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A series of polycyclic 1,4-dihydropyridines has been synthesized, viz., 1,4dihydrobenzothieno[3,2-b]pyridine-5,5-dioxides with electron-acceptor substituents at position 3. Their alkylation, chemical oxidation, and reactivity in electrochemical oxidation have been studied. The effect of a sulfonyl group in the indene segment on properties (pK, electrochemical oxidation potential) of the dihydrobenzothienopyridine system is considered.

 $5-0xo-4, 5-dihydro-1, 4-indeno[1, 2-b] pyridines (I) with an electron acceptor substituent X in the <math>\beta$ -position are known [1, 2].



I a d f $R=C_6H_5$, b, e, \hat{g} $R=C_6H_4OCH_3$ -p, $C R=C_6H_4NO_2$ -p; $a-C X=COOC_2H_5$, d-g $X=CSOC_2H_5$: II a, r R=H, b, s $R=CH_3$, c, d, l, o, t w, z $R=C_6H_5$, e $R=C_6H_4CH_2$, f, m, p, u, x, $R=C_6H_4OCH_3$ -p, g $R=C_6H_4OH$ -p, h $R=C_6H_4B$ -p, i $R=C_6H_3(OCH_3)_2$ -o,mj, n d, v, y, aa $R=C_6H_4NO_2$ -p, k $R=C_6H_5CH=CH$: a b, d, f $J=X=COOC_2H_5$, c, e, k $X=COOCH_3$; l-n $X=COCH_3$, o-q X=CN, r-v, $X=COSC_2H_5$, w- y, $X=CSOC_2H_5$, z, aa $X=CSSC_2H_5$: III a $R=C_6H_5D$, $R=C_6H_4B$ -p, $CR=C_6H_4CI$ -p, d, f $R=C_6H_4NO_2$ -p, e $R=C_6H_4OCH_3$ -p; a c $X=COOCH_3$, b, d $X=COOC_2H_5$, e, f $X=COSC_2H_5$

The present work offers a study of a new series of polycyclic 1,4-dihydropyridines, viz., 1,4-dihydrobenzothieno[3,2-b]pyridine-5,5-dioxides (IIa-aa, IIIa-f). The purpose of the work was to study the chemical, physicochemical, and biological properties of a new series of substances with a 1,4-dihydropyridine ring and to find the distinctive properties due to the introduction of a sulfonyl group instead of carbonyl in the indene segment.

The starting materials, 1-thionaphthenone-3-dioxide-1,1 and its arylindene derivatives, were synthesized analogously to [3, 5]. Compounds such as IIc-q, t-aa were obtained by condensation of 2-arylidene-1-thionaphthenone-3-dioxides-1,1 with enamine components IVa-g (esters of β -aminocrotonic IVa,b, and β -aminothiocrotonic acids IVe,f, etc.) in acetic acid with brief heating (method A). We also developed an improved method (method B), the condensation of 2-arylidene-1-thionaphthenone-3-dioxides-1,1 with acetothioacetic esters and other β -diketones or their derivatives in the presence of ammonium acetate. Thus we avoided the synthesis of the unstable sulfur-containing β -aminocrotonic esters, and increased the yields of the desired products II substantially. Dihydrobenzothienopyridine-5,5-dioxides (IIa,r) and the 4-methyl derivatives (IIb,s) are available via the reaction of 1-thionaphthenone-3-dioxide-1,1 with enamine and aldehyde components, analogous to [2].

Compounds IIh, j are oxidized by nitrogen oxides to the respective pyridines Va, b. Some II compounds were also alkylated at nitrogen by methyl iodide in acetonitrile in the presence of alkali to form N-methyldihydrobenzothienopyridines (IIIa-f).

UV, IR, and PMR spectroscopic data confirm the structures of compounds IIa-aa, IIa-f, and Va,b (Tables 1 and 2).

The general picture of the electronic structures of compounds II is close to that of the carbonyl analogs Ia-g, but II shows a 80-100 nm hypsochromic shift of the long-wave

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	P	Yield, %	20	- 80	28	34	54 99	32	73	12	75	67 90	2 2	87	000	88 (90)	85	79 60 (93)	62	(66) 19 19	50 (90) 60 (95)	96 96	49	202	67	74	88
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	Ö	c	59,0 60.2	65,4	66,1 50,8	64,2	54.8 54.8	62,6	59,1	68.5	66,1	0,00	65.9	60,1	56,1	63.5	61,8	57,0 63.5	61,8	57,0	55.0	66,1	55,7	000	62,6	57,9	59,4
	Empirical formula		C ₁₆ H ₁₅ NO,S CueH ₂₂ NO,S	C20H17NO4S	C21H19NO4S ConHigCINO4S	C22H21NO.S	C21H18BrNO4S	C2aH23NO ₆ S	C21H18N2O65 ConHaNO.S	C ₂₀ H ₁₇ NO ₃ S	C ₂₁ H ₁₀ NO ₄ S	C201161/2050	C2aH16N2O3S	CluH ₁₃ N ₃ O ₄ S	CIGHISNOSS2 CueHeNOSS2	C21H19NO3S2	C22H21NO4S2	C21H18N20552 C21HaN0255	C ₂₂ H ₂₁ NO ₄ S ₂	C21H18N2O5S2	CalH19N0233 CalH18N0053	C ₂₁ H ₁₉ NO ₄ S	C22H20BrNO4S	Carl and Solvers	C ₂₅ H ₂₃ NO ₄ S ₂	C22H20N2O552	C21H16BINO4S C21H16N2O6S
	Found, %	s	10,0 9.4		0, 4 0, 4	4,7	x v v v	6.9	2 0 2 0	9,4 4,6	ר~ ע ∞ ס	0 0 0 0		67 V 80 0	0 0 0 0 0	15,9	14,6	12.8	14,7	14,1	21.4	7,9	6,7 7,0		14,1	13,8	7,2
		z	4,6 3.7	3,6	4 e.		4 0 7 0	0,0 0,0	~ C	4,0	4,0	- «	7,4	11,3	4,4	3	0 0 0	0 0 0 0	3,2	0°5 77	- 0 0	4,0	0, u 0, u	6.4 6.4	3,2	6,2	6,8
		=	5,0	6 8 8	5,3 - 5,3	6,4	0,1 1,4	5,1	4 r. 0 0	200 000	2,2	4 7 7 7	4,1	3,1	4 G 0 C		5,2 7,5	4 4 0 8	4,8	4 - 0 u	4.1	2,0,2	4,3	, 4 7	5,0	4.5	3,84
			58,6 60.5	66,0	65,8 59,5	64,2	02,8 55,2	62,3	59,6 67,2	68,0	66,4	01.0	65,5	60,5 2,05	57,0 57,0	62,9	62,2	50,9 63.0	61,6	56,7	54.8	66,0	56,3	60.5 60.5	62,3	58,2	59,1
les (Va,D)	and the second sec	Amax, 1111	207, 218, 260 (sh), 278, 403 205 218, 260 (sh), 278, 380	207, 221, 260 (sh), 280, 375	207, 221, 260 (su), 280, 375 907 991 960 980 (sh), 375	207, 220, 258, (sh.), 278, 377	201, 220, 260 (30), 260, 378 207, 221, 260, 280 (sh), 375	207, 220, 260 (sh), 280, 380	20/, 218 (str), 238, 378 207, 220 (str), 258, 278, 378	207, 224, 258, 289, 389	207, 224, 257, 289, 390	201, 210 (301), 203, 334 907 919 958 974 (sh) 375	207, 222, 266, 276, 378	207, 215 (sh), 266, 375	201, 223, 264 (au.), 292, 405 207 223, 264 (sh) 292 383	207, 222, 257, 292, 387	207, 224, 257, 291, 387	201, 220 (su), 202 (su), 290, 391 207, 224, 257, 313, 402	207, 226, 258, 303, 405	207, 222 (sn), 268 (sn), 292, 405	207, 209, 310 (sh), 410	206, 220, 263 (sh), 282, 375	206, 221, 263 (st), 282, 375 906, (th) 991 958 (th) 989 379	204. 220. 281. 380	206, 225, 263 (sh.), 297, 385	206, 223 (sh), 258 (sh), 294, 390 213 200	213, 221 (sh), 263, 284
DIXOTD-C.		p. du	323 978	289-291	275-277	276	2/2 288	257	268-271 930-939	297-300	275	219	296	283	247	255-258	255	200-200 256	265	281	251	204 - 207	196-198	230	215-217	168	195
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*Yields obtained by method B in parentheses; otherwise, by method A.

TABLE 1. 1,4-Dihydrobenzothieno[3,2-b]pyridine-5,5-dioxides (IIa-aa and IIIa-f) and Benzothieno[3,2-b]pyri-

1268



IV **a** $X = COOCH_3$, **b** $X = COOC_2H_5$, **c** $X = COCH_3$, **d** X = CN, **e** $X = COSC_2H_5$, **f** $X = CSOC_2H_5$, **g** $X = CSSC_2H_5$; **v a** $R = C_6H_4B_7-\rho$, $X = COOC_2H_5$; **b** $R = C_6H_4NO_2\cdot\rho$, $X = COOC_2H_5$

maximum [2]. The long-wave maximum lies in the 372-420 nm region, depending on the kind of substituents at positions 3 and 4. The substituent effect at position 4 follows the same regularities as in the 5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridines [2]. The hypsochromic shift of the long-wave maximum of about 15-20 nm takes place in going from the sulfones that are unsubstituted at position 4 (IIa,r) to the 4-methyl (IIb,s) and 4-aryl (IId,t) derivatives (Table 1). Replacement of alkoxycarbonyl at position 3 by (ethylthio)carbonyl (IIr-v), ethoxythiocarbonyl (IIw-y), and (ethylthio)carbonyl (IIz,aa) causes, in that sequence, a gradual b thochromic shift of the long-wave maximum of about 15 nm. The color of the anion solution in aqueous alcoholic alkali also deepens in the same sequence from yellowish orange to dark red. The oxidized forms, pyridines Va,b, have no absorption in the above long-wave region.

In the IR spectra of compounds IIa-aa at 1145-1155 cm^{-1} we found the absorption maximum of the ring sulfonyl group; in the region of the alkoxycarbonyl and (ethylthio)carbonyl substituent double bonds there is oxo absorption around 1706 and 1640-1650 cm^{-1} , respectively, i.e., the thiol ether shows the typical 40-60 cm^{-1} reduction [6] in the location of the carbonyl maximum wavelength. Compounds IIk-q have an intense nitrile absorption maximum at 2210 cm^{-1} .

The oxidized forms — benzothienopyridines Va, b — are characterized by high-frequency carbonyl absorption bands in the 1720-1725 cm⁻¹ region.

The PMR spectra of compounds IIw-y (Table 2) show a shift of the methylene and methyl proton signals of the ethoxythiocarbonyl substituent toward the weak field, as compared with

Com-	PMR spectrum, δ, ppm (DMSO-d ₆)													
pound ¹ *	-CH ₂ CH ₃ ^{2*} (t, 3H)	2-CH ₃ ^{3*} (s, 3H)	(q, ^{2H})	4-CH	R and arom, protons	N-H** (s 1H)								
II a IIb	1, 31 1,29	2,38 2,38	4,18 4,18	3,53 s 4,08 q	7,46—7,87 (m 4H) 1,31 (d 3H); 7,49 7.92 (m 4H)	8,51 9,09								
ll¢ Ifd IJr IIv	(3,51) 1,09 1,13 1,27	2,40 2,41 2,17 2,30	3,97 2,71 2,89	5,06 s 5,09 s 3,42s 4,08 q	7,49-7,93 (H 4H) 7,20-8,02 (H 9H) 7,12-8,11 (H 9H) 7,56-7,93 (H 4H) 0.98 ($9,3H$); (H)	9,35 9,73 9,56 9,78								
IIt Ilu	1,02 1,02	2,22 2,33	2,71 2,71	5,07 s 4,98 s	7,60-8,04 (m 4H) 7,18-8,04 (m 9H) 3,62 (s, 3H): 6,67-8,04 (m 8H)	9,90 9,84								
IIV IIW IIX	1,03 1,22 1,24	2,40 2,38 2,38	2,71 4,33 4,33	5,24 s 5,49 s 5,42 s	7,44-8,13 (m, 8H) 7,16-8,00 (m, 9H) 3,60 (s, 3H) 6,67-8,00 (m, 8H)	10,04 9,82 9,78								
Ily Ila Ila Illa Illo Illc Illd Ille Illf	$1,33 \\ 1,11 \\ 1,02 \\ (3,60) \\ 1,18 \\ (3,60) \\ 1,18 \\ 1,13 \\ 1,16 \\ 1,16 \\ 1,13 \\ 1,16 \\ 1,16 \\ 1,18 \\ 1,13 \\ 1,16 \\ 1,18 \\ 1,13 \\ 1,16 \\ 1,1$	2,44 2,13 2,07 2,49 2,51 2,51 2,51 2,47 2,51	4,423.113,04	5,67 s 5,24 s 5,31 s 5,29 s 4,96 s 5,00 s 5,14 s 5,02 s 5,24 s	7,47-8,29 (m 8H) 7,18-8,09 (m 9H) 7,38-8,09 (m 9H) 7,24-8,02 (m 9H) 7,24-8,02 (m 8H) 7,29-8,00 (m 8H) 7,51-8,18 (m 8H) 6,76-7,96 (m 8H) 7,53-8,20 (m 8H)	10,07 9,60 9,73 (3,69) (3,66) (3,73) (3,71) (3,67) (3,71)								

TABLE 2. PMR Spectra of 1,4-Dihydrobenzothieno[3,2-b]pyridine-5,5-dioxides (IIa-d, r-aa and IIIa-e,h)

1* For IIa, b PMR spectrum was obtained in CDCl₃ with added DMSO-d₆.

2*Values for 3-CH₃ (s, 3H) in parentheses.

3*In DMSO-d; solution, signals overlap with those of solvent methyl.

3*Values for N-CH₃ (s, 3H) in parentheses.

TABLE 3. Ionization Constants (pK) and Long-Wave Absorption Maximum of 1,4-Dihydrobenzothieno[3,2-b]-pyridine-5,5-dioxides II in 50% Ethanol

Com- pound	pK±0.1	². _{max} , nm	Com- pound	p <i>K</i> ±0,1	λ _{max} . nm	Com- pound	pK±0,1	λ _{max} , nm
II a IIb IId IIf IIh II J	13,4 13,5 13,2 13,2 12,9 12,5	490 465 463 467 465 480	II/ IIO II r II s II t	12,5 11,5 12,6 12,7 12,3	480 455 503 478 480	IIU IIV IIW IIY IIZ	12,4 11,7 12,3 12,4 12,3	478 484 505 500 519

TABLE 4. Electrochemical Oxidation Half-Wave Potentials of 1,4-Dihydrobenzothieno[3,2-b]pyridine-5,5-dioxides (IIc, f, j, t, u, w, x) and 5-Oxo-4,5-dihydro-1H-indeno[1,2-b]pyridines (Ia-g)

Com- pound	$E_{1/2}, \mathbf{V}$	Com- pound	$E_{1/2}, \mathbf{V}$	Com- pound	<i>E</i> 1/2, V		
Ia Ib Ic Id Ie	1,10 1,15 1,23 1,08 —	f Ig IIC IIf IIj	1,10 1,05 1,33 1,35 1,43	IIt Ilu II w II x	1,35 1,32 1,28 1,20		

the ethoxycarbonyl derivatives IId, f, j and the thiol ethers IIt-v (Table 2). The methylene proton signals of ethoxycarbonyl have a certain paramagnetic shift relative to the protons of (ethylthio)carbonyl. An analogous weak field shift occurs in thioketones and thiomides at the G-H protons in α -position to thiocarbonyl [7, 8]. The same features of an XC shift of α -CH protons appear in sulfur-containing ester substituents, and in the protons of -0CH₂CH₃ and -SCH₂CH₃ segments of these groups in esters of the simplest thiocarboxylic acids [9]. Introduction of a sulfonyl group (structure II) instead of carbonyl (structure I) increases the pK by 0.5-0.7 units on average (Table 3). Substituents at position 4 increase the acidity of II in the sequence: CH₃ < H < C₆H₄R, in agreement with the increase in their electron acceptor properties.

Replacement of the cyclic oxo group (structure I) by sulfonyl (structure II) increases the electrochemical oxidation potentials by 0.15-0.27 V (Table 4).

The nature of the electron acceptor substituent X at the β -position of the 1,4-dihydropyridine ring has relatively little effect on the electrochemical oxidation potential and the pK values.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in mineral oil and hexachlorobutadiene. UV spectra were obtained on a Specord UV-vis instrument in $4 \cdot 10^{-3}$ M ethanol solutions. PMR spectra were obtained in Perkin-Elmer R 12 A (60 MHz) and Bruker WH 90/DS (90 MHz) instruments. Internal standards were HMDS and TMS. Electrochemical oxidation potentials were determined by a previously described procedure with a LP-7 automatic recording polarograph in acetonitrile using a rotating platinum microelectrode [10].

Ionization constants were determined spectrophotometrically [11] using the analytical anion wave in the long-wave region.

Properties of the synthesized substances are shown in Table 1.

<u>2-Methyl-1,4-dihydrobenzothieno[3,2-b]pyridine-5,5-dioxides (IIa, r).</u> To 0.91 g (5 mmole) of 1-thionaphthenone-3-dioxide-1,1 in 5 ml of toluene was added 7 mmole of the corresponding β -aminocrotonic ester IVb,e. The mixture wasboiled with excess paraformalde-hyde for 30 min, then about half of the toluene was distilled off. Upon cooling a yellow material precipitated which was crystallized from acetic acid.

 $\frac{2-\text{Methyl}-4-\text{aryl}-1,4-\text{dihydrobenzothieno}[3, 2-b]pyridine-5,6-\text{dioxides (IIc-q, t-aa)}.$ A) A mixture of 50 mmole of 2-arylidene-1-thionaphthenone-3-dioxide-1,1, 55 mmole of the corresponding β -aminovinyl component IVa-g, and 25 ml of acetic acid was boiled for 30 min. After cooling a yellow material precipitated, which was crystallized from acetic acid, ethanol, or DMFA.

B) A mixture of 10 mmole of 2-arylidene-1-thionaphthenone-3-dioxide-1,1 15 mmole of the corresponding sulfur-containing acetoacetic ester, 10 ml of acetic acid, and 7.7 g (100 mmole) of ammonium acetate was boiled for 10 min. After cooling, the yellow precipitate was separated and crystallized from acetic acid, ethanol, or DMFA.

<u>1,2-Dimethyl-4-aryl-1,4-dihydrobenzothieno[3,2-b]pyridine-5,5-dioxides (IIIa-f)</u>. In 60 ml of acetonitrile there was dissolved 3 mmole of IIc,e,h,j,u,v; 0.16g (4 mmole) of finely crushed sodium hydroxide was added, and the mixture was boiled for 5 min. To the red solution was added 4.32 g (30 mmole) of methyl iodide, and the mixture was heated on the water bath until the red color disappeared. The solvent was distilled off in vacuum, the residue was dissolved in 30 ml of water, and the yellow material was crystallized from ethanol or acetic acid.

<u>2-Methyl-4-arylbenzothieno[3,2-b]pyridine-5,5-dioxides (Va,b).</u> The corresponding compound IIh, j was dissolved in 3 ml of glacial acetic acid, l g (15 mmole) of sodium nitrite was added, and after 10 min the mixture was diluted with 10 ml of water. The color-less precipitate was crystallized from acetic acid.

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