**1,5-Dimethyl-2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-on-4-ium Iodide (7).** A.—Compound **5** (50 mg) was heated just above its melting point in a sublimation tube for 5 min. Thereafter the tube was connected to vacuum (0.1 mm) and the temperature was raised to 240° to sublime off traces of the demethylated products. The residue (46 mg) was pure **7**: mp 249–250°; mass spectrum *m/e* 225 ($M^+$ − MeI); ir (KBr) 1672 $cm^{-1}$ (CO); nmr (DMSO-$d_6$) $\tau$ 1.26 (s, $H_3$), 2.94 (d, $H_7$), 1.68 (d, $H_8$), 2.46 (m, Ph), 6.04 (s, 1-Me), 6.22 (s, 5-Me), $J_{7,8}$ = 9.9 Hz.

*Anal.* Calcd for $C_{14}H_{14}IN_3O$: C, 45.80; H, 3.85; N, 11.45. Found: C, 45.65; H, 3.81; N, 11.80.

B.—A mixture of **3** (0.45 g), MeOH (30 ml), and MeI (0.5 g) was heated in an autoclave at 160° for 3 hr. The solvent was evaporated and the residue was crystallized from EtOH (0.35 g, 48%), mp 249–250°. The compound was identical with the product obtained as described under A.

**1-Methyl-2-phenyl-5-trideuteriomethyl-3,7,8-trideuterioimidazo[1,2-*b*]pyridazin-6(5*H*)-on-4-ium iodide (9)** was obtained from **8** in the same manner as described for the nondeuterated compound **7** under A: mp 249–250°; mass spectrum *m/e* 231 ($M^+$ − MeI), 228 ($M^+$ − $CD_3I$); nmr (DMSO-$d_6$) $\tau$ 6.03 (s, 1-Me), 2.44 (m, Ph).

**Demethylation of 1,5-Dimethyl-2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-on-4-ium Iodide.**—The compound **7** (183 mg) was heated in a sublimation tube at 240° (0.1 mm) for 2 hr. The sublimate (28 mg) was identified as 5-methyl-2-phenylimidazo-[1,2-*b*]pyridazin-6(5*H*)-one (**3**). The residue was composed of the starting material as the main component and a small amount of 6-hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium anhydro salt (**6**) as shown by thin layer chromatography (DC Fertigplatten Kieselgel F-254, Merck, MeOH as solvent).

**Rearrangement of 6-Methoxy-2-phenylimidazo[1,2-*b*]pyridazine.**—The methoxy compound **2** (225 mg) was heated in a sealed tube at 240° for 2 hr. The dark residue was treated with MeOH (5 ml) and purified by column chromatography (column diameter 18 mm, length 10 cm, filled with alumina type 507 C Fluka, for elution MeOH was used). The purified solution was evaporated to dryness and the residue (150 mg) was a mixture of three compounds.

A solution of this mixture (30 mg) in MeOH (2 ml) was submitted to tlc (PSC Fertigplatten Kieselgel F-254, MeOH and $CHCl_3$, 1:30, as solvent) and the spots were separated and eluted with MeOH. Upon evaporation of each solution there were obtained the starting compound **2** (7 mg) and 5-methyl-2-phenylimidazo[1,2-*b*]pyridazin-6(5*H*)-one (**3**) (17 mg).

When the same tlc procedure was applied, but MeOH was used as solvent, the spot with $R_f$ 0.48 afforded after elution with MeOH pure 6-hydroxy-1-methyl-2-phenylimidazo[1,2-*b*]pyridazin-4-ium anhydro salt (**6**) (4 mg), identified by its melting point and ir spectrum when they were compared with those of an authentic specimen.

**6-Hydroxy-1-methylimidazo[1,2-*b*]pyridazin-4-ium Anhydro Salt (10).**—A suspension of 6-chloro-1-methylimidazo[1,2-*b*]-pyridazin-4-ium iodide[1] [1.95 g; nmr (DMSO-$d_6$) $\tau$ 1.32 (d, $H_2$), 1.08 (dd, $H_8$), 1.73 (d, $H_7$), 0.92 (dd, $H_8$), 5.75 (s, NMe), $J_{2,3}$ = 2.1, $J_{3,8}$ = 0.6 $J_{7,8}$ = 9.6 Hz] in aqueous KOH (1.12 g of KOH in 7 ml of water) was heated under reflux for about 10 min until a complete dissolution was achieved. After cooling, neutralization with concentrated hydrochloric acid, and evaporation to dryness, the residue was sublimed at 220° (0.1 mm) (0.7 g, 47%): mp 125–127°; mass spectrum *m/e* 149 ($M^+$); nmr (DMSO-$d_6$) $\tau$ 2.25 (d, $H_2$), 2.06 (dd, $H_3$), 3.53 (d, $H_7$), 2.30 (dd, $H_8$), 6.30 (s, NMe), $J_{2,3}$ = 2.0, $J_{3,8}$ = 0.6, $J_{7,8}$ = 9.5 Hz.

*Anal.* Calcd for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.43; H, 4.85; N, 27.87.

**6-Hydrazino-1-methylimidazo[1,2-*b*]pyridazin-4-ium Iodide (11).**—A mixture of 6-chloro-1-methylimidazo[1,2-*b*]pyridazin-4-ium iodide[1] (1.48 g) and hydrazine hydrate (5 ml, 80%) was heated under reflux for 10 min. Upon cooling the separated product was filtered off, washed with water, and crystallized from EtOH (0.8 g, 54%), mp 260°.

*Anal.* Calcd for $C_7H_{10}IN_5$: C, 28.88; H, 3.46; N, 24.07. Found: C, 28.87; H, 3.70; N, 24.51.

**Registry No.**—**1**, 34876-76-1; **2**, 1844-61-7; **3**, 1845-04-1; **4**, 34876-79-4; **5**, 34876-80-7; **6**, 34876-81-8; **7**, 34876-82-9; **8**, 34876-83-0; **9**, 34876-84-1; **10**, 34876-85-2; **11**, 34876-86-3.

**Acknowledgment.**—We are indebted to Dr. V. Kramer and Dr. J. Marsel, Institute J. Stefan, for recording the mass spectra.

# Ion Radicals. XXV. The Reactions of Thianthrene and Phenothiazine Perchlorates with Nitrite Ion, Pyridine, and Other Nucleophiles[1]

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Reaction of thianthrene perchlorate (**1**) with sodium nitrite in nitromethane solution gave thianthrene 5-oxide (**2**) and nitric oxide, each in greater than 90% yield. Reaction with $^{18}O$-labeled nitrite ion showed that the oxygen in **2** came from the nitrite ion. Reaction of **1** with sodium nitrate gave **2** (92, 98%) and nitrogen dioxide (71, 75%). Reaction of **1** with pyridine in nitromethane solution gave 73% of *N*-(2-thianthrenyl)pyridinium perchlorate (**3**) and 90% of thianthrene (**4**), the yields being calculated after compensation for the reaction of **1** with residual water in the pyridine. Reaction of solid **1** with neat pyridine was violent and was accompanied by explosion and flame unless carried out with small amounts of **1**, in which case the products were again **3** and **4**. Attempts to prepare **3** directly by the oxidation of **4** with iodine and silver perchlorate in the presence of pyridine failed. Reaction of phenothiazine perchlorate (**5**) with nitrite ion gave 3-nitrophenothiazine (96%) and phenothiazine (**6**) (100%). Oxidation of **6** with iodine and silver nitrite in acetonitrile solution gave 3-nitrophenothiazine in 70% yield. Reaction of **5** with pyridine gave *N*-(3-phenothiazinyl)pyridinium perchlorate (**7**) (78, 84%), **6** (72, 80%), and 3,10′-biphenothiazine (**8**) (2.1, 9%). Attempts to prepare **7** directly by the oxidation of **6** with iodine and silver perchlorate in the presence of pyridine gave mixtures of **7** and unidentified green solids whose separation was too difficult to achieve. Reaction of **5** with chloride and bromide ion gave the 3- and 3,7-dihalogenophenothiazines in approximately 75 and 8% yields, respectively, and, in each case, **6** in 85–90% yield. Reaction of **5** with fluoride ion gave only **6** (38%), **8** (17%), and an unidentified green solid.

In earlier publications, we have described the reactions of thianthrene perchlorate (**1**) with water,[4] electron-rich aromatics,[5] and dry ammonia.[1a] In each of these reactions the nucleophile attacked the thianthrene ring at sulfur (the 5 position) to form a 5-sub-

(1) (a) Part XXIV: H. J. Shine and J. J. Silber, *J. Amer. Chem. Soc.*, **94**, 1026 (1972). (b) Part XXIII: C. V. Ristagno and H. J. Shine, *J. Org. Chem.*, **36**, 4050 (1971). Supported by the National Science Foundation, Grant No. GP-25989X.

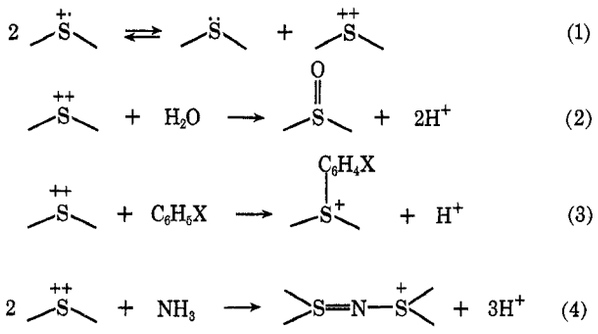
(2) Taken in part from the Ph.D. dissertation of Juana J. Silber, Texas Tech University, Jan 1972.

(3) Postdoctoral Fellow. We thank Texas Tech University for support of one of us (T. O.) under Grant No. 191-4719.

(4) Y. Murata and H. J. Shine, *J. Org. Chem.*, **34**, 3368 (1969).

(5) J. J. Silber and H. J. Shine, *ibid.*, **36**, 2923 (1971).

stituted thianthrene. In each case thianthrene was also formed. Kinetic data in two cases[4,5] allowed us to propose that the reactions involved the thianthrene dication which was formed by disproportionation of the cation radical when **1** was placed in solution. These reactions are illustrated with eq 1–3, in which only the 5 position of the thianthrene ring is shown.



Equation 4 illustrates the reaction with ammonia in which the heteroatom analog of the allylic cation is formed as part of the union of two thianthrene rings. The equations show that thianthrene is always an essential product of reaction.

The reaction of pyridine with aromatic hydrocarbons undergoing chemical[6] and anodic[7-10] oxidation has received quite a lot of attention. We have reported on the reaction between perylene perchlorate and pyridine,[1b] and have now studied the analogous reactions of **1** and phenothiazine perchlorate (**5**) with pyridine.

Reactions of cation radicals with nitrite and nitrate ions are not as well known. Oxidation of phenothiazine by ferric chloride in the presence of nitrite ion gave 3-nitrophenothiazine in good yield, and the reaction is thought to involve the phenazothionium ion.[11] Reaction of perylene perchlorate with nitrite ion gave good yields of 3-nitroperylene. The reaction can be carried out with *in situ* formation of the cation radical by using solutions of perylene, iodine, and silver nitrite.[12]

Anodic nitration, in which the involvement of cation radicals might be assumed, seems to have been confined to the oxidation of aromatics in nitric acid solution.[13,14]

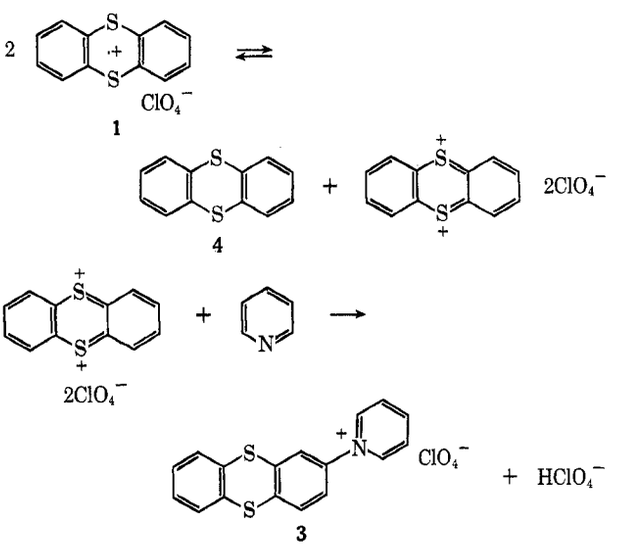
Since 2-nitrothianthrene is not readily prepared,[15] we thought that reaction of **1** with nitrite ion might be a convenient way of making that compound. We found this not to be the case, and our findings led also to a study of the reaction of **1** with nitrate ion. Reactions of phenothiazine perchlorate (**5**) with nitrite ion, halide ions, water, and hydroxide ion were also studied.

(6) J. Rochlitz, *Tetrahedron*, **23**, 3043 (1967).
(7) H. Lund, *Acta Chem. Scand.*, **11**, 1323 (1957).
(8) G. Manning, V. D. Parker, and R. N. Adams, *J. Amer. Chem. Soc.*, **91**, 4584 (1969).
(9) V. D. Parker and L. Eberson, *Tetrahedron Lett.*, 2839, 2843 (1969); *Acta Chem. Scand.*, **24**, 3542 (1970).
(10) L. Marcoux, *J. Amer. Chem. Soc.*, **93**, 537 (1971).
(11) J. Danecke and H.-W. Wanzlick, *Justus Liebigs Ann. Chem.*, **740**, 52 (1970).
(12) C. V. Ristagno and H. J. Shine, *J. Amer. Chem. Soc.*, **93**, 1811 (1971).
(13) M. J. Allen, "Organic Electrode Processes," Reinhold, New York, N. Y., 1958, p 162.
(14) F. Fichter, "Die Chemische Reaktion," herausgegeben von K. F. Bonhoeffer. Band VI. "Organische Elektrochemie," Theodor Steinkopf Verlag, Dresden and Leipzig, 1942, p 143.
(15) S. Krishna, *J. Chem. Soc.*, **123**, 156 (1923).

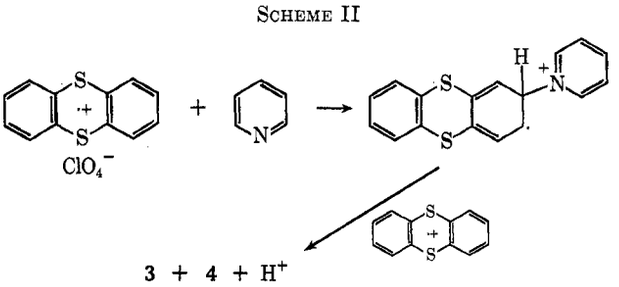
## Results and Discussion

**Reactions of Thianthrene Perchlorate (1).**—Reaction of pyridine with **1** was very rapid. When carried out in solution (nitromethane) the color of **1** was discharged within seconds. Reaction of **1** with neat pyridine was violent and accompanied on one occasion by flame and explosion. Controlled reaction of **1** with neat pyridine was achieved by adding small amounts of **1** to swirling pyridine, and led, as with reaction in solution, to essentially equimolar amounts of *N*-(2-thianthrenyl)pyridinium perchlorate (**3**) and thianthrene (**4**). We do not have kinetic evidence on which to base a mechanism for this reaction, since reaction was too fast to be adapted to kinetic study by the spectrophotometric technique used earlier.[4,5] By analogy with the earlier work we would recognize reaction as occurring with the dication formed by disproportionation of the cation radical (Scheme I), although we cannot rule out the stepwise sequence of Scheme II.

SCHEME I



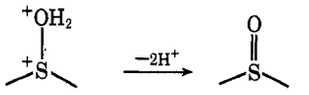
SCHEME II



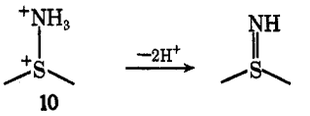
Marcoux has shown recently that anodic pyridination of 9,10-diphenylanthracene *via* the disproportionation route is not unreasonable.[10]

The identity of **3** was established by analysis and Zincke degradation to known 2-aminothianthrene. Substitution at nitrogen rather than at ring carbon of pyridine is consistent with our findings of the electrophilic nature of the earlier reactions, which, in fact, involve the thianthrene dication.[4,5] One would anticipate therefore that in the pyridination reaction the dication would not readily attack the 3 position of pyridine. The reaction we observe is very fast. There-

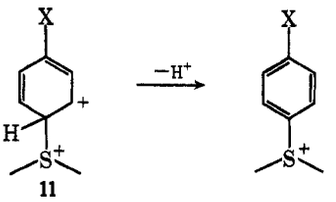
fore, we can understand that a pyridinyl carbon atom is not involved in bonding with the thianthrene ring. It is necessary to stress also that *N*-pyridinyl bonding occurs at the 2 and not the 5 position of the thianthrene ring. In all of our earlier reactions with other nucleophiles the contrary occurred.[4,5] The reason, we believe, is that in the earlier reactions the dicationic intermediate (depicted as **9**–**11**), formed in the first step of



**9**

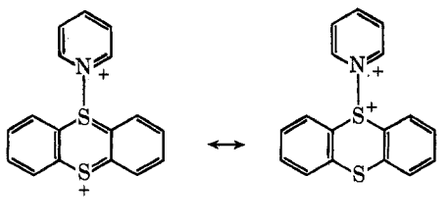


**10**



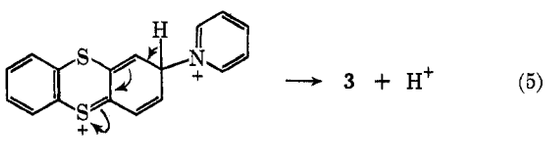
**11**

reaction of the nucleophile with the thianthrene dication, can easily lose either one or two protons and form a stable product. This is not the case if pyridination occurs at the 5 position. The product (**12**) would re-



**12**

main dicationic and for this reason its formation is likely to be reversible. In contrast, attack of pyridine at the 2 position of the thianthrene dication would be followed by proton loss (eq 5) and give the monocationic product, **3**.

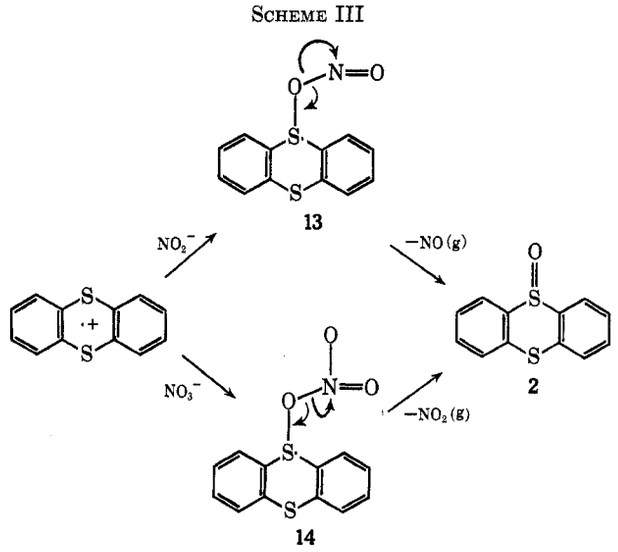


(5)

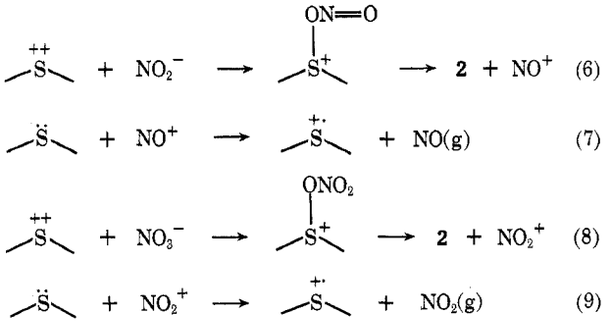
Attempts to prepare **3** by oxidation of thianthrene (**4**) with iodine and silver perchlorate in the presence of pyridine failed. Iodine–silver perchlorate in nitromethane in the absence of pyridine oxidized **4** only slowly. Purple solutions were obtained, characteristic of the cation radical, and these gave, finally, thianthrene 5-oxide (**2**) as product, apparently from reaction with the residual water in the solvent.[4] Although oxidation was slow, silver iodide precipitated early in reaction, presumably from reaction of iodine with silver perchlorate.[16] If carried on long enough, reaction led to almost total oxidation of **4** to **2**. On the other hand, only **4** was recovered from reactions of **4** with iodine–silver perchlorate in the presence of pyridine. We believe that the iodine becomes complexed by pyridine[17] and is no longer available for oxidation of thianthrene. These reactions were not pursued further.

Reaction of nitrite ion with **1** is quite unlike the analogous reactions with perylene[12] and phenothiazine (see later) perchlorates. These lead to ring nitration. In contrast, **1** is converted into thianthrene 5-oxide (**2**). The same occurs in reaction of **1** with nitrate ion. Furthermore, reaction of **1** with $^{18}O$-labeled nitrite ion (1.6 atom %) gave **2** with an $^{18}O$ content (1.3 atom %) that could have come only from the nitrite ion. We propose that these reactions involve the cation radical (Scheme III). Our reasons for so doing are

SCHEME III



deductive because once again reactions were too fast for kinetic study by our spectrophotometric technique.[4,5] Scheme III designates reaction *via* the negatively charged oxygen of the ambident nitrite ion at a position of high positive charge density, which is in accord with the way in which this nucleophile is understood to react. An intermediate radical (**13**) is formed, which can decompose into a stable product (**2**) and a stable radical (nitric oxide). The intermediate **14** in the nitrate reaction is shown to decompose analogously, the stable radical being nitrogen dioxide. If the reaction were to involve the dication rather than the cation radical (see eq 1) the nitrosonium ion (eq 6) and nitro-



(6)

(7)

(8)

(9)

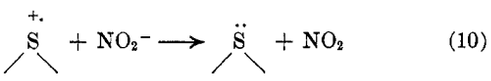
nium ion (eq 8) would be formed, and these would have to undergo subsequent reduction by thianthrene (eq 7 and 9) to account for the products. The cation

(16) N. W. Alcock and T. C. Waddington, *J. Chem. Soc.*, 2510 (1962).

(17) R. Foster, "Organic Charge-Transfer Complexes," Academic Press, New York, N. Y., 1969, p 276.

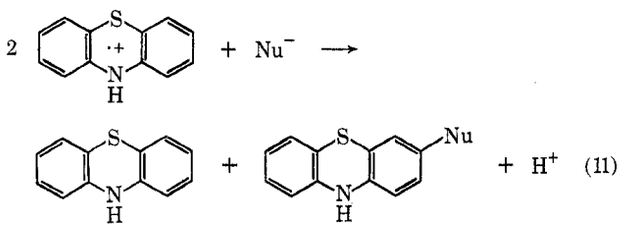
radical formed also (eq 7 and 9) would have to reenter into disproportionation (eq 1). While we cannot rule out these sequences (eq 1, 6, and 7; eq 1, 8, and 9), we feel that the two electrophiles, $NO^+$ and $NO_2^+$, would not be limited to the oxidation reactions of eq 7 and 9, but would also attack the thianthrene ring. However, no ring-substituted products were obtained, the only organic product detected by tlc being **2**.

Yet another route to product formation needs to be considered. Thianthrene (**4**)[18] and other organic sulfides[19,20] are oxidized to sulfoxides by dinitrogen tetroxide. If electron exchange between the cation radical and nitrite ion were to occur (eq 10) the two



products (**4** and nitrogen dioxide) would be available for whatever oxidation pathway dinitrogen tetroxide and **4** engage in. We do not believe that this (eq 10) is the way in which nitrite ion and **1** react, however. In none of our work have we been able to detect the formation of **4**. If reaction were to occur according to eq 10 we might expect some **4** to survive. Further, when nitrogen was bubbled through a solution while **1** reacted with nitrite ion there was no fall in yields of **2** and nitric oxide, and again no sign of formation of **4**. If electron exchange (eq 10) preceded oxidation we would anticipate that some nitrogen dioxide would be carried out of solution by the nitrogen-gas carrier. Thianthrene was not detected (tlc) in reactions of **1** with nitrate ion and, in analogy with the reasoning given above, we feel that electron exchange between cation radical and nitrate ion (to give **4** and $NO_3$) does not take place either. Thus, we feel that Scheme III best describes our results.

**Reactions of Phenothiazine Perchlorate (5).**—In contrast with **1**, phenothiazine perchlorate does not undergo nucleophilic reactions at sulfur.[11] Reaction with nitrite ion, pyridine, chloride, and bromide ion led to phenothiazine and a 3-substituted phenothiazine according to the following stoichiometry (eq 11).



In the case of pyridine, of course, appropriate changes in eq 11 are necessary. We do not know yet the mechanisms of these reactions. The possibilities of either direct reaction with the cation radical or reaction with the dication formed in disproportionation need to be considered and solved by kinetic work. Reaction of **5** with chloride and bromide ion may involve electron exchange first, followed by halogenation by molecular halogen. Chlorination and bromination of phenothiazine occur very readily,[21] although ordinarily polyhalogenated phenothiazines are formed. Preparation of monochloro- and monobromophenothiazine is usually achieved by reductive halogenation of the 5-oxide (see Experimental Section). In the reaction of **5** with bromide ion, the yields of products were not affected much when nitrogen was bubbled through the solution while reaction was occurring. The formation of both 3,7-dichloro- and 3,7-dibromophenothiazine in our reactions suggests that the reactions are not simple nucleophilic substitutions and mechanistic exploration of the reactions is needed.

Iodide ion, if used in excess, reduces **5** completely. Iodine will oxidize phenothiazine and, depending on the conditions, phenazothionium periodide[21] or 3,10′-biphenothiazine (**8**)[22] are obtained. We have used iodine as the oxidant in the direct "nitration" of phenothiazine by nitrite ion. Obviously, therefore, phenothiazine and iodine form an easily reversible redox system, and it is understandable that reduction of the cation radical by iodide ion could be achieved only by using an excess of iodide ion. We encounter also the same experience with iodide ion and **5** as with iodide and **1**[4] and perylene perchlorate,[1b] namely, that, although iodide ion is a good nucleophile, it is too easily oxidized by the cation radical to permit nucleophilic substitution in the ring.

Nucleophilic substitution by fluoride ion did not occur even though oxidation of fluoride ion by the cation radical is not possible. Apparently, fluoride ion is not sufficiently nucleophilic, as was discovered in the perylene perchlorate case.[1b] Fluorination of aromatics by xenon fluoride was once thought to involve reaction between the aromatic cation radical and fluoride ion, but this is now believed not to be the case.[23]

Reaction of **5** with fluoride ion systems gave phenothiazine (**6**), 3,10′-biphenothiazine (**8**), and an unidentified green solid (or solids).[24] The same behavior was observed in reactions of **5** with water and hydroxide ion solutions. These are not unexpected results. The dimer **8** appears to be formed from the phenothiazine cation radical in basic or weakly acidic solutions. Tsujino has reported that the dimer is a major product of reaction of phenothiazine in 90% sulfuric acid, and represents the cation radical as undergoing deprotonation in that medium.[25] We feel that this cannot be correct since the esr spectrum of the cation radical is so well established, not only in acid solutions,[26,27] but also in acetonitrile,[26,28] and the cation radical is stable even in acetic acid solution.[27] Furthermore, we have found that solutions of **5** in acetonitrile obey Beer's law at the maxima 437 and 515 nm over the concentrations tested, namely 1.6–15.2 $\times 10^{-4}$ *M*. Deprotonation and dimerization would certainly be encouraged in these circumstances (acetic acid and acetonitrile) as com-

(18) R. D. Whitaker and C. L. Bennett, *Quart. J. Fla. Acad. Sci.*, **28**, 329 (1965).
(19) R. D. Whitaker and C. L. Bennett, *ibid.*, **28**, 137 (1965).
(20) R. D. Whitaker and H. H. Sisler, *J. Org. Chem.*, **25**, 1038 (1960).
(21) C. Bodea and I. Silberg, *Advan. Heterocycl. Chem.*, **9**, 321 (1968).
(22) (a) Y. Tsujino, *Tetrahedron Lett.*, 2545 (1968); (b) *Nippon Kagaku Zasshi*, **90**, 490 (1969).
(23) M. J. Shaw, H. H. Hyman, and R. Filler, *J. Org. Chem.*, **36**, 2917 (1971).
(24) The nature of green solid(s) from phenothiazine reactions is discussed by Bodea and Silberg, ref 21, p 377.
(25) Y. Tsujino, *Nippon Kagaku Zasshi*, **90**, 809 (1969). We thank Professor Kimio Ohno for translating this article.
(26) J.-P. Billon, G. Cauquis, and J. Combrisson, *J. Chim. Phys.*, **61**, 374 (1964).
(27) H. J. Shine and E. E. Mach, *J. Org. Chem.*, **30**, 2130 (1965).
(28) S. Odiot and F. Tonnard, *J. Chim. Phys.*, **61**, 382 (1964).

pared with solution in 90% sulfuric acid. Therefore, we feel that dimerization occurs when **5** reacts with bases, and this is what has complicated the reactions with most of the nucleophiles used by us, *i.e.*, pyridine, fluoride ion, water, and hydroxide ion. These reactions may be complicated further because the dimer **8** is easily oxidized[22,25] giving rise to the so-called green products.

Deprotonation, dimerization, and oxidation of the dimer are undoubtedly the cause of the complexity of the reaction of phenothiazine with iodine, silver perchlorate, and pyridine. Instead of the pyridinium compound (**7**) a mixture of colored solids was obtained in which **7** was present but could not be separated cleanly. Phenothiazine, its dimer **8**, and **7** have now been found to undergo anodic oxidation in acetonitrile at closely similar potentials, and both oxidized **8** and oxidized **7** appear to react with pyridine.[29] It is not surprising, therefore that our attempt at the pyridination of **6** in the presence of excess of iodine–silver perchlorate should have given a mixture of products.

Reaction of **5** with nitrite ion was clean and gave an excellent yield of 3-nitrophenothiazine. Until recently this compound was not easily made. Direct reaction either by the ferric chloride–nitrite ion[11] or our iodine–silver nitrite method now gives 3-nitrophenothiazine in good yield. Reaction of **6** with nitrite ion in acidic media is described as giving colored products[30] while reaction in acetic acid–chloroform gave pure 3,7-dinitrophenothiazine.[31]

## Experimental Section

Acetonitrile was Eastman anhydrous grade (<0.01% water). Nitromethane and methylene chloride were Eastman Spectro Grade and were redistilled over phosphorous pentoxide. Each solvent was stored over molecular sieve in a septum-capped bottle and removed by syringe when needed.

Phenothiazine was crystallized from butanol, phenothiazine 5-oxide from ethanol, and thianthrene from acetone.

**Thianthrene perchlorate** (**1**) was prepared by the oxidation of thianthrene with perchloric acid.[4] Iodimetric assay gave 98–100% cation radical content consistently.

**Phenothiazine perchlorate** (**5**) was prepared either from disproportionation of an equimolar mixture of phenothiazine and phenothiazine 5-oxide in 70% perchloric acid (Billon's methods[32]) or by the oxidation of phenothiazine with iodine, as follows. A solution of 420 mg (2 mmol) of silver perchlorate in 3 ml of acetonitrile was added to a solution of 400 mg (2 mmol) of phenothiazine and 270 mg (1 mmol) of iodine in 40 ml of methylene chloride. After 30 min of stirring the precipitate was filtered off and the filtrate was poured into 180 ml of dry ether. The green-black crystalline precipitate was filtered on glass paper and dried under vacuum, and gave 210 mg (35%) of **5**.

A sample of **5** prepared by Billon's method was analyzed.[33]

*Anal.* Calcd for $C_{12}H_9NO_4SCl$: C, 48.48; H, 3.17; N, 4.70; S, 10.94; Cl, 12.02. Found: C, 48.24; H, 3.04; N, 4.69; S, 10.73; Cl, 11.87.

Thereafter, **5** samples were assayed iodimetrically. A weighed amount of **5** was dissolved in a solution of tetrabutylammoniun iodide (TBAI) in acetonitrile. The liberated iodine was titrated potentiometrically with sodium thiosulfate after adding a small amount of water.[1b] Phenothiazine is oxidized by iodine. Therefore, iodimetric assay was successful only if a severalfold excess of TBAI was used. Analyses were consistently in the range of 95–98% cation radical content. After titration, the solution was extracted with benzene, placed on a column of silica, and eluted with benzene to give phenothiazine in 90% and better yield.

Solutions of **5**, prepared in a sealed apparatus under vacuum in acetonitrile which had been degassed by the freeze–thaw technique, obeyed Beer's law over the range of concentrations used, namely 1.6–15.2 $\times 10^{-4}$ *M*, at 437 nm ($\epsilon$ 6020) and 515 (10,300), the two maxima in the visible spectrum of the phenothiazine cation radical.[27]

**Halogenophenothiazines.**—Authentic samples were prepared for spectroscopic characterization by reductive halogenation of phenothiazine 5-oxide.[34] Each pair of mono- and dihalogenophenthiazines was separated by column chromatography [silica gel, petroleum ether (bp 30–60°)–ethyl ether, 2:1]. 3-Chlorophenothiazine, mp 200–202° (benzene) (lit.[35] mp 201–201.5°), had $\lambda_{max}$ (methylene chloride) at 320 nm ($\epsilon$ 4.13 $\times 10^3$) and 258 (3.85 $\times 10^4$). 3,7-Dichlorophenothiazine, mp 220–221° (benzene) (lit.[22b] mp 219–220°), had $\lambda_{max}$ (methylene chloride) at 322 nm ($\epsilon$ 5.45 $\times 10^3$) and 260 (4.6 $\times 10^4$). 3-Bromophenothiazine, mp 182–183° (benzene) (lit.[36] mp 181.5°), had $\lambda_{max}$ (methylene chloride) at 320 nm ($\epsilon$ 5.0 $\times 10^3$) and 258.5 (4.7 $\times 10^4$). 3,7-Dibromophenothiazine, mp 199–200° dec (lit.[37] mp 206–207° dec), had $\lambda_{max}$ (methylene chloride) at 324 nm ($\epsilon$ 6.7 $\times 10^3$) and 261 (5.9 $\times 10^4$).

**Reaction of 1 with Nitrite Ion.**—To stirred solution of 33.9 mg (0.107 mmol) of **1** in 20 ml of dry nitromethane was added an excess (500 mg, 6.6 mmol) of solid, dry sodium nitrite. Some sodium nitrite remained undissolved. The purple color of the solution turned a yellowish-brown immediately, and slowly became colorless. (When a similar reaction was carried out under nitrogen the yellow-brown color was not observed, indicating that it was caused by the air oxidation of nitric oxide to nitrogen dioxide.) Tlc of the filtered colorless solution gave only one spot identified as thianthrene 5-oxide (**2**). Column chromatography (10% ether in benzene on a silica column) gave **2**, mp 143° (ethanol). Spectroscopic assay in acetonitrile at 242 nm ($\epsilon$ 1.67 $\times 10^4$) gave a yield of 88%. Similar experiments gave yields of 95 and 100%.

**Quantitative Assay of Nitric Oxide.**—Reaction of **1** with nitrite ion gave nitric oxide as the second product. This was assayed twice in separate experiments. The experiments were carried out under a stream of nitrogen in an apparatus and gas-bottle chain which had been flushed with dry nitrogen for 4 hr previously. The nitric oxide formed in the reaction was carried into a series of two bottles, each containing 100 ml of sulfuric acid and 2 ml of nitric acid. At the end of the reaction the nitrosylsulfuric acid in the absorption bottles was determined by the permanganate–ferrous ammonium sulfate method.[38] The two experiments beginning with 85.2 and 78.3 mg of **1**, respectively, gave 96 and 90% of theoretical nitric oxide and 91 and 89% of theoretical **2**.

**Reaction of 1 with $^{18}O$-Nitrite Ion.**—Labeled nitrite ion was prepared with the use of 1.6% enriched $^{18}O$ water.[39] Reaction with **1** was carried out, and mass spectrometry showed that the $^{18}O$ content of the isolated **2** was 1.3 atom %.

**Reaction of 1 with Nitrate Ion.**—Sodium nitrate was used as described for sodium nitrite. The purple color of the solution of **1** changed to brown even under a nitrogen atmosphere, indicating the formation of nitrogen dioxide. Thianthrene 5-oxide was determined as described above. Nitrogen dioxide was determined by absorption in sulfuric acid and titration by the permanganate–ferrous ammonium sulfate method.[38] Two experiments beginning with 70.9 and 74.6 mg of **1** gave 73 and 84% of nitrogen dioxide and 92 and 98% of **2**.

**Reaction of 5 with Nitrite Ion.**—A solution of 90 mg (0.301 mmol) of **5** in 10 ml of acetonitrile was added dropwise to a suspension of 1 g of sodium nitrite in 10 ml of acetonitrile. The

(29) Private communication from Dr. L. S. Marcoux.
(30) Reference 21, p 408.
(31) Reference 21, p 350.
(32) J.-P. Billon, *Bull. Soc. Chim. Fr.*, 1923 (1961).
(33) Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.
(34) H. Gilman and J. Eisch, *J. Amer. Chem. Soc.*, **77**, 3862 (1955).
(35) E. A. Nodiff and M. Hausmann, *J. Org. Chem.*, **29**, 2453 (1964).
(36) J. Cymerman-Craig, W. P. Rogers, and G. P. Warwick, *Aust. J. Chem.*, **8**, 252 (1955).
(37) S. Bodea and M. Raileanu, *Justus Liebigs Ann. Chem.*, **631**, 194 (1960).
(38) G. C. Whitmarck, C. J. Holdord, E. St. Clair Gantz, and G. B. L. Smith, *Anal. Chem.*, **23**, 464 (1951).
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orange solution was diluted with 20 ml of benzene, washed with 0.1 *M* sodium hydroxide and water, and evaporated to dryness under vacuum. The residue, 65 mg, was chromatographed on a silica column. Elution with benzene gave 31 mg (0.155 mmol, 100%) of phenothiazine, mp 181–183°; elution with benzene–ether gave 35 mg (0.143 mmol, 96%) of deep violet 3-nitrophenothiazine, mp 210–211° (lit.[11] mp 212°), $\lambda_{max}$ (ethanol) 454, 309, and 246 nm. Continued elution with ether gave 2 mg of unidentified orange solid.

Elemental analysis[33] of the 3-nitrophenothiazine was in excellent agreement with required values.

**Reaction of Phenothiazine with Iodine and Silver Nitrite.**—To a solution of 1.0 g (5 mmol) of phenothiazine and 635 mg (2.5 mmol) of iodine in 100 ml of acetonitrile was added 770 mg (5 mmol) of silver nitrite in 20 ml of acetonitrile. Silver iodide was filtered off and the solvent was removed under vacuum, giving 1.16 g of black residue. Chromatography on a silica column gave 854 mg (3.5 mmol, 70%) of crude 3-nitrophenothiazine, mp 198–199°. Crystallization from benzene gave mp 210°.

**Reaction of 1 with Pyridine.**—Reaction was carried out either in neat pyridine or in nitromethane solution. *Reaction in neat pyridine is violent and may be hazardous. On one occasion the mixture burst into flames.* No trouble was encountered with the use of small amounts of **1** and rapid swirling of the mixture. Addition of pyridine to a solution of **1** in nitromethane caused rapid change from a purple to a yellow solution. When nitromethane was used pyridinium perchlorate precipitated and was filtered off before proceeding further. The disadvantage to using nitromethane was that, although the solvent was dried, residual water reacted with the **1** and gave more thianthrene 5-oxide than was obtained with the use of dry, neat pyridine. When **1** reacts with water, both thianthrene 5-oxide and thianthrene are formed.[4] When **1** reacts with pyridine, both *N*-(2-thianthrenyl)-pyridinium perchlorate (**3**) and thianthrene are formed. Therefore, all reactions gave four products: thianthrene, thianthrene 5-oxide, **3**, and pyridinium perchlorate. These were separated and assayed as follows. The solution (whether in pyridine alone or in nitromethane–pyridine) was evaporated to dryness under vacuum to remove excess pyridine. Solid pyridinium perchlorate, if present, was filtered off before evaporation. The dry residue was dissolved in nitromethane and extracted with small amounts of cyclohexane until tlc of the nitromethane solution showed absence of thianthrene and its 5-oxide. The cyclohexane portions were combined and evaporated to dryness. The residue was dissolved in acetonitrile and analyzed spectroscopically for thianthrene and the 5-oxide.

The nitromethane solution, containing **3** and pyridinium perchlorate, was evaporated to dryness. The residue was washed with water to remove pyridinium perchlorate, and repeatedly with benzene or cyclohexane to remove traces of thianthrene and thianthrene 5-oxide. Crystallization from aqueous methanol gave yellow **3**, mp 206–207°, $\lambda_{max}$ (acetonitrile) 255 nm ($\epsilon$ 2.3 $\times$ $10^4$).

*Anal.* Calcd for $C_{17}H_{12}NO_4S_2Cl$: C, 51.84; H, 3.04; N, 3.60; S, 16.28; Cl, 9.00. Found: C, 51.94; H, 2.86; N, 3.84; S, 16.31; Cl, 8.87.

Quantitative assay of **3**, before the washed and dried solid residue was crystallized, was made spectroscopically in acetonitrile at 255 nm. A typical reaction of **1** (53.7 mg, 0.170 mmol) with Eastman Spectro Grade pyridine (not dried further) gave 19.4 mg (0.089 mmol) of thianthrene, 11.2 mg (0.048 mmol) of thianthrene 5-oxide, and 12.5 mg (0.032 mmol) of **3**. A typical reaction of **1** (90.8 mg, 0.287 mmol) in nitromethane solution gave 30.3 mg (0.140 mmol) of thianthrene, 25.2 mg (0.108 mmol) of thianthrene 5-oxide, and 10.3 mg (0.026 mmol) of **3**. After compensating for reaction with water these results correspond with 87 and 73% yields of **3**, respectively.

**Degradation of 3 into 2-Aminothianthrene.**—Aqueous sodium hydroxide (15%, 5 ml) was added to a solution of 27.5 mg of **3** in 30 ml of methanol under a nitrogen atmosphere. A red precipitate and solution formed during 3 hr of stirring. These were extracted with benzene, the benzene was removed under vacuum, and the red residue was dissolved in 5 ml of methanol. To this was added 15 ml of concentrated hydrochloric acid, and the mixture was stirred for 15 hr. The yellow solution was made alkaline and extracted with benzene. Tlc showed 2-aminothianthrene and one other spot ($R_f$ 0) only. Column chromatography (benzene on silica gel) gave 43% of 2-aminothianthrene, mp 255–256° (ethanol), shown to be identical with an authentic sample.[40]

**Reaction of 5 with Pyridine.**—To a stirred solution of 1.21 g (4.05 mmol) of **5** in acetonitrile was added 0.4 ml (4.9 mmol) of pyridine. The solution became green immediately but turned orange-red over a period of 5 hr. Evaporation of the solvent and extraction of the residue with benzene left a dark residue. The benzene-soluble portion was evaporated, giving 467 mg of a green solid. Chromatography of this solid on a silica column gave 290 mg (72%, based on the stoichiometry of the reaction) of phenothiazine, mp 185–186°, and 50 mg (0.126 mmol, 2.1%) of 3,10′-biphenothiazine (**8**), mp 196–198° (acetonitrile) (lit.[22] mp 199–200°), nmr spectrum in agreement with nmr of authentic compound, $\lambda_{max}$ (methylene chloride) 319 nm ($\epsilon$ 0.95 $\times$ $10^4$) and 259 (1.04 $\times$ $10^5$). Crystallization of the dark residue gave 600 mg (1.59 mmol, 78%) of brick-red *N*-(3-phenothiazinyl)-pyridinium perchlorate (**7**), mp 260–261° (aqueous ethanol).

*Anal.* Calcd for $C_{17}H_{13}N_2O_4SCl$: C, 54.2; H, 3.48; N, 7.43; S, 8.51; Cl, 9.41. Found: C, 54.1; H, 3.73; N, 7.98; S, 8.58; Cl, 9.80.

Compound **7** had $\lambda_{max}$ (acetonitrile) at 412 nm ($\epsilon$ 4.4 $\times$ $10^3$), 282 (1.07 $\times$ $10^4$), and 252 (3.75 $\times$ $10^4$).

In a similar experiment employing 154 mg of **5** and 50 $\mu$l of pyridine, the products were separated by tlc, removed from the tlc plate, and assayed spectroscopically, giving 80% of phenothiazine, 84% of **7**, and 9% of **8**.

**Reaction of 5 with Chloride Ion.**—A solution of 400 mg (1.44 mmol) of tetrabutylammonium chloride in 10 ml of acetonitrile was added to a stirred solution of 362 mg (1.21 mmol) of **5** in acetonitrile. After 3 hr the green solution was evaporated and the residue was extracted with benzene. The washed and dried benzene solution was evaporated to give 265 mg of brown residue. This was placed on a silica column and eluted with benzene to give 261 mg of yellow solid. Weighed samples of the solid were streaked on a silica gel tlc plate and developed with 2:1 petroleum ether–ether. The three tlc bands were removed and assayed spectrophotometrically, giving, in two separate assays, 42 and 43% of phenothiazine, 35 and 32% of 3-chlorophenothiazine, and 4.8 and 4.3% of 3,7-dichlorophenothiazine.

**Reaction of 5 with Bromide Ion. A.**—The procedure was the same as above, with the use of 446 mg of **5** and 1.0 g of potassium bromide. Two separate assays of tlc bands gave 46 and 48% of phenothiazine, 40 and 37% of 3-bromophenothiazine, and 4.2 and 4.1% of 3,7-dibromophenothiazine.

**B.**—A sample of 65 mg of **5** was treated with potassium bromide as above while a stream of nitrogen passed through the solution. Assay of products gave 50% of phenothiazine, 37% of 3-bromophenothiazine, and 4.1% of 3,7-dibromophenothiazine.

**Reaction of 5 with Fluoride Ion.**—Potassium fluoride and **5** (157 mg) were used as above. A green benzene solution was obtained, portions of which, by tlc separation (2:1 petroleum ether–ether) and spectroscopic analysis (methylene chloride) gave 38% of phenothiazine and 17% of 3,10′-biphenothiazine. A green band remained at the base of the tlc plate. On the upper edge of the green band was another, small band, light pink in color. These were not identified. They did not correspond with phenothiazine 5-oxide. The pink band may have been 3-phenothiazone.

Treatment of the green benzene solution with 1% aqueous sodium hydroxide caused the green color to disappear. The light brown solution was streaked on a silica plate and developed as earlier. The phenothiazine (19%) and 3,10′-biphenothiazine (35%) bands were followed by a series of three or four overlapping bands, and no attempt was made to separate and identify them.

**Reaction of 5 with Water.**—Water (2 ml) was added to a stirred solution of 157 mg (0.503 mmol) of **5** in 20 ml of acetonitrile. The solution became green. Work-up as in the fluoride ion reaction gave 33% of phenothiazine and 25% of 3,10′-biphenothiazine. The base of the tlc plate contained the green and pink bands observed in the fluoride ion reaction. Treatment of the benzene solution with 1% aqueous sodium hydroxide and work-up as in the fluoride ion case gave an identical chromatogram, consisting of the phenothiazine (19%) and 3,10′-biphenothiazine (45%) bands followed by the overlapping group of three or four bands.

(40) Prepared by Dr. C. F. Dais. See H. J. Shine, C. F. Dais, and R. J. Small, *J. Org. Chem.*, **29**, 21 (1964).

**Reaction of 5 with Hydroxide Ion.**—Aqueous sodium hydroxide (1%, 50 ml) was added to a solution of 2.62 g (8.78 mmol) of **5** in 100 ml of acetonitrile. The solution became green and a green solid precipitated. Extraction with chloroform and repeated chromatography of the chloroform soluble material on silica columns gave 300 mg (1.5 mmol, 17%) of phenothiazine, 210 mg (0.53 mmol, 6%) of 3,10′-biphenothiazine, and 24 mg (0.11 mmol, 1.3%) of 3-phenothiazone. At least four other products were present but were not identified.

**Registry No.**—**1**, 21299-20-7; **2**, 2362-50-7; **3**, 34874-72-1; **5**, 34874-73-2; **7**, 34874-74-3; phenothiazine, 92-84-2.

# 7,8,9-Trimethoxy-1,2,3,4,4a,5,6,10b-octahydro- and 7,8,9-Trimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridines. Synthesis and Stereochemistry of Certain 6-Substituted and 5,6-Disubstituted Derivatives[1]

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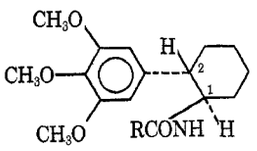
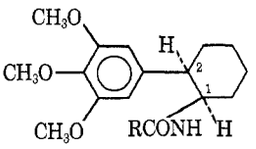
The diastereomers of 6-methyl and of 6-*o*-hydroxyphenyl derivatives of 7,8,9-trimethoxy-4a,10b-*trans*-1,2,3,4,-4a,5,6,10b-octahydrophenanthridine, obtained by the Pictet–Spengler reaction, were characterized by nmr. 7,8,9-Trimethoxy-4a,10b-*trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (**7**), its 6-methyl derivative **9**, and the 4a,10b-cis isomer **8** and its methyl derivative **10** were prepared by the Bischler–Napieralski reaction from the appropriate amides **3**–**6**. Conformations of **8** and **10** were established by nmr in deuteriochloroform and rotational isomerism of the amides is discussed. Catalytic hydrogenation of **9** and **10** yielded only the isomer having the methyl group trans to H-4a in each case, compounds **11** and **15**, respectively. The conformation of the cis compound **15** was established by nmr. Epimerization studies of the hydrochloride salts of the *N*-methyl derivatives of **11** and **12** (compounds **16** and **17**, respectively) in formic acid showed that for **16** the equilibrium is essentially in the direction of a single epimer having the two methyl groups trans to each other, while at equilibrium **17** shows a mixture with at least 75% of the epimer having the methyl groups trans.

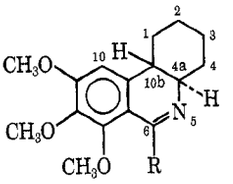
In a preceding paper[2] we have discussed the stereochemistry and epimerization of salts of N-substituted 7,8,9-trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,-4a,5,6,10b-octahydrophenanthridines prepared from *trans*- (**1**) and *cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamine[3] (**2**) *via* the Pictet–Spengler reaction. The present paper deals with the stereochemistry of 6-substituted and 5,6-disubstituted derivatives and their preparation by the same route and by the Bischler–Napieralski cyclodehydration of the appropriate amides of **1** and **2**. The 7,8,9-trimethoxy-1,2,3,4,4a,10b-hexahydrophenanthridine intermediates of the Bischler–Napieralski reaction were of interest from a pharmacological standpoint in addition to being potential sources of specific stereoisomers of the 6-substituted octahydro series because of probable stereoselectivity in the catalytic hydrogenation step, as was actually shown to be the case (*vide infra*).



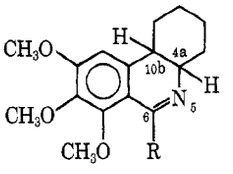
**3**, R = H
**5**, R = $CH_3$



**4**, R = H
**6**, R = $CH_3$



**7**, R = H
**9**, R = $CH_3$



**8**, R = H
**10**, R = $CH_3$

## Results and Discussion

**7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,-3,4,4a,10b-hexahydrophenanthridines and 6-Methyl Derivatives.**—A wide variety of condensing agents and solvents have been used in the Bischler–Napieralski reaction.[4] In the present study yields of better than 90% of the hydrochloride salts of **7**, **8**, **9**, and **10** were obtained by use of phosphorus oxychloride in chlorobenzene with the appropriate amides **3**–**6**.

The nmr spectra of amides **3**, **4**, and **6** show the presence of amide C–N bond rotational isomers, but no evidence of two isomers was found in **5**. The ratio of isomers, estimated from the integration of the signals of the aromatic hydrogens which give a singlet for each isomer, was found to be about 6:1 for **3**, 5:4 for **4**, and 7:1, or more, for **6**. Published data on isomerism of secondary amides[5] indicate a usual predominance of the isomer having a trans orientation of the N substituents and the R or H on the carbonyl carbon. Our results are in agreement with this. In the formamides **3** and **4** the signal of the formyl hydrogen of the major isomer in each case gives a doublet with a coupling constant of 2 Hz between the formyl and NH protons, while the doublet for the minor isomer has a coupling constant of 12 Hz, consistent with a trans orientation of the coupled hydrogens in the minor isomer. This assignment is also supported by the fact that the signal of the formyl hydrogen, or the acyl methyl group, of the minor isomer is at higher field than that of the major isomer in each case. Molecular models in-

(1) This investigation was supported by Grant MH 12204 from the National Institute of Mental Health, U. S. Public Health Service. The compounds were submitted to Eli Lilly and Company for pharmacological evaluation.

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(4) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1951).

(5) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1971).