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2-METHYLTHIENO-, THIONAPHTHENO-, AND THIENOTHIENOPYRIDINES

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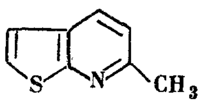
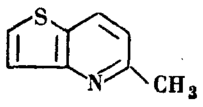
A general method for preparing 2-methylthieno-, thionaphtheno-, and thienothienopyridines has been developed. 2-Methylthieno [2, 3-b]-, -[3, 2-b] pyridines and 2-methylthionaphtheno [2, 3-b]-, -[3, 2-b] pyridines, which are new heterocyclic bases with a condensed thiophene ring, have been synthesized. Certain constants of these heterocyclic bases are quite close to those of the quinaldine and 2-methylnaphthoquinolines which are isosteric with them.

Previously the present authors prepared isomeric heterocyclic bases with a condensed thiophene ring, 2-methylthionaphthenopyridines [4], and the isosteric natures of the groups $-CH = CH-$ and $-S-$ were investigated with reference to examples drawn from among these.

The present paper describes the isomeric 2-methylthienopyridines I and II, which are isosteric with the quinaldine III.



I



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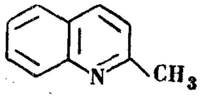
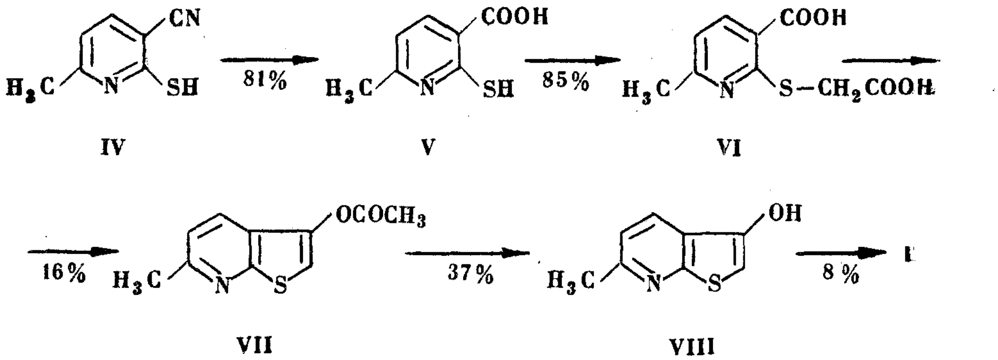


III

Before synthesizing 2-methylthieno [2, 3-b] pyridine (I), we knew that unsuccessful attempts had been made to prepare this base by various methods, particularly by the Doebner-Miller or Skraup method, starting from a double stannic salt of 2-aminothiophene hydrochloride [5]. In this connection it was planned to synthesize I from a pyridine derivative, viz., 2-methyl-5-cyano-6-mercaptopyridine (IV)

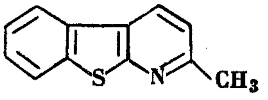


The starting 2-methyl-5-cyano-6-mercaptopyridine IV was prepared by reacting the sodium salt of formylacetone with cyanoacetamide in the presence of piperidine acetate [6]. Hydrolysis of the pyridine IV with hydrobromic acid gave 2-methyl-6-mercaptopyridine-5-carboxylic acid (V) which was converted by reaction with an aqueous sodium hydroxide solution of monochloroacetic acid, into 2-methyl-6(carboxymethylmercapto)-pyridine-5-carboxylic acid (VI). Heating the latter with acetic anhydride cyclized it to 2-methyl-4'-hydroxythieno [2, 3-b] pyridine (VIII). Lithium aluminum hydride reduction of the latter in ethereal solution gives the starting 2-methylthieno [2, 3-b] pyridine (VII), hydrolyzed by sulfuric acid solution to 2-methyl-4'-hydroxythieno [2, 3-b] pyridine (VIII). Lithium aluminum hydride reduction of the latter in ethereal solution gives the starting 2-methylthieno [2, 3-b]-pyridine (I).

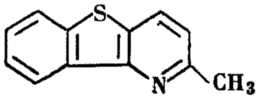
The multiple stages of this synthesis, the poor yield in the last stage, and the impossibility of preparing the isomeric base II by this method, necessitated departure from the plan of synthesis described, and passing to careful examination of the possibility of preparing 2-methylthieno [2, 3-b] pyridine using the Doebner-Miller or Skraup synthesis. However, numerous attempts to obtain the required base by reacting the double tin salts of 2-or 3-aminothiophene hydrochloride with compounds such as crotonaldehyde, paraldehyde, the sodium salt of formylacetone, etc. in the presence of various condensing agents, were unsuccessful. It was then decided to employ acetoacetaldehyde diethylacetal, with its two mobile ethoxy groups on the same carbon atom, for reacting with the double tin salt of

2-aminothiophene hydrochloride. The first attempt to close the pyridine ring in alcohol solution at 65-75° in the presence of anhydrous zinc chloride, gave 2-methylthieno [2, 3-b] pyridine in 20% yield [19].

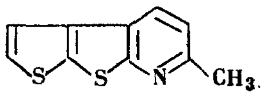
2-Methylthieno [3, 2, -b] pyridine (II), 2-methylthionaphtheno [2, 3-b] pyridine (IX), and 2-methylthionaphtheno [3, 2-b] pyridine (X), were synthesized by extending this method to the double tin salts of 3-aminothiophene [2], and 2- and 3-aminothionaphthene [4] hydrochlorides respectively.



IX

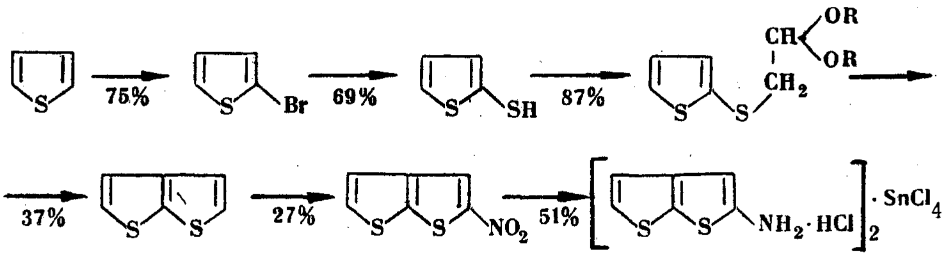


X



XI

The relative ease of closing of the pyridine ring, and the simplicity of the method

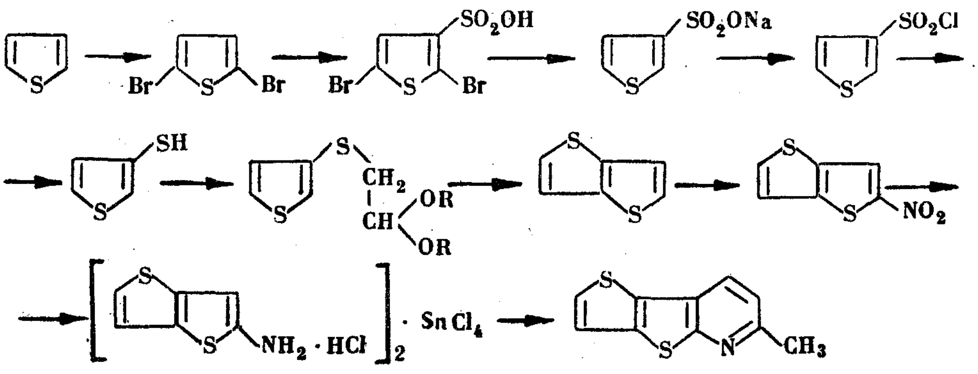


XII

XIII

indicated the use of this method for synthesizing an entirely new heterocyclic base with two thiophene rings condensed with the pyridine ring, viz., 2-methylthieno [2, 3-b]thieno [2, 3, -b] pyridine (XI). For this purpose the double tin salt of 2-aminothieno [2, 3-b] thiophene (XIII) was synthesized. It was necessary to make a departure from preparing thieno [2, 3-b] thiophene (XII) by reacting citric acid with phosphorus pentasulfide, since the yield does not exceed 1.5% [7], and the following synthetic route was therefore worked out (in conjunction with N. N. Mikheeva).

Reaction of dioxane dibromide with thiophene in ether gives 2-bromothiophene [8], which is converted, via its Grignard compound, to 2-thiophenthiol. Reaction of the latter with bromoacetaldehyde dimethylacetal converts it to 2-(2', 2'-dimethoxyethylsulfide) thiophene [10], from which thieno [2, 3-b]thiophene is obtained by treatment with phosphorus pentoxide in phosphoric acid. Nitration of thieno [2, 3-b] thiophene with concentrated nitric acid in acetic anhydride gives 2-nitrothieno [2, 3-b] thiophene [11], reduced by tin and hydrochloric acid to the double tin salt of 2-aminothieno [2, 3-b] thiophene. 2-Methylthieno [2, 3-b] thieno [2, 3-b] pyridine (XI) is synthesized in 23% yield by a method analogous to that used for the bases IX and X. The isomeric base 2-methylthieno [3, 2-b] thieno [2, 3-b] pyridine (XIV) could also be synthesized in a similar way.



XIV

The table gives certain constants for the heterocyclic bases synthesized, for their picrates, and for the quinaldine and naphthoquinoline bases isosteric with them.

Constants of the Heterocyclic Bases Prepared

Base	Appearance	Mp, °C	Bp, °C (mm pressure)	Picrate mp, °C
2-methylthieno [2, 3-b] pyridine	Yellow Oil	–	88–90(3)	210–211
2-methylthieno [3, 2-b] pyridine	Yellow Oil	–	95–98(5)	188–189
Quinaldine	Yellow Oil	–	110(10)[12]	191[13]
2-methylthieno [2, 3-b] thieno [2, 3-b] pyridine	Colorless plates	84–85	–	229–230
2-methylthieno [3, 2-b] thieno [2, 3-b] pyridine	Colorless plates	82–83	–	170–171
2-methylthionaphtheno [2, 3-b] pyridine	Yellow Oil	–	158–160(5)	222–223
2-methylthionaphtheno [3, 2-b] pyridine	Yellow Oil	–	163–165(5)	177–178
2-methyl-β-naphthoquinoline	Colorless plates	82[14]	–	224[15]
2-methyl-α-naphthoquinoline	Yellow Oil	–	324–326[15]	226[15]

Experimental

2-Methyl-5-cyano-6-mercaptopyridine (IV) was prepared by reacting 32.4 g sodium salt of formylacetone with 30 g cyanoacetamide in 200 ml water in the presence of piperidine acetate, with heating. Yield 36.5 g (81.1%). Light yellow plates mp 235-236°. ([6] gives 235°.)

2-Methyl-6-mercaptopyridine-5-carboxylic acid (V). A mixture of 24 g IV and 85 ml 48% hydrobromic acid was refluxed for 3 hr 30 min. The solution was filtered hot, cooled, and poured into thrice its volume of ice water, and air-dried. Yield 21.7 g (81%) mp 246-247° (reprecipitated from alkali solution, and crystallized from alcohol), light yellow plates. Found: N 8.17%. Calculated for $C_7H_7NO_2S$: N 8.25%.

2-Methyl-6-(carboxymethylmercapto) pyridine-5-carboxylic acid (VI). 1.9 g monochloroacetic acid in 10 ml water, neutralized with 2.2 g soda, was added to a solution of 3.1 g V in 15 ml 10% aqueous sodium hydroxide, at 10-15°. The next day the mixture was refluxed for 2 hr, then cooled, filtered, and carefully neutralized with dilute (1:1) hydrochloric acid, with cooling, until acid to congo red. The precipitate was filtered off, carefully washed with water, and air-dried. Yield 3.5 g (85%), mp 194-195° (alcohol), grayish prisms. Found: N 6.17%. Calculated for $C_9H_9NO_4S$: N 6.14%.

2 Methyl-4-acetoxythieno [2, 3-b] pyridine (VII). 40 g VI was dissolved with heating and stirring in 1300 ml acetic anhydride. The solution was refluxed for 3 hr, cooled and filtered, the anhydride vacuum-distilled off, and the residue treated 3 times with 300 ml dry ether, the extracts filtered, the anhydride vacuum-distilled off, and distilled. Yield 5.9 g (16.2%) bp 137-140° (2 mm), light yellow oil, with the characteristic odor of pyridine bases. Found: N 6.81%. Calculated for $C_{10}H_9NO_2S$: N 6.76%.

2-Methyl-4-hydroxythieno [2, 3-b] pyridine (VIII). 2 g VII and 30 ml 10% sulfuric acid were heated on a steam bath, under nitrogen and with stirring, for 1 hr. After cooling the reaction product was extracted with 200 ml ether, and the ethereal solution dried over magnesium sulfate. The ether was distilled off, the residue dried in air. Yield 0.42 g (25%). mp 113-115° (50% alcohol), pale brown prisms. Found: N 8.34%. Calculated for C_8H_7NOS: N 8.47%.

2-Methylthieno [2, 3-b] pyridine (I).

(a) 2.4 g lithium aluminum hydride was added to 320 ml dry ether, and the whole refluxed and stirred for 10 min. 6.1 g VIII was added gradually, and refluxing continued for 18 hr. 20 ml ether was then carefully added to the mixture after cooling, followed by 40 ml water and 50 ml dilute (1:1) hydrochloric acid. The ether was evaporated in a vacuum, the reaction mixture made alkaline to litmus with 10% aqueous sodium hydroxide solution, and the base steam-distilled off. The distillate was extracted with 300 ml ether, the ethereal extract dried over potash, the ether distilled off, and the residue vacuum-distilled. Yield 0.46 g (8.3%) bp 122-125° (13 mm). Light yellow oil having the characteristic odor of pyridine bases. Picrate: Light yellow needles, mp 210-211° (alcohol). Found: N 14. 76%. Calculated for $C_{14}H_{10}N_4O_7S$: N 14. 81%.

(b) 32.4 g acetoacetaldehyde diethylacetal was added dropwise, with energetic stirring, to a mixture of 64 g of the double tin salt of 2-aminothiophen hydrochloride, 250 ml dry alcohol, and 6 g fused anhydrous zinc chloride at 65-75°. Stirring was continued at the same temperature for 1 hr after addition was ended, after which the mixture was brought to the boil in 1 hr. Next it was cooled to room temperature, 6 g anhydrous zinc chloride was added with stirring, the whole heated to boiling, and stirred under reflux for 2 hr. The alcohol was distilled off, the residue treated, with cooling, with 10% aqueous sodium hydroxide solution, until alkaline to litmus, and the base steam-distilled off. The distillate was repeatedly extracted with 1000 ml ether in all, the ether extracts bulked and dried over potash, the ether distilled off, and the residue vacuum-distilled. Yield 3.6 g (20.1%) bp 88-89°. Slightly yellowish oil with the characteristic odor of pyridine bases. Found: N 9.28%. Calculated for C_8H_7NS: N 9.39%. Picrate: pale yellow needles, mp 210-211° (alcohol). Found N 14.78%. Calculated for $C_{14}H_{10}N_4O_7S$: N 14.81%.

2-Methylthienol [3, 2-b] pyridine (II). Prepared from 64 g of the double tin salt of 3-aminothiophene hydrochloride, 250 ml dry alcohol, 6 g fused anhydrous zinc chloride, and 31. 8 g acetoacetaldehyde dimethylacetal. Yield 9. 5 g(53%), bp 95-98° (5 mm). Slightly yellowish oil with a characteristic pyridine base odor. Found: N 9.31%. Calculated for C_8H_7NS: N 9.39%. Picrate: light yellow plates mp 188-189° (alcohol). Found N 13.67%. Calculated for $C_{14}H_{10}N_4O_7S$: N 14.81%.

2 Methylthionaphtheno [2, 3-b] pyridine (IX). Prepared from 76 g of the double tin salt of 2-aminothiophene hydrochloride, 500 ml dry alcohol, 9 g fused anhydrous zinc chloride, and 31.8 g acetoacetaldehyde dimethylacetal. Yield 3.2 g (13.6%), bp 158-160° (5 mm). Slightly yellowish oil with the characteristic pyridine-base odor. Found: N 6.91%. Calculated for $C_{12}H_9NS$: N 7.02%. Picrate: slightly yellowish needles mp 222-223° (alcohol). Found: N 12. 99%. Calculated for $C_{18}H_{12}N_4O_7S$: N 13. 07%.

2 Methylthionaphtheno [3, 2-b] pyridine (X). Prepared from 63 g of the double tin salt of 3-aminothionapthene hydrochloride, 400 ml dry alcohol, 7 g fused anhydrous zinc chloride, 26. 4 g acetoacetaldehyde dimethylacetal. Yield 3.0 g (15.2%), bp 164-165° (5 mm). Pale yellow oil, with the characteristic pyridine base odor. Found: N 6. 97%. calculated for $C_{12}H_9NS$: N 7.02%. Picrate: pale yellow needles, mp 177-178° (alcohol). Found: N 12.96%. Calculated for $C_{18}H_{12}N_4O_7S$: N 13. 07%.

2-Bromothiophene was prepared by reacting 264 g dioxane dibromide in 60 ml ether with 84 g thiophene, dissolved in 400 ml ether, at 0°. Yield 123.7 g (75%). Bp 54-55° (20 mm). The literature [8] gives bp 43-44° (15 mm).

2-Thiophenthiol. 164 g 2-bromothiophene was added to 31 g magnesium ribbon in 1500 ml anhydrous ether, and the mixture refluxed for 1 hr 30 min. Then 31.6 g sulfur was added. Yield 81 g (69.5%). Bp 46-48° (2 mm). The literature [9] gives bp 54° (5 mm).

2-(2'-Dimethoxyethylsulfide) thiophene was prepared by reacting 15 g bromoacetaldehyde dimethylacetal with 56.5 g 2-thiophenthiol in a solution of sodium ethoxide. Yield 89.5 g (87.6%). Colorless liquid, bp 115-120° (2 mm). The literature [10] gives bp 120-124° (bath temperature) (1 mm).

Thieno [2, 3-b] thiophene (XII) was prepared by heating 75 g phosphorus pentoxide with 16 g 2-(2'-dimethoxyethylsulfide) thiophene dissolved in 200 ml dry benzene. Yield 4.2 g (37.5%). Colorless liquid, bp 82-85° (3 mm). The literature [10] gives bp 75-80° (1 mm).

2-Nitrothieno [2, 3-b] thiophene was prepared by nitrating 2 g thieno [2, 3-b] thiophene with 0.65 ml nitric acid (d 1.5) in 4 ml acetic anhydride at 0°. Yield 0.7 g (27.2%). Light yellow prisms, mp 122-123°. The literature [11] gives mp 122-123°.

Double tin salt of 2-aminothieno [2, 3-b] thiophene hydrochloride (XIII). Over a period of 30 min, 30 g tin metal was added to a suspension of 18.5 g 2-nitrothieno [2, 3-b] thiophene in 185 ml concentrated hydrochloric acid, energetically stirred, and at 25-30°, stirring continued for a further 2 hr after the addition had ended, the temperature was raised to 35°, and stirring continued until all the tin had dissolved. The mixture was cooled, the precipitate filtered off, washed with a small amount of alcohol and ether, and air-dried. Yield 33. 1 g (51. 4%). Light yellow prisms.

2-methylthieno [2, 3-b] thieno [2, 3-b] pyridine (XI). 26.4 g acetoacetaldehyde dimethylacetal was added dropwise to an energetically stirred mixture, held at 65-75%, of 64 g of the double tin salt XIII, 250 ml anhydrous alcohol, and 5 g fused zinc chloride. After completion of addition, the mixture was stirred for 1 hr more, and then heated to boiling in an hour. Next it was cooled to 40°, 5 g zinc chloride was added over one hr, the whole heated to boiling and then refluxed for 2 hr 30 min. The alcohol was distilled off, 10% sodium hydroxide solution added to the residue, with cooling, until the reaction to litmus was alkaline, and the mixture steam-distilled. The colorless crystals in the distillate were filtered off, washed with water, and vacuum dried over solid caustic alkali. Yield 2.9 g (14.1%) (petrol ether), colorless plates, mp 84-85°. Found N 6.71%. Calculated for $C_{10}H_7NS_2$: N 6.82%. Picrate, yellowish-green plates, mp 229-230° (alcohol). Found N 12.33%, calculated for $C_{16}H_{10}N_4O_7S_2$: N 12.89%.

2, 5-Dibromothiophene was prepared by treating 84 g thiophene in glacial acetic acid with 320 g bromine. Yield 210 g (81%), bp 210-212°. The literature [16] gives bp 210. 5-211°.

Thiophene-3-sulfochloride was prepared by the action of 80 g phosphorus pentachloride on sodium thiophen-3-sulfonate, the latter being prepared by treating 2, 5-dibromothiophene-3-sulfonic acid with 5% sodium amalgam. (The 2, 5-dibromo acid was made by sulfonating 2, 5-dibromothiophene with 60 ml pyrosulfuric acid). Yield 46.3 g (50.8%), mp 42-43° (from ether). The literature [17] gives mp 43°.

3-Thiophenthiol was made by reducing 5 g thiophene-sulfochloride by heating with 16 g tin metal and hydrochloric acid under nitrogen. Yield 1.65 g (42.7%), bp 49-51° (2 mm). The literature [18] gives mp 171°.

3-(2', 2'-Diethoxyethylsulfide) thiophene was synthesized by the action of 40 g bromoacetaldehyde diethylacetal on 23.2 g 3-thiophenthiol in a solution of sodium ethoxide. Yield 34.5 g (74. 3%), mp 125-130° (2 mm). The literature gives [10] bp 115-120° (bath) (1 mm).

Thieno [3, 2-b] thiophene was prepared by heating 4.64 g 3-(2', 2'-diethoxyethylsulfide) thiophene dissolved in 120 ml dry benzene, with 24 g phosphorus pentoxide. Yield 2.1 g (75%), mp 53-54° (from petrol ether). The literature [11] gives mp 123-124°.

Double tin salt of 2 aminothieno [3, 2-b] thiophene hydrochloride. 40 g tin was added over 30 min to a vigorously stirred suspension of 26.4 g 2-nitrothieno [3, 2-b] thiophene in 240 ml concentrated hydrochloric acid at 30-35°. Stirring was continued for 2 hr after addition was complete. Then the mixture was heated to 40°, and stirring continued till the tin was completely dissolved. The precipitate which separated after cooling was filtered off, washed with a small quantity of alcohol and then of ether, and finally air dried. Yield of light gray prisms 41. 0 g (64%).

2-methylthieno [3, 2-b] thieno [2, 3-b] pyridine (XIV). 23 g acetoacetaldehyde dimethylacetal were added dropwise in an hour to a vigorously stirred mixture of 55 g of the double tin salt of 2-aminothieno [3, 2-b]-thiophene hydrochloride, 250 ml anhydrous alcohol, and 5 g fused anhydrous zinc chloride, held at 65-75°. The rest of the synthesis was similar to that for the [2, 3-b] isomer. Yield 2.6 g (14.9%), mp 83-84° (petrol ether), snow-white plates. Found N 6.65%. Calculated for $C_{10}H_7NS_2$: N 6. 82%. Picrate: light yellow prisms, mp 170-171° (from alcohol). Found N 12.81%. Calculated for $C_{16}H_{10}N_4O_7S_2$: N 12.89%.

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