prolonged heating is to be avoided. The compounds are difficult to free from metals and also from moisture to which they cling tenaciously especially at the temperature (52°) at which it is practical to dry them.

Attempted preparation of 6,7-di-i-propyl-8-1'-D-ribityl)lumazine. When method A was employed starting with 4-(1'-D-ribitylamino)-5-nitroso-2,6-dihydroxypyrimidine and a 3-mole excess of 2,5-dimethyl-3,4-hexanedione the yield of 6,7-di-*i*-propyl-8-(1'-D-ribityl)lumazine (determined spectrophotometrically) was less than 2%. When the condensation was attempted at *p*H 9 the yield was again less than 2%. Similar results were obtained with the boric acid method described for the preparation of 6,7-di-*i*-propyl-8-methyllumazine.

6,7-Di-i-propyl-8-methyllumazine. To a hot solution of 393 mg. of 5-amino-4-methylamino-2,6-dihydroxypyrimidine in 20 ml. of water were added 0.7 ml. of 2,5-dimethyl-3,4-hexanedione, 23 ml. of ethanol, and 960 mg. of boric acid. The solution was heated at 80° for 45 min. The yield, determined spectrophotometrically, was 612 mg. (94%).

The solution was applied immediately to a column (2 cm. diameter) of 60 g. of acid-washed alumina prepared with absolute alcohol. The green, fluorescent pteridine was eluted with 95% ethanol. The eluate was evaporated under reduced pressure, the residue was dissolved in hot water, and upon chilling it deposited 260 mg. of yellow crystals (40%). The physical properties are summarized in Tables III and IV.

5,6,7,8-Tetrahydro-9-(1'-D-ribityl)isoalloxazine. The isoalloxazine derivative was prepared from 500 mg. of 4-(1'-D-ribitylamino)-5-nitroso-2,6-dihydroxypyrimidine and 380 mg. of 1,2-cyclohexanedione as outlined in Method B. After purification by column chromatography and transfer into and out of benzyl alcohol, the aqueous extracts were evaporated to *ca.* 2 ml. Addition of alcohol and chilling brought about the precipitation of 45 mg. (9%) of 5,6,7,8-tetrahydro-9-(1'-D-ribityl)isoalloxazine. The compound could be recrystallized from water; m.p. 261–263° dec. $\lambda_{max}^{0.1N\ H_2SO_4}$ 413 mμ (log ε 4.00), 309 mμ (3.75), 258 mμ (4.14); λ_{min} 338 mμ (3.28), 296 mμ (3.61), 233 mμ (3.85). $\lambda_{max}^{0.1N\ NaOH}$ 374 mμ (log ε 3.74), 317 mμ (4.39), 245 mμ (4.29); λ_{min} 343 mμ (3.53), 276 mμ (3.87), 225 mμ (4.05).

Anal. Calcd. for $C_{15}H_{20}O_6N_4$: C, 51.2; H, 5.7; N, 15.9. Found: C, 51.2; H, 5.7; N, 15.7.

6,7-Diphenyl-8-(1'-D-ribityl)lumazine. Method B was followed. After the material had been applied to a column of acid alumina and eluted with 50% ethanol, the eluate was evaporated to dryness. The residue was taken up in water and extracted with ether to remove excess benzil. The lumazine was then transferred into and out of benzyl alcohol. After evaporation of the water the material was dissolved in a small amount of dioxane and precipitated by addition of ether. The properties of the compound are summarized in Tables III and IV.

The preparation of 8-methyllumazines. To 4-methylamino-5-amino-2,6-dihydroxypyrimidine in water were added a 3- to 7-mole excess of α-diketone, a volume of ethanol equal to that of the water used, and a drop of 2*N* hydrochloric acid. The solution was refluxed 30–50 min., then cooled and evaporated under reduced pressure. The residue was taken up in ethanol or ethanol-water, applied to 50–70 g. of acid-washed alumina (prepared in absolute alcohol in a 2-cm. diameter column), and eluted with ethanol. The eluate was evaporated and the residue recrystallized. A summary of the properties is given in Tables III and IV.

Paper chromatography. The ascending method was used with Whatman No. 3 MM filter paper and Schleicher and Schuell No. 507, acid washed. Position of spots was determined by fluorescence and/or quenching under ultraviolet light. The red color of the nitrosopyrimidine derivatives could be detected in daylight. The composition of the solvent systems used for the development of the chromatograms were *n*-butyl alcohol:ethanol:water—50:15:36, water saturated with *t*-amyl alcohol, or *i*-butyric acid:*N* ammonia:0.1*M* ethylenediamine tetraacetate—100:60:1.6.[22]

Materials. Sugars of C. P. grade were purchased from Pfanstiehl Laboratories, Inc. The ion exchange resins Dowex AG 50 W X-8 (200–400 mesh) and Dowex AG 1 X-10 (200–400 mesh) and the acid-washed alumina were obtained from California Corp. for Biochemical Research. 3,4-Hexanedione, 4,5-octanedione, and 2,3-dimethyl-3,4-hexanedione were prepared by acyloin condensation of the appropriate esters[23] followed by oxidation of the ketol with cupric acetate.[24] The remaining diketones were purchased from Aldrich Chemical Co. and Eastman Kodak Co.

SALT LAKE CITY, UTAH

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4-Sulfanilamidopyridazines

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3,4,6-Trichloropyridazine (II) condenses in dimethylformamide solution with sulfanilamide or its acetyl derivative to give 4-sulfanilamido-3,6-dichloropyridazine (III) or its acetyl derivative (IV). The latter is dehalogenated and hydrolyzed to 4-sulfanilamidopyridazine (V). Replacement of one chlorine atom in IV gives 4-sulfanilamido-3(or 6)-hydroxy-6(or 3)-chloropyridazine (VIa or b) and 4-sulfanilamido-3(or 6)-methoxy-6(or 3)-chloropyridazine (VIIIa or b). VI (a or b) is dehalogenated to 4-sulfanilamido-3(or 6)-hydroxypyridazine (VIIa or b).

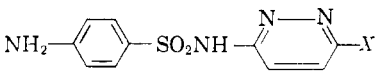
Rogers and English[1] and Druey *et al.*[2] described the synthesis of 3-sulfanilamido-6-chloropyridazine (Ia), an intermediate for the chemotherapeutically used 3-sulfanilamido-6-methoxypyridazine (Ib), from dichloropyridazine and sulfanilamide. 3-Sulfanilamidopyridazine (Ic) was obtained from Ia[3] and from 3-aminopyridazine.[4]

(1) U. S. Patent 2,671,086 (March 2, 1954); *Chem. Abstr.*, **49**, 1824 (1955).

(2) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

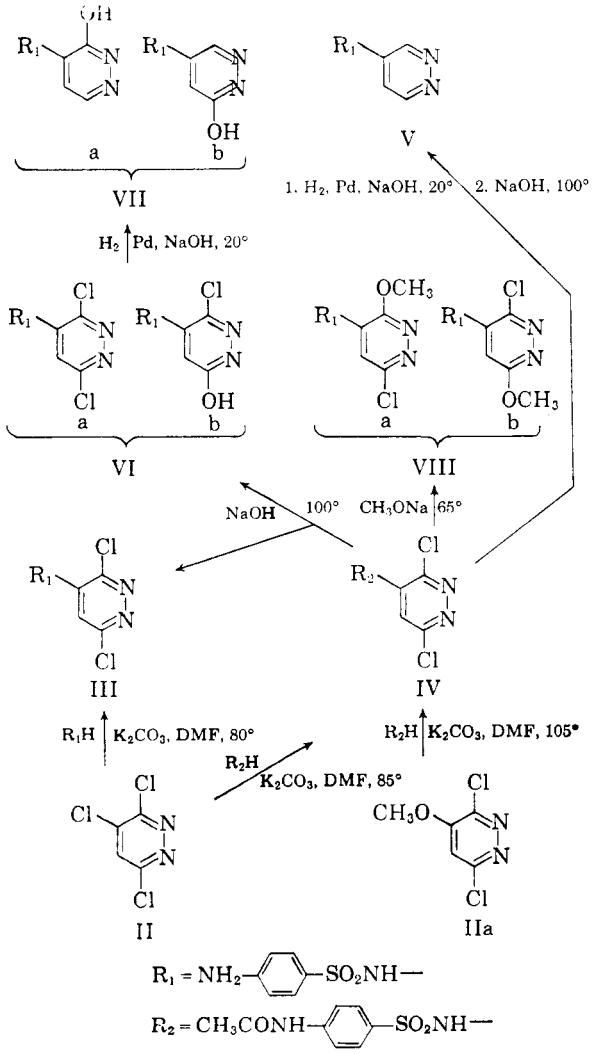
(3) J. H. Clark, J. P. English, G. R. Jansen, H. W. Marson, M. M. Rogers, and W. E. Taft, *J. Am. Chem. Soc.*, **80**, 980 (1958).

(4) C. Grundmann, *Ber.*, **81**, 1 (1948).



I.
a. $X = Cl$
b. $X = OCH_3$
c. $X = H$

In view of the therapeutic significance of 3-sulfanilamidopyridazines it was of interest to prepare the hitherto unknown 4-sulfanilamidopyridazine (V) and some of its derivatives. Melting 3,4,6-trichloropyridazine (II), which contains a highly reactive chlorine atom in position 4,[5,6] with sulfanilamide in the presence of potassium carbonate, failed to give 4-sulfanilamido-3,6-dichloropyridazine (III). We found, however, that when this reaction was performed in dimethylformamide (DMF) at 80°, the synthesis of III went smoothly.[7] The unexpected highly acidic properties of III caused initial difficulties in the isolation of this sulfonamide. This compound is soluble in an aqueous solution of sodium bicarbonate and is not precipitated by acetic acid, a property not often met in N_1-heterocyclic sulfonamides. Further 4-acetylsulfanilamide-3,6-dichloropyridazine (IV) was readily obtained from N_4-acetyl-sulfonamide, II and potassium carbonate in dimethylformamide solution at 80–85° in yields of 90%. IV was also obtained unexpectedly from 4-methoxy-3,6-dichloropyridazine (IIa), N_4-acetylsulfanilamide, potassium carbonate in dimethylformamide at 105°, which can serve as an unambiguous proof for the constitution of IV and of III.



Catalytic dehalogenation of IV, followed by saponification of the acetyl group results in 4-sulfanilamidopyridazine (V).

Boiling 4-acetylsulfanilamido-3,6-dichloropyridazine (IV) with aqueous sodium hydroxide yields 4-sulfanilamido-3(or 6)-hydroxy-6(or 3)-chloropyridazine (VIa or b),[8] and 4-sulfanilamido-3,6-dichloropyridazine (III) was isolated as a by-product. Catalytic dehalogenation of VI(a or b) yields 4-sulfanilamido-3(or 6)-hydroxypyridazine (VIIa or b).

The reaction of IV with sodium methoxide in boiling methanol gives 4-sulfanilamido-3(or 6)-methoxy-6(or 3)-chloropyridazine (VIIIa or b). Attempts to substitute the second chlorine atom proved unsuccessful. Heating IV for six hours with an excess of sodium methoxide in methanol to 130° in an autoclave resulted in the formation of VIII (a or b) and an amorphous substance insoluble in methanol.

The bacteriostatic activities *in vitro* against *streptococcus hemolyticus* and *staphylococcus aureus* of the sulfonamides V, VI (a or b), VII (a or b), and VIII (a or b) were not as high as the activity of 3-sulfanilamido-6-methoxypyridazine (Ib).

EXPERIMENTAL

All melting points were determined on a calibrated Fischer-Johns block. 3,4,6-Trichloropyridazine[9] was prepared according to Mizzoni and Spoerri[10] and 4-methoxy-3,6-

(5) K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta*, **39**, 1756 (1956).

(6) Tsukasu Kuraishi, *Chem. and Pharm. Bull.*, **4**, 137 (1956).

(7) The macrocyclic polysulfonamide *N,N'*-ditosyl-*N,N'*-alkylenebenzidine has been prepared from *N,N'*-ditosylbenzidine, alkylene bromides and potassium carbonate in dimethylformamide. [Hermann Stetter and Ernst Egon Roos, *Ber.*, **88**, 1390 (1955).]

(8) Tsukasu Kuraishi (*Chem. and Pharm. Bull.*, **6**, 331 (1958)) has prepared 4-amino-3-hydroxy-6-chloropyridazine and established its constitution. Condensation of this compound with *p*-acetylaminobenzenesulfonyl chloride should give 4-acetylsulfanilamido-3-hydroxy-6-chloropyridazine, and its saponification should result in 4-sulfanilamido-3-hydroxy-6-chloropyridazine (VIa). A comparison of VIa with compound VIa or b described in this paper could establish the structure of the latter; however the danger of contracting chronic eczema prevented the execution of these experiments.

(9) 3,4,6-Trichloropyridazine causes extended eczema and great care should be taken in handling it. (J. Druey, *Angew. Chem.*, **70**, 9 (1958).

(10) R. H. Mizzoni and P. E. Spoerri, *J. Amer. Chem. Soc.*, **76**, 2201 (1954).

dichloropyridazine according to Eichenberger *et al.*[5] All substances were dried over phosphorus pentoxide at 0.1–0.2 mm. and 80–106°. C,H- and S- analyses were obtained from the microanalytical laboratory of the Weizmann Institute of Science, Rehovoth, and Cl-determinations from Mr. Rosenfeld of this laboratory.

4-Sulfanilamido-3,6-dichloropyridazine (III). To a well stirred solution of 7.3 g. of trichloropyridazine (II) (0.04 mole) and 9.5 g. of sulfanilamide (0.055 mole) in 80 ml. of dimethylformamide was added 20.7 g. of potassium carbonate and the mixture stirred for 1 hr. at 80° (bath temperature) while moisture was excluded. The salts were filtered from the hot dimethylformamide solution and washed with dimethylformamide. The solvent was removed from the combined filtrates *in vacuo* on a water bath. The syrupy residue was digested with three portions of ether, which were discarded. The syrup was dissolved in 100 ml. of water and adjusted to *p*H 4.5 by means of *N* hydrochloric acid. The precipitate containing excess sulfanilamide was filtered and discarded. The filtrate was then adjusted with a further quantity of *N* hydrochloric acid to *p*H 2–1.8. The precipitate was filtered, washed and dried yielding 5 g. of crude III, m.p. 188–190°. It was twice crystallized from 90% aqueous methanol (1 g./20 ml.) giving 3.2 g. of pale yellow crystals, m.p. 200–201°.

Anal. Calcd. for $C_{10}H_8Cl_2N_4O_2S$: C, 37.6; H, 2.53; Cl, 22.5; S, 10.05. Found: C, 38.04; H, 2.89; Cl, 22.26; S, 10.36.

4-Acetylsulfonamido-3,6-dichloropyridazine (IV). A. *From 2,4,6-trichloropyridazine* (II). To a well stirred solution of 30 g. of 2,4,6-trichloropyridazine (II) (0.16 mole) and 46.2 g. of acetylsulfanilamide (0.22 mole) in 210 ml. of dimethylformamide was added 82 g. of potassium carbonate. The mixture was heated under exclusion of moisture for 1 hr. at 80° (bath temperature) and for another hour at 85°. The salts were filtered from the hot dimethylformamide solution and washed with dimethylformamide. The solvent was removed *in vacuo*. The residue, a yellowish syrup, was digested three times with ether, dissolved in 250 ml. of water, and allowed to stand overnight in the ice box. The solution was seeded with acetylsulfanilamide; after scratching and cooling, the excess of acetylsulfanilamide (6.5 g.) was filtered. IV was precipitated from the filtrate with hydrochloric acid, filtered, and repeatedly washed with water and ether, yielding 60 g. of crude IV. The crude product was stirred and boiled under reflux for 1 hr. with 1200 ml. of methanol, cooled, filtered, washed with methanol, and dried, giving 52 g. of a white powder, almost pure IV, m.p. 255–258° dec.

The analytical sample, white crystals m.p. 255–260° dec. was obtained by crystallizing this product twice from acetone (1 g./30 ml.).

Anal. Calcd. for $C_{12}H_{10}N_4O_3SCl_2$: C, 39.86; H, 2.79; Cl, 19.66. Found: C, 39.88; H, 2.88; Cl, 19.23.

B. *From 4-methoxy-3,6-dichloropyridazine* (IIa). To a well stirred solution of 3.5 g. of 4-methoxy-3,6-dichloropyridazine (IIa) and 5.8 g. of acetylsulfanilamide in 20 ml. of dimethylformamide was added 10 g. of potassium carbonate and the mixture heated for 3 hr. at 105° (bath temperature). Potassium carbonate was filtered from the hot mixture and washed with dimethylformamide. The solvent was removed *in vacuo*, the residue digested with ether, and the syrup dissolved in 40 ml. of water. In the manner described in the previous experiment 0.4 g. of acetylsulfanilamide was recovered and 3.5 g. of crude IV was precipitated with hydrochloric acid. This was redissolved in sodium bicarbonate solution and reprecipitated with hydrochloric acid, giving 2.4 g. of a white crystalline powder, m.p. 248–250°. A crystallization from acetone raised the m.p. to 257° dec.

Anal. Found: Cl, 19.66.

The melting point of a mixture with the material prepared from trichloropyridazine (II) was not depressed.

4-Sulfanilamido-3(or 6)-hydroxy-6(or 3)-chloropyridazine (VIa or b). A solution of 11.5 g. of 4-acetylsulfanilamido-3,6-dichloropyridazine (IV) (0.032 mole) in 85 ml. of 2*N* aqueous sodium hydroxide solution was boiled for 3 hr. under reflux and the filtered solution adjusted with diluted acetic acid to *p*H 4.6. The precipitate was filtered, washed, and dried, giving 7.4 g. of a white powder. The crude product was boiled with 75 ml. of methanol under reflux, cooled, and filtered, leaving behind a residue of 6.3 g. of VI (a or b), which was crystallized twice from dimethylformamide methanol (1:1) yielding 4.3 g. white crystals, m.p. 262–265°.

Anal. Calcd. for $C_{10}H_9ClN_4O_3S$: C, 39.90; H, 3.02; Cl, 11.8. Found: C, 39.98; H, 3.21; Cl, 11.94.

The methanol filtrate gave on evaporation 0.8 g. of a yellowish substance m.p. 190°. This was crystallized twice from 60% aqueous acetone, giving crystals, m.p. 200°, identical with 4-sulfanilamido-3,6-dichloropyridazine (III).

Anal. Found: Cl, 22.0.

4-Sulfanilamido-3(or 6)-methoxy-6(or 3)-chloropyridazine (VIIIa or b). 4-Acetylsulfonamido-3,6-dichloropyridazine (IV) (10.8 g., 0.03 mole) was added to 130 ml. of 1.25*N* sodium methoxide–methanol solution and boiled under reflux for 8 hr. The solution was evaporated on the steam bath, the residue dissolved in water, the sulfonamide precipitated with acetic acid at *p*H 4.6, dissolved in sodium carbonate solution and reprecipitated, giving 8 g. of a pale yellow powder, m.p. 195–198°. The methanol solution of the sulfonamide was boiled with charcoal, filtered and concentrated to 40 ml., from which was obtained 7 g. of crystals m.p. 200°. A second crystallization from methanol did not raise the melting point.

Anal. Calcd. for $C_{11}H_{11}ClN_4O_3S$: C, 41.96; H, 3.53; Cl, 11.20. Found: C, 42.02; H, 3.64; Cl, 10.64.

4-Sulfanilamidopyridazine (V). To the solution of 2.5 g. of 4-acetylsulfanilamido-3,6-dichloropyridazine (II) in 60 ml. 0.5*N* sodium hydroxide was added 1.5 g. of 10% palladium on charcoal, previously reduced. The mixture was shaken for 5 hr. with hydrogen at a pressure of 4 atm. The catalyst was filtered and the crude acetyl V, weighing 2 g., precipitated at *p*H 4.6. This material (1.7 g.) was warmed with 9.5 ml. of 2*N* sodium hydroxide on a boiling water bath for 3 hr., 10 ml. of water was added and 1.5 g. of sulfonamide precipitated with acetic acid at *p*H 4.6. This was crystallized twice by dissolving in 4 ml. of hot dimethylformamide and adding 4 ml. of hot methanol, which gave colorless crystals m.p. 260–261°.

Anal. Calcd. for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.03; S, 12.08. Found: C, 48.05; H, 4.08; S, 12.54.

4-Sulfanilamido-3(or 6)-hydroxypyridazine (VIIa or b). Prereduced 10% palladium on charcoal (2.2 g.) was added to a solution of 3.8 g. of 4-sulfanilamido-3(or 6)-hydroxy-6(or 3)-chloropyridazine (VIa or b) in 100 ml. of 0.4*N* sodium hydroxide and shaken for 5 hr. with hydrogen at a pressure of 4 atm. hydrogen. The solution was filtered from the catalyst and acidified with diluted acetic acid giving 2.8 g. of almost pure VIIa or b. This was crystallized twice from methanol yielding 2 g. of colorless crystals, m.p. 240–242°.

Anal. Calcd. for $C_{10}H_{10}N_4O_3S$: C, 45.06; H, 3.79; S, 12.01. Found: C, 45.23; H, 3.93; S, 11.93.

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