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5,5'-BIPYRIDYL-2,4,6,2',4',6'-HEXAONE DERIVATIVES (HYDURILIC ACIDS): SYNTHESES, MECHANISM OF C-C-BOND FORMATION AND PROPERTIES OF THE DIMERIC BARBITURIC ACID DERIVATIVES[¶]

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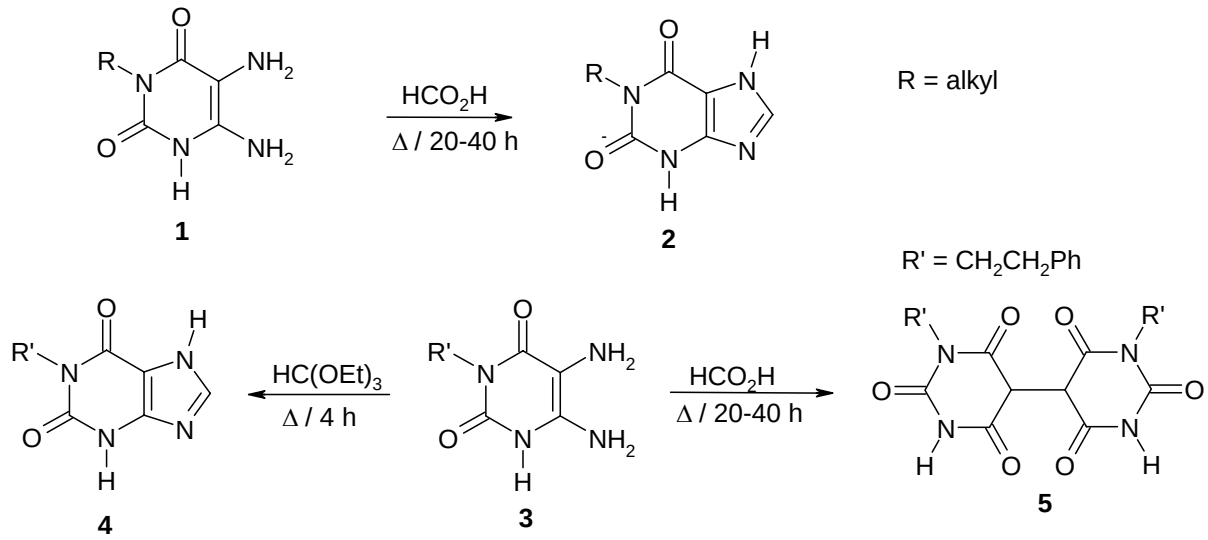
[¶]Dedicated to the memory of Dr. John William Daly, a brilliant and unique scientist, a great teacher, and an admirable person

Abstract – A series of hydurilic acid derivatives (5,5'-bipyrimidinyl-2,4,6,2',4',6'-hexaones) including several new derivatives was synthesized from 5,6-diaminouracils. Mechanisms for their formation are proposed and discussed. Furthermore, a new method for the preparation of pyrimidine-2,4,5,6-tetraone-5-oxime derivatives (violuric acids) was found starting from 5-amino-6-nitrosouracils.

INTRODUCTION

In the course of our efforts to synthesize novel xanthine derivatives as adenosine receptor antagonists[1] we had developed a general synthesis of 1-monosubstituted xanthines.[2] The conversion of 3-substituted 6-aminouracils[3] to the corresponding 5,6-diaminouracil derivatives (**1**) and subsequent condensation with formic acid for 20 to 40 h generally provided 1-monosubstituted xanthines (**2**) in high yields[2] (Scheme 1). One striking exception had been observed: the reaction of 5,6-diamino-3-(2-phenylethyl)uracil **3** with formic acid under reflux conditions did not lead to the corresponding 1-substituted xanthine derivative **4**, but gave an unknown compound (**5**) in high yield. The desired 1-(2-phenylethyl)xanthine **4** could meanwhile be synthesized from **3** in a yield of 92 % using triethylorthoformate after a reaction time of only 4 h under reflux conditions.[2] The present study was aimed at elucidating the structure of the new product **5**, the synthesis and characterization of analogs, and the mechanism of their formation.

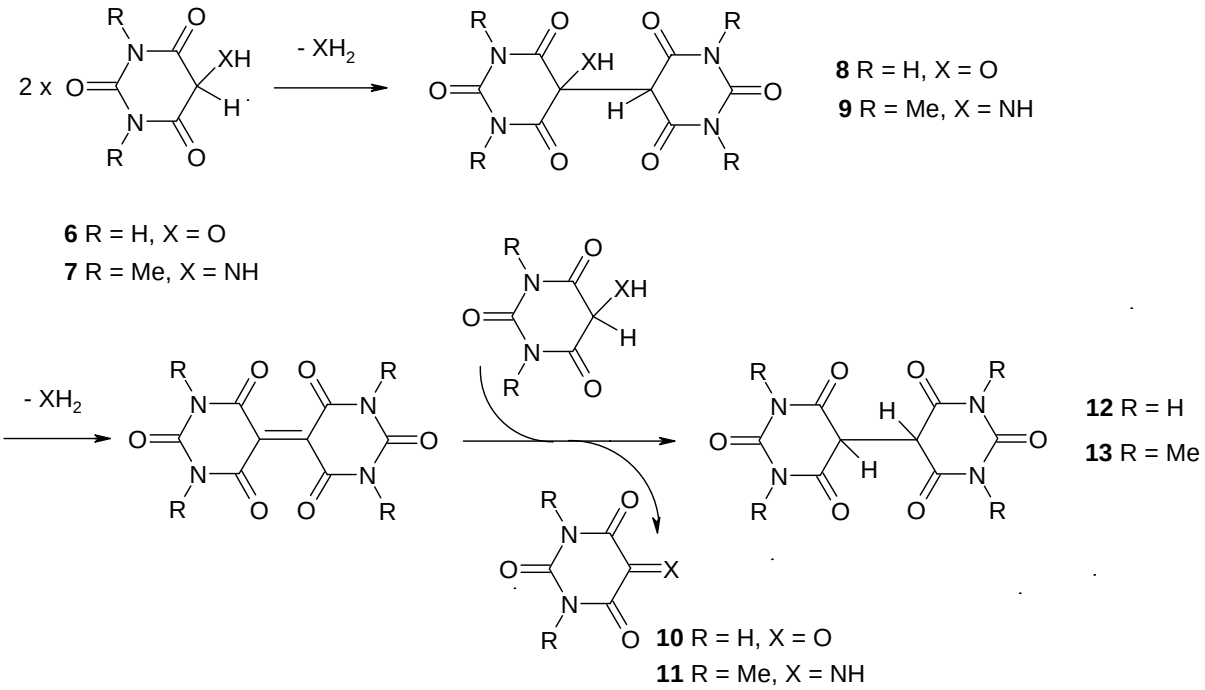


Scheme 1. Formation of 1-substituted xanthine derivatives from 5,6-diamino-3-alkyluracils and unexpected formation of 1,1'-bis-(2-phenylethyl)-[5,5']bipyrimidinyl-2,4,6,2',4',6'-hexaone (**5**) from 5,6-diamino-3-(2-phenylethyl)uracil (**3**).

RESULTS AND DISCUSSION

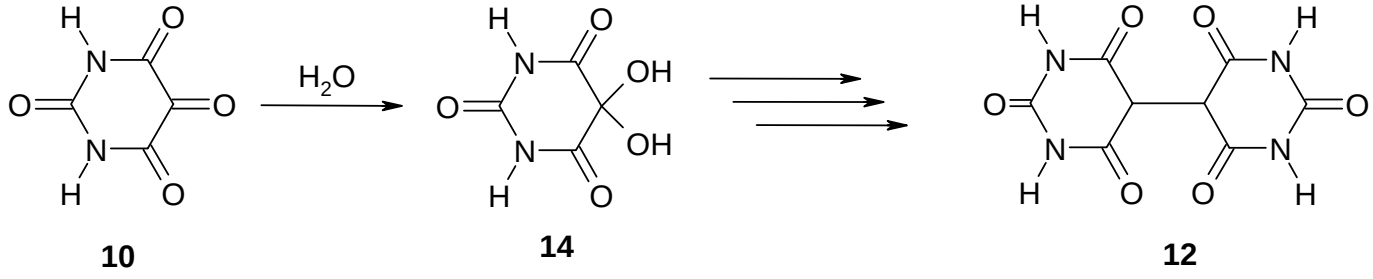
The structure of product **5** was elucidated by a combination of analytical methods including chromatography, spectroscopy, and elemental analysis. All observations taken together proved the formation of a symmetrical 1,1'-bis-(2-phenylethyl)-substituted [5,5']bipyrimidinyl-2,4,6,2',4',6'-hexaone **5** (Scheme 1). Presumably a mixture of stereoisomers was formed which could not be isolated. The fact that the CH-acidic isomers can easily be converted either into the corresponding enantiomer or into the meso-form could be a possible explanation for the difficulty in separating the stereoisomers.

The related, N-unsubstituted compound **12** (Scheme 2) with the trivial name hydurilic acid was first prepared and characterized by Bayer as early as 1863.[4] The 5,5'-connected dimer of barbituric acid had been obtained from 5-hydroxypyrimidine-2,4,6-trione (5-hydroxybarbituric acid, **6**) by heating in glycerol at 150 °C in a yield of 50 %,[4] or in the absence of solvent at 190-200 °C in a lower yield of 34 %.[5] Alternatively, 5-amino-1,3-dimethylpyrimidine-2,4,6-trione (5-amino-1,3-dimethylbarbituric acid, **7**) has been used as starting material. In the presence of two equivalents of methyl isocyanate as ammonia scavenger a 54 % yield of tetramethyl hydurilic acid (**13**) was obtained after a reaction time of 16 h at 100 °C in a sealed tube.[6] Based upon these findings a plausible pathway, involving three starting molecules, can be postulated to describe the aforementioned reactions (Scheme 2). Condensation reactions, including the formation of a carbon-carbon bond, are followed by elimination of pyrimidine-2,4,5,6-tetraone (alloxane, **10**) or 5-imino-1,3-dimethylpyrimidine-2,4,6-trione (**11**), respectively.



Scheme 2. Proposed pathway for the formation of hydurilic acid (**12**) from 5-hydroxybarbituric acid (**6**) and its tetramethyl derivative (**13**) from 5-amino-1,3-dimethylbarbituric acid (**7**).

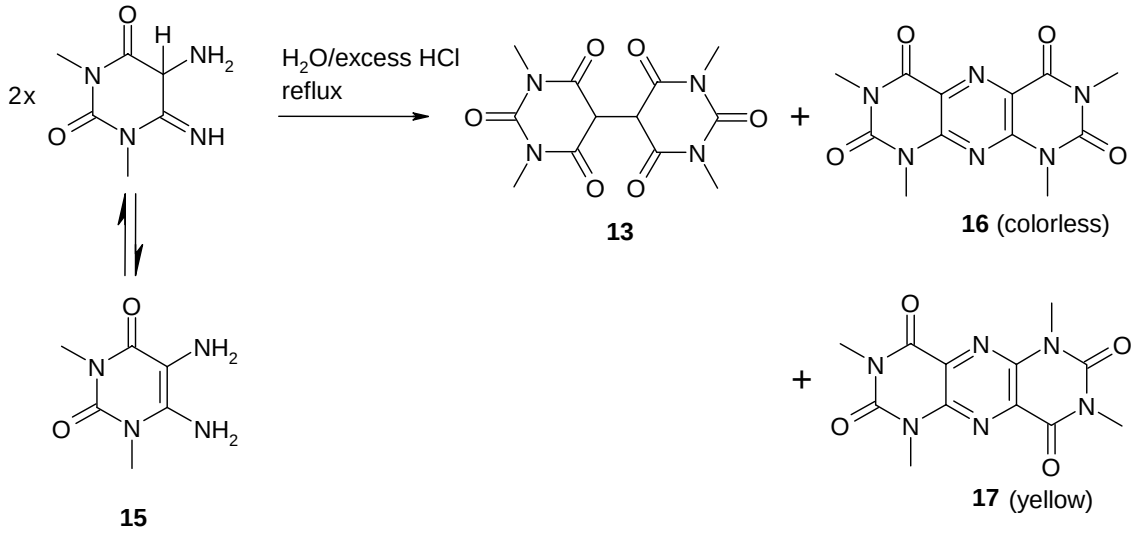
In this context it is noteworthy that the by-product of the described reactions, alloxane (**10**), was reported to provide hydurilic acid itself at 170 °C in a sealed tube. The presence of a large excess of water as well as the absence of water was shown to prevent the formation of **12**.[7] Due to the observed water-sensitivity alloxane hydrate **14** (see scheme 3) could be postulated as the initial molecule for the formation of **12** from **10**. Several different reaction steps have to be considered involving nucleophilic attacks, elimination of water or other molecules, and disproportionation reactions.



Scheme 3. Formation of unsubstituted hydurilic acid (**12**) from alloxane (**10**).

The formation of tetramethyl hydurilic acid **13** (Scheme 4) by refluxing of 5,6-diamino-1,3-dimethyluracil **15** in aqueous solution containing various concentrations of mineralic acid was first described by Bredereck using sulfuric acid;[8] he obtained **13** in 19 % yield. Independently, Blicke and Godt obtained a maximal yield of 54 % of **13** by using an aqueous solution of two equivalents of hydrochloric acid in water.[9] From the reaction mixtures both groups isolated the colorless pyrazine

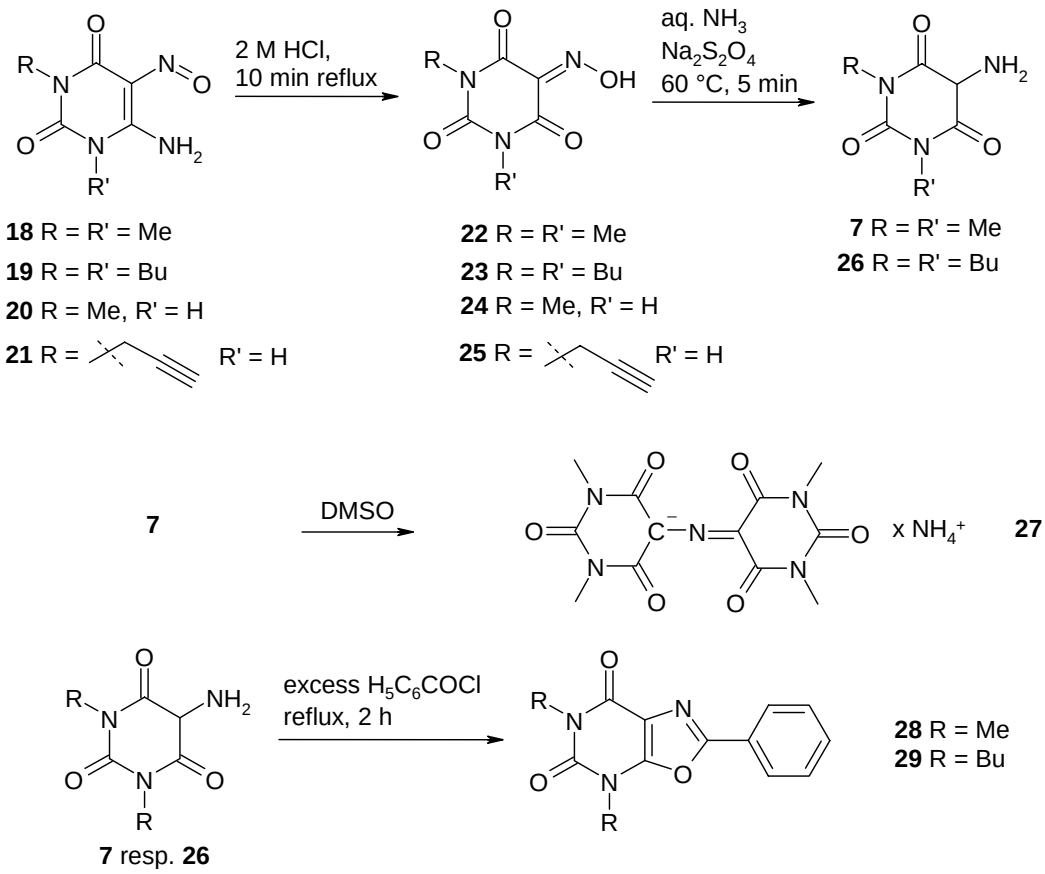
derivative 1,3,7,9-tetramethyl-(1*H*,3*H*,7*H*,9*H*)-pyrimido[5,4-*g*]pteridine-2,4,6,8-tetrone (**16**)[10] in yields of 31 %,[9] and 23 %, respectively[8] in addition to hydurilic acid derivative **13**. A careful reinvestigation of this reaction showed that the yellow isomer 1,3,6,8-tetramethyl(1*H*,3*H*,6*H*,8*H*)pyrimido[4,5-*g*]pteridine-2,4,7,9-tetrone (**17**)[11] was formed as well. Due to its physicochemical properties **17** remained in the mother liquor, when the reaction mixture was worked up as described by the authors (Scheme 4). It was found by Blicke and Godt[9] that the formation of **13** became predominant when the concentration of hydrochloric acid was increased. Our reinvestigation showed that the formation of pyrazine derivatives could not completely be suppressed, even in the presence of a large excess of hydrochloric acid.



Scheme 4. Formation of hydurilic acid and pyrazine derivatives from 5,6-diamino-1,3-dimethyluracil (**15**).

In contrast to Blicke and Godt[9] Bredereck presented a proposal for a detailed reaction mechanism correlating the formation of the reduced hydurilic acid derivative with the oxidized pyrazine ring system.[8] Since the nature of the redox reactions proposed by Bredereck[8] still remained unclear, additional experiments were performed to obtain more information about this reaction. Assuming that under vigorous aqueous acidic conditions at least a partial hydrolysis of the diaminouracil **15** would take place prior to any C-C-bond formation, a hydrolysis product of **15** should also lead to the hydurilic acid derivative **13** under the same reaction conditions.

5-Amino-1,3-dimethylbarbituric acid (**7**, Scheme 2) was selected to investigate its potential conversion to 1,1',3,3'-tetramethylhydurilic acid (**13**) under reflux conditions in the presence of an excess of aqueous hydrochloric acid. Starting compound **7** could easily be prepared by reduction of the appropriate pyrimidine-2,4,5,6-tetraone-5-oxime (violuric acid) derivative **22**[12] using sodium dithionite in aqueous ammonia solution (Scheme 5).



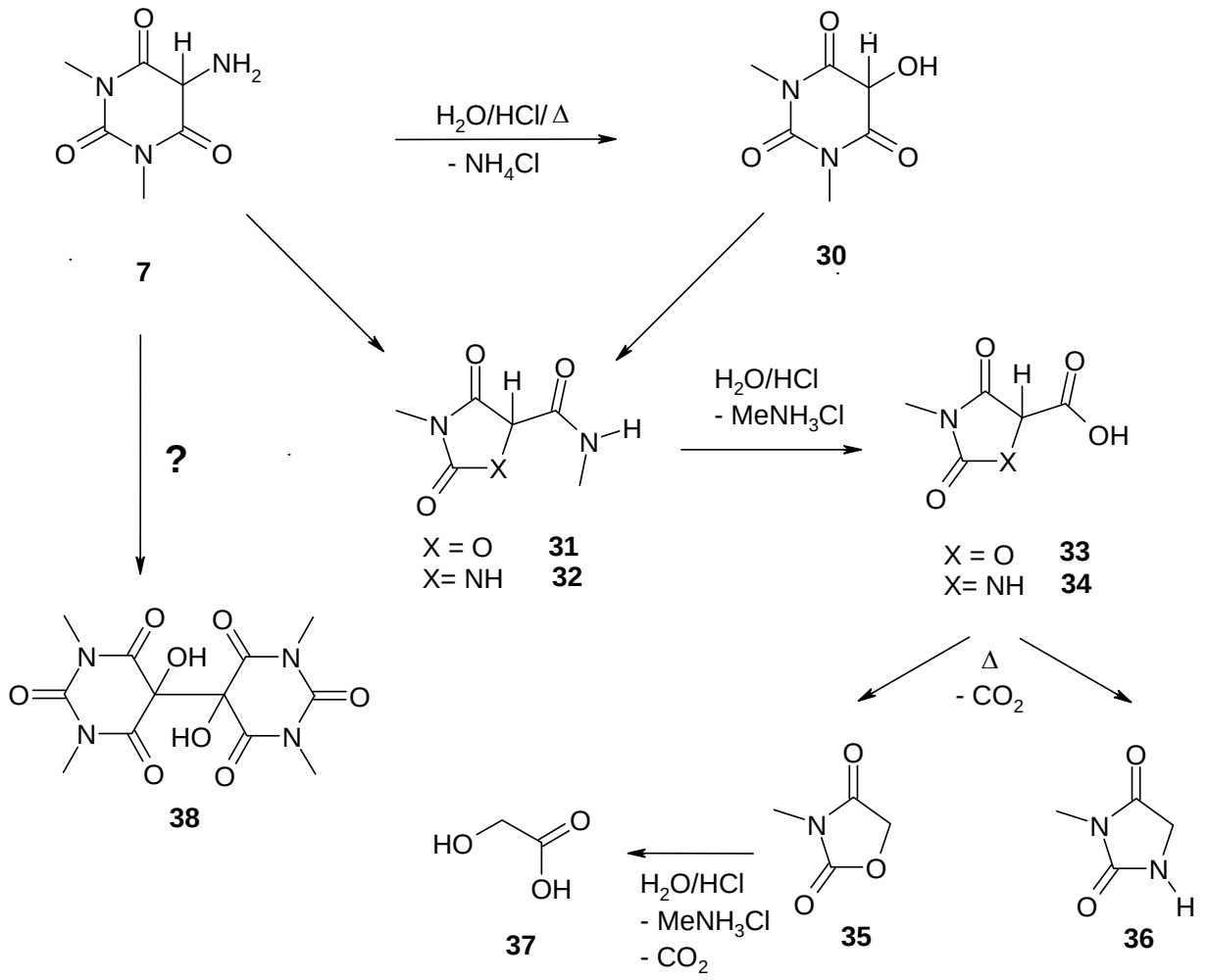
Scheme 5. Synthesis of violuric acids and 5-aminobarbituric acids and reactions of 5-amino-1,3-dimethylbarbituric acid (**7**).

The formation of **22** was achieved by hydrolysis of the corresponding 6-amino-5-nitrosouracil **18** in diluted aqueous hydrochloric acid under reflux conditions. To prove the general applicability of this method, a range of mono- and disubstituted violuric acid derivatives (**22**-**25**) was prepared. In all cases highly pure products were obtained with yields of around 80 % for the di-substituted and ca. 40 % for the mono-substituted derivatives. We observed that the cleavage of the derivatives **22**-**25** by diluted hydrochloric acid proceeded very slowly even under reflux conditions. To the best of our knowledge this route has not yet been described for the preparation of violuric acid derivatives.

The reduction of the purple solutions of violuric acid derivatives **22** and **23** at 60 °C provided the colorless 5-aminobarbituric acids **7** and **26** after short reaction times of less than 5 min. Although the colorless solids are extremely sensitive to oxidation, derivative **7** could be characterized by ^{1}H and ^{13}C NMR spectroscopy. The solution of **7** in d_6-DMSO had to be measured immediately since it soon turned to deep purple due to the oxidation of **7** by the solvent yielding the oxidation product murexoin **27** (confirmed by TLC analysis).[13] Further characterization of **7** and **26** was achieved by derivatization with an excess of benzoyl chloride under reflux conditions yielding the corresponding 4,6-dialkyl-2-phenyl-4*H*,6*H*-oxazolo[5,4-*d*]pyrimidine-5,7-diones **28** and **29**.[14,15]

Aqueous solutions of freshly prepared **7** containing an excess of hydrochloric acid were refluxed, varying the reaction times from 1 h up to 18 h (scheme 6). After cooling to rt the aqueous colorless reaction mixtures were extracted with dichloromethane. Due to complex separation problems of water-soluble reaction products, the aqueous phases were not investigated in detail, but were considered to contain mainly decomposition products, such as methylammonium chloride. In all cases evaporation of the organic solvent led to a solid residue consisting of a mixture of colorless products, none of which could be identified as tetramethylhydurilic acid **13** or a pyrazine derivative. One main product could easily be crystallized from diethyl ether. An ^{1}H NMR spectrum showing only two singlets at 3.08 (3H) and 4.68 ppm (2H), a ^{13}C NMR spectrum with four peaks at 25.9, 68.0, 156.0 and 170.4 ppm and a molecular mass of 155 pointed to a small molecule. Together with the melting point of 133 °C (Lit.: 133-134 °C)[16] all data indicated the formation of 3-methyloxazolidine-2,4-dione **35**[16] (Scheme 6). After a reaction time of 1 h compound **35** was obtained in a yield of 17 %, and after a reaction time of 3 h the yield was increased to 35 %. After 18 h a significant decrease in the yield was observed, and hydroxyacetic acid (**37**) was detected in the crude dichloromethane extract. Besides compound **35** another small heterocyclic compound was observed in the crude extract. Comparison with literature NMR data confirmed the formation of 3-methylimidazolidine-2,4-dione (3-methylhydantoine, **36**).[17] Compound **36** was obtained in a yield of about 5 % after a reaction time of 3 h. Longer reaction times did not significantly alter the yield of **36**, but the enrichment of **36** in comparison with **35** in the crude organic extract indicated that the hydantoin derivative was more stable than the oxazolidine derivative under vigorous aqueous acidic conditions. Without providing any experimental details, Techow[12] had reported on the crystallization of 5,5'-dihydroxy-1,3,1',3'-tetramethyl[5,5']bipyrimidyl-2,4,6,2',4',6'-hexaone (**38**, Scheme 6) from the neutralized reaction mixture after refluxing a solution of **7** in aqueous hydrochloric acid. This observation, which would involve a C-C-bond formation, could not be confirmed by our own experiments.

The formation of oxazolidine-2,4-diones (e.g. **35**) by a ring-contraction reaction from 5-hydroxybarbituric acid derivatives (e.g. **30**) is well known[18] but has typically been performed in alkaline solution or under virtually neutral conditions.[19] Several plausible mechanisms have been discussed[19] and led to an understanding of the observed reaction (Scheme 6). Presuming the hydrolysis of **7** to the 5-hydroxybarbituric acid derivative **30**, the following ring contraction leads to the intermediate **31**. A competing process is the intramolecular reaction of the starting compound **7** yielding the intermediate **32**. Hydrolysis of the resulting amide derivatives (**31** and **32**) followed by decarboxylation of the intermediates **33** and **34** would complete the formation of **35** and **36** (Scheme 6).

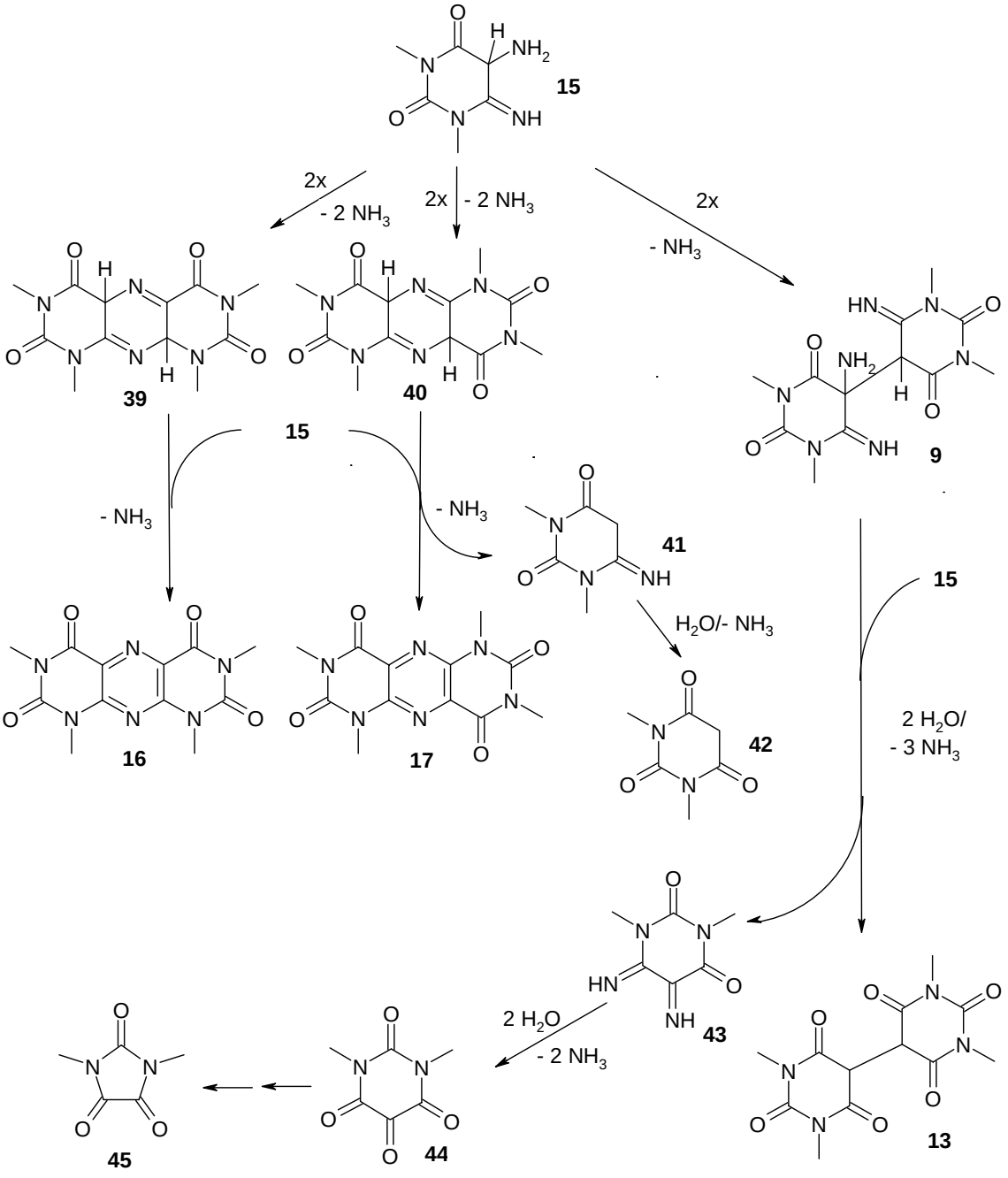


Scheme 6. Reaction of 5-amino-1,3-dimethylbarbituric acid (**7**) with an excess of hydrochloric acid under reflux.

In consideration of the above mentioned results, the mechanism proposed by Bredereck[8] concerning the formation of hydurilic acids from 5,6-diaminouracils upon catalysis by mineralic acids in water under reflux conditions has to be revised. Apparently the complete hydrolysis to a 5-hydroxybarbituric acid derivative could not be the first step since this would be followed by ring contraction.

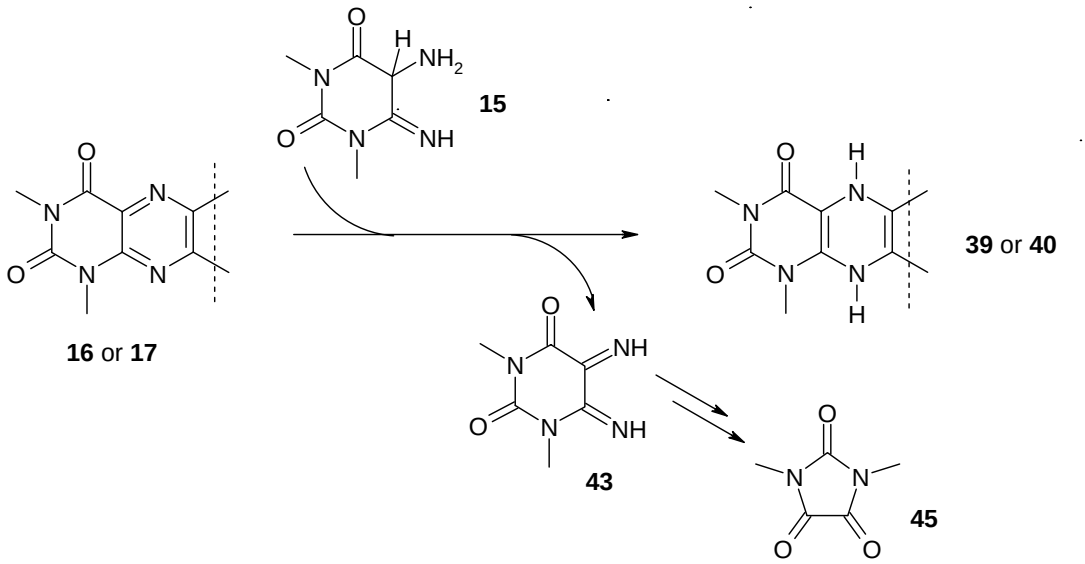
In order to obtain more information about the actual intermediates, the reaction of 5,6-diamino-1,3-dimethyluracil (**15**) was investigated in more detail (Scheme 7). As shown above, conversion of the vinylic amino group of 5-amino-1,3-dimethyl-6-nitrosouracil (**18**) into a carbonyl group yielding violuric acid derivative **22** was completed within less than 10 min already (Scheme 5). We therefore stopped the reaction of **15** in refluxing hydrochloric acid after 0.5 h already: the formation of **13** as well as that of pyrazine derivatives **16** and **17** (see Scheme 4) was observed to be already at an advanced stage after that short reaction time. TLC analysis of the crude reaction mixtures showed that further products had been formed besides **13**, **16** and **17**. Two further products were isolated by extraction of the crude reaction mixture and subsequent column chromatography:

1,3-dimethylimidazolidine-2,4,5-trione (dimethylparabanic acid, **45**)[20] and 1,3-dimethylbarbituric acid (**42**).[21] Compound **45** as a final product might be explained through decomposition of the alloxane derivative **44** similar to the formation of the 5-membered ring systems described in Scheme 6. The formation of **42** is more surprising since this derivative was neither observed nor expected before in this context. However, the formation of **42** could be explained by oxidation of the pyrazine precursor **39** (resp. **40**) by the starting compound **15** forming the final pyrazine derivative **16** (resp. **17**) as well as the intermediate **41**, which is subsequently hydrolyzed to **42** (Scheme 7).



Scheme 7. Reaction of 5,6-diamino-1,3-dimethyluracil (**15**) with an excess of hydrochloric acid under reflux.

Another possibility for the formation of compound **45** has to be considered. The pyrazine derivatives **16** (resp. **17**) may be reduced by the 5,6-diaminouracil **15** leading to **39** (resp. **40**). The resulting intermediate **43** would lead to the stable dimethylparabanic acid (**45**) as described above (Scheme 8).



Scheme 8. Reduction of pyrazine derivatives (**16** or **17**) by 5,6-diamino-1,3-dimethyluracil (**15**).

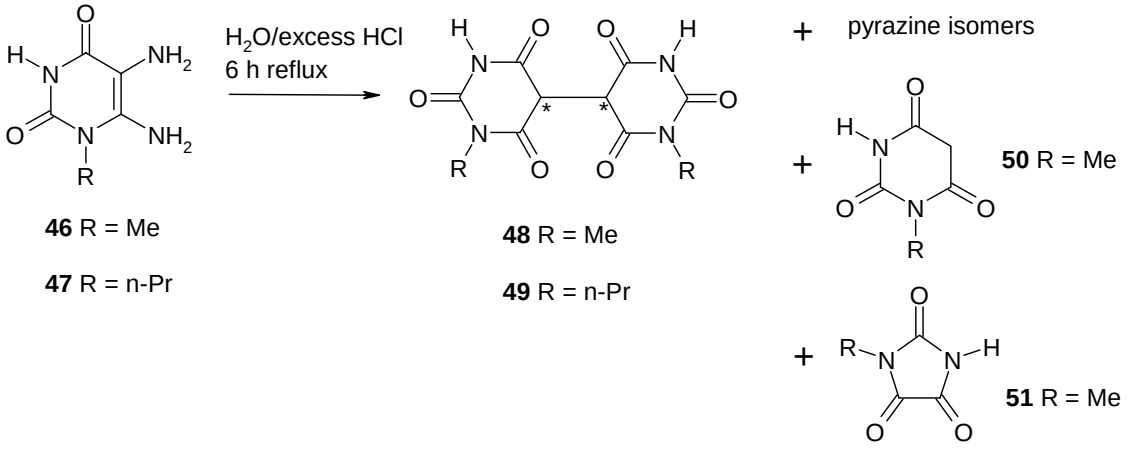
During the course of the above mentioned reaction a purple coloration was observed after ca. 10 min. Within the following 10 min the reaction mixture turned yellow. These changes of color could be associated with the formation of the well-known deep violet purpuric acid derivatives (compound **27**, Scheme 5). They consist of two pyrimidyl ring systems linked by a nitrogen atom forming a large delocalized π-electron system. Structurally similar pyrazine precursors can be postulated for the reaction investigated and could provide a plausible explanation for the purple color. Subsequent oxidation to the final pyrazine derivatives would explain a further change of color from purple to yellow. The remaining color can be assigned to the yellow pyrazine isomer **17**. These observations indicate that the formation of pyrazines should be completed after a reaction time of only 25 min.

Since the 5-unsubstituted barbituric acid (**42**) could still be detected after a reaction time of 12 h, the compound obviously does not participate in the formation process of hydurilic acid derivative **13**. This observation is well in agreement with the finding by Biltz that **42** itself does not lead to **13** under strongly acidic conditions in the presence of an oxidizing agent.[5] However, not even traces of the oxazolidine derivative **35** could be extracted from the reaction mixture. The absence of **35** is a further proof that a complete hydrolysis of the 5,6-diaminouracil **15** to the 5-hydroxybarbituric acid **30** cannot be the initial step in the reaction investigated. Both amino groups of the starting compound **15** appear to be essential

not only for the formation of pyrazines but also for the C-C-bond formation of two uracil ring systems finally resulting in the C5-C5'-bond of derivative **13** (Scheme 4).

In order to gain more information about the properties of hydurilic acid derivatives a series of derivatives were prepared. Tetramethylhydurilic acid (**13**) was best prepared as previously described by Blicke and Godt.[9] Further purification was achieved by column chromatography. 5,6-Diamino-1-alkyluracils were selected as starting compounds for 1,1'-disubstituted hydurilic acids. Since the reaction of 1-methyl- or 1-propyl-5,6-diaminouracil (**46** and **47**) with concentrated formic acid did not lead to hydurilic acids (see Scheme 1) the reaction was performed with an excess of hydrochloric acid under reflux conditions. After reaction times of less than 1 h the crude hydurilic acid derivatives **48** and **49**, contaminated by corresponding pyrazine derivatives, precipitated from the cold reaction mixtures (Scheme 9). Due to its physicochemical properties the purification of **48** (a purity of about 80 % was determined for the crude product) proved to be extraordinary difficult and could not satisfactorily be achieved with standard methods. In contrast, compound **49** could easily be obtained in a pure form by recrystallisation from isopropanol. Both 1,1'-substituted hydurilic acids were obtained in moderate yields of about 20 %. Consistent with our theory as described above, longer reaction times did not result in higher yields.

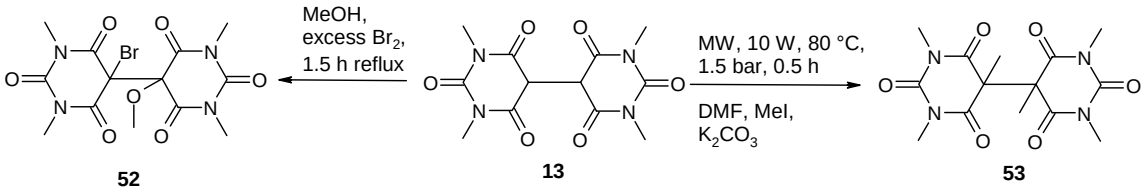
The conversion of the diaminouracil **46** confirmed our proposed reaction mechanism. Next to the desired compound **46** and pyrazine derivatives the formation of the corresponding C5-unsubstituted barbituric acid (**50**)[21] and the parabanic acid derivative **51**[20] were observed as side-products and characterized by comparison with literature NMR data. The small heterocyclic compounds **50** and **51** were extracted from the crude reaction mixture with dichloromethane and subsequently purified by column chromatography (Scheme 9).



Scheme 9. Formation of 1,1'-disubstituted hydurilic acid derivatives.

The preparation of hydurilic acids from 5,6-diaminouracils was observed to be associated with a number of difficulties: a) the yield is limited due to the reaction mechanism, b) the co-formation of pyrazine derivatives appears to be inevitable or can at least not easily be suppressed, c) especially less lipophilic derivatives cannot be purified easily. The easy formation of the 1,1'-di-(2-phenylethyl)hydurilic acid **5** (Scheme 1) from the corresponding 5,6-diaminouracil **3** remained an exception.

5,5'-Unsubstituted hydurilic acids show characteristic NMR spectra as discussed below. In order to obtain a broader basis of information 5,5'-disubstituted hydurilic acid derivatives were additionally prepared (Scheme 10). The known 5-bromo-5'-methoxytetramethylhydurilic acid (**52**) was obtained as previously described starting from tetramethylhydurilic acid **13** with an excess of bromine in methanol under reflux conditions.[22] The methylation of **13** using an excess of methyl iodide in DMF in the presence of a potassium carbonate under microwave irradiation (10 W, 80 °C, 1.5 bar, 0.5 h) yielded hexamethylhydurilic acid (**53**, Scheme 10).



Scheme 10. Formation of 1,1',3,3'-tetramethyl-5,5'-substituted hydurilic acid derivatives.

The previously described hydurilic acid derivatives **13**, **48**, **52** and **53** as well as the new derivatives **5** and **49** were investigated by ^{1}H and ^{13}C NMR spectroscopy.[22] The ^{1}H NMR spectra of all N-methyl substituted derivatives showed singlets for the N-methyl groups in the typical range from 3.08 (**48**) to 3.37 ppm (**52**). The C5 H-atom of the C5-unsubstituted derivatives were exchangeable, and appeared as very broad singlets within a small range from 4.85 to 4.99 ppm (compounds **5**, **13**, **48** and **49**, measured in DMSO-d_6). The NH-signals for the derivatives **5**, **48** and **49** were consistently observed around 11.7 ppm. In the ^{13}C NMR spectra the NCH_3 signals for the derivatives **13**, **48**, **52** and **53** appeared in the expected region around 29 ppm. The chemical shifts for unsubstituted C5-atoms (derivatives **5**, **13**, **48** and **49**) were observed around 48.5 ppm, showing very little variation. One remarkable effect could be observed comparing the spectra of tetramethylhydurilic acid **13** measured in $CHCl_3$ and in DMSO-d_6, respectively. The peak for the C5-atoms at 48.2 ppm appeared broadened and not very clear when DMSO-d_6 was used as a solvent, while in $CDCl_3$ the signal appeared very clear and well pronounced. This effect could be explained by a reduced tendency of the CH-acidic compound to form enol-tautomers in the non-polar $CDCl_3$. The well pronounced C2 signals of all derivatives investigated did not show any significant variations and were observed in the typical region around 150 ppm. In contrast to this the C4- and the

C6-signals, respectively, of the C5-unsubstituted derivatives **5**, **13**, **48** and **49**, appeared around 166 ppm appeared broadened and were only weak. Again, this effect could be explained by the formation of tautomers. The spectra of the C5-substituted derivatives **52** and **53** provided the proof for this assumption: the formation of tautomers could be blocked by substitution of the C5-positions so that the C4/C6-signals appeared clearly and well defined.

CONCLUSIONS

A series of differently substituted hydurilic acids was prepared from 5,6-diaminouracil derivatives including several new derivatives. The reaction mechanism was investigated in detail, and a new pathway was postulated based on the isolation and structural determination of intermediate products. The products were characterized by spectroscopic methods and 5,5'-unsubstituted derivatives not previously described in the literature were shown to tautomerize in polar solvents such as DMSO.

EXPERIMENTAL

1,1',3,3'-Tetramethyl[5,5']bipyrimidinyl-2,4,6,2',4',6'-hexaone (13): The compound was prepared as previously described.[9] ^{1}H NMR ($CDCl_3$) ppm: 3.31 (s, 12H, NCH_3), 4.65 (s sharp, 2H, C5H); ^{13}C NMR ($CDCl_3$) ppm: 29.1 (NCH_3), 48.72 (s sharp, C5), 151.0 (C2), 166.28 (C4/C6); ^{1}H NMR (DMSO-d_6) ppm: 3.15 (s, 12H, NCH_3), 4.99 (s br), 2H, C5H); ^{13}C NMR (DMSO-d_6) ppm: 28.6 (NCH_3), 48.7 (br, C5), 151.4 (C2), 167.1 (br, C4/C6).

1,1'-Dimethyl[5,5']bipyrimidinyl-2,4,6,2',4',6'-hexaone (48):[8,22] Freshly prepared 5,6-diamino-1-methyluracil (**46**, 1 g, < 6 mmol, containing an undetermined amount of water) was refluxed in a mixture of concentrated hydrochloric acid (5 mL) and water (5 mL). After 1 h the reaction was stopped and the yellow solution was evaporated under reduced pressure. The residue was crystallized from a minimum of water at 4 °C. After ca. 12 h the precipitate was filtered off under reduced pressure, washed with little water and dried at 70 °C yielding 160 mg of a pale yellow (due to impurities of the corresponding yellow pyrazine derivatives) solid. For the (colorless) **48** a purity of about 80 % was determined by ^{1}H NMR spectroscopy. Until now no satisfactory purification method could be developed. ^{1}H NMR (DMSO-d_6) ppm: 3.08 (s, 6H, CH_3), 4.85 (s, 2H, C5-H), 11.72 (s, 2H, NH); ^{13}C NMR (DMSO-d_6) ppm: 27.68, 48.31 (C5), 150.9 (C2), 167.6 and 168.4 (br, C4,C6).

1,1'-Dipropyl[5,5']bipyrimidinyl-2,4,6,2',4',6'-hexaone (49): Freshly prepared 5,6-diamino-1-propyluracil (**47**, ca. 850 mg, 4,6 mmol) was refluxed in a mixture of concentrated hydrochloric acid (3 mL) and water (5 mL). After 30 min a colorless solid precipitated and the reaction

was stopped. The precipitation was completed at 4 °C and the crude product (270 mg) was filtered off under reduced pressure. The solid was washed with water and recrystallized from isopropanol yielding 155 mg of colorless crystals (20 %). Alternatively the crude product could be purified by column chromatography on silica gel: eluting first with CH_2Cl_2/MeOH (5 : 1) in order to separate the impurities (pyrazine derivatives) and finally with CH_2Cl_2/MeOH (3 : 1): mp 215 °C; ^{1}H NMR (DMSO-d_6) ppm: 0.81 (br s, 6H, CH_3), 1.48 (br s , 4H, CH_2), 3.65 (br s, 4H, NCH_2), 4.87 (s, 2H, C5-H), 11.68 (s, 2H, NH); ^{13}C NMR (DMSO-d_6) ppm: 11.0 (CH_3) , 20.8 (CH_2), 42.3 (NCH_2), 48.5 (C5), 150.7 (C2), 167-169 (br, C4,C6); EIMS (*m/z*, %) 338 (M^+ , 10) 170 ($M/2H^+$, 100). Anal. Calcd for $C_{14}H_{18}N_4O_6$: C, 49.7; H, 5.36; N, 16.56. Found: C, 49.6; H, 5.33; N, 16.53.

1,1'-Diphenylethyl[5,5']bipyrimidinyl-2,4,6,2',4',6'-hexaone (5): 5,6-Diamino-3-(2-phenethyl)uracil (**3**, 1.2 g, 4.9 mmol) was suspended in 30 mL of formic acid (98%). The mixture was refluxed for 28 h. The excess of formic acid was distilled off and the residue was suspended in water. The precipitate was collected by filtration and washed with water. Further purification was achieved by dissolution of the compound in 1 M NaOH solution, precipitation by acidification using acetic acid and crystallization from a small amount of $CHCl_3$ yielding colorless crystals (66 % yield): mp 195 °C; ^{1}H NMR ($CDCl_3$): 2.87 (m, 4H, PhC*H*$_2$), 4.05 (m, 4H, NCH_2), 4.53 (s, 2H, C5-H), 7.17-7.30 (m, 10H, $H_{arom.}$), 8.61 (s, 2H, NH) ppm; ^{13}C NMR ($CDCl_3$) ppm: 33.8, 43.3, 48.2, 126.8, 128.6, 128.88, 128.92, 138.44, 137.50, 149.2 (C2), 166.0 (br, C4,C6) ppm; EIMS (*m/z*, %) 462 (M^+, 9) 104 ($[CH_2CH_2Ph]^+$, 100), FDMS (*m/z*, %) 462 (M^+ , 100); Anal. Calcd for $C_{24}H_{22}N_4O_6$: C, 62.3; H, 4.79; N, 12.1. Found: C, 62.2; H, 4.73; N, 12.2. TLC analysis: ($CHCl_3$: MeOH = 3:1, R_f = 0.95).

5-Bromo-5'-methoxy-1,1',3,3'-tetramethyl[5,5']bipyrimidinyl-2,4,6,2',4',6'-hexaone (52): The compound was prepared from **13** as previously described[22] (mp ca. 240 °C (dec.); lit mp 245-247 °C).[22] ^{1}H NMR ($CDCl_3$) ppm: 3.31 (s, 3H, OCH_3), 3.36 (s, 6H, NCH_3), 3.37 (s, 6H, NCH_3). ^{13}C NMR ($CDCl_3$) ppm: 29.6 (NCH_3), 30.4 (NCH_3), 56.9 (OCH_3), 64.9 (C5), 84.9 (C5), 150.2 and 150.5 (C2 or C2'), 161.5 and 162.8 (C4/C6 or C4'/C6').

1,1',3,3',5,5'-Hexamethyl[5,5']bipyrimidinyl-2,4,6,2',4',6'-hexaone (53):[22] A suspension of **13** (60 mg, 0.19 mmol), K_2CO_3 (0.055 g, 0.38 mmol) and methyl iodide (1 mL, 16 mol) in DMF (1 mL) was placed in a 10 mL pressure tube and irradiated by microwave for 0.5 h (10 W, 80 °C, 1.5 bar). Subsequently the mixture was evaporated under reduced pressure. After the addition of water (75 mL) the residue was extracted twice, with 50 mL CH_2Cl_2 each. The organic extracts were dried over K_2CO_3, filtered, evaporated and concentrated. The product was crystallized with Et_2O: 50 mg colorless crystals (77 %),

mp 258.7-259.1 °C; ^{1}H NMR ($CDCl_3$) ppm: 1.86 (s, 6H, C5CH_3), 3.25 (s, 12 H, NCH_3); ^{13}C NMR ($CDCl_3$) ppm: 21.5 (C5CH_3), 29.1 (NCH_3), 55.7 (C5), 150.3 (C2), 170.6 (C4/C6); EIMS (*m/z*, %) 338 (M^+ , 2) 170 ($M/2H^+$, 100). Anal. Calcd for $C_{14}H_{18}N_4O_6$: C, 49.7; H, 5.36; N, 16.56. Found: C, 49.5; H, 5.61; N, 16.60.

1,3-Dimethylpyrimidine-2,4,5,6-tetraone-5-oxime (22): A suspension of 6-amino-5-nitroso-1,3-dimethyluracil **18** (4.6 g, 25 mmol) in 35 mL of diluted hydrochloric acid (2 M) was heated under reflux until an almost decolorized mixture was obtained (ca. 10 min). The colorless product was crystallized from the reaction mixture at 4 °C, filtered off under reduced pressure, washed with water and dried at 70 °C (84 % yield): mp 144.9-145.5 °C (lit.[23], mp 141 °C). ^{1}H NMR ($CDCl_3$): (a single tautomer) 3.38 (s, 3H, NCH_3), 3.41 (s, 3H, NCH_3), 15.91 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): 27.9 (NCH_3), 29.0 (NCH_3), 135.5, 149.2, 156.2, 160.4 ppm; ^{1}H NMR (DMSO-d_6): 3.12 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 14.70 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6): 27.7 (NCH_3), 28.4 (NCH_3), 135.8, 150.8, 153.7, 158.3 ppm.

1-Methylpyrimidine-2,4,5,6-tetraone-5-oxime (24): A suspension of 6-amino-5-nitroso-3-methyluracil **20** (2.1 g, 12 mmol) in 15 mL of diluted hydrochloric acid (2 M) was heated under reflux until an almost decolorized mixture was obtained (ca. 10 min). The colorless product was crystallized from the reaction mixture at 4 °C, filtered off under reduced pressure, washed with water and dried at 70 °C (39 % yield): mp 208.3 °C (lit.[24], mp 202-203 °C (dec.)); ^{1}H NMR (DMSO-d_6): (mixture of two tautomer forms ca. 1 : 0.9) 3.05 (s, 3H, NCH_3), 3.11 (s, 3H, NCH_3), 11.51 (br s, 1H), 11.06 (s, 1H), 14.70 (br s, 2H) ppm; ^{13}C NMR (DMSO-d_6) ppm: 26.8 (NCH_3), 27.5 (NCH_3), 135.9, 136.4, 150.18, 150.24, 154.1, 154.8, 158.3, 159.1 ppm.

1,3-Dibutylpyrimidine-2,4,5,6-tetraone-5-oxime (23):[25] A mixture of finally ground 6-amino-1,3-dibutyl-5-nitrosouracil **19** (3.2 g, 12 mmol) and 30 mL of diluted hydrochloric acid was heated under stirring and vigorous reflux. After cooling to rt the mixture was diluted with 100 mL of water and extracted with 150 mL of Et_2O. The ether extract was filtered, dried over $MgSO_4$, filtered again and evaporated. The product was crystallized from petroleum ether (82 % yield): mp 74.5-75.2 °C; ^{1}H NMR ($CDCl_3$) ppm: (a single tautomer) 0.94 (m, 6H, CH_3), 1.36 (m, 4H, CH_2), 1.36 (m, 4H, CH_2), 1.60 (m, 4H, CH_2), 3.93 (m, 4H, NCH_2), 16.00 (br s, 1H), ^{13}C NMR ($CDCl_3$) ppm: 13.56, 13.62, 20.0, 29.7, 29.8, 41.6, 42.5, 135.5, 148.8, 156.0, 160.4.

1-Prop-2-ynylpyrimidine-2,4,5,6-tetraone-5-oxime (25): A suspension of 6-amino-5-nitroso-3-prop-2-ynyluracil **21** (1.2 g, 6 mmol) in 9 mL of diluted hydrochloric acid (2 M) was heated under reflux for 10 min. The hot solution was filtered in order to remove a small amount of decomposed material. Subsequently the off-white solid was allowed to crystallize at 4 °C, filtered under reduced pressure, washed with water and dried at 70 °C (39 % yield): mp > 173 °C (dec.); ^{1}H NMR (DMSO-d_6): (mixture of two tautomers, ca. 1 : 0.9) 3.13 (t, J = 2.5 Hz, 1H), 3.14 (t, J = 2.5 Hz, 1H), 4.41 (d, J = 2.5 Hz, 2H), 4.47 (d, J = 2.5 Hz , 2H), 11.64 (br s, 1H), 11.73 (s, 1H), 14.76 (br s, 2H) ppm; ^{13}C NMR (DMSO-d_6): 29.6, 30.2, 73.62, 73.64, 78.86, 78.88, 135.64, 136.30, 149.3, 149.4, 153.2, 163.7, 158.1, 158.3 ppm; EIMS (m/z, %) 195 (M^+ , 100).

5-Amino-1,3-dimethylpyrimidine-2,4,6-trione (7):[12] A deep-purple solution of 1,3-dimethylpyrimidine-2,4,5,6-tetraone-5-oxime **22** (1 g, 5.4 mmol) in 20 mL 12.5% aq NH_4OH was prepared and heated at 60 °C. Subsequently sodium dithionite (ca. 2.5 g) was rapidly added under stirring until the color turned yellowish. The solution was concentrated under reduced pressure to two-thirds of the original volume. After cooling to rt the air-sensitive, colorless crystals were filtered off and washed with water, EtOH and Et_2O and directly used for following steps (56 % yield): mp 200 °C; ^{1}H NMR (DMSO-d_6): 3.08 (s, 6H, NCH_3), 8.12 (s br, 3H, NH_2, OH) ppm; ^{13}C NMR (DMSO-d_6): 26.9 (NCH_3), 83.3, 152.1, 158.6 ppm.

5-Amino-1,3-dibutylpyrimidine-2,4,6-trione (26): A deep-purple mixture of 1,3-dibutylpyrimidine-2,4,5,6-tetraone-5-oxime **23** (1 g, 3.9 mmol) in 30 mL 12.5% aq NH_4OH was prepared and heated at 80 °C. Subsequently the solution was decolorized by the addition of sodium dithionite (2.7 g) upon stirring. The mixture was heated at 60 °C for additional 10 min, filtered to remove some unconverted starting material and concentrated under reduced pressure to two-thirds of the original volume. After cooling to rt colorless needles were rapidly filtered off, washed with water and directly used for following steps (yield: 1.0 g, max. 3.7 mmol, containing an undetermined percentage of water). Due to its extreme air-sensitivity compound **26** was only characterized by derivatization with benzoyl chloride yielding 4,6-dibutyl-2-phenyl-4*H*,6*H*-oxazolo[5,4-*d*]pyrimidine-5,7-dione (**29**).

4,6-Dimethyl-2-phenyl-4*H*,6*H*-oxazolo[5,4-*d*]pyrimidine-5,7-dione (28): The compound was prepared as previously described:[14] mp 234 °C (lit., mp 247 °C;[15] 240-242 °C[26]).

^{1}H NMR ($CDCl_3$): 3.42 (s, 3H, NCH_3), 3.63 (s, 3H, NCH_3) 7.46-7.48 (m, 3H, $H_{arom.}$), 8.01-8.04 (m, 2H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): 28.8 (NCH_3), 30.6 (NCH_3), 112.6 (C3a), 125.5, 126.5, 129.0, 131.3 ($C_{arom.}$), 150.2, 154.4, 156.5, 156.6 (C2, C4, C6, C7a) ppm.

4,6-Dibutyl-2-phenyl-4*H*,6*H*-oxazolo[5,4-*d*]pyrimidine-5,7-dione (29): A mixture of freshly prepared 5-amino-1,3-dibutylpyrimidine-2,4,6-trione **26** (1 g, 3.7 mmol) was refluxed with an excess of benzoyl chloride (3 mL, 25.8 mmol) for 0.5 h, cooled to rt, treated with 5% NaOH solution (50 mL), refluxed again for 10 min and finally stirred at rt until the viscous residue turned into a solid. The solid was extracted twice with 50 mL CH_2Cl_2 each, dried over K_2CO_3, filtered over silica gel and concentrated under reduced pressure leading to a highly pure product. Colorless needles were obtained by recrystallization from CH_2Cl_2 : petroleum ether (1 : 6) (ca. 30 % yield): mp 91 °C, ^{1}H NMR ($CDCl_3$): 0.93 (t, *J* = 7.6 Hz, 3H, CH_3), 0.99 (t, *J* = 7.6 Hz, 3H, CH_3), 1.37 (m, 2H, CH_3CH_2), 1.42 (m, 2H, CH_3CH_2), 1.63 (m, 2H, $CH_2CH_2CH_2$), 1.80 (m, 2H, $CH_2CH_2CH_2$), 4.02 (m, 2H, NCH_2), 4.08 (m, 2H, NCH_2), 7.45-7.50 (m, 3H, $H_{arom.}$), 8.00-8.05 (m, 2H, $H_{arom.}$) ppm; ^{13}C NMR ($CDCl_3$): 13.6, 13.8, 19.9, 20.1, 29.9, 30.3, 42.0 (NCH_2), 44.5 (NCH_2), 112.7 (C3a), 125.7, 126.5, 129.0, 131.3 (C_{aromat}), 149.7, 154.3, 156.4, 156.5 (C2, C4, C6, C7a) ppm; EIMS (m/z, %) 341 (M^+ , 100).

Reaction of 5-amino-1,3-dimethylpyrimidine-2,4,6-trione (7) with hydrochloric acid: Typical procedure: Freshly prepared **7** (1,1 g, ca. 6 mmol) was dissolved in a mixture of concentrated hydrochloric acid (10 mL) and water (10 mL) and heated under reflux. After 3 h the reaction was stopped. The colorless solution was cooled to rt, diluted with a concentrated aqueous solution of NaCl (50 mL) and extracted four times, with 50 mL CH_2Cl_2 each. The organic extracts were dried over $MgSO_4$, filtered and evaporated. The colorless solid residue (300 mg) was investigated by NMR spectroscopy indicating the formation of **35** (88 %) and **36** (12 %). Recrystallisation with CH_2Cl_2/Et_2O (1 : 5) afforded pure **35** (220 mg, 32 %).

3-Methyloxazolidine-2,4-dione (35): mp 133 °C; ^{1}H NMR ($CDCl_3$): 3.08 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), ppm; ^{13}C NMR ($CDCl_3$): 25.9 (NCH_3), 68.0 (CH_2), 156,0 (C2), 170.4 (C4) ppm; EIMS (m/z, %) 155 (M^+, 100).

Reaction of 5,6-diamino-1,3-dimethyl-1*H*-pyrimidine-2,4,dione (15) with hydrochloric acid: Typical procedure: Freshly prepared **15** (0.5 g, ca. 6 mmol) was dissolved in a mixture of concentrated hydrochloric acid (3 mL) and water (3 mL) and heated under reflux. After 1 h the yellow solution was cooled to rt and extracted three times, with 75 mL CH_2Cl_2 each. The organic extracts were dried over $MgSO_4$, filtered and evaporated. The product (260 mg) was separated by column chromatography on silica gel (eluent: CH_2Cl_2 /MeOH 7 : 1). The separated products **13**, **16**, **17**, **42** and **45** were characterized by their physico-chemical properties (TLC, mp, fluorescence) and NMR spectroscopy followed by comparison with literature data as far as accessible. Since part of the individual compounds remained in

the aqueous phase yields could not be precisely determined. Due to the extractive method which was selected for separation only qualitative results could reliably be obtained.

1,3,7,9-Tetramethyl-(1*H*,3*H*,7*H*,9*H*)-pyrimido[5,4-*g*]pteridine-2,4,6,8-tetrone (16):[27] colorless crystals: mp > 360 °C; ^{1}H NMR ($CDCl_3$) 3.52 (s, 6H, NCH_3), 3.72 (s, 6H, NCH_3) ppm, ^{13}C NMR ($CDCl_3$): 29.1 (NCH_3), 29.9 (NCH_3), 123.6, 149.4, 150.3, 157.9 ppm.

1,3,6,8-Tetramethyl-(1*H*,3*H*,6*H*,8*H*)-pyrimido[4,5-*g*]pteridine-2,4,7,9-tetrone (17):[11] blue fluorescent yellow crystals: ^{1}H NMR ($CDCl_3$) 3.55 (s, 6H, NCH_3), 3.80 (s, 6H, NCH_3) ppm, ^{13}C NMR ($CDCl_3$): 29.4 (NCH_3), 30.1 (NCH_3), 129.0, 144.3, 150.0, 158.6 ppm.

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