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CONDENSED ISOQUINOLINES. 7.* SYNTHESIS OF DERIVATIVES OF THE NEW HETEROCYCLIC SYSTEM THIENO[3',2':5,6]-PYRIMIDO[1,2-b]ISOQUINOLINE

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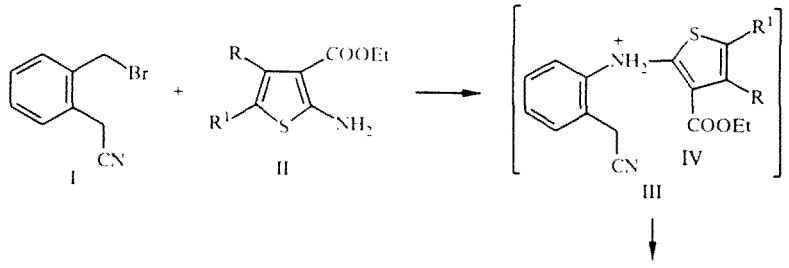
4-Oxo-6,11-dihydro-4H-thieno[3',2':5,6]-pyrimido[1,2-b]isoquinolines have been synthesized by the reaction of o-bromo-methylphenylacetonitrile with esters of substituted 2-aminothiophene-3-carboxylic acids. They were characterized as the hydrobromides and as the free bases. The tautomerism of the bases in DMSO solution is discussed.

We showed previously [2] that the reaction of o-bromomethylphenylacetonitrile (I) with anthranilic acid methyl ester leads to 5-oxo-7,12-dihydro-5H-isoquino[2,3-a]quinazoline. It seemed of interest to extend this type of reaction to heterocyclic analogs of anthranilic acid. With this aim the reaction of the bromonitrile (I) with the methyl esters of a series of 2-aminothiophene-3-carboxylic acids (II) has been studied. It was expected that derivatives of the new heterocyclic system thienopyrimido-isoquinoline might be formed by analogy with the previous case. There is no information in the literature on this system. In addition the compounds expected would contain thieno[2,3-d]pyrimidine fragments, so are potentially new biologically active substances (see for example [3] and the literature cited therein).

It was found that heating a mixture of equimolar quantities of aminoesters (II) with the bromonitrile (I) in 2-propanol leads to 4-oxo-6,11-dihydro-4H-thieno-[3',2':5,6]pyrimido[1,2-b]isoquinolines (III). It is evident that the reaction occurs as a sequence of conversions, comprising the alkylation of the aminoester (II) by the bromonitrile (I), the intramolecular addition of the amino group to the nitrile in the alkylation product (IV), and amidation of the ester group by the imine salt in the intermediate isoquinolinimine (V). The absence from the IR and PMR spectra of the compounds obtained of signals for the nitrile, ester, secondary amino, and primary imino group salts exclude the stopping of the process at the stages of the intermediate compounds (IV) and (V). Signals were observed in the high field region of the PMR spectra of compound (III) for the aliphatic protons of the substituent R and two two-proton singlets at 4.54-4.78 and 5.60-5.65 ppm for the methylene protons at $C_{(6)}$ and $C_{(11)}$ respectively (full data of the PMR spectra are given in Table 1). The IR spectra of the compounds obtained were characterized by the presence of strong bands for the stretching vibrations of C=O (1710), $C{=}N^+$ (1610), and N^+-H (v br 2250 cm^{-1}).



*For Communication 6, see [1].

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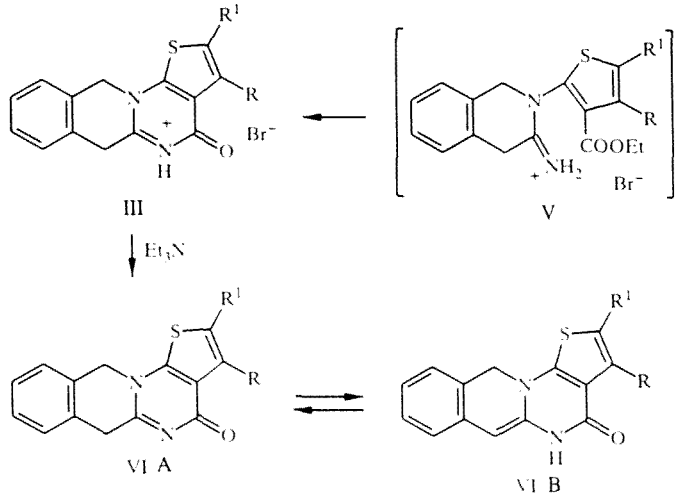
TABLE 1. Characteristics of 4-Oxo-6,11-dihydro-4H-thieno[3′,2′:5,6]pyrimido[1,2-b]isoquinolines

Compound	R	R^1	Mp, °C	Empirical formula	PMR spectra, ppm			
					$C_{(6)}H_2$, s	$C_{(11)}H_2$, s	NH	R, R^1
III a	CH_3	CH_3	250...253 (decomp.)	$C_{16}H_{15}BrN_2OS$	4,70	5,60	Exch.	s, 2,62 (6H)
III b	$-(CH_2)_4-$		348...350 (decomp.)	$C_{18}H_{17}BrN_2OS$	4,68	5,59	Exch.	m, 2,04 (4H); m, 3,03 (4H)
III c	$-(CH_2)_3-$		335...340 (decomp.)	$C_{17}H_{15}BrN_2OS$	4,45	5,49	Exch.	m, 2,51 (2H); m, 3,02 (4H)
III d	C_2H_5	H	248...249 (decomp.)	$C_{16}H_{15}BrN_2OS$	4,78	5,65	Exch.	t, 1,51 (3H); q, 3,11 (2H)
III e	H	C_6H_5	272...275 (decomp.)	$C_{20}H_{15}BrN_2OS$	4,54	5,63	Exch.	
VI a	CH_3	CH_3	233...235 (decomp.)	$C_{16}H_{14}N_2OS$	4,16, 4,94	5,23	s, 10,45	s, 2,43 (6H)
VI b	$-(CH_2)_4-$		290...295 (decomp.)	$C_{18}H_{16}N_2OS$	4,09, 4,91	5,15	s, 10,41	m, 1,74 (4H); m, 2,84 (4H)
VI c	$-(CH_2)_3-$		268...270 (decomp.)	$C_{17}H_{14}N_2OS$	4,11, 4,91	5,17	s, 10,40	m, 2,44 (2H); m, 2,89 (4H)
VI d	C_2H_5	H	170...171	$C_{16}H_{14}N_2OS$	4,12, 4,91	5,22	s, 10,51	t, 1,27 (3H), q, 2,87 (2H)
VI e	H	C_6H_5	240...242	$C_{20}H_{14}N_2OS$	4,16, 5,02	5,31	s, 10,52	

*Descriptions of the complex multiplets of aromatic protons are omitted.



II—VI a R = R^1 = CH_3, b R + R^1 = $-(CH_2)_4-$, c R + R^1 = $-(CH_2)_3-$, d R = H, R^1 = C_2H_5, e R = C_6H_5, R^1 = H

Salts (III) are converted by the action of triethylamine into the free bases (VI). These compounds have similar spectral characteristics to those of the salts (III) with the exception of the regular changes on going from salt to base. Thus in the IR spectra the ν_{N-H} band disappears but the $\nu_{C=O}$ and $\nu_{C=N}$ bands underwent low frequency shifts to 1630 and 1690 cm^{-1} respectively. In the PMR spectra of the free bases (in DMSO-D_6), the singlets of both methylene groups were displaced towards high field and the deprotonation affected the position of the signals of the $C_{(12)}H_2$ group protons. An interesting feature of these spectra proved to be the presence of two further signals of low intensity at 4.91-5.02 and 10.41-10.52 ppm assigned to the

TABLE 2. Elemental Analysis Data of the Synthesized Compounds

Compound	R^1	R^2	Found, %			Empirical formula	Calculated, %		
			N	S	Br		N	S	Br
IIIa	CH_3	CH_3	7,86	9,03	22,03	$C_{16}H_{15}BrN_2OS$	7,71	8,83	22,00
IIIb	$-(CH_2)_4-$		7,14	8,20	20,24	$C_{18}H_{17}BrN_2OS$	7,20	8,24	20,52
IIIc	$-(CH_2)_3-$		7,40	8,46	21,64	$C_{17}H_{15}BrN_2OS$	7,46	8,54	21,29
IIId	C_2H_5	H	7,72	8,84	22,26	$C_{16}H_{15}BrN_2OS$	7,71	8,83	22,00
IIIe	H	C_6H_5	6,63	7,84	19,46	$C_{20}H_{15}BrN_2OS$	6,81	7,80	19,43
VIa	CH_3	CH_3	10,21	11,34	—	$C_{16}H_{14}N_2OS$	9,92	11,35	—
VIb	$-(CH_2)_4-$		9,11	10,61	—	$C_{18}H_{16}N_2OS$	9,08	10,40	—
VIc	$-(CH_2)_3-$		9,44	10,85	—	$C_{17}H_{14}N_2OS$	9,52	10,89	—
VId	C_2H_5	H	10,09	11,60	—	$C_{16}H_{14}N_2OS$	9,92	11,35	—
VIe	H	C_6H_5	8,32	9,93	—	$C_{20}H_{14}N_2OS$	8,48	9,70	—

signals of the protons at 7-H and 5-H of the N−H tautomers of structure B. The basis for such an assignment is the low integrated intensity of the signal of the $C_{(7)}$ protons of tautomer A compared with the intensity of the signal for the methylene group at $C_{(12)}$, the position of which is evidently the same for both tautomers. The content of N−H tautomers B in DMSO solution was 10-15% determined from the integrated intensity of the signals indicated. The presence of a tautomeric equilibrium in solutions of compound (VI) was confirmed by the spectra recorded in the presence of D_2O. As a result of deuterium exchange the signal of the $C_{(6)}H_2$ of the C−H tautomer (VIA) and the signals of the $C_{(6)}H$ and $N_{(5)}H$ of the N−H tautomer, (VIB) disappeared. The possibility of tautomeric conversion of the structurally similar 5-oxo-7,12-dihydro-5H-isoquino[2,3-a]quinazoline was considered previously in [4] on the basis of an analogous facile deuterium exchange, however, the presence of the N−H tautomer was not recorded in solutions of this compound.

EXPERIMENTAL

The IR spectra of compounds in KBr disks were recorded on a Pye Unicam SP3 300 instrument. The NMR spectra of solutions of compounds in DMSO-D_6 were obtained on a Bruker WP 100 SY instrument, the internal standard being TMS. All salts (III) were recrystallized from a nitromethane−acetic acid mixture and base (VI) from 2-propanol.

The characteristics of compounds are given in Table 1. The data of elemental analysis were in agreement with calculated values.

4-Oxo-6,11-dihydro-4H-thieno[3′,2′:5,6]pyrimido[1,2-b]isoquinoline Hydrobromides (III). A solution of bromonitrile (I) (0.01 mole) and aminoester (II) (0.01 mole) in 2-propanol (30 ml) was boiled for 4 h. The solid which precipitated from the reaction mixture on cooling was filtered off and washed on the filter with 2-propanol. Yield was 77-85%.

To obtain the free bases, the salts (III) were treated with an excess of triethylamine, the mixture was brought to boiling, the excess of triethylamine evaporated in vacuum, and the residue treated with water. The solid was filtered off, washed with water, and then with 2-propanol.

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