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Cinnoline Chemistry. IX. 5-, 6-, 7- and 8-Halogen Substituted 4-Mercaptocinnolines and Related Compounds (1).

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A series of 4-mercaptocinnolines (4) monosubstituted with halogen in the benzenoid ring was obtained when the corresponding 4-hydroxycinnolines were treated with phosphorus pentasulfide in either pyridine or toluene. On prolonged heating in either or the two solvents, the halogen atom in 6-chloro- and 6-bromo-4-hydroxycinnoline was simultaneously substituted with a mercapto group, thus yielding 4,6-dimercaptocinnoline. Nucleophilic substitution of the halogen atom was also observed in the reaction of 6-fluoro- and 7-fluoro-4-hydroxycinnoline, while 8-halo-4-hydroxycinnoline gave exclusively 8-halo-4-mercaptocinnoline. From the reaction of 5-halo-4-hydroxycinnoline the only identified products were 5-halo-4-mercaptocinnolines. Previously unknown 4-hydroxycinnolines were synthesized. 4-Alkylmercaptocinnolines and 4,6-dialkylmercaptocinnolines of pharmacological interest were prepared from the parent mercaptocinnoline or from the corresponding chlorocinnoline.

The nucleophilic displacement of halogens in heteroaromatic compounds with phosphorus pentasulfide was recently reported (5). In certain instances this same nucleophilic displacement of halogen in the benzenoid portion of the cinnoline ring has been observed. The electron density in the 5-, 6-, 7- and 8-positions of cinnoline is high compared to the electron density at the carbon atoms in the nitrogen containing ring (6), and only a very few examples of nucleophilic substitution reactions are known to occur in the benzenoid ring of cinnolines. The Bücherer reaction has been used in the synthesis of aminocinnolines (7), and the exchange of bromine atoms and nitro groups with chlorine has been demonstrated. Thus, 4,6-dichloro- and 4,6,7-trichlorocinnoline were formed when 6-bromo-4-hydroxycinnoline (8) and 6-nitro-7-chloro-4-hydroxycinnoline (9), respectively, were allowed to react with a mixture of phosphoryl chloride and phosphorus pentachloride at elevated temperatures. The difficulty in avoiding this exchange was demonstrated in this laboratory, since a series of 6-bromo-4-alkylthiocinnolines prepared from 6-bromo-4-hydroxycinnoline (10) via 6-bromo-4-chlorocinnoline all showed high carbon and hydrogen content, indicating that some of the bromine had been substituted with chlorine.

Likewise, it was found that treatment of 6-bromo- (III) and 6-chloro-4-hydroxycinnoline (I) (10) with phosphorus pentasulfide in refluxing pyridine for 3 hours gave high yields of 4,6-dimercaptocinnoline (II). When 6-fluoro-4-hydroxycinnoline (IV) was treated in the same manner, partial degradation of the organic material occurred, and only a small amount of 4,6-dimercaptocinnoline (II) could be isolated together with some 6-fluoro-4-mercaptocinnoline (V).

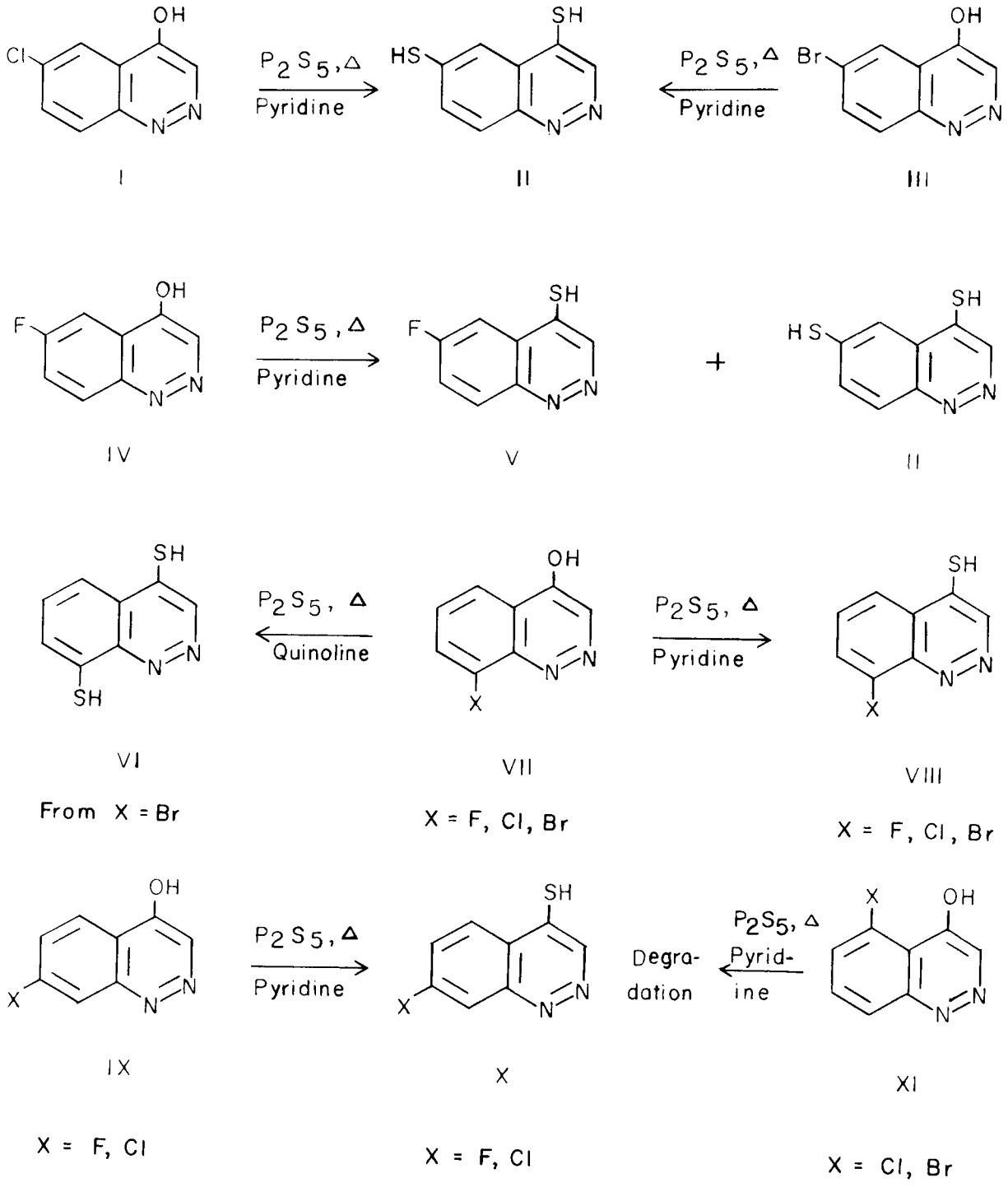
When 4-hydroxycinnoline substituted with fluorine, chlorine or bromide in the 8-position (VII) was treated with phosphorus pentasulfide in pyridine solution, only the corresponding 8-halo-4-mercaptocinnoline (VIII) could be isolated. In the hope that higher temperatures would promote the substitution of the halogen atom, 8-bromo-4-hydroxycinnoline was allowed to react with phosphorus pentasulfide in refluxing quinoline for 10 hours. From the reaction mixture was isolated a dark brown solid which decomposed above 360° and contained 29.3% sulfur. (4,8-Dimercaptocinnoline (VI) requires 33.0% S.) All attempts to purify this material have been unsuccessful. The infrared spectrum of the material was not informative.

Treatment of 7-fluoro- and 7-chloro-4-hydroxycinnoline (IX) with phosphorus pentasulfide in dry pyridine solution under reflux for 3-6 hours gave 7-fluoro- and 7-chloro-4-mercaptocinnoline (X). A similar treatment of 5-chloro- and 5-bromo-4-hydroxycinnoline (XI) resulted in complete degradation of the organic material.

In order to prepare 6-fluoro-, 6-chloro- and 6-bromo-4-mercaptocinnoline by allowing the corresponding 4-hydroxycinnoline to react with phosphorus pentasulfide, toluene replaced pyridine as the solvent. Even under these conditions a large amount of 4,6-dimercaptocinnoline (II) was formed from 6-chloro- and 6-bromo-4-hydroxycinnoline (XII) together with some monomercapto compound. 6-Fluoro-4-mercaptocinnoline (V) was formed in good yield from 6-fluoro-4-hydroxycinnoline (IV) by heating for 6 hours in dry toluene.

By the same procedure 5-chloro-, 6-chloro-, 8-fluoro-, 8-chloro- and 8-bromo-4-mercaptocinnolines were obtained. In these cases no displacement of the halogen atom was observed. 7-Fluoro-4-mercaptocinnoline (XV) was also obtained in good yield by this method, but a small amount of 4,7-dimercaptocinnoline (XVI) could be isolated from one such synthesis. The formation of 4,7-dimercaptocinnoline was not observed when 7-chloro-4-hydroxycinnoline was treated with phosphorus pentasulfide in toluene. Likewise, in pyridine solution neither fluorine nor chlorine were displaced in the 7-position. 7-Bromo-4-hydroxycinnoline was not available for study.

FLOW SHEET NO. I



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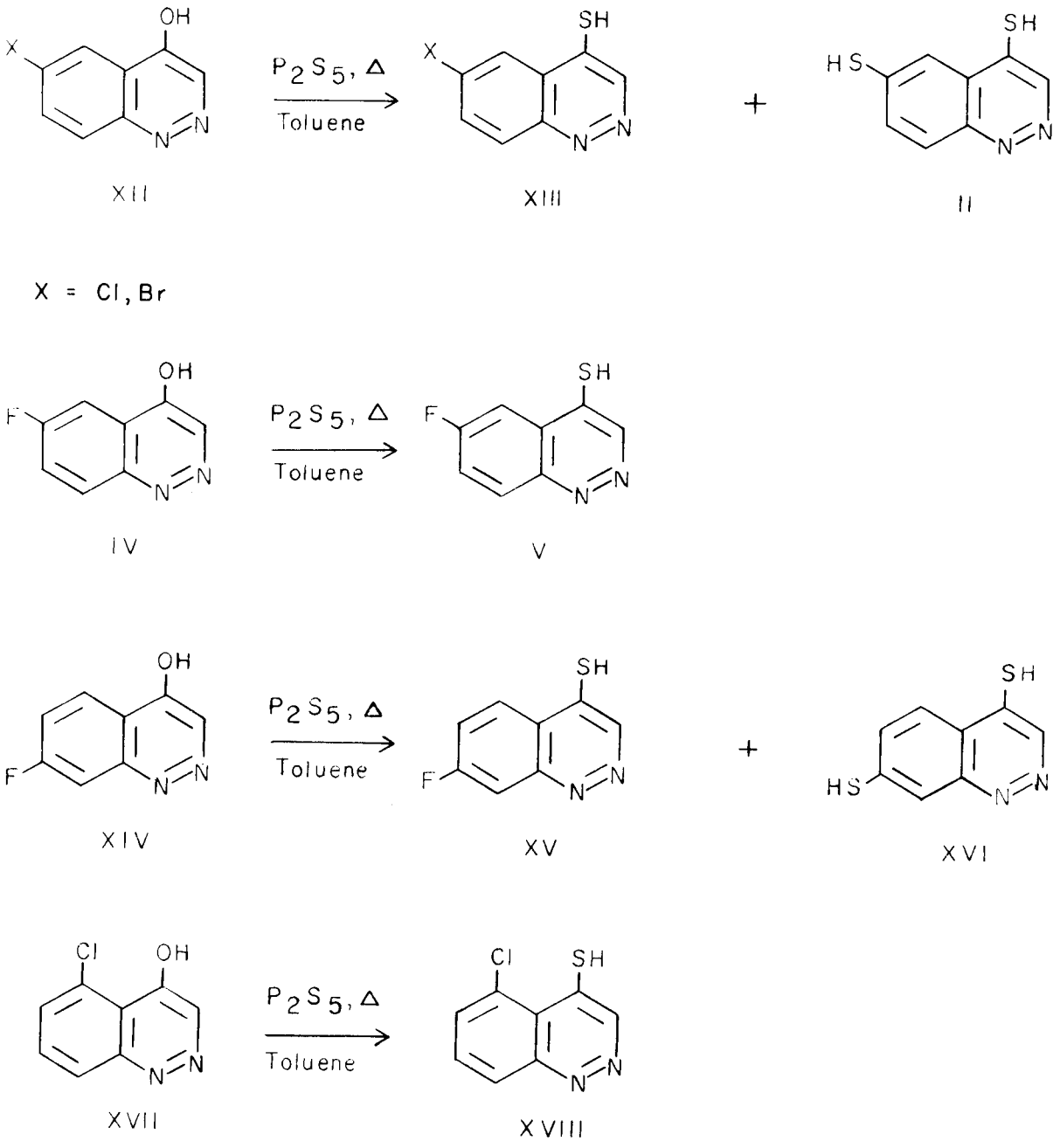
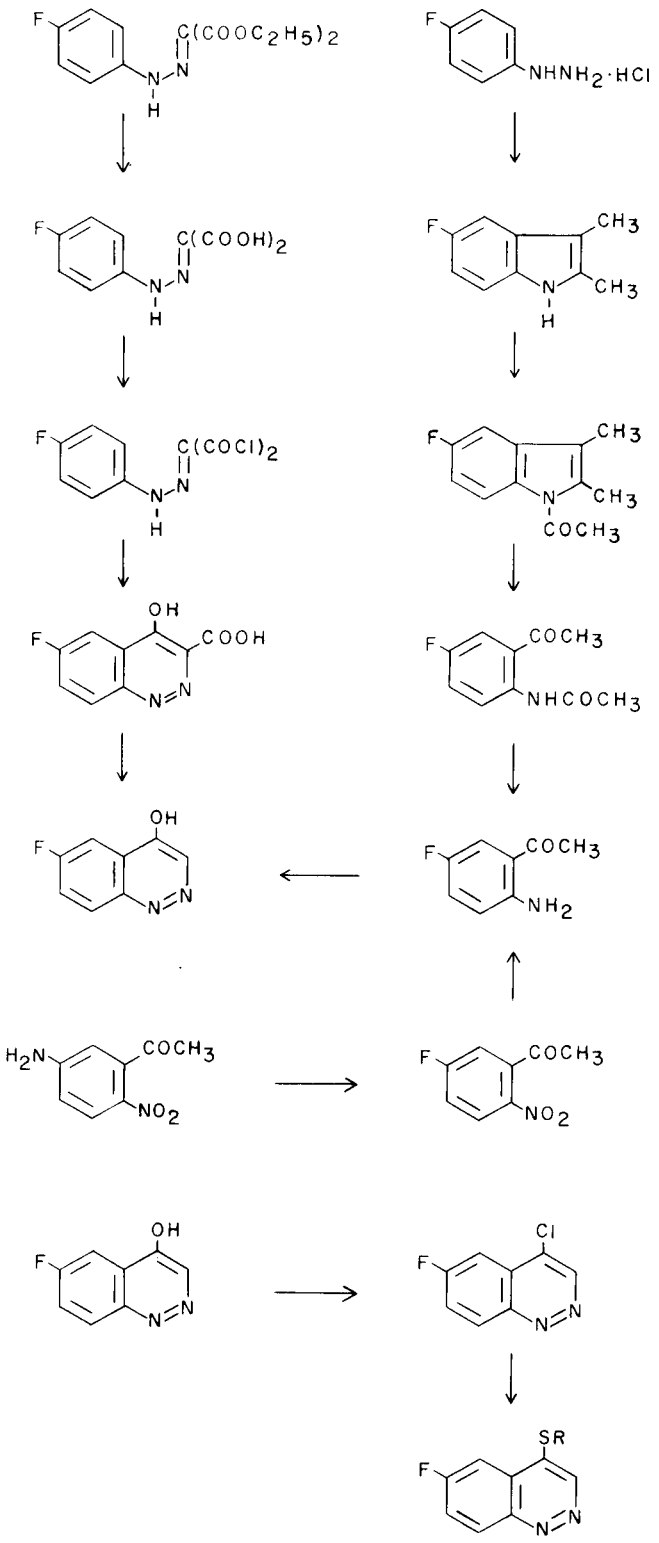


In dry toluene 5-chloro-4-mercaptocinnoline (XVIII) was obtained in good yield from 5-chloro-4-hydroxycinnoline (XVII) and phosphorus pentasulfide. However, under these conditions 5-bromo-4-hydroxycinnoline failed to react. In one experiment a small, but significant amount of a bromine-free, alkali-soluble compound, m.p. 208-209°, empirical formula $(C_8H_4N_2S_2)_n$ was obtained from 5-bromo-4-hydroxycinnoline and phosphorus pentasulfide in toluene. The infrared spectrum of the isolated compound indicated the absence of NH and C=S groups. A series of ring stretching bands in the region 1600-1330 cm^{-1} showed that the cinnoline ring system was intact. The infrared and ultraviolet spectra of the material were not sufficiently revealing to allow an unequivocal assignment of the structure.

It is suspected that the amount of water present in the solvent is the determining factor in many of these reactions. Several authors (11) have noted that addition of water to pyridine or the use of commercial pyridine without drying facilitates the isolation of the products from the reaction of uracil and related compounds with phosphorus pentasulfide. However, this does not mean that the substitution process is facilitated

FLOW SHEET NO. 2



by the presence of water, but that unwanted side reactions seem to be suppressed.

Attempts to use carbon disulfide as the solvent in the preparation of 6-chloro- and 6-bromo-4-mercaptocinnoline from the corresponding 4-hydroxycinnolines proved to be unsatisfactory. A yield of only 5% of the mercapto compound could be isolated after 24 hours on the steam bath. The balance of the starting material was recovered.

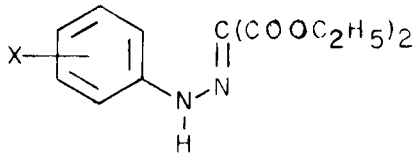
The reaction of the 4-hydroxycinnolines with phosphorus pentasulfide in pyridine solution for a few minutes was the most satisfactory method for the preparation of the 4-mercaptocinnolines. The hydroxyl group is substituted almost immediately during an initial exothermic reaction, whereas the halogen is not displaced. The 4-mercaptocinnolines listed in table VI could all be prepared in good yield by this procedure.

A series of S-alkyl derivatives were prepared for their potential antitumor activity. In most instances the alkylated derivatives were prepared from the mercapto compound by reaction with the appropriate alkyl chloride. Due to the difficulties in preparing 6-fluoro- and 6-bromo-4-mercaptocinnoline, the alternative method, conversion of the 4-hydroxycinnoline to the 4-chlorocinnoline followed by reaction of the latter with sodium alkylmercaptide, was attempted.

The general synthetic routes to the 4-hydroxycinnolines are illustrated in Flow Sheet No. 2 with 6-fluoro-4-hydroxycinnoline as the model compound. The desired 4-hydroxycinnolines were prepared by the method of Barber *et al.* (12). A halogen substituted aniline was diazotized and coupled with ethyl malonate, forming an ethyl mesoxalate phenylhydrazone which was saponified with sodium hydroxide to the mesoxalic acid. The mesoxalyl chloride phenylhydrazone was obtained by treatment of the acid with phosphorus pentachloride in refluxing chloroform solution, and this acid chloride was then cyclized to a 4-hydroxycinnoline-3-carboxylic acid by treatment with titanium tetrachloride in nitrobenzene. A *m*-substituted mesoxalyl chloride phenylhydrazone can cyclize to either the *o*- or *p*-position, giving two isomeric cinnoline derivatives. Barber *et al.* (12) reported that in three instances, namely, mesoxalyl chloride 3,4-dichlorophenylhydrazone, mesoxalyl chloride 3-bromo-4-methylphenylhydrazone and mesoxalyl chloride *m*-chlorophenylhydrazone, only one isomer was obtained. The product from the cyclization of mesoxalyl chloride *m*-chlorophenylhydrazone could be assigned the structure 5-chloro-4-hydroxycinnoline-3-carboxylic acid, since, on decarboxylation, it yielded a chloro-4-hydroxycinnoline (m.p. 330-332°), which was different from 7-chloro-4-hydroxycinnoline (m.p. 276-277°) reported by Atkinson and Simpson (13). Likewise, the product from the ring closure of mesoxalyl chloride 3,4-dichlorophenylhydrazone could be assigned the structure 5,6-dichloro-4-hydroxycinnoline-3-carboxylic acid by comparison of the decarboxylated product with the other possible isomer, 6,7-dichloro-4-hydroxycinnoline, reported by Keneford and Simpson (14). The structure of the cyclization product from mesoxalyl chloride 3-bromo-4-methylphenylhydrazone is yet to be determined.

In the case of mesoxalyl chloride *m*-chlorophenylhydrazone the results of Barber *et al.* (12) were confirmed in that the 5-chloro-4-hydroxycinnoline-3-carboxylic acid was definitely the predominant product. In one experiment this isomer was the sole product. In another experiment a small amount of the 7-chloro isomer was isolated after the decarboxylation of the chloro-4-hydroxycinnoline-3-carboxylic acids. The exact amount of the 7-chloro isomer formed is not

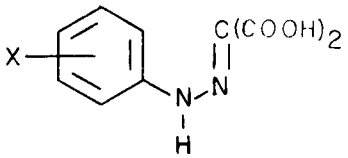
Table I. Ethyl Mesoxalate Phenylhydrazones.



X	m.p. °C.	Yield %	Calculated C	H	N	Found C	H	N
o-fluoro	57.5-58.0 (a)	67	55.31	5.36	9.93	55.02	5.38	9.94
o-bromo	70.5-71.0 (a)	90	45.48	4.41	8.16	45.78	4.50	7.95
m-fluoro	44.5-45.5 (b)	38	55.31	5.36	9.93	55.55	5.22	10.15
m-bromo	56.5-57.5 (a)	56	45.48	4.41	8.16	44.94	4.46	8.14
p-fluoro	64-65 (b)	77	55.31	5.36	9.93	55.34	5.10	10.07

(a) Recrystallized from ethanol. (b) Recrystallized from petroleum ether.

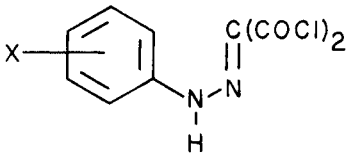
Table II. Mesoxalic Acid Phenylhydrazones.



X	m.p. °C.	Yield %	Calculated C	H	N	Found C	H	N
o-fluoro	168.0 (a)	64	47.80	3.12	12.40	47.73	3.08	12.15
o-bromo	350 (b)	77	37.64	2.46	9.76	37.20	2.58	9.92
m-fluoro	170.0 (a)	61	47.80	3.12	12.40	48.03	3.45	12.28
m-bromo	169-170 (b)	30	37.64	2.46	9.76	37.88	2.49	10.22
p-fluoro	171-172 (a)	52	47.80	3.12	12.40	47.99	3.32	12.43

(a) Recrystallized from ethyl acetate. (b) Recrystallized from glacial acetic acid.

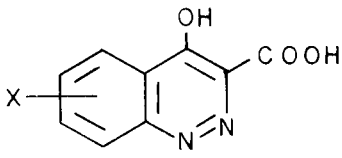
Table III. Mesoxalyl Chloride Phenylhydrazones.



X	m.p. °C.	Yield %	Calculated C	H	N	Found C	H	N
o-fluoro	92.5-93.5 (a)	84	41.08	1.92	10.65	40.75	1.80	10.99
o-bromo	143.0-144.0 (a)	75	33.36	1.56	8.65	33.16	1.84	8.60
m-fluoro	122.5-123.0 (a)	91	41.08	1.92	10.65	41.91 (b)	2.54 (b)	10.79
m-bromo	124-125 (a)	68	33.36	1.56	8.65	33.26	1.82	8.91
p-fluoro	71 (a)	74	41.08	1.92	10.65	41.10	2.58	

(a) Recrystallized from ethanol. (b) In spite of the poor C and H values, pure 7-fluoro-4-hydroxycinnoline-3-carboxylic acid (Table IV) was obtained.

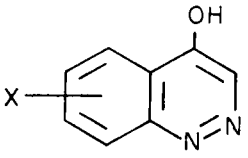
Table IV. 4-Hydroxycinnoline-3-carboxylic Acids.



X	m.p. °C.	Yield %	Calculated C	H	N	Found C	H	N
8-fluoro	254-255 (a)	81	51.93	2.42	13.46	52.19	2.87	13.59
8-bromo	256-257 (a)	69	40.16	1.87	10.41	40.14	2.09	10.18
7-fluoro	267-268 (a)	88	51.93	2.42	13.46	52.26	2.38	13.54
5- and 7-bromo	256-257 (a)	79	40.16	1.87	10.41	39.84	1.87	10.36
6-fluoro	264 (a)	31	51.93	2.42	13.46	52.09	2.59	13.04

(a) Recrystallized from glacial acetic acid.

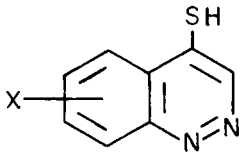
Table V. 4-Hydroxycinnolines.



X	m.p. °C.	Yield %	Calculated C	H	N	Found C	H	N
8-fluoro	262-263 (a)	65	58.55	3.07	17.07	59.04	3.34	17.12
8-bromo	190-192 (a)	60	42.70	2.24	12.46	42.61	2.43	12.32
7-fluoro	226-227 (a)	52	58.55	3.07	17.07	58.70	2.81	17.01
5-bromo	325-327 (a)	77	42.70	2.24	12.46	43.22	2.61	12.36
7-bromo	285-286 (a)	77	42.70	2.24	12.46	43.00	2.31	12.39
6-fluoro	267 (a)	47	58.55	3.07	17.07	58.13	2.88	17.35

(a) Recrystallized from methanol.

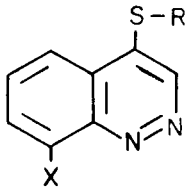
Table VI. 4-Mercaptocinnolines.



X	m.p. °C.	Color	Calculated C	H	N	S	Found C	H	N	S
8-fluoro	232 (a)	orange	53.32	2.80	15.55	17.79	53.79	2.94	15.81	17.78
8-chloro	228 (a)	blue	48.85	2.56	14.24	16.30	48.35	2.80	14.50	16.61
8-bromo	270-271 (a)	violet-blue	39.85	2.09	11.61	13.29	40.45	2.16	11.60	13.20
5-chloro	192-193 (a)	red	48.85	2.56	14.24	16.30	49.20	2.96	14.23	15.83
7-fluoro	241-242 (a)	orange-red	53.32	2.80	15.55	17.79	53.50	2.76	15.31	17.79
7-chloro	208-209 (a)	orange	48.85	2.56	14.24	16.30	48.88	2.68	13.63	15.90
6-fluoro	179-180 (a)	orange	53.32	2.80	15.55	17.79	53.73	3.04	15.54	18.04
6-chloro	181-182 (a)	dark red	48.85	2.56	14.24	16.30	49.37	2.71	14.18	16.22
6-bromo	187-189 (a)	purple	39.85	2.09	11.61	13.29	40.23	2.35	11.12	13.53

(a) Recrystallized from methanol.

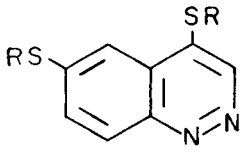
Table VII. 4-Alkylmercaptocinnolines.



R	X	Cinnoline g.	RCl g.	Yield %	m.p. °C	Empirical Formula	Calculated C	H	Found C	H
ethyl	H	3.2	10.0	77	98 (b)	$C_{10}H_{10}N_2S$	63.11	5.29	63.00	4.75
benzyl	H	1.6	3.0	40	141 (a)	$C_{15}H_{12}N_2S$	71.40	4.79	71.47	4.42
o-chlorobenzyl	H	1.6	3.2	72	136 (c)	$C_{15}H_{11}ClN_2S$	62.81	3.86	62.29	3.50
p-chlorobenzyl	H	1.6	3.2	86	178 (c)	$C_{15}H_{11}ClN_2S$	62.81	3.86	62.49	3.53
2,4-dichlorobenzyl	H	1.6	4.0	41	153 (c)	$C_{15}H_{10}Cl_2N_2S$	56.09	3.14	55.86	2.89
2,4-dichlorobenzyl	F	1.8	4.9	45	151 (a)	$C_{15}H_9Cl_2FN_2S$	53.11	2.67	53.10	2.80
2,4-dichlorobenzyl	Br	1.5	3.0	38	194 (c)	$C_{15}H_9BrCl_2N_2S$	45.03	2.27	44.90	2.58

(a) Recrystallized from ethanol. (b) Recrystallized from cyclohexane. (c) Recrystallized from benzene.

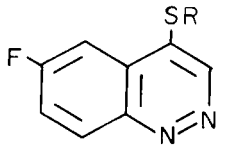
Table VIII. 4,6-Dimercaptocinnolines.



R	RCl g.	Yield %	m.p. °C	Empirical Formula	Calculated C	Calculated H	Found C	Found H
methyl	5.0	44	162 (a)	$C_{10}H_{10}N_2S_2$	54.01	4.53	54.09	4.16
benzyl	3.0	52	128 (a)	$C_{22}H_{18}N_2S_2$	70.53	4.84	70.46	4.81
o-chlorobenzyl	3.2	48	148 (a)	$C_{22}H_{16}Cl_2N_2S_2$	59.58	3.64	60.11	3.69
p-chlorobenzyl	3.2	48	162 (a)	$C_{22}H_{16}Cl_2N_2S_2$	59.58	3.64	59.35	3.52
2,4-dichlorobenzyl	4.0	34	145 (a)	$C_{22}H_{14}Cl_2N_2S_2$	51.56	2.75	51.51	2.61
3,4-dichlorobenzyl	4.0	42	128-130 (a)	$C_{22}H_{14}Cl_2N_2S_2$	51.56	2.75	51.28	2.62

(a) Recrystallized from benzene-cyclohexane 1:1.

Table IX. 6-Fluoro-4-alkylmercaptocinnolines.



R	RSH g.	Yield %	m.p. °C	Empirical Formula	Calculated C	Calculated H	Found C	Found H
benzyl	2.5	76	79 (b)	$C_{15}H_{11}FN_2S$	66.67	4.10	67.01	3.95
o-chlorobenzyl	3.1	58	114 (c)	$C_{15}H_{10}ClFN_2S$	59.13	3.31	59.03	3.10
p-chlorobenzyl	3.1	63	162 (a)	$C_{15}H_{10}ClFN_2S$	59.13	3.31	59.01	3.10
3,4-dichlorobenzyl	3.8	67	178 (a)	$C_{15}H_9Cl_2FN_2S$	53.13	2.67	52.96	2.53

(a) Recrystallized from ethanol. (b) Recrystallized from methanol. (c) Recrystallized from benzene-cyclohexane 1:1.

known, due to difficulties in the separation procedure. There were no significant differences in the conditions of the two cyclization reactions, but it is suspected that small variations in the temperature during the beginning of the reaction may account for the different results. The cyclization reaction was exothermic and difficult to control. Correlative studies between experimental conditions and the ratio of the yields of the isomers formed have not been undertaken.

The structure of the compounds formed by cyclization of mesoxalyl chloride *m*-fluoro- and *m*-bromophenylhydrazones could be determined from the ultraviolet spectra of the decarboxylated products, 5- or 7-fluoro-4-hydroxycinnoline and 5- or 7-bromo-4-hydroxycinnoline, respectively. The ultraviolet spectra of 6-fluoro-, 6-chloro- and 6-bromo-4-hydroxycinnoline were almost identical. Likewise, the spectra of 8-fluoro-, 8-chloro- and 8-bromo-4-hydroxycinnoline were almost identical. It was therefore expected that the same similarity of the spectra within each of the 5- and 7-substituted series would occur. The spectrum of the only isolated product (m.p. 226-227°) obtained from mesoxalyl chloride *m*-fluorophenylhydrazone was practically identical with the spectrum of 7-chloro-4-hydroxycinnoline. In the same manner the structure 5-bromo-4-hydroxycinnoline was assigned to the main product (85-90%, m.p. 325-327°) from mesoxalyl chloride *m*-bromophenylhydrazone, because of its close resemblance to the spectrum of 5-chloro-4-hydroxycinnoline. From the mixture of the isomeric 5- and 7-bromo-4-hydroxycinnolines was isolated a minute amount of the pure 7-bromo-4-hydroxycinnoline, m.p. 285-286°. The ultraviolet spectrum of this isomer showed the same close resemblance to the spectrum of 7-chloro-4-hydroxycinnoline as did that of 7-fluoro-4-hydroxycinnoline. The same relationship between the ultraviolet spectra of cinnolines substituted with halogen in the same position was shown by the 4-mercaptocinnolines. The spectral data of these compounds will be reported in a forthcoming paper.

The experimental data of the halogen substituted 4-hydroxycinnolines and their intermediates are listed in tables I - V. A few observations made in this laboratory on the synthetic procedures will be mentioned in the experimental part. The 4-mercaptocinnolines and their alkyl derivatives are listed in tables VI - IX.

6-Fluoro-4-hydroxycinnoline was prepared by the method of Barber *et al.* (12) in the low overall yield of 5% from *p*-fluoroaniline. This compound was also prepared by diazotation of 2-amino-5-fluoroacetophenone as described by Schofield and Simpson (10). Two routes leading to 2-amino-5-fluoroacetophenone were investigated. Both routes included five synthetic stages from commercially available materials, *m*-nitroacetophenone and *p*-fluoroaniline, respectively. As seen in

the flow sheet, reduction, acetylation and nitration (13) of *m*-nitroacetophenone led to 2-nitro-5-aminoacetophenone, which was then converted into 2-nitro-5-fluoroacetophenone. Reduction of this compound gave 2-amino-5-fluoroacetophenone in an overall yield of 7.5%. The final stage, cyclization of 2-amino-5-fluoroacetophenone to 6-fluoro-4-hydroxycinnoline, proceeded with a yield of 70%, giving an overall yield of 5% from *m*-nitroacetophenone, the same yield obtained by the method of Barber *et al.* (12). By the other route to 2-amino-5-fluoroacetophenone, *p*-fluoroaniline was diazotized and reduced with sodium bisulfite to *p*-fluorophenylhydrazine hydrochloride (14), which with methyl ethyl ketone in a Fischer indole synthesis gave 2,3-dimethyl-5-fluoroindole. Acetylation of this compound and oxidative cleavage of the acetylation product gave 2-acetamino-5-fluoroacetophenone, which was hydrolyzed to 2-amino-5-fluoroacetophenone in an overall yield of 32%. A final total yield of 22% of 6-fluoro-4-hydroxycinnoline from *p*-fluoroaniline represents the most favorable route.

All of the mercapto- and substituted mercaptocinnolines have been screened either against experimental rodent tumors or in cell culture or both. The activity of a compound is considered to be statistically significant if the T/C is 0.53 or less in S-180 or AC-755. In the LE-1210 system, the activity is considered to be statistically significant if the T/C is 1.25 or more. In the cell culture system (KB cells), the activity of the compound is considered to be statistically significant if the ED_{50} is 4 μg/ml. or less. The slope is simply the difference in response for a one-log difference in dose, the response being the ratio of the growth of the test sample to that of the untreated control. The following compounds exhibited statistically significant activity: 4-(2,4-dichlorobenzylthio)cinnoline, T/C = 0.17 (AC-755); 4,6-bis-(2,4-dichlorobenzylthio)-cinnoline, T/C = 0.45 (SA-180); 4-benzylthiocinnoline, ED_{50} = 1.3 μg/ml., slope = -0.56, (cell culture).

EXPERIMENTAL

All melting points are uncorrected. In the preparation of the halogen substituted 4-hydroxycinnolines the procedure described by Barber *et al.* (12) was followed in detail. However, a few observations made in this laboratory regarding each of the steps shall be reported.

Ethyl mesoxalate phenylhydrazones (Table I).

The ethyl mesoxalate phenylhydrazones were formed by coupling a diazotized aniline with ethyl malonate. The product separated from an aqueous-alcoholic solution, usually in good yield, (These were crude, but in satisfactory purity for the next step.) but in certain cases, these hydrazones showed considerable solubility in the solvent. A second crop could often be obtained on dilution of the filtrate with water. The initial product obtained could be used in the next stage without further purification, but it is recommended that the second crop be recrystallized (from ethanol or petroleum ether (30-60° BP)) before the saponification, since the presence of impurities lowered the yield of the mesoxalic acid phenylhydrazones.

Mesoxalic acid phenylhydrazones (Table II).

The crude mesoxalic acid phenylhydrazones prepared by saponification of their esters were usually obtained in almost quantitative yields. Purification of these crude products was necessary before conversion into the acid chlorides. In the hands of Barber, *et al.* (12) glacial acetic acid was a satisfactory recrystallization solvent. In this laboratory mesoxalic acid *p*-fluoro- and *p*-chlorophenylhydrazones were readily decarboxylated when these compounds were heated in this solvent. This decarboxylation was more rapid when Norite was present. In these instances ethyl acetate was a more satisfactory recrystallization solvent.

Mesoxalyl chloride phenylhydrazones (Table III).

The mesoxalyl chlorides were prepared from the parent acids on treatment with phosphorus pentachloride in refluxing chloroform solution. Purification of the acid was essential for the success of this reaction. A few attempts to use the crude mesoxalic acid phenylhydrazones resulted in the formation of a large amount of tarry material, from which the acid chloride could not be isolated. The crude mesoxalyl chloride, separating from the reaction mixture on addition of petroleum ether, could however, after a few washings with petroleum ether, be used directly in the next step.

4-Hydroxycinnoline-3-carboxylic acids (Table IV).

The mesoxalyl chloride phenylhydrazones on treatment with titanium tetrachloride in nitrobenzene followed by hydrolysis with sodium hydroxide were converted into 4-hydroxycinnoline-3-carboxylic acids. The formation of both 5- and 7-halogen substituted cinnoline derivatives from the mesoxalyl chloride *m*-halogen substituted phenylhydrazones was mentioned in the introduction. Separation of the isomers at this stage was not attempted. Yields reported in Table IV are crude.

4-Hydroxycinnolines (Table V).

Barber *et al.* (12) reported several procedures for the decarboxylation of the 4-hydroxycinnoline-3-carboxylic acids, of which heating in benzophenone at 190-210° was preferred in this laboratory. The decarboxylation was usually completed in less than 30 minutes. The suspension of the carboxylic acid in benzophenone changed during this period into a dark colored solution, from which the crude 4-hydroxycinnolines were obtained on addition of petroleum ether. The crude products were purified by treatment with activated charcoal in a solution of sodium hydroxide followed by recrystallizations from methanol. The separation of the 5- and 7-halogen substituted 4-hydroxycinnolines was performed by repeated crystallizations from methanol, aqueous ethanol (the fluoro derivatives), or mixtures of dimethyl formamide and methanol. Yields reported in Table V are crude.

2-Nitro-5-fluoroacetophenone.

To a mixture of 30 g. (0.167 mole) of 2-nitro-5-aminoacetophenone (16) in 120 ml. of 6 N hydrochloric acid was added dropwise at 0° a solution of 12 g. of sodium nitrite in 30 ml. of water. A solution of fluoroboric acid (100 ml.) prepared according to the procedure in "Organic Synthesis" (18) was added to the clear solution and the reaction mixture was allowed to stand at 5° for 2 hrs. The yellow precipitate was collected and dried in air. The yield of crude fluoroborate was 38 g. (82%), m.p. 125° dec.

The crude fluoroborate (10 g.) was mixed with powdered barium sulfate (30 g.) and heated over a free flame according to the procedure in "Organic Reactions" (19). The reaction mixture was then steam distilled for 2 hrs. and the aqueous distillate was extracted with ether. Almost pure 2-nitro-5-fluoroacetophenone (1.2 g., 24%) was obtained. Recrystallization from water gave pale yellow prisms, m.p. 53°.

Anal. Calcd. for $C_8H_6FNO_3$: C, 52.48; H, 3.27. Found: C, 52.57; H, 3.18.

2-Amino-5-fluoroacetophenone.

Method A. 2-Nitro-5-fluoroacetophenone was reduced with iron and acetic acid as described for 2-amino-5-chloroacetophenone by Simpson *et al.* (16). From 48 g. (0.26 mole) of 2-nitro-5-fluoroacetophenone there was obtained 38 g. (95%) of 2-amino-5-fluoroacetophenone, recrystallized from cyclohexane, m.p. 72-73°.

Anal. Calcd. for C_8H_8FNO: C, 62.73; H, 5.23. Found: C, 62.58; H, 4.72.

Method B. A mixture of 2-acetamino-5-fluoroacetophenone (74 g., 0.38 mole), 200 ml. of ethanol, 200 ml. of concentrated hydrochloric acid and 50 ml. of water was gently heated under reflux on a steam bath for 2 hrs. The solution was concentrated to half the volume under reduced pressure and the resulting solution made alkaline with 2 N sodium hydroxide. Extraction with ether gave 57 g. (99%) of 2-amino-5-fluoroacetophenone, m.p. 74°.

5-Fluoro-2,3-dimethylindole.

A mixture of *p*-phenylhydrazine hydrochloride (17) (40 g., 0.246 mole), 80 ml. of ethanol, methyl ethyl ketone (40 ml., 0.45 mole), and 100 ml. of 2 N sodium hydroxide solution was heated under reflux on a steam bath for 2 hrs. After cooling, the mixture was extracted with ether and the dried ether extract was evaporated to dryness. The residue was added to 350 g. of dry zinc chloride and the mixture heated to 180° for five min. whereupon an exothermic reaction ensued. When the reaction had subsided inorganic material was dissolved in 0.5 N hydrochloric acid, and the brown precipitate of the indole was filtered off, washed with water and dried in air. Recrystallization from petroleum ether gave pure 5-fluoro-2,3-dimethylindole, m.p. 98°.

Anal. Calcd. for $C_{10}H_{10}FN$: C, 73.58; H, 6.18. Found: C, 73.13; H, 5.64.

N-Acetyl-5-fluoro-2,3-dimethylindole.

Acetylchloride (40 ml.) was added to 8.0 g. (0.05 mole) of 5-fluoro-2,3-dimethylindole and the solution heated under reflux on a steam bath for 2 hrs. Excess acetylchloride was removed under reduced pressure and the residue distilled *in vacuo*. The yield of N-acetyl-5-fluoro-2,3-dimethylindole was 5.3 g. (53%), m.p. 71°.

Anal. Calcd. for $C_{12}H_{12}FNO$: C, 70.23; H, 5.90. Found: C, 70.11; H, 5.31.

2-Acetamino-5-fluoroacetophenone.

To a well stirred solution containing 90 g. (0.44 mole) of N-acetyl-5-fluoro-2,3-dimethylindole in 900 ml. of glacial acetic acid was added 90 g. of chromic anhydride and 90 ml. of water during 1 hr. During this time the temperature was maintained at 40°. The reaction mixture was then heated to 70° for 8 hrs., then allowed to stand overnight at room temperature. The clear, green solution was poured into 1 l. of ice water and the aqueous solution extracted with chloroform. Evaporation of the dried extract gave 67 g. (79%) of crude 2-acetamino-5-fluoroacetophenone, m.p. 110-112°. Recrystallization from water raised the melting point to 135°.

6-Fluoro-4-hydroxycinnoline.

To a solution of 2-amino-5-fluoroacetophenone (36 g., 0.235 mole) in 420 ml. of hydrochloric acid was added dropwise a solution of 18 g. of sodium nitrite in 30 ml. of water. During the addition the temperature was maintained at 0° and after the diazotation was completed the temperature was maintained at 80° for 4 hrs. The solution was then concentrated under reduced pressure until precipitation began and 100 ml. of water added whereupon saturation with potassium carbonate afforded a brown solid (28 g., 70%), m.p. 240-245°. Recrystallization from ethanol gave white needles of 6-fluoro-4-hydroxycinnoline, m.p. 267°.

4-Chloro-6-fluorocinnoline.

6-Fluoro-4-hydroxycinnoline (4.0 g., 0.024 mole) was dissolved in 30 ml. of phosphoryl chloride and the solution heated under reflux for 15 min. Excess phosphoryl chloride was removed under reduced pressure, the residue poured onto crushed ice and sodium acetate added to *p*H 2. Extraction with ether and evaporation of the dried extract gave 3.3 g. (74%) of crude 6-fluoro-4-chlorocinnoline, m.p. 81-83°. Recrystallization from cyclohexane gave pale yellow needles, m.p. 89°.

Anal. Calcd. for $C_8H_4ClFN_2$: C, 52.62; H, 2.21; N, 15.35. Found: C, 52.31; H, 2.34; N, 15.28.

4-Mercaptocinnolines (Table VI).

The 4-mercaptocinnolines in table VI were prepared from the corresponding 4-hydroxycinnoline with an excess of phosphorus pentasulfide in either boiling pyridine or boiling toluene. In general, products with the most satisfactory purity and yield were obtained by boiling a few minutes in pyridine solution or by several hrs. heating in toluene.

Pyridine method. The halogen substituted 4-hydroxycinnoline (0.005 mole) dissolved in 20 ml. of pyridine dried over potassium hydroxide was heated to boiling and phosphorus pentasulfide (1.11 g., 0.0025 mole) was then added in small portions. After the vigorous reaction had subsided, the mixture was heated under gentle reflux for 2-10 min. and the excess pyridine removed under reduced pressure. The residue was treated with 20 ml. of ice water and the aqueous solution left on the steam bath for 1 hr. Sodium hydroxide (1 N) was added to *p*H 8-9, the solution treated with activated charcoal and filtered. Acidification with concentrated hydrochloric acid precipitated the 4-mercaptocinnoline, which was recrystallized from absolute or aqueous methanol.

Toluene method. A suspension of the 4-hydroxycinnoline (0.005 mole) and excess phosphorus pentasulfide in 50 ml. of dry toluene was heated under reflux for 6-8 hrs. The reaction mixture was left overnight, and the solid filtered off. This was dissolved in a 0.5 N sodium hydroxide solution and left on the steam bath for 2-3 hrs. The product was isolated as described above under the pyridine method.

4,6-Dimercaptocinnoline.

6-Chloro-4-hydroxycinnoline (9.0 g., 0.05 mole) or 6-bromo-4-hydroxycinnoline (11.3 g., 0.05 mole) and phosphorous pentasulfide (44.4 g., 0.1 mole) were dissolved in 400 ml. of pyridine dried over potassium hydroxide. The solution was heated under reflux for 3 hrs. and pyridine was evaporated off under reduced pressure. The residue was poured onto a mixture of crushed ice and water (400 g.) and the dark brown suspension was left on the steam bath for 2 hrs. The solution was made alkaline (*p*H 8-9) with 1 N sodium hydroxide solution and, after filtration, the crude 4,6-dimercaptocinnoline precipitated on dropwise addition of concentrated hydrochloric acid. The crude product was redissolved in 0.5 N sodium hydroxide, treated with activated charcoal, filtered and reprecipitated with concentrated hydrochloric acid. The product obtained in this way was used for the preparation of the 4,6-dialkylmercaptocinnolines.

Purification of the 4,6-dimercaptocinnoline proved to be rather difficult due to its low solubility in all organic solvents. Ethanol and methanol were the most suitable solvents for recrystallization, from which the compound separated as a microcrystalline brownish orange powder, m.p. 245° dec. The sulfur content of the samples purified in this way varied from 30.8% to 35.0%. The theoretical amount of sulfur in 4,6-dimercaptocinnoline is 33.01%.

Anal. Calcd. for $C_8H_6N_2S_2$: C, 49.45; H, 3.11; N, 14.42. Found: C, 49.07; H, 3.10; N, 14.11.

4,7-Dimercaptocinnoline.

7-Fluoro-4-hydroxycinnoline (0.82 g., 0.005 mole) was heated under reflux with phosphorus pentasulfide (1.11 g., 0.0025 mole) in 50 ml. of toluene for 6 hrs. The solid residue was filtered and treated with 50 ml. of 0.5 N sodium hydroxide for 1 hr. on the steam bath. The solution was treated with charcoal, filtered and cooled to room temperature. An orange brown solid was precipitated by dropwise addition of concentrated hydrochloric acid. The crude product (0.77 g., 86%) was dried in the air and recrystallized from methanol. Part of the material was only slightly soluble in methanol, and was separated from the solution by decantation. 7-Fluoro-4-mercaptocinnoline could be isolated from the solution. The slightly soluble material was recrystallized twice from a large amount of methanol giving a microcrystalline, orange powder, m.p. 231-233°.

Anal. Calcd. for $C_8H_6N_2S_2$: C, 49.39; H, 3.11; N, 14.39; S, 33.01. Found: C, 49.16; H, 3.19; N, 14.09; S, 32.88.

4-Alkylmercaptocinnolines from the corresponding 4-mercaptocinnolines.

In a typical experiment 0.01 mole of a 4-mercaptocinnoline was dissolved in 50 ml. of 2 N sodium hydroxide solution and 10 ml. of ethanol. The alkyl chloride (*ca.* 0.025 mole) was added and the mixture was stirred at room temperature for 5 hrs. The solid was filtered off, washed with methanol, and the pure 4-alkylmercaptocinnoline was obtained on recrystallization from suitable solvents. The data on these compounds are recorded in tables VII and VIII.

6-Fluoro-4-alkylmercaptocinnolines (Table IX).

The sodium alkylmercaptides were prepared from the appropriate alkylmercaptans and the equivalent amount of sodium amide in benzene. The resulting solution was added to an equivalent amount of 6-fluoro-4-chlorocinnoline, and the reaction mixture was heated under reflux for 5 hrs. The mixture was cooled to room temperature and the inorganic material was filtered off. The filtrate was concentrated and cooled to room temperature, and the separated 6-fluoro-4-alkylmercaptocinnoline was collected and recrystallized.

Acknowledgment.

This investigation was supported by a PHS research grant No. CA-04327 from the National Cancer Institute, Public Health Service. The authors are grateful to Mrs. Ruby Ju, Miss Yoko Tokushige and Dr. K. Abe, Tanabe Seiyaku Co., Ltd., Tokyo, for the analytical data reported.

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Received March 12, 1964 Albuquerque, New Mexico