Compounds VIIa-c were treated with hydrogen chloride in dioxane at 20°C for 1 h, after which ether was added to precipitate IIa-c, which were purified by reprecipitation from alcohol by the addition of ether.

Compound VIId was dissolved in alcohol, an alcohol solution of HCl and ether were added successively, and the precipitated IId was recrystallized from alcohol.

LITERATURE CITED

1. M. D. Mashkovskii, Medicinals [in Russian], Vol. 1, Meditsina, Moscow (1972), p. 133.
2. L. E. Kholodov, V. G. Yashunskii, R. A. Al'tshuler, M. D. Mashkovskii, L. F. Roshchina, S. I. Shershneva, F. Ya. Leibel'man, O. N. Volzhina, and N. A. Petrova, Khim.-Farm. Zh., No. 1, 50 (1973).
3. S. Tanajama, T. Fujita, et al., Jpn. J. Pharm., 20, 413 (1970).
4. Z. A. Olvyanishnikova, T. M. Ivanova, V. E. Sviridova, and V. G. Yashunskii, Khim. Geterotsikl. Soedin., No. 2, 170 (1978).
5. K. Masuda and T. Kamija, Chem. Pharm. Bull., 19, 72 (1971).
6. S. V. Rogozhin, Yu. A. Davidovich, S. M. Andreev, and A. I. Yurtanov, Dokl. Akad. Nauk SSSR, 211, 1365 (1973).
7. S. V. Rogozhin, Yu. A. Davidovich, S. M. Andreev, and A. I. Yurtanov, Dokl. Akad. Nauk SSSR, 212, 108 (1973).
8. G. W. Anderson, F. M. Callahan, and J. E. Limmerman, J. Am. Chem. Soc., 89, 178 (1967).
9. S. V. Rogozhin, Yu. A. Davidovich, N. A. Samoilov, N. V. Mironova, A. I. Yurtanov, and S. M. Andreev, Izv. Akad. Nauk SSSR, No. 2, 428 (1972).
10. E. Schnabel, Ann. Chem., 702, 188 (1967).
11. H. U. Daeniker and J. Druey, Helv. Chim. Acta, 45, 2426 (1962).
12. W. Shiefken, Ann., 562, 6 (1948).

NEW METHODS FOR THE SYNTHESIS OF AMIDES OF BENZO[b]THIOPHENE-2-CARBOXYLIC ACID

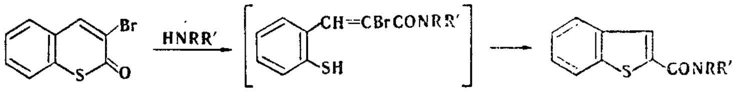
V. L. Savel'ev, T. G. Afanas'eva,
and V. A. Zagorevskii

UDC 547.733.735.07

The reaction of 3-bromothiocoumarin with nitrogen bases, during which the thiocoumarin system is converted to a benzothiophene system, was studied. A new method for the synthesis of amides of benzo[b]thiophene-2-carboxylic acid is proposed.

In contrast to 3-halocoumarins, little study has been devoted to the reaction of 3-halothiocoumarins with nucleophilic reagents. Only a communication [1] that 3-bromothiocoumarin (I) is converted to benzo[b]thiophene-2-carboxylic acid (II) when it is heated with a solution of potassium hydroxide is available. No information on the reaction of 3-halothiocoumarins with nitrogen bases is available in the literature.

We carried out the reaction of 3-bromothiocoumarin I with ammonia in dimethyl sulfoxide (DMSO) at 20°C with a number of amines in refluxing absolute benzene; the corresponding amides (III) of benzo[b]thiophene-2-carboxylic acid as the only products in all cases (except for the reaction with piperidine).



I IV III a-h

III a R=R'=H; b R=H, R'=n-C_4H_9; c R=H, R'=$C_6H_5CH_2$; d R+R'=—$(CH_2)_4$—; e R+R'=—$(CH_2)_5$—; f R+R'=$CH_2CH_2OCH_2CH_2$; g R+R'=$CH_2CH_2N(CH_3)CH_2CH_2$; h R=H, R'=$CH_2CH_2CH_2NCH_2CH_2OCH_2CH_2$

Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow 125315. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1340-1342, October, 1978. Original article submitted October 14, 1977.

0009-3122/78/1410-1085$07.50

TABLE 1. Benzo[b]thiophene-2-carboxylic Acid Amides (IIIa-h)

Compound	Reaction time, h	R_f[a]	mp, °C[b,c]	Found, %		Empirical formula	Calc., %		Yield, %
				N	S		N	S	
IIIa	48	0,15	174—176 (176[4])	8,0	18,0	C_9H_7NOS	7,9	18,1	70
IIIb	5	0,29	98—99,5	6,2	13,5	$C_{13}H_{15}NOS$	6,0	13,7	86
IIIc	10	0,42	145—146 (142—143[4])	5,2	11,8	$C_{16}H_{13}NOS$	5,2	12,0	72
IIId	7	0,21	93—95	6,1	13,8	$C_{13}H_{13}NOS$	6,1	13,9	76
IIIe	5	0,36	123—125 (125[4])	5,7	13,3	$C_{14}H_{15}NOS$	5,7	13,1	82
III f	6	0,21	97—98,5 (99—99,5[4])	5,7	12,8	$C_{13}H_{13}NO_2S$	5,7	13,0	97
IIIg[d]	6	0,46	254—257 (269—271[3])	9,4	10,6	$C_{14}H_{17}ClN_2OS$[e]	9,4	10,8	81
IIIh	5	0,47	115—117	9,2	10,5	$C_{16}H_{20}N_2O_2S$	9,2	10,4	83

[a] In chloroform for IIIa, g, h, and in benzene for IIIb-f. [b] The melting points of amides IIIa-h that we obtained from 3-bromocoumarin (I) and acid chloride V were completely identical. [c] Compounds IIIb, d, e were recrystallized from 70% alcohol, IIIc was recrystallized from alcohol, IIIf was recrystallized from petroleum ether, and IIIh was recrystallized from benzene—heptane. [d] Hydrochloride. [e] Found: Cl 12.1%. Calculated: Cl 11.9%.

In the case of the reaction with piperidine amide IIIe is formed in a mixture with a small amount of 4-piperidinothiocoumarin [according to the results of thin-layer chromatography (TLC)], from which the amide is separated by crystallization from 70% alcohol. It is interesting to note that a complex mixture of products, from which 3-piperidino-2,3-dihydrobenzofuran-2-carboxylic acid piperidide, α,β-dipiperidino-o-hydroxycinnamic acid piperidide, and 3- and 4-piperidinocoumarins, in addition to benzofuran-2-carboxylic acid piperidide, were isolated, is formed in the reaction of 3-bromocoumarin with piperidine under similar conditions [2]. This difference between 3-bromothiocoumarin (I) and 3-bromocoumarin can probably be explained by the higher rate of cyclization (because of the high nucleophilicity of the thiophenoxide ion) of the intermediate o-mercapto-α-bromocinnamic acid piperidide (IV) to amide IIIe as compared with the cyclization of the intermediate o-hydroxy-α-bromocinnamic acid piperidine.

The structure of amides IIIa-h was confirmed by the UV spectral data and independent synthesis by reaction of benzo[b]thiophene-2-carboxylic acid chloride (V) with ammonia and the corresponding amines in absolute benzene by the method in [3].

As in the case of the UV spectrum of acid II, two absorption maxima at 227-230 and 277-287 nm are observed in the UV spectra of amides IIIa-h.

Compounds with fungicidal, local anesthetic, analgetic, and anticonvulsant activity have been found among various amides of benzothiophene-2-carboxylic acid, which up until now have been obtained from acid II or its chloride (V); some of these compounds act as CNS antidepressants and depressants [3-6]. Our proposed method for the synthesis of benzothiophene-2-carboxylic acid amides from 3-bromothiocoumarin may therefore be of definite preparative interest.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds ($2.5 \cdot 10^{-5}$–$5 \cdot 10^{-5}$ M) were recorded with a Perkin—Elmer 402 spectrometer. The course of the reactions and the purity of the compounds obtained were monitored by TLC on activity IV aluminum oxide with chloroform or benzene as the solvent.

Acid II was obtained from 3-bromothiocoumarin (I) by the method in [1]. UV spectrum, λ_{max} (log ε): 230 (4.24), 241 (inflection), 277 (inflection), and 284 nm (4.12). Acid chloride V was obtained by the method in [7].

Benzothiophene-2-carboxylic Acid Amides (IIIa-h). A) A solution of 0.6 g (2.5 mmole) of bromide I in 7 ml of absolute DMSO was saturated with ammonia in the course of 30 min, after which the mixture was allowed to stand at 20°C for 48 h. It was then diluted with water, and the precipitate was removed by filtration, washed with warm water, and recrystallized from benzene to give amide IIIa. UV spectrum, λ_{max} (log ε): 228 (4.36), 245 (4.32), 279 (inflection), and 287 nm (4.33).

B) A 12.5-mmole sample of the corresponding amine was added to a solution of 0.6 g (2.5 mmole) of bromide I in 15 ml of absolute benzene, and the mixture was refluxed for 5-10 h until starting I vanished. It was then cooled. In the case of IIIc the precipitate was removed by filtration, washed with water, and recrystallized from alcohol (an additional amount of substance was isolated from the benzene solution after washing with 10% hydrochloric acid and water and evaporation). In the remaining cases the precipitated amine hydrobromide was removed by filtration and washed with benzene, and the combined solutions were washed with 10% hydrochloric acid and water and evaporated. The crystalline residues were recrystallized from a suitable solvent; oily IIIg was converted to the hydrochloride by treatment with an ether solution of hydrogen chloride. The hydrochloride was purified by precipitation from alcohol by the addition of ether.

Data for amides IIIa-h are presented in Table 1.

LITERATURE CITED

1. W. D. Cotterill, C. J. France, R. Livingstone, and J. R. Atkinson, J. Chem. Soc., Perkin Trans. I, No. 6, 817 (1972).
2. V. A. Zagorevskii, V. L. Savel'ev, N. V. Dudykina, and S. L. Portnova, Zh. Org. Khim., 3, 642 (1967).
3. E. Campaigne and T. Bosin, J. Med. Chem., 10, 945 (1967).
4. R. W. Goettsch and G. A. Wiese, J. Am. Pharm. Assoc., 47, 319 (1958).
5. W. B. Wright and H. J. Brabander, West German Patent No. 1936721 (1970); Chem. Abstr., 73, 120496 vP (1970).
6. W. B. Wright and H. J. Brabander, US Patent No. 3734915 (1973); Chem. Abstr., 79, 42558z (1973).
7. R. Royer, P. Demerseman, J.-P. Lechartier, and A. Cheutin, J. Org. Chem., 27, 3808 (1962).