DMF DIETHYLACETAL: KEY COMPONENT IN THE SYNTHESIS OF ISOMERIC PERIDOTHIENOPYRIMIDINES

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Earlier we synthesized derivatives of 3-cyano-4-aminopyridine-2-thiones, based on which, using the thorpe-Ziegler reaction, we obtained a series of substituted thieno[2, 3-]pyridines Ia-d [2]. The compounds Ia-d obtained contain in the 4 position of the pyridine ring a secondary (NHPh) or tertiary (Me_2N) amino group along with 3-amino- and carbonyl-containing groups in the 2, 3 positions of the thiophene ring. This makes it possible to investigate alternative heterocyclizations connected with participation of the indicated functional group substituents. Among condensed thienopyrimidines, up to the present time a whole series of derivatives have been observed which have pronounced biological activity [3-6]. Therefore the goal of this work was to search for synthesis methods for key compounds of this type, which then could be sued to search for compounds with antituberculosis and antiviral activity.

As the starting system for carrying out pyrimidine cyclization, we initially chose the 2-carbamide derivative (Ia), and as the cyclization agent we chose the diethylacetal of N,N-dimethylformamide (II). Upon heating the components in toluene solution, the reaction occurred at two centers; in this case, the expected pyrimidine cyclization did not occur, but we separated in good yield the bis-dimethylaminomethylene derivative IIIa; i.e., under these conditions, the reaction occurred at both primary amino groups: the amino group at the 3 position of the thiophene ring and the carbamide NH_2 group. Formation of this type of compound was observed earlier also in other series, in particular in synthesis of pyrimido-[4,5-f]pyrrolizines [1].

In hydrolysis of the compound obtained, we might expect formation of different types of products: complete or partial hydrolysis of the amidine moieties (up to the starting Ia or the corresponding N-formyl derivatives), cyclization at the NHPh group with formation of angular compounds of type IV or formation of condensed pyrimidines (IV) and (V).

In fact, we found that upon heating the bis-amidine IIIa in aqueous acetic acid, only one orientation is realized: a compound is isolated in almost quantitative yield which according to elemental analysis, mass, IR, and ^1H NMR spectra corresponds to the structure of a representative of a new heterocyclic system, 2-(N-formylcarbamido)-5-phenylthieno-[2,3,4-e,d]pyrido[4,3-d]pyrimidine (IVa). In the ^1H NMR spectrum of this compound (in DMSO-d_6), we observe signals from the N-phenyl ring at 7.66-7.70 ppm (m, 5H), doublets from the aromatic protons in the 6,7 positions of the tricycle: 8.43 ppm (7-H) and 6.36 ppm (6-H) ($^3J_{6H-7H}$ = 5.6 Hz), a single from the aromatic proton in the 4 position at 8.33 ppm, and finally broadened doublest characteristic for the formylamino group at 9.21 (d, 1H, CHO) and 10.73 (d, 1H, NH) ppm with spin-spin coupling constant $^3J_{CHO-NH}$ = 9.7 Hz. Thus protonation of the amidine moiety leads to acceleration of cyclization at the NH group in the 4d position of the pyridine ring; the process of pyrimidine cyclization is accompanied by hydrolysis of the acylamidine group in the 2 position with formation of an amide group.

Analogously, upon reaction of the ethoxycarbonyl derivative Ib with the acetal II, we obtained the amidine IIIb, from which upon heating in acetic acid we synthesized the tricyclic pyrimidine IVb.

It is quite understood that when a dimethylamino group is present on the pyrimidine ring, only cyclization of another type is possible: with formation of a derivative of pyrido[3,2:4',5'[thieno[3,2-d]pyrimidine (V). With the goal of obtaining these compounds by reaction of the aminoethoxycarbonyl derivative Ic with the acetal II, we obtained the amidine IIIc, heating of which with primary amines in acetic acid leads to 3-substituted-4-

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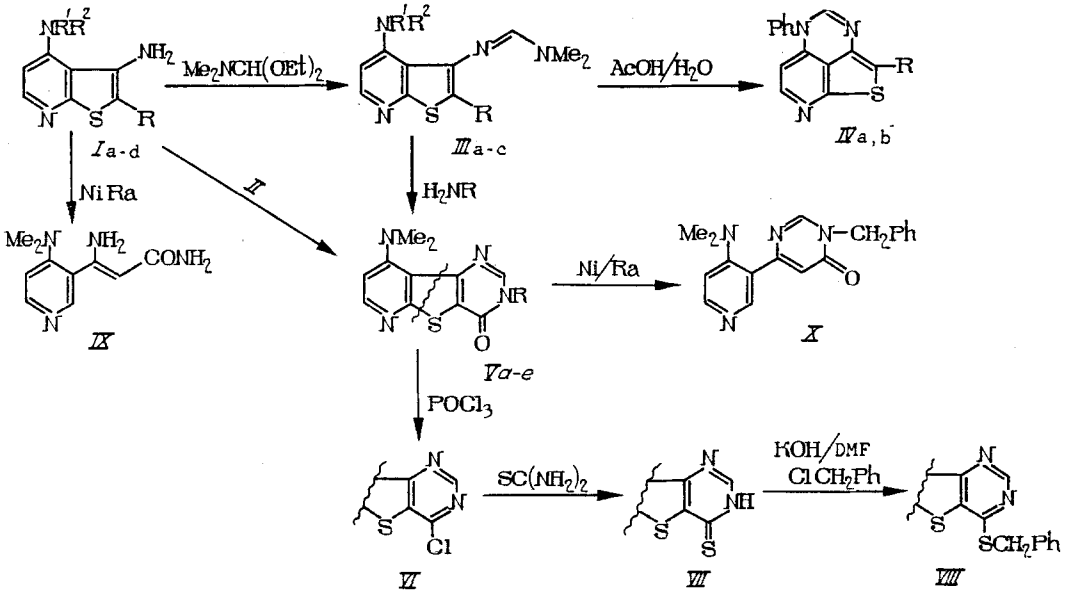
oxo-3,ing anilino derivatives Ia, b: while the latter are condensed with II in boiling toluene in 1 h, boiling for 9 h is required for compounds Ic, d.

This circumstance is probably due to the higher degree of steric shielding of the amino group in the 3 position of thienopyridines Ic, d by the dimethylamino group in the 4 position, compared with the NHPh substituent, which follows from consideration of Deriding molecular models.

In order to determine the feasibility of using compounds of type V for synthesis of various derivatives of this tricyclic system, for the example of N-unsubstituted pyrimidin-2-one (Vf) we synthesized the chloro- (VI), mercapto- (VII), and benzylmercapto derivatives (VIII), as shown below.



R^1=H, R^2=Ph (Ia-b; IIIa,b); R^1=R^2=Me (Ic,d IIIc); R=$CONH_2$ (Ia), $CONHCH_2Ph$ (Id); CON=$CHNMe_2$ (IIIa; COOEt (Ib,c; IIIb,c; IVb); CONHCHO (IVa), CH_2Ph (Va); Ph (Vb); C_6H_4Cl-p (Vc); C_6H_4Me-p (Vr); C_6H_4·OMe-*n* (Ve); H (Vf).

In our work, we studied desulfurization of both the bicycle Ia and the tricyclic derivative Va under the action of Raney nickel. The first method opens up to possibility of synthesis of α-pyridyl-3-enamines; the second method, 6-(pyridyl-3)-pyrimidine derivatives. In both cases, we established that the desulfurization process proceeds with difficulty, and large excesses of Raney nickel are required. Nevertheless, using the indicated method we could obtain in moderate yields compounds IX and X, the synthesis of which by other methods is a complicated problem.

EXPERIMENTAL (CHEMICAL)

The mass spectra of the synthesized compounds were obtained on the MAT-112 spectrometer, ionizing radiation 50 eV, ionization chamber temperature 140°C. The ^1H NMR spectra were recorded on the XL-200 spectrometer, internal standard TMS. The melting points were determined on a Boetius heating stage.

The characteristics of the synthesized compounds are presented in Table 1. The elemental analysis results correspond to the calculated values.

2-[(B-Benzyl)carbamido]-3-amino-4-dimethylaminothieno[2,3-b]pyridine (Id). The synthesis was done according to the technique in [2].

2-[(N,N-Dimethylaminomethylene)carbamido]-3-[(N,N-dimethylaminomethylene)amino]-4-anilinothieno[2,3-b]pyridine (IIIa). DMF diethylacetal (4.4 g, 30 mmoles) was added to a suspension of 2.84 g (10 moles) compound Ia in 10 ml absolute alcohol and boiled for 1 h. The reaction mass was cooled and the precipitate was filtered. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.12; 3.14; 3.15; 3.18 ppm (s 2 NMe_2, 3H each); 6.87 (d, 1H, 5-H, $^3J_{H5,H6}$ = 5.6 Hz; 7.10-7.45 (m, 5H, Ph); 8.02; 8.52 (s, 1H each, N = CH); 8.19 (d, 1H 6-H), 10.40 (br, s, 1H, NH).

TABLE 1. Physicochemical Properties of Synthesized Compounds

Compound	Yield, %	m.p., °C (solvent)	Empirical formula
Id	82	183—185 (acetonitrile)	$C_{17}H_{18}N_4S$
IIIa	76	256—259 (toluene)	$C_{20}H_{22}N_6SO$
IIIb	81	179—181 (alcohol)	$C_{19}H_{20}N_4SO_2$
IIIc	63	145—147 (toluene)	$C_{15}H_{20}N_4SO_2$
IVa	94	284—286 (DMF)	$C_{16}H_{10}N_4SO_2$
IVb	87	235—237 (aq. DMF)	$C_{17}H_{13}N_3SO_2$
Va	91	54—56 (alcohol)	$C_{18}H_{16}N_4SO$
Vb	62	191—193 (toluene)	$C_{17}H_{14}N_4SO$
Vc	75	232—234 (DMF)	$C_{17}H_{13}N_4SOCl$
Vd	77	222—225 (benzene-hexane)	$C_{18}H_{16}N_4SO$
Ve	64	206—208 (toluene)	$C_{18}H_{16}N_4SO_2$
Vf	90	300 (DMF)	$C_{11}H_{10}N_4SO$
VI	88	166—168	$C_{11}H_9N_4SCl$
VII	76	300 (DMF)	$C_{11}H_{10}N_4S_2$
VIII	83	176—176	$C_{18}H_{18}N_4S_2$
IX	56	216—217 (2-propanol)	$C_{10}H_{14}N_4O$
X	61	125—127 (ethylacetate)	$C_{18}H_{18}N_4O$

4-Phenylamino-3-[N,N-dimethylaminomethylene)-carbamido]-2-ethoxycarbonylthieno[2,3-b]pyridine (IIIb). Obtained analogously to compound IIIa.

4-Dimethylamino-3-[(N,N-dimethylaminomethylene)-carbamido]-1-ethoxycarbonylthieno-[2,3-b]pyridine (III). Acetal II (3.3 g, 21 mmoles) was added to a solution of 2.65 g (10 moles) compound Ic in 10 ml dry toluene and boiled for 9 h. The reaction mass was cooled and the precipitate was filtered.

2-(N-Formylcarbamido)-5-phenylthieno[2,3,4-e,d]pyrido[4,3-d]pyrimidine (IVa). A 25 ml portion of 70% acetic acid was added to 3.94 g (10 mmoles) bis-amidine IIIa and heated at 100°C for 30 min. the precipitate was filtered and washed with water $M^+ \cdot 322$.

2-Ethoxycarbonyl-5-phenylthieno[2,3,4-e,d]pyrido[4,3-d]pyrimidine (IV). Obtained analogously to compound IVa.

3,4-Dihydro-3-benzyl-9-dimethylaminopyrido-[3,2:4′,5′]thieno[3,2-d]pyrimidin-4-one (Va. Method A. Benzylamine (0.32 g, 3 mmoles) and 0.05 g p-toluenesulfonic acid was added to a solution of 0.64 g (2 mmoles) amidine IIIc in 15 ml dry toluene and boiled for 5 h. The reaction mass was evaporated under vacuum and the residue was ground with cold isopropanol. Yield, 44%. Method B. Acetal II (1.47 g) was added to a solution of 1.63 g compound Id in 30 ml alcohol and boiled for 10 h. The reaction mass was cooled and the precipitate was filtered. $M^+ \cdot$ 336. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.11 (s, 6H, NMe_2); 5.28 (s, 25, CH_2); 6.75 (d, 1H, 8-CH; $^3J_{H7,H8}$ = 5.5 (Hz); 7.33-7.38 (m 5H, Ph); 8.29 (s, 1H, 2-CH); 8.39 (d, 1H, 7-CH).

the 3-Aryl derivatives of 2,4-Dihydro-9-dimethylaminopyrido[3,2:4′,5′]thieno[3,2-d]pyrimidin-4-one (Vb-e). The corresponding aniline (15 moles) was added to a solution of 3.2 g (10 mmoles) compound IIIc in 10 ml glacial AcOH and heated at 80°C for 20 min. Then the reaction mass was poured into 75 ml cold water; this was neutralized to pH 7 and the precipitate was filtered. ^1H NMR spectrum for compound Vb ($CDCl_3$), δ ppm: 3.17 (s, 6H, NMe_2); 6.80 (d; 1H, 8-CH, $^3J_{H7,H8}$ = 5.6 Hz); 7.49-7.59 (m, 5H, Ph); 8.31 (s, 1H, 2-CH); 8.44 (d, 1H, 7-CH).

3,4-Dihydro-9-dimethylaminopyrido-[3,2;4,5]thieno]3,2-d]pyrimidin-4-one (Vf). Acetal II 4.41 g, mmoles) was added to a suspension of 2.36 g (10 mmoles) bicycle Ib in 20 ml alcohol and boiled with stirring for 9 h. The reaction mass was evaporated under vacuum. 40 ml 70% AcOH was added to the residue and boiled for 40 min. The precipitate was filtered, washed with water, and dried. Obtained: Vf. ^1H NMR spectrum (DMSO-d_6), δ ppm: 3.08 (s, 8.33 (s, 1H, 2-CH); 8.36 (d, 1H, 7-CH); 12.80 (br.s, 1H, NH).

4-Chloro-9-dimethylaminopyrido[3,2:4′,5′]thieno-[3,2-d]pyrimidine (VI). Phosphorus oxychloride (30 ml) and 1 g triethylamine hydrochloride was added to 2.24 g (9 mmoles) compound Vf. The reaction mass was boiled for 5 h. The excess $POCl_3$ was driven off under vacuum. The residue was poured over ice; the pH was brought up to 8 with a solution of NH_3 and it was extracted with chloroform. The extract was dried over $Na_2|SO_4$ and evaporated under vacuum. Obtained: VI.

3,4-Dihydro-9-dimethylaminopyrido[3,2:4′,5′]thieno-[3,2-d]pyrimidin-4-thione (VII). Thiourea (1.14 g, 15 mmoles) was added to a solution of 2.65 g (10 mmoles) of the chloro derivative VI in 30 ml toluene and boiled for 2 h. The reaction mass was cooled. A 60 ml portion of 10% NaOH was added and this was stirred for 30 min. The aqueous layer was separated and acidified with AcOH to pH 5-6. The precipitate of thione VII was filtered.

4-Benzylmercapto-9-dimethylaminopyrido[3,2:4′,5′]thieno[3,2-d]pyrimidine (VIII). A solution of 0.31 g (5.5 mmoles) KOH in 10 ml water was added of a solution of 1.31 g (5 mmoles) thione VII in 10 ml DMF and stirred for 15 min. Then 0.63 g (5 mmoles) benzyl chloride was added and this was stirred for 30 min. The precipitate of compound VIII was filtered.

β-Amino-β-(4-dimethylaminopyrid-3-yl)acrylamide (IX). Raney nickel (25-30 g) was added to a boiling solution of 4.72 g (20 mmoles) bicycle Ia in 300 ml alcohol in small portions over the course of 3-4 h. The end of the reaction was determined chromatographically from the disappearance of the starting compound. The reaction mass was filtered. The filtrate was evaporated under vacuum and the residue was crystallized M^+·206. ^1H NMR spectrum (DMF-d_7), δ, ppm: 2.97 (s, 6H, NMe_2); 4.76 (s, 1H, = CH); 6.30 6.80 (strongly broadened signals, 1h each, $CONH_2$; 6.75 (d, 1H, $^3J_{5H,6H}$ = 5.9 Hz); 7.60 (strongly broadened signals, 1H each, 2H, NH_2); 8.19 (d, 1H, 6-H).

3.Benzyl-6-(4-dimethylaminopyrid-3-yl)pyrimidin-4-one (X). Obtained analogously to compound IX. Obtained analogously to compound IX. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.83 (s, 6H, NMe_2); 5.16 (s, 2H, CH_2); 6.72 (s, 1H = CHCO); 6.74 (d, 5-CH, $^3J_{H5,H6}$ = 5.8 Hz); (narrow multiplet, 5H, Ph); (narrow multiplet, 5H, Ph); 8.25 (s, 1H, 2-CH); 8.30 (d, 1H, 6-CH); 8.44 (s, 1H, -N = CHN-).

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