

SOME CHEMISTRY OF 3-(2'-TETRAHYDOPYRANYLTHIO)INDOLE,
A MODEL STUDY IN SULFUR EXTRUSION

by

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ABSTRACT

3-(2'-Tetrahydropyranylthio)indole, VI, was synthesized from 3-thioindole, X, by treatment with 2-chlorotetrahydropyran, VIII, under basic conditions. This compound was used as a model system to study the feasibility of synthesizing biologically important C-nucleosides by first connecting the sugar to the base through a bridging sulfur atom and then extruding the sulfur atom with formation of the required carbon-carbon bond.

The hemithioketal, VI, is inert to phosphines and phosphites under a variety of conditions. Treatment of the hemithioketal with silver perchlorate in tetrahydrofuran produced a silver complex as evidenced by thin-layer chromatography analysis. Treatment of the complex with hydrochloric acid to precipitate the silver yielded a complex reaction mixture from which was isolated the starting hemithioketal, VI, 3-thioindole, X, and the disulfide of 1-(2'-tetrahydropyranylthio)indole, XVa. When the silver complex was treated with methyl iodide and the resulting reaction mixture was subjected to thin-layer chromatography, 3-methylthioindole, XVI, 1-(2'-tetrahydropyranyl)-3-methylthioindole, XVIII, and the bis-tetrahydropyranyl derivative, XVII, were isolated. It is apparent that carbon sulfur bond cleavage results in the formation of the carbonium ion of tetrahydropyran, XXI, which alkylates an indole nucleus in the one position to produce XV, XVII and XVIII. There is no evidence to indicate that the desired rearrangement to 3-(2'-tetrahydropyranyl)indole, VII, has occurred.

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Special thanks are given to William R. Anderson, Jr., and Harold A. Smith who supplied NMR and mass spectral data.

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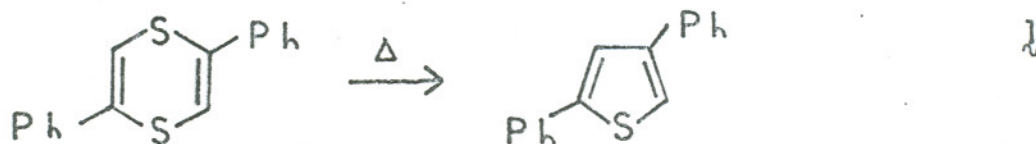
Finally, I wish to express my appreciation to my wife, Linda. Without her, graduate school would have been far less rewarding.

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INTRODUCTION

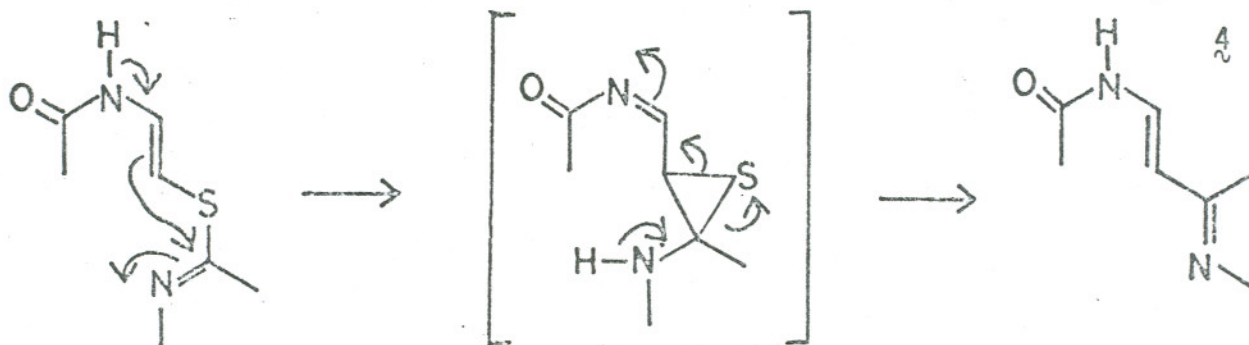
Extrusion reactions occurring within cyclic systems are well known.¹⁻³ A typical example is shown in equation 1. There are, however, relatively

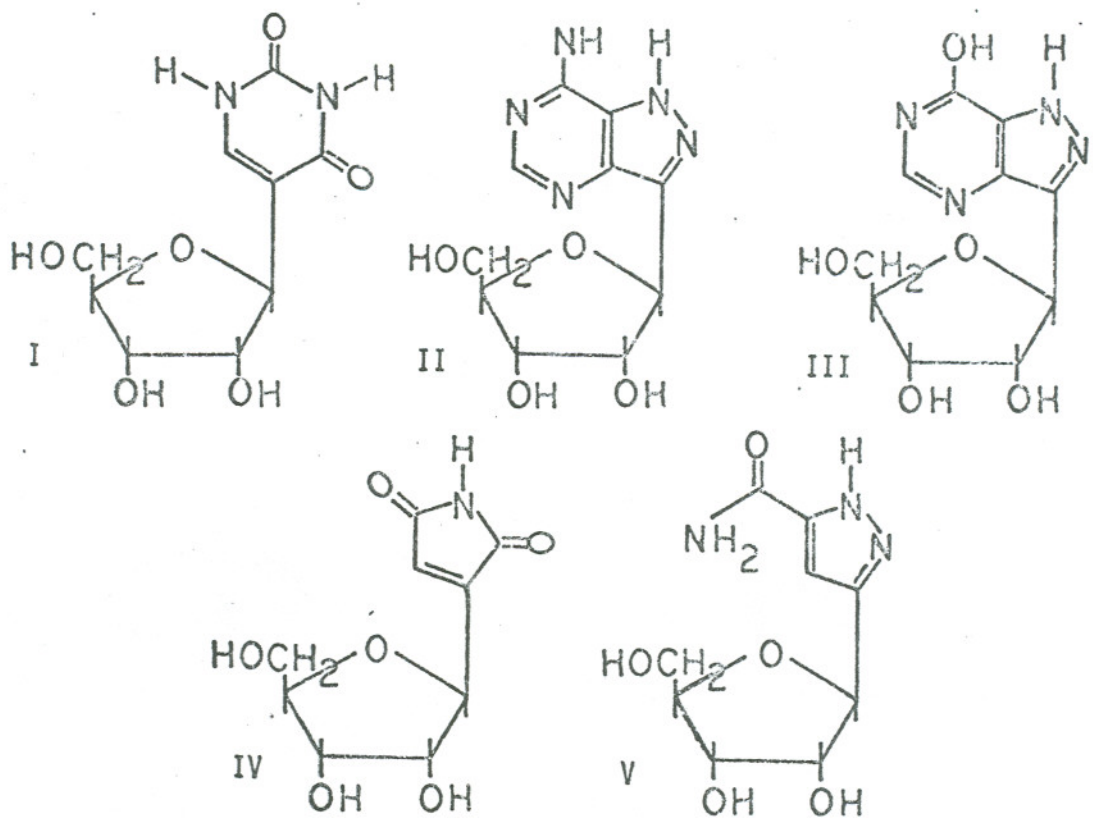


few examples of extrusion reactions resulting in carbon-carbon bond formation linking two moieties not already connected elsewhere. The Ramberg-Bäcklund reaction⁴ and the reductive coupling of alcohols,⁵ two reactions of this type, are shown in equations 2 and 3 respectively. Eschenmoser

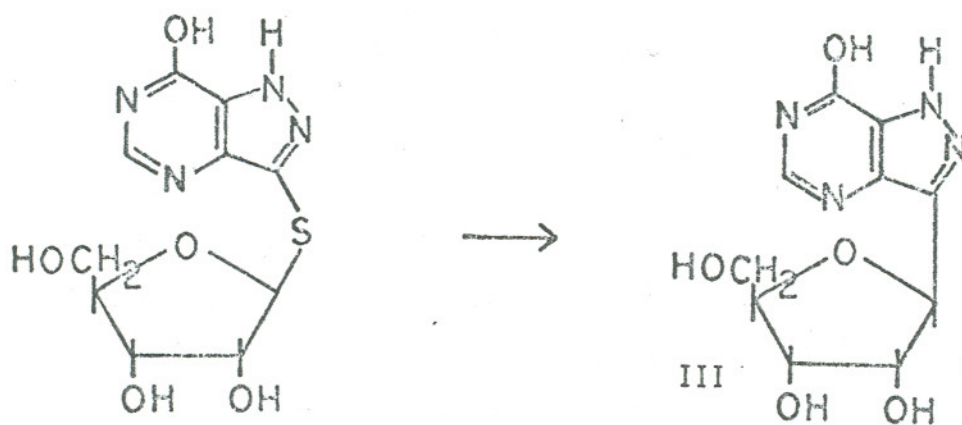


and coworkers⁶⁻⁹ have utilized several extrusion reactions in work directed toward the synthesis of vitamin B₁₂. As illustrated in equation 4, the



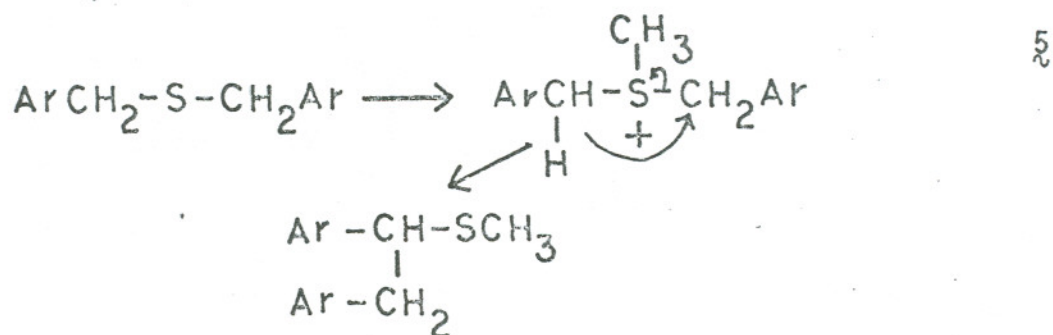


toward a synthesis of formycin, II. All these procedures are lengthy, low yield processes. The potential synthesis of C-nucleosides by sulfur extrusion, exemplified in equation 6, has the considerable advantage of starting from simple sugar and base derivatives.



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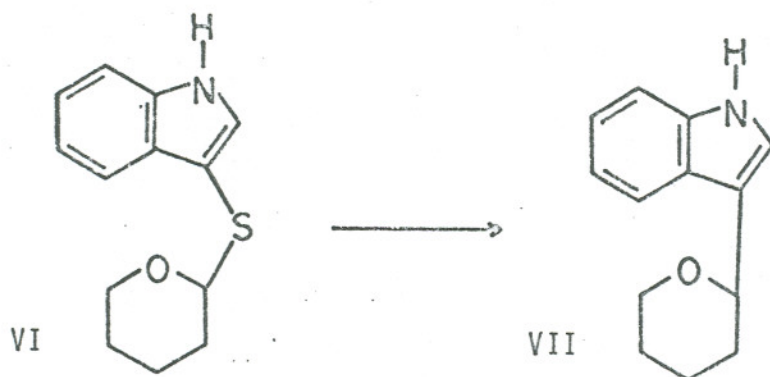
reactions are thought to proceed through an episulfide intermediate. A similar sequence was used by Felner and Schenker in their synthesis of anisomycin.¹⁰ It should also be noted that in addition to phosphines and phosphites, Eschenmoser, *et al.*, also used nickel perchlorate in reactions in which sulfur was extruded. Another approach used by Boekelheide and coworkers¹¹⁻¹³ involved the formation of a sulfonium salt and subsequent rearrangement using strong base (a Stevens rearrangement). This is shown in equation 5.



Consideration of these reactions suggested the possibility that biologically important C-nucleosides might be synthesized via a sulfur extrusion reaction from an intermediate in which the nitrogen base was linked to the sugar moiety by the bridging sulfur atom.

Five such C-nucleosides--pseudouridine (5-ribosyl uracil), I; formycin, II; laurusin (formycin B), III; showdomycin, IV and pyrazomycin, V--are now known. Pseudouridine, I, occurs widely in nucleic acids (particularly in transfer RNA's¹⁴⁻¹⁵) while formycin, II;¹⁶ laurusin, III;¹⁷ showdomycin, IV;¹⁸ and pyrazomycin, V,¹⁹ are antibiotics. Because of their biological importance,²⁰⁻²¹ the syntheses of these compounds have received a considerable amount of attention. Syntheses of pseudouridine, I,²²⁻²³ and showdomycin, IV,²⁴ have been reported; and two research groups, Sprinzl and coworkers²⁵ and Acton, *et al.*,²⁶ have reported work directed

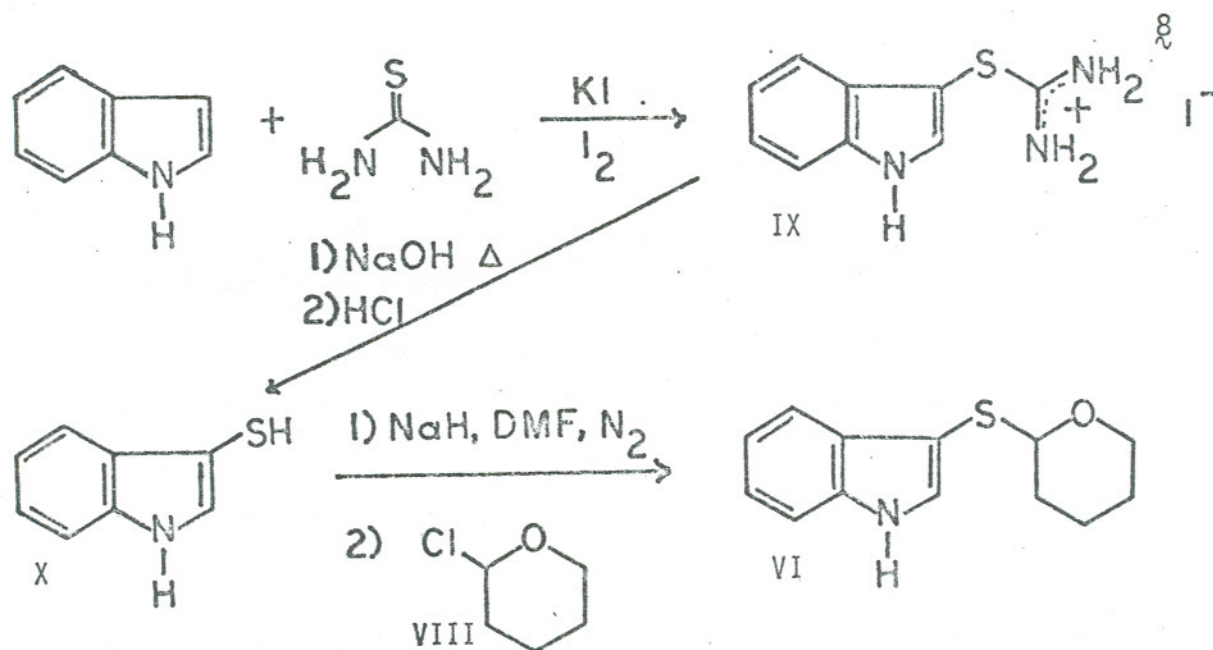
For our initial investigation, a model compound, 3-(2'-tetrahydropyranylythio)indole, VI, was chosen. This model was chosen because of the availability of starting materials and the structural similarities of the system to those of the C-nucleosides. This thesis describes a synthesis of VI and a number of reactions which were investigated in attempts to carry out the desired sulfur extrusion and rearrangement shown in equation 7.



DISCUSSION

Synthesis of 3-(2'-tetrahydropyranylthio)indole, VI.

3-(2'-Tetrahydropyranylthio)indole, VI, was synthesized according to the scheme shown in equation 8. 2-Chlorotetrahydropyran, VIII, was easily



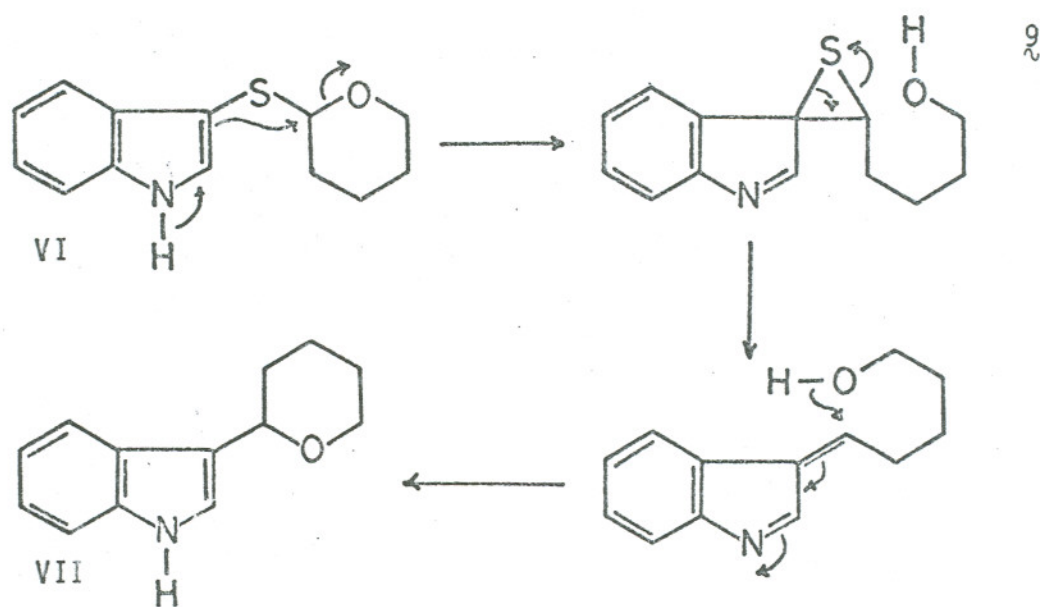
prepared after the manner of Booth and Ouellette,²⁷ by addition of anhydrous hydrogen chloride to dihydropyran in ether solution. 3-Thioindole, X, has been prepared by the reduction of the corresponding disulfide with glucose,²⁸ and in much higher yield by a procedure described by Harris.²⁹ In this procedure S-(3-indolyl)isothiuronium iodide, IX, was prepared by treatment of an equimolar mixture of thiourea and indole in aqueous methanol with a solution of potassium iodide and iodine in the same solvents. The thiol, X, was easily generated from the isothiuronium salt, IX, by heating in aqueous base followed by acidification.

Attempts to prepare the hemithioketal, VI, by reaction of the thiol, X, with 2-chlorotetrahydropyran, VIII, failed. In all cases several

products were formed which were not isolated and characterized. However, generation of the mercaptide in dimethylformamide using sodium hydride and subsequent addition of the 2-chlorotetrahydropyran produced the desired hemithioketal, VI, in moderate yield. The reaction is very sensitive to conditions, and air and water must be carefully excluded.

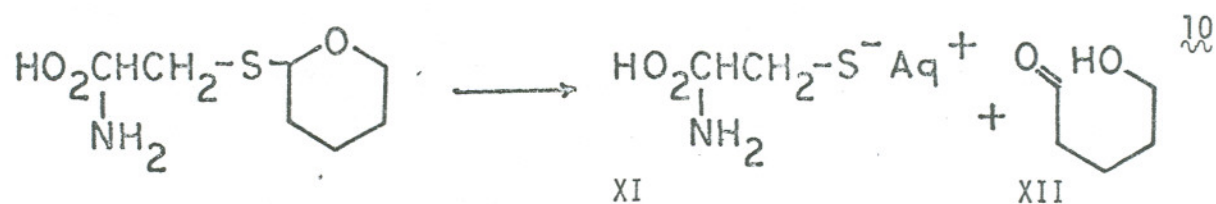
Reaction of 3-(2'-tetrahydropyranylthio)indole, VI, with phosphines and phosphites.

One may envisage the extrusion of sulfur from the hemithioketal, VI, using a phosphine or phosphite (equation 9) in a manner analogous to the procedures described by Eschenmoser.⁶⁻⁹ However, treatment of the hemithioketal, VI, with various phosphines and phosphites under either acidic or basic conditions yielded only starting material.

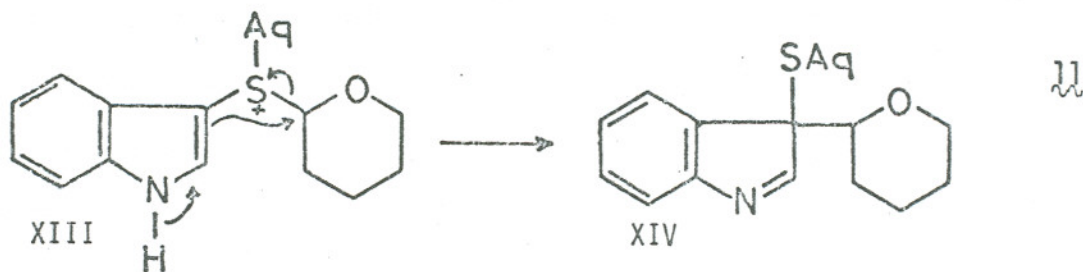


Reaction of 3-(2'-tetrahydropyranyltio)indole, VI, with aqueous silver nitrate.

Another approach to the sulfur extrusion was suggested by the observation of Holland and Cohen³⁰ that treatment of the tetrahydropyranyl derivative of cysteine with aqueous silver nitrate at 0° resulted in the immediate precipitation of the silver mercaptide of cysteine, XI, and formation of 5-hydroxyvaleraldehyde, XII. This is shown in equation 10.



Treatment of hemithioketal, VI, with aqueous silver nitrate yielded the expected silver derivative of 3-thioindole and 5-hydroxyvaleraldehyde, XII. It seemed possible that if the coordination of silver ion with the sulfur took place in the absence of external nucleophiles capable of attacking the tetrahydropyranyl ring, intramolecular displacement of sulfur might occur (equation 11).

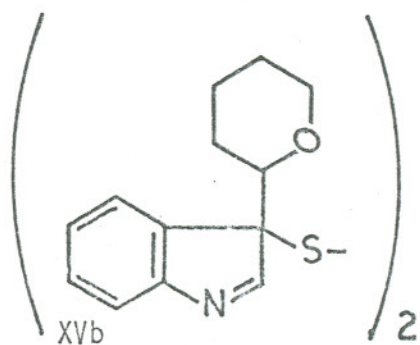
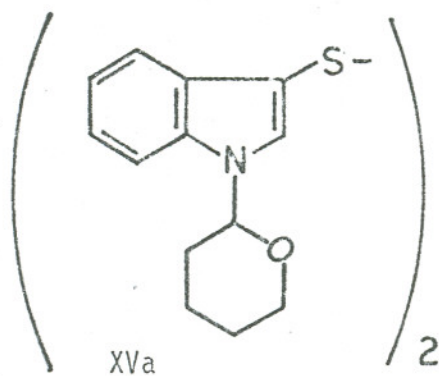


Reaction of 3-(2'-tetrahydropyranyltio)indole, VI, with silver perchlorate.

Combination of equimolar amounts of silver perchlorate (chosen because of its availability in the anhydrous state, its solubility in organic solvents, and the low nucleophilicity of the perchlorate ion) and the hemithioketal, VI, in pyridine at room temperature gave no reaction. When the combination was heated under reflux for two hours, many products were produced as shown by thin-layer chromatography. When the reactants were mixed in benzene instead of pyridine at room temperature, instant precipitation occurred. Treatment of the dark brown precipitate (presumed to be a silver salt or salts) with a saturated solution of hydrogen sulfide in ether gave, once again, a complex mixture of products. If the reaction was carried out at -78° (dry ice--acetone bath) in toluene, an immediate white precipitate was produced which darkened with warming to produce the same complex mixture as before. Addition of pyridine to the complex formed at -78° prior to warming prevented any further reaction and starting material was recovered. It was concluded on the basis of these experiments that the activity of the silver ion was greatly influenced by the extent of interaction of the silver ion with the solvent. After much experimentation, it was discovered that tetrahydrofuran moderated the reaction to the extent that it proceeded at a reasonable rate at room temperature, producing fewer products than were observed using other solvents.

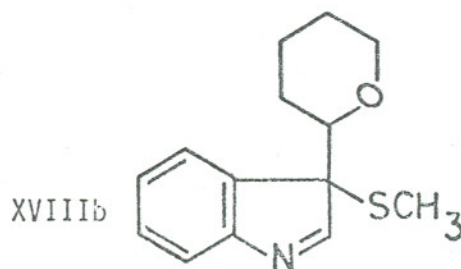
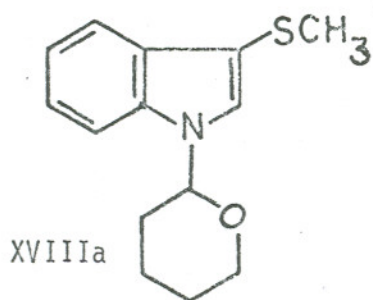
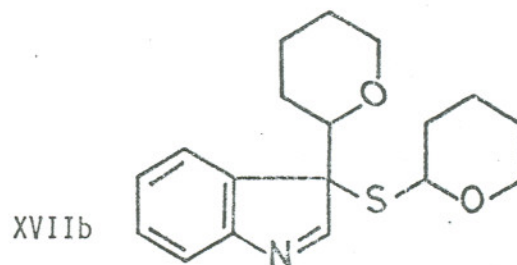
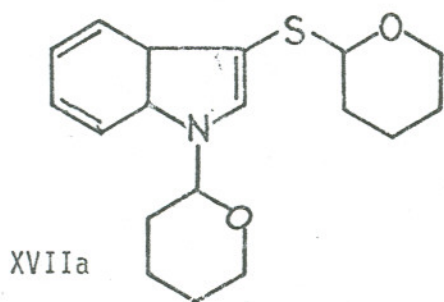
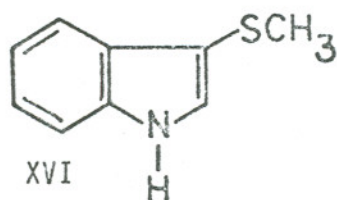
Combination of the silver perchlorate and the hemithioketal, VI, in tetrahydrofuran at -78° gave a clear colorless solution. Analysis by thin-layer chromatography indicated the presence of uncomplexed starting material. The solution turned yellow with warming, and at some point during the reaction a precipitate usually formed which accounted for approximately 25% of the combined weight of hemithioketal and silver perchlorate added.

There appeared to be no basic difference in reactions run at various temperatures between -15° and 25° other than the rate of appearance of the color and of the precipitate. In most cases, the precipitate redissolved with time, and in a few instances no precipitation occurred. In all cases, analysis by thin-layer chromatography indicated the absence of free hemithioketal, VI, in the mixture. All of the material present was very polar, apparently as a result of coordination with silver ion. No obvious correlation of the course of the reaction with parameters such as temperature and concentration of reactants was observed. Addition of water to the mixture caused no visible reaction, and treatment of such solutions with hydrochloric acid to remove silver ion produced results similar to those obtained when no water was added prior to workup. Treatment of the precipitated complex and the complex in solution with hydrochloric acid followed by thin-layer chromatographic analysis gave similar mixtures of products, the main difference being that the soluble complex yielded starting material as the major component, while the precipitated complex yielded none. Isolation of the major components of the reaction by thin-layer chromatography yielded the starting hemithioketal, VI, 3-thioindole, X, the disulfide of 3-thioindole, and a compound exhibiting nuclear magnetic resonance (NMR) and mass spectra consistent with both structures XVa and XVb (see Experimental).



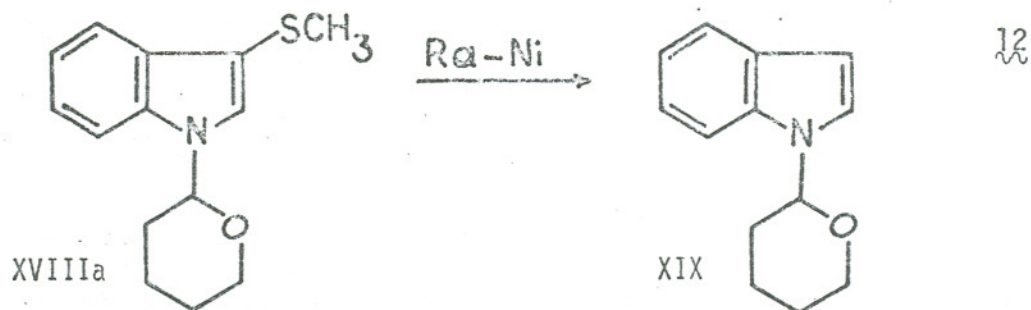
Reaction of methyl iodide with the silver complex of VI.

Addition of methyl iodide to the silver complex of VI in tetrahydrofuran below room temperature gave no reaction. When the reaction was carried out at room temperature a precipitate of silver iodide was formed over a period of several hours. The major products of the reaction were isolated by column and thin-layer chromatography (see Table 2). In addition to a relatively small amount of the starting hemithioketal, VI, 3-methylthioindole, XVI, a compound exhibiting NMR and mass spectra consistent with structures XVIIa and XVIIb, and a compound exhibiting NMR and mass spectra consistent with structures XVIIIa and XVIIIb (see Experimental) were isolated.



Elucidation of structures.

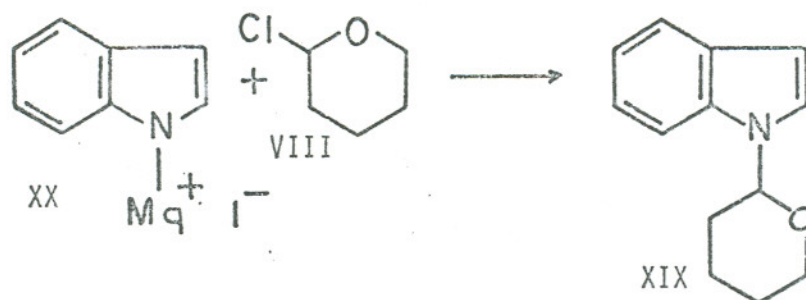
Treatment of compound XVIII with Raney nickel gave 1-(2'-tetrahydropyranyl)indole, XIX (equation 12). This structure was clearly indicated on the basis of spectral data. The utility of nuclear magnetic resonance



for assigning structures of indole derivatives was first discussed by Cohen *et al.*³¹ The proton in the three position of indole is found at δ 6.38 (CCl₄), and is coupled to both the proton in the two position and the proton on nitrogen. Alkylation of the nitrogen eliminates coupling to that position and the three proton occurs as a doublet, $J=3.5$ cps.³² The three proton in 1-(2'-tetrahydropyranyl)indole, XIX, is clearly seen as a doublet at δ 6.36, $J=3.5$ cps. (see Table 1). The infrared spectrum for XIX shows no N-H absorption, and the mass spectrum exhibits a parent ion at m/e 201 and other ions consistent with structure XIX (see Experimental).

Although structure XIX was clearly indicated by consideration of the spectral data, comparison was made with authentic material synthesized by another route. In an attempt to prepare 3-(2'-tetrahydropyranyl)indole, the indole Grignard reagent, XX,³³ was treated with 2-chlorotetrahydropyran, VIII, (equation 13). Unexpectedly, the only product other than unreacted indole obtained in anything but trace amounts was 1-(2'-tetrahydropyranyl)indole, XIX.

This result was surprising since a search of the literature failed to reveal a single example of exclusive alkylation at the one position using the Grignard reagent.³⁴



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Once the structure of XIX had been unambiguously determined, the detailed structural assignment for compounds XV, XVII and XVIII were made on the basis of their nuclear magnetic resonance spectra. The chemical shift of the two protons on the tetrahydropyranyl ring occurs in the range δ 4.80-4.84 when attached to sulfur and in the range δ 5.32-5.40 when attached to nitrogen. In all cases, mass spectral data were consistent with proposed structures and a strong parent ion was always observed.

TABLE 1
NMR Data

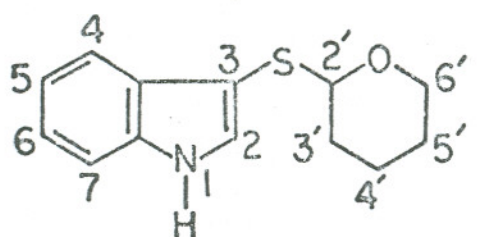
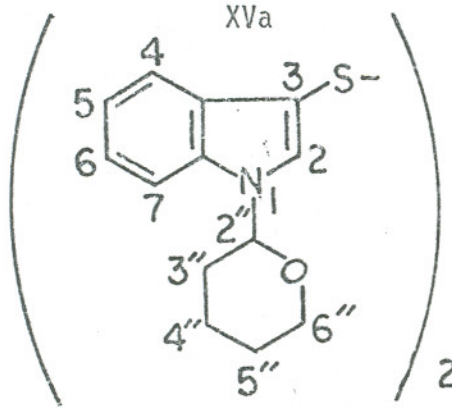
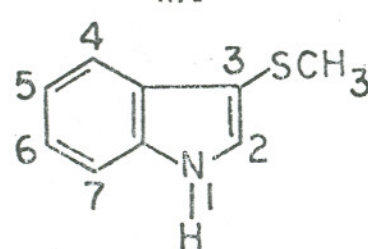
Compound	Proton	Chemical Shift ppm	Multiplicity	J (cps)
 <p>VI</p>	1	8.39	(s)	
	2	6.84	(d)	3.0
	4	7.64	(m)	
	5-7	7.05	(m)	
	2'	4.84	(d of d)	
	3'-5'	1.4-2.0	(m)	
	6'a	3.45	(m)	
	6'b	4.16	(m)	
 <p>XVa</p>	2-7	6.9-7.7	(m)	
	2''	5.39	(m)	
	3''-5''	1.5-2.1	(m)	
	6''a	3.78	(m)	
	6''b	4.00	(m)	
 <p>XVI</p>	SCH ₃	2.32	(s)	
	1	7.88	(s)	
	2,5-7	7.05-7.24	(m)	
	4	7.68	(m)	

TABLE 1 (cont'd.)

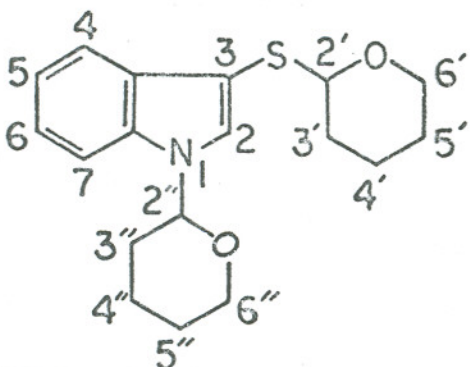
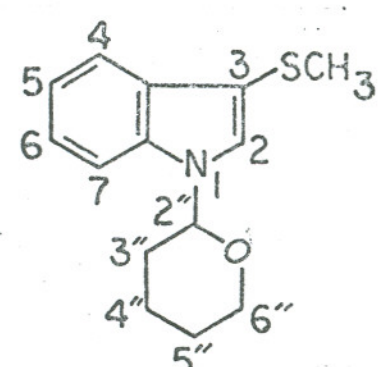
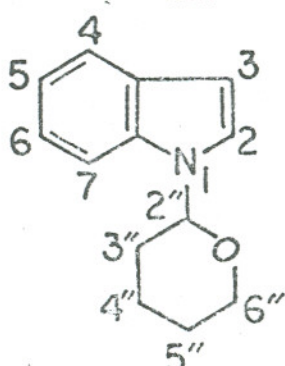
Compound	Proton	Chemical Shift ppm	Multiplicity	J (cps)
 <p>XVII</p>	2-7	6.9-7.7	(m)	
	2'	4.80	(m)	
	2''	5.38	(m)	
	3'-5', 3''-5''	1.5-2.1	(m)	
	6'a, 6''a	3.4-3.8	(m)	
	6'b, 6''b	3.9-4.2	(m)	
 <p>XVIII</p>	SCH ₃	2.29	(s)	
	2,5-7	7.0-7.4	(m)	
	4	7.62	(m)	
	2''	5.32	(m)	
	3''-5''	5.32	(m)	
	6'a	3.60	(m)	
 <p>XIX</p>	2	7.05	(d)	3.5
	3	6.36	(d)	3.5
	4-7	6.9-7.5	(m)	
	2''	5.4	(d of d)	
	3''-5''	1.4-2.1	(m)	
	6'a	4.58	(m)	
6'b	4.96	(m)		

TABLE 2
Thin-Layer Chromatography R_f Values

Compound	Chloroform:Acetone 95:5	Hexane:Acetone 3:1
VI	.65	
X	.82	
XVa	.91	
XVIa	.80	
XVIIa	.90	
XVIIIa	.95	.41
XIX		.48
Indole	.87	.69
3,3'-Diindolyl disulfide	.53	

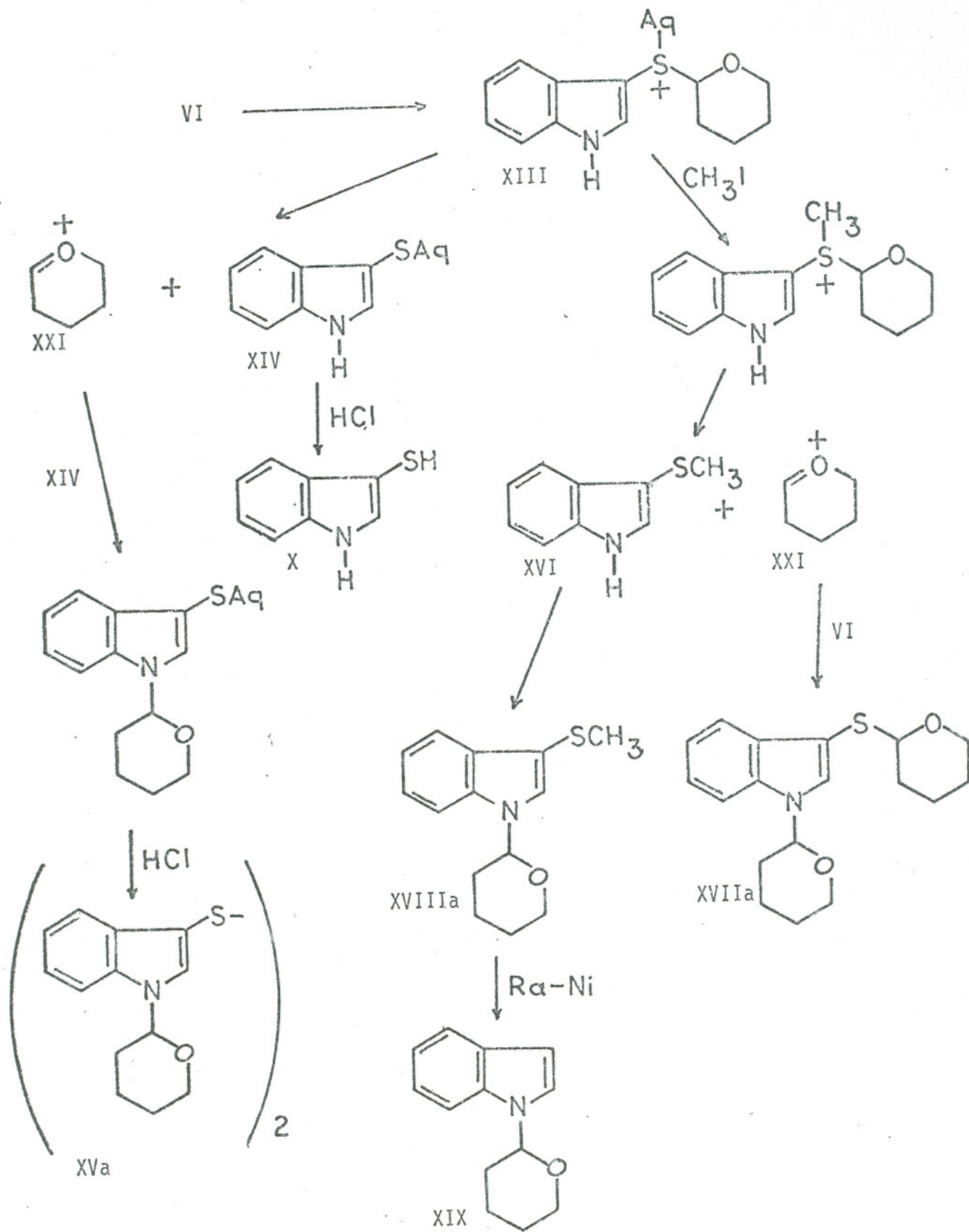
Conclusion.

Silver ion coordinates with the sulfur in 3-(2'-tetrahydropyranylthio)indole, VI, inducing carbon-sulfur bond cleavage to form the silver mercaptide and the carbonium ion of tetrahydropyran, XXI, which alkylates a 3-thioindole nucleus in the one position to give ultimately XVa (see Figure 1). The reaction of methyl iodide with the silver complex gives analogous results. Compounds XVIIa and XVIIIa are formed as a result of attack by the carbonium ion, XXI, on 3-(2'-tetrahydropyranylthio)indole, VI, and 3-methylthioindole, XVI, respectively (see Figure 1). Comparison of the respective NMR spectra with that of the product, XIX, of the Raney nickel reaction with XVIII has eliminated the alternative structures XVb, XVIIb and XVIIIb as possible assignments.

It is certain that XVIIa is the result of an intermolecular reaction. However, the possibility exists that XVa and XVIIIa could be the result, at least in part, of a 1,4-alkyl shift. There is no evidence that rearrangement of the tetrahydropyranyl ring to the three position of the indole occurs.

It is likely that the use of tetrahydrofuran to moderate the activity of the silver ion also serves to stabilize the carbonium ion of tetrahydropyran, XXI. It should be stressed that the various reactions yielded a large number of products, and many remain to be characterized.

FIGURE 1



EXPERIMENTAL

General Comments.

Infrared spectra of CCl_4 solutions were determined with a Perkin-Elmer 337 grating spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian HA-100 spectrometer. All spectra were run in CCl_4 and all chemical shifts expressed in parts per million downfield from an internal standard of tetramethylsilane. Mass spectra were obtained with a CEC Model 21-110B mass spectrometer. The first number denotes m/e and the number in parentheses is the relative percent of the base peak. All thin-layer chromatography (TLC) was done on silica gel using either hexane:acetone 3:1 or chloroform:acetone, 95:5 as the developing solvent (see Figure 2). All melting points were determined on a microscope hot stage and are uncorrected.

2-Chlorotetrahydropyran, VIII.²⁷

In 50 ml. of ether were dissolved 8.4 gm. (0.1 m) of dihydropyran. Dry HCl was bubbled in (with stirring) at 0° for half-hour. The yellow solution was distilled under reduced pressure and the portion collected boiled between $45-49^\circ$ (Lit. $35-36^\circ$, 12 mm press.),²⁷ 8.64 gm. (72% theory).

S-(3-indolyl)isothiuronium iodide, IX.²⁹

A mixture of 2.34 gm. (0.02 m) of indole and 1.52 gm. (0.02 m) of thiourea was dissolved in 100 ml. methanol and 100 ml. water. Iodine, 5.09 gm. (0.02 m), and potassium iodide, 3.32 gm. (0.02 m), in the same

solvents, were added. Over a period of two hours the dark solution gradually lightened to a pale yellow. The solvent was evaporated and the residue washed several times with water and several times with ether yielding 6.20 gm. (97% theory) of yellow crystals, m.p. 212-215° (Lit. 214-216°).²⁹ Product can be used without further purification; however, a pure product can be obtained by extraction of the color from an aqueous solution with ethyl acetate and subsequent recrystallization from hot water.

3-Thioindole, X.²⁹

Under a nitrogen atmosphere, 3.19 gm. (0.01 m) of S-(3-indolyl)isothiuronium iodide, IX, were dissolved in 500 ml. water, heated to between 80° and 100° and treated with an equivalent amount of sodium hydroxide. After 5-10 minutes, the thiol was precipitated with hydrochloric acid. After the solution had cooled, the cream colored plates were collected, dissolved in dichloromethane, and dried over sodium sulfate. The solvent was taken off under reduced pressure and the thiol used immediately in the next step. Great care must be exercised in order to prevent oxidation to the disulfide.

3-(2'-Tetrahydropyranylthio)indole, VI.

Dimethylformamide, 250 ml., distilled from CaH₂ was placed in a 500 ml. flask. The system was evacuated and purged with nitrogen several times. An oil dispersion of 0.5 gm. sodium hydride was added. To this was added (while stirring) 1.5 gm. (0.01 m) of 3-thioindole, X. An immediate reaction took place: hydrogen gas was being evolved. After 2 hrs., 1.2 gm. (0.01 m) of 2-chlorotetrahydropyran, VIII, was added to the solution. The color of

the solution changed from yellow to brown. After several hrs., the reaction mixture was poured into ether, extracted several times with water and treated twice with activated charcoal. The product, VI, was then recrystallized from a solution of hexane and ether giving 0.56 gm. (34% theory) cream colored crystals, m.p. 84-85°.

NMR: 6H (m) 1.4-2.0, 1H (m) 3.45, 1H (m) 4.16, 1H (q) 4.84, 1H (d) 6.84, 3H (m) 7.05, 1H (m) 7.64, 1H (s) 8.39.

Mass spec.: 234 (5), 233 (28), 151 (6), 150 (11), 149 (100), 121 (11), 120 (5), 117 (12), 85 (37), 77 (11), 67 (6), 57 (13), 55 (10), 43 (10), 41 (13), 39 (7).

Anal. calc'd for $C_{13}H_{15}NOS$: C, 66.90; H, 6.49; N, 6.00. Found: C, 66.99; H, 6.34; N, 5.82.

Reaction of 3-(2'-tetrahydropyranylthio)indole, VI, with various phosphines and phosphites.

In all instances, a few milligrams of 3-(2'-tetrahydropyranylthio)-indole, VI, were treated with a few milligrams of triphenyl phosphine, tributyl phosphine, trimethyl phosphite, triethyl phosphite or tributyl phosphite in dimethyl formamide or pyridine at temperatures ranging from room temperature to the reflux temperature of the solvent. In the case of the liquid phosphines and phosphites the reactions were also run neat. In no instance was there any evidence of reaction. Acid and base catalysis had no effect.

Reaction of 3-(2'-tetrahydropyranylthio)indole, VI, with aqueous silver nitrate.

A solution of 23.3 mg. (0.1 mm) of 3-(2'-tetrahydropyranylthio)indole,

VI, in 5 ml. of aqueous methanol and a solution of 17.0 mg. (0.1 mm) in 5 ml. of water were cooled in an ice bath and then combined. An immediate white precipitate formed which quickly turned yellow. The precipitate was filtered and 5-hydroxyvaleraldehyde, XII, was recovered from the filtrate as its dinitrophenylhydrozone, m.p. 110-112° (Lit. 109°),³⁵ accounting for 58% of the theoretical amount. The silver salt was treated with methanolic hydrochloric acid and the precipitated silver chloride collected. TLC analysis of the filtrate showed the major component to have the same R_f as 3-thioindole, X, and a minor component with the same R_f as the disulfide of 3-thioindole, X.

Reaction of 3-(2'-tetrahydropyranylythio)indole, VI, with silver perchlorate in pyridine.

A few mg. of 3-(2'-tetrahydropyranylythio)indole, VI, and a corresponding amount of silver perchlorate were dissolved in 10 ml. of pyridine. After several hrs., no reaction had occurred, based on TLC analysis of the reaction mixture. The solution was then refluxed for 2 hrs. producing a dark solution with some black precipitate, presumably silver sulfide; attempts to separate components of the reaction mixture by chromatographic techniques failed.

Reaction of 3-(2'-tetrahydropyranylythio)indole, VI, with silver perchlorate in benzene.

A few mg. of 3-(2'-tetrahydropyranylythio)indole, VI, were dissolved in a few ml. of dry benzene and cooled in an ice bath. A few mg. of anhydrous silver perchlorate were dissolved in a small amount of dry benzene

and cooled in an ice bath. The solutions were combined and an immediate white precipitate resulted which rapidly darkened. Treatment of the precipitate with a saturated ether solution of hydrogen sulfide yielded a black precipitate and a dark solution containing many products based on TLC analysis. When the same reaction was repeated in toluene in a dry ice--acetone bath, the white precipitate was stable until the solution was warmed turning it dark as before and resulting in many products after treatment with hydrogen sulfide. Addition of pyridine to the reaction mixture at -78° prevented any reaction and the starting hemithioketal, VI, was recovered.

Reactions of 3-(2'-tetrahydropyranylthio)indole, VI, in tetrahydrofuran with silver perchlorate.

A few mg. 3-(2'-tetrahydropyranylthio)indole, VI, dissolved in dry tetrahydrofuran (THF) were combined with an equivalent amount of anhydrous silver perchlorate dissolved in dry tetrahydrofuran. Concentrations in various reactions ranged from 0.01 to 0.002 m/l. When the two solutions were combined at -78° (dry ice--acetone bath) a colorless solution resulted. TLC analysis of the solution showed the presence of uncomplexed starting material. No change was observed after several hrs. at -78° . When warmed, the solution turned yellow and in most cases a yellow precipitate was formed and no uncomplexed starting material was evident by TLC analysis. Collection of the precipitate by filtration and weighing showed it to account for approximately 25% of the combined weight of the thioketal and silver perchlorate. Both the precipitated and soluble complex were treated with either hydrogen sulfide in ether or aqueous hydrochloric acid and subsequent addition of water and extraction with ether yielded similar complex mixtures of products. The main product from the soluble complex

was the starting hemithioketal, VI. Correspondingly, the precipitated complex gave none. Isolation of the major components of the reaction by preparative TLC yielded the starting hemithioketal, VI, 3-thioindole, X, the disulfide of 3-thioindole and a compound assigned as the disulfide of 1-(2'-tetrahydropyranyl)-3-thioindole, XIVa, white crystals, m.p. 136-140°. NMR: 5H (m) 6.9-7.7, 1H (m) 5.39, 1H (m) 4.00, 1H (m) 3.78, 6H (m) 1.5-2.1. Mass spec.: 27 (7), 29 (12), 39 (7), 41 (14), 43 (11), 55 (14), 57 (16), 67 (10), 77 (10), 84 (5), 85 (60), 104 (5), 117 (20), 120 (6), 121 (8), 148 (20), 149 (100), 150 (10), 151 (5), 201 (5), 231 (4), 232 (5), 233 (17), 234 (3), 261 (3), 262 (9), 263 (5), 264 (19), 265 (4), 348 (4), 432 (4), 464 (3).

The precipitate formed would usually dissolve completely after several hrs. at room temperature. In a few instances no precipitate formed. Several reactions were run between -15° and 25°. The only observed effect with temperature was the rate at which color and the precipitation occurred. At room temperature the color developed instantly, precipitation occurred in a few minutes and redissolved after several hours. Treatment with HCl before precipitation, after precipitation and after the precipitate had redissolved appeared to have no major effect on the complexity of the reaction or distribution of the products, except in those instances where the precipitate was filtered. In this case, the starting hemithioketal, VI, was by far the predominant product.

If water was added to the complex already formed in THF, no change was observed either in the appearance or the outcome of the reaction. However, if water was present at the time the reagents were combined, the silver salt of 3-thioindole, X, was precipitated.

Reactions of silver complex of VI with methyl iodide.

To the solution of the silver complex of VI prepared in THF, an excess of methyl iodide was added. There was no immediate reaction, but after several hrs. at room temperature a yellow precipitate of silver iodide formed. At lower temperatures no reaction occurred. The precipitate was filtered, water was added to the filtrate and the solution extracted with ether. Major components of the reaction were separated by preparative TLC. Isolated were the starting hemithioacetal, VI, and 3-methylthioindole, XVI, NMR: 3H (s) 2.32, 4H (m) 7.05-7.24, 1H (m) 7.68, 1H (s) broad.

1-(2'-tetrahydropyranyl)-3-(2''-tetrahydropyranylthio)indole, XVIIa, NMR: 12H (m) 1.5-2.0, 2H (m) 3.4-3.8, 2H (m) 3.9-4.2, 1H (m) 4.80, 1H (m) 5.38, 5H (m) 6.9-7.7.

Mass spec.: 317 (11), 234, (8), 233 (43), 163 (7), 151 (5), 150 (10), 149 (100), 148 (11), 117 (6), 85 (63), 84 (8), 83 (5), 77 (5), 69 (8), 67 (12).

1-(2'-tetrahydropyranyl)-3-methylthioindole, XVIIIa, NMR: 6H (m) 1.5-2.1, 3H (s) 2.29, 1H (m) 3.60, 1H (m) 4.00, 1H (q) 5.32, 4H (m) 7.0-7.4, 1H (m) 7.62.

Mass spec.: 247 (51), 209 (5), 179 (5), 174 (5), 165 (6), 164 (13), 163 (100), 162 (10), 149 (9), 148 (32), 133 (14), 132 (7), 121 (5), 120 (11), 117 (6), 85 (50), 77 (7), 67 (10), 57 (14), 55 (9), 43 (14), 41 (17), 39 (7), 29 (15), 27 (6).

Reaction of Raney nickel with 3-(2'-tetrahydropyranylthio)indole, VI; 3-methylthioindole, XVI; and 1-(2'-tetrahydropyranyl)-3-methylthioindole, XVIIIa.

A few mg. of 3-(2'-tetrahydropyranylthio)indole, VI, in methanol was treated with a large excess of Raney nickel. After stirring for half-hour

at room temperature, the solution was filtered and the solvent evaporated. The product had TLC characteristics identical with indole and the characteristic odor of indole. A few mg. of 3-methylthioindole, XVI, were treated in the same way with the same result. Analogous treatment of 1-(2'-tetrahydropyranyl)-3-methylthioindole, XVIIIa, with Raney nickel gave 1-(2'-tetrahydropyranyl)indole, XIX.

NMR: 6H (m) 1.4-2.1, 1H (m) 4.58, 1H (m) 4.96, 1H (q) 5.4, 1H (d) 6.36, 4H (m) 6.9-7.5, 1H (d) 7.05.

Mass spec.: 203 (6), 202 (9), 201 (44), 145 (5), 144 (7), 143 (14), 130 (13), 118 (14), 117 (100), 116 (11), 90 (10), 89 (11), 85 (16).

I.R.: 2925, 2835, 1510, 1455, 1310, 1220.

1-(2'-Tetrahydropyranyl)indole, XIX.

A solution of methyl magnesium iodide was prepared from 0.23 gm. (0.01 m) of magnesium and 1.4 gm. (0.01 m) of methyl iodide in anhydrous ether. There was a small amount of gray flocculent precipitate present. Indole, 0.7 gm. (6.0 mm), was added and after stirring for approx. 3 hrs., 0.72 gm. (6.0 mm) of 2-chlorotetrahydropyran was added. After the yellow solution had been stirred approx. 1 hr., water was added to it. The ether phase was extracted several times with water and brine and dried over sodium sulfate. 1-(2'-Tetrahydropyranyl)indole, XXI, was separated from the recovered indole by preparative TLC. IR and NMR spectra were identical with those of the product formed from the reaction of Raney nickel with 1-(2'-tetrahydropyranyl)-3-methylthioindole, XVIIIa.

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