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NEW CONVENIENT SYNTHESIS OF SUBSTITUTED 6,9-DIHYDROPYRIDO[3′,2′:4,5]THIENO[3,2-*b*]PYRIDINES AND 6,9-DIHYDROPYRIDO[3′,2′:4,5]THIENO[3,2-*d*]PYRIMIDINES

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1,4-Dihydro-3-cyano-2-pyridinethiolates react with 2-bromo-1-(4-bromophenyl)ethylidenemalononitrile or N-cyanochloracetamidine to give 6,9-dihydropyrido[3′,2′:4,5]thieno[3,2-b]pyridines or 6,9-dihydropyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidines, respectively.

Some hydrogenated pyridine derivatives display various biological properties including cardiotonic activity [1]. Special interest is found in hydrogenated pyridines condensed with other heterocycles, which combine several useful properties in a single molecule. Bicyclic hydrogenated systems have been studied by several workers [2-7] but tricyclic systems of this class have not yet been described.

We have developed a new synthesis for dihydropyridothienopyridines and dihydropyridothienopyrimidines using 1,4-dihydro-3-cyano-2-pyridinethiolates (I), 2-bromo-1-(4-bromophenyl)ethylidenemalononitrile (II), and N-cyanochloracetamidine (III). Reagents II and III have similar three-dimensional and electronic structure with a labile halogen atom bound to an acidic methylene unit. The electron-withdrawing group responsible for the acidity of the methylene unit contains a CN moiety in the α-position capable of condensation. This accounts for the similarity of their reactions with I and the conditions, under which these reactions proceed. However, there are definite differences in the behavior of II and III.

The first step features regioselective alkylation of dihydropyridinethiolates I by II and III at the sulfur atom to give IV and V, respectively. When 2-bromoethylidenemalononitrile II is used, this reaction proceeds readily with the piperidine salt of II, while in the case of N-cyanochloracetamidine III whose halogen atom is less active in nucleophilic substitution, the piperidine salt of I must be converted to the potassium salt by adding to KOH to the reaction mixture.

The replacement of the halogen atom by sulfur in II and III markedly enhances the acidity of the methylene group, thereby facilitating the Thorpe–Ziegler condensation in products IV and V. This condensation proceeds spontaneously under the reaction conditions. Thus, IV and V could not be isolated. This condensation leads to closure of a thiophene ring to give dihydrothienopyridines VI and VII, respectively.

The amino and cyano groups in VI and VII are favorably arranged for closure of a six-membered ring, which, as shown in our previous work [8], may be catalyzed either by acid or base. Cyclization in the case of the malononitrile derivatives proceeds spontaneously under the reaction conditions and VI could not be isolated. The final products, 6,9-dihydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines (VIII) were obtained directly. Spontaneous cyclization is not found for the cyanoamidine derivatives, in which the electrophilicity of the nitrile group is reduced due to conjugation with the nitrogen atom, and VII may be isolated from the reaction mixture. Products VII undergo acid-catalyzed closure of the diaminopyrimidine ring using HCl in methanol to give 6,9-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines (IX).

The mildness of the conditions in all steps permits retention of the unaltered 1,4-dihydropyridine system and this method is the only procedure yielding triply fused hydrogenated pyridines. Thus, we are the first to report a regioselective synthesis for functionally substituted 6,9-dihydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines and 6,9-dihydro-pyrido[3′,2′:4,5]-thieno[3,2-*d*]pyrimidines.

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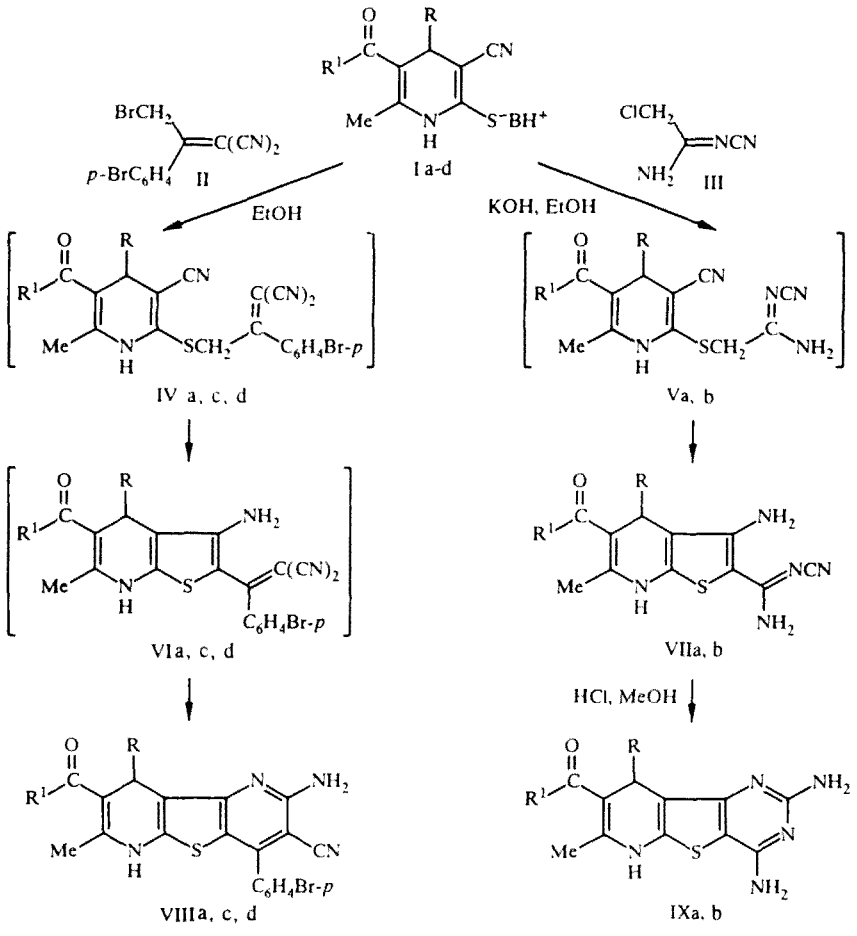

B = piperidine , I, IV—IX a R = C_6H_4OMe-*p*, R^1 = OEt; b R = C_6H_4F-*p*, R^1 = Me; c R = $C_6H_4NO_2$-*o*, R^1 = Me; d R = 2-thienyl , R^1 = OEt

EXPERIMENTAL

The IR spectra were taken on a Specord M-80 spectrometer for KBr pellets. The ^1H NMR spectra were taken on a Bruker WM-250 spectrometer at 250 MHz in DMSO-d_6. The elemental analysis was carried out on a Perkin-Elmer C,H,N analyzer. The yields and indices of the products are given in Table 1.

Starting reagents Ia-Id [2], II [10], and III [11] were obtained according obtained according to reported procedures.

3-Amino-2-(aminocyanoiminomethyl)-4,7-dihydrothieno[2,3-*b*]pyridines (VIIa,b). A sample of 5.0 mmoles KOH as a 10% aqueous solution and 5.1 mmoles N-cyanochloracetamidine III were added to a solution of 5 mmoles Ia or Ib in 20 ml ethanol. The mixture was maintained for 0.5 h at room temperature. Water was added until slight turbulence was noted and the mixture was left to crystallize overnight. Crystalline VII was filtered off, washed with water, and dried in the air.

2-Amino-6,9-dihydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines (VIIIa,c,d). A sample of 5.1 mmoles 2-bromo-1-(4-bromophenyl)ethylidenemalononitrile II was added to a solution of 5.0 mmole Ia, Ic, or Id. The mixture obtained was maintained for 10 min at 40°C and for about 16 h at room temperature. The crystalline precipitate of VIII was filtered off, washed with ethanol and hexane, and dried in the air.

2,4-Diamino-6,9-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines (IXa,b). A sample of 2 ml 35% hydrochloric acid was added to a suspension of 5.0 mmoles thienopyridine VIIa or VIIb in 20 ml methanol and stirred for 2 h at room temperature. The reaction mixture was then neutralized by adding aqueous sodium carbonate. The crystalline precipitate of IX was filtered off, washed with ethanol and hexane, and dried in the air.

TABLE 1. Physical Indices of Products

Compound	Mp, °C	Chemical formula	Found, % / Calculated, %			IR spectrum, cm^{-1}	PMR spectrum in DMSO-d_6, ppm, coupling constant (J), Hz	Yield, %
			C	H	N			
VIIa	276	$C_{20}H_{21}N_5O_3S$	58,44 58,38	5,09 5,14	17,23 17,02	3428, 3302, 3207 (NH), 2184, 2153 (CN), 1697 (C=O), 1645 (C=N)	1,15 (3H, t, J = 7, $CH_2\underline{CH_3}$), 2,25 (3H, s, 6-CH_3), 3,66 (3H, s, OCH_3), 3,93 (2H, q, J = 7, $\underline{CH_2}CH_3$), 4,95 (1H, s, 4-H), 6,74 and 7,16 (4H, AA'BB', H_{Ar}), 6,75 (2H, s, 3-NH_2), 7,34 (2H, s, NH_2 amidine), 9,95 (1H, s, 7-NH)	99
VIIb	196...197	$C_{18}H_{16}FN_5OS$	58,39 58,52	4,38 4,37	19,20 18,96	3452, 3324, 3180 (NH), 2178, 2138 (CN), 1668 (C=O), 1608 (C=N)	2,12 (3H, s, 6-CH_3), 2,31 (3H, s, $COCH_3$), 5,17 (1H, s, 4-H), 6,98 (2H, s, 3-NH_2), 7,05 (2H, t, J = 9, 3,5-H_{Ar}), 7,32 (2H, d. d, J_1 = 9, J_2 = 5,5, 2,6-H_{Ar}), 7,39 (2H, s, NH_2 amidine), 10,07 (1H, s, 7-NH)	81
VIIIa	208...209	$C_{28}H_{23}BrN_4O_3S$	58,52 58,44	4,10 4,03	9,65 9,74	3460, 3322 (NH), 2210 (CN), 1690 (C=O), 1625 (C=N)	1,20 (3H, t, J = 7, $CH_2\underline{CH_3}$), 2,40 (3H, s, 7-CH_3), 3,69 (3H, s, OCH_3), 4,05 (2H, q, J = 7, $\underline{CH_2}CH_3$), 5,32 (1H, s, 9-H), 6,70 (2H, s, 2-NH_2), 6,76 and 7,27 (4H, AA'BB', H-9_{Ar}), 7,56 and 7,82 (4H, AA'BB', $H_{4\text{-}Ar}$), 10,21 (1H, s, 6-NH)	82
VIIIc	210...212	$C_{26}H_{18}BrN_5O_3S$	55,68 55,72	3,33 3,24	12,65 12,50	3480, 3380 (NH), 2210 (CN), 1645 (C=O), 1604 (C=N), 1533 (NO_2)	2,15 (3H, s, 7-CH_3), 2,37 (3H, s, $COCH_3$), 6,01 (2H, s, 2-NH_2), 6,34 (1H, s, 9-H), 7,37 (1H, d.d.d, J_1 = 8,4, J_2 = 6,7, J_3 = 2,1, 4'-H 9_{Ar}), 7,50 and 7,75 (4H, AA'BB', 4_{Ar}), 7,54...7,69 (2H, m, 5',6'-$H_{9\text{-}Ar}$), 7,85 (1H, d.d, J_1 = 8,4, J_2 = 1, 3'-$H_{9\text{-}Ar}$), 13,5 (1H, br.s, 6-NH)	41
VIIId	270	$C_{25}H_{19}BrN_4O_2S_2$	54,51 54,45	3,42 3,47	10,02 10,16	3450, 3290 (NH), 2210 (CN), 1680 (C=O), 1620 (C=N)	1,20 (3H, t, J = 7, $CH_2\underline{CH_3}$), 2,38 (3H, s, 7-CH_3), 4,09 (2H, q, J = 7, $\underline{CH_2}CH_3$), 5,65 (1H, s, 9-H), 6,78 (2H, s, 2-NH_2), 6,83 (2H, m, 3',4'-$H_{9\text{-thienyl}}$), 7,19 (1H, d, J = 5, 5'-$H_{9\text{-thienyl}}$), 7,56 and 7,80 (4H, AA'BB', $H_{4\text{-}Ar}$), 10,33 (1H, s, 6-NH)	55
IXa	185...186	$C_{20}H_{21}N_5O_3S$	58,31 58,38	5,22 5,14	17,16 17,02	3480, 3350 (NH), 1695 (C=O), 1610 (C=N)	1,15 (3H, t, J = 7, $CH_2\underline{CH_3}$), 2,32 (3H, s, 7-CH_3), 3,65 (3H, s, OCH_3), 4,01 (2H, q, J = 7, $\underline{CH_2}CH_3$), 5,19 (1H, s, 9-H), 5,70 (2H, s, 2-NH_2), 6,50 (2H, s, 4-NH_2), 6,73 and 7,16 (4H, AA'BB', H_{Ar}), 9,89 (1H, s, 6-NH)	67
IXb	216...217	$C_{18}H_{16}FN_5OS$	58,48 58,52	4,33 4,37	19,15 18,96	3324, 3210 (NH), 1652 (C=O), 1600 (C=N)	2,08 (3H, s, 7-CH_3), 2,38 (3H, s, $COCH_3$), 5,32 (1H, s, 9-H), 5,80 (2H, s, 2-NH_2), 6,57 (2H, s, 4-NH_2), 7,01 (2H, t, J = 8,5, 3'-, 5'-H_{Ar}), 7,38 (2H, d.d, J_1 = 8,5, J_2 = 5,5, 2'-, 6'-H_{Ar}), 10,04 (1H, s, 6-NH)	80

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REFERENCES

1. A. Sausins and G. Duburs, Heterocycles, **27**, 269 (1988).
2. V. P. Litvinov, V. K. Promonenkov, Yu. A. Sharanin, A. M. Shestopalov, L. A. Rodinovskaya, V. Yu. Mortikov, and V. S. Bogdanov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 2101 (1985).
3. Yu. A. Sharanin, A. M. Shestopalov, L. A. Rodinovskaya, V. N. Nesterov, V. E. Shklover, Yu. T. Struchkov, V. K. Promonenkov, and V. P. Litvinov, Zh. Org. Khim., **22**, 2600 (1986).
4. Yu. A. Sharanin, M. P. Goncharenko, and A. M. Shestopalov, Zh. Org. Khim., **21**, 2470 (1985).
5. A. A. Krauze, R. O. Vitolinya, M. Z. Romanova, and G. Ya. Dubur, Khim.-farm. Zh., **22**, 855 (1988).
6. A. A. Krauze, E. E. Liepin'sh, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 4, 563 (1988).
7. A. A. Krauze, E. E. Liepin'sh, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 1, 115 (1990).
8. V. L. Ivanov, V. A. Artemov, L. A. Rodinovskaya, A. M. Shestopalov, V. N. Nesterov, and V. P. Litvinov, Khim. Geterotsikl. Soedin., No. 1, 115 (1996).
9. V. L. Ivanov, V. A. Artemov, L. A. Rodinovskaya, A. M. Shestopalov, V. N. Nesterov, and V. P. Litvinov, Khim. Geterotsikl. Soedin., No. 1, 115 (1996).
10. M. Susse and S. Johne, J. Prakt. Chem., **323**, 647 (1981).
11. K. R. Huffman and F. C. Schaefer, J. Org. Chem., **28**, 1812 (1963).