6. R. P. Mariella, J. Callahan, and A. O. Jibril, J. Org. Chem., 20, 1721 (1955).
7. H. Henecka, Chem. Ber., 82, 36 (1949).
8. H. M. Wuest, J. A. Bigot, T. J. do Boer, B. v. d. Wal, and J. P. Wibaut, Recl. Trav. Chim., 78, 226 (1959).
9. B. R. Baker, M. V. Querry, S. R. Safir, and S. Bernstein, J. Org. Chem., 12, 144 (1947).
10. B. V. H. Sokol and J. J. Ritter, J. Am. Chem. Soc., 70, 3517 (1948).

RESEARCH ON THIENOPYRIDINES AND PYRIDOTHIENOPYRIMIDINES. 2.* SOME TRANSFORMATIONS OF 2-CARBETHOXY-3-AMINO-4,6-DIMETHYLTHIENO[2,3-b]PYRIDINE

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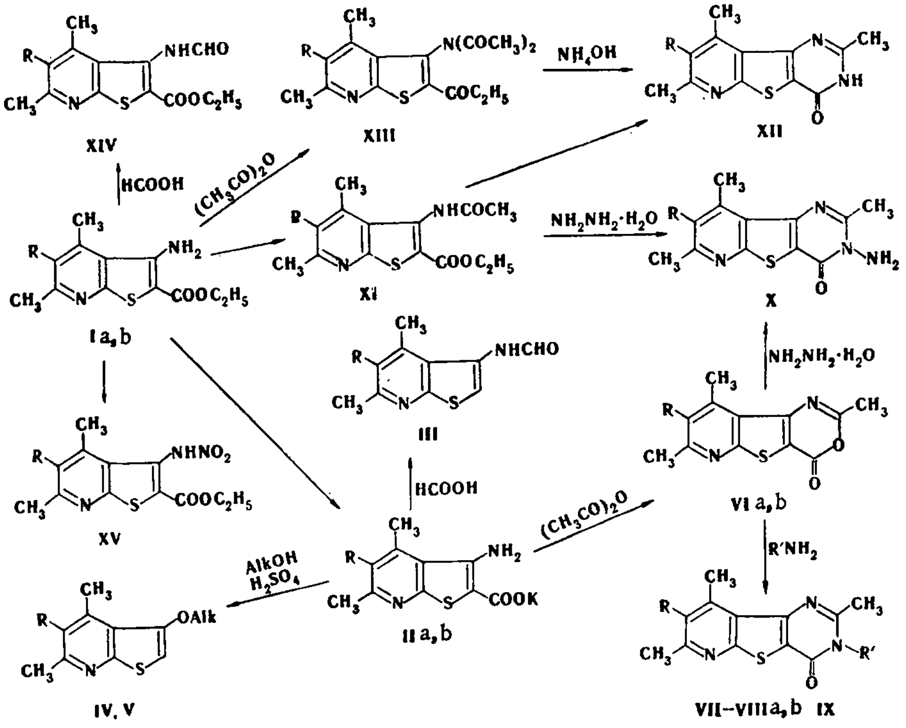
In our previous communication [1] we described the synthesis of a number of 3-aminothieno[2,3-b]pyridines from the corresponding substituted 2-chloro-3-cyanopyridines. The present paper is devoted to a study of the transformations of one of the representatives of these compounds, viz., 2-carbethoxy-3-amino-4,6-dimethylthieno[2,3-b]pyridine (Ia).

Brief heating of Ia in an alcohol solution of potassium hydroxide gives potassium 3-amino-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate (IIa) [2], refluxing of which with formic acid leads to decarboxylation and the formation of the N-formyl derivative (III). As demonstrated in [2], when IIa is heated with methanol or butanol in the presence of aqueous



I–IIa, VIb R=H; b $R=NO_2$; III–V, X–XV R=H; IV $Alk=CH_3$; V $Alk=C_4H_9$; VIIa R=H; $R'=(CH_2)_3N(CH_3)_2$; VIIb $R=NO_2$; $R'=(CH_2)_3N(CH_3)_2$; VIIIa R=H; $R'=(CH_2)_2N(C_2H_5)_2$; VIIIb $R=NO_2$; $R'=(CH_2)_2N(C_2H_5)_2$; IX R=H; $R'=C_6H_5$

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*See [1] for communication 1.

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sulfuric acid, it undergoes decarboxylation accompanied by replacement of the amino group by an alkoxy group; the 3-methoxy- and 3-butoxy derivatives (IV and V), respectively, were obtained.

When IIa is refluxed with acetic anhydride, it is converted to an oxazinone (VIa) in which the endocyclic oxygen atom is readily replaced by a primary amine or hydrazine residue to give 3-substituted pyrido[3',2'-4,5]thieno[3,2-d]pyrimidines (VII-X).

Potassium 3-amino-5-nitro-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate (IIb), which was obtained from nitro compound Ib [1], was also converted to an oxazinone (VIb); reaction of the latter with the corresponding amines gave VIIb and VIIIb. As we have previously noted [1], the ester group in 3-aminothienopyridine Ia cannot be converted to an amide or hydrazide group under ordinary conditions. It was found that if the amino group in this compound is first acetylated by means of acetyl bromide in dioxane, the resulting monoacetyl derivative (XI) reacts with ammonia and hydrazine hydrate; the resulting amide and hydrazide immediately undergo cyclization and are converted to three-ring structures XII and X. As indicated above, the latter compound was also obtained by the action of hydrazine hydrate on oxazinone VIa. One acetyl group is split out to give XII when diacetyl derivative XIII, obtained by refluxing Ia in acetic anhydride [3], is treated with ammonium hydroxide. It should be noted that 2-carbethoxy-3-formamido-4,6-dimethylthieno[2,3-b]pyridine (XIV), obtained by heating Ia with formic acid, does not form a three-ring compund with hydrazine hydrate; instead, XIV undergoes hydrazinolysis to give Ia. Only nitramine XV, the structure of which was proved by the IR, UV, and PMR spectra, was obtained in an attempt to introduce a nitro group in the pyridine ring of thienopyridine Ia by the action of nitric acid in acetic anhydride. The IR spectrum of XV does not contain the two absorption bands at 3200-3500 cm^{-1} that are characteristic for the NH_2 group; instead, one absorption band at 3240 cm^{-1} (NH) is observed. The third absorption band (at 330-390 nm) vanishes in the UV spectrum of XV; this is characteristic for all of the N-substituted 3-aminothieno[2,3-b]pyridines. The singlet unresolved signal at 7.14 ppm, which corresponds to the proton in the 5 position, is retained in the PMR spectrum of XV, and this constitutes evidence in favor of the absence of a substituent attached to C_5.

EXPERIMENTAL

The IR spectrum of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of ethanol solutions were recorded with an EPS-3 spectrophotometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The individuality of the compounds obtained was confirmed by chromatography on Silufol UV-254 plates; the plates were developed in UV light.

3-Formamido-4,6-dimethylthieno[2,3-b]pyridine (III). A suspension of 10 g (0.0386 mole) of potassium 3-amino-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate (IIa) [2] in 100 ml of formic acid was refluxed for 3 h and 40 min, after which the excess formic acid was removed by distillation, and the residue was triturated in 150 ml of water. The aqueous suspension was made alkaline to pH 5 with 40% sodium hydroxide solution, and the precipitate was removed by filtration and washed with water to give 7.93 g (99.1%) of XIII in the form of almost colorless crystals with mp 188.5-189.5°C (aqueous methanol). IR spectrum: 3380 (NH) and 1665 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 237 (4.35) and 288 nm (4.24). Found: C 58.2; H 5.0; N 13.5%. $C_{10}H_{10}N_2OS$. Calculated: C 58.2; H 5.0; N 13.6%.

3-Butoxy-4,6-dimethylthieno[2,3-b]pyridine (V). A suspension of 2.6 g (9.98 mmole) of IIa in a mixture of 50 ml of butanol, 10 ml of water, and 5 ml of concentrated sulfuric acid was refluxed for 2 h and 40 min, after which it was cooled and poured into water. The butanol layer was separated, washed several times with water to remove the sulfuric acid, and dried with magnesium sulfate. The solvent was then removed, and the oily residue was triturated with ether. The resulting precipitate was separated, treated with 5% aqueous sodium hydroxide, washed with water, and dried. The solid was then triturated with hexane, the insoluble material was separated, and the hexane filtrate was evaporated to give 0.78 g (31.2%) of V in the form of yellowish crystals with mp 51-51.5°C (petroleum ether). Found: C 66.1; H 7.2; S 13.7%. $C_{13}H_{17}NOS$. Calculated: C 66.3; H 7.3; S 13.6%.

A similar procedure was used to obtain IV with mp 97-98°C (aqueous methanol) (mp 99-101°C [2]).

2,7,9-Trimethyl(1,3)oxazino[5,4-d]thieno[2,3-b]pyrid-4-one (VIa). A suspension of 11.71 g (0.045 mole) of IIa in 31.4 ml of acetic anhydride was refluxed for 1 h and 40 min, after which it was cooled, and the precipitate was removed by filtration and washed with acetic anhydride and water to give 8.61 g (78%) of VIa as fine colorless needles with mp 218-219°C (alcohol) (mp 206-207°C [3]). IR spectrum: 1750 cm^{-1} (CO).

Similar treatment of IIb gave 2,7,9-trimethyl-8-nitro(1,3)oxazino[5,4-d]thieno[2,3-b]-pyrid-4-one (VIb), with mp 226-228°C (alcohol), in 46% yield. Found: C 49.4; H 3.3; N 14.3%. $C_{12}H_9N_3O_4S$. Calculated: C 49.5; H 3.1; N 14.4%.

2,7,9-Trimethyl-3-dimethylaminopropylpyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-one (VIIa). A mixture of 5 g (20.3 mmole) of VIa with 10.52 g of dimethyllaminopropylamine was heated gradually with stirring to 150°C and maintained at this temperature for 7-10 min. It was then cooled, and the precipitate was removed by filtration and washed with hexane to give 4.17 g (62.1%) of VIIa with mp 121-122.5°C (hexane). Found: C 61.9; H 6.7; N 17.3; S 9.5%. $C_{17}H_{22}N_4OS$. Calculated: C 61.8; H 6.7; N 17.0; S 9.7%.

Similar treatment of VIa with diethylaminoethylamine gave VIIIa with mp 87.5-88°C (hexane), in 53% yield. Found: C 62.4; H 7.1; N 16.0; S 9.3%. $C_{18}H_{24}N_4OS$. Calculated: C 62.8; H 7.0; N 16.3; S 9.3%.

The reaction of 0.5 g (2.03 mmole) of VIa and 2 ml (2.04 g) of aniline (after heating at 150-155°C for 2 h and 30 min) gave 0.42 g (84%) of IX with mp 241.5-242.5°C (from 50% alcohol). Found: C 67.5; H 4.5; N 12.9; S 9.8%. $C_{18}H_{15}N_3OS$. Calculated: C 67.3; H 4.7; N 13.0; S 10.0%.

The reaction of nitrooxazinone VIb with dimethylaminopropylamine gave VIIb, with mp 156-157.5°C (alcohol), in 90.6% yield. Found: C 54.7; H 5.8; N 18.3; S 8.8%. $C_{18}H_{15}N_3OS$. Calculated: C 54.5; H 5.6; N 18.7; S 8.5%.

The reaction of VIb and diethylaminoethylamine gave VIIIb, with mp 148-150°C (alcohol), in 74.5% yield. Found: C 55.7; H 5.9; N 18.0; S 8.5%. $C_{18}H_{23}N_5O_3S$. Calculated: C 55.5; H 6.0; N 18.0; S 8.3%.

2,7,9-Trimethyl-3-aminopyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-one (X). A) A 2.5-ml [5.575 g (111 mmole)] sample of hydrazine hydrate was added to a hot solution of 0.5 g (2.03 mmole) of VIa in 50 ml of absolute alcohol, and heating was continued. A copious precipitate formed after a few minutes. The mixture was refluxed for another 10 min, after which it was cooled, and the precipitate was removed by filtration to give 0.4 g (61%) of X in the form of colorless needles with mp 315-317.5°C (dec., butanol). IR spectrum: 3270, 3200 (NH_2), 1665, 1630 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 248 (4.54), 285 (3.96), 294 (4.10), 327 (3.81), and 339 nm (3.68) shoulder. Found: C 55.4; H 4.4; N 21.5; S 12.3%. $C_{12}H_{12}N_4OS$. Calculated: C 55.4; H 4.6; N 21.5; S 12.3%.

B) A 2-ml [2.06 g (41.2 mmole)] sample of hydrazine hydrate was added to a solution of 0.36 g (1.23 mmole) of XI in 20 ml of absolute ethanol; a precipitate formed almost immediately. The mixture was then heated at 50-70°C for 30 min, after which it was cooled, and the precipitate was removed by filtration to give 0.3 g (90.9%) of X with mp 315-317°C (dec.). No melting-point depression was observed for a mixture of this product with a sample of X obtained by method A.

2-Carbethoxy-3-acetamino-4,6-dimethylthieno[2,3-b]pyridine (XI). A 10.35 ml [17.25 g (0.14 mole)] sample of acetyl bromide was added dropwise with vigorous stirring to a suspension of 6.25 g (0.025 mole) of Ia in 48 ml of dry dioxane, and the resulting viscous mass was stirred at 20°C for 30-40 min and at 80°C for 30 min. The mixture was then cooled to 20°C and poured into 200 ml of water, and the solution was treated with charcoal and neutralized to pH 7 with ammonium hydroxide. The precipitate was removed by filtration and washed with water to give 7.15 g (99.2%) of XI in the form of colorless crystals with mp 195-195.5 °C (alcohol). IR spectrum: 3300 (NH); 1720, 1670 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 238 (4.24) and 298 nm (4.23). Found: C 57.6; H 5.5; N 9.7%. $C_{14}H_{16}N_2O_3S$. Calculated: C 57.5; H 5.5; N 9.6%.

2,7,9-Trimethylpyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-one (XII). A) A suspension of 1 g (3.42 mmole) of XI in 25 ml of 25% NH_4OH was stirred at room temperature for 14 h, and the resulting precipitate was removed by filtration, washed with ammonium hydroxide and water, and treated with 5% sodium hydroxide solution. The alkaline filtrate was acidified with glacial acetic acid, and the precipitate was removed by filtration to give 0.34 g (40.6%) of XII in the form of colorless crystals that were soluble in aqueous alkali solutions and melted above 360°C. IR spectrum: 3310 (NH) and 1680 cm^{-1} (CO). Found: C 59.0; H 4.8; N 17.1; S 13.3%. $C_{12}H_{11}N_3OS$. Calculated: C 58.8; H 4.5; N 17.1; S 13.1%.

B) A suspension of 0.5 g of XIII [3] in 15 ml of 25% ammonium hydroxide was stirred at 20°C for 5 h, after which it was cooled, and the precipitate was removed by filtration, washed with water, and dried to give 0.29 g (90%) of XII with mp > 360°C that was soluble in aqueous alkali solutions. Found: C 58.8; H 4.4; N 16.9; S 12.9%. $C_{12}H_{11}N_3OS$. Calculated: C 58.8; H 4.5; N 17.1; S 13.1%.

2-Carbethoxy-3-formamido-4,6-dimethylthieno[2,3-b]pyridine (XIV). A solution of 1.94 g (7.75 mmole) of Ia in 20 ml of formic acid was refluxed for 16 h, after which the solvent was evaporated to dryness, and the residue was treated with 40 ml of water. The mixture was neutralized to pH 6 with 40% sodium hydroxide, and the precipitate was removed by filtration, washed with water, dried, refluxed with 30 ml of absolute alcohol, and removed by filtration to give 1.37 g (60.7%) of XIV as colorless crystals with mp 267-268.5°C (alcohol). IR spectrum: 3270 (NH); 1715, 1650 cm^{-1} (CO). Found: C 56.0; H 4.8; S 11.6%. $C_{13}H_{14}N_2O_3S$. Calculated: C 56.1; H 5.1; S 11.5%.

2-Carbethoxy-3-nitramino-4,6-dimethylthieno[2,3-b]pyridine (XV). A mixture of 0.76 ml of acetic anhydride and 0.8 ml of nitric acid (sp. gr. 1.5) was added with cooling to a suspension of 2.42 g (9.68 mmole) of Ia in 10 ml of acetic anhydride at such a rate that the temperature did not rise above 40°C. A yellow precipitate formed. The mixture was stirred at 20°C for 1 h and 15 min, after which the precipitate was removed by filtration and washed successively with acetic anhydride and water to give 1.08 g (36%) of XV in the form of light-yellow crystals with mp 116-117°C (alcohol). IR spectrum: 3240 (NH) and 1715 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 238 (4.25) and 298 nm (4.18). PMR spectrum (in deuterochloroform), δ: 1.37 ($COOCH_2CH_3$, t), 2.63 (4-CH_3, 6-CH_3, s), 4.36 ($COOCH_2CH_3$, q), 7.03 (5-H, broad s), and 10.14 ppm (NH). Found: C 48.8; H 4.4; N 14.3; S 11.0%. $C_{12}H_{13}N_3O_4S$. Calculated: C 48.8; H 4.4; N 14.2; S 10.9%.

LITERATURE CITED

1. V. I. Shvedov, T. P. Sycheva, and T. V. Sakovich, Khim. Geterotsikl. Soedin., No. 10, 1331 (1979).
2. K. Gewald, M. Hentschell, and U. Illgen, J. Prakt. Chem., 316, 1030 (1974).
3. F. Guerrera, M. A. Siracusa, and V. Tornetta, Il Farmaco, Ed. Sci., No. 1, 21 (1976).