[1]Benzopyrano[3,4-*d*]pyrimidines and [1]Benzothiopyrano[3,4-*d*]pyrimidines. Two New Heterocyclic Ring Systems (1)

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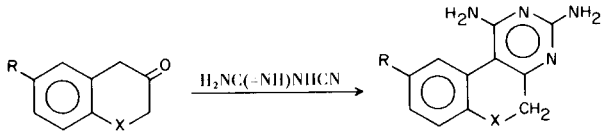
In a recent paper (2), condensation of 2-tetralone with cyanoguanidine under fusion conditions was shown to give 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (**1a**) exclusively. That the product was angular rather than linear in structure was proved by alternative, unequivocal synthesis from 1-cyano-3,4-dihydro-2-methoxynaphthalene, and also by dehydrogenation with selenium dioxide. Compound **1a** is but one of a larger number of tricyclic 2,4-diaminopyrimidine ring systems that can be viewed as conformationally rigid analogs of the antimalarial drug pyrimethamine (3,4). As part of a continuing search for new dihydrofolate reductase inhibitors and antimalarial agents, we were interested in modifications of **1a** involving replacement of the 6-CH_2 group by a polar atom. In this note, we should like to report the synthesis of oxygen and sulfur analogs **1b-1d** *via* the cyanoguanidine condensation route. To our knowledge, these are the first reported examples of the [1]benzopyrano[3,4-*d*]pyrimidine and [1]benzothiopyrano[3,4-*d*]pyrimidine ring systems (5).



1a, X = CH_2, R = H
1b, X = O, R = H
1c, X = O, R = Cl
1d, X = S, R = H

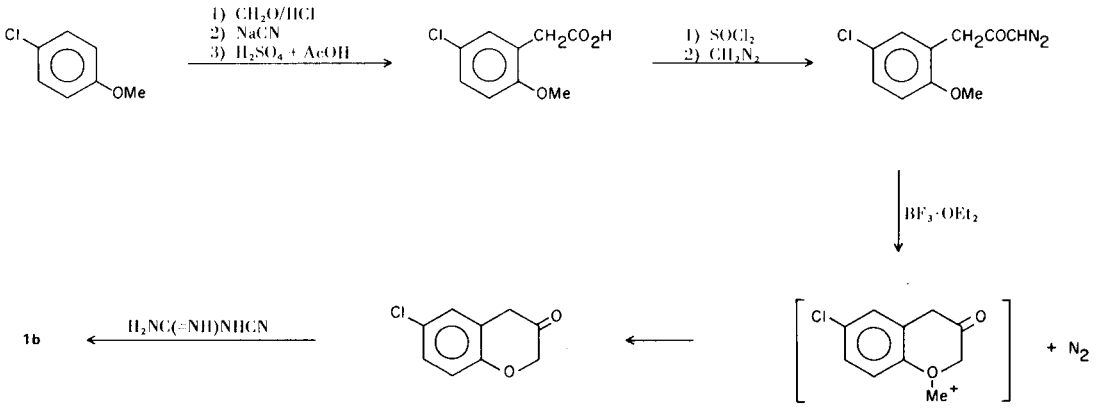
Chroman-3-one, the ketone precursor required for the synthesis of **1b** *via* the above reaction, was prepared from 1-diazo-3-(*o*-anisyl)-2-propanone and boron trifluoride etherate according to Scheffer and Moore (6). Thiochroman-3-one was obtained by the recently described method of Lumma and Berchtold (7,8) which involves Dieckmann cyclization of ethyl *o*-(carbethoxymethylthio)phenylacetate with sodium hydride in tetrahydrofuran, followed by acid hydrolysis and decarboxylation. 6-Chlorochroman-3-one, an unknown compound prior to this work, was synthesized from 5-chloro-2-methoxyphenylacetic acid (9) *via* the six-step sequence shown in Chart I. The 20% overall yield of 6-chlorochroman-3-one approximated that of chroman-3-one itself, indicating that the electron-withdrawing effect of the aromatic chlorine substituent is not large enough to impede oxonium salt formation in the cyclization step.

Preliminary experiments involving condensation of chroman-3-one with cyanoguanidine under simple fusion conditions (10) proceeded only in low yield and with extensive decomposition. Some improvement in the appearance of the crude product was noted when dimethylformamide was added as a solvent, but after column chromatographic purification on silica gel, the final yield of **1b** was still only 8%. Similar results were obtained with 6-chlorochroman-3-one, the yield of purified **1c** being 11%. The major portion of the product appeared to consist of neutral tars resulting from polymerization of the starting ketones.

In striking contrast to the behavior of the chroman-3-ones, the reaction of thiochroman-3-one proceeded cleanly and afforded a 54% yield of **1d**. In this case, a modified procedure involving addition of morpholine and *p*-toluenesulfonic acid to the reaction mixture was used. This approach was selected on the basis of an earlier observation (11) that enamines of ketones and aldehydes sometimes react more satisfactorily with cyanoguanidine than the carbonyl compounds themselves. In the present instance, the morpholine enamine of thiochroman-3-one was presumably generated *in situ*, but isolation of the intermediate was not attempted. Extension of this enamine modification to the reaction of 6-chlorochroman-3-one failed to raise the yield of **1c**.

A reasonable interpretation of the above findings can be made on the basis of the spectral properties of chroman-3-one and thiochroman-3-one. The electron-withdrawing effect of oxygen upon the adjacent methylene group should be much greater than the effect of sulfur, in accord with the relative positions of these atoms in the periodic table. This is supported by the nmr chemical shifts of the $ArOCH_2CO$- protons in chroman-3-one (τ 5.68) (6) and the $ArSCH_2CO$- protons in thiochroman-3-one (τ 6.45) (7). The strong $\delta^-O-CH_2\delta^+$ dipole in chroman-3-one

CHART I



should oppose polarization of the carbonyl double bond to a greater extent than the $\delta-S-CH_2\delta+$ dipole in thiochroman-3-one, and the infrared data suggest that this is indeed the case. The carbonyl band of chroman-3-ones appears at a frequency of 1730 cm^{-1}, while that of thiochroman-3-one and 2-tetralone occurs at about 1720 cm^{-1}. Thus, thiochroman-3-one ought to resemble 2-tetralone with respect to the reactivity of its keto group (12), whereas chroman-3-one might be expected to behave somewhat differently.

ULTRAVIOLET ABSORPTION SPECTRA OF CH_2CH_2-, OCH_2-, AND SCH_2-BRIDGED 2,4-DIAMINO-5-PHENYLPYRIMIDINE ANALOGS IN 95% ETHANOL

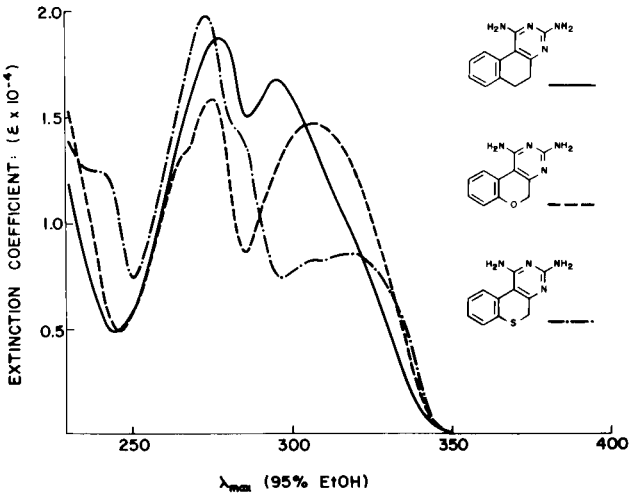


Figure 1.

As indicated in Figure 1, replacement of the 6-CH_2 group in **1a** by oxygen and sulfur causes interesting changes in the ultraviolet absorption spectrum. These are apparently due to a combination of two separate effects: 1) resonance interaction of unshared oxygen and sulfur electrons with the phenyl ring, and 2) variations in molecular geometry stemming from changes in bond lengths and bond angles in the $X-CH_2$ bridge. It is important to note that the fundamental two-peak pattern, with a conjugation band in the 300 mμ region, which is characteristic of **1a** and other types of 2,4-diamino-5-phenylpyrimidine derivatives, is also present in the spectra of **1b** and **1d**. This indicates clearly that condensation with cyanoguanidine takes place at the 4-position of chroman-3-one and thiochroman-3-one, and not at the 2-position (13). The lower-wavelength band in the spectra of **1a-1d** appears to be relatively insensitive to the change from a methylene group to a polar atom. This band probably does not involve conjugation of the unshared electron pairs on oxygen or sulfur with the π-orbital system, since such an interaction would produce a bathochromic shift rather than the small hypsochromic shift actually observed. The longer-wavelength band, on the other hand, undergoes a bathochromic displacement relative to **1a** (11 mμ for **1b** and 24 mμ for **1d**) suggesting some resonance interaction of unshared oxygen and sulfur electrons with the adjacent π-electron system. The substantial loss of intensity of this band in the case of **1d** may indicate distortion of the bridged biphenyl-like chromophore stemming from the large size of the sulfur atom.

In summary, analysis of the ultraviolet spectral data of **1b-1d** provides further support for the view that chroman-3-one and thiochroman-3-one should behave like 2-tetralone (2) in condensing with cyanoguanidine at the more resonance-stabilized benzylic carbon.

EXPERIMENTAL (14)

6-Chlorochroman-3-one.

A mixture of 5-chloro-2-methoxyphenylacetic acid (9) (8.0 g., 0.040 mole) and thionyl chloride (8 ml.) was stirred under reflux for 1 hour. After removal of excess thionyl chloride under reduced pressure, trituration with benzene (20 ml.) and fractional distillation gave 8.0 g. (91%) of 5-chloro-2-methoxyphenylacetyl chloride, b.p. 114-118° (0.5 mm.). A solution of this acid chloride in ether (20 ml.) was added dropwise with stirring to an ether solution of diazomethane (prepared from 45 g. of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) (15), and the reaction mixture was kept at room temperature for 18 hours. The light yellow solution of diazoketone was poured gradually (15 minutes) into a solution of boron trifluoride etherate (16 g.) in ether (200 ml.) with stirring and ice-bath cooling. The mixture was washed with water (2 x 100 ml.) and then 3% sodium bicarbonate (2 x 100 ml.), rinsed with water, dried over sodium sulfate and sodium carbonate overnight, and evaporated to dryness. Fractional distillation of the combined crude product from two parallel runs gave 6.0 g. (20% overall yield) of light yellow liquid, b.p. 115-120° (0.1 mm.), solidifying in the receiver upon refrigeration; ν max (potassium chloride) 3450, 1730 (C=O), 1480, 1250 (C–O), 1040, 830 cm^{-1}.

Anal. Calcd. for $C_9H_7ClO_2$: C, 59.20; H, 3.87. Found: C, 59.21; H, 3.80.

1,3-Diamino-5*H*-[1]benzopyrano[3,4-*d*]pyrimidine (**1b**).

A mixture of chroman-3-one (1.0 g., 0.0068 mole), cyanoguanidine (1.0 g., 0.012 mole), and dimethylformamide (1 ml.) was stirred under nitrogen for 1 hour while being heated gradually to 180-190° (oil bath temperature). After slight cooling, ice (10 g.) was added, the reaction mixture was stirred with a spatula until all lumps were broken up, and the solid was filtered and washed with water (3 x 20 ml.). Recrystallization of the dried solid from ethanol gave 1.2 g. of crude **1b**. A 1 g. portion of this was dissolved in dimethylformamide (5 ml.) and placed on a silica gel column (3 x 35 cm.), which was washed successively with chloroform (500 ml.) and ether (500 ml.) to remove dark-colored impurities. The column was then eluted with 4:1 ether-ethanol (1000 ml.), the product being monitored by ultraviolet absorption; further elution with absolute ethanol extracted no additional material. Evaporation of the ether-ethanol eluate to dryness and recrystallization of the resulting yellow powder from ethanol (charcoal) gave 0.12 g. (8%) of colorless prisms, m.p. 232-233° dec.; ν max (potassium chloride) 3450, 3230, 1650, 1570, 1480, 1210, 750 cm^{-1}; λ max (ethanol) mμ (ϵ x 10^{-3}) 266 (12.7, infl.), 275 (15.7), 306 (14.5).

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.86; H, 4.65; N, 26.22.

1,3-Diamino-9-chloro-5*H*-[1]benzopyrano[3,4-*d*]pyrimidine (**1c**).

The reaction of 6-chlorochroman-3-one (1.0 g., 0.0054 mole) and cyanoguanidine (1.0 g., 0.012 mole) in dimethylformamide (3 ml.) was carried out as described for **1b**. Purification of the crude product by the same procedure of silica gel chromatography used for **1b** and crystallization from ethanol gave 0.15 g. (11%) of pale yellow prisms, m.p. 250-251° dec.; ν max (potassium chloride) 3500, 3380, 3250, 1640, 1580, 1450, 1210, 820 cm^{-1}; λ max (ethanol) mμ (ϵ x 10^{-3}) 246 (9.3, infl.), 270 (12.9, infl.), 278 (15.4), 318 (15.7).

Anal. Calcd. for $C_{11}H_9ClN_4O$: C, 53.13; H, 3.65; N, 22.53. Found: C, 53.16; H, 3.71; N, 22.25.

1,3-Diamino-5*H*-[1]benzothiopyrano[3,4-*d*]pyrimidine (**1d**).

A mixture of thiochroman-3-one (1.0 g., 0.0061 mole), cyanoguanidine (1.0 g., 0.012 mole), dimethylformamide (2 ml.), morpholine (8 ml.), and *p*-toluenesulfonic acid (10 mg.) was stirred at 120-130° (internal) for 24 hours. The condenser was then removed and the mixture heated slowly to 190-200° (oil bath temperature) for 1 hour. After slight cooling, the contents of the flask were poured into ice water (30 ml.), and the solid was collected and washed with water. The dried brown powder was treated with warm dimethylformamide (10 ml.), and the insoluble portion was filtered off, washed with hot 95% ethanol (30 ml.), and dried, yield 0.55 g., m.p. 270-272° dec. The combined dimethylformamide solution and ethanol wash were concentrated and placed on a silica gel column (3.5 x 30 cm.), which was washed successively with chloroform (500 ml.), 1:1 chloroform-ether (500 ml.), and ether (500 ml.), and then eluted with 4:1 ether-ethanol (500 ml.). Recrystallization of the evaporated ether-ethanol eluate from ethanol (charcoal) gave another 0.2 g. of analytically pure colorless plates, m.p. 268-270° dec.; ν max (potassium chloride) 3350, 3210, 1650, 1640, 1570, 1560, 1430, 770 cm^{-1}; λ max (ethanol) mμ (ϵ x 10^{-3}) 240 (12.8, infl.), 273 (19.8), 284 (13.2, infl.), 311 (8.1, infl.), 320 (8.3). The total yield was 0.75 g. (54%).

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33. Found: C, 57.50; H, 4.45; N, 24.45.

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(1) This investigation was supported in part by Research Contract DA-49-193-MD-3008 from the U. S. Army Medical Research and Development Command, Office of the Surgeon General, and Research Career Development Award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. This is publication No. 701 from the Army Research Program on Malaria.

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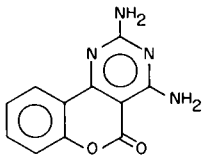

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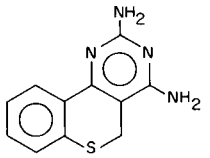

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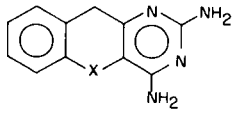
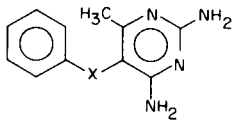
(12) In agreement with this interpretation, yields of **1a** from 2-tetralone are found to be comparable to those of **1d** from thiachroman-3-one (S. K. Sengupta, private communication; see also reference 10a).

(13) Cyclization at the 2-position would give derivatives of the unknown 10*H*-[1]benzopyrano[3,2-*d*]pyrimidine and 10*H*-[1]-benzothiopyrano[3,2-*d*]pyrimidine ring systems. The products, **i** and **ii**, would be expected to display ultraviolet absorption characteristics resembling those of 6-alkyl-2,4-diamino-5-phenoxypyrimidines and 6-alkyl-2,4-diamino-5-phenylthiopyrimidines. The longest wavelength band of 2,4-diamino-6-methyl-5-phenoxypyrimidine (**iii**) occurs at 287.5 mμ [E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Am. Chem. Soc.*, 73, 3753 (1951)], while that of 2,4-diamino-6-methyl-5-phenylthiopyrimidine (**iv**) is shifted to 289 mμ [E. A. Falco, B. Roth, and G. H. Hitchings, *J. Org. Chem.*, 26, 1143 (1961)]. The clear divergence between these values and the maxima observed with **1b-1d** constitutes indirect proof for the angular nature of our products.



i (X = O)
ii (X = S)



iii (X = O)
iv (X = S)

(14) Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were measured with a Perkin-Elmer Model 137B double beam recording spectrophotometer. Melting points were taken in Pyrex capillary tubes in a modified Wagner-Meyer apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, 10, 584 (1938)]. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

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