SUBSTITUTED HYDRAZIDES OF HYDROXYCARBOXYLIC ACIDS

LXV. PIPERIDINO-, MORPHOLINO-, AND N-METHYLPIPERAZINOACETYL DERIVATIVES OF THE TOLYLHYDRAZIDES OF DIARYL- AND DIALKYLGLYCOLIC ACIDS*

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A number of β-chloroacetyl-β-tolylhydrazides of diaryl- and dialkylglycolic acids have been obtained by the reaction of the hydrazides with acetyl chloride. The chloroacetyl derivatives, on heating with piperidine, morpholine, or N-methylpiperazine, are converted into the corresponding β-(aminoacetyl)-β-tolylhydrazides of diaryl- and dialkylglycolic acids. The IR and UV spectra of these compounds are examined, and also the spectra of their halochromic salts, and their basicity.

The β-(aminoacetyl)-β-phenylhydrazides of diaryl- and dialkylglycolic acids, containing heterocyclic amine residues, have been shown to possess significant analgesic activity [2-4]. In order to investigate further this group of compounds, we have synthesized the piperidino-, morpholino-, and N-methylpiperazinoacetyl derivatives of the tolylhydrazides of diaryl- and dialkylglycolic acids.

The reaction of tolylhydrazides [5-7] with chloroacetyl chloride in benzene has yielded the β-chloroacetyl-β-tolylhydrazides of a number of diaryl- and dialkylglycolic acids (Table 1).

*For part LXIV, see [1].

TABLE 1. $XC_6H_4N(COCH_2Cl)NHCOC(OH)R_2$

Compound	X	R	mp, °C (from toluene)	Molecular formula	Found, % Cl	Found, % N	Calculated, % Cl	Calculated, % N	Yield, %
I	o-CH_3	C_6H_5	173—174[a]	$C_{23}H_{21}ClN_2O_3$	8.55	6.75	8.69	6.85	97
II		p-$CH_3OC_6H_4$	182—183	$C_{25}H_{25}ClN_2O_5$	7.51	6.15	7.59	5.98	94
III		C_3H_7	173—174	$C_{17}H_{25}ClN_2O_3$	10.34	8.14	10.42	8.22	75
IV		C_4H_9	146—146,5	$C_{19}H_{29}ClN_2O_3$	9.52	7.77	9.63	7.59	95
V	m-CH_3	C_6H_5	203—204b	$C_{23}H_{21}ClN_2O_3$	8.70	6.30	8.69	6.85	97
VI		p-$CH_3C_6H_4$	210—211	$C_{25}H_{25}ClN_2O_3$	8.30	7.10	8.13	6.98	99
VII		p-$CH_3OC_6H_4$	187—188[a]	$C_{25}H_{25}ClN_2O_5$	7.35	6.13	7.59	5.98	75
VIII		C_2H_5	166,5—167,5	$C_{15}H_{21}ClN_2O_3$	11.23	8.77	11.36	8.96	87
IX		C_3H_7	181,5—182	$C_{17}H_{25}ClN_2O_3$	10.36	7.94	10.42	8.22	93
X		C_4H_9	159—160[c]	$C_{19}H_{29}ClN_2O_3$	9.52	7.51	9.63	7.59	99
XI	p-CH_3	C_6H_5	193—194	$C_{23}H_{21}ClN_2O_3$	8.49	6.93	8.69	6.85	93
XII		p-$CH_3C_6H_4$	199—200	$C_{25}H_{25}ClN_2O_3$	8.27	6.80	8.13	6.98	99
XIII		p-$CH_3OC_6H_4$	163—164[a]	$C_{25}H_{25}ClN_2O_5$	7.47	5.92	7.59	5.98	92
XIV		C_2H_5	181—181,5	$C_{15}H_{21}ClN_2O_3$	11.28	8.86	11.36	8.96	98
XV		C_3H_7	185—186[c]	$C_{17}H_{25}ClN_2O_3$	10.35	8.33	10.42	8.22	98
XVI		C_4H_9	183—184[a]	$C_{19}H_{29}ClN_2O_3$	9.54	7.71	9.63	7.59	95

a) From alcohol. b) From glacial acetic acid. c) From benzene.

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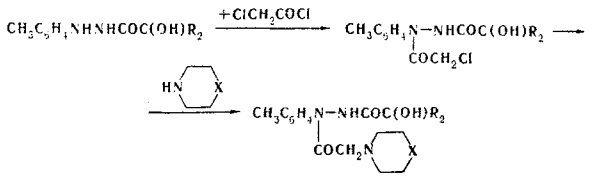
TABLE 2.

$XC_6H_4N(COCH_2N(CH_2CH_2)Y)-NHCOC(OH)R_2$

Compound	X	Y	R	mp, °C (from benzene)	Molecular formula	N, % found	N, % calculated	Yield, %
XVII	*o*-CH_3	CH_2	C_6H_5	109—110	$C_{28}H_{31}N_3O_3$	9.37	9.19	99
XVIII	*o*-CH_3	CH_2	*p*-$CH_3OC_6H_4$	91—92	$C_{30}H_{35}N_3O_5$	8.04	8.12	86
XIX	*o*-CH_3	CH_2	C_3H_7	117—118[a]	$C_{22}H_{35}N_3O_3$	10.80	10.79	96
XX	*o*-CH_3	CH_2	C_4H_9	129—130[b]	$C_{24}H_{39}N_3O_3$	9.97	10.07	97
XXI	*m*-CH_3	CH_2	C_6H_5	132—133	$C_{28}H_{31}N_3O_3$	9.28	9.19	98
XXII	*m*-CH_3	CH_2	*p*-$CH_3C_6H_4$	163—164	$C_{30}H_{35}N_3O_3$	8.85	8.84	99
XXIII	*m*-CH_3	CH_2	*p*-$CH_3OC_6H_4$	164—165	$C_{30}H_{35}N_3O_5$	8.03	8.12	89
XXIV	*m*-CH_3	CH_2	C_2H_5	133—134	$C_{20}H_{31}N_3O_3$	11.67	11.63	89
XXV	*m*-CH_3	CH_2	C_3H_7	109—110	$C_{22}H_{35}N_3O_3$	10.65	10.79	90
XXVI	*m*-CH_3	CH_2	C_4H_9	85—86	$C_{24}H_{39}N_3O_3$	9.89	10.07	90
XXVII	*p*-CH_3	CH_2	C_6H_5	164—165[c]	$C_{28}H_{31}N_3O_3$	9.04	9.19	93
XXVIII	*p*-CH_3	CH_2	*p*-$CH_3C_6H_4$	182—183[c]	$C_{30}H_{35}N_3O_3$	8.73	8.84	87
XXIX	*p*-CH_3	CH_2	*p*-$CH_3OC_6H_4$	198—199[b]	$C_{30}H_{35}N_3O_5$	8.15	8.12	99
XXX	*p*-CH_3	CH_2	C_2H_5	184—185	$C_{20}H_{31}N_3O_3$	11.64	11.63	95
XXXI	*p*-CH_3	CH_2	C_3H_7	162—163	$C_{22}H_{35}N_3O_3$	10.76	10.79	96
XXXII	*p*-CH_3	CH_2	C_4H_9	162—163[c]	$C_{24}H_{39}N_3O_3$	10.20	10.07	97
XXXIII	*o*-CH_3	O	C_6H_5	107—108	$C_{27}H_{29}N_3O_4$	9.11	9.15	98
XXXIV	*o*-CH_3	O	*p*-$CH_3OC_6H_4$	140—141[c]	$C_{29}H_{33}N_3O_6$	8.13	8.09	99
XXXV	*o*-CH_3	O	C_3H_7	117—118[a]	$C_{21}H_{33}N_3O_4$	10.63	10.74	99
XXXVI	*o*-CH_3	O	C_4H_9	125—126	$C_{23}H_{37}N_3O_4$	9.93	10.02	99
XXXVII	*m*-CH_3	O	C_6H_5	164—165	$C_{27}H_{29}N_3O_4$	9.14	9.15	81
XXXVIII	*m*-CH_3	O	*p*-$CH_3C_6H_4$	151—152[a]	$C_{29}H_{33}N_3O_4$	8.93	8.84	81
XXXIX	*m*-CH_3	O	*p*-$CH_3OC_6H_4$	142—143	$C_{29}H_{33}N_3O_6$	8.07	8.09	99
XL	*m*-CH_3	O	C_2H_5	140—141[c]	$C_{19}H_{29}N_3O_4$	11.60	11.50	94
XLI	*m*-CH_3	O	C_3H_7	115—116	$C_{21}H_{33}N_3O_4$	10.70	10.74	87
XLII	*m*-CH_3	O	C_4H_9	129—130	$C_{23}H_{37}N_3O_4$	9.92	10.02	84
XLIII	*p*-CH_3	O	C_6H_5	181—182	$C_{27}H_{29}N_3O_4$	9.19	9.15	98
XLIV	*p*-CH_3	O	*p*-$CH_3C_6H_4$	200—201	$C_{29}H_{33}N_3O_4$	8.77	8.84	80
XLV	*p*-CH_3	O	*p*-$CH_3OC_6H_4$	180—181	$C_{29}H_{33}N_3O_6$	8.02	8.09	81
XLVI	*p*-CH_3	O	C_2H_5	181—182	$C_{19}H_{29}N_3O_4$	11.40	11.50	86
XLVII	*p*-CH_3	O	C_3H_7	161—162	$C_{21}H_{33}N_3O_4$	10.77	19.74	87
XLVIII	*p*-CH_3	O	C_4H_9	168—169	$C_{23}H_{37}N_3O_4$	10.00	10.02	82
XLIX	*o*-CH_3	NCH_3	C_4H_9	128—129[c]	$C_{24}H_{40}N_4O_3$	12.83	12.96	85
L	*m*-CH_3	NCH_3	*p*-$CH_3OC_6H_4$	112—113[a]	$C_{30}H_{36}N_4O_5$	10.44	10.53	96
LI	*m*-CH_3	NCH_3	C_4H_9	129—130[c]	$C_{24}H_{40}N_4O_3$	12.80	12.96	66
LII	*p*-CH_3	NCH_3	C_6H_5	174—175	$C_{28}H_{32}N_4O_3$	11.78	11.86	66
LIII	*p*-CH_3	NCH_3	*p*-$CH_3OC_6H_4$	160—161[c]	$C_{30}H_{36}N_4O_5$	10.67	10.53	66
LIV	*p*-CH_3	NCH_3	C_4H_9	131—132[a]	$C_{24}H_{40}N_4O_3$	12.75	12.98	85

a) From CCl_4. b) From alcohol. c) From toluene.

On heating the chloroacetyl derivatives in benzene with an excess of piperidine, morpholine, or N-methylpiperazine, the corresponding aminoacetyl compounds are obtained (Table 2):



R = C_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, C_2H_5, C_3H_7, C_4H_9; X = CH_2, O, NCH_3

The IR spectra of CCl_4 solutions of all the compounds show two bands in the 3000-cm^{-1} region, at 3625 and 3340 cm^{-1}. These are due to the stretching of the free OH and NH groups. In the crystalline state, there is a reduction in the intensity of the bands due to the vibrations of the OH and NH groups, indicating their involvement in hydrogen bonding. That the carbonyl group also participates in the formation of hydrogen bonds is indicated by a reduction in the frequency of the amide-I bands on passing from the dissolved to the crystalline state. The amide-I band, as in other arylhydrazides [8], is split (1696-1702 and 1676-1688 cm^{-1} in the crystals, and 1717 and 1690 cm^{-1} in solution). The stretching frequencies of the C—OH bond remain at 1060 cm^{-1} as in the starting tolylhydrazines [9] and other benzilic arylhydrazides [10]. As a result of the presence of the morpholine ring in XXXIII, XXXVII, and XLIII, bands appear at 870-877 and 804-824 cm^{-1}, which are attributed [11] to the vibration frequencies of the morpholine ring as a whole, and a band at 1118 cm^{-1} which results from the vibration of the C—O—C bonds in the morpholine ring.

TABLE 3. pK_{R^+} for β-(Aminoacetyl)-β-(p-tolyl)hydrazides of Di-(p-anisyl)glycolic Acid

Compound	pK_{R^+}	Compound	pK_{R^+}
XVIII	−9.31	XXXIX	−9.49
XXIII	−9.59	XLV	−9.45
XXIX	−9.54	L	−9.19
XXXIV	−9.22	LIII	−9.07

The spectrum of LII shows a band at 1167 cm^{-1}, attributed [12] to the vibration of the piperazine ring. The piperidinoacetyl derivatives show bands at 770, 870, and 119 cm^{-1} and are attributed [13, 14] to the piperidine ring.

The introduction of an aminoacetyl group into the hydrazide changes the nature of the UV spectrum to a considerable extent. By comparison with the spectra of the parent tolylhydrazides [7], the maximum undergoes smoothing, and the absorption curves show a smooth reduction with a small inflexion.

Diarylglycolic arylhydrazides exhibit the phenomenon of halochromism [15]. This property is also found in the aminoacetyl derivatives. The halochromic salts of the piperidino-, morpholino-, and N-methylpiperazinoacetyl derivatives of di-(p-anisyl)glycolic hydrazide possess a maximum at 570 nm (log ε 4.61), which corresponds to the absorption of the halochromic salts of the parent tolylhydrazides [16].

The basicity of the carbonyl carbon atom of the aminoacetyl derivatives of di(p-anisyl)glycolic hydrazide were determined by the spectrophotometric method [17, 18]. The pK_{R^+} values are given in Table 3.

We see from the results that the nature of the acyl residue has little effect on the basicity of the carbonyl carbon atom, since the pK_{R^+} values obtained are similar to those for the acetyl and benzoyl derivatives of di-(p-anisyl)glycolic phenyl- and p-tolylhydrazides [18].

EXPERIMENTAL

Benzilic β-(Chloroacetyl)-β-(o-tolyl)hydrazide (I). To a solution of 5 g of benzilic o-tolylhydrazide [5] in benzene was added 4.8 g (0.26 mmole) of chloroacetyl chloride, and the mixture was heated on a water bath for 1 h. The hydrazide (I) was isolated by evaporation of the solvent. It was soluble in benzene, toluene, alcohol, and glacial acetic acid.

Compounds II-XVI were obtained in a similar manner.

Benzilic β-(Piperidinoacetyl)-β-(o-tolyl)hydrazide (XVII). A benzene solution of 1 g of compound I was heated with 1.8 g (8 mmole) of piperidine on a water bath for 2 h. The product was isolated by removal of the solvent, and was soluble in benzene, toluene, and alcohol, and glacial acetic acid, but only sparingly soluble in water.

Compounds XVIII-LIV were obtained in a similar manner.

The IR spectra were recorded on an IKS-14 spectrophotometer, as pastes in Vaseline oil, or as solutions in CCl_4. The UV spectra were obtained on an SF-4 spectrophotometer, as solutions in alcohol. The halochromic solutions were prepared by adding 1 ml of an acetic acid solution of the aminoacetyl derivative of known concentration to 9 ml of H_2SO_4, of various percentage compositions. The spectra of the halochromic solutions were obtained on an SF-10 recording spectrophotometer.

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