MHz) δ 14.4, 18.6, 20.2, 28.4, 40.5, 43.0, 45.5, 58.8, 59.7, 63.6, 64.7, 108.1, 111.2, 147.5, 173.2; MS (EI), m/e (relative intensity) 268 (4), 253 (2), 241 (1), 223 (6), 200 (3), 195 (6), 154 (15), 139 (48), 113 (100), 99 (16), 86 (66); IR (neat) 1725 and 1645 cm^{-1}; GC t_R 20.17. Anal. Found: C, 67.14; H, 9.01.

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Condensation of 2,4-Diamino-6(1*H*)-pyrimidinone with 2-(Aminomethylene)cyclopentanone[1]

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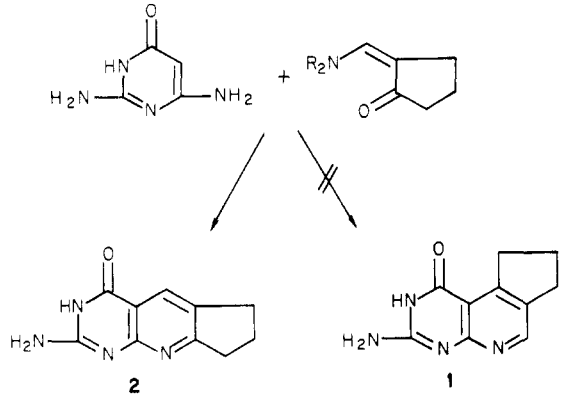
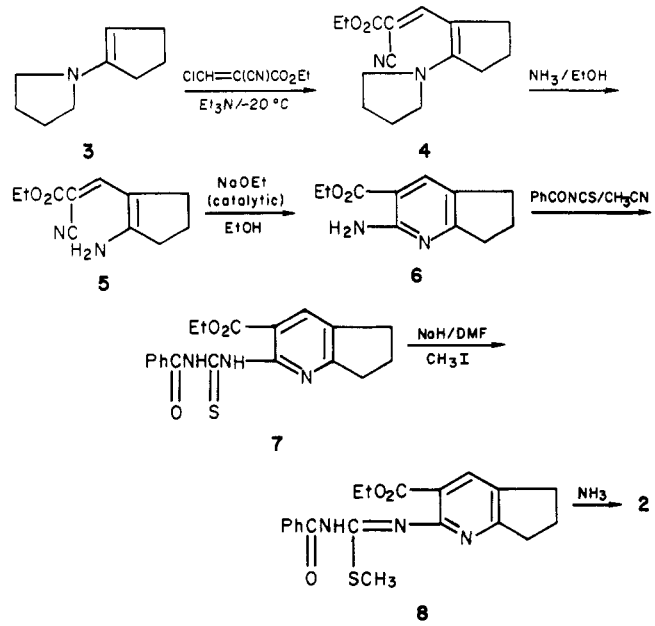
Interest in annulated 5-deazapteridines (pyrido[2,3-*d*]-pyrimidines) as potential inhibitors of dihydrofolate reductase and thymidylate synthetase prompted us to reinvestigate the structure of the product arising from the condensation of 2,4-diamino-6(1*H*)-pyrimidinone with 2-(aminomethylene)cyclopentanone, a reaction described in 1973 by Stark and Breitmaier.[2] At that time it could not be determined by these authors whether the product possessed the 5,6-annulated structure **1** or the 6,7-annulated isomeric structure **2**. Following the conditions described by Stark and Breitmaier, we obtained a compound whose physical characteristics corresponded precisely with those previously described. The same compound could be obtained by using 2-[(dimethylamino)methylene]cyclopentanone instead of the aminomethylene derivative. By an independent and unequivocal synthesis, we have been able to show that this compound does not possess structure **1** but is instead the 6,7-annulated isomer **2**.



2 **1**

Thus, treatment of 1-pyrrolidinocyclopentene with ethyl (chloromethylene)cyanoacetate[3] in the presence of 1 equiv of triethylamine at −20 °C in methylene chloride gave the alkylated enamine **4**, which was converted in high yield to the primary enamine **5** with ethanolic ammonia. Ring closure to **6** was then effected by treatment with a catalytic amount of sodium ethoxide in ethanol under reflux for 12 h. Although the usual conditions for pyrimidine annulation of *o*-amino esters with guanidine failed with **6**, we were able to convert **6** to **2** by reaction with benzoyl isothiocyanate to give **7**, which was then S-methylated with methyl iodide/sodium hydride/DMF to **8**. Aminolysis of **8** then gave **2**,[4] which was identical in every respect with the compound prepared by the procedure of Stark and Breitmaier.[2]



3 **4** **5** **6** **7** **8**

Since we have also shown by an unequivocal and independent synthesis that condensation of 2,4-diamino-6-(1*H*)-pyrimidinone with 1-[4-*tert*-butoxycarbonyl)-phenyl]-3-(aminomethylene)-4-piperidinone gives a linear pyrido[2,3-*d*]pyrimidine analogous to **2**,[5] it seems probable that all of the cycloalkeno-5-deazapteridines described by Stark and Breitmaier[2] possess 6,7-annulated structures.[6]

Experimental Section

1-(Pyrrolidino)-2-(2-carbethoxy-2-cyanoethylene)cyclopentene (4). Ethyl (chloromethylene)cyanoacetate[3] (4.65 g, 0.0365 mol) in 10 mL of methylene chloride was added dropwise to a solution of 5 g (0.0365 mol) of 1-pyrrolidinocyclopentene and 5 mL (0.0365 mol) of triethylamine in 100 mL of methylene chloride cooled to −20 °C. After addition was complete (10 min), the reaction mixture was stirred for 1 h and warmed to room temperature, and 10 mL of water was added. The organic phase was separated, dried ($MgSO_4$), and evaporated to give a red solid which was triturated with ethanol. Filtration then gave 4.6 g (48%) of **4** as yellow crystals, mp 153–154 °C.

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.23; H, 7.69; N, 10.77. Found: C, 69.14; H, 7.57; N, 10.51.

2-Amino-3-carbethoxy-5,6-trimethylenepyridine (6). A suspension of 2.0 g of **4** in 25 mL of saturated ethanolic ammonia was stirred at room temperature for 96 h, and the resulting precipitate of **5** was collected by filtration and recrystallized from acetic acid: yield 1.35 g (88%), mp 323–324 °C. Ring closure was then effected by heating 0.6 g of **5** for 18 h in 20 mL of ethanol

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(6) In footnote *a* to Table III (see ref 2), Stark and Breitmaier wrote that "Aufgrund neuerer Messungen der ^{13}C-^1H Kopplungskonstanten an den Cycloalkeno-5-desazapteridinen und analogen Verbindungen ist nicht auszuschliessen, dass die Zuordnung der ^{13}C-Signale von C-5 und C-7 in Abb. 2 und den Tab. 4-6 umzukehren ist. Dementsprechend wäre der Cycloalkenring in den Verbindungen 12–14 und 17–21 linear, d.h. in 6,7-Stellung des 5-Desazapteridins ankondensiert". A linear structure was later confirmed for the condensation product of 4-aminouracil with 2-(hydroxymethylene)-5α-dihydrotestosterone (Bouchon, G.; Stark, E.; Pech, H.; Breitmaier, E. *Chem. Ztg.* **1973**, *97*, 509). We thank Prof. Breitmaier for drawing our attention to this latter paper.

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containing a catalytic amount (0.1 g) of sodium ethoxide. Evaporation of the reaction mixture and chromatography of the residue on silica using ether as the eluent gave 0.23 g (38%) of **6** as colorless crystals, mp 121–122 °C after recrystallization from cyclohexane.

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.80; N, 13.59. Found: C, 64.17; H, 6.93; N, 13.65.

6,7-Trimethylene-5-deazapterin (2-Amino-6,7-trimethylene-4(3*H*)-pyrido[2,3-*d*]pyrimidinone) (2). Method A. A mixture of 0.5 g (0.0024 mol) of the *o*-amino ester **6** and 0.5 g (0.0029 mol) of benzoyl isothiocyanate in 25 mL of acetonitrile was heated under reflux for 2 h. Filtration then gave 0.51 g (56%) of the benzoylthiourea derivative **7**. This compound (0.36 g, 0.001 mol) was added in one portion to a slurry of 0.05 g of 60% sodium hydride/mineral oil in 10 mL of DMF, and the mixture was stirred at room temperature for 1 h. Methyl iodide (0.2 mL) was then added, and the mixture was stirred again for 1 h. The solvent was removed by evaporation under reduced pressure, and the residual S-methylated thiourea derivative **8** was suspended in 20 mL of saturated ethanolic ammonia and heated in a sealed glass tube at 120 °C for 2 h. The contents of the tube were then cooled and filtered to give 0.05 g (15% based upon **6**) of **2**: mp >250 °C; IR (Nujol) 3400–2300, 1710, 1675, 1600 cm^{-1}; NMR (TFA-d_1 + Me_4Si) δ 2.3–2.75 (m, 2 H), 3.3 and 3.5 (2t, 4 H, J = 6 Hz), 8.9 (s, 1 H).

Method B. A mixture of 2.78 g (0.018 mol) of 2-[(dimethylamino)methylene]cyclopentanone[7] and 1.89 g (0.015 mol) of 2,4-diamino-6(1*H*)-pyrimidinone in a mixture of 30 mL of water and 45 mL of acetic acid containing 1 drop of piperidine was heated under reflux for 2 h. The yellow precipitate which had separated was collected by filtration, washed with water, methanol, acetone, and ether, and dried at 100 °C (0.1 mm) for 4 h; yield 2.1 g (69%). This compound was identical in every respect with **2** prepared by method A and also identical with the condensation product of 2,4-diamino-6(1*H*)-pyrimidinone with 2-(aminomethylene)cyclopentanone, prepared as described by Stark and Breitmaier.[2]

Registry No. 1, 49739-08-4; 2, 91159-00-1; 3, 7148-07-4; 4, 91159-01-2; 5, 91159-02-3; 6, 68708-34-9; 7, 91159-03-4; 8, 91159-04-5; ClCH=C(CN)CO_2Et, 78872-04-5; PhCONCS, 532-55-8; 2,4-diamino-6(1*H*)-pyrimidinone, 56-06-4; 2-[(dimethylamino)methylene]cyclopentanone, 62041-55-8; 2-(aminomethylene)cyclopentanone, 42997-61-5.

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Synthesis and Carbon-13 NMR of an Unusual Tricyclic Barbituric Acid Derivative†

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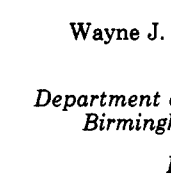
Bicyclic imides of the type illustrated in general structure **1** are of interest because they belong to a class of

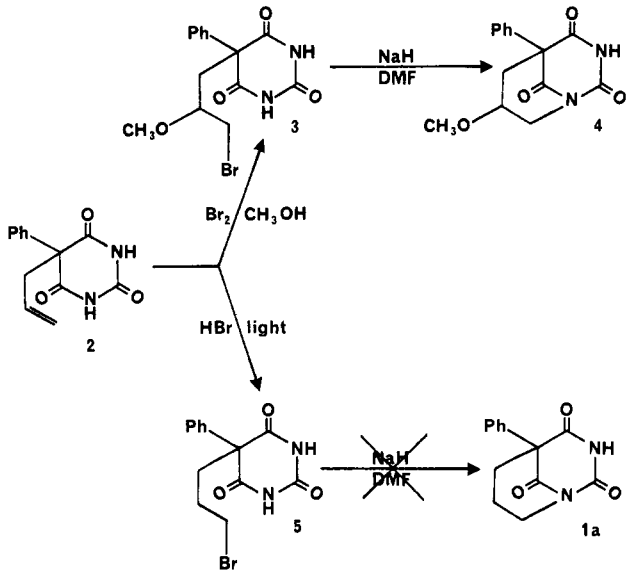


	X	
1a	CONH	barbituric acid
1b	NH	hydantoin
1c	O	2,4-oxazolidinedione

1

anti-Bredt bridgehead nitrogen amides.[1] These compounds were first proposed as potential stereoselective anticonvulsants by E. E. Smissman, whose synthetic efforts[2-11] revealed that structures with n = 1 were very resistant to formation. For example, despite numerous attempts by Smissman to prepare **1a** (n = 1) or analogues,[6-8] the only reported success[6] was for the preparation of methoxy-substituted bicyclic barbiturate **4** using the procedure illustrated in Scheme I. Surprisingly, similar synthetic approaches involving intermediates without the methoxy group, such as **5** in Scheme I, did not yield **1a**. Our interest[2] in these systems prompted us to repeat Smissman's synthesis of **4**. Here we report that the structural assignments for **4** and the immediate synthetic precursor **3** are incorrect, and we provide NMR evidence which shows that the correct structures are novel cyclized barbituric acid derivatives containing the amide acetal functionality.

Scheme I



Results and Discussion

5-Allyl-5-phenylbarbituric acid (**2**, Scheme I) was prepared from 5-phenylbarbituric acid according to the procedure of Vorm and Siegfried.[12] The ^1H and ^{13}C NMR assignments for **2** are presented in Table I and are consistent with the assigned structure. The reaction of **2** with Br_2 and CH_3OH according to the procedure of Smissman[6] produced a crystalline product that was identical in every respect (mp, IR, and ^1H NMR in CF_3CO_2H-d_1) to that reported as **3**. Furthermore, the electron-impact mass spectrum gave the anticipated molecular ion at m/e 356 and confirmed the presence of one bromine. However, the ^1H NMR spectrum of **3** run in Me_2SO-d_6 (shown as compound **6** in Table I) displayed two types of N–H resonances

† Dedicated to the memory of Prof. E. E. Smissman.

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