for analytical samples, mp 190–192 °C dec (lit.[4] mp 192–193 °C), after drying in vacuo over P_2O_5. Mother liquors were combined, the solvent removed, and the residue recrystallized from 70% aqueous trifluoroacetic acid to give an additional 0.6 g of **1**, mp 187–192 °C dec. The pure compound (**1**) showed: mass spectrum (20 eV) *m/e* 196 (M^+, 38%), 150 (17%), 123 (100%), 122 (9%), 105 (3%), 94 (3%), 77 (10%); NMR (10% D_2O in $(CD_3)_2CO$) δ 6.45 (s, 1 H, β-H), 6.87 (d, J = 8 Hz, 1 H, H_5), 7.20 (dd, J = 8, 2 Hz, 1 H, H_6), 7.45 (d, J = 2 Hz, 1 H, H_2) (enol form); UV (MeOH) λ_{max} 307 nm (mixture of enol and keto tautomers).

Registry No.—1 keto form, 4228-66-4; 1 enol form, 68307-79-9; 2, 59-92-7; 3, 68307-80-2.

References and Notes

(1) This research was supported by National Science Foundation (GM 17957) and National Institutes of Health (5-TO1-HL-05672) grants.
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Pteridines. 46. Unequivocal Synthesis of 2,4-Diamino-6(5*H*)-pteridinone (4-Amino-4-deoxyxanthopterin) and Xanthopterin from 5,7-Diaminofurazano[3,4-*d*]pyrimidine[1,2]

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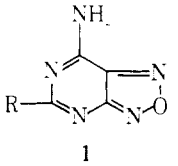
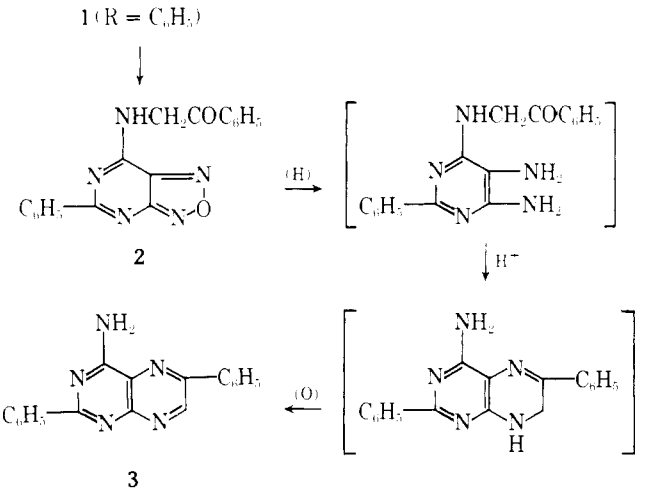
7-Aminofurazano[3,4-*d*]pyrimidines (**1**), which are readily prepared by lead tetraacetate oxidation of 4,6-diamino-5-



1

nitrosopyrimidines,[3] represent latent 4,5,6-triaminopyrimidines of considerable synthetic versatility. The 7-amino substituent (particularly when acylated) is remarkably reactive toward nucleophilic displacement reactions,[3,4] and the substituent thus introduced can be modified (e.g., by acylation) without incident. Reductive cleavage of the N–O–N linkage then generates a strongly nucleophilic 5-amino grouping which cyclizes with the newly introduced (and perhaps modified) adjacent substituent. The 6-amino group remaining from the reductive cleavage reaction is extruded as a substituent on the new fused heterocycle. In this way furazano[3,4-*d*]pyrimidines have been exploited as intermediates for the synthesis of adenines,[3,5] 4-aminopyrrolo[3,2-*d*]pyrimidines,[6] 4-amino-7-azapteridines,[7] and (in a few limited cases) 4-aminopteridines.[7] An example of the latter transformation is the unequivocal synthesis of 2,6-diphenyl-4-aminopteridine (**3**) from 5-phenyl-7-(benzoylmethylamino)-furazano[3,4-*d*]pyrimidine (**2**), prepared from 5-phenyl-7-aminofurazano[3,4-*d*]pyrimidine (**1**, R = C_6H_5) and aminoacetophenone, by reductive cleavage of the furazan ring, acid-catalyzed cyclization, and oxidation.

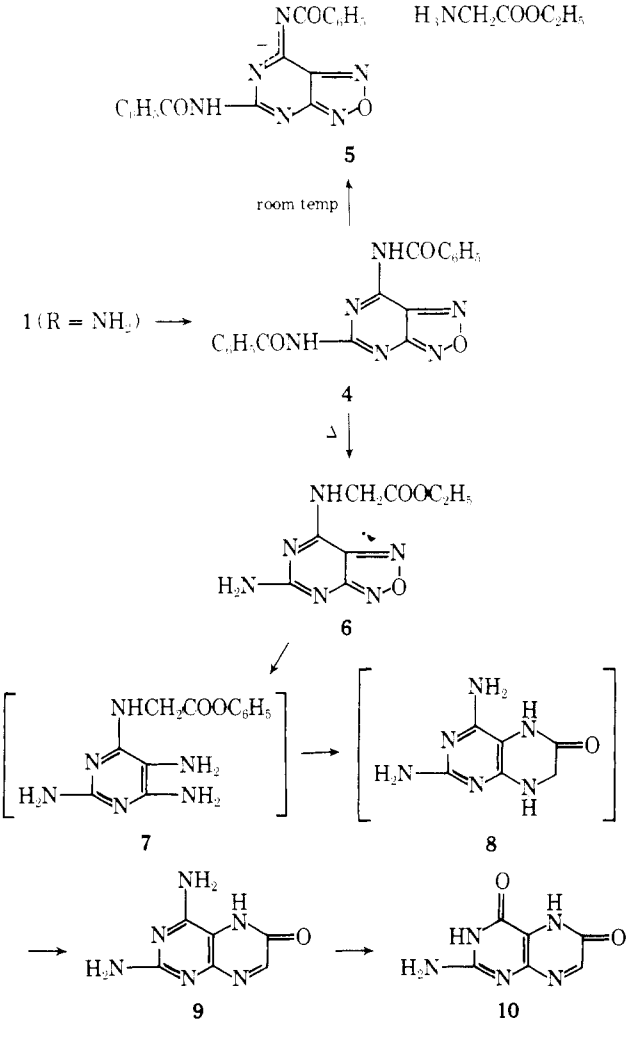
The present note describes an extension of this general synthetic method to the unequivocal synthesis of 4-amino-



2 **3**

4-deoxyxanthopterin (2,4-diamino-6(5*H*)-pteridinone) (**9**) and, by hydrolysis of the latter, a new synthesis of the naturally occurring insect pigment and antitumor agent xanthopterin (**10**).[8]

Fusion of 5,7-diaminofurazano[3,4-*d*]pyrimidine (**1**, R = NH_2) with benzoic anhydride at 200 °C gave 5,7-bis(benzoylamino)furazano[3,4-*d*]pyrimidine (**4**) in 91% yield. Although reaction of the latter intermediate with ethyl glycinate in THF at room temperature resulted only in the formation of a salt (**5**), heating a mixture of **4** and ethyl glycinate at 110 °C for 5 min resulted both in displacement of the 7-benzoylamino substituent and in aminolytic cleavage of the 5-benzoyl grouping to give 5-amino-7-(carbethoxymethylamino)fura-



5 **4** **6** **7** **8** **9** **10**

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zano[3,4-*d*]pyrimidine (**6**) in 71% yield. Catalytic reduction of **6** in methanol led to smooth reductive cleavage of the furazan ring to give (presumably) the intermediate pyrimidine **7** which, without isolation, cyclized upon treatment with *p*-toluenesulfonic acid at room temperature to 2,4-diamino-7,8-dihydro-6(5*H*)-pteridinone (**8**). This latter compound proved to be too unstable for isolation, but treatment with iodine in aqueous base resulted in smooth dehydrogenation to 2,4-diamino-6(5*H*)-pteridinone (4-amino-4-deoxyxanthopterin) (**9**). Hydrolysis of **9** with refluxing 5% sodium hydroxide then gave xanthopterin (**10**) itself, identical in every respect with an authentic sample.[8]

In view of the remarkable effect on biological activity of replacement of the 4-"hydroxy" group in pterins by an amino substituent (cf. folic acid and aminopterin),[9] the biological (and antitumor) activity of **9** should be of particular interest.

Experimental Section

5,7-Bis(benzoylamino)furazano[3,4-*d*]pyrimidine (4). A flask containing 4.0 g of 5,7-diaminofurazano[3,4-*d*]pyrimidine and 40 g of solid benzoic anhydride was placed in an oil bath maintained at 200 °C. The resulting suspension was stirred for 1 h, during which time all solid material dissolved. The yellow solution was cooled to room temperature to give a solid yellow mass which was slurried in 100 mL of ether and stirred for 1 h. The pale yellow crystals were collected by filtration, washed with ether, and dried in vacuo, yield 8.6 g (91%). An analytical sample, mp 270–271 °C, was obtained by recrystallization from DMF: IR (KBr) ν_{max} 1660, 1620, 1585, 1445 cm^{-1}.

Anal. Calcd for $C_{18}H_{12}N_6O_3$: C, 60.00; H, 3.36; N, 23.33. Found: C, 59.93; H, 3.45; N, 23.51.

Salt of 5,7-Bis(benzoylamino)furazano[3,4-*d*]pyrimidine and Ethyl Glycinate (5). To a suspension of 1.8 g of 5,7-bis(benzoylamino)furazano[3,4-*d*]pyrimidine in 12 mL of THF was added 1 g of ethyl glycinate, and the resulting mixture was stirred vigorously until all solid material dissolved. The yellow solution was then allowed to stand at room temperature for 30 min. The colorless crystals which had separated were collected by filtration, washed with ethanol, and air-dried: yield 1.35 g (58%); mp 167–169 °C; NMR (CF_3COOH) δ 0.83 (t, 3 H), 3.6–4.1 (m, 4 H), 7.0–8.0 (m, 10 H); IR (KBr) ν_{max} 3450, 3400, 3320, 1725, 1640 cm^{-1}.

Anal. Calcd for $C_{22}H_{21}N_7O_5$: C, 57.01; H, 4.57; N, 21.16. Found: C, 57.01; H, 4.78; N, 21.02.

5-Amino-7-(carbethoxymethylamino)furazano[3,4-*d*]pyrimidine (6). A flask containing a suspension of 3.6 g of 5,7-bis(benzoylamino)furazano[3,4-*d*]pyrimidine in 9 mL of ethyl glycinate was placed in an oil bath at 110 °C. After 1 min of stirring at this temperature, a red solution resulted which, within 5 min, solidified to a purple mass. The reaction mixture was cooled to room temperature and slurried in 25 mL of ethanol, and the purple solid was collected by filtration, washed free of color with cold ethanol, and dried: yield 1.69 g (71%); mp 245–246 °C dec (from dioxane); NMR (Me_2SO-d_6) δ 1.16 (t, 3 H), 4.13 (q, 2 H), 4.26 (s, 2 H), 7.19 (br s, 2 H); IR (KBr) ν_{max} 3450, 3360, 1735, 1660, 1600 cm^{-1}.

Anal. Calcd for $C_8H_{10}N_6O_3$: C, 40.33; H, 4.23; N, 35.28. Found: C, 40.52; H, 4.42; N, 35.29.

2,4-Diamino-7,8-dihydro-6(5*H*)-pteridinone (8). A suspension of 235 mg of 5-amino-7-(carbethoxymethylamino)furazano[3,4-*d*]-pyrimidine in 70 mL of methanol was stirred with 120 mg of 5% Pd–C under 1 atm of hydrogen until 3 mmol of hydrogen had been consumed (ca. 45 min). The catalyst was removed by filtration, and 5 mg of *p*-toluenesulfonic acid was added to the filtrate, which was then allowed to stand at room temperature for 3 h. During this period, colorless crystals started to separate from the solution, and this process was aided by refrigeration. The precipitate was collected by filtration, washed with ethanol and ether, and dried: yield 120 mg; mp >250 °C dec. Because of its instability, this material was not further purified and was used directly in the next reaction: NMR (Me_2SO-d_6) δ 3.80 (s, 2 H), 5.4 (br s, 2 H), 5.8 (br s, 2 H), 6.43 (br s, 1 H, N-8 H), 9.4 (br s, 1 H, N-5 H); IR (KBr) ν_{max} 3400, 3175, 1690, 1660, 1600 cm^{-1}.

2,4-Diaminopteridine-6(5*H*)-one (4-Amino-4-deoxyxanthopterin) (9). A solution of 100 mg of 2,4-diamino-7,8-dihydro-6(5*H*)-pteridinone in 8 mL of 0.5 N aqueous potassium hydroxide was cooled in an ice bath. To the stirred solution was added dropwise, over a period of 10 min, a solution of 200 mg of iodine in 2 mL of ethanol. After addition was complete, the reaction mixture was stirred at 0 °C for an additional 10 min and the product was then precipitated by addition of acetic acid to neutrality. The flocculent precipitate could be collected readily by filtration if the reaction flask was first warmed for several hours. An additional precipitation of this material from dilute potassium hydroxide with acetic acid gave 85 mg (74%): mp >350 °C; IR (KBr) ν_{max} 3340, 3150, 1650, 1515, 1410 cm^{-1}; UV (0.1 N HCl) λ_{max} (log ϵ) 245 (4.13), 275 (3.64), 354 (3.86), 367 (3.82) nm.

Anal. Calcd for $C_6H_6N_6O \cdot H_2O$: C, 36.73; H, 4.11; N, 42.84. Found: C, 37.00; H, 4.55; N, 43.24.

Xanthopterin (10). A solution of 100 mg of 2,4-diamino-6(5*H*)-pteridinone in 10 mL of 5% sodium hydroxide was stirred in a plastic flask for 24 h at 100 °C. The yellow solution was diluted with water to 20 mL and filtered, and the pH was adjusted to 2 with 6 N hydrochloric acid. The precipitate which had formed was collected by filtration and redissolved in 10 mL of 2% sodium hydroxide. Reprecipitation with acetic acid then gave 85 mg of pure xanthopterin, identical in all respects with authentic material.

Registry No.—**1** (R = NH_2), 30745-07-4; **4**, 68152-16-9; **5**, 68152-17-0; **6**, 68152-18-1; **8**, 26398-12-9; **9**, 1917-45-9; **10**, 119-44-8; ethyl glycinate, 459-73-4.

References and Notes

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Lithiation of *N,N*-Dimethyl-3-(phenylthio)-2-propenylamine

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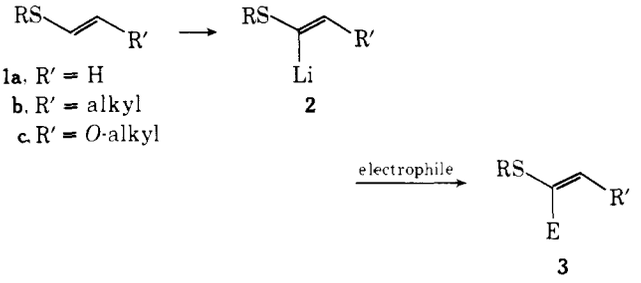
The α lithiation of vinyl sulfides (**1a,b**) is facile, and the resulting anions **2** constitute synthetic equivalents of acyl anions.[1] Possible side reactions are Michael-type additions of the metalating agent to the terminal of the olefinic bond, leading to saturated carbanions stabilized by the sp^3–d overlap.[2,3] α deprotonation, however, can be achieved exclusively by observing low temperatures and by the use of less nucleophilic metalating agents such as lithium diisopropylamide.[4,5]



1a, R′ = H
b, R′ = alkyl
c, R′ = *O*-alkyl

2

3

The latter fact is indicative of the considerable thermodynamic acidity of the α proton in such substrates ($pK_a \leq 30$).

In analyzing the directing influence of additional hetero-

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