Isothiocyanates. XLIV. Preparation and properties of some substituted benzhydryl isothiocyanates

[a]J. KALAMÁR, [b]Ľ. DROBNICA, [c]K. ANTOŠ, [d]J. SURÁ, and [a]D. MRAVEC

[a]*Department of Organic Technology, Slovak Technical University, 880 37 Bratislava*

[b]*Department of Microbiology and Biochemistry, Slovak Technical University, 880 37 Bratislava*

[c]*Department of Textile, Cellulose, and Paper, Slovak Technical University, 880 23 Bratislava*

[d]*Department of Organic Chemistry, Slovak Technical University, 880 37 Bratislava*

Received 11 April 1974

Synthesis of 2-, 3-, 4-, and 4,4′-substituted benzhydryl isothiocyanates with halo, methyl, methoxy, nitro, and isothiocyanato groups as substituents is described. The obtained i.r. spectral data indicate that *p*-substituents in the substituted benzhydryl isothiocyanates similarly as in benzyl isothiocyanates affect ν_{as}(NCS) so that a linear correlation with σ_m and σ_p values is valid. The reactivity of —NCS group with OH^- ions and $-NH_2$ group of glycine respectively was studied spectrophotometrically. The obtained reaction rates of glycine addition do not point to a possibility of this correlation.

The substituted benzhydryl isothiocyanates showed selective activity against gram-positive bacteria, mycobacteria [1], and some plasmodia [2]. Results of tests against intestine parasites were also published [3].

The basic benzhydryl isothiocyanate was prepared from benzhydrylamine through the appropriate thiuram disulfide [4] as well as by rearrangement of benzhydryl thiocyanate [5—7]. Further compounds prepared by rearrangement of the appropriate thiocyanates were 2-chlorobenzhydryl isothiocyanate [8], 4-methylbenzhydryl isothiocyanate, and 4-nitrobenzhydryl isothiocyanate [9], 4-chlorobenzhydryl isothiocyanate [7, 9], 4,4′-dimethylbenzhydryl isothiocyanate, and 4,4′-dichlorobenzhydryl isothiocyanate [6]. The i.r. spectra of benzhydryl isothiocyanates were taken in [10]. The kinetics of benzhydryl thiocyanate rearrangements was also studied [6, 9, 11].

The aim of this work was to synthesize a series of substituted benzhydryl isothiocyanates for studying their physicochemical properties. The preparation was mostly accomplished by reaction of the appropriate benzhydrylamines with thiophosgene. 3- and 4-Nitro derivatives were prepared by isomerization of the corresponding thiocyanates.

Experimental

Melting points were determined on a Kofler block and the refractive indices by a Hilger refractometer. The u.v. spectra were measured on a Specord UV-VIS Zeiss spectrophotometer at 25 ± 0.2°C (concentration of isothiocyanate 5×10^{-5} M in methanol). The i.r. spectra were taken on a UR-20 Zeiss Jena spectrophotometer in the region of 2000—2200 cm^{-1} (maximum of —NCS group) using KBr cells of 0.16 mm thickness; concentration of isothiocyanate 0.1 M in chloroform.

Preparation of the starting benzhydrylamines for isothiocyanates (*I—XVI*) was described in [12]. The new-synthesized benzhydrylamines (derivatives *XVIIa—XXIIIa*) were prepared by the same procedure and are listed in Table 1.

4-Nitrobenzhydryl isothiocyanate (*XXV*) and 3-nitrobenzhydryl isothiocyanate (*XXIV*) not reported previously were prepared by isomerization of thiocyanates according to [6, 9]. Their yields and physicochemical properties are given in Table 2.

3-Nitrobenzhydrol

A mixture of 3-nitrobenzophenone (78.5 g; 0.346 mole) and aluminium isopropylate (72.1 g; 0.353 mole) was heated in absolute isopropyl alcohol (1050 ml) at the bath temperature 105 ± 2°C for 8 hrs. Acetone formed in the course of reaction was simultaneously distilled off and determined. When the reaction was over, the solvent was distilled off *in vacuo* and the distillation residue was decomposed with a mixture of ice (200 g) and 50% hydrobromic acid (150 ml). The formed organic layer was extracted with diethyl ether and dried. After removing the solvent, the residue was used to prepare 3-nitrobenzhydryl bromide without further purification. Yield 77 g, *i.e.* 97.2% of theoretical amount.

For $C_{13}H_{11}NO_3$ (229.24) calculated: 68.12% C, 4.84% H, 6.11% N; found: 67.91% C, 4.73% H, 6.24% N.

Table 1

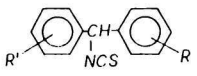
Substituted benzhydrylammonium chlorides

No.	Formula	*M*	Calculated/found % C	% H	% N	Yield [%]	M.p. [°C]	Note
XVIIa	$C_{13}H_{13}ClFN$	237.7	65.69	5.51	5.88	66	234—239	6 hrs
			65.78	5.60	5.93			without catalysis
XVIIIa	$C_{13}H_{13}ClFN$	237.7	65.69	5.51	5.88	57	235—239	6 hrs
			65.58	5.57	5.90			without catalysis
XIXa	$C_{13}H_{13}ClFN$	237.7	65.69	5.51	5.88	58	222—223	7 hrs
			65.75	5.48	5.82			without catalysis
XXa	$C_{13}H_{12}ClF_2N$	255.7	61.07	4.73	5.48	44.8	235—236	6 hrs
			61.16	4.81	5.41			without catalysis
XXIa	$C_{13}H_{13}ClIN$	345.6	45.18	3.79	4.05	52	222—226	6 hrs
			45.25	3.69	4.17			without catalysis
XXIIa	$C_{13}H_{13}ClIN$	345.6	45.18	3.79	4.05	71	217—232	3 hrs
			45.23	3.83	4.15			with catalysis
XXIIIa	$C_{13}H_{13}ClIN$	345.6	45.18	3.79	4.05	81	232—233	3 hrs
			45.21	3.71	4.12			with catalysis

The substituents of compounds *XVIIa—XXIIIa* were the same as in compounds *XVII—XXIII* (see Table 2).

Table 2

Characterization and yields of the substituted benzhydryl isothiocyanates



No.	R	R′	Formula	*M*	Calculated/found % C	% H	% N	% S	% Hal	Yield [%]	Found/literature data M.p. [°C] B.p. [°C/torr]	Refractive index n_D^{20}	Density d_{20} [g cm^{-3}]
I	H	H	$C_{14}H_{11}NS$	225.32						80 80 [13][a]	60 59–60 [4–7]		
II	2-Cl	H	$C_{14}H_{10}ClNS$	259.76						75 46 [8][b]	143/0.05 186–189/1.5 [8]	1.6138	1.2219
III	3-Cl	H	$C_{14}H_{10}ClNS$	259.76	64.73 64.50	3.88 3.72	5.39 5.18	12.34 12.30	13.65 13.35	62	154/0.1	1.6329	1.2384
IV	4-Cl	H	$C_{14}H_{10}ClNS$	259.76						81 89 [7][b]	153/0.1 175–179/3–4 [7]	1.6345 n_D^{25} 1.6165 [9]	1.2335
V	4-Cl	4-Cl	$C_{14}H_9Cl_2NS$	294.21						85 [6][c]	85 84–85 [6]		
VI	2-Br	H	$C_{14}H_{10}BrNS$	304.21	55.27 55.13	3.31 3.29	4.60 4.40	10.54 10.81	26.27 26.32	45	147/0.07 150–152/1.1 [9]	1.6505	1.4175
VII	3-Br	H	$C_{14}H_{10}BrNS$	304.21	55.27 55.42	3.31 3.64	4.60 4.45	10.54 10.75	26.27 26.55	60	155/0.1		
VIII	4-Br	H	$C_{14}H_{10}BrNS$	304.21	55.27 55.30	3.31 3.17	4.60 4.45	10.54 10.79	26.27 26.25	78	154/0.1	1.6484	1.4227
IX	4-Br	4-Br	$C_{14}H_9Br_2NS$	383.11	43.89 43.90	2.36 2.15	3.66 3.58	8.37 8.20	41.71 41.80	85	109		
X	2-OCH_3	H	$C_{15}H_{13}NOS$	255.34	70.55 70.32	5.13 5.20	5.49 5.28	12.56 12.45		50	32; 148/0.1		
XI	4-OCH_3	H	$C_{15}H_{13}NOS$	255.34	70.55 71.00	5.13 5.10	5.49 5.35	12.56 12.50		70	36; 135/0.05		
XII	4-OCH_3	4-OCH_3	$C_{16}H_{15}NO_2S$	285.37	67.34 67.40	5.29 5.20	4.91 4.86	11.21 11.03		45	48		

Table 2 (Continued)

No.	R	R′	Formula	*M*	Calculated/found % C	% H	% N	% S	% Hal	Yield [%]	Found/literature data M.p. [°C] B.p. [°C/torr]	Refractive index n_D^{20}	Density d_{20} [g cm^{-3}]
XIII	3-CH_3	H	$C_{15}H_{13}NS$	239.34	75.27	5.47	5.85	13.40		70	139/0.2		
					75.30	5.40	5.63	13.15					
XIV	4-CH_3	H	$C_{15}H_{13}NS$	239.34						75 [9][c]	36; 136/0.05 139—141/0.1 [9]	n_D^{25} 1.6165 [9]	
XV	4-CH_3	4-CH_3	$C_{16}H_{15}NS$	253.37						80 [6][c]	51 50.5—51 [6]		
XVI	4-NCS	H	$C_{15}H_{10}N_2S_2$	282.39	63.80	3.56	9.92	22.71		25	55; 130/0.003		
					63.74	3.52	9.71	22.53					
XVII	2-F	H	$C_{14}H_{10}FNS$	243.31	69.11	4.14	5.76	13.18	7.81	83	135/0.7	1.6112	1.2046
					69.14	4.17	5.69	13.29	7.60				
XVIII	3-F	H	$C_{14}H_{10}FNS$	243.31	69.11	4.14	5.76	13.18	7.81	70	140/0.5	1.6104	1.20516
					69.05	4.17	5.56	13.25	7.73				
XIX	4-F	H	$C_{14}H_{10}FNS$	243.31	69.11	4.14	5.76	13.18	7.81	79	139/0.7	1.6060	
					68.93	4.07	5.83	12.95	7.69				
XX	4-F	4-F	$C_{14}H_9F_2NS$	261.30	64.35	3.47	5.36	12.27	14.54	90	141/0.7	1.5935	
					64.21	3.50	5.25	12.11	14.39				
XXI	2-I	H	$C_{14}H_{10}INS$	351.21	47.87	2.87	3.99	9.13	36.13	84	182/0.7	1.6781	1.812
					47.72	2.85	3.75	8.97	35.80				
XXII	3-I	H	$C_{14}H_{10}INS$	351.21	47.87	2.87	3.99	9.13	36.13	64	184/0.7	1.6752	
					47.56	2.70	3.75	9.25	36.30				
XXIII	4-I	H	$C_{14}H_{10}INS$	351.21	47.87	2.87	3.99	9.13	36.13	81	184/0.7		
					47.63	2.82	3.85	8.95	36.31				
XXIV	3-NO_2	H	$C_{14}H_{10}N_2O_2S$	270.31	62.20	3.72	10.36	11.86		36[d]	68		
					62.12	3.65	10.20	11.51					
XXV	4-NO_2	H	$C_{14}H_{10}N_2O_2S$	270.31						42[c] 50 [6, 9][c]	53 52.4—53.6 [6, 9]		

a) The isothiocyanate was prepared by reaction of benzhydrylamine with thiophosgene.

b) The yield was related to the appropriate benzhydryl chloride. The preparation was accomplished through thiocyanate in one step.

c) The isothiocyanate was prepared by rearrangement of the appropriate thiocyanate.

3-Nitrobenzhydryl bromide

3-Nitrobenzhydrol (74 g; 0.323 mole) in anhydrous diethyl ether (150 ml) was saturated with hydrogen bromide and heated for 1 hr under reflux. After removing the solvent, the residue was distilled *in vacuo*. The fraction boiling in the temperature range of 183—193°C/0.2 torr was collected. Yield 75.1 g, *i.e.* 79.6% of theoretical amount.

For $C_{13}H_{10}NBrO_2$ (292.13) calculated: 53.45% C, 3.45% H, 4.8% N, 27.35% Br; found: 53.40% C, 3.39% H, 4.86% N, 27.11% Br.

3-Nitrobenzhydryl thiocyanate

To a solution of 3-nitrobenzhydryl bromide (75.1 g; 0.257 mole) in anhydrous acetone (400 ml), potassium thiocyanate (25 g; 0.257 mole) was added and the reaction mixture was stirred for 24 hrs at laboratory temperature. The precipitated potassium bromide (32 g) was filtered and acetone was distilled off *in vacuo*. The distillation residue was extracted with benzene (400 ml). The organic layer was washed with water and after drying, benzene was distilled off. The crystalline residue was recrystallized from the mixture of benzene—diethyl ether. Yield 38 g, *i.e.* 54.7% of theoretical amount.

For $C_{14}H_{10}N_2SO_2$ (270.31) calculated: 62.21% C, 3.73% H, 10.36% N, 11.86% S; found: 62.34% C, 3.64% H, 10.52% N, 11.75% S.

Preparation of benzhydryl isothiocyanates (I—XXIII) from benzhydrylamines and thiophosgene

The appropriate benzhydrylammonium chloride (0.1 mole) in water (100 ml), dichloroethane (30 ml), and powdery calcium carbonate (11 g; 0.11 mole) were allowed to react at 25°C with thiophosgene (7.6 ml; 11.5 g; 0.1 mole) in dichloroethane (30 ml; added during 10 min) for 2 hrs. After raising the temperature of the solution to 35°C, the unaltered carbonate was filtered off. The dichloroethane layer was distilled with water vapour. The distillation residue was extracted with benzene and the extract was purified with charcoal. After evaporation the products were distilled *in vacuo* or crystallized from the mixture of *n*-heptane—diethyl ether (1 : 1, v/v). Their yields and physicochemical properties are in Table 2.

Kinetic measurements

The kinetics of addition of OH^- ions and $-NH_2$ group, respectively to $-NCS$ group was followed by the method described in [14]. The measurements were accomplished at 25 ± 0.2°C in 0.1 M borate buffer of pH 9.8. The initial glycine concentrations (base form) (2×10^{-2} M) in the reaction mixture and the concentration of isothiocyanate in the reaction mixture (lower than 5×10^{-5} M), limited by solubility of the compound in water, secured the pseudomolecular course of reaction. The reaction mixture containe buffer (17.9 ml), stock aqueous solution of glycine (2 ml), and stock dioxan solution of the isothiocyanate (0.1 ml). The nature of the spectra of isothiocyanate and the reaction product determined the choice of a suitable wavelength at which the extinction was read in certain intervals. The reaction rate of isothiocyanate with OH^- ions was measured similarly. With some isothiocyanates preliminary measurements were accomplished at several temperatures (20—40°C). The rate constants of the chosen studied isothiocyanates are given in Table 3.

Table 3

Spectral data and rate constants

No.	λ_{max} [nm] log ε	k_{NH_2} [l mol^{-1} min^{-1}]	k_{OH} [l mol^{-1} min^{-1}]	ν_{as}(NCS) [cm^{-1}]
I	258 3.49	4.01 ± 0.14	11.57 ± 0.27	2062
II	252 3.13	2.22 ± 0.2	4.94 ± 0.09	2054
III	247 3.52	6.35 ± 0.4	18.32 ± 0.48	2052
IV	275 3.86	3.72 ± 0.19	6.72 ± 0.47	2053
V	256 3.48	4.15 ± 0.06	8.88 ± 0.19	2046
VI	250 3.21	2.75 ± 0.16	3.61 ± 0.1	2050
VII	—	—	—	2051
VIII	244 3.70	2.41 ± 0.07	4.4 ± 0.23	2052
IX	234 3.46	0.69 ± 0.1	3.42 ± 0.23	2044
X	255 3.52	6.34 ± 0.42	7.60 ± 0.12	2062
XI	274 3.52	12.55 ± 0.53	23.5 ± 2.0	2058
XII	—	—	—	2062
XIII	—	—	—	2061
XIV	254 3.50	3.12 ± 0.06	5.95 ± 0.13	2060
XV	252 3.38	1.43 ± 0.04	3.28 ± 0.07	2060
XVI	273 3.97	2.04 ± 0.05	4.08 ± 0.27	2046
XVIII	—	—	—	2062
XXII	—	—	—	2060
XXIV	—	—	—	2042
XXV	—	—	—	2040

Results and discussion

In this work described benzhydryl isothiocyanates were synthesized from the appropriate benzhydrylamines and thiophosgene in dichloroethane and water in the presence of calcium carbonate as a neutralizing agent. Isothiocyanates were isolated from the dichloroethane layer by removing the organic solvent and thiophosgene residues by distillation with water vapour. In this manner, isothiocyanates practically without thiophosgene ingredient were prepared. It was difficult to remove thiophosgene by other methods (*e.g.* by repeated distillation *in vacuo* or crystallization). Isothiocyanates were further purified according to their nature either by distillation under high vacuum or crystallization or by combination of these two methods. By this procedure, a series of new-synthesized isothiocyanates of high purity and yield was obtained. For instance, the prepared 4-methylbenzhydryl isothiocyanate, regarding the advantage of the mentioned procedure, was identified as a solid crystalline compound of m.p. 36°C while this com-

pound prepared by rearrangement of the appropriate thiocyanate was described in the literature [9] as a liquid. It can be stated that the reaction of benzhydrylamines with thiophosgene affording isothiocyanates proceeded with high degree of conversion and the loss in yields was only due to isolation and purification processes.

The investigated isothiocyanates showed two bands in the i.r. spectra at 2100 cm^{-1}. In contrast to benzyl isothiocyanates [15], the second band was here only a shoulder. The position of the main maximum of the absorption band ν_{as}(NCS) depended on the nature of the substituent and it was possible to correlate this band position with the Hammett σ constants (Table 3, Fig. 1).

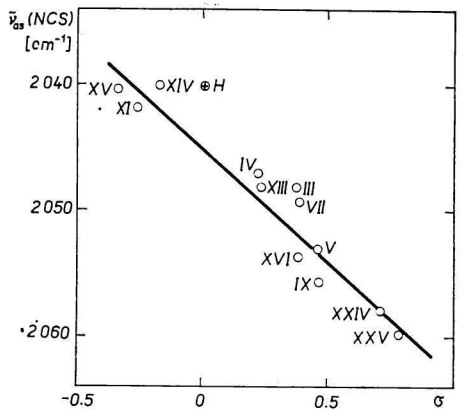


Fig. 1. Dependence of the vibration wavenumbers of the substituted benzhydryl isothiocyanates on the Hammett σ constants ($\varrho = -18.133$, $r = 0.95$).

The kinetics of addition of OH^- ions and $-NH_2$ group of glycine, respectively to —NCS group was followed by the method elaborated for studying the reactivity of aromatic isothiocyanates [14]. Comparison of the rate constants of the studied isothiocyanates indicated only slight differences in the reactivities of the individual derivatives. While the rate constant values of a similar series of substituted phenyl isothiocyanates varied in the range of 4—60 l mol^{-1} min^{-1} and those of the substituted benzyl isothiocyanates in the 2.74—7.64 l mol^{-1} min^{-1} range [15], in the case of benzhydryl isothiocyanates this region was 0.684—13.08 l mol^{-1} min^{-1}. The reactivity of —NCS group bound to aromatic ring through methylene group can be affected mainly by inductive effects of the substituents. These values of the rate constants indicated that the reactivity of the studied derivatives was not influenced significantly by substituents. The course of these reactions was influenced by further factors such as the bulkiness of the substituent and other sterical effects, the flexibility of the molecule, and the solubility of the derivatives. Probably owing to these factors, linear relationship was not found between the rate constants and the nature of the substituents. Similar phenomenon was observed with substituted benzyl isothiocyanates in our work [15] where the σ constants could have not been correlated with kinetic data.

References

1. Kalamár, J., Drobnica, Ľ., Antoš, K., Nemec, P., Bencze, K., and Kristian, P., *Czechoslov. Patent* 140 213 (1970); *British Patent* 1 200 689 (1970).
2. Kretschmar, W., *The Metabolism of Malaria Parasites* (Plasmodium *Berghei*, *Pl.*

Vickei) and the Antimalarial Activity of Isothiocyanates. Second International Symposium on Isothiocyanates, Smolenice, Nov. 1969.
3. Augustín, J., Drobnica, Ľ., Nemec, P., Antoš, K., Kalamár, J., and Kristian, P., *J. Antibiot.* ***21***, 497 (1968).
4. Braun, J. V. and Deutsch, H., *Ber.* ***45***, 2188 (1912).
5. Wheeler, H. L., *J. Amer, Chem. Soc.* ***26***, 345 (1904).
6. Iliceto, A., Fava, A., Mazzucato, U., and Radici, P., *Gazz. Chim. Ital.* ***90***, 919 (1960).
7. Najer, H. and Giudicelli, R., *Bull. Soc. Chim. Fr.* ***27***, 960 (1960).
8. Winthrop, S. O., Sybulski, S., Gavin, G., and Grant, G. A., *J. Amer. Chem. Soc.* ***79***, 3496 (1957).
9. Iliceto, A., Fava, A., Mazzucato, U., and Rossetto, O., *J. Amer. Chem. Soc.* ***83***, 2729 (1961).
10. Foffani, A., Mazzucato, U., Miotti, U., and Semerano, G., *Accademia nazionale dei lincei, Estratto dei Rendiconti della Classe di Scienze fisiche, matematiche e naturali,* Serie VIII, Vol. *XXIX*, fasc. 5 — Novembre 1960, p. 355.
11. Fava, A., Iliceto, A., Ceccon, A., and Koch, P., *J. Amer. Chem. Soc.* ***87***, 1045 (1965).
12. Kalamár, J. and Ryban, B., *Chem. Zvesti* ***20***, 70 (1966).
13. Kalamár, J., Bencze, K., and Křenek, P., *Chem. Zvesti* ***21***, 350 (1967),
14. Drobnica, Ľ. and Augustín, J., *Collect. Czech. Chem. Commun.* ***30***, 99 (1965).
15. Antoš, K., Štullerová, A., Knoppová, V., and Kristian, P., *Chem. Zvesti* ***19***, 353 (1965).

Translated by A. Kardošová