1-Phenyl-3-oxo-4-methyldihydrothieno[3,4-b]indole (XXVI). A 0.7-g (0.0025 mole) sample of II-hydrochloride was refluxed in 20 ml of alcohol and 5 ml of concentrated HCl for 4 h, after which the mixture was cooled to precipitate XXVI (Table 3) with Rf 0.56.

The same method was used to prepare XXVII and XXVIII.

Bis(1-methyl-2-hydroxymethyl-3-indolylphenylmethyl) Sulfide (XXIX). A 1.4-g (0.005 mole) sample of XXVI was reduced in ether with 0.40 g (0.012 mole) of LiAlH₄. After decomposition of the excess LiAlH₄ with water, the precipitate was removed by filtration, and the ether layer was dried with anhydrous Na₂SO₄ and evaporated to give XXIX, which was crystallized from cyclohexane. The yield of product with mp 75° was 0.78 g (56%). Found: N 5.2; S 6.0%; C₃₄H₃₂N₂SO₂. Calculated: N 5.8; S 6.0%.

2-(1-Methyl-2-indolyl)-4-methylthiazole Hydrochloride (XXX). A 1.37-g (0.01 mole) sample of bromoacetone was added to 1.92 g (0.01 mole) of thioamide I in 15 ml of ethanol saturated with HCl, after which the mixture was refluxed for 5 min. It was then cooled to precipitate 2.4 g (86%) of XXX with mp 215° (from alcohol). Substance XXX was not affected by refluxing in HCl. The 2-(1-methyl-2-indolyl)-4-methylthiazole base is incapable of forming acetyl derivatives under the influence of acetic anhydride. Found: C 12.6; N 4.9; S 11.0%. C₁₄H₁₀NS·HCl. Calculated: C 12.7; N 5.6; S 11.4%.

LITERATURE CITED


DERIVATIVES OF CONDENSED SYSTEMS BASED ON PYRIMIDINE, PYRAZINE, AND PYRIDINE

XXXVI.* SYNTHESIS OF PYRIMIDO[4,5-b]-1,4-THIAZIN-6-ONES AND PYRIMIDO[4,5-b]-1,5-THIAZEPIN-6-ONES

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Pyrimido[4,5-b]-1,4-thiazin-6-one and pyrimido[4,5-b]-1,5-thiazepin-6-one derivatives were obtained by reaction of 5-amino-6-chloropyrimidines with thioglycolic acid and 5-amino-6-mercaptopypyrimidines with β-bromopropionyl chloride. The IR spectra of the compounds are presented.

We have previously reported the synthesis of pyrimido[4,5-b]-1,4-thiazin-6-ones by reaction of 5-amino-6-mercaptopypyrimidines with α-halo acids [2]. During a biological study of these compounds it was observed that they inhibit the enzymes of folic acid metabolism and have antitumorigenic activity [3]. In this connection we obtained a number of new derivatives and homologs of pyrimido[4,5-b]-1,4-thiazin-6-one and investigated some of their properties.

4-Alkoxypyrimitothiazin-6-ones IV and V were obtained by reaction of 4-alkoxy-5-amino-6-chloropyrimidines I and II with thioglycolic acid. In the reaction of 4,6-dichloro-5-aminopyrimidine (III) with thioglycolic acid both chlorine atoms are replaced by carboxymethylthio groups to give derivative VI. This method for the synthesis of pyrimidothiazin-6-ones [4] has an advantage over the method described in [2] with respect to the number of steps involved.

*See [1] for communication XXXV.
Compounds IV and V are readily alkylated to give methyl derivatives VII and VIII, in the IR spectra of which the NH absorption band present in the spectra of starting IV and V is absent and the absorption band of an amide group (1678-1680 cm\(^{-1}\)) is retained. Oxidation of IV with peracetic acid yielded sulfonic acid XI, the structure of which was proved by identification with a sample obtained by oxidation of 4-methoxy-5-amino-6-mercaptopypirimidine (IX) to X and subsequent demethylation.

For biological study it was of interest to obtain pyrimido[4,5-b]-1,5-thiazepin-6-one derivatives, which are homologs of IV-VI. With this end in mind, we obtained the corresponding 6-thiopropionic acids XII and XIII by reaction of IX and 2,5-diamino-4-methyl-6-mercaptopypirimidine (X) with \(\beta\)-bromopropionic acid. An attempt to cyclize XII and XIII under the influence of SOCl\(_2\) or POCl\(_3\) was unsuccessful. We therefore used the more reactive haloalkanoic acid chlorides as the carbonyl component in this reaction. Initially in the case of IX and chloroacetyl chloride we ascertained that in acetone containing K\(_2\)CO\(_3\) pyrimidothiazin-6-one IV, rather than the product of acylation of the ring nitrogen atom is formed. Similarly, 2-amino-4-methylpyrimido[4,5-b][1,4]-thiazin-6-one (XIV) was obtained by reaction of X with chloroacetyl chloride. Thus under the indicated conditions the 5-NH\(_2\) groups is acylated and the SH group is alkylated, and the ring N(1) atom does not participate in the reaction.

5-(2-Bromopropionyl)aminopyrimidine (XV) was isolated in the reaction of pyrimidine IX with \(\beta\)-bromopropionyl chloride. The alternative structures – products of alklylation and acylation of the S or N(1) atoms – are excluded by the results of elementary analysis, by the absence in the IR spectra of absorption of an NH\(_2\) group, by the presence of absorption bands of an amide group, and by the chemical transformations of XV. Thus the reaction of XV with CH\(_3\)I gave derivative XVI, the structure of which as the SCH\(_3\) rather than the NCH\(_3\) derivative was proved by the presence in its PMR spectrum of the signal of an SCH\(_3\) group (2.62 ppm). Heating XV in acetonitrile gave pyrimido[4,5-b]-1,5-thiazepin-6-one (XVII), the structure of which was proved by the presence in its IR spectrum of bands of an amide group (1670 and 3230 cm\(^{-1}\)) and by reactions: like cyclic lactams, XVII is readily alkylated by CH\(_3\)I to give the 5-methyl derivative (XIX). The IR spectrum of XIX does not contain the NH band that is present in the spectrum of starting XVII, but the band of an amide carbonyl group (1675 cm\(^{-1}\)) is retained. Oxidation of thiazepinone XVII gave acid XVIII, the IR spectrum of which contains, in addition to bands of SO\(_2\) groups (1125 cm\(^{-1}\)) and a carboxyl group (1725 cm\(^{-1}\)), bands of an NH\(_2\) group (3380, 3490, and 1610 cm\(^{-1}\)). The intensity of the bands related to the NH\(_2\) group decrease markedly when acid XVIII is deuterated; this confirms the correctness of the above assignments. These data make it possible to reject alternative structures XX and XXI for acid XVIII and starting pyrimidothiazepinone XVII and consequently to exclude the possibility of migration of the acyl residue from the 5-NH\(_2\) group to the 6-mercaptop group under the conditions...