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Synthesis and Structure Determination of Thiazolo- and Thiazinopteridinones

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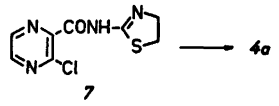
A method for structure determination of dihydro derivatives of thiazolo- and thiazinopteridinones based on the UV and mass spectra of the hydrolysis products is described.

Previously we described the synthesis of isomeric 2,3-dihydro-thiazolo[3,2-*a*]pyrimidinones,[1,2] identified on the basis of UV and mass spectra of the hydrolysis products. In the present paper we extend the synthesis to the following dihydro derivatives of thiazolo- and thiazinopteridinones, representing the novel ring systems: 5*H*-thiazolo[2,3-*b*]pteridine (*3a* and *3c*), 4*H*,6*H*-thiazino[2,3-*b*]pteridine (*3b* and *3d*), 5*H*-thiazolo[3,2-*a*]pteridine (*4a*), and 3*H*,6*H*-thiazino[3,2-*a*]pteridine (*4b* and *4d*). Again, UV and mass spectra of the products formed by hydrolysis of the ring systems permit unequivocal structure assignment by reasoning similar to that previously employed.[1,2]

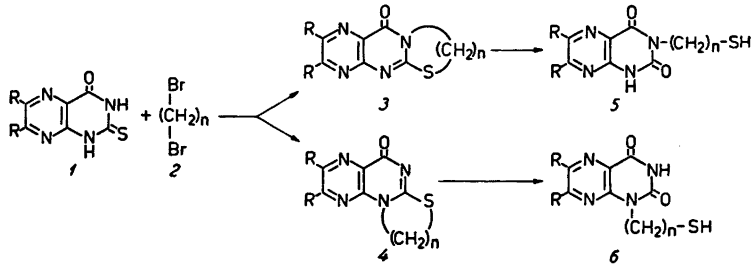
Reaction of the sodium salt of a 2-thiolumazine (*1*) with an α,ω-dibromoalkane in 2-propanol, in the presence of sodium hydrogen carbonate, afforded dihydrothiazolo- or dihydrothiazinopteridinones (Scheme 1). With 2-thiolumazine (*1*, R = H) only one isomer, *3a* or *3b*, could be detected, whereas 6,7-dimethyl-2-thiolumazine (*1*, R = CH_3) afforded a major (*3c* or *3d*) and a minor (*4c* or *4d*) isomer.

Reaction of 3-chloropyrazinoyl chloride with 2-amino-2-thiazoline in chloroform gave the 3-chloropyrazinecarboxamide (*7*) in high yield and as the sole product. Heating of 7 in DMF resulted in ring closure to *4a* (Scheme 2).

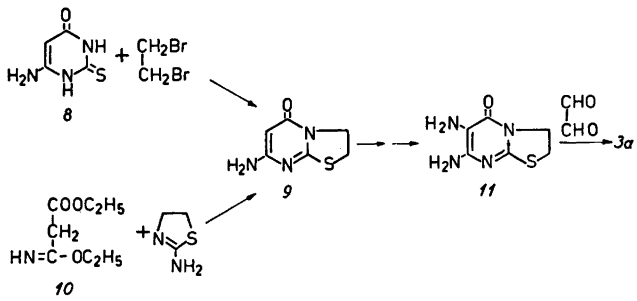


Scheme 2.

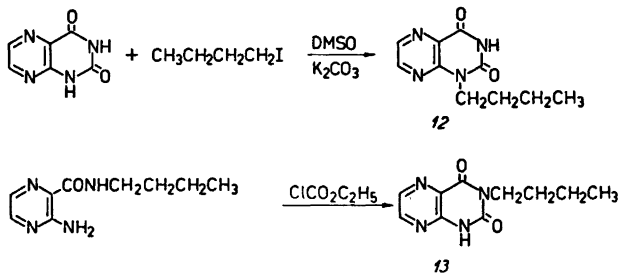
Analogously, reaction of 6-amino-2-thiouracil (*8*) with 1,2-dibromoethane gave solely the 2,3-dihydro-7-amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (*9*) (Scheme 3), formed also as the only product in the reaction of ethyl 2-carbethoxyacetimidate (*10*) and 2-amino-2-thiazoline. Nitrosation of *9*, followed by reduction, afforded 2,3-dihydro-6,7-diamino-5*H*-thi-



Scheme 1. *3 – 6 a*: R = H, *n* = 2; *b*: R = H, *n* = 3; *c*: R = CH_3, *n* = 2; *d*: R = CH_3, *n* = 3.



Scheme 3.



Scheme 4.

azolo[3,2-*a*]pyrimidin-5-one (*11*) convertible to *3a* upon reaction with glyoxal in hydrochloric acid.

Hydrolysis of *3* and *4* in aqueous alkali or acid resulted in opening of the thiazoline ring and formation of the 1- or 3-(ω-mercaptoalkyl)-lumazines (*5* and *6*) (Scheme 1). As model compounds 1- and 3-butyllumazine (*12* and *13*) were synthesized, the latter by an unambiguous route (Scheme 4).

Mass spectrometry. In a search for means of distinguishing between compounds of type *3* and *4*, their mass spectra were compared (Table 1). Conspicuously characteristic is the different character of the base peaks, consisting for compounds *3* of the molecular ions, and for compounds *4* of the $M^+ - CO$ ions.

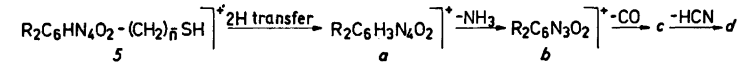
Mass spectrometric data for the hydrolysis products, *5* and *6*, and for the synthetic analogues, *12* and *13*, are listed in Table 2.

The typical fragmentation pattern of compounds of type *5* and of *13* analogous to the fragmentation pattern of 3-alkyluracils,[1,2] is shown in Scheme 5.

An alternative path for the 3-(3-mercaptopropyl)lumazines (*5b* and *5d*) produces ions one mass unit higher. A possible course of this fragmentation is outlined in Scheme 6. The unusual fragmentation, *i.e.* loss of the side chain with transfer of three hydrogen atoms and formation of the ion *e* was confirmed by high resolution mass spectrometry * on *5b*.

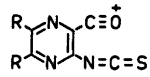
Contrary to the uracil series, the mass spectra of compounds *6* and *12* exhibit ions of the same type as outlined in Scheme 5 for compounds *5*. Significantly, however, *6* and *12* also fragment in a manner characteristic for type *6* compounds

* The author is indebted to Dr. Gustav Schroll, Department of General and Organic Chemistry, University of Copenhagen, for the high resolution mass spectral data.



Scheme 5.

Table 1. Relative intensities (in %) of the most abundant ions in the mass spectra of *3* and *4*.



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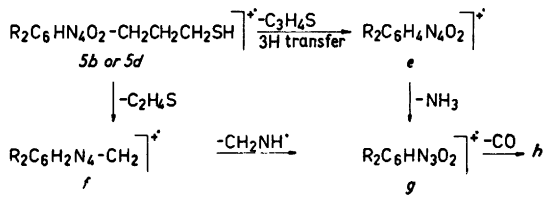
Comp.	M+	M+−CH_3	M+−CO	M+−CHO	M+−SH	Y	Y−CO	M+−CH_3CN	M+−CH_3CN−CO
3a	100		3	14		6	7		
3b	100	26	3	5	16	13	12		
3c	100					3	4	77	28
3d	100	24	4		15	16	10	39	56
4a	36		100	15					
4c	75		100	11			3		
4d	83		100	7	5	9		3	4

Table 2. Relative intensities (in %) of the most abundant ions in the mass spectra of *5*, *6*, *12*, and *13*.

Comp.	M+	M+−SH	*a*	*b*	*c*	*d*	*e*	*f*	*g*	*h/n*	*i*	*j*	*k*	*l*	*m*
5a	2		100	24	33	12									
5b	34	15	67	38	52	26	100	95	28	35	5			11	3
5c	12		100	15	36	4									
5d	55	23	80	19	49	9	39	100	21	51	3			9	9
13	46		100	42	44	21	11	48	15	19	7			8	3
6a	4		100	6	6	10					3	22	13	38	3
6c	29		100		6	4					3	31	21	22	20
6d	25	100	13	12	10	7	4	23		9	4	33	18	37	13
12	93		100	25	21	22	12	43	8	57	9	65	28	60	80

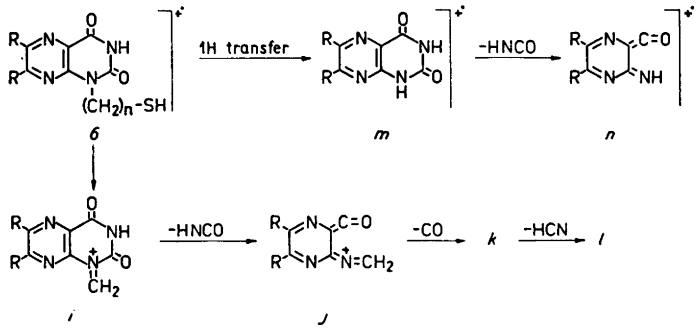


Scheme 6.

(Scheme 7). Thus, the ions *i*−*l*, particularly *j* and *k*, clearly identify them as originating from 1-substituted lumazines. Hence, the tricyclic compounds whence they derive must be thiazolo- or thiazino[3,2-*a*]pteridinones.

UV spectroscopy. The UV spectra of compounds *3* and *4* were recorded (see Experimental); a distinction between the two types of compounds on the basis of their UV spectra is hardly possible.

In Table 3, the UV spectra of the hydrolysis products *5* and *6* and of the two *N*-butyllumazines, *12* and *13*, in ethanol and in 0.1 N sodium hydroxide, respectively, are listed. The maxima at 330 nm are bathochromically displaced in base for both types of compounds, but in the 1-alkyllumazine series the displacement is only 5−10 nm, while the 3-alkyllumazines exhibit an alkali shift of 30−40 nm. These results are in agreement with previously reported data for



Scheme 7.

Table 3. UV spectra of the 1- or 3-substituted lumazines. $\lambda_{max}[\lambda_{infl}]$ nm (log ε).

Comp.	In EtOH				In 0.1 N NaOH			
5a	207(3.99)	234(4.12)		327(3.83)	219(4.44)	243(4.29)	270 (4.02)	364(3.79)
5b	206(4.00)	235(4.14)		325(3.48)	218(4.34)	243(4.26)	[267](4.01)	360(3.76)
5c	209(4.14)	236(4.13)		330(3.85)	220(4.48)	243(4.27)	272 (4.05)	364(3.86)
5d	209(4.18)	237(4.11)		331(3.96)	221(4.26)	245(4.31)	[270](4.09)	363(3.87)
13	206(3.96)	235(4.17)		327(3.84)	220(4.14)	248(4.22)	[270](3.94)	365(3.74)
6a	206(3.99)	237(4.11)		329(3.80)	218(4.34)	241(4.27)		338(3.75)
6c	210(4.15)	235(4.06)	250 (4.02)	332(3.92)	219(4.40)	243(4.32)		341(3.93)
6d	211(4.09)	235(4.03)	251 (3.98)	332(3.90)	224(4.17)	245(4.34)		341(3.96)
12	206(3.96)	236(4.12)	[250](3.96)	331(3.81)	218(4.38)	243(4.20)		338(3.80)

N-alkyluracils,[1,2] where a bathochromical shift in base was exhibited only by the 3-alkyl derivatives. Clearly, UV spectroscopy of the products formed by hydrolysis of the ring systems constitutes an efficient tool for structure assignment of compounds of type *3* and *4*.

EXPERIMENTAL

Melting points are uncorrected. Mass spectra were recorded with an LKB 9000 mass spectrometer fitted with an all-glass heated inlet system; an ionizing potential of 70 eV was used. UV spectra were recorded on a Unicam s.p. 820 recording spectrophotometer. Thin layer chromatography (TLC) were performed on silica gel (Merck) without fluorescence indicator; solvent system: butanol – acetic acid – water (4:1:5). Spots were visualized in UV light.

2,3-Dihydro-5H-thiazolo[2,3-b]pteridin-5-one (3a). To a refluxing suspension of $NaHCO_3$ (25.9 g) and 1,2-dibromoethane (87.2 g) in 2-propanol (210 ml) was added a solution of 13.9 g of 2-thiolumazine (*1*, R = H) and 3.1 g of NaOH in 750 ml of 60 % 2-propanol. The mixture was refluxed for 1 h and evaporated. The residue was suspended in 150 ml of water and the insoluble compound filtered off. Yield 7.71 g (50 %). After recrystallizations from DMF the m.p. was > 300 °C. Anal. $C_8H_6N_4OS$: C, H, N, S. UV [EtOH (log ε)]: 231(3.91), 261(4.05), 280(4.05), 232(3.80) nm.

2,3-Dihydro-1H,6H-thiazino[2,3-b]pteridin-6-one (3b). Reaction of 13.0 g of 2-thiolumazine and 44.1 ml of 1,3-dibromopropane in the same manner as described above for *3a* yielded, after treatment with water, a sticky compound. One recrystallization from DMF gave 4.77 g (30 %). After two recrystallizations from DMF the m.p. was 293 – 294 °C (dec.). Anal. $C_9H_8N_4OS$: C, H, N, S. UV [EtOH (log ε)]: 243(3.98), 295(4.15), 337(3.76) nm.

2,3-Dihydro-7,8-dimethyl-5H-thiazolo[2,3-b]-pteridin-5-one (3c) and 1,2-Dihydro-7,8-dimethyl-5H-thiazolo[3,2-a]pteridin-5-one (4c). To a refluxing suspension of 28.2 g of $NaHCO_3$ and 43.7 ml of 1,2-dibromoethane in 260 ml of 2-propanol was added a solution of 17.11 g of 6,7-dimethyl-2-thiolumazine [4] (*1*, R = CH_3) and 3.29 g of NaOH in 935 ml of 60 % 2-propanol. The mixture was refluxed for 1 h. The precipitate was filtered off and the filtrate evaporated. The residue was extracted with boiling EtOH. The EtOH was evaporated yielding 17.81 g (92 %) of a crude product, shown by TLC to consist of two compounds. The mixture was

recrystallized three times from DMF without achieving separation of the two components. Part of the recrystallized compound (3.80 g) was fractionated on an alumina column. Elution with $CHCl_3$ afforded 2.85 g of *3c* (m.p. 269–271 °C). Further elution with MeOH-$CHCl_3$ (1:3) gave 0.62 g of *4c*, m.p. > 300 °C. *3c*. Recrystallization from ethanolic DMF afforded pure *3c*, m.p. 271–272 °C (dec). Anal. $C_{10}H_{10}N_4OS$: C, H, N, S. TLC: $R_F = 0.33$. UV [EtOH (log ε)]: 248(4.04), 284(4.11), 327(388) nm. *4c*. Compound *4c* was recrystallized from ethanolic DMF; m.p. > 300 °C. Anal. $C_{10}H_{10}N_4OS$: C, H, N, S. TLC: $R_F = 0.17$. UV [EtOH (log ε)]: 225(4.12), 261(4.21), 334(4.01), 343(sh, 3.97) nm.

2,3-Dihydro-8,9-dimethyl-4H,6H-thiazino[2,3-b]pteridin-6-one (3d) *and 1,2-dihydro-8,9-dimethyl-3H,6H-thiazino[3,2-a]pteridin-6-one* (4d). To a refluxing suspension of 50.4 g of $NaHCO_3$ and 61.5 ml of 1,3-dibromopropane in 350 ml of 2-propanol was added, over a period of 3 h, a solution of 53.2 g of the sodium salt of 6,7-dimethyl-2-thiolumazine (*1*, R = CH_3) in 1250 ml of 50 % 2-propanol. The mixture was refluxed for 2 h, and cooled. The precipitate was filtered off, and the filtrate was evaporated. Water (200 ml) and chloroform (250 ml) were added to the residue. The layers were separated, and the aqueous phase was extracted with 150 ml of chloroform. The combined chloroform extracts were dried and evaporated. The residue was triturated with 200 ml of acetone yielding 19.1 g. The crude product was shown by TLC to consist of two compounds. R_F = 0.49 and $R_F = 0.35$. *3d*. Three recrystallizations from ethanol yielded *3d*, m.p. 227–229 °C (dec.) (68 % of the crude product). Anal. $C_{11}H_{12}N_4OS$: C, H, N, S. TLC: $R_F = 0.49$. UV [EtOH (log ε)]: 246(4.06), 295(4.18), 333(3.83) nm. *4d*. The crude product (14.7 g) was extracted with two 750 ml portions of boiling ethyl acetate yielding 1.74 g of an insoluble compound. The latter was fractionated on an alumina column. The column was eluted with ethyl acetate, mixtures of ethyl acetate and chloroform, and chloroform, in this order. The last fractions contained the isomer with $R_F = 0.35$. After recrystallisation from ethanol, 0.90 g of pure *4d* was obtained. M.p. 297–300 °C (dec.). Anal. $C_{11}H_{12}N_4OS$: C, H, N, S. UV [EtOH (log ε)]: 222(4.13), 261(4.16), 295(sh, 3.96), 325(4.06), 339(sh, 3.99) nm.

3-Chloro-N-(2-thiazolinyl)pyrazinecarboxamide (*7*). A suspension of 14.0 g of 3-hydroxypyrazinecarboxylic acid [5] in 100 ml of thionyl chloride and 0.5 ml of DMF was refluxed for 1 h. The dark solution obtained was evaporated. The residue was dissolved in 70 ml of dry $CHCl_3$ and added, over a period of 1 h, to a suspension of 25.5 g of 2-amino-2-thiazoline in 150 ml of $CHCl_3$. The temperature was kept at 10 °C during the addition. The mixture was stirred at room temperature for 2 h and the precipitate was collected, suspended in 100 ml of water, and stirred for 1 h at room temperature. The insoluble compound (10.3 g) was collected and washed with water. When the reaction mixture was left at room temperature for 2 days an additional crop (10.7 g) separated. The two portions were combined and recrystallized twice from ethanolic DMF yielding 15.1 g (62 %), m.p. 177–178 °C (dec.). Anal. $C_8H_7ClN_4OS$: C, H, Cl, N, S.

1,2-Dihydro-5H-thiazolo[3,2-a]pteridin-5-one (*4a*). A solution of 11.2 g of *7* in 50 ml of DMF was refluxed for 4 h. After cooling, the precipitate (8.14 g, 86 %) was collected and recrystallized twice from DMF. M.p. 258–260 °C. Anal. $C_8H_6N_4OS$: C, H, N, S. UV [EtOH (log ε)]: 221(4.11), 261(4.14), 288(sh, 3.76), 328(3.91), 345(sh, 3.81) nm.

2,3-Dihydro-7-amino-5H-thiazolo[3,2-a]pyrimidin-5-one (*9*). (*a*) In the same manner as described above for *3a*, 6-amino-2-thiouracil (*8*) (21.5 g) was reacted with 1,2-dibromoethane (80 ml). After treatment with water 14.0 g (56 %) was obtained. After two recrystallizations from ethanolic DMF, the m.p. was 274–277 °C. Anal. $C_6H_7N_3OS$: C, H, N, S. UV [EtOH (log ε)]: 223(4.19), 273(3.72) nm.

(*b*) A mixture of 3.45 g of 2-amino-2-thiazoline and 7.80 g of ethyl 2-carbethoxyacetimidate [6] in 50 ml of ethanol was stirred at room temperature for 2 h and then refluxed for 3 h. The mixture was cooled and the precipitate (2.28 g, 40 %) was collected. The filtrate was evaporated to half its volume and left at room temperature for several days when a further amount of compound had separated (2.41 g, 34 %). The two crops were combined and recrystallized from ethanolic DMF, yielding *9* m.p. 272–275 °C. The identity with the compound prepared above was established by IR, UV, and TLC.

2,3-Dihydro-6-nitroso-7-amino-5H-thiazolo-[3,2-a]pyrimidin-5-one. To a 35 °C warm solution of *9* (8.45 g) in 300 ml of 10 % acetic acid was added a solution of 3.80 g of $NaNO_2$ in 20 ml of water. The mixture was stirred at room temperature for 5 h. Yield 9.11 g (92 %). Recrystallizations of a small sample from DMF yielded a pure compound, m.p. 239–242 °C (dec.). Anal. $C_6H_6N_4O_2S$: C, H, N, S.

2,3-Dihydro-6,7-diamino-5H-thiazolo[3,2-a]-pyrimidin-5-one (*11*). To a suspension of 0.99 g of the nitroso compound in 30 ml of boiling water, sodium dithionite was added in small portions until the blue colour disappeared. After refluxing for a further 5 min the solution was cooled. Yield 0.54 g (58 %), m.p. 204–207 °C (dec.) (from water). Anal. $C_6H_6N_4OS$: C, H, N, S. UV [EtOH (log ε)]: 223(4.20), 295(3.85) nm.

2,3-Dihydro-5H-thiazolo[2,3-b]pteridin-5-one (3a) *from* 11 *and glyoxal*. Compound *11* (0.46 g) was dissolved in 4 ml of boiling 3 N HCl. The heating was discontinued, and 0.97 ml of a 30 % aqueous solution of glyoxal was added. The mixture was cooled, the precipitate (0.42

g, 82 %, m.p. > 300 °C) was collected and identified by IR, UV, and TLC as the previously synthesized *3a*.

3-(2-Mercaptoethyl)lumazine (5a). A suspension of 3.83 g of *3a* in 50 ml of 3 N NaOH was refluxed for 2 h. The solution obtained was acidified with HCl and the precipitate collected. Yield after one recrystallization from 40 % aqueous EtOH: 2.95 g (57 %), m.p. 212–213 °C. Anal. $C_8H_8N_4O_2S$: C, H, N, S.

3-(3-Mercaptopropyl)lumazine (5b). A suspension of 0.44 g of *3b* in 5 ml of 3 N NaOH was kept at 50 °C for 10 min. The mixture was stirred at room temperature for 2 h and the resulting solution was acidified. The precipitate (0.41 g, 86 %) was collected and recrystallized from EtOH. M.p. 192–194 °C. Anal. $C_9H_{10}N_4O_2S$: C, H, N, S.

3-(2-Mercaptoethyl)-6,7-dimethyllumazine (5c). The compound was prepared by hydrolysis of *3c* by the general procedure described above for *5a*. The yield was 93 %. After recrystallizations from aqueous EtOH, the m.p. was 258–262 °C. Anal. $C_{10}H_{12}N_4O_2S$: C, H, N, S.

3-(3-Mercaptopropyl)-6,7-dimethyllumazine (5d). A suspension of 0.30 g of *3d* in 10 ml of 3 N hydrochloric acid was refluxed for 1 h. The precipitate (0.28 g, 88 %, m.p. 221–223 °C) was recrystallized from ethanol without change in m.p. Anal. $C_{11}H_{14}N_4O_2S$: C, H, N, S.

1-(2-Mercaptoethyl)lumazine (6a). Hydrolysis of *4a* with 3 N NaOH yielded after acidification, 80 % of *6a*. After recrystallizations from EtOH the m.p. was 213–215 °C. Anal. $C_8H_8N_4O_2S$: C, H, N, S.

1-(3-Mercaptoethyl)-6,7-dimethyllumazine (6c). Hydrolysis of *4c* with 3 N NaOH yielded 84 %, m.p. 214–216 °C (from EtOH). Anal. $C_{10}H_{12}N_4O_2S$: C, H, N, S.

1-(3-Mercaptopropyl)-6,7-dimethyllumazine (6d). Hydrolysis of *4d* with 3 N NaOH yielded 77 %, m.p. 193–194 °C (from EtOH). Anal. $C_{11}H_{14}N_4O_2S$: C, H, N, S.

1-Butyllumazine (12). To a solution of 4.15 g of lumazine in 50 ml of DMSO was added 3.3 g of K_2CO_3, followed by 1.47 g of butyl iodide. The mixture was stirred at 90 °C for 3 h, cooled, and poured onto ice (100 g). The precipitate was removed and the filtrate acidified with HCl. Extraction with chloroform and evaporation of the chloroform yielded an oil, from which a solid compound could be isolated after trituration with water. The compound (1.13 g, 64 %) was recrystallized twice from acetonitrile. M.p. 174–176 °C (dec.). Anal. $C_{10}H_{12}N_4O_2$: C, H, N.

3-Amino-N-butylpyrazinecarboxamide. A suspension of 6.0 g of methyl 3-aminopyrazinecarboxylate [7] in 30 ml of butylamine was refluxed for 2.5 h. The solution was evaporated and the residue was recrystallized from ligroin (b.p. 80–110 °C). Yield 6.2 g (82 %), m.p. 56–57 °C. Anal. $C_9H_{14}N_4O$: C, H, N.

3-Butyllumazine (13). A solution of 6.2 g of 3-amino-*N*-butylpyrazinecarboxamide in 120 ml of ethyl chloroformate was refluxed for 7 h. The solution was evaporated, and the oily residue was added to a solution of 6.0 g of sodium in 300 ml of EtOH. The solution was refluxed for 4 h and evaporated. The residue was dissolved in 50 ml of water and acidified. The precipitate (6.1 g, 89 %) was recrystallized from EtOH. M.p. 214–215 °C (dec.). Anal. $C_{10}H_{12}N_4O_2$: C, H, N.

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