ANTIMYCOBACTERIAL THIOBENZANILIDES*

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Dedicated to Professor Otto Exner on the occasion of his 65th birthday.

A group of 30 thiobenzanilides active against *Mycobacterium kansasii* have been synthesized and their ^{1}H NMR and UV spectra and R_M values (TLC on silica gel impregnated with methylsilicone oil) have been measured. From the correlation between the chemical shifts of the thioamide proton in the ^{1}H NMR spectra and the Hammett constants it can be concluded that the substituents in both aromatic rings uniformly affect the electron density of the thioamide group. The antimycobacterial activity is probably connected with local molecular parameters and can be considered to be approximately additive with respect to both parts of the molecule.

One of our long-term projects concerns investigation of the dependence between lipophilicity and antituberculous activity of potential antituberculotics. The problem of relations between lipophilicity of molecules and general antibacterial activity was dealt with by Lien et al.[1]. They found that the most active inhibitors of growth of gram-negative bacteria exhibit the logarithm of the distribution coefficient octanol–water at the value of 4, whereas the growth inhibitors for gram-positive bacteria show values of about 6. These data found were related to the structure of cell wall whose increasing lipophilicity prevents penetration of lipophilic substances into the bacterium. In the report mentioned[1] no example was given concerning mycobacteria. Formally mycobacteria can be considered gram-positive bacteria, but in contrast to other bacterial strains of this group they contain strongly lipophilic mycolic acids (2,3-dialkyl-3-hydroxypropionic acids with 78–95 carbon atoms) in their cell wall. Therefore the conclusions derived from other gram-positive bacteria cannot be valid here.

In the context of systematic studies of compounds containing a thiocarbonyl group, we therefore decided to investigate the relations between structure of thio-

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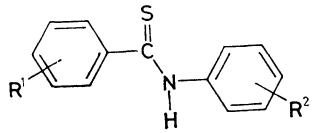
benzanilides and tuberculostatic activity of these compounds against *Mycobacterium kansasii*. *Mycobacterium kansasii* causes some tuberculous diseases and current antituberculotics are less efficient against it. The antituberculotic activity of thiobenzamides was pointed out by Mollin et al.[2] The aim of the present study was to synthesize 30 thiobenzanilides, to experimentally determine some of their molecular



parameters (the chemical shift of the thioamide proton in ^{1}H NMR spectra, wavenumber of the absorption maximum in UV spectra, the R_M values of partition chromatography on thin layers). For the purpose of study of antimycobacterial activity in vitro we chose the Sauton protein-free synthetic medium which represents a simple system suitable for studies of mechanism of activity of antimycobacterial compounds. The variations of substituents were carried out according to Topliss[3], which is advantageous if the activity order of the substances prepared should be used in searching the molecular parameters important for the activity. When planning the experiments we hoped that the regularities found would be describable by regression equations.

EXPERIMENTAL

Chemicals. All the thiobenzanilides studied were prepared by the procedure according to Pravdić and Hahn[4]: a 3 h refluxing of 1 mol of the corresponding benzanilide with 0·5 to 0·75 mol phosphorus pentasulfide in pyridine. The reaction mixture was then cooled and poured onto water, the raw product was collected by suction and repeatedly recrystallized from methanol or ethanol. The substances for analysis and further measurements and biological tests were dried over phosphorus pentoxide under the pressure of 1·5 kPa 3 days. Thiobenzanilide (*I*), 61%, m.p. 101–103°C (ref.[5] gives m.p. 98°C); 4′-methoxythiobenzanilide (*II*), 41%, m.p. 133–135°C (ref.[6] gives m.p. 133°C); 4′-methylthiobenzanilide (*III*), 40%, m.p. 129–132°C (ref.[6] gives m.p. 131°C); 4′-chlorothiobenzanilide (*IV*), 69%, m.p. 149°C (ref.[6] gives m.p. 149°C); 3′,4′-dichlorothiobenzanilide (*V*), 66%, m.p. 148–150°C (ref.[7] gives m.p.142–146·5°C); 4′-bromothiobenzanilide (*VI*), 55%, m.p. 152°C (ref.[8] gives m.p. 152–153°C); 4-methoxythiobenzanilide (*VII*), 84%, m.p. 153°C (ref.[9] gives m.p. 153–154°C); 4,4′-dimethoxythiobenzanilide (*VIII*), 80%. m.p. 147–149°C (ref.[10] gives m.p. 148°C); 4-methoxy-4′-methylthiobenzanilide (*IX*), 85%, m.p, 158°C (ref.[10] gives m.p. 157°C); 4′-chloro-4-methoxythiobenzanilide (*X*), 94%, m.p. 181°C (ref.[11] gives m.p. 182°C); 4-methylthiobenzanilide (*XIII*), 94%, m.p. 142–145°C (ref.[12] gives m.p. 142–144°C); 4,4′-dimethylthiobenzanilide (*XV*), 86%, m.p. 169–171°C (ref.[13] gives m.p. 165–166°C); 4-chlorothiobenzanilide (*XIX*), 47%, m.p. 157–159°C (ref.[14] gives m.p 157–159°C); 4-chloro-4′-methoxythiobenzanilide (*XX*), 50%, m.p. 171–173°C (ref.[2] gives m.p. 168–172°C); 4-chloro-4′-methylthiobenzanilide (*XXI*), 51%, m.p. 180–182°C (ref.[2] gives m.p. 178–182°C); 4,4′-dichlorothiobenzanilide (*XXII*), 66%, m.p. 208–209°C (ref.[15] gives m.p. 206–207°C). Properties of newly prepared compounds are presented in Table I.

Physical Measurements

^1H NMR Spectra. The ^{1}HNMR spectra were measured with a Tesla BS 497 (100 MHz) apparatus in dimethyl sulfoxide at 21°C. The chemical shift values δ (ppm) of the proton of thioamide group referenced to internal tetramethylsilane are presented in Table II.

UV Spectra. The UV spectra were measured with a Specord UV-VIS apparatus (Zeiss Jena, G.D.R.) in aqueous solutions. The results are summarized in Table II.

Measurements of Lipophilicity. These measurements were carried out by TLC (Silufol UV 254, Kavalier-Votice; silica gel with starch as the binding agent and with an UV indicator; impregnated with silicone oil Lukoil M 100; the impregnation was accomplished by capillary elevation of 5% Lukoil solution in ether overnight, subsequent 12 h drying at room temperature, and repeated impregnation from the opposite side of the plate). The samples for chromatography were dissolved in chloroform. The chromatograms were developed with aqueous methanol (MeOH concentrations 40, 50, and 60 vol. %). Various combinations of the compounds along with the unsubstituted thiobenzanilide (*I*) as a standard were placed on the individual plates. For each compound the estimation was repeated at least six times, and standardization was carried out with the use of Eqs (*1*) and (*2*) (as in one of our earlier papers[16]) to eliminate random effects.

$$(R_M)_{exp} - (R_M)_{st} = \Delta R_M \qquad (1)$$

$$R_M = [\sum_1^m (R_M)_{st}]/m + [\sum_1^n \Delta R_M]/n\,, \qquad (2)$$

where $(R_M)_{exp}$ means the value of R_M of the compound followed in the given experiment, $(R_M)_{st}$ is the R_M value of the standard in this experiment, n is number of measurements of the compound followed ($n \geqq 6$), m is number of determination of the standard ($m = 30$). The standardized R_M values for each methanol concentration as well as those extrapolated to 0% methanol in the mobile phase are summarized in Table III.

Microbiological Evaluation

The microbiological tests were carried out on a synthetic liquid medium without proteins (by Sauton) with *Mycobacterium kansasii* PKG 8 (the collection of Dr Runyon, Salt Lake City). The antibacterial substances were dissolved in dimethyl sulfoxide prior to addition to the medium. The concentrations of 4, 7, 15, 31, 62, 125, 250, 500, 1 000 and 2 000 μmol/l, and exceptionally 750 μmol/l were used. The values of minimum inhibitory concentrations were read after 14 days incubation at 37°C and the logarithms of these data are given in Table II.

Calculations

The regression equations were calculated on a table computer IQ-151 using a Multireg-H program. The calculations of the Free–Wilson analysis were carried out on a Tesla SM 14-20 computer with the use of an adapted program by Purcell[17].

DISCUSSION

In quantitative evaluations of relations between chemical structure and biological activity one usually solves regression equations involving structural parameters as independent variables. If the structure is described by parameters connected with

TABLE I
Thiobenzanilides

Compound	R^1	R^2	Yield %	M.p. °C	Formula (M.w.)	Calculated/Found					
						% C	% H	% N	% S	% Cl	% Br
XI	4-OCH_3	3′,4′-Cl_2	70	134	$C_{14}H_{11}Cl_2NOS$	53·85	3·55	4·48	10·27	22·71	
					(312·2)	53·71	3·52	4·42	10·25	22·58	
XII	4-OCH_3	4′-Br	72	179	$C_{14}H_{12}BrNOS$	52·18	3·75	4·34	9·94		24·79
					(322·2)	51·90	3·78	4·34	9·76		24·71
XIV	4-CH_3	4′-OCH_3	98	137—140	$C_{15}H_{15}NOS$	70·04	5·87	5·44	12·45		
					(257·3)	70·05	5·85	5·42	12·35		
XVI	4-CH_3	4′-Cl	88	203—205	$C_{14}H_{12}ClNS$	64·24	4·62	5·35	12·24	13·54	
					(261·8)	64·35	4·53	5·49	12·36	14·06	
XVII	4-CH_3	3′,4′-Cl_2	97	146—149	$C_{14}H_{11}Cl_2NS$	56·77	3·74	4·73	10·82	23·93	
					(296·2)	56·85	3·66	4·95	10·64	23·65	
XVIII	4-CH_3	4′-Br	89	210—212	$C_{14}H_{12}BrNS$	54·91	3·94	4·57	10·46		26·09
					(306·2)	54·95	4·01	4·71	10·48		26·01
XXIII	4-Cl	3′,4′-Cl_2	44	129—131	$C_{13}H_8Cl_3NS$	49·31	2·54	4·42	10·12	33·59	
					(316·6)	49·12	2·57	4·32	10·28	33·52	

XXIV	4-Cl	4′-Br	52	118	$C_{13}H_9ClBrNS$	47·80	2·77	4·28	9·81	10·85	24·46
					(326·6)	47·85	2·80	4·27	9·95	10·50	24·80
XXV	3-Br	H	95	116—117	$C_{13}H_{10}BrNS$	53·43	3·44	4·79	10·97		27·34
					(292·2)	53·38	3·51	4·94	11·03		27·38
XXVI	3-Br	4′-OCH_3	96	99—100	$C_{14}H_{12}BrNOS$	52·18	3·75	4·34	9·94		24·79
					(322·2)	52·37	3·74	4·47	10·07		24·73
XXVII	3-Br	4′-CH_3	95	101—103	$C_{14}H_{12}BrNS$	54·91	3·94	4·57	10·46		26·09
					(306·2)	54·95	4·01	4·71	10·57		26·37
XXVIII	3-Br	4′-Cl	83	117—118	$C_{13}H_9ClBrNS$	47·80	2·77	4·28	9·81	10·85	24·46
					(326·6)	48·16	2·87	4·41	10·09	10·54	24·98
XXIX	3-Br	3′,4′-Cl_2	95	119—121	$C_{13}H_8Cl_2BrNS$	43·24	2·23	3·87	8·87	19·63	22·12
					(361·1)	43·44	2·31	3·86	8·71	19·70	22·20
XXX	3-Br	4′-Br	96	136—138	$C_{13}H_9Br_2NS$	42·07	2·44	3·78	8·63		43·06
					(371·1)	42·59	2·56	4·05	8·69		43·21

physical and physico-chemical characteristics of the substances (lipophilicity and, as the case may be, its square, electronic parameter and possibly also steric parameter), then this approach is called the Hansch procedure[17-21]. Most often used are the substituent constants. Attempts at interpretation of antimycobacterial activity by means of the Hansch analysis using published substituent constants[18-21] gave

TABLE II

The sum of the Hammett substituent constants ($\sum\sigma$), the proton chemical shifts (δ, ppm) of thioamide group, wavelength of the absorption maxima in UV spectra (λ, nm) and logarithm of the minimum inhibitory concentration (log MIC, μmol/l) against *Mycobacterium kansasii*

Compound	$\sum\sigma$	δ	λ	log MIC[a]
I	0	11·73	260	1·792
II	−0·27	11·60	270	1·792
III	−0·17	11·64	263	2·097
IV	0·23	11·78	263	1·792
V	0·45	11·88	263	1·491
VI	0·23	11·78	267	1·491
VII	−0·27	11·51	276	1·792
VIII	−0·54	11·39	290	2·398
IX	−0·44	11·44	288	2·875
X	−0·04	11·57	278	2·699
XI	0·18	11·65	287	1·792
XII	−0·04	11·56	291	2·398
XIII	−0·17	11·62	270	1·792
XIV	−0·44	11·50	278	1·792
XV	−0·34	11·54	270	2·097
XVI	0·06	11·69	278	3·301
XVII	0·28	11·77	270	1·792
XVIII	0·06	11·68	270	3·000
XIX	0·23	11·78	267	2·097
XX	−0·04	11·68	277	1·792
XXI	0·06	11·70	270	2·097
XXII	0·46	11·85	270	2·097
XXIII	0·68	11·93	270	1·491
XXIV	0·46	11·84	267	2·398
XXV	0·39	11·86	263	1·491
XXVI	0·12	11·73	257	1·792
XXVII	0·22	11·78	263	1·491
XXVIII	0·62	11·92	257	2·097
XXIX	0·84	11·99	250	1·491
XXX	0·62	11·91	263	1·792

[a] For comparison: log MIC isonicotinohydrazide 1·491 μmol/l.

only statistically insignificant equations ($r \approx 0{\cdot}4$). Therefore we tried to directly measure the physical properties of the compounds prepared. The values of chemical shifts of the proton in thioamide group (^{1}H NMR spectra) was followed as the electronic parameter. However, the values empirically obtained correlated with the Hammett constants of both the substituent groups varied (σ_1 and σ_2 relate to substituents of the thioacyl and anilide moieties of the molecule, respectively). The values

TABLE III

R_M values of partition TLC in various concentration of methanol in water (vol. %) the R_M values extrapolated to 0% methanol and the sum of the hydrophobic substituent constants ($\sum\pi$)

Compound	$R_M(60)$	$R_M(50)$	$R_M(40)$	$R_M(0)$	$\sum\pi$
I	−0·114	0·212	0·556	1·893	0
II	−0·119	0·210	0·643	2·150	−0·03
III	−0·075	0·255	0·778	2·452	0·60
IV	−0·007	0·534	1·033	3·120	0·73
V	0·284	0·868	1·443	3·763	1·45
VI	0·058	0·602	1·094	3·175	1·19
VII	−0·166	0·208	0·556	1·962	−0·03
VIII	−0·161	0·160	0·650	2·257	−0·06
IX	0·105	0·400	0·866	2·607	0·57
X	0·085	0·524	0·891	2·778	0·70
XI	0·243	0·764	1·522	3·125	1·42
XII	0·121	0·559	1·092	2·792	1·16
XIII	−0·152	0·345	0·788	2·677	0·60
XIV	−0·682	0·104	0·556	3·088	0·57
XV	−0·023	0·382	0·954	2·050	1·20
XVI	0·133	0·617	1·301	3·604	1·33
XVII	0·321	0·886	1·484	3·804	1·05
XVIII	0·090	0·627	1·426	4·054	1·79
XIX	0·105	0·461	1·038	2·867	0·73
XX	0·040	0·430	0·993	2·870	0·70
XXI	0·194	0·667	1·168	3·111	1·33
XXII	0·246	0·782	1·348	3·547	1·46
XXIII	0·471	1·090	1·664	4·058	1·18
XXIV	0·264	0·831	1·280	3·332	1·92
XXV	0·031	0·471	1·403	4·065	0·96
XXVI	0·022	0·592	1·487	4·363	0·93
XXVII	0·226	0·768	1·591	4·274	1·56
XXVIII	0·773	1·281	1·985	4·376	1·69
XXIX	0·750	1·411	1·966	4·416	1·41
XXX	0·493	0·980	1·862	4·534	2·15

of chemical shifts supply similar information as the sum of the Hammett constants does, see Eqs (*3*) and (*4*).

$$\delta = 0{\cdot}418\,(\sigma_1 + \sigma_2) + 11{\cdot}663 \qquad (3)$$

$$r = 0{\cdot}967 \quad s = 0{\cdot}04 \quad F = 406{\cdot}83 \quad n = 30$$

$$\delta = 0{\cdot}482\sigma_1 + 0{\cdot}304\sigma_2 + 11{\cdot}661 \qquad (4)$$

$$r = 0{\cdot}974 \quad s = 0{\cdot}04 \quad F = 251{\cdot}41 \quad n = 30$$

For the lipophilicty parameer we took the R_M values from partition TLC. However, the correlations with published values of hydrophobic substituent constant were less significant than those of the above-mentioned relations between the electronic parameters. Within the range of methanol concentrations in the mobile phase, the value of correlation coefficient increased with decreasing methanol concentration in the mobile phase. As an example given is Eq. (*5*) correlating the R_M values (obtained in 40% methanol) with the sum of hydrophobic substituent constants.

$$(R_M)_{40} = 0{\cdot}590\,(\pi_1 + \pi_2) + 0{\cdot}586 \qquad (5)$$

$$r = 0{\cdot}828 \quad s = 0{\cdot}238 \quad F = 61{\cdot}18 \quad n = 30$$

However, even the application of experimentally obtained electronic and lipophilic parameters did not lead to any more significant increase of correlation of the antimycobacterial activity with structural parameters in the equations of the Hansch type.

Therefore, we extended the number of currently used parameters by another independent parameter, the wavelength of the absorption maximum in the UV spectra. The dependence of antituberculous activity on this parameter has already been described in literature[22,23] for some groups of compounds. The wavelength values of the absorption maxima can be considered an electronic parameter which does not correlate with the Hammett constants[19]. But even the introduction of this parameter into the equations of the Hansch type did not result in any substantial increase of statistical significance of the correlation equations with the antimycobacterial activity in the compound set followed ($r \approx 0{\cdot}52$). We stopped further attempts at looking for the equations of the Hansch type.

For subsequent studies we adopted the analysis according to Free and Wilson[24]. This approach takes the resulting biological activity as being additive with regard to the effects of individual molecular fragments. The analysis led to more favourable results (Table IV). Using the Topliss analysis[3] we could infer from the order of substituent contributions to the antimycobacterial activity at both of the varied parts of the molecule that in the anilide moiety of the molecule a parabolic relationship

exists between the activity and lipophilicity of substituents, whereas in the thioacyl section the dependence is linear with respect to both electronic and lipophilicity parameters. The relation was expressed by Eq. (*6*) in which π^- constants (derived from substituted anilines[25]) were preferred for the anilide section of the molecule. The indexes denoting the individual parts of the molecule are analogous to those in Eq. (*4*). The value of correlation coefficient is somewhat increased, if also in the thioacyl section the hydrophobicity constants are more adapted to the set studied and the π^{th} constants (derived from thiobenzamides[26]) are used (Eq. (*7*)).

$$\log \text{MIC} = 0{\cdot}477\pi_1 - 1{\cdot}452\sigma_1 - 0{\cdot}692\,(\pi_2^-)^2 + 1{\cdot}035\pi_2^- + 1{\cdot}749 \qquad (6)$$

$$r = 0{\cdot}747 \quad s = 0{\cdot}34 \quad F = 7{\cdot}90 \quad n = 30$$

$$\log \text{MIC} = 0{\cdot}644\pi_1^{th} - 1{\cdot}862\sigma_1 - 0{\cdot}692\,(\pi_2^-)^2 + 1{\cdot}035\pi_2^- + 1{\cdot}669 \qquad (7)$$

$$r = 0{\cdot}769 \quad s = 0{\cdot}33 \quad F = 9{\cdot}05 \quad n = 30$$

The dependence of antimycobacterial activity on physical and physico-chemical properties of some parts of the molecule (i.e. on local molecular parameters) is typical of strongly lipophilic compounds[27-29]. We presume that these substances operate in the cell wall or on the surface of cell wall, and the transport into the molecule

TABLE IV

The Hammett substituent constants (σ), the hydrophobic substituent constants (π, π^{th}, π^-) and the activity contributions of Free–Wilson analysis (Δ log MIC)

Substituent	σ^a	π^a	π^{th}	π^-	Δ log MIC^e
4-H	0	0	0	—	−0·268
4-OCH_3	−0·27	−0·03	0·00[b]	—	0·315
4-CH_3	−0·17	0·60	0·42[b]	—	0·285
4-Cl	0·23	0·73	0·90[b]	—	−0·015
3-Br	0·39	0·96	1·02[b]	—	−0·318
4′-H	0	0	—	0	−0·218
4′-OCH_3	−0·27	−0·03	—	−0·12[c]	−0·097
4′-CH_3	−0·17	0·60	—	0·48[c]	0·121
4′-Cl	0·23	0·73	—	0·93[c]	0·387
3′4′-Cl_2	0·45[d]	1·45	—	1·72[c]	−0·399
4′-Br	0·23	1·19	—	1·13[c]	0·206
μ_0[f]	—	—	—	—	2·010

[a] From ref.[18]; [b] from ref.[26]; [c] from ref.[20]; [d] from ref.[30]; [e] $r = 0{\cdot}807$, $s = 0{\cdot}337$, $F = 4{\cdot}15$, $n = 30$; [f] parent structure.

of mycobacterium does not make itself felt. Therefore, it is impossible to find equations of the Hansch type which adopt the lipophilicity of a molecule as a whole. Therefore, we accepted Eq. (*7*) as a working hypothesis.

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