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One-Step Synthesis of Lumazine and Xanthine: First Co-Crystal of Lumazine and Perchloric Acid with a Unique Monohydrated Hydronium Ion ($H_5O_2^+$) Mediated Supramolecular Assembly of the Lumazine Dimer

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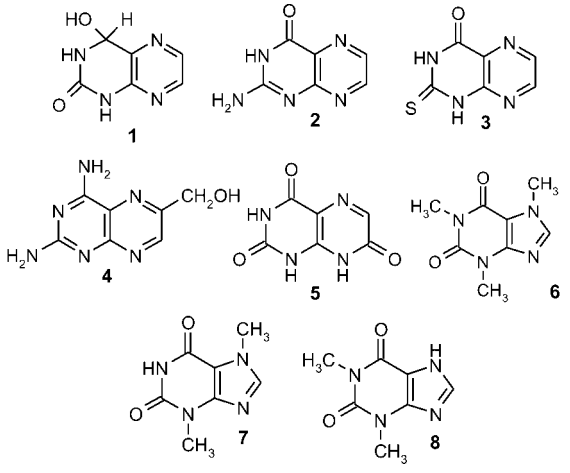
Keywords: Pterins / Lumazine / Perchloric acid / Supramolecular chemistry / Hydrogen bonds

A perchloric acid mediated one-step synthesis of lumazine derivatives from pterins and xanthine from guanine is reported. However, 2-pivaloylamino derivatives of pterins underwent simple hydrolysis of the pivaloylamino group generating free pterin compounds, but the 2-oxo derivatives, that is, the lumazine compounds, were not obtained. A novel supramolecular assembly is constructed by the unique hydrogen bonding of $H_5O_2^+$ bridging two hydrogen-bonded dimers of lumazine to form the co-crystal **21** with aqueous perchloric acid. In contrast, N^2-pivaloyl-6-bromo-5-deazapterin was simply hydrolysed to form the protonated deazapterin **22**, which forms a unique six-membered cyclic hydrogen-bonded structure leading to the generation of a polymeric supramolecular assembly.

Introduction

The versatility of pterin (pterin, xanthopterin, chrysopterin, lumazine and leucettidine) and purine derivatives (adenine, guanine and xanthine) in the synthesis of natural products like folic acid, biopterin, neopterin and the anticancer drug methotrexate as well as other biologically important building blocks of RNA and DNA and pigments has been well documented.[1] Xanthine oxidase and related enzymes can convert xanthopterin into leucopterin and pterin into isoxanthopterin.[2] Bergmann and Kwietny undertook a kinetic study of the oxidation of pteridine, pteridinones, pteridinediones and pteridinetriones by milk xanthine oxidase.[3] The co-ordination chemistry of pteridine, lumazine and 5-deazapterin derivatives has been the subject of intense research for many years, and thus they have been studied from a variety of perspectives by many different research groups.[4] Metal complexes of pteridine derivatives have been shown to be useful as cofactors, for example, molybdenum cofactor, and as biological carriers for some analogous compounds such as molybdopterin and tetrahydropterin. However, many features of their mechanism of action are still controversial but it is known that pteridine and pterin derivatives act by inhibiting xanthine oxidase, a key enzyme in the biosynthesis of DNA precursors and a generator of free radicals.[5] We have recently reported the first microwave-assisted regiospecific synthesis of 6-substituted pterins.[6]

The conversion of pteridinamines into pteridinones can be done by alkaline or acidic hydrolysis.[7] Lumazine derivatives have been made in several ways, for example, by oxidation of the covalent 3,4-hydrate of 2(1*H*)-pteridinone **1**,[8] by treatment of 2-amino-4(3*H*)-pteridinone (**2**) with nitrous acid[9] or by oxidative hydrolysis of 2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3**) by ammoniacal hydrogen peroxide.[10] 6-Hydroxymethylpterin has also been synthesised by the hydrolysis of 6-hydroxymethyl-2,4-diaminopteridine (**4**).[11] 2-Amino-4,7(3*H*,8*H*)-pteridinedione has been converted into 2,4,7(1*H*,3*H*,8*H*)-pteridinetrione (**5**) by refluxing in 6 M hydrochloric acid.[12]



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Xanthine is also a very important key constituent of tea and cocoa beans, for example, caffeine (**6**), theobromine (**7**) and theophylline (**8**). Also, xanthine derivatives have been synthesised by different methods, for example, by oxidation with nitric oxide in the presence of dioxygen,[13] with methanococcus vannieliii[14] or with concentrated HCl and $NaNO_2$ in water.[15]

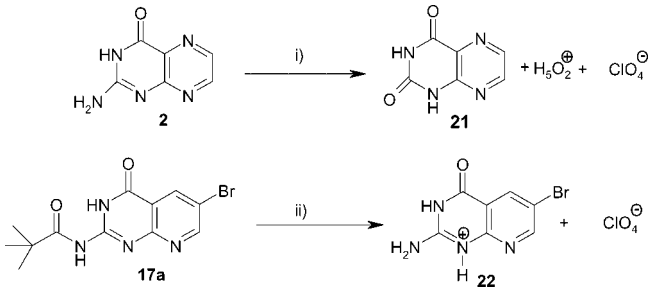
The most noticeable physical properties of the tautomeric pteridinones are their resistance to melting and their poor solubility in water and indeed in most other solvents. Their solubility in water decreases markedly as the number of oxo substituents increases. These effects clearly result from intermolecular hydrogen bonding which is exceptionally powerful within the crystal lattice.[16] It has been reported that metal-coordinated $[H_5O_2]^+$ forms strong hydrogen bonds with the oxygen atom of a carboxylate group[17] and also that it forms a microporous layer structure.[18] With the lumazine dimer, the existence of the guest unit $[H_5O_2]^+$ allows the formation of a unique supramolecular assembly containing these dimers. The sheet structure formed from the hydrogen-bonded lumazine dimer and $[H_5O_2]^+$ is distinctive among other supramolecular structures that have been reported.

Result and Discussion

We report[19] here a useful, straightforward, economic and efficient one-step method for the synthesis of lumazine derivatives in good yield by conversion of the amino group in pterins to the oxo group with perchloric acid (Table 1). Thus the pterin derivatives **2**, **11**, **13**, **15**, **17** and **18** and also guanine **20** afford the corresponding lumazine derivatives **9**, **10**, **12**, **14**, **16** and xanthine **19**. The isolation of crystalline ammonium perchlorate as a byproduct from the above hydrolysis suggests the removal of the amino group in the presence of perchloric acid as the ammonium perchlorate salt. But with a pivaloyl-protected amino group, for example, in compounds **2a**, **11a**, **13a**, **15a**, **17a**, **18a** and **20a**, only hydrolysis of the pivaloylamino groups takes place, affording compounds **2**, **11**, **13**, **15**, **17**, **18** and **20**. By hydrolysis of the pivaloyl derivatives of pterin or other analogous pivalamides or acetamides, the perchlorate salts of pterin and other analogues may also be isolated. Also further conversion of the amino group thus liberated from the hydrolysis of the pivaloyl derivatives of pterin to the corresponding oxo group was also successful by treatment with excess perchloric acid and warming. We neutralised the perchlorate reaction products and isolated the free heterocyclic bases for structural confirmation. All the compounds made here have been well characterised by spectroscopic studies as well as by comparison with authentic samples. The reaction conditions and yields are summarised in Table 1.

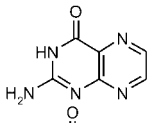
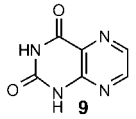
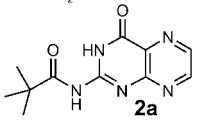
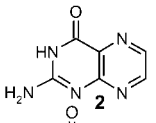
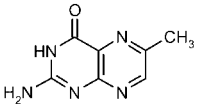
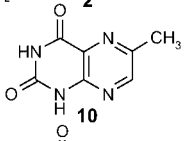
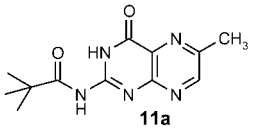
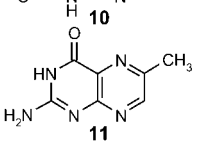
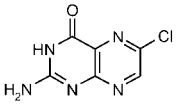
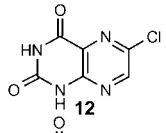
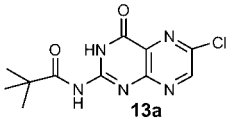
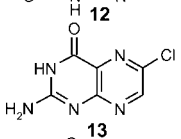
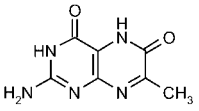
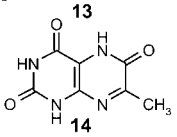
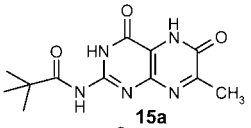
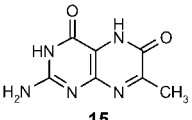
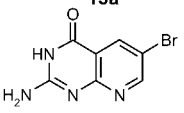
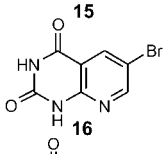
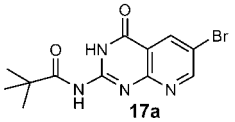
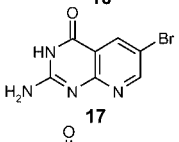
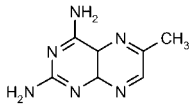
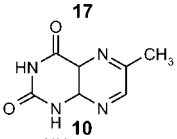
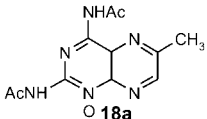
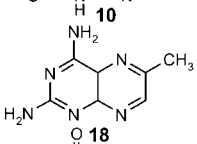
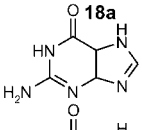
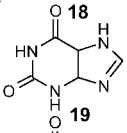
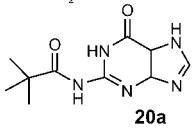
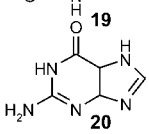
The starting materials shown in Table 1 were prepared in our laboratory by reported literature procedures. Starting materials **2** and **2a** were made by condensing 2,5,6-triaminopyrimidin-4(3*H*)-one hydrochloride with glyoxal and subsequent pivaloylation by heating at reflux with pivalic anhydride.[20] Similarly, starting 6-methylpterin (**11**) and its 2-pivaloyl derivative **11a** were made by following our microwave procedure.[6a,21] 2-Amino-6-chloropterin (**13**) and its pivaloyl derivative **13a** were prepared by Taylor and Roy's procedure.[22] 7-Methylxanthopterin (**15**) was prepared by condensation of 2,5,6-triaminopyrimidin-4(3*H*)-one hydrochloride with pyruvic acid at room temperature[28c] and pivaloyl derivative **15a** was obtained by heating at reflux with pivalic anhydride.[19] The starting compounds 6-bromo-5-deazapterin (**17**) and its 2-pivaloyl derivative **17a** [intermediates for an important anticancer drug lometrexol (5,10-dideaza-5,6,7,8-tetyrahydrofolic acid) developed by Taylor et al.[23] (Table 1, Entries 9 and 10)] were also prepared by their reported procedure.[24] Starting 2,4-diamino-6-methylpteridines **18** and **18a** were made[25] by condensing 2,4,5,6-tetraaminopyrimidine hydrochloride with methyl glyoxal and subsequent acetylation by heating at reflux with acetic anhydride.

We also report[19] here the first synthesis of the perchloric acid co-crystal of lumazine **21** derived from pterin **2** by mild conversion of the 2-amino group to the oxo group with perchloric acid (Scheme 1) and also the synthesis of the perchlorate of 6-bromo-5-deazapterin (**22**) under the same conditions from N^2-pivaloyl-6-bromo-5-deazapterin (**17a**), as well as their X-ray structures and supramolecular assembly. Interestingly, lumazine forms a co-crystal of perchloric acid: the lumazine ring cannot be protonated so instead the proton goes on the water-forming $H_5O_2^+$ which binds the hydrogen-bonded dimer of lumazine. In contrast, in the case of deazapterin, its perchlorate salt is isolated, as proven by X-ray structures. This is probably because lumazine is a weaker base than deazapterin which has a more basic guanidine moiety. New co-crystal **21** derived from lumazine and aqueous perchloric acid and the 6-bromo-5-deazapterin perchlorate (**22**) were characterised by ^1H and ^{13}C NMR spectroscopy. The structures and the supramolecular assembly of **21** and **22** were confirmed by single-crystal X-ray analysis.



Scheme 1. Reagents and conditions: (i) 70% perchloric acid, 70–80 °C, 25 min; (ii) 70% perchloric acid, 70–80 °C, 15 min.

Table 1. Products isolated by the reaction of perchlorate with pterin, N^2-pivaloylpterin, 5-deazapterin and xanthine systems.

Entry	Starting material[a]	Product[b]	Reaction condition	Yield[c]	Reference
1		 **9**	25 min	46%	9
2	 **2a**	 **2**	15 min	55%	20
3		 **10**	45 min	42%	26
4	 **11a**	 **11**	15 min	62%	21
5		 **12**	50 min	59%	19
6	 **13a**	 **13**	15 min	65%	22
7		 **14**	45 min	54%	27
8	 **15a**	 **15**	15 min	62%	28
9		 **16**	30 min	56%	19
10	 **17a**	 **17**	15 min	68%	24
11		 **10**	25 min	61%	26
12	 **18a**	 **18**	15 min	66%	25
13		 **19**	15 min	69%	29
14	 **20a**	 **20**	7 min	75%	13

[a] All the prepared starting materials (Entries 1 to 14) were characterised by their ^{1}H NMR spectra which are identical to the reported data. [b] The ^{1}H NMR spectroscopic data of compounds **9**, **10**, **12**, **14**, **15a**, **16**, **18a**, **19**, **20a**, **21** and **22** and the ^{13}C NMR spectra of compounds **21** and **22** are given in the Experimental Section. [c] Yields refer to the isolated products.

The synthesis of deazapterin perchlorate **22** from **17a** is the result of hydrolysis of the pivaloylamino group, whereas the synthesis of lumazine **21** results from the conversion of the amino group into the corresponding oxo group. However, **22** can be further converted into oxo compound **16** by simply decanting the liquid from the solid, adding a fresh excess of perchloric acid and warming.

The notoriously poor solubility of pterin compounds in common organic solvents and also in water (as reported by Taylor: "resembling nothing more than brick dust, in their appearance and ease of handling"), which results from multiple intramolecular hydrogen bonds, restricts their chemistry and causes problems in obtaining single crystals suitable for X-ray analysis. For this reason there are only a few X-ray-determined structures of complexes containing pterin ligands. Moreover, lumazine compounds are more insoluble than pterins due to the replacement of the 2-amino group by a 2-oxo group and thus lumazine crystals are important to enable their structural confirmation. By our methods, perchlorate salts that are water-soluble can be easily prepared and easily made crystalline.

Here we have further demonstrated the dimeric existence of lumazine compounds in contrast to pterins which form polymeric structures. Similarly folate, having a pterin moiety, also exists as a cyclic hydrogen-bonded tetramer,[30] which also forms a liquid-crystalline mesophase. The single crystal of a lumazine–sodium complex has been studied and the crystal structure of this compound shows a metal-coordinated dimeric structure[31] stabilised by water coordination. We report here the single-crystal X-ray structure of the co-crystal formed between the neutral lumazine molecule and aqueous perchloric acid **21** (Figure 1).

The lumazine molecule typically associates to form a dimer through N–H···O hydrogen bonds involving one of the lactam moieties (which has an imide NH) of each molecule. This stable dimer is further extended forming a hydrogen-bonded supramolecular assembly through intermolecular hydrogen bonds involving $H_5O_2^+$ (a hydronium ion hydrogen-bonded to one water molecule)[32] as a bridge between the unused oxygen of the urea-type lactam carbonyl and one pyrazine nitrogen atom of the adjacent ring through O–H···O and O–H···N hydrogen bonds (Figure 2).

This unique supramolecular assembly of a lumazine dimer mediated by $H_5O_2^+$ is exceptional.[33] The relative orientation of the hydrogen atoms in $H_5O_2^+$ allows the interconnected lumazine molecules to form a wing-like sheet. The counter-cation $H_5O_2^+$ is slightly bent [O(1)–H(1)–O(2), 161°]. Here a very short O(1)–O(2) distance of 2.404 Å is comparable to the distance reported in the literature.[34] The three-dimensional supramolecular structure is achieved by participation of the ClO_4^- ions, where each ClO_4^- ion binds to four different wing-like sheets (Figure 3b).

An important point to note in the crystal structure is that the lumazine moiety itself is not protonated by perchloric acid; the protonation happens on a water molecule (hydronium ion) which is then further hydrated forming a $H_5O_2^+$ unit which binds a dimer of lumazine to another dimer for supramolecular stability. Also the bonds H^+–$H_2O(1)$ (1.27 Å) and H^+–$H_2O(2)$ (1.16 Å) are considerably longer than normal O–H (0.97 Å) bonds, that is, the hydrated hydronium ion which is neutralised by the perchlorate ion bonded to the NH hydrogen of the lactam not used in the dimeric or supramolecular network (unlike the other lactam which is an imidic NH). The lumazine layers are connected by perchlorate ions through N–H···O hydrogen bonding (Figure 3a).

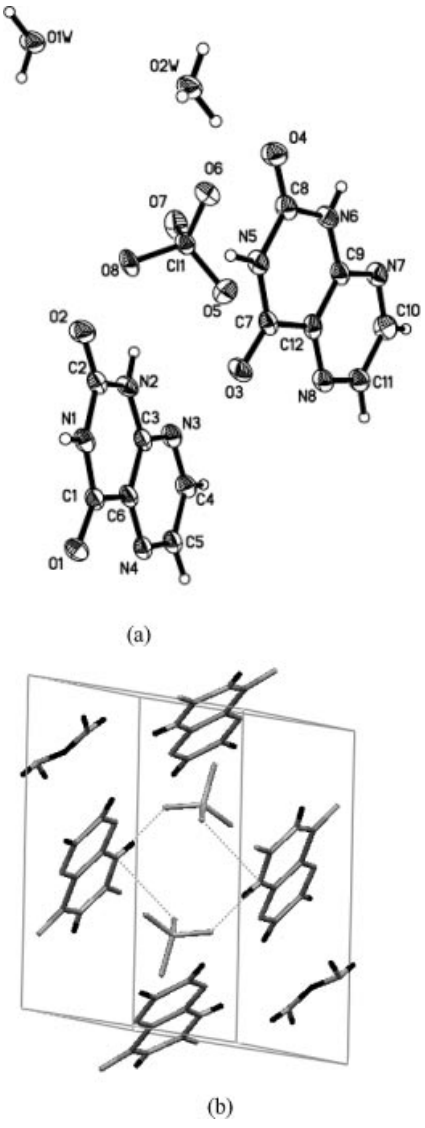


Figure 1. X-ray crystal structure of lumazine perchlorate **21**: (a) ORTEP diagram with the atom numbering scheme; (b) packing of molecules in the crystal lattice.

The lumazine molecules are almost planar. The angles found at the carbonyls C(4)=O(10) and C(2)=O(9) in **21** correspond to the usual values of these functional groups of 122.15, 123.23, 114.60° and 121.75, 122.76, 115.49°. However, they deviate markedly from those measured in guanine hydrochloride monohydrate by X-ray diffraction (116, 136 and 108°).[35]

The crystal structure of compound **21** shows the way in which the molecules of **21** organise themselves with guest water molecules. The crystal packing of **21** contains various

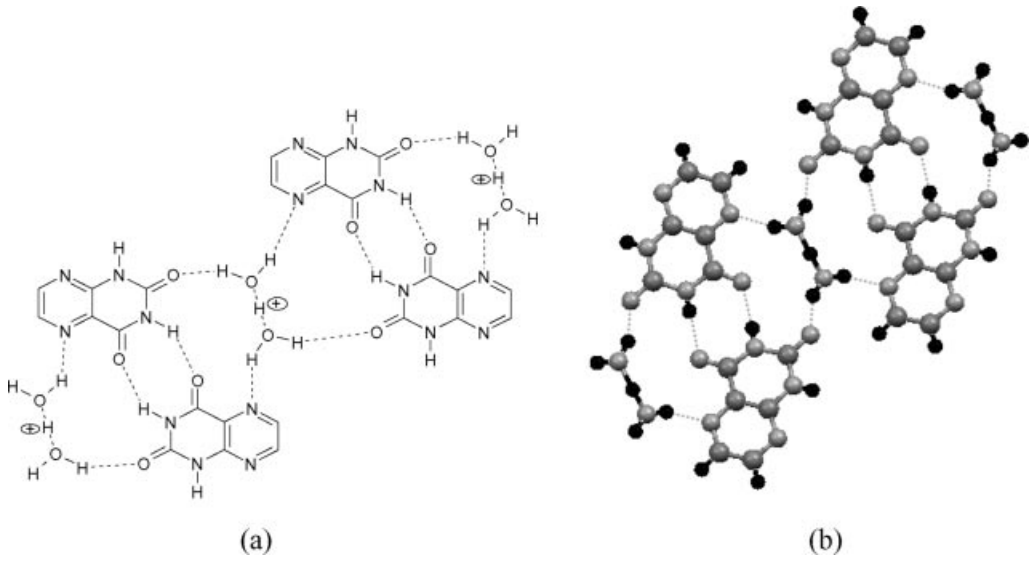


Figure 2. (a) The three types of hydrogen bonds formed by lumazine and the $H_5O_2^+$ ion in the X-ray structure of the supramolecular assembly. (b) Hydrogen bonding in the supramolecular network of **21** (perchlorate is excluded for clarity).

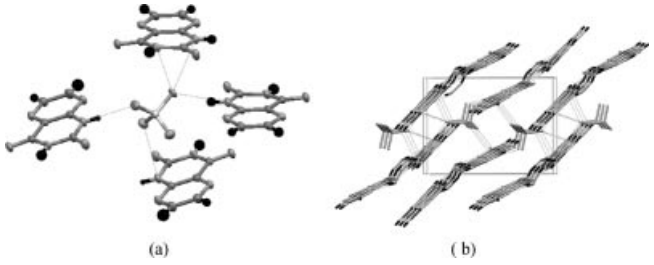


Figure 3. (a) The sets of parallel lumazine layers with only one type of hydrogen bond (N–H···O) formed with the perchlorate ion. (b) ClO_4^- ion binding with four wing-like sheets.

types of noncovalent interactions (from strong to weak hydrogen bonds and π–π interactions) which all contribute to generate a supramolecular co-crystal of lumazine and aqueous perchloric acid. The ^{1}H NMR spectra of lumazine **9** (Figure 4a) and its perchloric acid co-crystal **21** (Figure 4b) in [D$_6$]DMSO are compared in Figure 4. The chemical shift values (δ = 10.07 and 7.88 ppm) of the two pyrimidine lactam protons H_a and H_b in lumazine **9** are shifted downfield (δ = 11.91 and 11.66 ppm) when it is complexed with the perchlorate ion (compound **21**), whereas the pyrazine protons H_c and H_d are little affected. Possibly the water peak which appears at δ = 3.4 ppm in the NMR spectrum of lumazine in [D$_6$]DMSO is at δ = 4.8 ppm in lumazine perchlorate hydrate suggesting protonation of water, as demonstrated also by the structure of the co-crystal of the lumazine hydronium hydrate perchlorate. Thus the X-ray structure and the NMR data for lumazine hydronium hydrate perchlorate in the solid and solution state show good correlations. The proton peaks in the NMR spectrum of co-crystal **21** are more clearly resolved showing complexation.

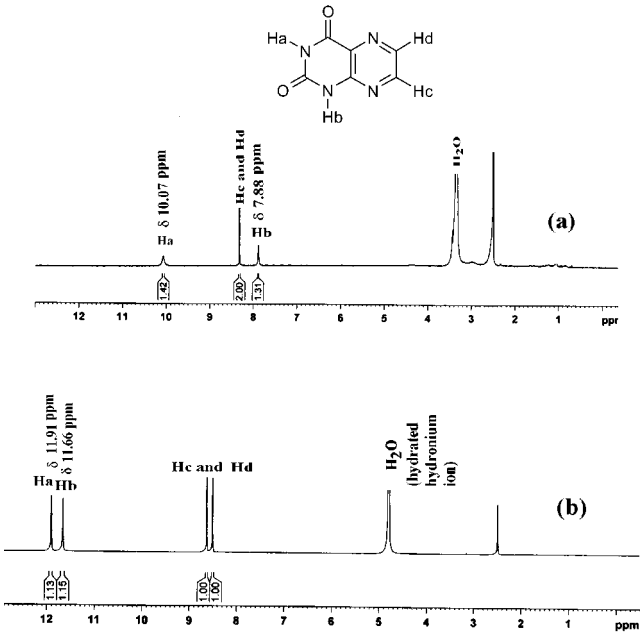


Figure 4. Comparison of the ^{1}H NMR spectra in [D$_6$]DMSO of (a) lumazine (**9**) and (b) the co-crystal of lumazine and aqueous perchloric acid (**21**).

We also report here the single-crystal structure of 6-bromo-5-deazapterin perchlorate (**22**) (Figure 5). The X-ray analysis of the perchlorate salt of 6-bromo-5-deazapterin (**22**) which is protonated on N(1) of the pyrimidine ring suggests a polymeric supramolecular ribbon structure (instead of a dimeric supramolecular structure as in the above lumazine **21**) in which the carbonyl group of the lactam moiety binds the pyrimidine amino group of a second molecule forming a six-membered intermolecular N–H···O hy-

drogen-bonding arrangement (Figure 6a). In this case protonation helps to form a stable six-membered intermolecular hydrogen-bonded system which is relatively rare compared with six-membered intramolecular hydrogen-bonded systems which are common.

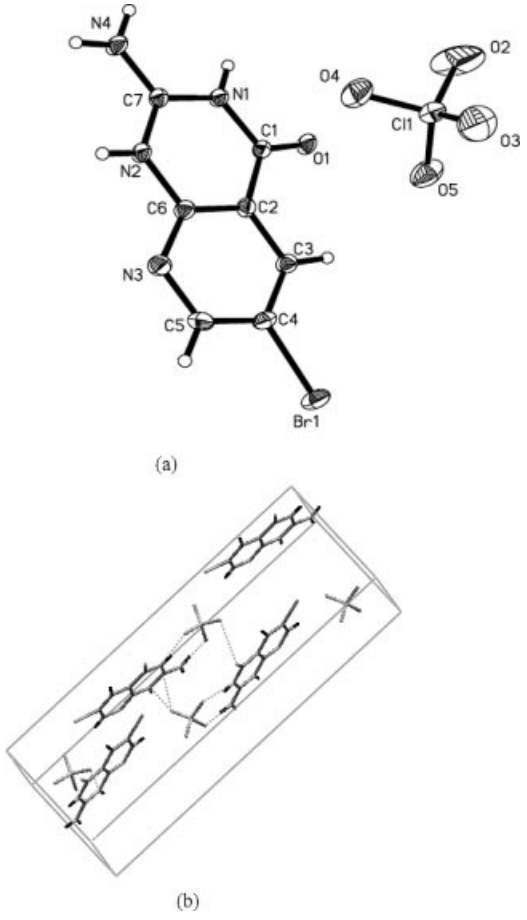


Figure 5. X-ray structure of 6-bromo-5-deazapterin perchlorate (**22**): (a) ORTEP diagram of the compound with the atom numbering scheme; (b) packing of the molecules in the crystal lattice.

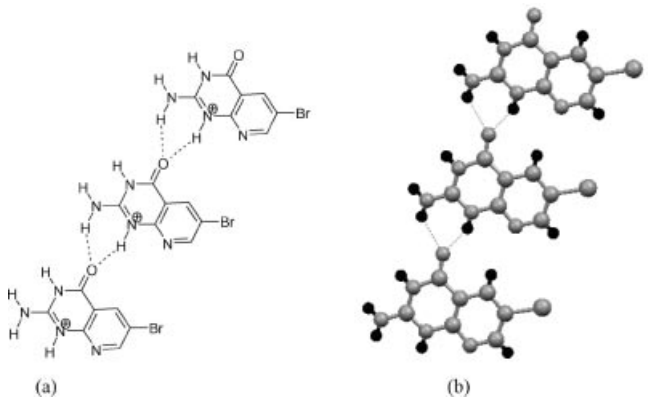


Figure 6. (a) One type of hydrogen-bonded, ribbon-like structure in the supramolecular self-assembly formed by deazapterin, as determined by X-ray analysis. (b) Hydrogen bonding in a supramolecular network of **22** (perchlorate is excluded for clarity).

The interpenetrating parallel layers are connected by a perchlorate ion (Figure 7a). There are two sets of parallel chains with each chain forming an intermolecular hydrogen bond with another chain parallel to it and also to another chain not parallel to it through ClO_4^- ions. This type of propagation of the chain gives rise to an interpenetrating ladder-like supramolecular structure (Figure 7b). Here the 6-bromo-5-deazapterin molecules and ClO_4^- ions are situated alternately at the diagonal.

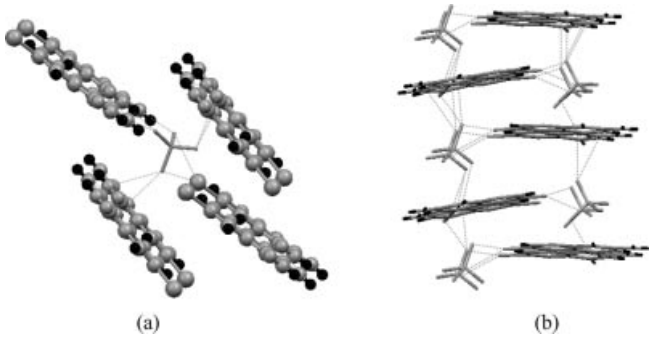


Figure 7. (a) The parallel layers in deazapterin **22** bound to the perchlorate ion. (b) Interpenetrating ladder-like structure of compound **22**.

The ^1H NMR spectra of 6-bromo-5-deazapterin (**17**) (Figure 8a) and its perchlorate crystal **22** (Figure 8b) in $[D_6]$DMSO are shown in Figure 8. It can be observed that the amine proton in compound **17** shifts from its normal position (δ = 6.49 ppm) to a more downfield (δ = 8.27 ppm) position in 6-bromo-5-deazapterin perchlorate (**22**).

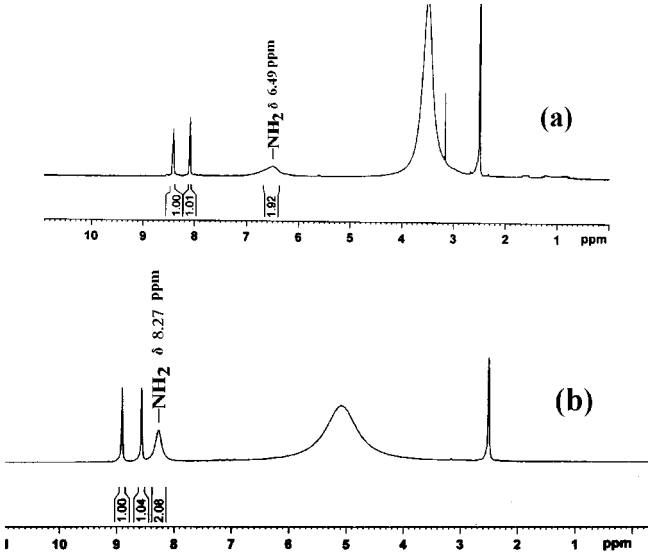


Figure 8. Comparison of the ^1H NMR spectra in $[D_6]$DMSO: (a) 6-bromo-5-deazapterin (**17**) and (b) 6-bromo-5-deazapterin perchlorate (**22**).

The molecule 6-bromo-5-deazapterin (Figure 9) is protonated at N(1).[36,37] Both the pyrimidine and pyridine rings are planar with the amino group consisting of the atoms N(9), H(13) and H(14) and the atoms H(12), H(15),

O(10), H(16), Br(11) and H(17) lying in the same respective planes. The angle between plane 1 (pyrimidine ring) and plane 2 (pyridine) is 3.16° giving an overall planar molecular structure. The chlorate ion exhibits its shortest distance with respect to the atoms H(15) (2.22 Å), H(12) (2.429 Å), H(13) (2.380 Å) and H(14) (2.073 Å). Also the bonds N(1)–C(2) (1.33 Å), C(2)–N(3) (1.35 Å) and C(2)–N(9) (1.31 Å) are considerably shorter than typical single bonds (1.54 Å). Based on these results, the positive charge can be assumed to be strongly delocalised over the centres N(1), C(2), N(3) and N(9) (Figure 9). Thus in this study the structures of the two perchlorate salts, the unique monohydrated hydronium ion ($H_5O_2^+$) mediated supramolecular assembly of the lumazine dimer and the polymeric six-membered cyclic intermolecular hydrogen-bonded assembly of 6-bromo-5-deazapterin, are compared.

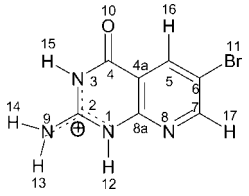


Figure 9. Delocalised positive charge on protonation of the deazapterin system, from bond lengths measured by X-ray analysis.

Conclusions

A one-step synthesis of lumazine from pterin and xanthine from guanine, including a series of analogous compounds, is reported. In its supramolecular assembly, a H^+-mediated dimeric guest water ($H_5O_2^+$) binds two dimers of lumazine **21** which itself is not protonated, in contrast to the more basic 5-bromodeazapterin **22**. To the best of our knowledge this is the first report of a perchlorate or perchloric acid co-crystal of deazapterin, pterin or lumazine, which are easy to make by this procedure, and the isolation of these as crystalline solids is a unique advantage. Also these unique layer structures have attracted considerable interest in recent years in the studies of crystal engineering, molecular recognition and supramolecular chemistry.[38]

Experimental Section

General: All commercially available chemical reagents were used without further purification. Technical solvents were distilled by standard methods. All the reactions were carried out in 70% perchloric acid. ^{1}H NMR spectra were recorded either with a Bruker AM 300L MHz or a Bruker 400 MHz spectrometer. ^{13}C NMR spectra were recorded with a Bruker 400 MHz spectrometer. For NMR, DMSO and $CDCl_3$ were used as solvents, unless otherwise mentioned, using TMS as internal standard. Chemical shifts are expressed in δ units and ^{1}H–^{1}H, ^{1}H–^{13}C coupling constants in Hz. IR spectra were recorded with a JASCO FT/IR-460 plus spectrometer, using KBr discs. Melting points are uncorrected. UV/VIS spectra were recorded, using spectroscopic grade CH_3OH, with a JASCO V-530. Crystal data were collected with a Bruker SMART APEX2 CCD area detector diffractometer equipped with a low-temperature device. Cell refinement: APEX2; data reduction: SAINT (Bruker, 2005); programs used to solve structures: SHELXTL (Sheldrick, 1998); molecular graphics: SHELXTL; softwares used to prepare material for publication: SHELXTL and PLATON (Spek, 2003).

Representative Reaction Procedure: N^2-pivaloyl-6-bromo-5-deazapterin (**17a**; 500 mg, 0.65 mmol) was dissolved in perchloric acid (70%, 4 mL) with warming for 15 min at 70–80 °C, and then the reaction mixture was kept at room temp. The acid was neutralised with solid Na_2CO_3. The colourless crystalline solid, **17**, was filtered, washed well with ice-cold water and dried in a desiccator (250 mg, 68%).

A mixture of 6-bromo-5-deazapterin (**17**; 200 mg, 0.82 mmol) and perchloric acid (70%, 2 mL) was heated at 110–130 °C with stirring for 30 min. The reaction mixture was cooled, neutralised, and the precipitated white solid was collected by filtration, washed with ethanol and ether and then dried to give compound **16** (105 mg, 56%).

2,4(1*H*,3*H*)-Pteridinedione (Lumazine) (9): M.p. >300 °C. FTIR (KBr): $\tilde{\nu}$ = 3360, 1655, 1625, 1434, 1345, 1209, 1144, 800 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.07 (br. s, 1 H, N^{3}H), 8.32 (d, J = 1.9 Hz, 2 H, C^6-H and C^7-H), 7.88 (br. s, 1 H, N^{1}H) ppm. $C_6H_4N_4O_2$ (164.12): calcd. C 43.91, H 2.46, N 34.14; found C 43.79, H 2.50, N 34.21.

6-Methyl-2,4(1*H*,3*H*)-Pteridinedione (6-Methyllumazine) (10): M.p. 325–328 °C. FTIR (KBr): $\tilde{\nu}$ = 3346, 1685, 1610, 1440, 1336, 1231, 1144, 826 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.47 (br. s, 1 H, N^{3}H), 8.38 (s, C^7-H), 7.95 (br. s, 1 H, N^{1}H), 2.66 (s, 3 H, C^6-CH_3) ppm. $C_7H_6N_4O_2$ (178.15): calcd. C 47.19, H 3.39, N 31.45; found C 47.25, H 3.47, N 31.56.

6-Chloro-2,4(1*H*,3*H*)-Pteridinedione (6-Chlorolumazine) (12): M.p. >250 °C. UV (CH_3OH): λ_{max} (logε) = 372 (1.77), 263 (2.24), 211 (2.341) nm. FTIR (KBr): $\tilde{\nu}$ = 3341, 1637, 1589, 1434, 1336, 1213, 1144, 829 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.44 (s, C^7-H), 7.69 (br. s, 1 H, NH) ppm. $C_6H_3ClN_4O_2$ (198.57): calcd. C 36.29, H 1.52, N 28.22; found C 36.21, H 1.47, N 28.19.

7-Methyl-2-pivaloylamino-4,6(3*H*,5*H*)-pteridinedione (2-Pivaloylaminochrysopterin) (15a): 2,5,6-Triaminopyrimidin-4(3*H*)-one dihydrochloride (2.0 g) was stirred in water(15 mL) at room temperature. A solution of pyruvic acid (1.5 g) and water (5 mL) was added at a low temperature (below 5 °C) over a period of 40–50 min with vigorous stirring. The brown solution was then stirred and allowed to reach room temperature. Stirring was continued further for 12 h. The separated solid was filtered through a sinter funnel, washed well with water followed by ethanol and then dried in vacuo. The solid compound **15** (1.2 g, 70%, m.p. >350 °C) after pivaloylation with pivalic anhydride and a catalytic amount of DMAP followed by silica gel column chromatography afforded a cream-coloured solid **15a** (1.4 g, 78%). M.p. 258–260 °C. FTIR (KBr): $\tilde{\nu}$ = 3478, 3152, 1700, 1669, 1617, 1482, 1380, 1245 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.19 (br. s, 1 H, NHCOCMe$_3$), 11.54 (br. s, 1 H), 9.46 (br. s, N^{3}H), 8.87 (br. s, N^{5}H), 3.66 (s, 3 H, C^7-CH_3), 2.22 (s, 9 H, CMe$_3$) ppm. $C_{12}H_{15}N_5O_3$ (277.28): calcd. C 51.98, H 5.45, N 25.26; found C 52.10, H 5.56, N 25.39.

7-Methyl-2,4,6(1*H*,3*H*,5*H*)-Pteridinetrione (14): M.p. >350 °C. FTIR (KBr): $\tilde{\nu}$ = 3424, 1628, 1402, 1370, 1333, 1142, 825 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.87 (br. s, 2 H, N^{3}H and N^{5}H), 7.00 (br. s, 1 H, N^{1}H), 3.22 (s, 3 H, C^7-CH_3) ppm. $C_7H_6N_4O_3$ (194.15): calcd. C 43.30, H 3.11, N 28.86; found C 43.41, H 3.71, N 29.01.

6-Bromo-2,4(1*H*,3*H*)-pyrido[2,3-*d*]pyrimidinedione (6-Bromo-5-deazalumazine) (16): M.p. >300 °C. UV (CH_3OH): λ_{max} (logε) = 333 (0.962), 277 (1.627), 215 (1.697) nm. FTIR (KBr): $\tilde{\nu}$ = 3259, 3072, 1678, 1592, 1556, 1470, 1378, 1296, 830 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 9.19 (d, J = 1.4 Hz, C^5-H), 8.85 (d, J = 2.4 Hz, C^7-H), 8.54 (br. s, 2NH) ppm. $C_7H_4BrN_3O_2$ (242.03): calcd. C 34.74, H 1.67, N 13.36; found C 34.60, H 1.57, N 13.42.

2,4-Bis(acetylamino)-6-methylpteridine (18a): M.p. 230–232 °C (ref.[25] 234–236 °C). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.54 (br. s, 1 H, N*H*$COCH_3$), 8.86 (s, 1 H, C^7-H), 8.2 (br. s, 1 H, N*H*$COCH_3$), 2.68 (s, 3 H, C^6-CH_3), 2.68 (s, 3 H, $COCH_3$), 2.60 (s, 3 H, $COCH_3$) ppm. $C_{11}H_{12}N_6O_2$ (260.25): calcd. C 50.77, H 4.65, N 32.29; found C 50.98, H 4.80, N 32.38.

Xanthine (19): M.p. >300 °C. FTIR (KBr): $\tilde{\nu}$ = 3005, 1703 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 11.46 (br. s, 1 H, N^3H), 8.97 (s, 1 H), 6.99 (br. s, 2 H, N^1H and N^5H) ppm. $C_5H_4N_4O_2$ (152.11): calcd. C 39.48, H 2.65, N 36.83; found C 39.59, H 2.73, N 36.76.

Typical Procedure for the Synthesis of Pterin Perchlorate Salts: Compound **2** or **17a** (100 mg) was dissolved in perchloric acid (70%, 0.5 mL) by warming for 25 min at 70–80 °C and then the reaction mixture was kept at room temperature. After several days, light-yellow needle-shaped crystals were separated which were collected by filtration and dried (45 mg, 62%).

Lumazine–Aqueous Perchloric Acid Co-Crystal (21): M.p. >350 °C. FTIR (KBr): $\tilde{\nu}$ = 3054, 1713, 1566, 1464, 1081, 625 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 11.91 (br. s, 1 H, N^3H), 11.66 (br. s, 1 H, N^1H), 8.61 (d, J = 2.3 Hz, 1 H, C^6-H), 8.52 (d, J = 2.4 Hz, 1 H, C^7-H) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO): δ = 160.9, 149.8, 149.4, 148.1, 140.0, 127.9 ppm. MS (ESI): *m*/*z* (%) = 351 (64) [2M (lumazine dimer) + Na]$^+$, 187 [M + Na]$^+$. $C_6H_9N_4O_8Cl$ (300.61): calcd. C 26.81, H 3.35, N 20.85; found C 25.77, H 3.16, N 20.66. Crystal data: formula for **21** = $2(C_6H_4N_4O_2)\cdot ClO_4\cdot 2(H_2O)$-H, M = 464.75, triclinic, *Cc* (No.9), a = 8.4636(9), b = 24.2785(4), c = 7.7545(1) Å, α = 90, β = 113.0230(10), γ = 89.955(7)°, V = 887.63(16) Å^3, Z = 2, D_c = 1.739 g/cm^3, μ(Mo-K_α) = 0.294 mm^{-1}, F(000) = 476, crystal size = 0.07 × 0.26 × 0.26 mm, temperature = 100.0(1) K, radiation (Mo-K_α) = 0.71073 Å, $\theta_{Min-Max}$ = 1.8–25.0°, total unique data, R(int) = 11742, 3123, 0.077, observed data = 2234 [$I > 2.0\sigma(I)$], Nref = 3123, Npar = 332, R = 0.0528, wR_2 = 0.1442.

6-Bromo-5-deazapterin Perchlorate Salt (22): M.p. >300 °C. FTIR (KBr): $\tilde{\nu}$ = 3430, 3290, 2625, 1587, 1480, 1446, 1088, 625 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 8.91 (s, 1 H, C^5-H), 8.57 (s, 1 H, C^7-H), 8.27 (br. s, 2 H, NH) ppm. ^{13}C NMR (400 MHz, 2% CF_3COOD/[D_6]DMSO): δ = 183.5, 177.8, 122.0, 119.0, 116.1, 113.1, 69.9 ppm. MS (ESI): *m*/*z* (%) = 243 (100) [MH (of deazapterin itself as found)]$^+$. $C_7H_6N_4O_5BrCl$ (341.5): calcd.C 24.60, H 1.75, N 16.40; found C 24.49, H 1.66, N 16.45. Crystal data: formula for **22** = $C_7H_6BrN_4O\cdot ClO_4$, M = 341.51, monoclinic, space group *Cc* (No. 9), a = 8.4636 (9), b = 24.2785 (4), c = 7.7545 (1) Å, α = 90, β = 113.0230 (10), γ = 90°, V = 1136.97(3) Å^3, Z = 4, D_c = 1.995 g/cm^3, μ(Mo-K_α) = 3.871 mm^{-1}, F(000) = 672, crystal size = 0.25 × 0.30 × 0.31 mm, temperature = 100.0(1) K, radiation (Mo-K_α) = 0.71073 Å, $\theta_{Min-Max}$ = 1.7–30.0°, total unique data, R(int) = 13570, 3272, 0.024, observed data = 3161 [I > 2.0σ(I)], Nref = 3272, Npar = 187, R = 0.0305, wR_2 = 0.0786.

CCDC-631453 (**21**) and -295219 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): General experimental methods, crystallography studies, ^1H NMR spectra of known compounds **9**, **10** and **14** and also of new compounds **12**, **15a**, **16**, **18a**, **19**, **21** and **22**, ^{13}C NMR spectra of **21** and **22**. The crystallographic data of compounds **21** and **22** are also described.

Acknowledgments

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