Cyclization of Ylidenemalononitriles. VII. Studies on Sulfur-containing Heterocyclic Systems. (1a)

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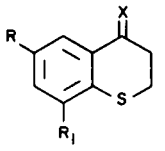
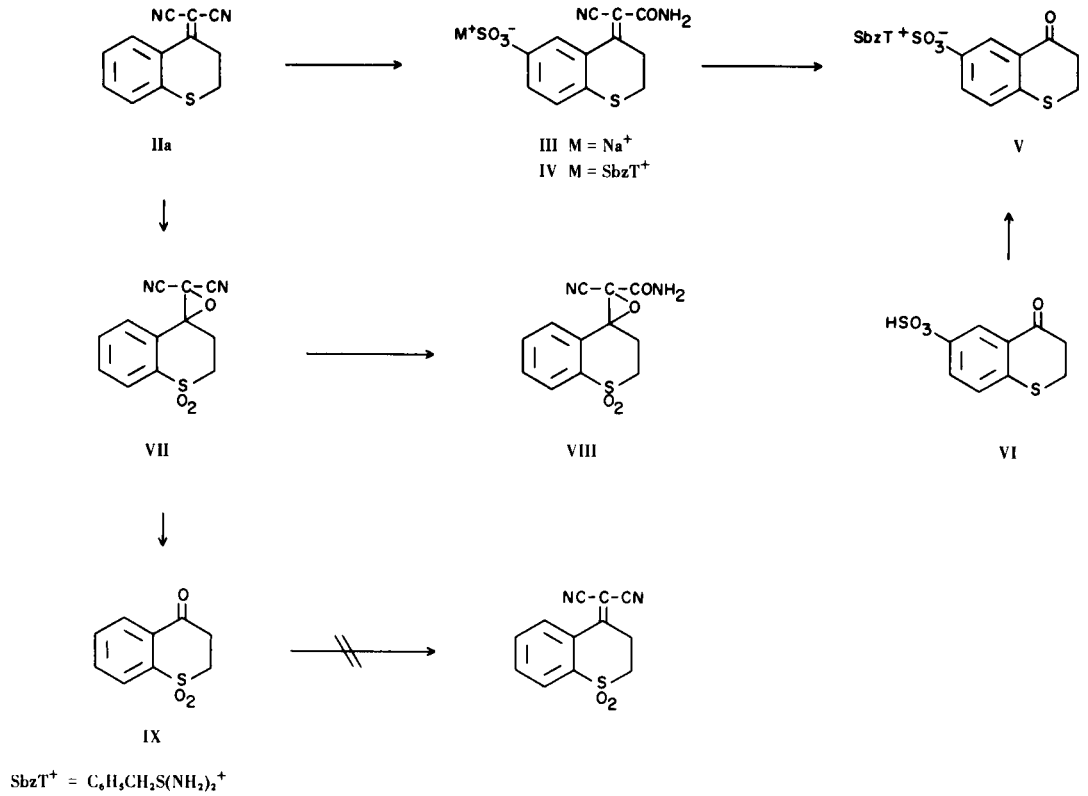
Ring closure of ylidenemalononitrile adducts has been extended to the syntheses of isomeric sulfur heterocycles. The malononitrile derivatives of thiochromanone, thiochromone and *iso*-thiochromanone have been synthesized, and results of the acidic ring closure experiments on these compounds are reported. The thiochromanone adducts gave an interesting disproportionation reaction, and experiments designed to support the proposed route are presented.

Ylidenemalononitriles have been employed as an annelation technique in a large variety of carbocyclic ring systems (2), but few applications of this procedure to heterocyclic compounds have been described. Attempts to cyclize ylidenemalononitriles in the quinolone and chromanone series were reported recently (3) and preliminary data for thiochromanones (I) were reported several years ago (4). It is this latter example which we wish to elaborate in this paper.



I X = O (R = R_1 = H)
IIa X = C(CN)$_2$ (R = R_1 = H)
IIb X = C(CN)$_2$ (R = CH_3, R_1 = H)
IIc X = C(CN)$_2$ (R = H, R_1 = CH_3)

CHART I



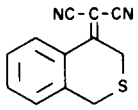
$SbzT^+$ = $C_6H_5CH_2S(NH_2)_2^+$

Thiochroman-4-ylidenemalononitrile (IIa) was prepared from the corresponding ketone (5) by a procedure reported earlier (2). Ring closure for malononitrile adducts (2) in concentrated sulfuric acid produced only a water soluble sulfonic acid, isolated as the sodium (III) or *S*-benzylthiuronium salt (IV) (Chart I). From elemental analyses, infrared and nmr spectral data, structures III and IV were assigned to these two products. In addition, IV could be converted to V by heating in aqueous ethanol. The structure of V was confirmed by its synthesis *via* sulfonation of thiochroman-4-one to form VI and precipitation of the *S*-benzylthiuronium salt (V).

Cyclization of IIa was attempted with polyphosphoric acid, polyphosphoric acid-chlorobenzene (6), acetic acid-hydrochloric acid (7), hydrogen fluoride (8), Hoesch conditions (9) and trifluoroacetic acid but only starting material was recovered. Heating in 85% phosphoric acid led to reversal of the condensation reaction, producing I.

Since the above experiments indicated that IIa could not readily be cyclized, several experiments were necessary to determine the role of the sulfur atom. Oxidation of the sulfur to a sulfone would deactivate the benzene ring. Treatment of IIa with hydrogen peroxide produced the epoxidized sulfone (VII), and extended reaction periods led to the cyanoacetamide derivative (VIII). In acid, VII was converted to IX but IX resisted reaction with malononitrile. Structure VII was confirmed by elemental analysis, infrared data and a positive periodic test (10).

A second approach removed the sulfur atom to a position from which it could not have electronic participation with the benzene ring. Synthesis of *iso*thiochromanylidenemalononitrile (X), and treatment with concentrated sulfuric



X

acid gave a black solid melting above 300°. Reported (11) sensitivities of benzylthiolacetic acid and *iso*thiochromanone in concentrated sulfuric acid appear to have been carried through to the malononitrile adduct (X).

A final maneuver was blockage of the position most likely to undergo sulfonation. A methyl group was placed *para* (*ortho* ruled out on steric grounds) to the sulfur atom (IIb). As reported (4), treatment of IIb with sulfuric acid produced three products; XI, XII, and XIII (Chart II), which were explained as arising *via* a disproportionation of XII. A detailed discussion of this mechanism is outlined in reference 4. Compound XII is the analog of that obtained for α-tetralone (2a). In addition, a small amount of XIV, arising from hydrolysis/decarboxylation of XI, has been found in the mother liquors.

Reaction periods have an influence on product distribution and further data, which supports the disproportionation/air oxidation scheme of the earlier paper (4), is available. That XII was initially formed and disproportionated to XI and XIII is indicated since maximum amount of XII was obtained after two hours stirring in concentrated sulfuric acid at room temperature, followed by standard work up procedure. The amount of XII began to diminish with an increase in XI and XIII as the reaction time in concentrated acid was increased up to six hours. After a reaction time of four and up to six hours, the yield of XII was at its lowest point, and the yield of XI was equal to XIII. Between six and ten hours, the amount of XII began to increase at the expense of XI with an accompanying slight increase in XIII. After a reaction time of fifteen hours, the point at which the study was terminated, nearly equal amounts of XI and XII with almost twice as much XIII was produced. These yields were based on the total product isolated, and as the reaction time increased more water soluble materials were evident and less isolable products. These latter materials were most likely sulfonated cyclized derivatives (3b), particularly in light of decreased over-all yield of isolable cyclized products (XI, XII, XIII). The yields of XIV seemed to remain static throughout these varied reaction times.

These results support the suggestion (4) that XII was initially formed and disproportionated gradually to XI and XIII in equal amounts. This was confirmed by warming XII in a concentrated sulfuric acid solution for several hours, pouring over ice to obtain XI and XIII. However, after six hours, the disproportionation mechanism seemed to be supplemented by an oxidation pathway, since XI decreased, while XII and XIII increased. This result may be due to air oxidation of XI to XII, with disproportionation or air oxidation of XII to XIII. Verification of the conversion of XI to XII and XIII was obtained when XI, placed in concentrated sulfuric acid and allowed to stand at room temperature for 24 hours, produced XII and XIII. Likewise, treating a sulfuric acid solution of XI with a stream of oxygen produced XII and XIII. Under the same conditions, XII yielded XI, XII, and XIII with a yield of XI and XII less than XIII, indicating that both oxidation and disproportionation are occurring in acid solution. Compound XI also produced XIV, in addition to XII and XIII, when its acid solution was warmed briefly at 70°, indicating that XIV is produced by hydrolysis and decarboxylation of XI.

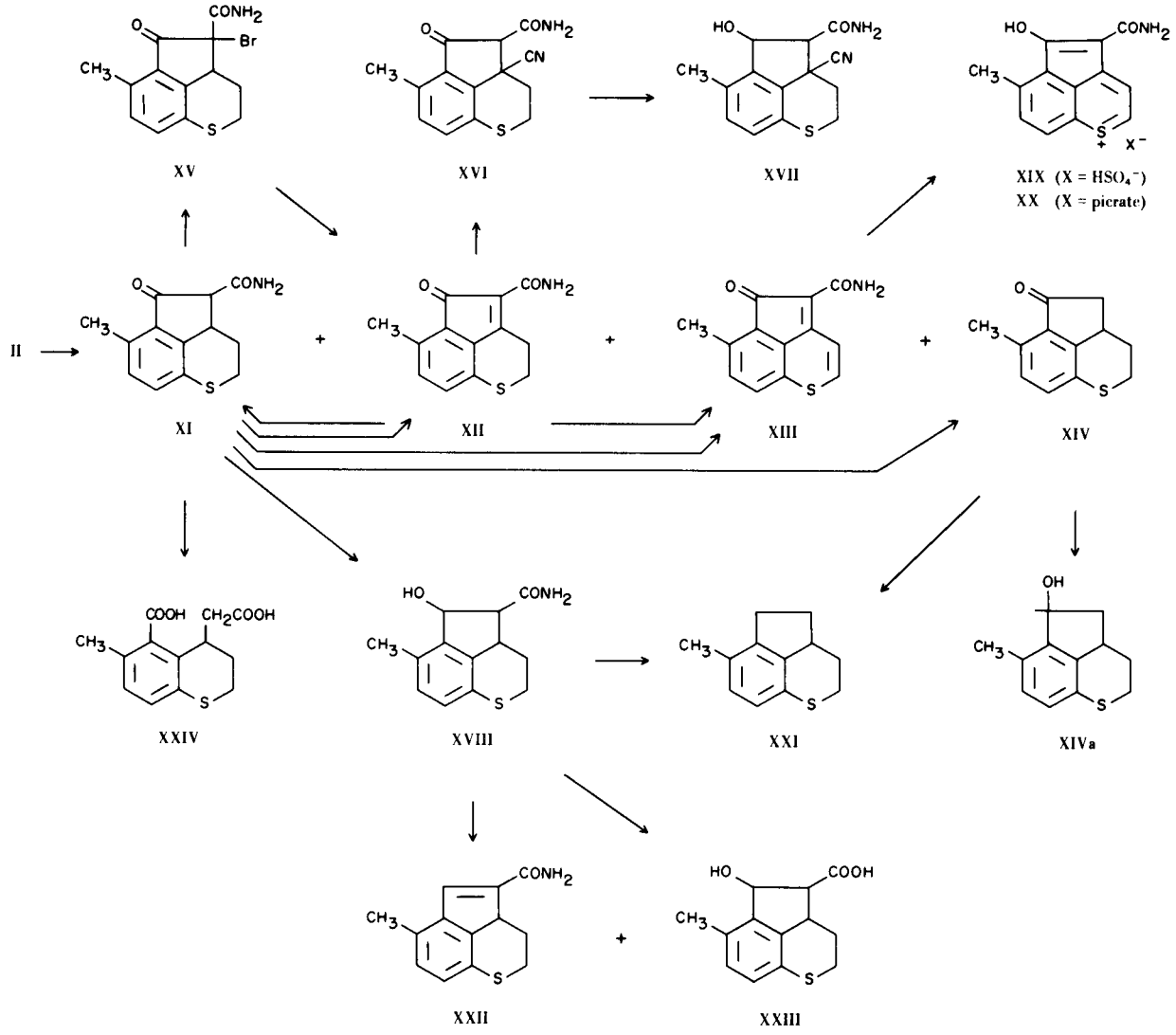
Further investigation showed that XI or XII could be converted directly to XIII upon treatment with 30% palladium on charcoal catalyst, but the transformation of XI to XII was not observed under these conditions. However, bromination of XI followed by dehydrobromination of the α-bromoketone (XV) proceeded to a mixture of XII and

XIII. (The appearance of the latter products apparently depends upon whether or not the elimination follows initial dehydrogenation or dehydrohalogenation, and may be influenced by stereochemical requirements).

The structural formulas proposed for compounds XI, XII and XIII have been confirmed by infrared, ultraviolet and nmr data (4). Michael addition of cyanide (12) to XII suggests that the double bond was in the five-membered ring with formation of XVI. Treatment of XII with base, followed by acidification always led to a product in which the double bond was conjugated with the ketone function. When the double bond is in the five-membered ring, the resulting indenones are reported to be colored (2b), whereas indanones are white. It is interesting that XI is orange and almost identical in color to XII. However, XI may exist as an enol, as it does in trifluoroacetic acid, where the nmr has the proper ratio of protons (2:3:5) for the enol structure. Sodium borohydride reduction of XVI, XIV, or XI gave alcohols XVII, XIVa or XVIII, respectively. These products were colorless or very light yellow, as expected for indanes.

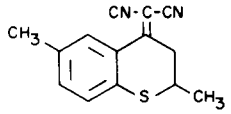
Several observations with these compounds are worthy of note (Chart II). Compound XIII was obtained as the bisulfate salt (XIX) and as the picrate (XX), but resisted catalytic reduction, bromination and conjugative addition. Numerous attempts to hydrolyze the amide group of XIII failed. In acid, compound XVIII yielded a 1:1 mixture of XXI and a green polymer, but in base produced XXII and XXIII. Formation of the completely reduced product, XXI, by acid hydrolysis of XVIII, must also involve a disproportionation of the product formed by hydrolysis, decarboxylation and dehydration of the XVIII,

CHART II

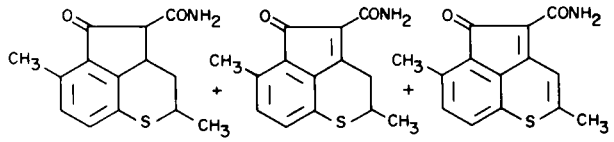


with concommitant polymerization of the more oxidized product of the disproportionation. Compound XXI was also prepared by Wolff-Kishner reduction of XIV. Various attempts to dehydrogenate XIV failed giving almost quantitative recovery of starting material. Finally, compound XII could be catalytically reduced to XI, while in base XI underwent ring opening to XXIV.

Evidence for the disproportionation route followed by XII might be obtained by blocking the position α to the sulfur atom in IIb. If the disproportionation proceeds by the mechanism proposed (4), hydride transfer should be prevented. We were unable to prepare the 2,2-dimethyl analog of IIb, but using a published approach (13), the monomethyl derivative (XXV) could be prepared and cyclized. A longer reaction time was required for appearance of the disproportionation products, XXVa and XXVc; XXVb was obtained in low yield. Since XXVa was isolated in highest yield (50%), this may indicate inhibition of the air oxidation step by methylation of position-2.



XXV

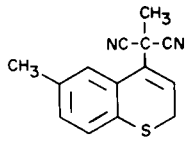


XXVa XXVb XXVc

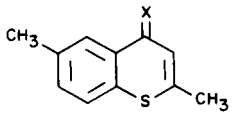
Our attempts to prepare the 3-methyl analog of IIb by alkylation yielded a stable 2*H*-thiochromene (XXVI) when IIb was treated with sodium hydride and methyl iodide. Thiochromenes generally polymerize readily and the monomeric existence of XXVI is unique.

To substantiate the idea that it is necessary to block the six-position of the aromatic ring to inhibit sulfonation, 8-methylthiochroman-4-ylidenemalononitrile (IIc) was synthesized. When treated with sulfuric acid, a water soluble product was obtained. Salting of the aqueous acid mixture gave a product exhibiting characteristics of the sodium sulfonate as determined by infrared spectroscopy. It appears, therefore, that the six-position must be blocked for cyclization of the sulfur heterocycles to occur.

Extension of the ylidenemalononitrile cyclization to thiochromones (*i.e.*, XXVII) was easily possible since these heterocycles were readily available by the reaction of *p*-toluenethiol and β-ketoesters in the presence of polyphosphoric acid (14). In the case studied, cyclization of the malononitrile adduct (XXVIII) produced a small amount (20%) of XXVc. Products analogous to XXVa and XXVb could not be detected, as the remaining material was intractable. Treatment of XXVIII with sulfuric acid produced only *retro* products, XXVII and malononitrile. This anomaly apparently involves the participation of the sulfur lone pair of electrons acting through the conjugated double bond facilitating the reversibility.



XXVI



XXVII X = O
XXVIII X = $C(CN)_2$

TABLE I

Properties of Thiochromanylidenemalononitriles

Compound	Yield %	M.p. °C	Molecular Formula	Analysis (%) Carbon (Found)	Hydrogen (Found)	Nitrogen (Found)	Sulfur (Found)
IIa R = R_1 = H	89	119 -120	$C_{12}H_8N_2S$	67.89 (67.99)	3.77 (3.88)		15.11 (15.24)
IIb R = CH_3, R_1 = H	75	75.5- 78	$C_{13}H_{10}N_2S$	69.03 (69.15)	4.42 (4.62)	12.39 (12.33)	
X	32.5	106.5-109	$C_{12}H_8N_2S$	67.89 (67.84)	3.77 (4.01)	13.21 (13.14)	15.11 (15.43)
XXV	77	118 -119	$C_{14}H_{12}N_2S$	70.00 (70.04)	5.00 (5.29)	11.66 (11.28)	
IIc R = H, R = CH_3	44.3	133 -136	$C_{13}H_{10}N_2S$	69.03 (69.00)	4.42 (4.53)	12.39 (12.31)	14.16 (14.26)

EXPERIMENTAL (16)

3-Arylmercaptopropionic Acids.

These acids were prepared from sodium aryl sulfides and propiolactone, adapting Gresham's procedure (17): 3-phenylmercaptopropionic acid (17); 3-(*p*-tolymercapto)propionic acid (5,18,19); 3-(*o*-tolymercapto)propionic acid (18).

3-Arylmercaptobutyric Acids.

3-(*p*-Tolylmercapto)butyric acid was prepared by a slight modification of the literature procedure (13). A mixture of 44.6 g. (0.35 mole) of *p*-toluenethiol, 36.0 g. (0.42 mole) of crotonic acid, 1 ml. of piperidine and 1 ml. of Triton B was refluxed at 200° for 2 hours. The dark orange solution was subjected to vacuum distillation, yielding a colorless oil (100%), b.p. 140-144° (0.32 mm.).

4-Thiochromanones.

4-Thiochromanone (5), 6-methyl-4-thiochromanone (5,19), 8-methyl-4-thiochromanone (18) and 2,6-dimethyl-4-thiochromanone (13) were prepared by cyclizing the appropriate 3-arylpropionic acid in sulfuric acid.

Isothiochroman-4-one.

Benzylthioacetic acid (20,21,22) was prepared from α-toluenethiol and chloroacetic acid. Cyclization was achieved (20) with phosphorus pentoxide to give the ketone (m.p. 59-60°).

2,6-Dimethyl-4-thiochromones (XXVII).

This procedure was adapted from that used by Bossert (14). A polyphosphoric acid (600 g.) solution of 24.8 g. (0.20 mole) of *p*-toluenethiol and ethyl acetoacetate (0.20 mole) was stirred on a steam bath for 45 minutes. The brown solution was poured into 1 l. of water and allowed to stand overnight. The product was filtered and recrystallized from benzene/petroleum ether as white prisms (29 g., 77%) melting at 114°.

Ylidenemalononitriles.

The method used was described in previous papers (2) following the procedure of Mowry (23). Yields were improved by the use of xylene as solvent. Some of the physical properties of the dinitriles are listed in Table I.

The ylidenemalononitrile adduct of 2,6-dimethyl-4-thiochromone was prepared by allowing XXVII (0.01 mole) and malononitrile (0.12 mole) to react in 200 ml. of acetic anhydride at 140° for 3 hours. The product was filtered from acetic anhydride and recrystallized from benzene as yellow needles (7.6 g., 32%) of XXVII, melting at 184°, lit. m.p. 180° (14).

Sodium Thiochroman-4-ylidenecyanoacetamide-6-sulfonate (III).

A solution of 5 g. (0.24 mole) of IIa in 50 ml. concentrated sulfuric acid was allowed to stand at room temperature for 30 minutes. The black reaction mixture was poured into 200 ml. of ice-water. No tarring was evident. After standing overnight, the clear solution was filtered, chilled, and 20 g. of sodium chloride added. Stirring and scratching effected the crystallization of a bright yellow solid which was recrystallized from hot 95% ethanol. The purified product did not melt below 300° and was obtained in 92.8% yield; I.R. ν max (potassium bromide) 3400 (NH), 1650 (amide CO), 2220 (CN), 1200 (RSO_3-) and 1035 (RSO_3-) cm^{-1}; U.V. λ max (ethanol) (log ε) 306 (3.91), 274 (4.16) and 267-270 sh (4.13-4.14) mμ. The structure proposed was also confirmed by an nmr spectrum, which showed a series of complex multiplets for the aromatic hydrogens at 1.35-1.45 (1 H), 1.9-2.2 (1 H), 2.45-2.70 (1 H) and a broad band (methylene protons) at 6.4-6.9 (4 H) τ.

Anal. Calcd. for $C_{12}H_9N_2O_4S_2Na$: C, 43.37; H, 2.71; N, 8.43. Found: C, 43.53; H, 2.61; N, 8.34.

S-Benzylthiuronium Thiochroman-4-ylidenecyanoacetamide-6-sulfonate (IV).

The procedure of Chambers and Watt (24) was utilized. About 2 g. of the sodium salt of III was dissolved in the smallest amount of hot water, and a concentrated solution containing 2 g. of *S*-benzylthiuronium chloride was added to that of the sulfonate and shaken thoroughly with cooling in an ice bath. The bright yellow product was recrystallized from hot ethanol/water. This material melted and resolidified at 60-64°, then melted again at 179-180°; I.R. ν max (potassium bromide) 3220-3050 (NH^+, NH), 1650 (amide CO), 1200 (RSO_3-) cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}N_4S_3O_4$: C, 50.42; H, 4.20; N, 11.78; S, 20.17. Found: C, 50.69; H, 4.47; N, 11.97; S, 20.46.

When the recrystallization mixture was allowed to stand overnight to complete precipitation, the product redissolved. Concentration of the solvent gave an orange crystalline product melting at 197-198°, which exhibited no nitrile absorption in the infrared region of the spectrum. When analyzed, this material proved to be the keto-sulfonic acid salt (V) expected from hydrolysis of the cyanoacetamide function, by comparison to an authentic sample.

S-Benzylthiuronium 4-Thiochromanone-6-sulfonate (V).

Five g. of 4-thiochromanone (I) was heated on a steam bath with 50 ml. of concentrated sulfuric acid for 2 hours to give VI. The resulting dark red solution was poured onto crushed ice and saturated with sodium chloride. Then, 5 g. of *S*-benzylthiuronium chloride was added to the acidic solution with vigorous stirring. After 1 hour, a pale yellow product was collected and recrystallized from 50% ethanol/water to give a product melting at 197-198° in 66.4% yield; I.R. ν max (potassium bromide) 1660 (CO) cm^{-1}. This substance proved identical (infrared, melting point, mixture melting point) to the hydrolysis product (V) resulting from IV.

Anal. Calcd. $C_{17}H_{18}N_2O_4S_3$: C, 49.76; H, 4.39; N, 6.83; S, 23.41. Found: C, 49.73; H, 4.54; N, 6.93; S, 23.32.

3,3-Dicyano-6′-methylspiro[oxirane-2,4′-thiochroman] 1′,1′-Dioxide (VII).

After dissolving 10 g. (0.047 mole) of IIa in 200 ml. glacial acetic acid, 35 ml. of 30% hydrogen peroxide was added and the solution heated on a steam bath for 1 hour. The yellow solution turned black almost immediately. At the end of 1 hour, the solution was dark red, but clear; after pouring onto 1 l. of crushed ice, the pale yellow precipitate was recrystallized from dilute acetic acid, to give 8 g. (70%) of white crystals which melted at 210-212°; I.R. ν max (potassium bromide) 2250 (CN), 1310 (RSO_2R), 1255 (eposide), and 1145 (RSO_2R) cm^{-1}. A positive periodic acid test (10) for an epoxide was obtained and the product was identified as VII.

Anal. Calcd. for $C_{12}H_8N_2O_3S$: C, 55.38; H, 3.07; N, 10.76; S, 12.30. Found: C, 55.55; H, 3.33; N, 10.56; S, 12.40.

When the reaction time was extended to 2 hours, a white product (5.5 g., 46%) melting at 248-249° was isolated. This substance was recrystallized from dilute acetic acid and analyzed as the cyanoacetamide (VIII); I.R. ν max (potassium bromide) 3400 (NH), 3200 (NH), 1700 (amide CO), 2230 (CN), 1310 (RSO_2R), 1255 (epoxide), and 1145 (RSO_2R) cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_2O_4S$: C, 51.80; H, 3.60; N, 10.07; S, 11.51. Found: C, 52.03; H, 3.94; N, 10.01; S, 11.49.

Cyclization of 6-Methylthiochroman-4-ylidenemalononitrile (IIb).

To a solution of 60 ml. of concentrated sulfuric acid, 2 g. (0.009 mole) of IIb was gradually added with stirring. The color

of the mixture became dark red, greenish black and finally dark blue. This reaction mixture was allowed to stand for a given period of time (see discussion) at room temperature. At the end of the period, the blue medium was warmed on a steam bath to 70°, cooled to 50° and poured onto ice. After standing overnight, a maroon product was collected by suction filtration from a purple solution. This product was recrystallized from ethyl acetate as a fluffy reddish orange substance. Some black (purple) insoluble residue remained on the filter paper in trace quantities. Yields of 11.3-20.4% of XII melting at 216-219° were collected; I.R. ν max (potassium bromide) 3400 (NH), 1670 (amide CO) and 1700 (CO) cm^{-1}; U.V. λ max (95% ethanol) (log ϵ) 240-246 sh (4.38), 249 (4.40) and 277-295 (3.90) mμ. The indene structure was confirmed by nmr which showed bands at 2.83 τ (2H, singlet, C_7 and C_8 protons), 7.5 τ (3H, singlet, C_6 methyl) and two broad structured bands centered at 6.41 τ (2H) and 6.8 τ (2H) (C_2 and C_3 methylenes). In sulfuric acid this compound gave a purple solution. The R_f value taken on tlc was 0.65 (25).

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 63.67; H, 4.49; N, 5.71; S, 13.06. Found: C, 63.56; H, 4.79; N, 5.82; S, 13.43.

Evaporation of the red ethyl acetate mother liquor gave a red product XI which melted at 177-179°. Recrystallization from 96% ethanol or ethyl acetate/petroleum ether gave an orange recrystalline product melting 179-181° which dissolved in warm base and reprecipitated with hydrochloric acid giving an orange solid. In sulfuric acid the product produced a purple mixture. This product was obtained in 21.2-37% yields; I.R. ν max (potassium bromide) 3400 (NH), 1700 (CO) and 1665 (amide CO) cm^{-1}; U.V. λ max (95% ethanol) (log ϵ) 243 (4.28), 249 (4.32), 266-276 sh (4.01) and 330-350 (3.50) mμ. The structure of XI was confirmed by its nmr spectrum showing bands at 2.71-3.00 τ (2H, 4 sharp peaks, C_7 and C_8 protons) 7.5 τ (3H, singlet, C_6 methyl) 6.5 τ and 7.25 τ (5H, series of broad bands, C_2, C_3 and C_{3a} methylenes and methine). This data is consistent for an enol structure of XI. The R_f value taken on tlc was 0.55.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.16; H, 5.26; N, 5.67; S, 12.95. Found: C, 62.90; H, 5.23; N, 5.61; S, 12.97.

Upon standing several days a reddish product precipitated from the original aqueous reaction solution. Basification with ammonium hydroxide gave an additional quantity of the reddish product. This material was filtered, dried, and sublimed *in vacuo* (128°/1.25 mm) to yield XIV as white prisms (5% based on overall product isolation), m.p. 109-110° (ethanol), and XIII (35.6-54.8%), which remained in the reservoir of the sublimator, as maroon needles, m.p. 265-267° (DMF/water). Compounds XIII (15%) and XIV) (60%) were also isolated and separated by the sublimation technique upon treatment of XI with 100 ml. of 10% acid (hydrochloric or sulfuric) followed by stirring at room temperature and subsequent refluxing for 16 hours.

Compound XIII has I.R. ν max (potassium bromide) 3370 (NH), 1660 (amide CO) and 1650 (CO) cm^{-1}; U.V. λ max (95% ethanol) (log ϵ) 212 (4.59), 244 (4.28), 300 (4.29) and 355-365 sh (3.47) mμ; U.V. λ max (sulfuric acid) (log ϵ) 207 (2.17), 221-223 (4.26), 240 (4.25), 301 (4.40) and 3.71 (4.16) mμ. The nmr spectrum showed bands at 0.95-1.55 τ (2H, a series of four sharp peaks, C_2 and C_3 protons), 1.9-2.3 τ (2H, a series of four sharp peaks, C_7 and C_8 protons) and 7.15 τ (3H, singlet C_6 methyl). The R_f value taken on tlc was 0.475.

Anal. Calcd. for $C_{13}H_9NO_2S$: C, 64.19; H, 3.70; N, 5.76; S, 13.17. Found: C, 63.96; H, 3.77; N, 6.02; S, 13.11.

Compound XIV gave I.R. ν max (potassium bromide) 1700 (CO) cm^{-1}; U.V. λ max (hexane) (log ϵ) 212 (3.97), 237 (4.34), 243 (4.35), 264 (3.91), 273 (3.90) and 328-341 (3.50) mμ. The nmr showed bands at 6.72-7.07 τ (10H, multiplet) and 2.82-3.18 (2H multiplet C_7 and C_8 protons). The R_f value taken on tlc was 1.00.

Anal. Calcd. for $C_{12}H_{12}OS$: C, 70.58; H, 5.88; O, 7.83; S, 15.66. Found: C, 70.70; H, 5.72; O, 8.08; S, 15.74.

The 2,4-dinitrophenylhydrazone derivative derivative of XIV was recrystallized from ethyl acetate as red needles, m.p. 179° dec.

Anal. Calcd. for $C_{18}H_{16}N_4O_4S$: N, 14.58. Found: N, 14.65.

An efficient separation of XI, XII and XIII is obtained by Soxhlet extraction of the water insoluble mixture; XI and XII separated from XIII (ethyl acetate insoluble). XII precipitated from cooled ethyl acetate solution, and XI obtained by concentration of mother liquor.

Conversion of 4-Carbamoyl-2,3-dihydro-6-methyl-5*H*-cyclopenta[*d,e*]benzothiopyran-5-one (XII) into 4-Carbamoyl-2,3,3a,4-tetrahydro-6-methyl-5*H*-cyclopenta[*d,e*]benzothiopyran-5-one (XI) and 4-Carbamoyl-6-methyl-5*H*-cyclopenta[*d,e*]benzothiopyran-5-one (XIII).

After stirring a solution of 125 mg. of XII in 10 ml. concentrated sulfuric acid at room temperature for 3 hours, it was poured over ice and allowed to stand. The resulting product was collected by filtration and found to be a mixture of XI, XII, and XIII by thin layer chromatography. Refluxing 15% hydrochloric acid solution for 30 minutes produced the same results. (Under similar conditions XI gave XII and XIII.)

4-Bromo-4-carbamoyl-6-methyl-2,3,3a,4-tetrahydro-5*H*-cyclopenta[*d,e*]benzothiopyran-5-one (XV).

Dropwise addition of 1.60 g. (0.01 mole) of bromine in 5 ml. of acetic acid to a 40 ml. acetic acid solution of 2.49 g. (0.01 mole) of XI was carried out over a 10 minute period at 0°. The dark red solution was stirred at room temperature for 30 minutes after cessation of the bromine addition, poured over 200 ml. of ice water, filtered and recrystallized from 95% ethanol as bright red prisms, (3.21 g., 99%) m.p. 147-149° dec; I.R. ν max (potassium bromide) 3400 (NH), 3385 (associated NH) 1690 (CO) and 1670 (amide CO) cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}NO_2SBr$: C, 47.85; H, 3.68; N, 4.29. Found: C, 47.68; H, 3.61; N, 4.00.

Dehydrobromination of XV.

A solution of 50.0 mg. (16.0 mmoles) of XV in 4 ml. of *s*-collidine was refluxed with stirring for 5 minutes at which time a purple solution resulted. Warm benzene was added to the cooled solution and filtered to yield a water soluble material which gave a positive silver nitrate test (*s*-collidine hydrobromide).

The benzene mother liquor was washed with two 20 ml. portions of 10% hydrochloric acid saturated with sodium chloride, 20 ml. of saturated sodium chloride solution, 20 ml. of water and then dried over anhydrous magnesium sulfate. Upon evaporation of the benzene, a gummy material resulted which crystallized from ethyl acetate-hexane as a 1:1 mixture of XII and XIII; separated by fractional recrystallization from a small amount of ethyl acetate and thin layer chromatography.

The use of lithium chloride (26) as the dehydrobromination agent produced a 61% yield of a 3:1 mixture of XII and XIII.

3a-Cyano-4-carbamoyl-6-methyl-2,3,3a,4-tetrahydro-5*H*-cyclopenta[*d,e*]benzothiopyran-5-one (XVI).

In an approach similar to that reported for the α-tetralone derivative (12,27), a heterogeneous mixture of 125.0 mg. (0.5 mmole) of XII, 2.5 ml. of water, 2.0 ml. of *t*-butanol and 25.0 mg. (0.5 mmole) of sodium cyanide was warmed on a steam bath for 5 minutes at which time the solution became homogeneous and dark

red. The solution was allowed to stand at room temperature for 1 hour and acidified with 20% sulfuric acid to yield a red product (84 mg., 62%; ethyl acetate), m.p. 190-192°; I.R. ν max (potassium bromide) 3380 (NH), 2230 (CN), 1680 (CO), 1670 (associated CO) and 1655 (amide CO); U.V. λ max (95% ethanol) (log ϵ) 243 sh (4.17), 252 (3.92) and 339-347 (3.53) mμ.

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.77; H, 4.41; N, 10.29; S, 11.76. Found: C, 61.75; H, 4.45; N, 10.50; S, 11.88.

3a-Cyano-4-carbamoyl-6-methyl-2,3,3a,4-tetrahydro-5*H*-cyclopenta[*d,e*]benzothiopyran-5-ol (XVII).

To a 25 ml. aqueous solution of 320.0 mg. 1.17 mmoles of XVI, 300 mg. of sodium borohydride in 10 ml. of 2% sodium hydroxide solution was added dropwise over a period of 15 minutes. Stirring of the reddish solution overnight produced a color change to yellow. Neutralization and recrystallization of the product from aqueous ethanol gave white needles (257 mg., 80%), m.p. 207-209°; I.R. ν max (potassium bromide) 3345 (OH), 3200 (OH), 2230 (CN) and 1665 (amide CO) cm^{-1}; U.V. λ max (95% ethanol) (log ϵ) 220 (4.05), 261 (3.88), 291 (2.78) and 300 (2.78) mμ.

Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.28; H, 5.11; N, 10.22. Found: C, 61.40; H, 5.15; N, 10.28.

4-Carbamoyl-6-methyl-2,3,3a,4-tetrahydro-5*H*-cyclopenta[*d,e*]-benzothiopyran-5-ol (XVIII).

To a 25 ml. stirred, heterogeneous absolute ethanol mixture of 750 mg. (3.0 mmoles) of XI, 250 mg. of sodium borohydride in 10 ml. of water was added dropwise. The solution was stirred at room temperature for 2 hours becoming clear in 5 minutes. The precipitate was filtered and recrystallized from absolute ethanol as light yellow needles (450 mg., 60%), m.p. 193.5-195°; I.R. ν max (potassium bromide) 3400 (OH), 3395 (OH), 3210 (NH), 1660 (unassociated amide CO) and 1650 (associated amide CO) cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.90; H, 6.31; N, 5.82.

4-Carbamoyl-6-methyl-5*H*-cyclopenta[*d,e*]benzothiopyran-5-one Bisulfate (XIX).

A 0.1 g. sample of XIII was dissolved in concentrated sulfuric acid to give a reddish solution. This solution was cooled in an ice bath, and ethyl acetate was gradually added to the chilled mixture. The red precipitate was collected by filtration, washed thoroughly with ethyl acetate, dried and observed to decompose at temperatures greater than 240° but without melting below 300°; I.R. ν max (potassium bromide) 3500-2000 (salt) and 1670 (amide CO) cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}NO_6S_2$: C, 45.75; H, 3.23; N, 4.11. Found: C, 45.76; H, 3.45; N, 4.05.

The red picrate of XIII, recrystallized from chloroform/petroleum ether, melted in the range 216-218°; I.R. ν max (potassium bromide) 3000 (NH), 3100 (NH), 3000-2400 (salt), 1660 (CO) and 1640 (amide CO) cm^{-1}.

Anal. Calcd. for $C_{19}H_{12}N_4O_9S$: C, 48.31; H, 2.54; N, 11.86; S, 6.87. Found: C, 48.06; H, 2.58; N, 12.18; S, 6.82.

6-Methyl-2,3,3a,4-tetrahydro-5*H*-cyclopenta[*d,e*]benzothiopyran (XXI).

A solution of 1.0 g. (4.0 mmoles) of XVIII in 100 ml. of 50% sulfuric acid was heated with stirring at 160° for 11 hours. After 1 hour the solution became green and white crystals began to appear in the reflux condenser. After cessation of reflux and purification by sublimation of these crystals *in vacuo* (40°/0.33 mm.), white prisms (137 mg., 18%), of XXI (m.p. 55°) resulted; I.R. ν max (potassium bromide) 2895 (CH), 2850 (CH) cm^{-1}; U.V. λ max (95% ethanol) (log ϵ) 220 (4.27), 261 (3.98), 289 (2.91) and 300 (2.60) mμ. The nmr spectrum indicated only methylene/methyl and aromatic protons in a ratio of 9:3:2.

Anal. Calcd. for $C_{12}H_{14}S$: C, 75.73; H, 7.36. Found: C, 75.55; H, 7.28.

The blue-green acidic solution was poured over ice and allowed to stand overnight. The dark blue-green product could not be sublimed and was recrystallized from aqueous methanol as dark blue-green prisms, m.p. 320°, probably polymeric. Thin layer chromatography showed this material to be a single product. Extraction of the aqueous acidic solution with chloroform yielded a purplish gum which could not be crystallized nor purified.

Compound XIV could be converted quantitatively to XXI, identical to that obtained above, using Wolff-Kishner reduction conditions (28).

6-Methyl-2,3,3a,4-tetrahydro-5*H*-cyclopenta[*d,e*]benzothiopyran-5-ol (XIVa).

A 10 ml. absolute ethanol solution of 204 mg. (1.0 mmole) of XIV and 40 mg. (1.0 mmole) of sodium borohydride was stirred at room temperature for 2 hours. The solution was concentrated and the white product (155 mg., 75%) was recrystallized from aqueous ethanol as white needles, m.p. 115°; I.R. ν max (potassium bromide) 3320 (OH) cm^{-1}.

Anal. Calcd. for $C_{12}H_{14}OS$: C, 69.86; H, 6.80; O, 7.76. Found: C, 69.55; H, 7.09; O, 7.77.

4-Carbamoyl-2,3-dihydro-6-methyl-3a*H*-cyclopenta[*d,e*]benzothiopyran (XXII) and 4-Carboxyl-2,3,3a,4-tetrahydro-6-methyl-5*H*-cyclopenta[*d,e*]benzothiopyran-5-ol (XXIII).

A 25 ml. 10% sodium hydroxide solution of 1.20 g. (4.80 mmoles) of XVIII was heated under reflux for 11 hours. The starting material was initially insoluble in base but gradually became homogeneous and refluxing continued until there was no more ammonia evolved. The insoluble material was filtered (377 mg., 34%) and recrystallized from methanol as gray needles, m.p. 237.5-239.5°, identified as XXII; I.R. ν max (potassium bromide) 3400 (NH) and 1655 (amide CO) cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.53; H, 5.63; N, 6.06; O, 6.93. Found: C, 67.56; H, 5.69; N, 6.18; O, 6.94.

The mother liquor was neutralized with 7% hydrochloric acid solution and upon standing several days a product (408 mg., 34%) precipitated, which was soluble in bicarbonate solution with carbon dioxide evolution, and was recrystallized from ethyl acetate/petroleum ether as white needles, m.p. 200-201°, identified as XXIII; I.R. ν max (potassium bromide) 3455 (OH), 2880-2930 (OH, carboxylic acid, and associated acid CO) cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}O_3S$: C, 62.37; H, 5.60. Found: C, 62.08; H, 5.65.

(5-Carboxy-6-methylthiochroman-4-yl)acetic Acid (XXIV).

A solution of 3.20 g. (13.0 mmoles) of XI in 100 ml. of 20% sodium hydroxide was refluxed for 5 hours, accompanied by a distinct ammonia evolution. The blackish reaction solution was acidified with hydrochloric acid solution and allowed to stand overnight yielding a black product which was recrystallized from benzene (Norit) as cream prisms (2.0 g., 58%), m.p. 171°, identified as XXIV (compare 2a); I.R. ν max 2510-3100 (broad OH), 1660-1700 (broad acid CO) cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}O_4S$: C, 58.64; H, 5.26; O, 24.02; Eq. Wt., 133.1. Found: C, 58.61; H, 5.25; O, 24.36; Eq. Wt. (titration) 132.8.

Cyclization of 2,6-Dimethylthiochroman-4-ylidenemalononitrile (XXV).

Using a procedure identical to that for IIb, the following products were obtained after 4 hours reaction time with 2.4 g. (0.01 mole) of XXV in 60 ml. of concentrated sulfuric acid.

Compound XXVa was obtained as orange needles (1.3 g., 50%) from ethanol, m.p. 165°; I.R. ν max (potassium bromide) 3400 (NH), 1710 (CO), and 1670 (amide CO) cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.37; H, 5.75; N, 5.37. Found: C, 64.42; H, 5.72; N, 5.25.

The product XXVb was obtained as red-orange needles (209 mg., 8%) from ethyl acetate m.p. 199-200°; I.R. ν max (potassium bromide) 3410 (NH), 1700 (CO), and 1675 (amide CO) cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.86; H, 5.02; N, 5.40. Found: C, 65.01; H, 5.22; N, 5.25.

Nothing resulted from the purple mother liquor upon standing 4 days so it was basified with ammonium hydroxide and a maroon product (0.91 g., 35%) resulted which was recrystallized from dimethylformamide/water as maroon prisms, identified as XXVc by comparison to that product obtained using XXVIII in polyphosphoric acid (see below).

4-Carbamoyl-2,6-dimethyl-5*H*-cyclopenta[*d*,*e*]benzothiopyran-5-one (XXVc).

To 50.0 g. of polyphosphoric acid, 1.59 g. (6.6 mmoles) of 2,6-dimethylthiochroman-4-ylidenemalononitrile (XXVIII) was added and the resulting solution stirred at 130° for 105 minutes. The deep red solution was poured into ice water and the maroon product collected and crystallized from ethanol to give 0.52 g. of deep maroon needles, which was then recrystallized from benzene (0.32 g., 19%), m.p. 260°; I.R. ν max (potassium bromide) 3330 (NH) 3250 (CH) 1650 (CO Amide I) and 1540 (Amide II) cm^{-1}; U.V. λ max (ethanol) (log ϵ) 214 (4.60), 246 (4.30), 304 (4.31), 340-370 (broad sh) (3.5) mμ.

Anal. Calcd. for $C_{14}H_{11}NO_2S$: C, 65.36; H, 4.31; S, 12.44. Found: C, 65.52; H, 4.46; S, 12.40.

4-(1′,1′-Dicyanoethyl)-6-methyl-2*H*-thiochromene (XXVI).

To 75 ml. of a cooled, stirred dimethylsulfoxide solution of 2.26 g. (0.01 mole) of IIb, 0.5 g. (0.01 mole of 57% dispersion) of sodium hydride was added. To the resultant dark brown solution, 1.42 g. (0.01 mole) of methyl iodide was added dropwise, stirred at room temperature for 15 hours, poured over ice and the precipitated black product recrystallized from ethanol as white needles (1.0 g., 44%), m.p. 100-102°; I.R. ν max (potassium bromide) 2220 (CN) and 1620 (C=C) cm^{-1}

Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 70.00; H, 5.00. Found: C, 69.83; H, 5.37.

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