Synthesis of Thiopyrano[2,3-*d*]pyrimidines and Thieno[2,3-*d*]pyrimidines

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The reaction of 4-chloro-5-cyano-2-methylthiopyrimidine (I) with ethyl mercaptosuccinate (II) in refluxing ethanol containing sodium carbonate has afforded diethyl 5-amino-2-(methylthio)-7*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate (IV). Displacement of the methylthio group in IV with hydrazine gave the corresponding hydrazino derivative which underwent Schiff base formation with benzaldehyde or 2,6-dichlorobenzaldehyde. Treatment of IV in refluxing acetic anhydride afforded the corresponding diacetylated amino derivative. Partial saponification of IV with sodium hydroxide gave 5-amino-2-(methylthio)-7*H*-thiopyrano-[2,3-*d*]pyrimidine 6,7-dicarboxylic acid 6 ethyl ester (VIII). The reaction of 4-amino-6-chloro-5-cyano-2-phenylpyrimidine (XI) with II resulted in the formation of ethyl 4-amino-6-(ethoxycarbonyl)-5,6-dihydro-5-amino-2-phenylthieno[2,3-*d*]pyrimidine-6-acetate (XIII) which when subjected to hydrolysis gave ethyl 4,5-diamino-2-phenylthieno[2,3-*d*]pyrimidine-6-acetate isolated as the hydrochloride (XIV). Diazotization of IV with sodium nitrite in acetic acid unexpectedly afforded diethyl 5-(acetyloxy)-6,7-dihydro-6-hydroxy-2-(methylthio)-5*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate (XV). Several structural ambiguities were resolved by ir and pmr spectra.

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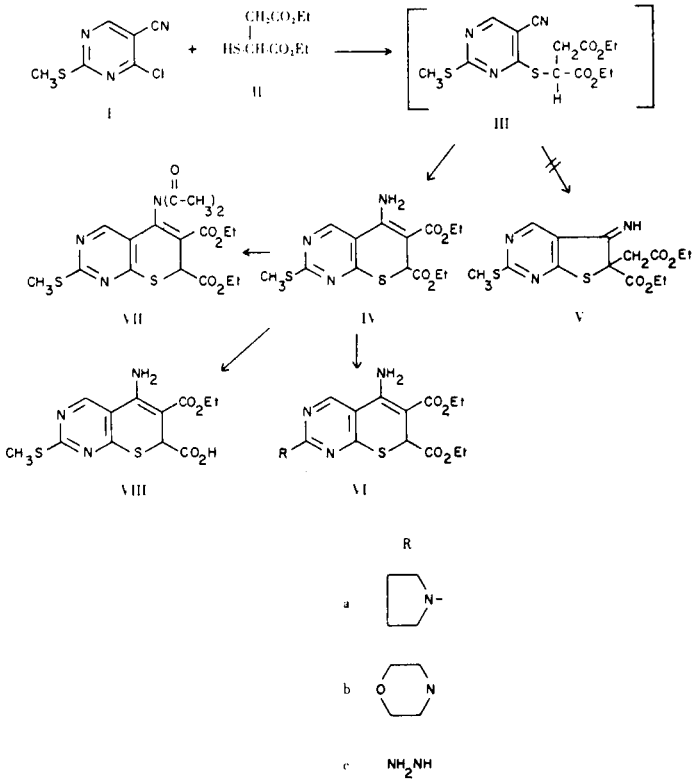
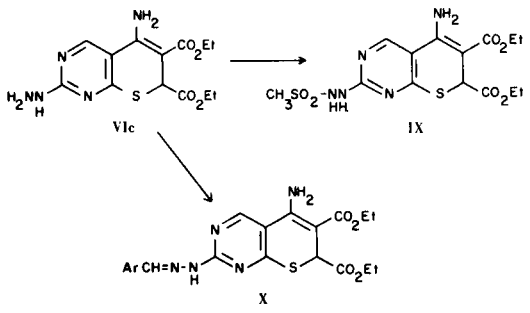
Previously, we reported a facile synthesis of thieno-[2,3-*d*]pyrimidines formed in a single step *via* the reaction of variously substituted 4-chloro-5-cyanopyrimidines with ethyl mercaptoacetates or mercapto-*N*-substituted acetamides (1). Further studies have shown that the reaction of ethyl mercaptosuccinate with 4-chloro-5-cyano-2-methylthiopyrimidine takes a different course forming diethyl 5-amino-2-(methylthio)-7*H*-thiopyrano[2,3-*d*]-pyrimidine-6,7-dicarboxylate (IV) instead of the isomeric thieno[2,3-*d*]pyrimidine (V) (Scheme I). The structural assignment of IV is substantiated by its infrared and proton magnetic resonance spectrum. The ir spectrum shows no nitrile absorption but ester C=O bands are found at 5.73 and 5.95 μ, corresponding to an unconjugated and chelated conjugated ester, respectively. The pmr spectrum shows the annelar methinyl proton as a singlet at 4.90 δ and the amino protons as a singlet at 6.92 δ which vanishes on deuteration. These spectral data clearly establish the thiopyrano[2,3-*d*]pyrimidine (IV) as the correct structure for the product.

Displacement of the methylthio group in IV by pyrrolidine resulted in the formation of diethyl 5-amino-2-(1-pyrrolidinyl)-7*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate (VIa). Similar nucleophilic displacement reactions were carried out with morpholine and hydrazine

Scheme I



Scheme II



Ar

a C_6H_5

b $2,6\text{-}Cl_2C_6H_3$

resulting in the formaiton of VIb and VIc, respectively. Treatment of IV in boiling acetic anhydride for several hours caused a diacetylation of the amino group to occur giving VII. When IV was treated with boiling 10% sodium hydroxide solution containing a few milliliters of ethanol, saponification of the 7-carbethoxy group resulted. Upon acidification, the mono ester VIII was obtained. The ir spectrum of the product indicated that the conjugated ester C=O band at 5.93 μ is still intact.

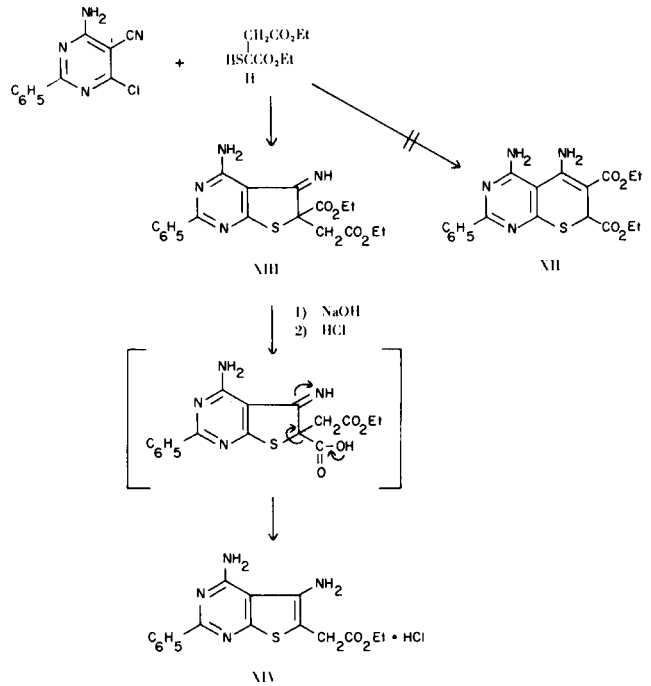
The reaction of diethyl 5-amino-2-hydrazino-7*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate (VIc) with methanesulfonyl chloride afforded IX (Scheme II). The hydrazino function of VIc also underwent reaction with benzaldehyde and 2,6-dichlorobenzaldehyde in refluxing ethanol to give the corresponding Schiff base derivatives Xa and Xb, respectively.

The reaction of 4-amino-6-chloro-5-cyano-2-phenylpyrimidine (XI) with diethyl mercaptosuccinate in refluxing ethanol containing sodium carbonate, surprisingly gave the thieno[2,3-*d*]pyrimidine XIII instead of the expected thiopyrano[2,3-*d*]pyrimidine XII (Scheme III). Formation of XII may be precluded by the fact that the two bulky amino groups adjacent to each other at the 4,5-positions represent a more sterically crowded and therefore less favorable arrangement. The thieno[2,3-*d*]-pyrimidine, on the other hand, affords less steric crowding in this regard. The infrared spectrum of XIII indicates the presence of two unconjugated ester C=O bands at 5.71 and 5.81 μ. The pmr spectrum also is in accord with the assigned structure. The pendant acetate methylene resonance appears as an A, B quartet pattern centered at 3.50 δ (J = 18 Hz). Magnetically non-equivalent methylene protons adjacent to an asymmetric center have been reported previously (2). The imino proton appears at 10.73 δ and disappears on deuteration.

Partial saponification of XIII with 15% sodium hydroxide solution followed by acidification with hydrochloric acid resulted in decarboxylation to afford ethyl 4,5-diamino-2-phenylthieno[2,3-*d*]pyrimidine-6-acetate hydrochloride (XIV).

Compound IV was diazotized with sodium nitrite in acetic acid and the resulting diazonium salt subjected to hydrolysis. The mass spectrum of the product indicated the molecular weight to be 416 or 60 mass units greater than the expected 5-hydroxy product. Combustion analysis and the molecular weight required a molecular formula of $C_{16}H_{20}N_2O_7S_2$. The infrared spectrum showed no conjugated ester carbonyl absorption but indicated instead unconjugated ester carbonyl absorptions at 5.65 and 5.70 μ. Apart from the proton patterns of the pyrimidine substituents and the ethyl ester groups, the pmr showed two non-coupled methinyl protons at 5.38 and 6.24 δ, a methyl singlet at 2.16 δ and a proton singlet at 6.40 δ which vanished on deuteration. The product failed to undergo acetylation with acetyl chloride. One structure which appears to best fit these data is XV.

Scheme III



Scheme IV

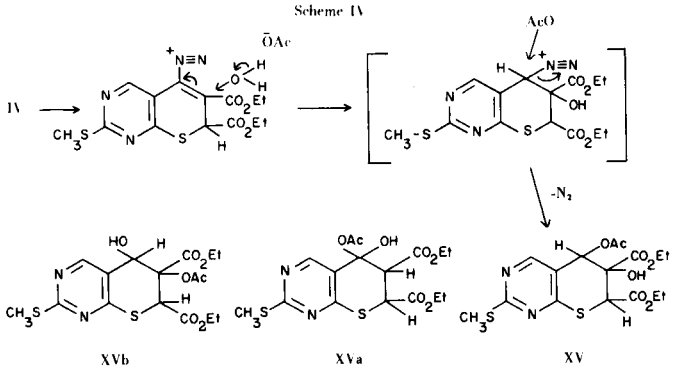
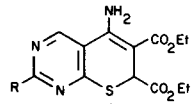


Table I

Diethyl 5-amino-2-substituted-7*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylates



Compound	R	M.p. °C	Recrystallization Solvent	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IV	CH_3S	115-117	ethanol	$C_{14}H_{17}N_3O_4S_2$	47.31	4.82	11.82	47.05	4.99	11.72
VIa		113-115	ethanol-petroleum ether	$C_{17}H_{22}N_4SO_4$	53.95	5.86	14.80	53.69	5.74	14.96
VIb		145-148	ethanol-water	$C_{17}H_{22}N_4SO_5$	51.76	5.63	14.20	51.65	5.63	14.18
VIc	$NHNH_2$	130	ethanol	$C_{13}H_{17}N_5SO_4$	46.01	5.05	20.64	45.84	4.99	20.99
IX	CH_3SO_2NHNH	210-212	ethanol	$C_{14}H_{19}N_5S_2O_6$	40.28	4.59	16.78	40.17	4.73	16.92
Xa	$C_6H_5CH{=}NNH$	220-222	ethanol	$C_{20}H_{21}N_5SO_4$	56.19	4.95	16.38	56.24	4.96	16.32
Xb	2,6 $Cl_2C_6H_3CH{=}NNH$	153-155	ethanol	$C_{20}H_{19}Cl_2N_5O_4S \cdot H_2O$	46.70	4.11	13.61	46.91	3.73	13.62

Other isomers which were considered alternative possibilities for the product are XVa and XVb. Since coupling of the methinyl protons does not occur, structure XVa is eliminated as a reasonable choice for the structure of the product. Structure XVb also does not appear too likely since one might expect the secondary alcohol function to acetylate readily and that coupling would occur between the OH and methinyl proton. Additional data involving the Lanthanide shift reagent $Eu(fod)_3$ provided further evidence that XV is the correct structural assignment. In deuteriochloroform, the addition of this reagent caused a downfield shift in all proton patterns. Apart from the OH proton, where the complex is formed, the biggest shift occurred with the uncoupled methinyl singlets which had the same order of magnitude in their shift. The approximately equal shifts of methinyl proton resonances are best explained by structure XV wherein the methinyl protons are approximately equi-distant from the OH complexing center. The methinyl protons in XVa and XVb, in contrast are not equi-distant from the complexing center and larger differences in their shift patterns therefore would be expected (3). At higher concentrations of shift reagent, the methylene pattern of the 6-carbethoxy group began to separate into multiple quartet patterns possibly due to adjacent surrounding chiral centers.

Formation of XV may be envisioned as proceeding through the addition of water across the 5,6-double bond of the diazonium salt in a Michael fashion. Acetolysis and loss of nitrogen from the resulting intermediate then leads to the product.

EXPERIMENTAL

Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide disks using a Perkin-Elmer (Model 21) spectrophotometer. Pmr spectra were obtained with a Varian A-60 spectrometer using deuteriochloroform or DMSO-d_6 as indicated. Chemical shifts were measured in ppm (δ) with respect to tetramethylsilane. The observed spectra are in accord with structural assignments.

Diethyl 5-Amino-2-(methylthio)-7*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate (IV).

A mixture of 9.27 g. (0.05 mole) of 4-chloro-2-methylthio-5-cyanopyrimidine, 10.3 g. (0.05 mole) of ethyl mercaptosuccinate and 5.3 g. (0.05 mole) of sodium carbonate in 200 ml. of ethanol was heated under reflux with stirring for 5 hours. The reaction mixture was filtered and the filtrate taken to dryness on a rotary evaporator. Trituration of the residue with water caused it to solidify. Recrystallization of the crude product from ethanol gave 6.4 g. of product, ir: μ 5.73 (unconjugated ester C=O), 5.95 (conjugated ester C=O): pmr (deuteriochloroform): δ 1.18 (t, 3, CH_2CH_3), 1.29 (t, 3, CH_2CH_3), 2.53 (s, 3, CH_3S), 4.09 (q, 2, CH_2CH_3), 4.22 (q, 2, CH_2CH_3), 4.90 (s, 1, CH-CO_2Et), 6.92 (s, 2, NH_2), 8.60 (s, 1-pyrimidine H).

Diethyl 5-Amino-2-(1-pyrrolidinyl)-7*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate (VIa).

A stirred mixture of 14.2 g. (0.04 mole) of IV and 28.4 g. (0.4 mole) of pyrrolidine in 150 ml. of ethanol was heated under reflux for 6 hours. The mixture was diluted with 200 ml. of water and was cooled in ice. The precipitate which formed was collected, dried and recrystallized from a mixture of ethanol-petroleum ether to give 3.9 g. of product, m.p. 113-115°; ir: μ 5.76 (unconjugated ester C=O), 5.97 (conjugated ester C=O).

Diethyl 5-Amino-2-hydrazino-7*H*thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate (VIc).

This compound was prepared from 16 g. (0.045 mole) of IV and 9.0 g. (0.18 mole) of hydrazine hydrate in 200 ml. of ethanol. The reaction mixture was heated under reflux for 4 hours, filtered and the filtrate diluted with 150 ml. of water. The resulting precipitate was recrystallized from ethanol to afford the analytical sample, ir: μ 3.0-3.3 (broad NH), 5.72 (unconjugated ester C=O), 5.98 (conjugated ester C=O).

Diethyl 5-(Diacetylamino)-2-methylthio-7*H*-thiopyrano[2,3-*d*]-pyrimidine-6,7-dicarboxylate (VII).

A stirred mixture of 13 g. of IV in 75 ml. of acetic anhydride was heated under reflux for 18 hours. The mixture was cooled in ice and diluted with 150 ml. of water. After standing at room temperature, the water was decanted from the reaction mixture leaving an oil which upon trituration with 25 ml. of ethanol solidified. Recrystallization from ethanol gave 6.49 g. of product, m.p. 118-120°: ir: μ 5.75 and 5.85 (ester and imide C=O absorptions).

Anal. Calcd. for $C_{18}H_{21}N_3O_6S_2$: C, 49.19; H, 4.82; N, 9.56. Found: C, 48.79; H, 4.81; N, 9.40.

5-Amino-2-(methylthio)-7*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylic Acid 6-Ethyl Ester (VIII).

To a mixture of 20 ml. of 10% aqueous sodium hydroxide and 15 ml. of ethanol was added 6.0 g. of IV. The mixture was heated to the boiling point, cooled in ice and acidified with concentrated hydrochloric acid to *p*H 7. The precipitate which formed was collected. Further acidification of the filtrate gave a second crop of crystals. The combined crops were recrystallized from a mixture of ethanol-petroleum ether to give 2.8 g. of product, m.p. 197-200°; ir: μ 2.95, 3.08 (NH_2), 5.93 (conjugated ester C=O), pmr (DMSO-d_6): 1.23 (t, 3, CH_2CH_3), 2.55 (s, 3, CH_3S), 4.23 (q, 2, CH_2CH_3), 4.91 (s, 1, CH-CO_2H), 7.99 (s, 2, NH_2), 8.83 (s, 1, pyrimidine H), 12.8 (s (broad), 1, CO_2H).

Anal. Calcd. for $C_{12}H_{13}N_3S_2O_4$: C, 44.04; H, 4.00; N, 12.84. Found: C, 43.86; H, 3.97; N, 12.78.

Diethyl 5-Amino-2-[2-(methylsulfonyl)hydrazino]-7*H*-thiopyrano-[2,3-*d*]pyrimidine-6,7-dicarboxylate (IX).

To a solution of 1.0 g. of VIc in 20 ml. of dry pyridine was added 0.34 g. of methanesulfonyl chloride. The reaction mixture was allowed to stand at room temperature for 1 hour and was then diluted with 25 ml. of water. The precipitate which formed was collected and recrystallized from ethanol giving the analytical sample; ir: μ 5.73 (unconjugated ester C=O), 5.97 (conjugated ester C=O), 7.50, 8.60 (SO_2).

Diethyl 5-Amino-2-(benzylidenehydrazino)-7*H*-thiopyrano[2,3-*d*]-pyrimidine-6,7-dicarboxylate (Xa).

A stirred mixture of 1.0 g. (0.003 mole) of VIc and 0.3 g. (0.003 mole) of benzaldehyde in 25 ml. of ethanol was heated under reflux for 4 hours. A few milliliters of water was added to

the reaction mixture which was then cooled in ice. The precipitate which was formed was collected and recrystallized from ethanol giving the analytical sample; ir: μ 5.72 (unconjugated ester C=O), 5.96 (conjugated ester C=O), 6.13 (C=N).

Ethyl 4-Amino-6-(ethoxycarbonyl)-5,6-dihydro-5-imino-2-phenylthieno[2,3-*d*]pyrimidine-6-acetate (XIII).

A mixture of 6.91 g. (0.03 mole) of 4-amino-6-chloro-5-cyano-2-phenylpyrimidine, 6.18 g. (0.03 mole) of diethyl mercaptosuccinate and 4.08 g. (0.03 mole) of sodium carbonate was heated under reflux with stirring for 7.5 hours. The reaction mixture was filtered while hot and on cooling the filtrate in ice, there was obtained 5.7 g. of product, m.p. 179-182°. Recrystallization from ethanol gave 4.6 g. of product, m.p. 181-184°; ir: μ 2.95-3.05 (NH_2) 5.77 (s), 5.81 (ester C=O absorption), pmr (DMSO-d_6) 1.13 (t, 3, CH_2CH_3), 1.17 (t, 3, CH_2CH_3), 3.50 (A,B q, 2 CH_2CO_2Et), 4.11 (q, 2, CH_2CH_3), 4.16 (q, 2, CH_2CH_3), 7.50 (m, 3, *m,p*-phenyl H'S), 8.35 (m, 2, *o*-phenyl H'S), 8.09 (s (broad), 2, NH_2).

Anal. Calcd. for $C_{19}H_{20}N_4O_4S$: C, 56.99; H, 5.03; N, 13.99. Found: C, 56.55; H, 5.06; N, 13.66.

Ethyl 4,5-Diamino-2-phenylthieno[2,3-*d*]pyrimidine-6-acetate Hydrochloride (XIV).

A solution containing 0.5 g. of XIII in 50 ml. of 15% sodium hydroxide solution was stirred at room temperature for 2 hours. The reaction mixture was then cooled in ice and acidified with concentrated hydrochloric acid. The resulting precipitate was collected and recrystallized from ethanol giving 0.1 g. of product, m.p. 226-229° d; ir: μ 5.75 (ester C=O absorption), 6.0 (C=N), pmr (DMSO-d_6): 1.07 (t, 3, CH_2CH_3), 3.45 (q, 2, CH_2CH_3), 3.93 (s, 2, CH_2CO_2Et), 7.39 (broad singlet, exchangeable protons), 7.06 (m, 3, *m,p*-phenyl H'S), 8.40 (m, 2, *o*-phenyl H'S).

Anal. Calcd. for $C_{16}H_{16}N_4O_2S \cdot HCl \cdot H_2O$: C, 50.19; H, 5.00; N, 14.63; Cl. 9.26. Found: C, 49.85; H, 4.77; N, 14.53; Cl, 9.22.

Diethyl 5-(Acetyloxy)-6,7-dihydro-6-hydroxy-2-(methylthio)-5*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate (XV).

To a solution of 1.2 g. (0.003 mole) of IV in 25 ml. of glacial acetic acid was added 0.2 g. (0.003 mole) of sodium nitrite. The mixture was stirred at room temperature for 1 hour and filtered. The filtrate was diluted with 20 ml. of water and heated on a steam bath for 1 hour. The reaction mixture was further diluted with 50 ml. of water and extracted with 50 ml. of ether. The ether layer was dried over magnesium sulfate, filtered and the ether removed by evaporation leaving an oil. The oil was dissolved in ethyl acetate and the solution was passed through a short alumina column. Evaporation of the ethyl acetate gave 0.1 g. of product m.p. 164-167°; ir: μ 3.25 (broad OH), 5.65, 5.70 (ester C=O absorption), pmr (DMSO-d_6) 1.17 (t, 3, CH_2CH_3), 1.23 (t, 3, CH_2CH_3), 2.16 (s, 3, $OC\text{-}CH_3$), 4.17 (q's, 4, $C\text{-}OCH_2CH_3$), 5.38 (s, 1, $SCHCO_2Et$), 6.24 (s, 1, Ac-OC*H*), 6.40 (s, 1, OH), 8.12 (s, 1, pyrimidine H).

Anal. Calcd. for $C_{16}H_{20}N_2O_7S_2$: C, 46.14; H, 4.84; N, 6.73. Found: C, 46.21; H, 4.88; N, 6.70.

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