ACETALS OF LACTAMS AND ACID AMIDES

# XXIX.* SYNTHESIS OF 1,8-NAPHTHYRIDINE AND PYRIDO[2,3-d]PYRIMIDINE DERIVATIVES

E. O. Sochneva, N. P. Solov'eva, and V. G. Granik

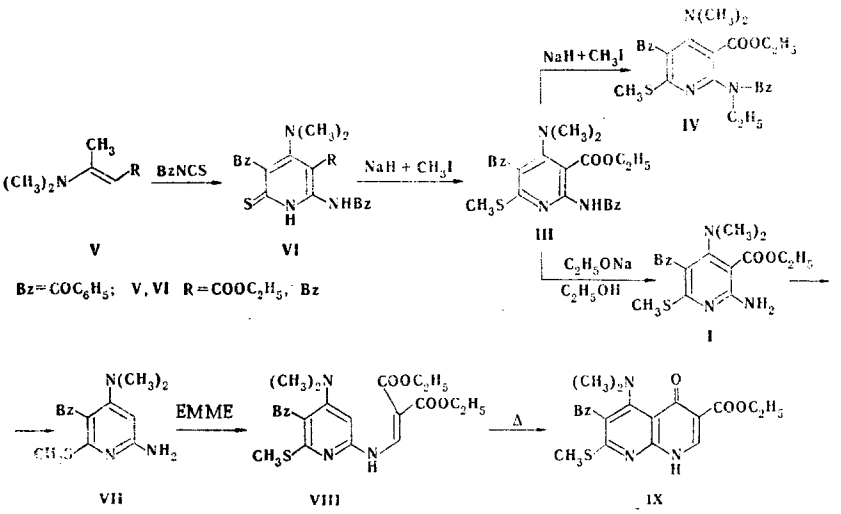
UDC 547.834.2'822.7'824'854

The reaction of acetals of amides and lactams with substituted 2-aminonicotinic acid esters was used to synthesize the corresponding amidines, which undergo cyclization to 1,8-naphthyridine derivatives when they are heated in the presence of acidic or basic catalysts and give pyrido[2,3-d]pyrimidine derivatives on reaction with amines.

It is known that anthranilic [2] and 4-aminopyrimidine-5-carboxylic [3] acid esters readily react with acetals of amides and lactams and that the resulting amidines undergo smooth cyclization to 4-quinolone and pyrido[2,3-d]pyrimidine derivatives, respectively, under acid or base-catalysis conditions.

The goal of the present research was to extend this reaction to the synthesis of 1,8-naphthyridine derivatives and to ascertain some factors that affect this sort of cyclization.

In the first step of the research we selected 2-amino-3-carbethoxy-4-dimethylamino-5-benzoyl-6-methylmercaptopyridine (I), obtained [4] by the reaction of $\beta$-dimethylaminocrotonic ester with benzoyl isothiocyanate (II) and subsequent S-methylation and debenzoylation of the intermediate 2-N-benzoyl-I (III), as the starting compound.† A similar "pyridine" synthesis can also be realized on the basis of other enaminocarbonyl compounds. For example, 2-N-benzamido-3,5-dibenzoyl-4-dimethylaminopyridine-6-thione (VI) was synthesized by reaction of II with 1-dimethylamino-1-methyl-2-benzoylethane (V).




The synthesis of a 1,8-naphthyridine derivative (IX) from aminocarbethoxypyridine I was accomplished via the usual scheme – by saponification of the carbethoxy group – and aminopyridine VII was obtained by de-

*See [1] for communication XXVIII.

†According to [4], III should be obtained in the absence of excess alkylating agent, since further alkylation at the 2-$NHCOC_6H_5$ group is possible. Thus 2-(N-ethyl-N-benzoyl)amino-3-carbethoxy-4-dimethylamino-5-benzoyl-6-methylmercaptopyridine (IV) is formed in the ethylation of III.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1671-1676, December, 1978. Original article submitted April 4, 1978.

0009-3122/78/1412-1359$07.50  

TABLE 1.

| Compound | 2-$CH_3$ | 3-$CH_3$ | 4-$CH_2$ | 5-$CH_2$ | N-$CH_3$ | 5-CH | 6-CH | 7-CH | 8-CH | $C_6H_5$ |
|---|---|---|---|---|---|---|---|---|---|---|
| XXIV | — | 6,83 (3-CH=) | | | 3,57 | 8,25 | 9,13 | — | — | 7,5—8,3 |
| XIX* | 3,35 | 1,90 | 2,58 | — | 3,13 | — | 6,75 | — | — | ⊢ |
| XXV | 4,25 | 3,37 | — | — | 3,48 | 8,27 | 9,06 | — | — | 7,6—8,4 |
| XXVI | 3,87 | 3,00 | 2,24 | — | 3,63 | — | 8,20 | 9,15 | — | 7,6—8,05 |
| XXVII | 4,05 | 2,18 | | 3,13 | 3,58 | — | — | 8,21 | 9,13 | 7,5—8,3 |

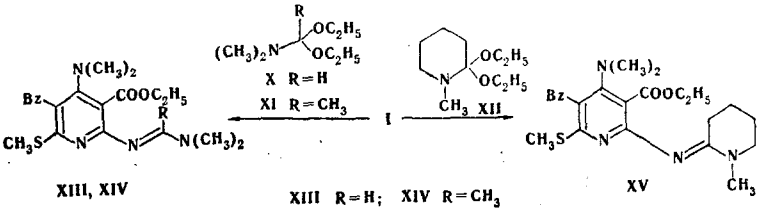
*There are signals of 6-C−$CH_3$ at 2.45 ppm and 7-C−$CH_3$ at 2.83 ppm.

TABLE 2. Synthesized Compounds

| Compound | mp, deg°C (solvent) | Found, % | | | | Empirical formula | Calculated, % | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | S | | C | H | N | S | |
| XIII | 110—112 (alcohol) | 61,0 | 6,5 | 13,4 | 7,7 | $C_{21}H_{26}N_4SO_3$ | 61,0 | 6,3 | 13,6 | 7,8 | 84 |
| XIV | 127—130 (alcohol) | 61,4 | 7,0 | 13,1 | 7,5 | $C_{22}H_{28}N_4SO_3$ | 61,7 | 6,6 | 13,1 | 7,5 | 86 |
| XV | 201—203 (isopropanol) | 63,3 | 6,3 | 12,2 | 7,7 | $C_{24}H_{30}N_4SO_3$ | 63,5 | 6,6 | 12,1 | 7,1 | 64 |
| XVII | 63—66 (heptane) | 62,7 | 7,7 | 16,8 | — | $C_{13}H_{19}N_3O_2$ | 62,7 | 7,7 | 16,9 | — | 91 |
| XXIV | 251—254 (alcohol) | 72,4 | 5,6 | 15,8 | — | $C_{16}H_{15}N_3O$ | 72,4 | 5,7 | 15,8 | — | 52 |
| XXV | 318 (DMF) | 73,3 | 5,6 | 14,8 | — | $C_{17}H_{15}N_3O$ | 73,6 | 5,5 | 15,1 | — | 32 |
| XXVII | 242—245 (DMF) | 74,9 | 6,2 | 13,7 | — | $C_{19}H_{19}N_3O$ | 74,7 | 6,3 | 13,8 | — | 71 |
| XXIX b | 155—158 (isopropanol) | 72,2 | 5,5 | 15,9 | — | $C_{16}H_{15}N_3O$ | 72,5 | 5,7 | 15,8 | — | 88 |
| XXIX c | 181—183 (isopropanol) | 73,1 | 6,6 | 15,3 | — | $C_{17}H_{17}N_3O$ | 73,0 | 6,1 | 15,1 | — | 73 |
| XXIX d | 225—227 (DMF) | 76,4 | 4,9 | 13,5 | — | $C_{20}H_{15}N_3O$ | 76,6 | 4,8 | 13,4 | — | 35 |
| XXXI a | 219—222 (DMF)−$H_2O$ 1 : 1) | 64,6 | 4,9 | 23,4 | — | $C_{13}H_{12}N_4O$ | 65,0 | 5,0 | 23,3 | — | 61 |
| XXXI b | 122—124 (DMF)−$H_2O$, 1 : 1) | 66,3 | 5,6 | 22,1 | — | $C_{14}H_{14}N_4O$ | 66,1 | 5,5 | 22,1 | — | 54 |
| XXXI c | 223—226 (DMF)−$H_2O$, 1 : 1) | 63,8 | 4,6 | 24,5 | — | $C_{12}H_{10}N_4O$ | 63,7 | 4,4 | 24,8 | — | 51 |

carboxylation. Reaction of the latter with ethoxymethylenemalonic ester (EMME) was used to synthesize N-heteryleneamine VIII, heating of which in Dowthern leads to 3-carbethoxy-5-dimethylamino-6-benzoyl-7-methylmercapto-4-naphthyridone (IX).

However, although complications were not observed in the reaction of I with dimethylformamide diethylacetal (X), dimethylacetamide diethylacetal (XI), and N-methylpiperidone diethylacetal (XII), we were unable to accomplish the naphthyridine synthesis on the basis of amidines XIII-XV. It should be noted that the "amidine" dimethylamino group appears in the PMR spectrum of XIII in the form of two signals (3.03 and 3.14 ppm) of equal intensity; this is probably associated with hindered rotation relative to the C−N bond. It is important that in the spectrum of amidine XIV this dimethylamino group shows up as a singlet (3.03 ppm). This difference between these similarly constructed compounds is evidently due to the fact that XIV contains steric hindrance to "amidine" conjugation,* and the order of the C−N bond is lower than in XIII. Hence the barrier to rotation is higher in amidine XIII.




The application of the usual methods [2, 3] for the cyclization of amidines was unsuccessful: We were unable to synthesize the corresponding naphthyridines from amidines XIV and XV either under acid-catalysis conditions (p-TsOH) or when we used a basic catalyst (BuONa).

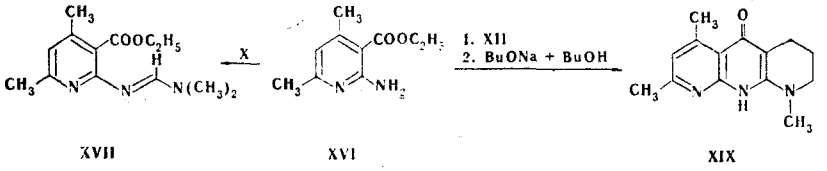
The lack of an analogy with amidines obtained on the basis of amide and lactam acetals and anthranilic and 4-aminopyrimidine-5-carboxylic acid derivatives [2, 3] led us to the assumption of steric hindrance to cyclization arising because of the presence of a bulky dimethylamino group in the 4 position of the pyridine ring. In the next stage of the research we therefore subjected 2-amino-3-carbethoxy-4,6-dimethylpyridine (XVI) [6],

*We have previously observed inhibition of conjugation in an amidine system due to steric hindrance in the case of N-(4-carbethoxy-5-pyrazolinyl)amidines [5].

i.e., a compound with a less bulky substituent in the 4 position, to reaction with acetal XII. This compound (XVI) also reacts smoothly with acetals X and XII, and, as in the case of amidine XIII, two singlets of equal intensity (at 2.98 and 3.02 ppm), which are related to the dimethylamino group, are observed in the PMR spectrum of amidine XVII, i.e., rotation of this group relative to the C–N bond is hindered.

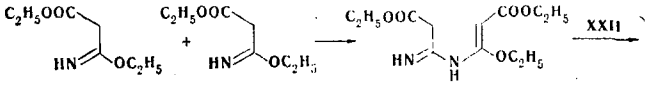
1,6,8-Trimethyl-5-oxo-1,2,3,4,5,10-hexahydropyrido[2,3-b]1,8-naphthyridine (XIX) can be synthesized, although in relatively low yield, by heating amidine XVIII, obtained from acetal XII and pyridine XVI, in a solution of BuONa in BuOH.

The structure of three-ring compound XIX was proved by means of its PMR (Table 1) and mass spectra. A molecular-ion peak with m/e 243 and $(M-H)^+$, $(M-CH_3)^+$, and $(M-OH)^+$ fragments are observed in the mass spectrum of XIX; the formation of the peak of the latter ion constitutes evidence for fragmentation of the substance from the hydroxy form. The presence in the spectrum of peaks with m/e 214, 199, 187, 173, and 159 can be explained by stepwise fragmentation of the saturated ring.

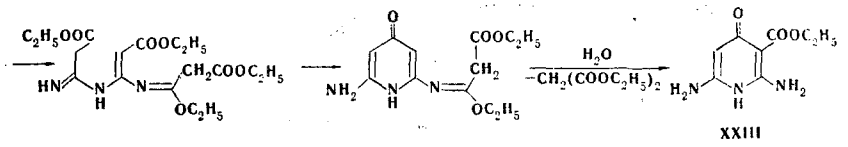



XVII XVI XIX

2-Amino-3-carbethoxy-6-phenylpyridine (XX), which was obtained by the method in [6] by reaction of formylacetophenone (XXI) with imino ester XXII, was next subjected to reaction; 2,6-diamino-3-carbethoxy-4-pyridone (XXIII), which is probably formed via the following scheme (by trimerization of XXII), was isolated as a side product:

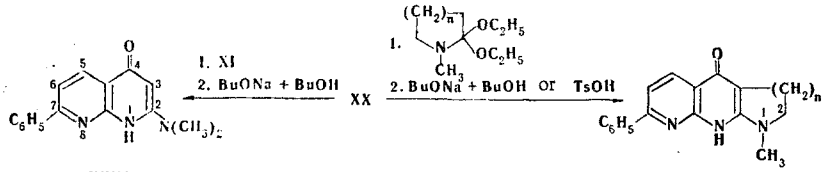



XXII XXII




XXIII

The absence of a substituent in the 4 position of the pyridine ring in XX has a distinct effect on the ability of amidines* synthesized from XX and amide and lactam acetals to undergo cyclization to naphthyridine derivatives (XXIV-XXVIII). Intramolecular cyclization proceeds smoothly and gives the products in good yields both in the presence of p-TsOH and in the case of catalysis by sodium butoxide (this was demonstrated in the case of the preparation of XXVI).

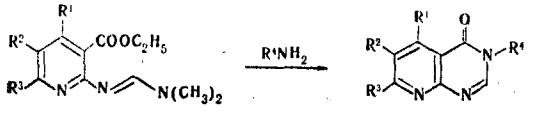



XXIV XXV–XXVII, n = 1–3

The structures of naphthyridone XXIV and three-ring compounds XXV-XXVII were confirmed by the PMR-spectral data (Table 1).

The synthesis of N-heterylamidines from amide and lactam acetals also makes it possible to use them for another purpose – for the preparation of pyrido[2,3-d]pyrimidine derivatives.

*The intermediate amidines were not isolated from the reaction mixture. The degree of their formation was monitored by chromatography, after which they were cyclized to 1,8-naphthyridine derivatives XXIV-XXVII.

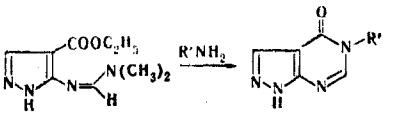


XIII, XVII, XXVIII XXIX

XIII $R^1$=$NMe_2$, $R^2$=Bz, $R^3$=SMe; XVII $R^1$=$R^3$=Me, $R^2$=H; XXVIII $R^3$=Ph, $R^1$=$R^2$=H;
XXIX a $R^1$=$PhCH_2NH$, $R^2$=Bz, $R^3$=SMe, $R^4$=$PhCH_2$; b $R^1$=$R^3$=Me, $R^2$=H, $R^4$=$PhCH_2$;
c $R^1$=$R^2$=Me, $R^3$=Ph, $R^4$=$PhCH_2CH_2$; d $R^1$=$R^2$=H, $R^3$=Ph, $R^4$=$PhCH_2$

Amidine XXIII was obtained from aminopyridine XX and dimethylformamide acetal X and, without isolation, was subjected to reaction with benzylamine. Substituted pyrido[2,3-d]pyrimidines (XXIXa-d) are formed from the amidines smoothly and in high yields. It is interesting to note that the dimethylamino group in the 4 position of the ring is replaced by a benzylamino group in the reaction of XIII with benzylamine. A singlet of an S-Me group at 2.47 ppm, a doublet from a methylene link of the $PhCH_2N$ group at 3.92 ppm, a singlet of a methylene group of 6-$CH_2Ph$ at 5.15 ppm, a triplet of a 4-NH group at 9.91 ppm, a 7-H singlet at 8.73 ppm, and a multiplet of protons of three phenyl rings at 6.8-7.8 ppm are observed in the PMR spectrum ($d_6$-DMSO + $CCl_4$) of the result resulting pyridopyrimidine XXIXa.

The reaction to obtain condensed pyrimidines from compounds that have carbethoxy and amidino groups in adjacent positions of the heteroring can also be extended to other variants. We have demonstrated this in the case of the previously synthesized [5] N-(4-carbethoxy-3-pyrazolinyl)amidines (XXX); as a result, we obtained 5-substituted derivatives of pyrazolo[3,4-d]pyrimidine (XXXIa-c).



XXX XXXIa-c

XXXI a R'=$C_6H_5CH_2CH_2$; b R'=$C_6H_5CH_2CH(CH_3)$;
c R'=$C_6H_5CH_2$

In conclusion, we note that if one assumes that the differences in the ability to undergo intramolecular cyclization of amidines to 1,8-naphthyridine derivatives depend on the volume of the grouping in the 4 position of the pyridine ring, it turns out that these cyclizations are considerably more sensitive to steric hindrance than the reactions to form condensed pyrimidines. This in turn implies differences in the transition states of these processes and makes it possible to assume that conversion of the ester group to an amido group primarily takes place in the preparation of pyrido[2,3-d]pyrimidines, whereas transamination of the amidine fragment occurs in the second step.

## EXPERIMENTAL

The IR spectra of mineral oil pastes of the compounds were obtained with a Perkin-Elmer 457 spectrometer. The PMR spectra of the compounds were obtained with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with an MKh-1303 mass spectrometer equipped for direct introduction of the samples into the source at an ionizing-emission energy of 50 eV.

2-(N-Ethyl-N-benzamido)-3-carbethoxy-4-dimethylamino-5-benzoyl-6-methylmercaptopyridine (IV). A 0.3-g (12.5 mmole) sample of sodium hydride was added to 5 g (11.2 mmole) of III in a mixture of 140 ml of DMF and 28 ml of dry toluene, and a solution of 1.75 g (11.2 mmole) of ethyl iodide in 10 ml of DMF was added with cooling and stirring. The mixture was then stirred at 20°C for 4 h, after which it was allowed to stand overnight. It was then subjected to vacuum evaporation, water was added to the residue, and the aqueous mixture was extracted with ether. Workup of the extract gave 2.85 g (52%) of IV with mp 124-126°C (from alcohol). Found: C 65.9; H 5.9; N 8.6; S 6.5%. $C_{27}H_{29}N_3O_4S$. Calculated: C 65.5; H 5.7; N 8.8; S 6.9%.

2-N-Benzamido-3,5-dibenzoyl-4-dimethylamino-6-mercaptopyrimidine (VI). A solution of 2 g (10.6 mmole) of enamino ketone V in 15 ml of dry chloroform was added dropwise with ice cooling in the course of 20 min to a solution of 3.42 g (21 mmole) of benzoyl isothiocyanate in 15 ml of dry chloroform, and the mixture was refluxed for 1 h. It was then cooled and filtered to give 0.55 g of VI. Workup of the mother liquor gave an additional 0.85 g of VI for an overall yield of 27% of a product with mp 260-262°C (from DMF). Found: C 69.4; H 4.8; N 8.8; S 6.6%. $C_{22}H_{22}N_3O_3S$. Calculated: C 69.9; H 4.8; N 8.7; S 6.7%.

2-N-(2,2-Dicarbethoxymethylene)-amino-4-dimethylamino-5-benzoyl-6-methylmercaptopyridine (VIII). A mixture of 2 g (6.9 mmole) of VII and 1.5 g (6.9 mmole) of EMME was heated at 150°C for 30 min, after which alcohol was added, and the mixture was filtered to give 2.5 g (79%) of VIII with mp 130-135°C (from alcohol). Found: C 60.6; H 6.0; N 9.2; S 6.9%. $C_{23}H_{26}N_3O_5S$. Calculated: C 60.5; H 5.7; N 9.2; S 7.1%.

3-Carbethoxy-5-dimethylamino-6-benzoyl-7-methylmercapto-1,8-naphthyrid-4-one (IX). A mixture of 1.5 g (3.3 mmole) of VIII and 22.5 g of Dowtherm was heated at 280°C for 30 min, after which it was cooled, a mixture (1:1) of hexane and ether was added, and the resulting mixture was worked up to give 1.1 g (81%) of IX with mp 158-161°C (from alcohol). PMR spectrum (in $CD_3OD$): 1.37 and 4.34 ($COOC_2H_5$), 2.49 ($SCH_3$), 2.67 ($NCH_3$), 8.45 (2-H), and 7.35-7.80 ($C_6H_5$) ppm. Found: C 58.5; H 5.8; N 9.5; S 7.5; $H_2O$ 4.2%. $C_{21}H_{21}N_4O_4S$. Calculated: C 58.9; H 5.4; N 9.8; S 7.5; $H_2O$ 4.2%.

2-(N',N'-Dimethylaminomethylene)amino-3-carbethoxy-4-dimethylamino-5-benzoyl-6-methylmercapto-pyridine (XIII). A mixture of 2 g (5.6 mmole) of I and 0.91 g (6.2 mmole) of acetal X in 15 ml of dry toluene was refluxed for 3 h, after which the toluene was removed by vacuum distillation to give 1.95 g (84%) of amidine XIII with mp 110-112°C (from alcohol). Found: C 61.0; H 6.5; N 13.4; S 7.7%. $C_{21}H_{26}N_4O_3S$. Calculated: C 61.0; H 6.3; N 13.6; S 7.8%. Amidines XIV, XV, XVII, and XVIII were similarly synthesized (Table 2).

2,6-Diamino-3-carbethoxy-4-pyridone (XXIII). The reaction was carried out by a known method [6]. The ether was then removed by distillation, aqueous alcohol was added, and the mixture was refluxed for 5 h. The precipitated XX was removed by filtration, and the mother liquor was worked up to give XXIII, with mp 194-196°C and $M^+$ 197, in 3% yield. IR spectrum: 1620, 1640 (C=O, C=C), 1730 ($COOOCH_3$), 3200, 3300, 3465 (CH, $CH_2$) $cm^{-1}$. Found: C 48.7; H 5.8%. $C_8H_{11}N_3O_3$. Calculated: C 48.7; H 5.6%.

1,6,8-Trimethyl-5-oxo-1,2,3,4,5,10-hexahydropyrido[2,3-b]naphthyridine (XIX). A mixture of 6 g (32 mmole) of XVI and 6.55 g (3.5 mmole) of N-methylvalerolactam diethylacetal (XII) in 50 ml of dry toluene was refluxed for 8 h, after which the toluene was removed by vacuum distillation, and the residue was added to a solution of BuONa (from 1.2 g of Na and 80 ml of BuOH). The mixture was refluxed for 4 h, and the precipitate was removed by filtration and dissolved in water. The aqueous solution was acidified to pH ~ 6 with dilute HCl and extracted with chloroform. The combined extracts were dried with $Na_2SO_4$ and subjected to evaporation to give 2.63 g (34%) of XIX with mp 218°C (from iso-PrOH) and $M^{+\cdot}$ 243. Found: N 17.24%. $C_{14}H_{17}N_3O$. Calculated: N 17.28%.

1-Methyl-5-oxo-8-phenyl-1,2,3,4,5,10-hexahydro[2,3-b]-1,8-naphthyridine (XXVI). A mixture of 2.1 g (8.71 mmole) of XX and 1.8 g (9.6 mmole) of XII in 20 ml of dry toluene was refluxed for 7 h, after which it was evaporated to dryness. The resulting amidine was cyclized by two methods.

A) The amidine was heated in the presence of a catalytic amount of TsOH at 180°C for 15 min, after which alcohol was added, and the mixture was worked up to give 1.85 g (73%) of XXVI with mp 258-260°C (from DMF). Found: C 74.3; H 6.0; N 14.5%. $C_{18}H_{17}N_3O$. Calculated: C 74.2; H 5.8; N 14.4%.

B) The amidine was refluxed in a solution of BuONa for 3 h, and the mixture was then worked up as in the case of XIX to give XXVI, with mp 258-260°C (from DMF), in 69% yield. Compounds XXIV, XXV, and XXVII were synthesized by method B (Table 2).

2-Methylmercapto-3-benzoyl-4-benzylamino-5-oxo-6-benzylpyrido[2,3-d]pyrimidine (XXIXa). A mixture of 1.25 g (3.02 mmole) of amidine XIII and 0.65 g (6.04 mmole) of benzylamine was heated at 175°C for 1.5 h, after which it was cooled, treated with alcohol, and worked up to give 0.7 g (56%) of XXIXa with mp 178-181°C (aqueous DMF). Found: C 70.4; H 4.8; N 11.3; S 6.4%. $C_{29}H_{24}N_4O_2S$. Calculated: C 70.7; H 4.9; N 11.4; S 6.5%. Pyridopyrimidines XXIXb-d and pyrazolo[3,4-d]pyrimidines XXXIa-c were similarly obtained (Table 2).

## LITERATURE CITED


1. V. G. Granik, I. V. Persianova, A. M. Zhidkova, N. B. Marchenko, R. G. Glushkov, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 12, 1666 (1978).
2. A. M. Zhidkova, V. G. Granik, R. G. Glushkov, T. F. Vlasova, O. S. Anisimova, T. A. Gus'kova, and G. N. Pershin, Khim. Geterotsikl. Soedin., No. 5, 670 (1974).
3. V. G. Granik, N. B. Marchenko, and R. G. Glushkov, Khim. Geterotsikl. Soedin., No. 11, 1549 (1978).
4. R. W. J. Carney, J. Wojtkunski, B. Fechtig, R. T. Puckett, B. Biffar, and G. de Stevens, J. Org. Chem., 36, 2602 (1970).
5. V. G. Granik, E. O. Sochneva, and I. V. Persianova, Khim. Geterotsikl. Soedin., No. 3, 379 (1978).
6. A. Dornow and P. Karlson, Ber., 73, 542 (1940).