278. *Tuberculostatic Hydrazides and their Derivatives.*

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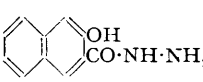
Many new hydrazides and their condensation products with various aldehydes and ketones have been prepared.

Tuberculostatic activity is shown to be widespread in this type of compound, and to be highly dependent on molecular structure.

The antitubercular properties of hydrazines and hydrazides have frequently been investigated (Jouin and Buu-Hoï, *Ann. Inst. Pasteur*, 1946, **72**, 580; Buu-Hoï, Royer, Jouin, Lecocq, and Guettier, *Bull. Soc. chim.*, 1947, **14**, 128; Buu-Hoï, Le Bihan, and Binon, *Rec. Trav. chim.*, 1951, **70**, 1099), and research in this field recently culminated in the discovery of drugs effective in human tuberculosis, notably *iso*nicotinhydrazide (Neoteben, Rimifon, Nydrazid) and its *N'-iso*propyl derivative (Marsalid) (cf. Offe, Siefken, and Domagk, *Naturwiss.*, 1952, **5**, 118; *Deut. med. Woch.*, 1952, **18**, 573; Fox, *Science*, 1952, **116**, 129; Bernstein, Lott, Steinberg, and Yale, *Amer. Rev. Tuberc.*, 1952, **65**, 357). Further, tuberculostatic activity has been shown to be present in a wide series of non-pyridinic hydrazides (Buu-Hoï, Xuong, Nam, and Binon, *Compt. rend.*, 1952, **235**, 329), although no compound has yet been found to approach *iso*nicotinhydrazide in that respect.

The present work records the preparation of a large number of hydrazides and of their condensation products with various aldehydes and ketones. These condensation products were investigated in view of the possibility of their being less toxic than the parent hydrazides, as a result of the blocking of the free NH_2-group.

The aromatic hydrazides found most active hitherto were 5-chlorosalicyl-, 2-hydroxy-1-naphth-, 4-hydroxybenz-, and 1-naphthylacet-hydrazide; 5-chlorosalicylhydrazide possessed a relatively low toxicity and is undergoing *in vivo* tests, especially with strains of *Mycobacterium tuberculosis* resistant to *iso*nicotinhydrazide. All the hydrazides studied gave sparingly soluble chelate compounds with copper salts, and the hypothesis has been put forward that this property might play a rôle in the tuberculostatic effects of hydrazides (Buu-Hoï *et al.*, *Compt. rend.*, 1952, **234**, 1925; 1952, **235**, 329). This theory has now been supported by lack of activity of copper derivatives such as that from 4-hydroxybenzhydrazide and copper sulphate, whereas the free hydrazide is tuberculostatic at a concentration of $1 : 10^{-5}$ (chelation with copper had already been postulated for the tuberculostatic thiosemicarbazones). In view of this hypothesis, compounds containing further chelating groups such as salicylhydrazide (I; R = H), 5-chloro- and 5-bromo-salicyl-

(I)  (II) 

hydrazide (I; R = Cl,Br), and 2-hydroxy-3-naphth-hydrazide (II) and their hydrazones have been specially considered. Table 1 lists the hydrazones prepared from the hydrazides of type (I); Table 2 contains those prepared from 2-hydroxy-3-naphth-hydrazide; Table 3,

Table 1. *Substituted* N'-*benzylidene* (*and analogous* *) *derivatives of* o- *and* p-*hydroxybenzhydrazide.*

Substituents in benzylidene residue	M. p.	Formula	N (%) Found	N (%) Reqd.
Derivatives of salicylhydrazide.				
3 : 4-$(OMe)_2$	197°	$C_{16}H_{16}O_4N_2$	9·2	9·3
2-OH-3-OMe	247	$C_{15}H_{14}O_4N_2$	9·5	9·8
3 : 4-CH_2O_2	271	$C_{15}H_{12}O_4N_2$	9·8	9·9
p-Cl	262	$C_{14}H_{11}O_2N_2Cl$	10·0	10·2
3 : 4-Cl_2 [1]	256	$C_{14}H_{10}O_2N_2Cl_2$	9·2	9·1
o-OH	284	$C_{14}H_{12}O_3N_2$	10·6	10·9
5-Cl-2-OH	287	$C_{14}H_{11}O_3N_2Cl$	9·3	9·6
3 : 5-Cl_2-2-OH [2]	274	$C_{14}H_{10}O_3N_2Cl_2$	8·5	8·6
3 : 5-Br_2-2-OH [3]	261	$C_{14}H_{10}O_3N_2Br_2$	6·6	6·8
3 : 5-I_2-2-OH [4]	258	$C_{14}H_{10}O_3N_2I_2$	5·2	5·5

TABLE 1. (Continued.)

Substituents in benzylidene residue	M. p.	Formula	N (%) Found	N (%) Reqd.
Derivatives of 5-chlorosalicylhydrazide.				
p-OMe	268°	$C_{15}H_{13}O_3N_2Cl$	9·0	9·2
p-OH	286	$C_{14}H_{11}O_3N_2Cl$	9·5	9·6
3 : 4-$(OMe)_2$	239	$C_{16}H_{15}O_4N_2Cl$	8·1	8·4
p-Cl	276	$C_{14}H_{10}O_2N_2Cl_2$	8·8	9·1
3 : 4-CH_2O_2	263	$C_{15}H_{11}O_4N_2Cl$	8·6	8·8
2-OH-3-OMe	266	$C_{15}H_{13}O_4N_2Cl$	8·4	8·7
3 : 4-Cl_2 [5]	264	$C_{14}H_9O_2N_2Cl_3$	8·1	8·2
o-OH	307	$C_{14}H_{11}O_3N_2Cl$	9·4	9·6
5-Cl-2-OH	310	$C_{14}H_{10}O_3N_2Cl_2$	8·3	8·6
3 : 5-Cl_2-2-OH [6]	297	$C_{14}H_9O_3N_2Cl_3$	7·6	7·8
3 : 5-Br_2-2-OH [7]	312	$C_{14}H_9O_3N_2Br_2Cl$	5·9	6·2
3 : 5-I_2-2-OH [8,19]	319	$C_{14}H_9O_3N_2ClI_2$	5·1	5·2
* 5-Propyl-2-thenylidene [9]	216	$C_{15}H_{15}O_2N_2ClS$	8·5	8·7
Derivatives of 5-bromosalicylhydrazide.				
p-OMe	267	$C_{15}H_{13}O_3N_2Br$	8·1	8·0
p-OH	292	$C_{14}H_{11}O_3N_2Br$	8·1	8·4
3 : 4-$(OMe)_2$	241	$C_{16}H_{15}O_4N_2Br$	7·1	7·4
p-Cl	275	$C_{14}H_{10}O_2N_2BrCl$	7·7	7·9
3 : 4-CH_2O_2	253	$C_{15}H_{11}O_4N_2Br$	7·8	7·7
2-OH-3-OMe	272	$C_{15}H_{13}O_4N_2Br$	7·4	7·7
3 : 4-Cl_2 [10]	274	$C_{14}H_9O_2N_2BrCl_2$	7·0	7·2
o-OH	316	$C_{14}H_{11}O_3N_2Br$	8·2	8·4
5-Cl-2-OH	313	$C_{14}H_{10}O_3N_2BrCl$	7·3	7·6
3 : 5-Cl_2-2-OH [11]	304	$C_{14}H_9O_3N_2BrCl_2$	6·8	6·9
3 : 5-Br_2-2-OH [12]	315	$C_{14}H_9O_3N_2Br_3$	5·5	5·7
* 5-Propyl-2-thenylidene [13]	222	$C_{15}H_{15}O_2N_2BrS$	7·3	7·6
Derivatives of 3 : 5-*dichlorosalicylhydrazide.*[19]				
3 : 5-Cl_2-2-OH [14]	286	$C_{14}H_8O_3N_2Cl_4$	6·8	7·1
3 : 5-Br_2-2-OH [15]	290	$C_{14}H_8O_3N_2Br_2Cl_2$	5·7	5·8
Derivatives of 3 : 5-*dibromosalicylhydrazide.*[19]				
3 : 5-Cl_2-2-OH [16]	238	$C_{14}H_8O_3N_2Br_2Cl_2$	5·5	5·8
3 : 5-Br_2-2-OH [17]	266	$C_{14}H_8O_3N_2Br_4$	4·7	4·9
Derivatives of p-*hydroxybenzhydrazide.*				
o-OH	280	$C_{14}H_{12}O_3N_2$	10·6	10·9
m-OH	271	$C_{14}H_{12}O_3N_2$	10·8	10·9
p-OH	273	$C_{14}H_{12}O_3N_2$	10·5	10·9
p-CH_2Ph·O	232	$C_{21}H_{18}O_3N_2$	8·2	8·1
3 : 5-I_2-4-OH [18,19]	270	$C_{14}H_{10}O_3N_2I_2$	5·2	5·5
p-OMe	226	$C_{15}H_{14}O_3N_2$	10·2	10·4
p-NMe_2	251	$C_{16}H_{17}O_2N_3$	14·6	14·8
3 : 4-CH_2O_2	238	$C_{15}H_{12}O_4N_2$	9·7	9·9
Cinnamylidene	232	$C_{16}H_{14}O_2N_2$	10·2	10·5
Citrylidene	140	$C_{17}H_{22}O_2N_2$	9·6	9·8
Glyoxal bis-derivative	300	$C_{16}H_{14}O_4N_4$	17·0	17·1
Derivatives of 3 : 5-*di-iodosalicylhydrazide.*[19]				
o-OH	247	$C_{14}H_{10}O_3N_2I_2$	5·2	5·5
3 : 5-Cl_2-2-OH	244	$C_{14}H_8O_3N_2Cl_2I_2$	4·8	4·9
3 : 5-Br_2-2-OH	268	$C_{14}H_8O_3N_2Br_2I_2$	4·0	4·2
3 : 5-I_2-2-OH	294	$C_{14}H_8O_3N_2I_4$	3·4	3·7

* In derivatives marked thus, the benzylidene group is replaced by that named.

[1] Found : Cl, 22·6. Reqd. Cl, 23·0%. [2] Found : Cl, 21·6. Reqd. : Cl, 21·8%. [3] Found : Br, 38·8. Reqd. : Br, 38·6%. [4] Found : I, 49·6. Reqd. : I, 50·0%. [5] Found : Cl, 31·2. Reqd. : Cl, 31·0. [6] Found : Cl, 29·5. Reqd. : Cl, 29·6%. [7] Found : C, 37·2; H, 2·2. Reqd. : C, 37·5; H, 2·0%. [8] Found : C, 31·2; H, 2·0. Reqd. : C, 31·0; H, 1·7%. [9] Found : S, 9·6. Reqd. : S, 9·9%. [10] Found : C, 43·0; H, 2·4. Reqd. : C, 43·2; H, 2·3%. [11] Found : C, 41·3; H, 2·4. Reqd. : C, 41·6; H, 2·2%. [12] Found : Br, 48·6. Reqd. : Br, 48·7%. [13] Found : S, 8·5. Reqd. : S, 8·7%. [14] Found : Cl, 35·7. Reqd. : Cl, 36·0%. [15] Found : C, 34·5; H, 2·0. Reqd. : C, 34·8; H, 1·7%. [16] Found : C, 34·6; H, 2·0. Reqd. : C, 34·8; H, 1·7%. [17] Found : Br, 56·0. Reqd. : Br, 55·8%. [18] Found : I, 49·6. Reqd. : I, 50·0%. [19] Pale yellow compounds; all the other substances were colourless; recrystallisation from ethanol or propanol. Salicylhydrazide was prepared by Struve and Radenhausen's method (*J. pr. Chem.*, 1895, **52**, 239).

TABLE 2. *Substituted N'-benzylidene (and analogous *) derivatives of 2-hydroxy-3-naphth-hydrazide.*[20]

Substituents in benzylidene residue	M. p.	Formula	N (%) Found	N (%) Reqd.
o-OH	301°	$C_{18}H_{14}O_3N_2$	9·0	9·2
2-OH-3-OMe	272	$C_{19}H_{16}O_4N_2$	8·0	8·3
p-OMe	288	$C_{19}H_{16}O_3N_2$	8·6	8·8
3 : 4-CH_2O_2	236	$C_{19}H_{14}O_4N_2$	8·5	8·4
3 : 5-Cl_2-2-OH [22]	291	$C_{18}H_{12}O_3N_2Cl_2$	7·2	7·5
3 : 5-Br_2-2-OH [23]	295	$C_{18}H_{12}O_3N_2Br_2$	6·1	6·0
3-OMe-4-$OC_{12}H_{25}$-*n*	140	$C_{31}H_{40}O_4N_2$	5·2	5·5
p-NMe_2 [21]	251	$C_{20}H_{19}O_2N_3$	12·8	12·6
p-Cl	266	$C_{18}H_{13}O_2N_2Cl$	8·4	8·6
o-Cl	263	$C_{18}H_{13}O_2N_2Cl$	8·3	8·6
2 : 4-Cl_2 [24]	261	$C_{18}H_{12}O_2N_2Cl_2$	7·6	7·8
3 : 4-Cl_2 [25]	251	$C_{18}H_{12}O_2N_2Cl_2$	7·5	7·8
5-Cl-2-OH	240	$C_{18}H_{13}O_3N_2Cl$	8·0	8·2
* 2-Methoxy-1-naphthylmethylidene [21]	223	$C_{23}H_{18}O_3N_2$	7·3	7·6
* 5-Acenaphthenylmethylidene	258	$C_{24}H_{18}O_2N_2$	7·6	7·7
* 3-Pyrenylmethylidene	262	$C_{28}H_{18}O_2N_2$	6·5	6·8

[20] This hydrazide was prepared by Franzen and Richler's method (*J. pr. Chem.*, 1908, **78**, 164). [21] Yellow prisms; all the other substances were colourless. Recrystallisation from ethanol or propanol. [22] Found : Cl, 18·8. Reqd. : Cl, 18·9%. [23] Found : Br, 34·2. Reqd. : Br, 34·5%. [24] Found : Cl, 19·5. Reqd. : Cl, 19·8%. [25] Found : Cl, 19·6%.

TABLE 3. *Substituted N'-benzylidene (and analogous *) derivatives of thiophen-2-carboxyhydrazides.*

Substituent in benzylidene residue	M. p.	Formula	N (%). Found	N (%). Reqd.
2 : 4-Cl_2 [27]	231°	$C_{12}H_8ON_2Cl_2S$	9·0	9·4
3-OMe-4-$OC_{12}H_{25}$-*n*	112	$C_{25}H_{36}O_3N_2S$	6·0	6·3
3 : 5-I_2-2-OH [26]	dec. 261	$C_{12}H_8O_2N_2I_2S$	5·4	5·6
Derivatives of 5-bromothiophen-2-carboxyhydrazide.				
3 : 4-Cl_2 [28]	237	$C_{12}H_7ON_2BrCl_2S$	7·2	7·4
p-Me	191	$C_{13}H_{11}ON_2BrS$	8·6	8·7
p-NMe_2 [26]	213	$C_{14}H_{14}ON_3BrS$	11·8	11·9
p-OH	245	$C_{12}H_9O_2N_2BrS$	8·4	8·6
o-OH	239	$C_{12}H_9O_2N_2BrS$	8·3	8·6
p-Cl	225	$C_{12}H_8ON_2ClBrS$	8·0	8·1
o-Cl	208	$C_{12}H_8ON_2ClBrS$	8·2	8·1
5-Br-2-OH [29]	232	$C_{12}H_8O_2N_2Br_2S$	6·8	7·0
5-Cl-2-OH	233	$C_{12}H_8O_2N_2BrClS$	7·7	7·8
3 : 5-Cl_2-2-OH	246	$C_{12}H_7O_2N_2Cl_2BrS$	7·0	7·1
3 : 5-I_2-2-OH [26]	255	$C_{12}H_7O_2N_2BrI_2S$	4·6	4·9
2-OH-3-OMe	249	$C_{13}H_{11}O_3N_2BrS$	7·7	7·9
p-OMe	187	$C_{13}H_{11}O_2N_2BrS$	8·1	8·3
5-Propyl-2-thenylidene [26]	154	$C_{13}H_{13}ON_2BrS_2$	7·5	7·8
* 5-Acenaphthenylmethylidene [26]	228	$C_{18}H_{13}ON_2BrS$	7·0	7·3
* 3-Pyrenylmethylidene [26]	288	$C_{22}H_{13}ON_2BrS$	6·2	6·5
Derivatives of 5-chlorothiophen-2-carboxyhydrazide.				
5-Br-2-OH	222	$C_{12}H_8O_2N_2BrClS$	7·6	7·8
2-OH-3-OMe	245	$C_{13}H_{11}O_3N_2ClS$	9·1	9·0
p-NMe_2	207	$C_{14}H_{14}ON_3ClS$	13·6	13·7
o-Cl [30]	210	$C_{12}H_8ON_2Cl_2S$	9·3	9·4
3 : 4-Cl_2 [31]	244	$C_{12}H_7ON_2Cl_3S$	8·1	8·4
o-OH	229	$C_{12}H_9O_2N_2ClS$	9·8	10·0
2 : 4-Cl_2 [32]	227	$C_{12}H_7ON_2Cl_3S$	8·1	8·4
5-Cl-2-OH [33]	219	$C_{12}H_8O_2N_2Cl_2S$	8·7	8·9
3 : 5-I_2-2-OH	264	$C_{12}H_7O_2N_2ClI_2S$	5·1	5·3
3-OMe-4-$OC_{12}H_{25}$-*n*	141	$C_{25}H_{35}O_3N_2ClS$	5·6	5·9
p-OMe	175	$C_{13}H_{11}O_2N_2ClS$	9·2	9·5
m-NO_2	239	$C_{12}H_8O_3N_3ClS$	13·4	13·6
5-*n*-Propyl-2-thenylidene [26]	153	$C_{13}H_{13}ON_2ClS_2$	9·0	9·0
5-Tetradecyl-2-thenylidene	107	$C_{24}H_{35}ON_2ClS_2$	6·2	6·0
5-Acenaphthenylmethylidene [26]	231	$C_{18}H_{13}ON_2ClS$	7·9	8·2
3-Pyrenylmethylidene [26]	288	$C_{22}H_{13}ON_2ClS$	7·0	7·2

* See asterisk to Table 1.

[26] Yellow prisms; all the other substances were colourless. Recrystallisation from ethanol. Thiophen-2-carboxyhydrazide was prepared by Curtius and Thyssen's method (*J. pr. Chem.*, 1902, **65**, 7). [27] Found : Cl, 23·5. Reqd. : Cl, 23·7%. [28] Found : S, 8·2. Reqd. : S, 8·5%. [29] Found : Br, 39·2. Reqd. : Br, 39·6%. [30] Found : Cl, 23·4. Reqd. : Cl, 23·7%. [31] Found : Cl, 31·7. Reqd. : Cl, 13·9%. [32] Found : Cl, 31·8%. [33] Found : Cl, 22·2. Reqd. : Cl, 22·5%.

TABLE 4. *Substituted* N'*-benzylidene* (*and analogous* *) *derivatives of nicotin- and* iso*nicotin-hydrazide.*

Substituents in benzylidene residue	M. p.	Formula	N (%) Found	N (%) Reqd.
Derivatives of nicotinhydrazide.				
p-OH [34]	248°	$C_{13}H_{11}O_2N_3$	—	—
3 : 4-$(OMe)_2$	158	$C_{15}H_{15}O_3N_3$	14·4	14·7
4-OH-3-OMe [34]	218	$C_{14}H_{13}O_3N_3$	—	—
o-Cl [34]	167	$C_{13}H_{10}ON_3Cl$	—	—
p-Cl	197	$C_{13}H_{10}ON_3Cl$	16·1	16·2
3 : 4-Cl_2 [36]	195	$C_{13}H_9ON_3Cl_2$	14·1	14·3
3-OMe-4-$OC_{12}H_{25}$	126	$C_{26}H_{37}O_3N_3$	9·5	9·6
* 5-Acenaphthenylidene [35]	212	$C_{19}H_{15}ON_3$	13·7	14·0
5-Cl-2-OH	206	$C_{13}H_{10}O_2N_3Cl$	14·9	15·2
o-OH [34]	194	$C_{13}H_{11}O_2N_3$	—	—
3 : 5-Cl_2-2-OH [37]	215	$C_{13}H_9O_2N_3Cl_2$	13·2	13·5
* 3-Pyrenylmethylidene [35]	260	$C_{23}H_{15}ON_3$	12·1	12·0
* Piperonylidene [34]	209	$C_{14}H_{11}O_3N_3$	—	—
* 9-Ethyl-3-carbazolylmethylidene	220	$C_{21}H_{18}ON_4$	16·2	16·4
* 1-Naphthylmethylidene	199	$C_{17}H_{13}ON_3$	15·4	15·3
* 2 : 4-Dichlorophenyl*iso*propylidene [38]	236	$C_{16}H_{13}ON_3Cl_2$	12·2	12·6
Derivatives of iso*nicotinhydrazide.*				
5-Cl-2-OH	232	$C_{13}H_{10}O_2N_3Cl$	15·0	15·2
3 : 5-Cl_2-2-OH [34, 39]	244	$C_{13}H_9O_2N_3Cl_2$	13·2	13·5
3 : 5-Br_2-2-OH [34, 40]	214	$C_{13}H_9O_2N_3Br_2$	10·1	10·5
3 : 5-I_2-2-OH [34, 41]	213	$C_{13}H_9O_2N_3I_2$	8·3	8·5
o-OH [42]	251	$C_{13}H_{11}O_2N_3$	—	—
2-OH-3-OMe	234	$C_{14}H_{13}O_3N_3$	15·2	15·5
p-NMe_2 [34]	199	$C_{15}H_{16}ON_4$	20·8	20·9
3 : 5-I_2-4-OH [34, 43]	dec. >250	$C_{13}H_9O_2N_3I_2$	8·2	8·5
* Cinnamylidene	201	$C_{15}H_{13}ON_3$	16·5	16·7
* 5-Acenaphthenylmethylidene [34]	200	$C_{19}H_{15}ON_3$	14·1	14·0
* 3-Pyrenylmethylidene [34]	259	$C_{23}H_{15}ON_3$	12·2	12·0
* 9-Ethyl-3-carbazolylmethylidene	244	$C_{21}H_{18}ON_4$	16·2	16·4
* 2 : 4-Dichlorophenyl*iso*propylidene [34, 44]	213	$C_{16}H_{13}ON_3Cl_2$	12·4	12·6

* See asterisk in Table 1.

[34] These substances, already reported in the literature (Meyer and Mally, *Monatsh.*, 1912, **33**, 399; Offe, Siefken, and Domagk, *Z. Naturforsch.*, 1952, **7**, [*B*], 462), are listed here in view of the differences in the m. p.s. [35] Yellow compounds; all the others were colourless. [36] Found : Cl, 24·3. Reqd. : Cl, 24·1%. [37] Found : Cl, 22·6. Reqd. : Cl, 22·9%. [38] Found : Cl, 21·0. Reqd. : Cl, 21·3%. [39] Found : Cl, 22·6. Reqd. : Cl, 22·9%. [40] Found : Br, 40·2. Reqd. : Br, 40·1.% [41] Found : I, 51·1. Reqd. : I, 51·5%. [42] Lit., m. p. 247°. [43] Found : I, 51·3. [44] Found : Cl, 21·0. Reqd. : Cl, 21·3%.

those from *N*-2-thenoylhydrazine and its 5-chloro- and 5-bromo-derivative; in Table 4 are listed the hydrazones from nicotin- and *iso*nicotin-hydrazide.

The activity of isatin in the Strecker degradation of amino-acids (cf. Moubasher, *J.*, 1951, 231, 1928) and its selection as a model for carboxylase (see Langenbeck, " Die organischen Katalysatoren," Springer-Verlag, Berlin, 1932) led us to prepare, for biological testing, a number of β-hydrazones derived from isatin (and some of its derivatives) with various hydrazides; these compounds are listed in Table 5.

The tuberculostatic activity *in vitro* of some compounds described in this work has already been reported (Buu-Hoï *et al.*, *locc. cit.*); other results are listed in Table 6.

In view of the high nitrogen content of the hydrazones, determination of nitrogen was more adequate than that of carbon and hydrogen.

EXPERIMENTAL

Halogenated Salicylhydrazides.—A mixture of methyl 5-chlorosalicylate (5 g.), 95% hydrazine hydrate (2·5 g.) and ethanol (50 c.c.) was refluxed for 5 hr.; the precipitate of *5-chlorosalicylhydrazide* formed on cooling (98% yield) crystallised as long, shiny, colourless needles, m. p. 222°, from ethanol (Found : C, 44·9; H, 4·0. $C_7H_7O_2N_2Cl$ requires C, 45·0; H, 3·8%). Similarly were prepared 3 : 5-*dichloro-*, prisms, m. p. 175°, from acetone (Found : C, 37·8; H, 2·9. $C_7H_6O_2N_2Cl_2$ requires C, 38·0; H, 2·7%), 5-*bromo-*, needles, m. p. 218°, from ethanol (Found : C, 36·1; H, 3·1. $C_7H_7O_2N_2Br$ requires C, 36·4; H, 3·0%), 3 : 5-*dibromo-*, prisms, m. p. 192°, from acetone (Found : C, 27·0; H, 2·2. $C_7H_6O_2N_2Br_2$ requires C, 27·1; H, 1·9%),

and 3 : 5-*di-iodo-salicylhydrazide*, needles, m. p. 218° (Found : N, 7·0; I, 62·5. $C_7H_6O_2N_2I_2$ requires N, 6·9; I, 62·9%).

β-*Naphthyloxyacethydrazide*.—This *hydrazide* formed leaflets, m. p. 172°, from ethanol (Found : C, 66·5; H, 5·5. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6%). It gave the following *N'*-derivatives : p-*anisylidene*, prisms, m. p. 182°, from ethanol–benzene (Found : N, 8·3. $C_{20}H_{18}O_3N_2$ requires N, 8·4%), p-*hydroxybenzylidene*, prisms, m. p. 206°, from ethanol (Found : N, 8·9. $C_{19}H_{16}O_3N_2$ requires N, 8·8%), *piperonylidene*, needles, m. p. 190° (Found : N, 7·8. $C_{20}H_{16}O_4N_2$ requires N, 8·0%), *veratrylidene*, prisms, m. p. 181°, from acetic acid (Found : N, 7·6. $C_{21}H_{20}O_4N_2$ requires N, 7·7%), and p-*chlorobenzylidene*, needles, m. p. 215°, from toluene (Found : N, 8·0. $C_{19}H_{15}O_2N_2Cl$ requires N, 8·3%).

Phenoxyacethydrazide.—This *compound* crystallised as needles, m. p. 108°, from methanol (Found : C, 57·6; H, 6·1. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0%), and gave a p-*anisylidene*, prisms, m. p. 138° (from methanol) (Found : N, 9·5. $C_{16}H_{16}O_3N_2$ requires N, 9·8%); p-*chlorobenzylidene*, m. p. 175° (from toluene) (Found : N, 9·5. $C_{15}H_{13}O_2N_2Cl$ requires N, 9·7%), and *piperonylidene* derivative, prisms, m. p. 201° (from ethanol) (Found : N, 9·5. $C_{16}H_{14}O_4N_2$ requires N, 9·4%).

TABLE 5. *Condensation products of isatins with hydrazides.*[45]

Hydrazide	M. p.	Formula	N (%) Found	N (%) Reqd.	M. p.	Formula	N (%) Found	N (%) Reqd
	Isatin				*5-Methylisatin*			
Phenylacet-	167°	$C_{16}H_{13}O_2N_3$	15·0	15·1				
Dodecan-					130°	$C_{21}H_{31}O_2N_3$	11·5	11·8
β-Naphthyloxyacet-					260	$C_{21}H_{17}O_3N_3$	11·5	11·7
Nicotin-	283	$C_{14}H_{10}O_2N_4$	20·6	21·1	266	$C_{15}H_{12}O_2N_4$	19·6	20·0
*iso*Nicotin-	296	,,	20·8	21·1	316	,,	19·8	20·0
Salicyl-	326	$C_{15}H_{11}O_3N_3$	14·6	14·9	312	$C_{16}H_{13}O_3N_3$	14·0	14·2
5-Chlorosalicyl-	311	$C_{15}H_{10}O_3N_3Cl$	13·0	13·3	316	$C_{16}H_{12}O_3N_3Cl$	12·4	12·7
5-Bromosalicyl	315	$C_{15}H_{10}O_3N_3Br$	11·5	11·7	313	$C_{16}H_{12}O_3N_3Br$	10·9	11·2
2-Hydroxy-3-naphth-	332	$C_{19}H_{13}O_3N_3$	12·4	12·7	323	$C_{20}H_{15}O_3N_3$	12·0	12·2
Adipic bishydrazide	232	$C_{22}H_{20}O_4N_6$	19·1	19·4				
Sebacic bishydrazide	192	$C_{26}H_{28}O_4N_6$	17·3	17·2				
5-Bromothiophen-2-carboxy-	242	$C_{13}H_8O_2N_3BrS$	11·8	12·0				
	5-Bromoisatin				*7-Methylisatin*			
Phenylacet-[46]	228	$C_{16}H_{12}O_2N_3Br$	11·4	11·7				
Dodecan-[47]	166	$C_{20}H_{26}O_2N_3Br$	9·8	10·0				
Phenoxyacet-[48]	201	$C_{16}H_{12}O_3N_3Br$	11·0	11·2				
β-Naphthyloxyacet-	252	$C_{20}H_{14}O_3N_3Br$	9·6	9·9				
Nicotin-[49]	292	$C_{14}H_9O_2N_4Br$	16·0	16·2	195	$C_{15}H_{12}O_2N_4$	19·9	20·0
*iso*Nicotin-[50]	318	,,	15·9	16·2	206	,,	19·8	20·0
Salicyl-[51]	318	$C_{15}H_{10}O_3N_3Br$	11·4	11·7				
					5-Chloroisatin			
5-Chlorosalicyl-	313	$C_{15}H_9O_3N_3ClBr$	10·4	10·6	[52] 314	$C_{15}H_9O_3N_3Cl_2$	11·6	12·0
5-Bromosalicyl-[53]	312	$C_{15}H_9O_3N_3Br_2$	9·3	9·6	309	$C_{15}H_9O_3N_3ClBr$	10·3	10·6
2-Hydroxy-3-naphth-	320	$C_{19}H_{12}O_3N_3Br$	10·0	10·2				
Adipic bishydrazide[54]	233	$C_{22}H_{18}O_4N_6Br_2$	14·4	14·2				
Sebacic bishydrazide[55]	242	$C_{26}H_{26}O_4N_6Br_3$	13·1	130				

[45] The reaction affects the 3-keto-group of isatin (cf. Struve, *J. pr. Chem.*, 1894, **50**, 307). [46] Found : Br, 22·0. Reqd. : Br, 22·3%. [47] Found : Br, 18·8. Reqd. : Br, 19·0%. [48] Found : Br, 21·0. Reqd. : Br, 21·4%. [49] Found : Br, 23·0. Reqd. : Br, 23·2%. [50] Found : Br, 23·1%. [51] Found : Br, 21·9. Reqd. : Br, 22·2%. [52] Found : Cl, 20·2. Reqd. : Cl, 20·3%. [53] Found : Br, 36·2. Reqd. : Br, 36·4%. [54] Found : Br, 26·8. Reqd. : Br, 27·1%. [55] Found : Br, 24·6. Reqd. : Br, 24·8%.

Derivatives of Phenylacethydrazide.—The following derivatives are recorded : p-*anisylidene*, leaflets, m. p. 171°, from methanol (Found : N, 10·2. $C_{16}H_{16}O_2N_2$ requires N, 10·4%); p-*chlorobenzylidene*, needles, m. p. 167°, from methanol (Found : N, 10·2. $C_{15}H_{13}ON_2Cl$ requires N, 10·3%); and *piperonylidene*, needles, m. p. 219°, from ethanol (Found : N, 9·8. $C_{16}H_{14}O_3N_2$ requires N, 9·9%).

Naphthylacethydrazides.—The 1-*naphthyl* compound crystallised as prisms, m. p. 169°, from methanol (Found : N, 13·8. $C_{12}H_{12}ON_2$ requires N, 14·0%); 2-*naphthylacethydrazide* had m. p. 189° (from methanol) (Found : N, 14·2. $C_{12}H_{12}ON_2$ requires N, 14·0%).

3 : 4-*Dichlorocinnamhydrazide*.—3 : 4-Dichlorocinnamic acid was best prepared by a Perkin reaction from 3 : 4-dichlorobenzaldehyde; its *ethyl* ester, prisms, m. p. 81° (from light petroleum) (Found : C, 53·6; H, 4·1. $C_{11}H_{10}O_2Cl_2$ requires C, 53·9; H, 4·1%), gave 3 : 4-*dichlorocinnamhydrazide*, m. p. 138° (from methanol) (Found : N, 12·2. $C_9H_8ON_2Cl_2$ requires N, 12·1%); *ethyl* 2 : 4-*dichlorocinnamate* had m. p. 52° (from light petroleum) (Found : C, 53·8; H, 4·1%).

2-*Hydroxy*-1-*naphth-hydrazide*.—This *compound* formed prisms (from methanol), decomp. > 206° (completely melted at 216°) (Found: N, 13·5. $C_{11}H_{10}O_2N_2$ requires N, 13·9%), and gave a 5-*chloro*-2-*hydroxybenzylidene* derivative as prisms, m. p. 240°, from ethanol (Found : N, 8·0. $C_{18}H_{13}O_3N_2Cl$ requires N, 8·2%).

Derivatives of N-*Lauroylhydrazine* (cf. Curtius, *J. pr. Chem.*, 1914, **89**, 511).—The 4-*chlorobenzylidene* derivative formed prisms, m. p. 102°, from ethanol (Found : N, 8·0. $C_{19}H_{29}ON_2Cl$ requires N, 8·3%); and the p-*dimethylaminobenzylidene* derivative pale yellow needles, m. p. 103°, from methanol (Found : N, 12·0. $C_{21}H_{35}ON_3$ requires N, 12·2%).

TABLE 6. *Tuberculostatic activities* in vitro.[a]

	Activity at concn. 1 in
N'-4-Hydroxybenzylidene*iso*nicotinhydrazide [b]	10^{-7}
N'-5-Chloro-2-hydroxybenzylidene*iso*nicotinhydrazide	10^{-7}
N'-5-Bromo-2-hydroxybenzylidene*iso*nicotinhydrazide	10^{-6}
N'-Cinnamylidene*iso*nicotinhydrazide	10^{-7}
N'-*p*-Chlorophenyl*iso*propylidene*iso*nicotinhydrazide	10^{-7}
N'-2 : 4-Dichlorophenyl*iso*propylidene*iso*nicotinhydrazide	10^{-6}—10^{-7}
N'-3 : 4-Methylenedioxybenzylidenephenylacethydrazide	$<10^{-4}$
N'-4-Hydroxy-3-methoxybenzylidenephenylacethydrazide	$<10^{-4}$
N'-3 : 4-Dimethoxybenzylidenephenylacethydrazide	$<10^{-4}$
p-Hydroxy-*N'*-*o*-hydroxybenzylidenebenzhydrazide	10^{-4}
p-Hydroxy-*N'*-*m*-hydroxybenzylidenebenzhydrazide	10^{-4}
p-Hydroxy-*N'*-*p*-hydroxybenzylidenebenzhydrazide	10^{-4}—10^{-5}
N'-Anisylidene-*p*-hydroxybenzhydrazide	10^{-5}
4-Hydroxy-*N'*-*p*-methoxyphenyl*iso*propropylidenebenzhydrazide	10^{-4}
N'-Citrylidene-*p*-hydroxybenzhydrazide	10^{-4}
N'-*p*-Dimethylaminobenzylidene-*p*-hydroxybenzhydrazide	$<10^{-4}$
N'-3-Chloro-4-hydroxybenzylidene-*p*-hydroxybenzhydrazide	10^{-4}
p-Hydroxy-*N'*-(4-hydroxy-3 : 5-di-iodobenzylidene)benzhydrazide	10^{-4}
N'-*p*-Chlorophenyl*iso*propylidene-*p*-hydroxybenzhydrazide	10^{-4}
N'-Cinnamylidene-*p*-hydroxybenzhydrazide	10^{-4}
Glyoxal bis-(*p*-hydroxybenzoylhydrazone)	$<10^{-4}$
Glucose *p*-hydroxybenzoylhydrazone	$<10^{-4}$
5-Chloro-*N'*-*p*-methoxybenzylidenesalicylhydrazide	10^{-4}
5-Chloro-*N'*-*p*-chlorobenzylidenesalicoylhydrazide	10^{-4}
N'-*p*-Anisylidene-5-bromosalicoylhydrazide	10^{-4}
5-Bromo-*N'*-*p*-chlorobenzylidenesalicylhydrazide	10^{-4}
N'-*p*-Anisylidene-β-naphthyloxyacethydrazide	10^{-4}
Complex from *p*-hydroxybenzhydrazide and $CuSO_4$	$<10^{-4}$
p-Hydroxybenzhydrazide	10^{-5}
2 : 5-Dihydroxy*iso*nicotinhydrazide	$<10^{-4}$
Pyrazinecarboxyhydrazide	10^{-5}

[a] Determined on *Mycobacterium tuberculosis var. hominis*, strain H37 Rv, in Dubos–Middlebrook medium (the inoculum was a 6-day old culture on Dubos medium, and the reading was taken after 3 weeks). [b] The high activity found for this substance is in accord with a recent work of Offe, Siefken and Domagk (*Z. Naturforsch.*, 1952, **7**, [*B*], 465).

Nicotin- and iso*Nicotin-hydrazide*.—These hydrazides were prepared by 30 min.' refluxing of a solution of the corresponding methyl ester (60 g.) and 95% hydrazine (15 g.) in ethanol (50 c.c.); after cooling, the precipitated hydrazide was collected and recrystallised from ethanol. Methyl nicotinate and *iso*nicotinate were conveniently prepared as follows : a mixture of the acid (80 g.), methanol (300 c.c.), benzene (300 c.c.), and sulphuric acid (60 c.c.) was refluxed for 2 hr.; next, the azeotropic mixture of methanol, benzene, and water was slowly distilled off (4—5 hr.); the viscous residue (100 c.c.) was poured on ice (150 g.) and basified with sodium carbonate to pH 8, and the free ester taken up in chloroform (yield, 72 g.).

Derivatives of Adipic and Sebacic Dihydrazides.—Adipic dihydrazide was prepared by Curtius' method (*J. pr. Chem.*, 1915, **91**, 4). It gave the following derivatives : *di*-p-*chlorobenzylidene*, leaflets, m. p. 248°, from ethanol (Found : N, 13·1. $C_{20}H_{20}O_2N_4Cl_2$ requires N, 13·4%); *di*-p-*methoxybenzylidene*, leaflets (from ethanol), m. p. 217° (Found : N, 13·4. $C_{22}H_{26}O_4N_4$ requires N, 13·7%); *dipiperonylidene*, needles, m. p. 234° (from ethanol) (Found : N, 12·6. $C_{22}H_{22}O_6N_4$ requires N, 12·8%); *divanillylidene*, prisms, m. p. 287° (from ethanol)

(Found : N, 12·8. $C_{22}H_{26}O_6N_4$ requires N, 12·7%); *bis*-(p-*dimethylaminobenzylidene*), needles, m. p. 224° (from ethanol) (Found : N, 19·1. $C_{24}H_{32}O_2N_6$ requires N, 19·3%); and *di*-5-*acenaphthenylmethylidene*, pale yellow leaflets, m. p. 212° (from ethanol) (Found : N, 11·0. $C_{32}H_{30}O_2N_4$ requires N, 11·2%). Sebacic dihydrazide (Steller, *J. pr. Chem.*, 1900, **62**, 216) gave the following derivatives: *di*-p-*chlorobenzylidene*, leaflets, m. p. 209° (from ethanol) (Found: N, 11·9. $C_{24}H_{28}O_2N_4Cl_2$ requires N, 11·8%); *di*-p-*methoxybenzylidene*, leaflets, m. p. 182° (from ethanol) (Found : N, 12·2. $C_{26}H_{34}O_4N_4$ requires N, 12·0%); *dipiperonylidene*, leaflets, m. p. 203° (from ethanol) (Found : N, 11·0. $C_{26}H_{30}O_6N_4$ requires N, 11·3%); *bis*-(p-*dimethylaminobenzylidene*, prisms, m. p. 164° (from ethanol) (Found : N, 16·9. $C_{28}H_{40}O_2N_6$ requires N, 17·1); and *di*-5-*acenaphthenylmethylidene*, faintly yellow leaflets, m. p. 194° (from ethanol) (Found: N, 10·2. $C_{36}H_{38}O_2N_4$ requires N, 10·0%).

n-*Dodecyl Vanillyl Ether*.—Prepared by alkylation of vanillin with *n*-dodecyl bromide and potassium hydroxide in ethanol, this *ether* had b. p. 256—258°/18 mm., and formed prisms, m. p. 57°, from ethanol (Found : C, 74·8 ; H, 10·1. $C_{20}H_{32}O_3$ requires C, 75·0; H, 10·0%); its *thiosemicarbazone* formed needles, m. p. 128°, from ethanol (Found : C, 64·0; H, 9·0. $C_{21}H_{35}O_2N_3S$ requires C, 64·1; H, 8·9%), its *semicarbazone* needles, m. p. 142°, from ethanol (Found : N, 11·0. $C_{21}H_{35}O_3N_3$ requires N, 11·1%), and its 4-*keto*-2-*thiazolinylhydrazone*, m. p. 188°, from acetic acid (Found : C, 63·4; H, 8·3. $C_{23}H_{35}O_3N_3S$ requires C, 63·7; H, 8·1%).

Other Hydrazines.—Further *compounds*, prepared by analogous methods, are recorded in the Tables.

Our thanks are offered to Professor M. Welsch (University of Liège) and Messrs. Société Belge de l'Azote (Liège) for some of the biological tests performed, and to Miss P. F. Boshell, M.A. (Oxon.), for assistance with this work.

THE RADIUM INSTITUTE, UNIVERSITY OF PARIS. [*Received, November 29th*, 1952.]