RESEARCH ON THIENOPYRIDINES AND PYRIDOTHIENOPYRIMIDINES.

3.* TRANSFORMATIONS OF 7,9-DIMETHYL-8-NITROPYRIDO[3',2':4,5]-THIENO[3,2-d]PYRIMIDIN-4-ONES

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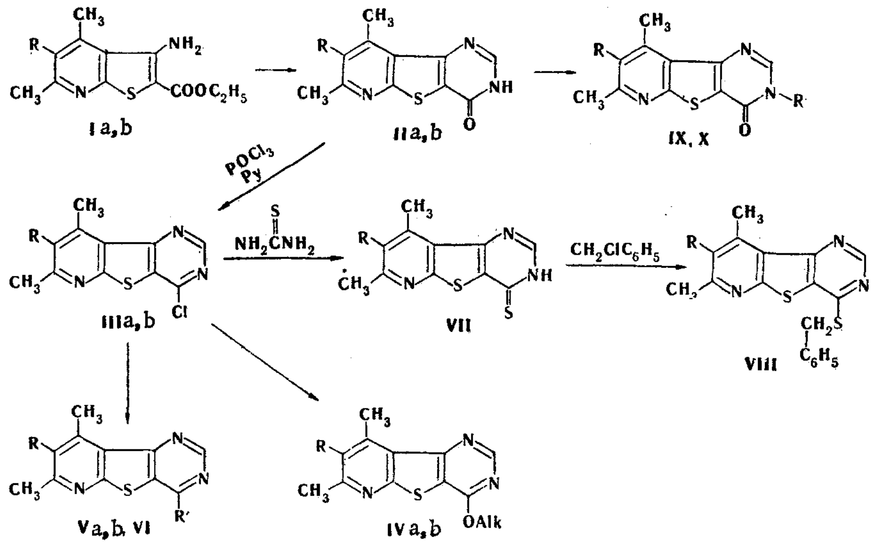
The present paper is a continuation of research on thienopyrimidines previously conducted by one of us [2,3]. In the present communication we describe the transformations of 7,9-dimethylpyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-ones (IIa,b) obtained by a well-known method, viz., by refluxing 4,6-dimethyl-2-carbethoxy-3-aminothieno[2,3-b]pyridines (Ia,b) in excess formamide. Some of these reactions were recently carried out with unsubstituted pyridothienopyrimidin-4-one [5].

4-Chloro derivatives IIIa, b were obtained by the action of phosphorus oxychloride on IIa, b; this reaction proceeds considerably more rapidly in the presence of pyridine, and the yield of IIIa is higher than when only phosphorus oxychloride is used. We have noted that the presence of a nitro group in the pyridine ring has a negative effect both on the cyclization with formamide and on replacement of the hydroxy group by chlorine: pronounced resinification was observed in the preparation of IIb and IIIb, and the yields of both nitro derivatives were lower.



I–III a R=H; b $R=NO_2$; IV a R=H; Alk=Me; b $R=NO_2$; Alk=Et; Va R=H; $R'=NHNH_2$; Vb $R=NO_2$; $R'=NHNH_2$; VI $R=NO_2$; $R'=NH(CH_2)_2NEt_2$; VII R=H

As expected, 4-chloro derivatives IIIa, b are capable of nucleophilic substitution reactions, and this makes it possible to introduce various groups in the 4 position; it was noted that the presence of a nitro group in the 8 position is responsible for the increased lability of the halogen atom and that reactions involving replacement of the chlorine in IIIb proceed more readily and give the products in higher yields than in the case of IIIa.

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*See [1] for communication 2.

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4-Alkoxy derivatives IVa, b were obtained by treatment of IIIa,b with sodium alkoxides in the corresponding alcohols; 4-hydrazino derivatives Va, b are formed by the action of hydrazine hydrate on IIIa,b, while VI was obtained from IIIb and diethylaminoethylamine.

The reaction of IIIa with thiourea converted it to a thione (VII), which can exist in thiolactam and thiolactim forms; the data from the IR spectrum indicate that the thione form is the preferred form. However, in the case of electrophilic substitution reactions in thione VII the equilibrium is shifted to favor the thiolactim form, and S-alkyl derivatives are formed. Thus 4-benzylmercapto-7,9-dimethylpyrido[3',2':4,5]thieno[3,2-d]pyrimidine (VIII) was obtained by the action of benzyl chloride on VII in the presence of sodium ethoxide.

In contrast to thione VII, the alkylation of the corresponding pyridothienopyrimidin-4-one (IIa) leads to substitution only in the 3 position. 3-Methyl and 3-benzyl derivatives (IX, X), the structures of which were proved by their IR spectra (from the absence of the absorption band characteristic for the NH group), were obtained by the action of dimethyl sulfate or benzyl chloride on IIa.

EXPERIMENTAL

The IR spectra 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 individuality of the compounds obtained was confirmed by chromatography on Silufol UV-254 plates; the plates were developed in UV light.

7,9-Dimethyl-8-nitropyride[3',2':4,5]thieno[3,2-d]pyrimidin-4-one (IIb). A mixture of 6 g (20.3 mmole) of Ib [6] and 58.2 ml of formamide was refluxed for 4 h, after which it was cooled, and the precipitate was removed by filtration and washed with formamide and water to give 2.64 g (47%) of yellow crystals with mp > 360°C [from dimethylformamide (DMF)]. IR spectrum: 3170 (NH) and 1665 cm^{-1} (CO). Found: C 48.0; H 3.0; S 11.3%. $C_{11}H_8N_4O_3S$. Calculated: C 47.8; H 2.9; S 11.6%.

Similarly, the reaction of 30 g of Ia [4, 6] and 342 ml of formamide (after refluxing for 2 h) gave 25.2 g (92%) of IIa with mp > 360°C (from DMF). IR spectrum: 3160 (NH) and 1660 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 247 (4.50), 286 (3.98), 295 (4.10), and 323 nm (3.85)

7,9-Dimethyl-4-chloropyride[3',2':4,5]thieno[3,2-d]pyrimidine (IIIa). A mixture of 1.8 g (7.78 mmole) of IIa, 11.9 ml [9.93 g (130 mmole)] of phosphorus oxychloride, and 1.19 ml of dry pyridine was refluxed for 1.5 h, after which it was cooled and poured into ice water. The aqueous mixture was treated with ammonium hydroxide to pH 4, and the precipitate was removed by filtration and washed with water to give 1.91 g (98.4%) of light-yellow crystals with mp 186.5-188.5°C (alcohol). UV spectrum, λ_{max} (log ε): 237 (4.44), 264 (4.12), 290 (4.27), 317 (3.62), 329 nm (3.65). Found: C 52.7; H 3.3; Cl 14.1%. $C_{11}H_8ClN_3S$. Calculated: C 52.9; H 3.2; Cl 14.2%.

Similarly, the reaction of 4.46 g (16.1 mmole) of IIb, 24.7 ml [41.37 g (270 mmole)] of phosphorus oxychloride, and 2.47 ml of dry pyridine gave 1.58 g (33.2%) of IIIb as almost colorless crystals with mp 185-187°C (alcohol). Found: C 45.0; H 2.4; Cl 12.1; N 19.1%. $C_{11}H_7ClN_4O_2S$. Calculated: C 44.8; H 2.4; Cl 12.0; N 19.0%.

4-Metoxy-7,9-dimethylpyride[3',2':4,5]thieno[3,2-d]pyrimidine (IVa). A 1.47-g (5.9 mmole) sample of IIIa was added to a solution of sodium methoxide, prepared from 0.2 g (0.0087 g-atom) of sodium metal and 45 ml of methanol, and the mixture was refluxed for 6 h. It was then cooled, and the precipitate was removed by filtration to give 0.77 g (53.5%) of colorless crystals with mp 151-153°C (alcohol). IR spectrum: 1140 cm^{-1} (C—O). UV spectrum, λ_{max} (log ε): 237 (4.52), 260 (4.21), 286 (4.21), 312 (3.64), 323 nm (3.66). Found: C 58.9; H 4.5; N 17.0; S 12.9%. $C_{12}H_{11}N_3OS$. Calculated: C 58.7; H 4.5; N 17.1; S 13.1%.

Similarly, the reaction of 0.5 g (1.7 mmole) of IIIb and sodium ethoxide gave 0.43 g (82.7%) of IVb with mp 177-180°C (alcohol). Found: N 18.3; S 10.5%. $C_{12}H_{12}N_4O_3S$. Calculated: N 18.4; S 10.5%.

4-Hydrazino-7,9-dimethylpyride[3',2':4,5]thieno[3,2-d]pyrimidine (Va). A 0.34-ml [0.34 g (6.79 mmole)] sample of hydrazine hydrate was added to a suspension of 0.8 g (3.20 mmole) of IIIa in 20 ml of absolute alcohol, and the mixture was refluxed for 9 h. It was then cooled, and the precipitate was removed by filtration to give 0.76 g (96.2%) of colorless crystals with mp 301-305.5°C (dec., butanol). Found: C 53.8; H 4.3; N 28.3; S 13.3%. $C_{11}H_{11}N_5S$. Calculated: C 53.9; H 4.5; N 28.6; S 13.1%.

Similarly, the reaction of 0.5 g (1.7 mmole) of IIIb and 0.18 ml [0.18 g (3.6 mmole)] of hydrazine hydrate in 10.6 ml of absolute alcohol (after refluxing for 4 h and 30 min) gave 0.45 g (91.5%) of light-yellow crystals of Vb with mp 296-297.5°C (dec., butanol). Found: C 46.1; H 3.6; N 28.6; S 11.0%. $C_{11}H_{10}N_6O_2S$. Calculated: C 45.5; H 3.5; N 28.9; S 11.0%.

4-Diethylaminoethylamino-7,9-dimethyl-8-nitropyrido[3',2':4,5]thieno[3,2-d]pyrimidine (VI). A mixture of 0.5 g (1.7 mmole) of IIIb and 2 ml of diethylaminoethylamine was heated at 150°C for 1 h, after which it was cooled, and the precipitate was removed by filtration and washed with water to give 0.42 g of product. Addition of water to the filtrate gave an additional 0.15 g of product for an overall yield of 0.57 g (89.2%) of light-yellow crystals with mp 204-206°C (alcohol). The product took on a greenish tint in light. Found: C 54.1; H 6.1; N 22.4; S 8.5%. $C_{17}H_{22}N_6O_2S$. Calculated: C 54.5; H 5.9; N 22.4; S 8.6%.

4-Mercapto-7,9-dimethylpyrido[3',2':4,5]thieno[3,2-]pyrimidine (VII). A 2.2-g (8.8 mmole) sample of IIIa was added to a solution of 0.74 g (9.72 mmole) of thiourea in 40 ml of ethanol, and the mixture was refluxed for 3 h and 30 min. It was then cooled, and the precipitate was removed by filtration to give 1.96 g (89.5%) of yellow crystals with mp > 320°C. IR spectrum: 3120 (NH) and 1220 cm^{-1} (C=S). UV spectrum, λ_{max} (log ε): 227 (4.43), 279 (4.08), 300 (4.11), 322 (3.98), 377 nm (4.00). Found: C 53.0; H 3.8; S 25.7%. $C_{11}H_9N_3S_2$. Calculated: C 53.4; H 3.7; S 25.9%.

4-Benzylmercapto-7,9-dimethylpyride[3',2':4.5]thieno[3,2-d]pyrimidine (VIII). A 0.5-g (2.02 mmole) sample of VII was added to a solution of sodium ethoxide, prepared from 0.054 g (2.3 mg-atom) of sodium metal and 42.5 ml of absolute ethanol, and the mixture was refluxed for 1 h. It was then treated with 0.64 ml [0.7 g (5.53 mmole)] of benzyl chloride, and the precipitate was removed by filtration and washed with water to give 0.54 g (79.4%) of light-yellow crystals with mp 151.5-153.5°C (alcohol). UV spectrum, λ_{max} (log ε): 228 (4.39), 245 (4.38); 299 (4.34), 328 (3.92), 339 nm (3.93). Found: C 63.9; H 4.4; S 19.1%. $C_{18}H_{15}N_3S_2$. Calculated: C 64.1; H 4.5; S 19.0%.

3,7,9-Trimethylpyrido[3',2':4.5]thieno[3,2-d]pyrimidin-4-one (IX). A 1-g (4.33 mmole) sample of IIa and 0.42 ml [0.56 g (4.46 mmole)] of dimethyl sulfate were added to a solution of sodium ethoxide, prepared from 0.76 g (0.033 g-atom) of sodium metal and 33 ml of absolute ethanol, and the mixture was refluxed for 18 h. The precipitate was removed by filtration and dissolved in 40 ml of water. The aqueous solution was extracted with chloroform, and the extracts were dried and evaporated to give 0.16 g (15%) of colorless crystals with mp 274-277°C (butanol). IR spectrum: 1670 cm^{-1} (CO). Found: C 58.9; H 4.6; N 17.1%. $C_{12}H_{11}N_3OS$. Calculated: C 58.8, H 4.5, N 17.1%.

3-Benzyl-7,9-dimethylpyrido[3,'2':4,5]thieno[3,2-d]pyrimidin-4-one (X). A 2-g (8.65 mmole) sample of IIa was added to a solution of sodium ethoxide, prepared from 0.21 g (9.13 mg-atom) of sodium metal and 64.5 ml of absolute ethanol, and the mixture was refluxed for 1 h. It was then treated with 1.1 ml [1.21 g (9.56 mmole)] of benzyl chloride, and the resulting mixture was refluxed for another 10 h. It was then cooled, and the precipitate was removed by filtration and washed with 5% sodium hydroxide solution and water to give 1.27 g (45.7%) of colorless crystals with mp 180-182°C (methanol). IR spectrum: 1660 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 248 (4.90), 286 (3.96), 297 (4.12), 324 (3.83), 336 nm (3.64). Found: C 69.9; H 4.6; N 13.0%. $C_{18}H_{15}N_3OS$. Calculated: C 67.3; H 4.7; N 13.1%.

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