[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XIX. THIOPHENE ISOSTERS

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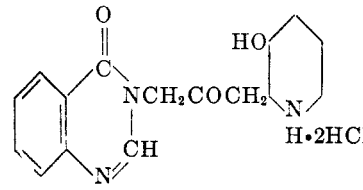
The general method for the synthesis of the Hydrangea alkaloid (I) involved coupling of 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine with 4-quin-



I

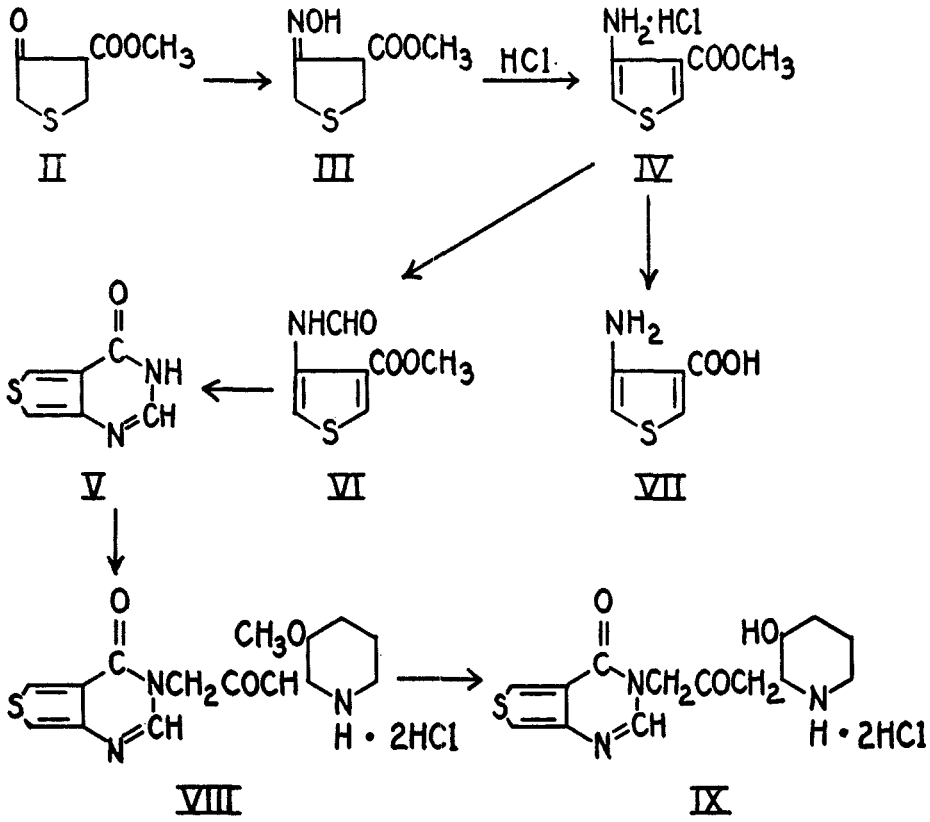
azolone followed by removal of the blocking groups by two stage strong acid hydrolysis (1). A series of related compounds with the benzene ring replaced by a heterocycle could theoretically be synthesized. However, it is imperative that the heterocycle be stable to strong acid. Secondly, the heterocycle should not be basic such as pyrimidine, pyridine, or imidazole since substitution of a basic group on the benzene ring of the alkaloid (I) caused loss of activity (2). One of the few heterocycles satisfying these conditions is thiophene. This communication describes the syntheses of 6,7- and 7,8-thia-4-quinazolones, two of the three possible thienopyrimidones, and conversion of the 6,7-thia-4-quinazolone to the alkaloid isoster (IX).

The most general method of synthesizing 4-quinazolone and its derivatives is by the Niementowski reaction (3), involving fusion of the proper anthranilic acid with formamide (3). This would require the preparation of the proper *o*-aminothenoic acid, none of which are described in the literature. However, Cheney and Piening (4) have described a synthesis of 2-alkyl-3-amino-4-thenoic esters by a general method. The parent amino ester (IV) has now been synthesized by their procedure.

3-Carbomethoxy-4-ketothiophane (II) (5) was converted to the oxime (III) and rearranged with hydrogen chloride (4) to the desired 3-amino-4-carbomethoxythiophene hydrochloride (IV). Saponification gave impure 3-amino-4-thenoic acid (VII) in low yield which was not readily purified due to its apparent instability. It seemed desirable at this point to convert the amino ester base (IV) directly to the thiaquinazolone (V). A test reaction with methyl anthranilate and formamide at 175° gave only 35% of 4-quinazolone after four hours. However, addition of ammonium formate to the fusion mixture raised the yield of 4-quinazolone to 71%. Application of these conditions to IV free base gave only traces of the desired V along with large amounts of tar. Since aminothiophene bases are notoriously unstable, the molecule was stabilized by formylation to VI.

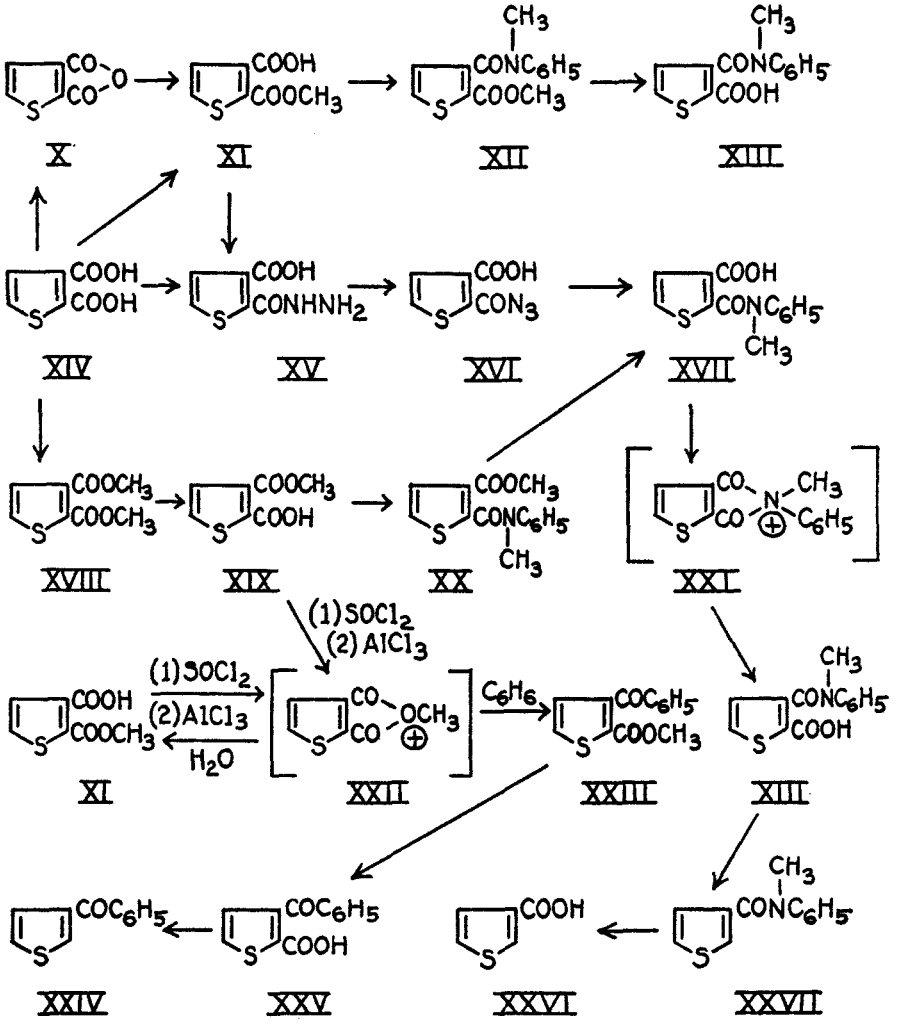
Treatment with ammonium formate and formamide at 145° for six hours gave a 50% yield of the desired thiaquinazolone (V).

Coupling of V with 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine (1) gave a gum which was hydrolyzed directly to VIII in 0.7% yield. Hydrobromic acid hydrolysis afforded the thiophene isoster of the Hydrangea alkaloid (IX) which was about 1/10 as active as the parent *dl*-alkaloid and had a chemotherapeutic index of 1–2.



The syntheses of 5,6-thia- and 7,8-thia-4-quinazolone (XLIII and XXXV) should be feasible from thiophene-2,3-dicarboxylic acid (XIV) by Curtius degradation of one or the other of the carboxyl groups. Modification of the procedure for permanganate oxidation of 2-aceto-3-methylthiophene (6) increased the yield from 13% (7) to 43%. The diacid (XIV) readily forms an anhydride (7), which gave a monomethyl ester, A, m.p. 123°. This same monomethyl ester was obtained in better over-all yield by partial esterification of the diacid (XIV). It follows that partial acid hydrolysis of the diester (XVIII) should give the isomeric monoester, since the ratio of the rates of esterification of the two carboxyls should be the same as the ratio of the rates of acid hydrolysis of the two esters. This has been found to be the case, an isomeric monoester B, m.p. 105°, being obtained.

For sake of discussion monoester A is arbitrarily assigned structure XI and monoester B structure XIX.



In order to prove the structure of monoester A, the carboxyl was converted to the methylanilide (XII) *via* the acid chloride, then saponified to the acid (XIII). Thermal decarboxylation gave the crude methylanilide (XXVII) which was hydrolyzed and the product shown to be identical with authenic 3-thenoic acid,[1] indicating that the assignment of the structure XI to monoester A was correct, *barring molecular rearrangements*. To check on this point, the hydrazide (XV) obtained from monoester A, was converted to the azide (XVI) and reacted with methylaniline to give the amide acid (XVII), isomeric with XIII. The amide

[1] We are indebted to Dr. Ellis V. Brown of Fordham University for an authentic sample of 3-thenoic acid (8).

acid (XVII) was also obtained from monoester B *via* XX. When the amide acid (XVII) was thermally decarboxylated, then hydrolyzed, the product was not 2-thenoic acid as expected, but was again 3-thenoic acid showing that the methylanilide acid actually having structure XVII does *rearrange* to XIII, probably *via* XXI.[2] Thus the structure proof was void and another was sought.

Reaction of the acid chloride from monoester A with benzene in the presence of aluminum chloride gave 2-carbomethoxy-3-benzoylthiophene (XXIII) along with some recovered monoester A. Hydrolysis and decarboxylation gave 3-benzoylthiophene (XXIV) isomeric with authenic 2-benzoylthiophene (9). *Barring molecular rearrangements* the structures were again proven. However, when the acid group of monoester B was converted to the acid chloride and condensed with benzene and aluminum chloride, 2-carbomethoxy-3-benzoylthiophene (XXIII) was obtained, identical with that obtained from monoester A. In addition the acidic fraction recovered was not ester B, as expected, but rearrangement to ester A had taken place. Thus one of the two acid chloride-esters underwent rearrangement during this operation, probably *via* the oxonium ion (XXII).

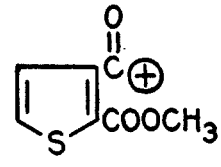
The facts that the phenyl group attached to the 3-carbonyl and that monoester A is obtained in both cases lends strong evidence, but not proof that the ester group of monoester A is at the 2-position since the carbonium ion (XXIIb) would be expected to react with water or benzene to give the carboxyl or benzoyl groups, respectively, at position 3.

The structures were proven through derivatives of 2-amino-3-thenoic acid quite unexpectedly. When the azide (XVI) from monoester A was refluxed in chloroform, the intermediate isocyanate cyclized to 6,7-thiaisatoic anhydride (XXVIII). It had been planned to react this with ammonia to give 2-amino-3-thenamide (XXIX) which could be cyclized to the desired 7,8-thia-4-quinazolone (XXXV) with formic acid, a method used with isatoic anhydride and its substituted derivatives to avoid going through unstable anthranilic acids (11). However, when XXVIII was treated under these conditions a neutral compound was isolated which analyzed for thienylurea (XXXI). When the formic acid treatment was omitted, the urea acid (XXXII) was obtained in good yield, rupture of the anhydride ring having occurred on the abnormal side of the hetero oxygen. When XXXII was heated with 89% formic acid decarboxylation took place rapidly and the product was again a thienylurea. The latter was identical with authenic 2-thienylurea obtained from 2-thenoic acid *via* the hydrazide (XXX) giving a complete structure proof of all the intermediates as written in the flow sheets.

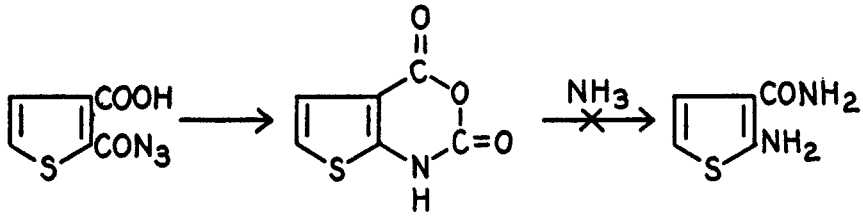
Treatment of the isatoic anhydride (XXVIII) with ammonium formate in 89% formic acid at 100° caused ring opening and formylation to 2-formamido-3-thenoic acid (XXXIII). This compound failed to give 7,8-thia-4-quinazolone (XXXV) when fused with ammonium formate and formamide under the usual conditions. Isatoic anhydride itself also gave N-formylanthranilic acid with ammonium formate in formic acid but it was readily convertable to 4-quina-

[2] The transfer of an amine from one carboxyl to the other in a diacid has been noted previously with a monomethylanilide of methylsuccinic acid (10).

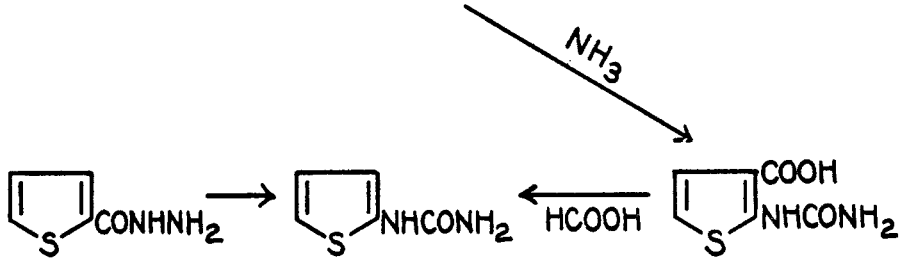
zolone by fusion with formamide and ammonium formate. The methyl ester (XXXIV), obtained from XXXIII with diazomethane, gave dark tars when fused with ammonium formate and formamide in contrast to VI.



XXII b



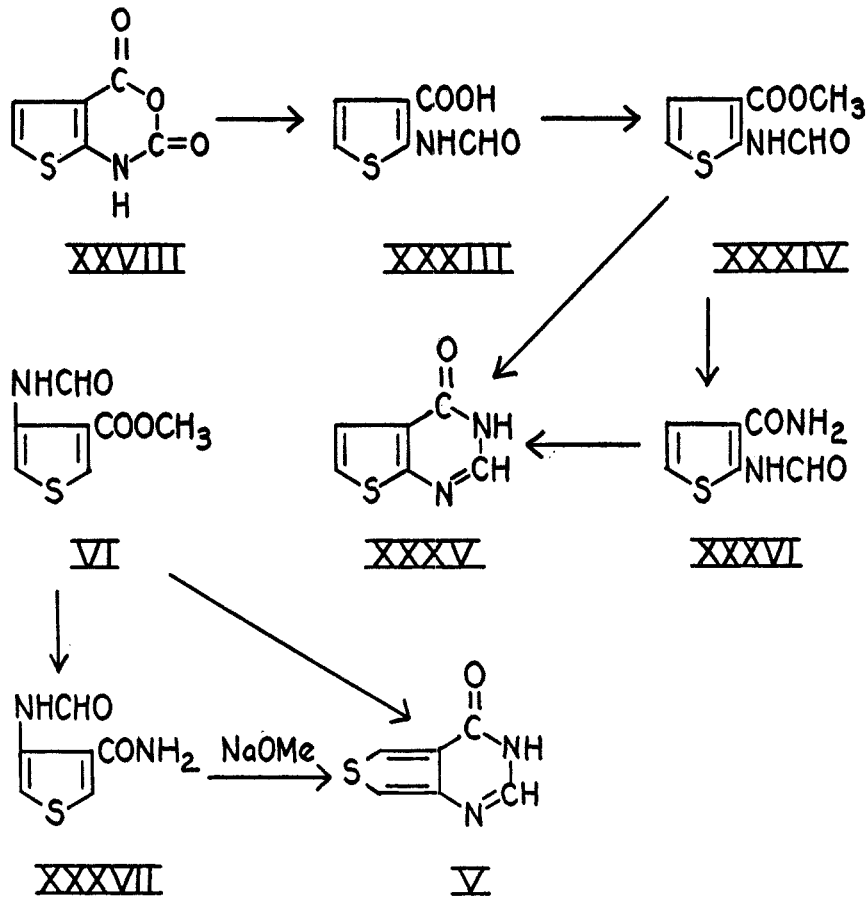
XVI XXVIII XXIX



XXX XXXI XXXII

Since considerably larger quantities of VI were available than XXXIV, a milder method for the preparation of V was sought which could be applied to XXXV. The action of ammonia in methanol at 25° on VI afforded the amide (XXXVII) in 71% yield. This was smoothly cyclized with methanolic sodium methoxide at 25° to the 6,7-thia-4-quinazolone (V) in 93% yield. The over-all yield from VI was 66% *via* the amide whereas direct fusion of VI to V proceeded in 50% yield as described earlier. The action of ammonia on methyl N-formylanthranilate led directly to 4-quinazolone. When 2-formamido-3-carbomethoxythiophene (XXXIV) was treated with methanolic ammonia, reaction was slow and a 4% yield of the desired 7,8-thia-4-quinazolone (XXXV) was obtained directly. Since 3-methylthiophene was no longer commercially available at this

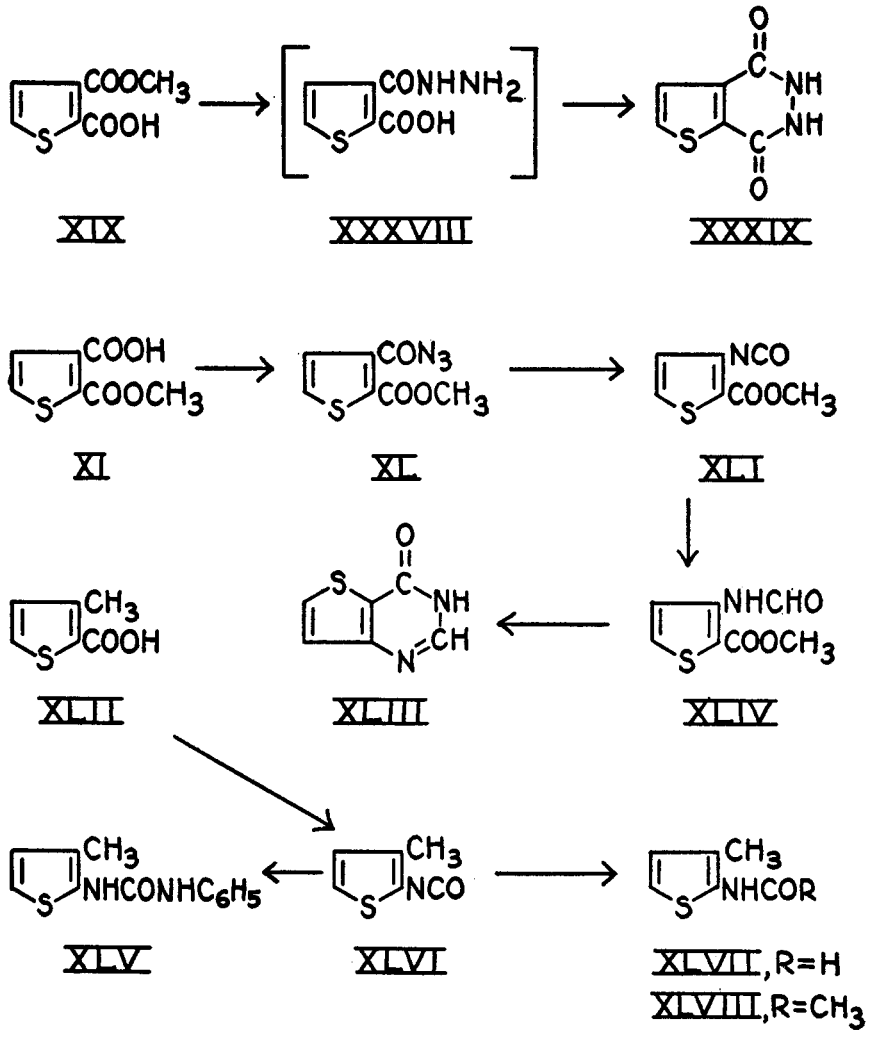
point, sufficient XXXV could not be obtained for preparation of this thiophene isoster of the Hydrangea alkaloid.



5,6-Thia-4-quinazolone (XLIII) could not be prepared from monoester B (XIX) in the same fashion. When XIX was treated with hydrazine in the same manner as described for monoester A, the intermediate hydrazide (XXXVIII) spontaneously cyclized to XXXIX, again showing the greater reactivity of the α-carboxyl than the β-carboxyl. A second method also failed; treatment of the acid chloride of monoester A (XI) with sodium azide, then Curtius rearrangement to the isocyanate (XLI), seemed to take place satisfactorily. Reaction with formic acid did not lead to the expected 2-carbomethoxy-3-formamidothiophene (XLIV) even though this sequence of reactions was satisfactory for conversion of 3-methyl-2-thenoic acid (XLII) to 2-formamido-3-methylthiophene (XLVII) and 2-acetamido-3-methylthiophene (XLVIII).

Acknowledgement: Thanks are given to Mr. Louis Brancone and staff for the

microanalyses, Messers. W. McEwen and J. Poletto for large scale preparation of some of the intermediates, and Dr. R. Hewitt and co-workers for the antimalarial assay.



EXPERIMENTAL

3-Carbomethoxy-4-oximinothiophane (III). A mixture of 20 g. of 3-carbomethoxy-4-ketothiophane (II) (5), 20 g. of hydroxylamine hydrochloride, 300 cc. of methanol, and 57 g. of barium carbonate was refluxed on the steam-bath for 16 hours. The filtered solution was evaporated *in vacuo* and the residue partitioned between water and ethyl acetate. The organic layer, dried with magnesium sulfate, was evaporated to dryness *in vacuo* leaving 21.4 g. (102%) of an oil which was 95% pure based on the nitrogen analysis.

Anal. Calc'd for $C_6H_9NO_3S$: N, 8.00. Found: N, 7.58.

The use of pyridine instead of barium carbonate gave a similar product in 83% yield, except that the product was darker.

3-Carbomethoxy-4-aminothiophene hydrochloride (IV). To a solution of 21.3 g. of III in 250 cc. of reagent ether was added 28 cc. of 5 *N* hydrogen chloride in methanol. After 18 hours at room temperature, the mixture was filtered and the product washed with ether; yield, 10.3 g., m.p. 203–205° dec. After standing one more day the filtrate deposited an additional 3.1 g. (total 57%) of product, m.p. 195–197° dec. Recrystallization of a sample of the first crop from methanol-ether afforded white needles, m.p. 203–205° dec.

Anal. Calc'd for $C_6H_7NO_2 \cdot HCl$: C, 37.2; H, 4.17; N, 7.24.

Found: C, 37.5; H, 4.44; N, 7.67.

An attempt to hydrolyze the ester with 10% sodium hydroxide to 4-amino-3-thenoic acid (VII) gave only a small amount of product which seemed quite unstable and was not readily purified.

3-Carbomethoxy-4-formamidothiophene (VI). A solution of 3.0 g. of IV and 2.0 g. of anhydrous sodium acetate in 15 cc. of 89% formic acid was heated on the steam-bath for one hour, then evaporated to dryness *in vacuo*. Addition of water gave 2.5 g. of crude insoluble product, m.p. 87–89°. This material was recrystallized from hot heptane, decanting from some insoluble tar; yield, 1.7 g. (59%), m.p. 94–96°. A second recrystallization gave white crystals, m.p. 94–96°.

Anal. Calc'd for $C_7H_7NO_3S$: C, 45.4; H, 3.82; N, 7.58.

Found: C, 45.5; H, 3.90; N, 7.88.

In a larger run employing 45 g. of IV it was more convenient to pulverize the crude, dry product with an equal amount of sand and isolate the product by Soxhlet extraction with petroleum ether (b.p. 40–100°); yield, 30.3 g. (71%), m.p. 90–92°.

4-Formamido-3-thenamide (XXXVII). A solution of 10 g. of VI in 150 cc. of methanol was saturated with ammonia and allowed to stand for 4 days. Concentration *in vacuo* gave 6.5 g. (71%) of product in three crops, m.p. between 187 and 194°. Recrystallization of a sample from water with the aid of Norit gave white crystals, m.p. 197–198°.

Anal. Calc'd for $C_6H_6NO_2S$: C, 42.3; H, 3.55; N, 16.5.

Found: C, 42.0; H, 3.88; N, 16.1.

Conversion of methyl anthranilate to 4-quinazolone. A mixture of 5 g. of methyl anthranilate, 5 g. of ammonium formate, and 4 cc. of formamide was heated in a bath at 175–180° for 4½ hours. Trituration with cold methanol gave 3.5 g. (71%) of 4-quinazolone, m.p. 195–197°, which was identified by mixture m.p.

Omission of the ammonium formate gave only 1.7 g. (36%) of 4-quinazolone.

Thieno[3,4-*d*]*pyrimidone-4* (*6,7-thia-4-quinazolone*) (V). (*A*). A mixture of 6 g. of VI, 6 g. of ammonium formate, and 25 cc. of formamide was heated in a bath at 140–145° for 6 hours during which time the product crystallized. The cold mixture was triturated with methanol; yield, 2.5 g. (50%), m.p. 269–271°. At the end of 4 hours at 140–145° the yield was 46% and 18% of unchanged VI was recovered. When the reaction was run at 160–165° for 90 minutes the yield was 31%, m.p. 268–270°. Several recrystallizations of the latter from methanol with the aid of Norit gave white crystals, m.p. 271–273°.

Anal. Calc'd for $C_6H_4N_2OS$: C, 47.3; H, 2.65; N, 18.4.

Found: C, 47.3; H, 2.84; N, 18.2.

Direct fusion of IV free base with the same reagents for 4 hours or for one hour at 125°, then 4 hours at 160–165° gave tars which contained traces of the desired product. Similar results were obtained at 175–180° for 4 hours.

(*B*). A suspension of 18 g. of 4-formamido-3-thenamide (XXXVII) in 130 cc. of 1 *N* sodium methoxide was stirred for 16 hours during which time solution was complete. After standing an additional 24 hours, the solution was clarified by filtration and evaporated to dryness *in vacuo*. The solid was dissolved in 50 cc. of water and the solution acidified with acetic acid. The product was collected and washed with water; yield, 14.7 g. (93%), m.p. 270–272°. A mixture with preparation *A* melted the same.

The amide was recovered unchanged when warmed briefly with aqueous alkali (11) or refluxed in acetic anhydride containing 0.25% phosphoric acid for one hour (12).

3-[*β-Keto-γ-*(*3-methoxy-2-piperidyl*)*propyl*]*-6,7-thia-4-quinazolone dihydrochloride* (VIII).

Condensation of 2.12 g. of 6,7-thia-4-quinazolone (V) with 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine in the usual manner (1) followed by hydrochloric acid hydrolysis of the crude gum (11) gave 40 mg. (0.7%) of tan crystals, m.p. 215° dec.

Anal. Calc'd for $C_{15}H_{19}N_3O_3S \cdot 2HCl$: C, 45.7; H, 5.38; N, 10.6.

Found: C, 46.0; H, 5.53; N, 10.5.

3-[β-Keto-γ-(3-hydroxy-2-piperidyl)propyl]-6,7-thia-4-quinazolone dihydrochloride (IX). Hydrolysis of VIII with 48% hydrobromic acid in the usual manner (1) gave IX as nearly white crystals from absolute alcoholic hydrogen chloride, m.p. 195–200° dec., with shrinkage at 152–154°.

Anal. Calc'd for $C_{14}H_{17}N_3O_3S \cdot 2HCl \cdot 1\frac{1}{2}H_2O$: C, 41.3; H, 5.40; N, 10.3.

Found: C, 41.5; H, 5.77; N, 10.7.

Thiophene-2,3-dicarboxylic acid (XIV). To a stirred mixture of 35 g. of 2-aceto-3-methylthiophene and 2.1 l. of water containing 280 g. of sodium hydroxide was added portionwise 195 g. of potassium permanganate over a period of 90 minutes. After being stirred an additional hour, the mixture was stirred on the steam-bath until a sample spotted on filter paper was no longer purple (2 hours). The mixture was cautiously acidified to about *p*H 3 with 50% sulfuric acid and again heated and stirred on the steam-bath for 30 minutes. The mixture was filtered hot and the manganese dioxide cake was washed with hot water. The manganese dioxide cake was stirred with 200 cc. of 5% sodium hydroxide, filtered, washed with water and the filtrate acidified. Extraction with 2 50-cc. portions of ethyl acetate gave 1.5 g. of product, m.p. 262–264° dec.

The original filtrate, from which some solid separated on cooling, was extracted with 5 250-cc. portions of ethyl acetate (a sixth extract did not contain any material). The first dried extract was evaporated separately *in vacuo* leaving 14.4 g. of solid, m.p. 195–197° dec. Trituration with cold ethyl acetate gave 4.6 g. of product, m.p. 257–259° dec. The remaining four extracts were combined, dried with magnesium sulfate, and evaporated *in vacuo* leaving 12.6 g. of product, m.p. 268–270° dec.; lit. m.p. 270° (7). The total yield was 18.7 g. (43%).

2-Carbomethoxy-3-thenoic acid (XI). (*A*). A solution of 13.4 g. of thiophene-2,3-dicarboxylic anhydride (7) in 70 cc. of methanol was refluxed on the steam-bath for 18 hours, then evaporated to dryness *in vacuo*. The residue (m.p. 100–110°) was recrystallized from toluene giving 7.1 g. (37%) of white crystals, m.p. 119–121°. Further recrystallizations gave a constant m.p. of 122–124°.

Anal. Calc'd for $C_7H_6O_4S$: C, 45.3; H, 3.26.

Found: C, 45.6; H, 3.50.

The filtrate from the 7.1 g. was evaporated to dryness *in vacuo*. The residue was heated on the steam-bath for about two hours with 6 *N* hydrochloric acid. The cooled mixture was filtered to give 48% of XIV, m.p. 266–268° dec.

(*B*). To a mixture of 14 g. of the diacid (XIV) and 70 cc. of methanol was added 0.56 cc. of acetyl chloride. The solution was refluxed 20 minutes, then immediately evaporated to dryness *in vacuo*. The residue was extracted with 20 cc. of hot toluene on the steam-bath and filtered from 2.6 g. (19%) of unchanged XIV, m.p. 263–265°. The filtrate on cooling deposited 5.2 g. of monoester, m.p. 118–120°, identical with preparation *A*. The filtrate was extracted with excess aqueous sodium bicarbonate and the extracts acidified to give an additional 3.3 g. (total 56%) of monoester, m.p. 112–115°. The toluene solution on evaporation to dryness *in vacuo* gave 3.0 g. (19%) of residual diester (XVIII) which solidified on cooling. The conversion to monoester based on diacid and diester not recovered was 89%.

Dimethyl thiophene-2,3-dicarboxylate (XVIII). To a mixture of 5 g. of diacid (XIV) and 25 cc. of methanol was added 0.2 cc. of acetyl chloride. The solution was refluxed three hours, then evaporated to dryness *in vacuo* leaving 5.5 g. (96%) of a low-melting solid (7).

3-Carbomethoxy-2-thenoic acid (XIX). A solution of 6.0 g. of diester (XVIII) in 26 cc. of acetone and 20 cc. of 6 *N* hydrochloric acid was allowed to stand at room temperature for 24 hours, then evaporated to dryness *in vacuo* (bath 40–45°). The residue was heated on the steam-bath with 20 cc. of toluene and filtered from 0.84 g. (16%) of diacid (XIV), m.p. 266–268° dec. The toluene was extracted with excess saturated aqueous sodium bicarbonate.

Acidification gave 2.4 g. (43%) of white crystals of monoester, m.p. 103–105°, unchanged on recrystallization from heptane. A mixture with XI (1:3) melted at 98–99°.

Anal. Calc'd for $C_7H_6O_4S$: C, 45.3; H, 3.26.

Found: C, 45.6; H, 3.51.

The toluene solution of neutral material gave 1.6 g. (28%) of unchanged diester on evaporation. Thus the conversion to monoester is 77% based on diester and diacid not recovered.

N-Methyl-2-carbomethoxy-3-thenanilide (XII). A solution of 2.0 g. of XI in 6.5 cc. of thionyl chloride was refluxed 30 minutes, gas evolution being complete in 20 minutes. The solution was evaporated to dryness *in vacuo* (bath 45°) and the evaporation repeated with 13 cc. of benzene. The residual acid chloride, dissolved in 13 cc. of benzene, was treated with 5 cc. of methylaniline with cooling. The methylaniline hydrochloride was removed by filtration. Addition of heptane to turbidity gave 2.1 g. (71%) of product, m.p. 85–88°. Two recrystallizations from heptane gave white crystals, m.p. 90–92°.

Anal. Calc'd for $C_{14}H_{13}NO_3S$: C, 61.1; H, 4.77; N, 5.08.

Found: C, 61.1; H, 5.19; N, 4.90.

Similarly, 0.50 g. of 3-carbomethoxy-2-thenoic acid (XIX) gave 0.43 g. (58%) of *N-methyl-3-carbomethoxy-2-thenanilide* (XX), m.p. 112–113°. Recrystallization from heptane afforded white crystals, m.p. 113–115°.

Anal. Calc'd for $C_{14}H_{13}NO_3S$: C, 61.1; H, 4.77; N, 5.08.

Found: C, 61.5; H, 4.89; N, 5.03.

N-Methyl-2-thenanilide was prepared in the same fashion from 2-thenoic acid in 59% yield, m.p. 82–84°, unchanged on recrystallization from heptane.

Anal. Calc'd for $C_{12}H_{11}NOS$: C, 66.3; H, 5.12; N, 6.46.

Found: C, 66.3; H, 5.10; N, 6.28.

The hydrolysis of this anilide was investigated since the methylanilide obtained on decarboxylation of XIII and XVII was not readily purified. A mixture of 1.00 g. of anilide, 3 cc. of acetic acid, and 5 cc. of 6 *N* hydrochloric acid was refluxed 6 hours, then evaporated to dryness *in vacuo*. The residue was partitioned between water and ethyl acetate. The separated ethyl acetate layer was back-extracted with excess aqueous sodium bicarbonate. Acidification gave 0.30 g. (51%) of 2-thenoic acid, m.p. 125–126°. A one-hour hydrolysis gave only 17% of the acid and 65% of the anilide was recovered unchanged.

3-Carboxy-2-thenhydrazide (XV). A solution of 11.2 g. of XI and 10 cc. of 100% hydrazine hydrate in 58 cc. of absolute alcohol was refluxed for 2½ hours. The mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 45 cc. of water, filtered from a little insoluble material, and the filtrate acidified with acetic acid, then cooled. The product was collected and washed with water; yield, 8.7 g. (78%), m.p. 331–333° dec. and sublimation. Recrystallization from water gave white crystals, m.p. 329–331° dec. This compound was soluble in 1 *N* hydrochloric acid or aqueous sodium bicarbonate.

Anal. Calc'd for $C_6H_6N_2O_3S$: C, 38.7; H, 3.24; N, 15.1.

Found: C, 39.0; H, 3.58; N, 15.0.

The benzylidene derivative formed in 93% yield, m.p. 219–221°, when a hot solution of this hydrazide was treated with benzaldehyde. Recrystallization from 50% alcohol gave white crystals, m.p. 220–221°.

Anal. Calc'd for $C_{13}H_{10}N_2O_3S$: C, 56.8; H, 3.67; N, 10.2.

Found: C, 56.7; H, 3.99; N, 10.2.

When 3-carbomethoxy-2-thenoic acid (XIX) was treated with hydrazine under the same conditions, the desired hydrazide (XXXVIII) spontaneously cyclized to the dione (XXXIX), m.p. 333–336° dec. This compound was insoluble in 1 *N* hydrochloric or aqueous sodium bicarbonate, but was soluble in dilute sodium hydroxide as expected for a phthalazine-dione type. It did not form a benzylidene derivative. Recrystallization of a sample from water gave white crystals, m.p. 331–333° dec.

Anal. Calc'd for $C_6H_4N_2O_2S$: C, 42.7; H, 2.38; N, 16.7.

Found: C, 42.8; H, 2.84; N, 16.6.

N-Methyl-2-carboxy-3-thenanilide (XIII). A solution of 1.7 g. of the ester (XII) in 5 cc. of alcohol and 5 cc. of 10% sodium hydroxide was refluxed on the steam-bath for two hours, then concentrated nearly to dryness *in vacuo*. The residue was dissolved in 10 cc. of saturated aqueous sodium bicarbonate. Acidification gave 1.2 g. (74%) of product as white crystals, m.p. 153–155°, unchanged on recrystallization from toluene.

Anal. Calc'd for $C_{13}H_{11}NO_3S$: C, 59.7; H, 4.27; N, 5.36.

Found: C, 59.6; H, 4.49; N, 5.18.

N-Methyl-3-carboxy-2-thenanilide (XVII). (*A*). Hydrolysis of 230 mg. of the ester (XX) as described in the previous experiment gave 160 mg. (74%) of product, m.p. and mixture m.p. with preparation *B*, 169–170°.

(*B*). To a stirred solution of 2.3 g. of 3-carboxy-2-thenhydrazide (XV) in 50 cc. of 1 *N* hydrochloric acid and 50 cc. of chloroform cooled in an ice-bath to 5° was added dropwise over a period of 15 minutes, a solution of 1.04 g. of sodium nitrite in 3 cc. of water. The separated aqueous layer was extracted with 40 cc. more of chloroform. To the combined chloroform solutions was added 5.4 cc. of methylaniline. After 3 days at 3° the solution was extracted with excess aqueous sodium bicarbonate. Acidification gave 2.3 g. (71%) of product, m.p. 168–170°. Recrystallization from toluene afforded white crystals, m.p. 169–170°.

Anal. Calc'd for $C_{13}H_{11}NO_3S$: C, 59.7; H, 4.27; N, 5.36.

Found: C, 59.8; H, 4.19; N, 5.31.

A mixture of 0.50 g. of this acid, 1 cc. of quinoline, and a trace of copper oxide was heated in a bath at 165–180° for 90 minutes when carbon dioxide evolution was complete. The cooled residue was dissolved in 10 cc. of ethyl acetate and washed successively with 2 5-cc. portions of 3 *N* hydrochloric acid, 5 cc. of saturated aqueous sodium bicarbonate, and water. Evaporation of the ethyl acetate solution *in vacuo* left 0.35 g. of crude anilide (XXVII) as an oil.

Hydrolysis of 0.31 g. of this anilide by refluxing with 1 cc. of acetic acid and 3 cc. of 6 *N* hydrochloric acid for 24 hours followed by isolation of the bicarbonate-soluble fraction gave 70 mg. (38%) of 3-thenoic acid, m.p. 125–127°. Recrystallization from heptane gave white crystals, m.p. 133–135°, which gave no depression in m.p. when mixed with an authenic sample of 3-thenoic acid.[1]

When the isomeric N-methyl-2-carboxy-3-thenanilide (XIII) was decarboxylated and hydrolyzed the same 3-thenoic acid, m.p. and mixture m.p. 129–131°, was obtained in 40% yield.

2-Carbomethoxy-3-benzoylthiophene (XXIII). 2-Carbomethoxy-3-thenoic acid (XI) (3.5 g.) was converted to the acid chloride as described in the preparation of XII. To the acid chloride dissolved in 16 cc. of benzene was added 2.85 g. of anhydrous aluminum chloride. The mixture was refluxed on the steam-bath for one hour, then cooled and shaken with 19 g. of cracked ice and 8 cc. of 12 *N* hydrochloric acid until solution was complete. The separated benzene layer was extracted with excess aqueous sodium bicarbonate. Acidification gave 1.2 g. (34%) of unchanged monoester (XI), m.p. and mixed m.p. 112–115°. The benzene solution was dried with magnesium sulfate and evaporated to dryness *in vacuo* leaving 1.75 g. (38%) of crude product. Two recrystallizations from toluene gave yellow crystals, m.p. 126–128°.

Anal. Calc'd for $C_{13}H_{10}O_3S$: C, 63.5; H, 4.11.

Found: C, 63.8; H, 4.14.

(*B*). When the isomeric monoester *B* (XIX) was treated by procedure *A*, 1.95 g. (61%) of crude ketone was obtained. Recrystallization from toluene gave yellow crystals, m.p. and mixture m.p. with preparation *A*, 126–128°. From the bicarbonate-soluble fraction there was isolated 31% of monoester *A* (XI), m.p. 108–113° and identified by mixture m.p.'s.

3-Benzoyl-2-thenoic acid (XXV). A mixture of 400 mg. of pure XXIII, 2.6 cc. of 10% sodium hydroxide, and 2.6 cc. of methanol was refluxed on the steam-bath for 25 minutes. The solution was diluted with 5 cc. of water, washed with ethyl acetate, and acidified to

give 300 mg. (87%) of product, m.p. 142–144°. Recrystallization from toluene with the aid of Norit gave white crystals, m.p. 146–148°.

Anal. Calc'd for $C_{14}H_8O_3S$: C, 62.1; H, 3.47.

Found: C, 61.9; H, 3.65.

3-Benzoylthiophene (XXIV). A mixture of 190 mg. of XXV and 10 mg. of copper oxide was heated in a bath at 200–210° for ten minutes when carbon dioxide evolution was complete. The cooled residue was dissolved in ethyl acetate. The solution, washed with aqueous sodium bicarbonate and dried with magnesium sulfate, was evaporated to dryness *in vacuo* leaving 120 mg. (78%) of product which solidified on cooling. Recrystallization from aqueous methanol gave white crystals, m.p. 63°. A mixture with 2-benzoylthiophene (9), m.p. 55–56°, melted at 43–50°.

Anal. Calc'd for $C_{11}H_8OS$: C, 70.1; H, 4.28.

Found: C, 70.1; H, 4.59.

6,7-Thiaisatoic anhydride (XXVIII). To a stirred and ice-cooled solution of 10 g. of XV in 250 cc. of chloroform and 250 cc. of 1 *N* hydrochloric acid was added dropwise over a period of 15 minutes a solution of 4.85 g. of sodium nitrite in 13 cc. of water. The mixture was stirred an additional 15 minutes in the ice-bath. The yellow solid which separated was removed by filtration; wt., 1.9 g., m.p. 100° with explosive decomposition. The separated aqueous layer was extracted with 250 cc. of chloroform and the combined extracts dried with sodium sulfate at 0°. The chloroform solution was refluxed for four hours when gas evolution was essentially complete. After ½ hour a white solid had begun to separate. The mixture was cooled and the product collected; yield 4.3 g., m.p. 221–223° dec. An additional 0.9 g. was obtained by concentration of the filtrate.

The 1.9 g. of solid, m.p. 100° dec., appeared to be the intermediate azide (XVI) as judged by its m.p. and ready solubility in aqueous sodium bicarbonate. It was refluxed with 150 cc. of chloroform for 24 hours during which time nitrogen was evolved and the granular solid gradually changed to fine white needles. The cooled mixture was filtered; yield, 1.2 g., m.p. 208–210° dec. The total yield was 6.4 g. (70%). Recrystallization of a sample from ethyl acetate gave white crystals, m.p. 223–225° dec.

Anal. Calc'd for $C_6H_3NO_3S$: C, 42.7; H, 1.78; N, 8.28.

Found: C, 42.8; H, 2.16; N, 8.35.

Attempts to convert this compound to 2-amino-3-carbomethoxythiophene hydrochloride by refluxing in 1 *N* methanolic hydrogen chloride resulted in recovered starting material after 30 minutes. After 8 hours there was considerable decomposition and a small amount of starting material was the only product isolatable.

3-Carboxy-2-thienylurea (XXXII). A mixture of 300 mg. of XXVIII, 3.5 cc. of acetone, 1 cc. of water, and 0.21 cc. of 28% ammonia water was boiled gently on the steam-bath for ten minutes, then evaporated to dryness *in vacuo*. The residue was dissolved in 3 cc. of warm methanol and ethyl acetate was added to turbidity. Cooling gave 180 mg. (56%) of product, m.p. 184–185° dec. This compound is water-soluble and extractable from aqueous acid, but not from aqueous base showing that the structure was XXXII and not the expected 2-amino-3-thenamide.

Anal. Calc'd for $C_6H_6N_2O_3S$: C, 38.7; H, 3.24; N, 15.0.

Found: C, 39.0; H, 3.68; N, 15.0.

2-Thienylurea (XXXI) (*A*). The crude residue obtained from evaporation of the ammoniacal acetone solution from 500 mg. of XXVIII as in the preceding experiment was heated in 4 cc. of 89% formic acid for one hour on the steam-bath. The solution was diluted with 4 cc. of water, separated from some insoluble material, saturated with salt, and extracted with 3 10-cc. portions of ethyl acetate. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. The residual oil (450 mg.) solidified on standing. Two recrystallizations from toluene gave white crystals, m.p. 144–146°.

Anal. Calc'd for $C_5H_6N_2OS$: C, 42.3; H, 4.23; N, 19.7.

Found: C, 42.6; H, 3.99; N, 19.5, 19.5.

(*B*). A solution of 180 mg. of XXXII in 2.5 cc. of 89% formic acid was heated on the

steam-bath for one hour during which time carbon dioxide was evolved. The solution was evaporated to dryness *in vacuo* and the residue crystallized from toluene: white crystals, m.p. and mixture m.p. with preparation *A*, 142–143°.

(*C*). To a stirred solution of 4.4 g. of 2-thenhydrazide (XXX) (13) in 145 cc. of 1 *N* hydrochloric acid and 145 cc. of carbon tetrachloride cooled in an ice-bath was added 2.83 g. of sodium nitrite in 8 cc. of water over a period of 15 minutes while maintaining the temperature at 5–8°. After being stirred 15 minutes more, the aqueous layer was separated and extracted with 30 cc. of carbon tetrachloride. The combined organic extracts, dried with sodium sulfate at 0°, were refluxed for 15 hours during which time nitrogen was evolved.

An aliquot of the solution of 2-thienyl isocyanate equivalent to 1 g. of the hydrazide (XXX) was stirred with 41 cc. of 28% ammonia water for one hour. The mixture was concentrated to about 10 cc. *in vacuo*. The product was removed by filtration; yield, 0.28 g. (28%), m.p. 142–144°. Recrystallization from toluene gave white crystals, m.p. and mixture m.p. with preparation *A*, 146–147°.

An additional 0.34 g. (total 62%), m.p. 141–142° was isolated from the aqueous filtrate by saturation with salt and extraction with ethyl acetate.

2-Formamido-3-thenoic acid (XXXIII). The yield of this compound was poor due to decarboxylation if the conditions were not carefully controlled. The following procedure was the best of five reactions tried.

A mixture of 2.1 g. of XXVIII, 2.1 g. of ammonium formate, and 12 cc. of 99% formic acid was heated on the steam-bath with mixing until solution was complete (five minutes), then for exactly five minutes more. As much of the formic acid as possible was removed *in vacuo* in a bath at 40–45°. The residue was warmed very briefly with 15 cc. of water and filtered warm. The insoluble material consisted of 0.53 g. of unchanged anhydride (XXVIII), m.p. 215–216° dec. The filtrate was saturated with salt and extracted with 4 5-cc. portions of ethyl acetate. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. Trituration of the oily solid with chloroform gave 0.80 g. (50% based on XXVIII not recovered), m.p. 164–165° dec. The same yield could be obtained with recovered XXVIII. As the reaction time was increased the yield progressively decreased. Recrystallization of a sample from water gave white crystals, m.p. 191–193° dec.

Anal. Calc'd for $C_6H_5NO_3S$: C, 42.2; H, 2.94; N, 8.19.
Found: C, 42.5; H, 3.25; N, 7.94.

Attempts to convert this compound to 7,8-thia-4-quinazolone (XXXV) by fusion with formamide and ammonium formate at 140–145° for 1–6 hours failed to give any of the desired product whereas *o*-formamidobenzoic acid gave a 68% yield of 4-quinazolone, m.p. 206–207°.

When isatoic anhydride was treated with ammonium formate and formic acid as above until gas evolution was complete (45 minutes), a 69% yield of *o*-formamidobenzoic acid was obtained, identified by mixture m.p. No reaction took place at 100° when the ammonium formate was omitted.

Methyl 2-formamido-3-thenoate (XXXIV). To a dried methylene chloride solution of diazomethane (from 1 g. of nitrosomethylurea) was added portionwise 0.50 g. of crude XXXIII with ice-cooling. The reaction was complete five minutes after the addition. The excess diazomethane was destroyed with acetic acid. Evaporation to dryness *in vacuo* gave 0.45 g. (83%) of product, m.p. 65–75°. Recrystallization of a sample from methanol gave white crystals, m.p. 89–90°.

Fusion with formamide and ammonium formate at 140–145° for 3 hours gave a dark tar from which none of the desired 7,8-thia-4-quinazolone (XXXV) could be isolated.

7,8-Thia-4-quinazolone (XXXV). A solution of 1.5 g. of crude XXXIV in 30 cc. of methanol was saturated with ammonia and allowed to stand for 13 days. The solution was evaporated to dryness *in vacuo* leaving an oil with a little suspended solid. Addition of 3 cc. of methanol and filtration gave 0.05 g. (4%) of product, m.p. 210–212°. Recrystal-

lization from methanol afforded white needles, m.p. 210–211°. This compound is readily soluble in water.

Anal. Calc'd for $C_6H_4N_2OS$: C, 47.3; H, 2.65; N, 18.4.
Found: C, 47.7; H, 3.13; N, 18.3.

3-Methyl-2-thienyl isocyanate (XLVI). A mixture of 17.5 g. of 3-methyl-2-thenoic acid (XLII) (14) and 35 cc. of thionyl chloride was refluxed on the steam-bath for one hour, gas evolution being complete in 25 minutes. Volatile material was removed *in vacuo* (bath 40–45°) and the evaporation was repeated after the addition of 50 cc. of benzene. The residual acid chloride, dissolved in 90 cc. of acetone, was added dropwise with stirring and ice-cooling to a solution of 11.8 g. of sodium azide in 90 cc. of water at such a rate that the temperature was 5–8°. The mixture was stirred one hour more in the ice-bath, then diluted with 90 cc. of cold chloroform and 125 cc. of ice water. The separated aqueous layer was extracted with 90 cc. more of chloroform. The combined chloroform extracts, dried for a few minutes with calcium chloride at 0°, were refluxed on the steam-bath for 90 minutes when nitrogen evolution was complete. This measured solution of XLVI was used in portions in subsequent reactions.

Similarly, a chloroform solution of *2-carbomethoxy-3-thienyl isocyanate* (XLI) was prepared from XI.

The intermediate *3-methyl-2-thenoyl chloride* was characterized as its *anilide*, which formed white crystals from heptane, m.p. 128–130°.

Anal. Calc'd for $C_{12}H_{11}NOS$: C, 66.4; H, 5.11; N, 6.44.
Found: C, 66.1; H, 5.18; N, 6.43.

2-Acetamino-3-methylthiophene (XLVIII). The chloroform solution of XLVI from 5 g. of XLII was evaporated *in vacuo* (bath 30–35°). The residue was refluxed with 50 cc. of acetic acid for 20 hours, gas evolution being complete in 6 hours. The solution was evaporated to dryness *in vacuo* and the dark tar was extracted several times with hot heptane. The decanted extracts on cooling deposited 1.6 g. (29% based on XLII) of product, m.p. 118–120°. Recrystallization from heptane with the aid of Norit gave white crystals, m.p. 122–124°.

Anal. Calc'd for C_7H_9NOS: C, 54.2; H, 5.85; N, 9.03.
Found: C, 54.0; H, 6.07; N, 8.96.

An attempt to oxidize this compound to 2-acetamino-3-thenoic acid with potassium permanganate was unsuccessful. No product could be extracted from the acidified aqueous solution.

2-Uranilino-3-methylthiophene (XLV). To a chloroform solution of isocyanate (XLVI), from 2 g. of XLII, was added 1.6 cc. of aniline. After being refluxed for 10 minutes, the solution was evaporated to dryness *in vacuo* and the residue was triturated with heptane; yield, 1.3 g. (40% based on XLII), m.p. 203–204°. Recrystallization from dilute methanol gave white crystals, m.p. 204–206°.

Anal. Calc'd for $C_{12}H_{12}N_2OS$: N, 12.1. Found: N, 12.0.

An attempt to oxidize this compound to 2-uranilino-3-thenoic acid with potassium permanganate in acetone gave only water-soluble products from which the desired product could not be isolated.

2-Formamido-3-methylthiophene (XLVII). To a chloroform solution (14.3 cc.) of the isocyanate (XLVI), from 1.00 g. of XLII, was added 10 cc. of 99% formic acid. The solution was refluxed on the steam-bath for one hour when gas evolution was complete, then evaporated to dryness *in vacuo*. The dark residue (0.9 g.) was extracted several times with hot heptane. The extracts on cooling deposited 0.21 g. (21%) of product, m.p. 83–85°. Recrystallization from heptane gave white crystals, m.p. 84–86°.

Anal. Calc'd for C_6H_7NOS: C, 51.1; H, 4.99; N, 9.92.
Found: C, 51.0; H, 5.13; N, 10.1.

When 89% formic acid was employed in the above procedure, the yield was 19%, m.p. 80–82°. No product could be isolated when the reaction was run in 99% formic acid with no diluent.

When a chloroform solution of 2-carbomethoxy-3-thienyl isocyanate (XLI) was treated with 99% formic acid as described above none of the desired 2-carbomethoxy-3-formamidothiophene could be isolated. A small yield of *N,N'-bis-(2-carbomethoxy-3-thienyl)urea*, m.p. 200–202°, was obtained as white crystals from methanol.

Anal. Calc'd for $C_{13}H_{12}N_2O_5S_2$: C, 45.8; H, 3.55; N, 8.25.
Found: C, 45.6; H, 4.02; N, 7.84.

SUMMARY

6,7-Thia-4-quinazolone has been prepared *via* 3-carbomethoxy-4-oximinothiophane and 3-carbomethoxy-4-aminothiophene, then converted to the thiophene isoster of the Hydrangea alkaloid.

The monoesters of thiophene-3,4-dicarboxylic acid have been synthesized. Two rearrangements were encountered during attempted structure proofs. The 2-monoester was converted to 7,8-thia-4-quinazolone *via* 6,7-thiaisatoic anhydride.

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