SUBSTITUTED HYDRAZIDES OF HYDROCARBOXYLIC ACIDS

LXXXII. CHLOROPHENYL HYDRAZIDES OF DIARYL- AND DIALKYLGLYCOLIC ACIDS

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UDC 615.281.221.1:547.298.61

The arylhydrazides of diaryl- and dialkylglycolic acids synthesized earlier showed high antispasmodic activity [1] and the ability to suppress the growth of tubercular bacilli [2, 3]. The biological activity of these compounds depends to a large degree on the nature and position of substituents in the benzene ring on nitrogen. We studied the effect of chlorine in positions 3 or 4 of the benzene ring on nitrogen on the biological and chemical properties of the arylhydrazides indicated above. m-Chlorophenyl- and p-chlorophenylhydrazides of diaryl- and dialkylglycolic acids (III-XXI, Table 1) were synthesized upon reaction of ethyl esters of m- and p-chlorophenylhydrazides of oxalic acid (I, II) with aryl- and alkylmagnesium halides by the scheme [4]

$$\underset{\text{I, II}}{ClC_6H_4NHNHCOCOOC_2H_5} \xrightarrow{2RMgBr} \underset{\text{III—XXI}}{ClC_6H_4NHNHCOC(OH)R_2}$$

N-Benzoyl derivatives (XXII-XXXVI, Table 2) were obtained upon heating (III-XXI) with benzoyl chloride in benzene, and N-acetyl derivatives (XXXVII-LII, Table 2) were obtained upon heating with acetic anhydride.

The IR spectra (see Fig. 1) of compounds (III) and (XV) in the region of 3000 cm^{-1} in solution show three bands of free OH- and two NH-groups having frequencies of 3620, 3443, and 3343 cm^{-1}. Upon going to crystals the frequencies of these bands decreases as a result of formation of hydrogen bonds. The carbonyl also participates in formation of the latter, which is indicated by the decrease in frequency of its band from 1700 cm^{-1} in solution to 1680 cm^{-1} in crystals. The $\nu C=O$ bond in the tertiary hydroxyl has a frequency of 1054 cm^{-1}, as in the case of other arylhydrazides of benzylic acid [5]. In compound (XXXVII) a

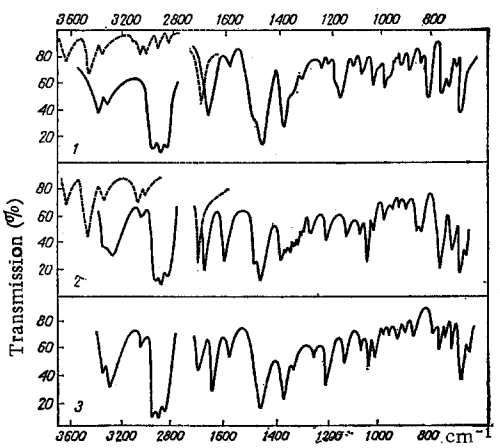

Fig. 1. IR spectra of chlorophenylhydrazides (spectra of solutions in carbon tetrachloride are depicted by a dotted line): 1, 2) m-chloro- and p-chlorophenylhydrazides of benzylic acid; 3) β-acetyl-β-m-chlorophenylhydrazides of benzylic acid.

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TABLE 1. Chlorophenylhydrazides of Diaryl- and Dialkylglycolic Acids

Compound*	R	Yield (%)	Mp (deg)†	UV spectra, alcohol as solvent				Found N (%)	Empirical formula	Calc. N (%)
				K-band		B-band				
				λ (nm)	lg ε	λ (nm)	lg ε			
III	C_6H_5	92	141—2	238	4,10	288	3,33	7,92, 8,00	$C_{20}H_{17}ClN_2O_2$	7,94
IV	m-$CH_3C_6H_4$	98	152—3	242	4,13	288	3,24	7,17, 7,20	$C_{22}H_{21}ClN_2O_2$	7,36
V	p-$CH_3C_6H_4$	96	183—4	242 (bend)	4,12	288	3,37	7,27, 7,10	$C_{22}H_{21}ClN_2O_2$	7,36
VI	o-$CH_3OC_6H_4$	94	158—9	238 (bend)	4,05	274	3,74	6,51, 6,63	$C_{22}H_{21}ClN_2O_4$	6,78
VII	p-$CH_3OC_6H_4$	96	152—3	234	4,40 0	274 282	3,64 3,64	6,55, 6,48	$C_{22}H_{21}ClN_2O_4$	6,78
VIII	m-ClC_6H_4	95	136—7	238	4,00	277	3,26	6,60, 6,43	$C_{20}H_{15}Cl_3N_2O_2$	6,64
IX	p-ClC_6H_4	92	180—1	224	4,42	278	3,33	6,36, 6,42	$C_{20}H_{15}Cl_3N_2O_2$	6,64
X	CH_3	90	124—5	—	—	—	—	12,41, 11,91	$C_{10}H_{13}ClN_2O_2$	12,25
XI	C_2H_5	91	95—6	240	3,99	288	3,25	11,13, 11,20	$C_{12}H_{17}ClN_2O_2$	10,91
XII	C_4H_9	89	122—3	240	3,99	288	3,26	8,69, 8,70	$C_{16}H_{25}ClN_2O_2$	8,96
XIII	C_5H_{11}	96	113—4	240	4,06	286	3,35	8,30, 8,16	$C_{18}H_{29}ClN_2O_2$	8,22
XIV	iso-C_5H_{11}	88	161—2	238	4,07	288	3,29	8,20, 8,30	$C_{18}H_{29}ClN_2O_2$	8,22
XV	C_6H_5	92	170—1	242	4,25	290	3,25	7,94, 7,65	$C_{20}H_{17}ClN_2O_2$	7,94
XVI	m-CH_3:C_6H_4	94	137—8	242	4,22	292	3,28	7,15, 7,30	$C_{22}H_{21}ClN_2O_2$	7,36
XVII	p-$CH_3C_6H_4$	86	170—1	226 240	4,21 4,21	290	3,22	7,39, 7,59	$C_{22}H_{21}ClN_2O_2$	7,36
XVIII	C_2H_5	98	133—3,5	242	4,12	292	3,16	10,63, 10,61	$C_{12}H_{17}ClN_2O_2$	10,91
XIX	C_4H_9	96	127—8	244	4,19	292	3,23	8,96, 8,81	$C_{16}H_{25}ClN_2O_2$	8,96
XX	C_5H_{11}	94	125—6	244	4,20	292	3,23	8,10, 8,05	$C_{18}H_{29}ClN_2O_2$	8,22
XXI	iso-C_5H_{11}	88	169—70	242	4,19	292	3,25	8,32, 8,00	$C_{18}H_{29}ClN_2O_2$	8,22

*Compounds (III)-(XIV) contain chlorine in the meta position, (XV)-(XXI) contain chlorine in the para position.

†Compounds (III, IV, V, VII, X, XI, XII, XV, XVII-XXI) were crystallized from toluene, (VI, XIII, XIV, XVI) were crystallized from alcohol, (VIII, IX) were crystallized from benzene.

TABLE 2. N-Benzoyl and Acetyl Derivatives of m- and p-Chlorophenylhydrazides of Diaryl- and Dialkylglycolic Acids $ClC_6H_4N(COR)NHCOC(OH)R_2$

Compound*	R	Yield (%)	Mp (deg)†	Found N (%)	Empirical formula	Calc. N (%)
XXII	C_6H_5	85	199—200	6,19; 6,00	$C_{27}H_{21}ClN_2O_3$	6,14
XXIII	m-$CH_3C_6H_4$	78	195—6	5,71; 5,88	$C_{29}H_{25}ClN_2O_3$	5,78
XXIV	p-$CH_3C_6H_4$	98	188—9	5,67; 5,58	$C_{29}H_{25}Cl_2N_2O_3$	5,78
XXV	p-$CH_3OC_6H_4$	75	205—6	5,62; 5,39	$C_{29}H_{25}ClN_2O_5$	5,42
XXVI	C_2H_5	92	179—180	7,80; 7,48	$C_{19}H_{21}ClN_2O_3$	7,77
XXVII	C_4H_9	90	227—8	6,90; 6,67	$C_{23}H_{29}ClN_2O_3$	6,73
XXVIII	C_5H_{11}	93	209—10	6,30; 6,05	$C_{25}H_{33}ClN_2O_3$	6,30
XXIX	iso-C_5H_{11}	93	199—200	6,22; 6,20	$C_{25}H_{33}ClN_2O_3$	6,30
XXX	C_6H_5	90	224—5	6,00; 6,15	$C_{27}H_{21}ClN_2O_3$	6,14
XXXI	m-$CH_3C_6H_4$	89	236—7	5,60; 5,51	$C_{29}H_{25}ClN_2O_3$	5,78
XXXII	p-$CH_3C_6H_4$	91	237—9	5,58; 5,47	$C_{29}H_{25}ClN_2O_3$	5,78
XXXIII	C_2H_5	92	192—3	7,48; 7,51	$C_{19}H_{21}ClN_2O_3$	7,77
XXXIV	C_4H_9	90	227—8	6,80; 6,67	$C_{23}H_{29}ClN_2O_3$	6,73
XXXV	C_5H_{11}	86	236—7	6,42; 6,16	$C_{25}H_{33}ClN_2O_3$	6,30
XXXVI	iso-C_5H_{11}	92	218—9	6,23; 6,10	$C_{25}H_{33}ClN_2O_3$	6,30
				CH_3CO		CH_3CO
XXXVII	C_6H_5	94	185—6	11,36	$C_{22}H_{19}ClN_2O_3$	10,91
XXXVIII	m-$CH_3C_6H_4$	91	156—7	10,35	$C_{24}H_{23}ClN_2O_3$	10,18
XXXIX	p-$CH_3C_6H_4$	91	192—3	10,60	$C_{24}H_{23}ClN_2O_3$	10,18
XL	p-$CH_3OC_6H_4$	90	188—9	10,04	$C_{24}H_{23}ClN_2O_3$	9,46
XLI	m-ClC_6H_4	92	167—8	9,50	$C_{22}H_{17}Cl_3N_2O_3$	9,28
XLII	p-ClC_6H_4	91	198—9	9,20	$C_{22}H_{17}Cl_3N_2O_3$	9,28
XLIII	C_2H_5	92	126—8	14,96	$C_{14}H_{19}ClN_2O_3$	14,40
XLIV	C_4H_9	94	159—160	12,54	$C_{18}H_{27}ClN_2O_3$	12,12
XLV	C_5H_{11}	95	194—5	11,38	$C_{20}H_{31}ClN_2O_3$	11,24
XLVI	iso-C_5H_{11}	95	179—180	11,10	$C_{20}H_{31}ClN_2O_3$	11,24
XLVII	C_6H_5	83	198—9	10,60	$C_{22}H_{19}ClN_2O_3$	10,91
XLVIII	m-$CH_3C_6H_4$	84	213—4	10,50	$C_{24}H_{23}ClN_2O_3$	10,18
XLIX	p-$CH_3C_6H_4$	86	195—7	10,08	$C_{24}H_{23}ClN_2O_3$	10,18
L	C_4H_9	91	203—4	11,91	$C_{18}H_{27}ClN_2O_3$	12,12
LI	C_5H_{11}	90	190—1	10,92	$C_{20}H_{31}ClN_2O_3$	11,24
LII	iso-C_5H_{11}	94	213—4	11,00	$C_{20}H_{31}ClN_2O_3$	11,24

* Compounds (XXII-XXIX, XXXVII-XLVI) contain chlorine in the meta position, (XXX-XXXVI, XLVII-LII) contain chlorine in the para position. For compounds (XXII-XXXVI) R' = C_6H_5 and R' = CH_3 for (XXXVII-LII).

† Crystallization solvent was glacial acetic acid for (XXXI), benzene for (XXXIII, XXXVII, XLIII, XLV), alcohol for (XXII, XXVI-XXVIII, XXXV, XXXVI, XL, XLVI, XLIX), and toluene for the remaining compounds.

second band of amide (I) occurs in connection with the presence of the N-acetyl group, which also occurs in N-acyl derivatives of other arylhydrazides of this group [6].

In the UV region (see Table 1) chlorophenylhydrazides of dialkylglycolic acids have two clearly expressed maxima with a wave length and extinction value similar to values for m-chloroaniline in compounds (XI-XIV) and for p-chloroaniline [7] for compounds (XVIII-XXI). Absorption of aryl groups, found on the carbinyl carbon, is superimposed on this spectrum in hydrazides of diarylglycolic acids, which introduces changes into both bands.

The series of synthesized arylhydrazides was examined for antitubercular activity. It is seen from Table 3 that all of the studied compounds have a high ability to suppress growth of tubercular bacilli; however, the activity falls sharply in the presence of serum. The position of chlorine in the benzene ring on nitrogen has an effect on activity: the activity is higher at the para-position. Substitution of hydrogen on the nitrogen bonded to the benzene ring by an acetyl group leads to a decrease in antitubercular activity.

The series of compounds was examined for antispasmodic activity; compound (XVIII) in a dose of 200 mg/kg showed 100% protection from spasms upon electric shock, compound (XIX) showed 80% protection, and compound (IV) showed 40% [8].

EXPERIMENTAL

m-Chlorophenylhydrazide of Ethyl Oxalate (I). We dissolved 9 g of m-chlorophenylhydrazine [9] in 30 ml of alcohol, added 11 g of diethyl oxalate, and left the mixture for 24 h. Yield of (I) was 14 g (91%); dis-

TABLE 3. Antitubercular Activity of Chlorophenylhydrazides of Disubstituted Glycolic Acids

Compound	Conc. (μg/ml) in which the preparation is active			
	strain Academia		strain H_{37} R_V	
	without serum	with serum	without serum	with serum
III	0,25	7,8	—	7,8
IV	0,5	15,6	—	15,6
V	0,5	1000	0,5	1000
VIII	0,25	15,6	0,5	125
IX	0,5	125	—	62,5
X	0,125	31,2	0,062	125
XIV	0,125	125	0,5	1000
XVI	<0,062	15,6	0,062	62,5
XVIII	0,25	125	0,25	31,2
XIX	0,125	31.2	<0,062	31,2
XX	<0,0075	125	<0,062	31,2
XXI	<0,062	250	<0,062	125
XLII	3,9	125	—	125

solves in alcohol, benzene, xylene, toluene; platelets with mp 131-132°C (from toluene). Found, %: N 11.30, 11.28. $C_{10}H_{11}ClN_2O_3$. Calculated, %: N 11.55.

p-Chlorophenylhydrazide of Ethyl Oxalate (II). Upon standing for 24 h a solution of 8.6 g of p-chlorophenylhydrazine [10] in 50 ml of alcohol and 8.4 g of diethyl oxalate yielded 12.6 g of (II) (85%); platelets, mp 154-155° (from toluene). Found, %: N 11.68, 11.71. $C_{10}H_{11}ClN_2O_3$. Calculated, %: N 11.55.

m-Chlorophenylhydrazide of Benzylic Acid (III). To a solution of phenylmagnesium bromide (from 2.4 g of magnesium and 15.7 g of bromobenzene) was added 4.9 g of compound (I). The reaction mass was heated for 30 min and decomposed with dilute hydrochloric acid. Yield was 6.9 g. The material dissolved in alcohol, benzene, toluene.

Compounds (IV-XIV) were obtained analogously from (I) and compounds (XV-XXI) were obtained from (II).

β-Benzoyl-β-m-chlorophenylhydrazide of Benzylic Acid (XXII). We dissolved 1 g of hydrazide (III) in 7 ml of benzene, added 1.5 g of benzoyl chloride, and heated the mixture for 40 min on a water bath with a reflux condenser. The reaction product separates out upon cooling. Yield was 1.3 g; the material dissolves in benzene, toluene, glacial acetic acid, alcohol.

Compounds (XXIII-XXXVI) were obtained analogously.

β-Acetyl-β-m-chlorophenylhydrazide of Benzylic Acid (XXXVII). We dissolved 1 g of compound (III) in 10 ml of acetic anhydride, heated the mixture on a water bath for 2 h, and diluted the reaction mass with water.

Materials (XXXVIII-LII) were obtained analogously.

IR spectra were measured on an IKS-14 spectrophotometer having LiF and NaCl prisms for pastes in mineral oil and solutions in carbon tetrachloride. UV spectra were taken on an SF-4 spectrophotometer. Antitubercular activity was studied by the method described in [2].

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