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L. F. TREFILOVA and I. Ya. POSTOVSKII

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Abstract

Full Text

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L. F. TREFILOVA and I. Ya. POSTOVSKII

SOME DIPHENYL DERIVATIVES AND THEIR TUBERCULOSTATIC ACTIVITY

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It is known that unsubstituted aniline has tuberculostatic action *in vitro* at a concentration of (2 10^{-4}) mol/l ((^1)). Para-substituted anilines —4-aminophenol, 4-methoxyaniline, 4-ethoxyaniline, 4-propoxyaniline—show greater activity: their tuberculostatic action appears at concentrations of (2 10^{-4}), (1 10^{-5}), (1.25 10^{-6}), (6.25 10^{-7}) mol/l ((^2)). A significantly more active compound than aniline proved to be 4-aminodiphenyl: it shows tuberculostatic action already at a concentration of (1.25 10^{-7}) mol/l ((^4)). Taking these observations into account, Ch. P. Ivanov and I. M. Panaiotov ((^5)) synthesized 4-hydroxy-4-aminodiphenyl and its alkyl ethers for testing their tuberculostatic activity.

Among derivatives of aromatic amines, azomethines and thiourea derivatives may be of interest as tuberculostatic compounds. The tuberculostatic activity of azomethines had already been studied earlier by Erlenmeyer and co-workers ((^6)) and by Bäuzer and co-authors ((^7)). The fungicidal action of certain azomethines is also known ((^8)). As for thiourea derivatives, they have more than once been the subject of investigations of their antitubercular and fungicidal properties ((^9)).

In the course of our investigations on the synthesis of compounds with possible antitubercular action, starting from 4-aminodiphenyl and its para-alkoxy derivatives, we obtained a series of new diphenyl derivatives, in particular azomethines (Table 1) and (N,N')-substituted thioureas (Table 2). In addition, azomethines —derivatives of 4-diphenylaldehyde—were obtained.

The azomethines (Table 1) were obtained in almost quantitative yield by heating, in alcoholic solution, equimolecular amounts of 4-aminodiphenyl and its (n)-alkoxy derivatives with various aromatic aldehydes (benzaldehydes 1-5, salicylic aldehyde 6-10, vanillin 11-15, para-acetylaminobenzaldehyde 16-20, cinnamic aldehyde 21-25, piperonal 26), and also with furfural 27-31 and 9-formylacridine 32. Azomethines from 4-diphenylaldehyde were synthesized by reaction of this aldehyde with aromatic amines (aniline 33, (n)-anisidine 34, sulfanilamide 35, 4-aminodiphenyl 36, and 4-amino-4-methoxydiphenyl 37). The azomethines obtained are yellowish or yellow crystalline substances that crystallize well from alcohol, acetone, and dioxane.

Derivatives of (N)-diphenyl-(N')-phenylthiourea (Table 2) were obtained in good yield (80-96%) by heating, in alcoholic solution, equimolecular amounts of 4-aminodiphenyl and its (n)-alkoxy derivatives with various mustard oils (allyl mustard oil 1-5, (n)-methoxyphenyl mustard oil 6-10, (n)-ethoxyphenyl mustard oil 11-15, (n)-chlorophenyl mustard oil 16-20). The thioureas obtained are colorless crystalline substances crystallizing from alcohol.

Table 1

No.	Compound	Substituent (X)	Empirical formula	M.p., °C	N, % found	N, % calc.
1	X-C_6H_4-C_6H_4-N=CH-C_6H_5	H	$C_{19}H_{15}N$	147-148[10]		
2	X-C_6H_4-C_6H_4-N=CH-C_6H_5	HO	$C_{19}H_{15}ON$	202-203[11]		
3	X-C_6H_4-C_6H_4-N=CH-C_6H_5	CH_3O	$C_{20}H_{17}ON$	173-174	4.99	4.88
4	X-C_6H_4-C_6H_4-N=CH-C_6H_5	C_2H_5O	$C_{21}H_{19}ON$	146-147	4.90	4.65
5	X-C_6H_4-C_6H_4-N=CH-C_6H_5	C_4H_9O	$C_{23}H_{23}ON$	180-181	4.29	4.25
6	X-C_6H_4-C_6H_4-N=CH-C_6H_4-OH	H	$C_{19}H_{15}ON$	140-141	5.29	5.13

No.	Compound	Substituent (X)	Empirical formula	M.p., °C	N, % found	N, % calc.
7	X-C_6H_4-C_6H_4-N=CH-C_6H_4-OH	HO	$C_{19}H_{15}O_2N$	210–212	4.85	4.84
8	X-C_6H_4-C_6H_4-N=CH-C_6H_4-OH	CH_3O	$C_{20}H_{17}O_2N$	193–194	4.65	4.62
9	X-C_6H_4-C_6H_4-N=CH-C_6H_4-OH	C_2H_5O	$C_{21}H_{19}O_2N$	185–186	4.64	4.41
10	X-C_6H_4-C_6H_4-N=CH-C_6H_4-OH	C_4H_9O	$C_{23}H_{23}O_2N$	175–176	4.17	4.06
11	X-C_6H_4-C_6H_4-N=CH-$C_6H_3(OH)(OCH_3)$	H	$C_{20}H_{17}O_2N$	185–186	4.82	4.62
12	X-C_6H_4-C_6H_4-N=CH-$C_6H_3(OH)(OCH_3)$	HO	$C_{20}H_{17}O_3N$	254–255	4.64	4.39
13	X-C_6H_4-C_6H_4-N=CH-$C_6H_3(OH)(OCH_3)$	CH_3O	$C_{21}H_{19}O_3N$	186–187	4.41	4.20

No.	Compound	Substituent (X)	Empirical formula	M.p., °C	N, % found	N, % calc.
14	X-C_6H_4-C_6H_4-N=CH-$C_6H_3(OH)(OCH_3)$	C_2H_5O	$C_{22}H_{21}O_3N$	182–183	4.30	4.03
15	X-C_6H_4-C_6H_4-N=CH-$C_6H_3(OH)(OCH_3)$	C_4H_9O	$C_{24}H_{25}O_3N$	129–130	4.07	3.73
16	X-C_6H_4-C_6H_4-N=CH-C_6H_4-$NHCOCH_3$	H	$C_{21}H_{18}ON_2$	235–236	8.55	8.91
17	X-C_6H_4-C_6H_4-N=CH-C_6H_4-$NHCOCH_3$	HO	$C_{21}H_{18}O_2N_2$	244–246	8.66	8.84
18	X-C_6H_4-C_6H_4-N=CH-C_6H_4-$NHCOCH_3$	CH_3O	$C_{22}H_{20}O_2N_2$	263–264	8.34	8.13
19	X-C_6H_4-C_6H_4-N=CH-C_6H_4-$NHCOCH_3$	C_2H_5O	$C_{23}H_{22}O_2N_2$	273–279	8.06	7.82
20	X-C_6H_4-C_6H_4-N=CH-C_6H_4-$NHCOCH_3$	C_4H_9O	$C_{25}H_{26}O_2N_2$	244–245	7.44	7.25

No.	Compound	Substituent (X)	Empirical formula	M.p., °C	N, % found	N, % calc.
21	X-C_6H_4-C_6H_4-N=CH-CH=CH-C_6H_5	H	$C_{21}H_{17}N$	189-190	4.88	4.94
22	X-C_6H_4-C_6H_4-N=CH-CH=CH-C_6H_5	HO	$C_{21}H_{17}ON$	210-211	4.71	4.68
23	X-C_6H_4-C_6H_4-N=CH-CH=CH-C_6H_5	CH_3O	$C_{22}H_{19}ON$	190-191	4.63	4.47
24	X-C_6H_4-C_6H_4-N=CH-CH=CH-C_6H_5	C_2H_5O	$C_{23}H_{21}ON$	181-182	4.54	4.28
25	X-C_6H_4-C_6H_4-N=CH-CH=CH-C_6H_5	C_4H_9O	$C_{25}H_{25}ON$	175-176	4.08	3.94
26	C_6H_5-C_6H_4-N=CH-benzodioxolyl	–	$C_{20}H_{15}O_2N$	144-145	4.82	4.65
27	X-C_6H_4-C_6H_4-N=CH-furyl	H	$C_{13}H_{13}ON$	106-107	5.70	5.66

No.	Compound	Substituent (X)	Empirical formula	M.p., °C	N, % found	N, % calc.
28	X-C_6H_4-C_6H_4-N=CH-furyl	HO	$C_{17}H_{13}O_2N$	266–267	5.35	5.32
29	X-C_6H_4-C_6H_4-N=CH-furyl	CH_3O	$C_{18}H_{15}O_2N$	126–127	5.03	5.05
30	X-C_6H_4-C_6H_4-N=CH-furyl	C_2H_5O	$C_{19}H_{17}O_2N$	157–158	4.83	4.81
31	X-C_6H_4-C_6H_4-N=CH-furyl	C_4H_9O	$C_{21}H_{21}O_2N$	165–166	4.51	4.39
32	C_6H_5-C_6H_4-N=CH-[[unclear: fused N-containing aromatic ring]]	—	$C_{26}H_{18}N$	205–206	7.98	7.82
33	C_6H_5-C_6H_4-CH=N-C_6H_5	—	$C_{19}H_{15}N$	150–151[12]		
34	C_6H_5-C_6H_4-CH=N-C_6H_4-OCH_3	—	$C_{20}H_{17}ON$	181–182	5.07	4.88

No.	Compound	Substituent (X)	Empirical formula	M.p., °C	N, % found	N, % calc.
35	C_6H_5-C_6H_4-CH=N-C_6H_4-SO_2NH_2	—	$C_{19}H_{16}O_2N_2S$	239-240	8.29	8.33
36	C_6H_5-C_6H_4-CH=N-C_6H_4-C_6H_5	—	$C_{25}H_{19}N$	245-246[13]		
37	C_6H_5-C_6H_4-CH=N-C_6H_4-C_6H_4-OCH_3	—	$C_{26}H_{21}ON$	241-243	3.99	3.86

The melting points and the results of analysis of the azomethines are given in Table 1, and those of the thioureas in Table 2.

Azomethines described in the literature are 1[10], 2[11], 33[12], 36[13] (Table 1), and the thiourea derivatives are 6[14], 11 and 16[15] (Table 2). The remaining compounds presented here were obtained for the first time.

In testing the tuberculostatic action of the azomethines *in vitro* against the virulent strain K_1 (human type), compounds 1, 6, 11, 13, 32 (Table 1) completely inhibited bacterial growth at drug concentrations from (1 10^{-6}) to (1 10^{-7}); the other compounds were less active, or exhibited no tuberculostatic activity at all.

The thiourea derivatives (Table 2) showed no activity at concentrations greater than (1 10^{-4}). Thus, thiourea derivatives with a diphenyl residue should be assigned to compounds weakly active with respect to the tubercle bacillus *in vitro*, although the corresponding phenyl compounds are distinguished by high activity.

Table 2

No.	Compound	Substituent (X)	Empirical formula	m.p., °C	N, % found	N, % calc.
1	X-diphenyl-NH-C(=S)-NHCH$_2$CH=CH$_2$	H	$C_{16}H_{16}N_2S$	159–160	10.57	10.44
2	X-diphenyl-NH-C(=S)-NHCH$_2$CH=CH$_2$	HO	$C_{16}H_{16}ON_2S$	237–238	10.01	9.85
3	X-diphenyl-NH-C(=S)-NHCH$_2$CH=CH$_2$	CH$_3$O	$C_{17}H_{18}ON_2S$	177–178	9.20	9.39
4	X-diphenyl-NH-C(=S)-NHCH$_2$CH=CH$_2$	C$_2$H$_5$O	$C_{18}H_{20}ON_2S$	169–170	8.94	8.97
5	X-diphenyl-NH-C(=S)-NHCH$_2$CH=CH$_2$	C$_4$H$_9$O	$C_{20}H_{24}ON_2S$	169–170	8.38	8.23
6	X-diphenyl-NH-C(=S)-NH-C$_6$H$_4$-OCH$_3$	H	$C_{20}H_{18}ON_2S$	183–194^(14)	–	–
7	X-diphenyl-NH-C(=S)-NH-C$_6$H$_4$-OCH$_3$	HO	$C_{20}H_{18}O_2N_2S$	245–246	8.33	8.00

No.	Compound	Substituent (X)	Empirical formula	m.p., °C	N, % found	N, % calc.
8	X-diphenyl-NH-C(=S)-NH-C_6H_4-OCH_3	CH_3O	$C_{21}H_{20}O_2N_2S$	206–207	8.05	7.69
9	X-diphenyl-NH-C(=S)-NH-C_6H_4-OCH_3	C_2H_5O	$C_{22}H_{22}O_2N_2S$	209–210	7.43	7.40
10	X-diphenyl-NH-C(=S)-NH-C_6H_4-OCH_3	C_4H_9O	$C_{24}H_{26}O_2N_2S$	202–203	7.11	6.89
11	X-diphenyl-NH-C(=S)-NH-C_6H_4-OC_2H_5	H	$C_{21}H_{20}ON_2S$	197–198^(15)	–	–
12	X-diphenyl-NH-C(=S)-NH-C_6H_4-OC_2H_5	HO	$C_{21}H_{20}O_2N_2S$	243–245	7.79	7.69
13	X-diphenyl-NH-C(=S)-NH-C_6H_4-OC_2H_5	CH_3O	$C_{22}H_{22}O_2N_2S$	210–212	7.50	7.40

No.	Compound	Substituent (X)	Empirical formula	m.p., °C	N, % found	N, % calc.
14	X-diphenyl-NH-C(=S)-NH-C_6H_4-OC_2H_5	C_2H_5O	$C_{23}H_{24}O_2N_2S$	211-212	7.14	7.14
15	X-diphenyl-NH-C(=S)-NH-C_6H_4-OC_2H_5	C_4H_9O	$C_{25}H_{28}O_2N_2S$	204-205	6.78	6.66
16	X-diphenyl-NH-C(=S)-NH-C_6H_4-Cl	H	$C_{19}H_{15}N_2SCl$	201-203*	8.39	8.27
17	X-diphenyl-NH-C(=S)-NH-C_6H_4-Cl	HO	$C_{19}H_{16}ON_2SCl$	246-247	7.99	7.90
18	X-diphenyl-NH-C(=S)-NH-C_6H_4-Cl	CH_3O	$C_{20}H_{17}ON_2SCl$	215-216	7.78	7.60
19	X-diphenyl-NH-C(=S)-NH-C_6H_4-Cl	C_2H_5O	$C_{21}H_{19}ON_2SCl$	216-218	7.33	7.32

No.	Compound	Substituent (X)	Empirical formula	m.p., °C	N, % found	N, % calc.
20	X-diphenyl-NH-C(=S)-NH-C_6H_4-Cl	C_4H_9O	$C_{22}H_{23}ON_2SCl$	206–207	6.86	6.82

* In (15) 195°.

It is interesting that azomethine, obtained from 4-diphenylaldehyde and aniline (33), has absolutely no effect on the growth of tubercle bacilli, whereas the isomeric azomethine, obtained from 4-aminodiphenyl and benzaldehyde (1), possesses high tuberculostatic activity, (0.2 10^{-6}). Compounds 34, 35, 36, and 37 also proved inactive. This indicates that, in the manifestation of antitubercular action, the essential role is played not so much by the diphenyl residue as by 4-aminodiphenyl.

The toxicity of the most active azomethines 1, 6, 11, and 13 (Table 1) was tested on white mice. The indicated azomethines proved to be considerably less toxic than 4-aminodiphenyl; however, in experiments on mice infected with the virulent strain K_1, they did not show a therapeutic effect.*

The microbiological tests of the compounds described here and the experiments on white mice were carried out by Candidate of Medical Sciences E. I. Chertkova (Sverdlovsk Scientific-Research Tuberculosis Institute).

Experimental Part

1. Preparation of 2-oxy-3-methoxybenzylidene-4-aminodiphenyl (11, Table 1). To a hot solution of 1.69 g (0.01 mole) of 4-aminodiphenyl in 4 ml of alcohol was added a hot solution of 1.52 g (0.01 mole) of vanillin in 4 ml of alcohol. The mixture was heated on a water bath for half an hour. After 10 min the solution becomes orange and small crystals precipitate from it. After cooling, the azomethine was filtered off and dried, m.p. 184–186°. Yield 2.9 g (95.7% of theory). The product was recrystallized from alcohol—yellow needles, m.p. 185–186° (for analysis see Table 1).

2. Preparation of N-4-(4′-methoxydiphenyl)-N′-(ethoxyphenyl)thiourea (13, Table 2). To a hot solution of 0.4 g

* It is evidently of interest to carry out further testing of the physiological action of the azomethines presented here, in particular their carcinogenic properties, if one takes into account that 4-aminodiphenyl shows a clearly carcinogenic action (16). The possibility is not excluded of finding among the azomethines of

diphenyl carcinostatic substances as well, especially since one of the azomethines of the fluorene series, related to the carcinogenic derivative of fluorene, showed anticancer action (17).

A solution of 0.36 g (0.002 mole) of *p*-ethoxyphenyl isocyanate in 3 ml of alcohol was added to 0.46 g (0.002 mole) of 4-methoxy-4-aminodiphenyl in 10 ml of alcohol. The mixture was heated on a water bath for 15 min; the small colorless crystals that precipitated after cooling were filtered off and dried, m.p. 210-212°. Yield 0.7 g (92% of theory). After recrystallization from alcohol, m.p. 211-212° (for analysis see Table 2).

Ural Polytechnic Institute
named after S. M. Kirov

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Note: Figure translations are in progress. See original paper for figures.