PYRIMIDINE DERIVATIVES.

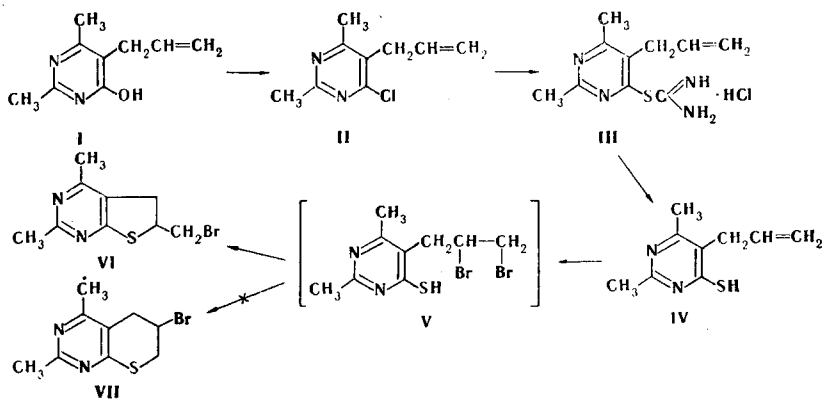
56.* NEW METHOD FOR THE SYNTHESIS OF THIENO[2,3-d]PYRIMIDINE

R. G. Melik-Ogandzhanyan,
A. S. Gapoyan, V. É. Khachatryan,
and V. S. Mirzoyan

UDC 547.859'735'818.07

A new scheme was developed for the synthesis of 2,4-dimethyl-5,6-dihydro-6-bromomethylthieno[2,3-d]pyrimidine by bromination of the corresponding 5-allyl-6-mercaptopyrimidine. It is shown that when the bromomethyl derivative is treated with sodium methoxide a molecule of hydrogen bromide is split out to give 2,4,6-trimethylthieno[2,3-d]pyrimidine. The structures of the synthesized compounds were proved by PMR spectroscopy and mass spectrometry.

In the development of research on the preparation of condensed heterocyclic compounds on the basis of pyrimidine [1, 2], which are of interest in the search for new antitumorigenic preparations, in the present research we studied methods for the construction of the thieno[2,3-d]pyrimidine (VI) system via the following scheme:



The starting 2,4-dimethyl-5-allyl-6-hydroxypyrimidine was obtained by condensation of acetamidine with ethyl allylacetoacetate by the method described in [2, 3].

The action of phosphorus oxychloride on hydroxypyrimidine I in the presence of dimethylaniline was used to synthesize chloropyrimidine II, which reacts with thiourea to give thiuronium salt III. The corresponding 4-mercaptopyrimidine IV was obtained by refluxing III with sodium ethoxide in ethanol.

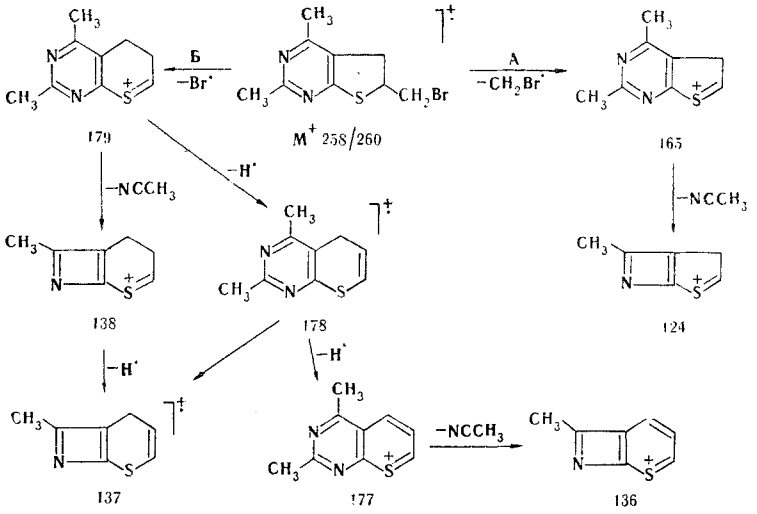
In the case of bromination of IV in ethanol, instead of the expected addition product V, we isolated cyclic 2,4-dimethyl-5,6-dihydro-6-bromomethylthieno[2,3-d]pyrimidine (VI) in the form of the hydrobromide; consequently, in addition to the addition of a molecule of bromine, this reaction proceeds with splitting out of hydrogen bromide to give a cyclic five-membered dihydrothiophene ring rather than a six-membered thiopyran ring (VII), which was proved unambiguously by analysis of the mass spectrum of the reaction product.

The mass spectrum of VI contains a peak of a molecular ion, which subsequently undergoes fragmentation via two principal pathways, viz., A and B,

*See [1] for Communication 55.

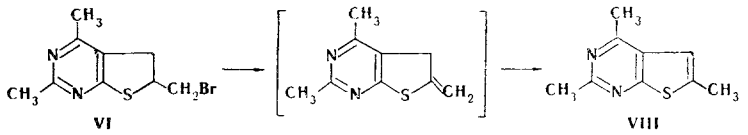
Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan, 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 118-120, January, 1982. Original article submitted February 9, 1981.

 0009-3122/82/1801-0100$07.50



via the scheme presented above. The peak of the ion with m/z 165* (pathway A) has high intensity (~60% of the maximum peak), and its formation is associated with the elimination of a CH_2Br radical; this is characteristic for α-substituted unsaturated five-membered heterorings. The maximum peak is the peak of the ion with m/z 124, which is formed from the ion with m/z 165 as a result of elimination of a molecule of acetonitrile. Pathway B involves ejection of a bromine atom from the molecular ion; the resulting ion with m/z 179 subsequently loses a hydrogen atom (to give an ion with m/z 178) and a cyanomethyl group (to give an ion with m/z 138).

Evidence in favor of the structure of VI is provided by the fact that when it is treated with sodium methoxide, a molecule of hydrogen bromide is split out to give 2,4,6-trimethylthieno[2,3-d]pyrimidine (VIII).



A signal of the proton attached to the C_5 atom of the thiophene ring (q, 6.82 ppm) and signals of methyl groups attached to the C_2 and C_4 atoms of the pyrimidine ring (2.65 and 2.63 ppm, respectively) and the C_6 atom of the thiophene ring (2.62 ppm) are observed in the PMR spectrum of VIII.

We made an attempt to carry out nucleophilic substitution of the bromine atom in VI by various amines (dimethylamine, diethylamine, piperidine, and morpholine); however, instead of the expected 2,4-dimethyl-5,6-dihydro-6-aminomethylthieno[2,3-d]pyrimidines, trimethyl derivative VIII is formed, i.e., the bases do not replace the bromine atom but promote splitting out of a molecule of hydrogen bromide.

EXPERIMENTAL

The mass spectrum was recorded with an MKh-1303 spectrometer at an ionization energy of 30 eV at 30-40°C below the melting point of the investigated compound with direct introduction of the sample into the ion source. The PMR spectra of 7% solutions of the compounds in D_2O (IV) and CCl_4 (VI, VIII) were recorded with a Varian T-60 spectrometer (60 MHz) with tetramethylsilane as the standard. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in ether–petroleum ether (4:1) (for I) and benzene–acetone (4:1) (for IV, VI, and VIII) systems with development in UV light.

2,4-Dimethyl-5-allyl-6-chloropyrimidine (II). A mixture of 3.2 g (0.02 mole) of 2,4-dimethyl-5-allyl-6-hydroxypyrimidine, 10 ml of freshly distilled phosphorus oxychloride, and 6 ml of dimethylaniline was heated on a water bath for 3-4 h, after which the excess phosphorus oxychloride was removed by distillation, and the residue was poured into ice water.

*In the scheme and in the text the numbers that characterize the ions are the mass-to-charge ratios (m/z).

The aqueous mixture was extracted with chloroform, the chloroform layer was dried over anhydrous sodium sulfate, and the solvent was removed by distillation. The residue was distilled *in vacuo* to give 2.5 g (70.0%) of a product with bp 93-95°C (1.3 hPa) and R_f 0.51. PMR spectrum: 2.42 (s, C_2-CH_3), 2.60 (s, C_4-CH_3), 3.45 (m, C_5-CH_2), and 5.40 ppm (m, C_5-CH=CH_2). Found: C 58.90; H 5.90; Cl 19.21; N 15.60%. $C_9H_{11}ClN_2$. Calculated: C 59.17; H 6.08; Cl 19.39; N 15.34%.

S-(2,4-Dimethyl-5-allyl-6-pyrimidinyl)thiourea Hydrochloride (III). A 5.5-g (0.03 mole) sample of pyrimidine I was added to 2.5 g (0.033 mole) of thiourea dissolved in 50 ml of acetone, and the mixture was heated with stirring on a water bath for 2-3 h. It was then cooled, and the resulting precipitate was removed by filtration, washed with acetone, and dried to give 7.55 g (97.4%) of a product with mp 156-157°C. Found: Cl 13.72; S 12.40%. $C_{10}H_{15}ClN_4S$. Calculated: Cl 13.70; S 12.38%.

2,4-Dimethyl-5-allyl-6-mercaptopyrimidine (IV). A 0.46-g (0.02 mole) sample of sodium metal dissolved in 30 ml of absolute ethanol was added to a solution of 2.6 g (0.01 mole) of derivative III in 20 ml of ethanol, and the mixture was heated on a water bath for 3-4 h. It was then cooled and acidified to pH 5-6 with concentrated hydrochloric acid. The precipitated crystals were removed by filtration, washed with cold water, and recrystallized from hexane to give 1.6 g (89.3%) of a product with mp 140-141°C and R_f 0.40. PMR spectrum: 2.60 (s, C_2-CH_3), 2.90 (s, C_4-CH_3), 3.53 (m, C_5-CH_2), 5.63 (m, C_5-CH=CH_2). Mass spectrum: M^+ 178. Found: C 59.85; H 6.50; N 15.21; S 17.44%. $C_9H_{12}N_2S$. Calculated: C 59.98; H 6.71; N 15.38; S 17.55%.

2,4-Dimethyl-5,6-dihydro-6-bromomethylthieno[2,3-d]pyrimidine (VI). A solution of 3.2 g (0.02 mole) of bromine in 20 ml of ethanol was added dropwise in the course of 15 min to a solution of 3.6 g (0.02 mole) of IV in 30 ml of ethanol, after which the mixture was refluxed for 4 h. It was then cooled, and the precipitated crystals were removed by filtration and dissolved in 50 ml of water. The aqueous solution was treated with 20 ml of 20% ammonium hydroxide, and the mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, the solvent was removed by distillation, and the residue was crystallized from hexane to give 3.1 g (60.2%) of a product with mp 57-58°C and R_f 0.44. PMR spectrum: 2.40 (s, C_2-CH_3), 2.55 (s, C_4-CH_3), 3.62 (m, C_5-CH_2), 4.00 (m, C_6-CH), and 3.35 ppm (m, C_6-CH_2Br). Mass spectrum: M^+ 258. Found: Br 32.00; S 12.60%. $C_9H_{11}BrN_2S$. Calculated: Br 32.13; S 12.85%.

2,4,6-Trimethylthieno[2,3-d]pyrimidine (VIII). A solution of 0.23 g (0.01 mole) of sodium metal in 40 ml of absolute methanol was added to a solution of 2.60 g (0.01 mole) of VI in 20 ml of methanol, and the mixture was refluxed for 3 h. The solvent was removed by distillation, the residue was poured into water, and the aqueous mixture was extracted with benzene. The extract was dried over anhydrous sodium sulfate, the solvent was removed by distillation, and the residue was crystallized from hexane to give 1.27 g (72.7%) of a product with mp 86-87°C and R_f 0.43. Found: C 61.17; H 5.00; N 5.90; S 18.20%. $C_9H_{10}N_2S$. Calculated: C 61.02; H 5.08; N 15.87; S 18.08%. M^+ 178.

A mixture of 2.60 g (0.01 mole) of VI, 0.02 mole of the corresponding amine, and 30 ml of benzene was heated in a sealed ampul at 150°C for 6-8 h, after which it was cooled and filtered. The benzene was removed from the filtrate by distillation, and the residue was distilled at 140-142°C (1.3 hPa). It was then crystallized from hexane to give a product with mp 86-87°C in 30-35% yield. With respect to its physicochemical properties the product was identical to VIII. The same compound (VIII) was formed by heating (at 80-100°C) bromo derivative VI with the corresponding amine in toluene, acetone, or without a solvent.

LITERATURE CITED

1. R. G. Melik-Ogandzhanyan, R. G. Mirzoyan, and A. A. Aroyan, Arm. Khim. Zh., 28, 53 (1975).
2. R. G. Melik-Ogandzhanyan, A. S. Gapoyan, V. É. Khachatryan, V. S. Mirzoyan, Zh. S. Manukyan, and S. A. Papoyan, Arm. Khim. Zh., 33, 1020 (1980).
3. Y. Hach, Chem. Listy, 45, 459 (1951).