-5-carboxylate (8). A mixture of 7 (1.0 g, 5 mmol), ethanolic NaOEt (1 N, 5 mL), and benzyl chloride (0.694 mL, 5.5 mmol) was refluxed in ethanol (25 mL) for 3 h, evaporated to dryness, triturated with water, and filtered. The precipitate on crystallization from ethanol afforded 8 (0.90 g, 62%); mp 174–175 °C (lit.[7] mp 174–179 °).

4-Hydroxy-2-(benzylthio)pyrimidine-5-carboxylic Acid (9). The above ester 8 (11.60 g, 40 mmol) was hydrolyzed by refluxing it in dilute alcohol (70%, 250 mL) containing KOH (8.96 g, 0.16 mol) to yield the acid 9 (9.2 g, 88%): mp 192–194 °C; λ_{max} (log ϵ) (EtOH) 302 (4.06), 258 (3.89) nm; (pH 2) 318 (4.06), 258 (3.84) nm, (pH 12) 294 (4.09), 252 (4.02) nm; ^{1}H NMR (Me_2SO-d_6) δ 4.50 (2 H, s, CH_2), 7.35 (5 H, m, C_6H_5), 8.60 (1 H, s, H-6) and 11.32 (2 H, bs, OH and COOH). Anal. Calcd for $C_{12}H_{10}N_2O_3S$: C, 54.95; H, 3.84; N, 10.68; S, 12.23. Found: C, 54.83; H, 3.93; N, 10.46; S, 12.06.

General Procedure for Reduction with Diborane. BH_3–THF complex in THF (1.0 M) was used as the reducing agent. All the reductions were carried out in THF except in case of isoorotic acid where pyridine was used. The reagent, BH_3–THF solution (3 mL, 3 mmol), was added dropwise to a magnetically stirred and ice-cooled solution of the substrate (1 mmol) in THF or pyridine (40 mL) under nitrogen. After the addition was over, the reaction mixture was stirred at 0 °C for 30 min and at ambient temperature for 1 h. The solvent was then evaporated in a rotary evaporator. The residue was treated with aqueous acetic acid (50%, 8 mL) and the mixture was again evaporated to dryness. The residue was digested with hot water (10 mL) for 5 min and filtered, whereby most of the boric acid formed went into the filtrate. The precipitate was crystallized from either water or alcohol.

5,6-Dihydrouracil (12): mp and mmp 278–280 °C.

Ethyl 5,6-dihydro-4-hydroxy-2-mercaptopyrimidine-5-carboxylate (13): mp 142–143 °C λ_{max} (log ϵ) (H_2O, pH 7 and 2) 273 (4.46) and 226 (4.23) nm; in alkaline pH (12) the compound underwent some transformation showing UV absorption maximum at 237 (log ϵ 4.39) nm; IR (KBr) 3200, 1750, 1720 cm^{-1}, ^{1}H NMR (Me_2SO-d_6) δ 1.19 (3 H, t, J = 8, CH_3), 3.65 (3 H, m, -CH_2CHCO_2Et), 4.10 (2 H, q, J = 8, -CO_2CH_2-), 9.25 (1 H, bs, -NHCO-), and 11.02 (1 H, bs, -SCNHCO-). Anal. Calcd for $C_7H_{10}N_2O_3S$: C, 41.57; H, 4.98; N, 13.86. Found: C, 41.52; H, 4.94; N, 13.93.

4-Hydroxy-5-(hydroxymethyl)-2-(benzylthio)pyrimidine (10): mp 175 °C; λ_{max} (log ϵ) (aqueous ethanol, 50%) 285 (3.89), 289 (3.89) and 281 (3.93) nm at pH 7, 2, and 12, respectively, with isosbestic point at 286 nm; IR (KBr) 3400 (OH), 1660 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.40 (1 H, bs, OH), 4.30 (2 H, s, CH_2OH), 4.43 (2 H, s, $ArCH_2S$-), 7.85 (5 H, m, C_6H_5), 7.85 (1 H, s, H-6). Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87; N, 11.28; S, 12.91. Found: C, 58.20; H, 4.86; N, 11.155; S, 12.75.

4-Hydroxy-5-(hydroxymethyl)-2-mercaptopyrimidine (1). To a solution of 10 (0.248 g, 1 mmol) in liquid ammonia (~30 mL) was added freshly cut sodium (0.086 g), affording a dark blue solution. The blue color was discharged by careful addition of ammonium chloride. The reaction was left in the hood to allow the ammonia to evaporate. The residue was dissolved in water (20 mL). Rotary evaporation to 5–6 mL followed by cooling gave needlelike crystals of final product 1 (0.076 g, 48% of theory). Physical data for 1: IR (KBr) 3300 (NH), 1650 and 1545 (amide carbonyl); ^{1}H NMR (Me_2SO-d_6) δ 4.17 (2 H, s, -CH_2-), 7.31 (1 H, s, vinyl), 8.80 (2 H, bs, D_2O exchangeable). Anal. Calcd for $C_5H_6N_2O_2S$: C, 37.96; H, 3.82; N, 17.72. Found: C, 38.05; H, 3.89; N, 17.62.

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Registry No. 1, 93185-31-0; 5, 23945-50-8; 6, 23945-44-0; 7, 38026-46-9; 8, 93185-32-1; 9, 93185-33-2; 10, 93185-34-3; 11, 5366-11-0; 12, 504-07-4; 13, 93185-35-4.

Aqueous Intermolecular Diels–Alder Chemistry: Vernolepin Revisited

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Since the first synthesis of the potent cytotoxic sesquiterpene vernolepin (2) was recorded in 1976,[1] several ingenious approaches have been completed and published.[2] Notable among them is Schlessinger's[2d] route that proceeds via the intermediacy of bicyclic enone 1,[3] which was prepared in 11 steps from ethyl crotonate. We detail below an alternate, direct six-step synthesis of 1 that features an

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(3) The configuration about the anomeric carbon in bicyclic enone 1 was previously incorrectly assigned by the Schlessinger group. The structure of 1 has been unambiguously established by single-crystal X-ray analysis (unpublished results, Indiana University).

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