# SUBSTITUTED HYDRAZIDES OF HYDROXYCARBOXYLIC ACIDS

## XXVIII. Morpholinoacetyl Derivatives of Phenylhydrazides of Diaryl and Dialkyl Glycolic Acids*

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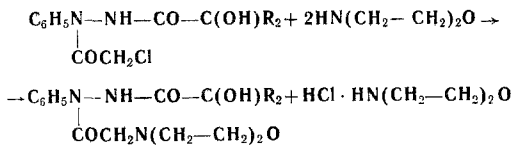
The action of morpholine on chloroacetyl derivatives of phenylhydrazides of diaryl- and dialkylglycolic acids gives hitherto undescribed morpholinoacetyl derivatives of the phenylhydrazides. Methiodides of a number of these compounds are prepared. The hitherto undescribed chloroacetyl derivatives of the phenylhydrazides of di(m-tolyl)-, di(o-anisyl)-, diamyl-, diheptyl-, and dioctylglycolic acids, and also the phenylhydrazide of diheptylglycolic acid are described.

Previously synthesized [2] diethylamino- and piperidinoacetyl derivatives of phenylhydrazines of diaryl- and dialkylglycolic acids have been found to have analgesic activity [3]. It was of interest to introduce into this group of compounds the morpholino group, which is found in a number of physiologically active compounds.

Introduction of the morpholino group was effected by heating chloroacetyl derivatives of phenylhydrazides of diaryl- and dialkyl-glycolic acids with excess morpholine.



*For Part XXVII see [1].

The starting chloroacetyl derivatives were prepared by reacting the phenylhydrazides of diaryl- and dialkylglycolic acids [4–6] with chloroacetyl chloride [2]. The newly prepared chloroacetyl derivatives are shown in Table 1. Table 2 gives the morpholinoacetyl derivatives. They are colorless crystalline substances, which are soluble in organic solvents. Heating a number of the morpholinoacetyl derivatives with methyl iodide in benzene gives methiodides [Table 3].

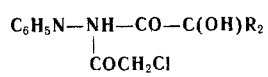
## EXPERIMENTAL

**Phenylhydrazide of diheptylglycolic acid.** A solution of Mg heptyl bromide was prepared from 35.8 g (0.2 mole) heptyl bromide and 4.8 g (0.2 g at) Mg, and to it was added 8.4 g (0.04 mole) ethyl ester of the β-phenylhydrazide of oxalic acid [7], the mixture heated for 30 min, and then decomposed with dilute HCl. The reaction product was extracted with ether. Yield 87.4%. Soluble in benzene, ether, EtOH, needles ex toluene, mp 96–97°. Found: N 7.71; 7.65%. Calculated for $C_{22}H_{38}N_2O_2$: N 7.73%.

**β-Morpholinoacetyl-β-phenylhydrazide of benzilic acid.** 1.5 g (0.004 mole) β-chloroacetyl-β-phenylhydrazide of benzilic acid [2] was heated on a water bath with 5 ml morpholine for 2 hr. The reaction product was isolated after diluting with water. Compounds VII–XIX were prepared similarly.

Table 1

Chloroacetyl Derivatives of Phenylhydrazides of Diaryl- and Dialkylglycolic Acids



| Compound | R | Mp, °C | Formula | Found, % | | Calculated, % | | Yield % |
|---|---|---|---|---|---|---|---|---|
| | | | | Cl | N | Cl | N | |
| I | *m*-$CH_3C_6H_4$ | 200–201 | $C_{24}H_{23}ClN_2O_2$ | 8.64 | 6.16; 6.80 | 8.41 | 6.63 | 87.6 |
| II | *o*-$CH_3OC_6H_4$ | 186–187 | $C_{24}H_{23}ClN_2O_5$ | 8.00 | 6.35; 6.46 | 7.82 | 6.17 | 90.1 |
| III | *n*-$C_5H_{11}$ | 176–177 | $C_{20}H_{31}ClN_2O_3$ | 9.37 | 7.01; 7.35 | 9.30 | 7.33 | 86.7 |
| IV | *n*-$C_7H_{15}$ | 175–176 | $C_{24}H_{39}ClN_2O_3$ | 7.88 | 6.29; 6.09 | 8.10 | 6.39 | 91.6 |
| V | *n*-$C_8H_{17}$ | 176–177 | $C_{26}H_{43}ClN_2O_3$ | 7.74 | 5.79; 5.74 | 7.62 | 6.01 | 93.3 |

*Compounds I–III crystallize from EtOH, IV, V from glacial AcOH.

Table 2

Morpholinoacetyl Derivatives of Phenylhydrazides of Diaryl- and Dialkylglycolic Acids

$C_6H_5N—NH—CO—C(OH)R_2$

$COCH_2N(CH_2—CH_2)_2O$

| Compound | R | Mp,* °C | Formula | N, % | | Yield % |
|---|---|---|---|---|---|---|
| | | | | Found, % | Calculated | |
| VI | $C_6H_5$ | 130—131 | $C_{26}H_{27}N_3O_4$ | 9.27; 9.29 | 9.44 | 98.1 |
| VII | $p$-$CH_3C_6H_4$ | 156—157 | $C_{28}H_{31}N_3O_4$ | 8.59; 8.71 | 8.88 | 90.6 |
| VIII | $m$-$CH_3C_6H_4$ | 180—181 | $C_{28}H_{31}N_3O_4$ | 9.27; 9.14 | 8.88 | 83.7 |
| IX | $o$-$CH_3C_6H_4$ | 121—122 | $C_{28}H_{31}N_3O_4$ | 8.58; 8.69 | 8.88 | 87.4 |
| X | $o$-$CH_3OC_6H_4$ | 112—114 | $C_{28}H_{31}N_3O_6$ | 8.06; 8.19 | 8.32 | 75.8 |
| XI | $C_6H_{11}$** | 191—192 | $C_{26}H_{39}N_3O_4$ | 8.79; 8.89 | 9.19 | 78.1 |
| XII | $C_2H_5$ | 154—155 | $C_{18}H_{27}N_3O_4$ | 11.98; 11.93 | 12.03 | 80.3 |
| XIII | $n$-$C_3H_7$ | 122—123 | $C_{20}H_{31}N_3O_4$ | 11.12; 11.13 | 11.14 | 93.0 |
| XIV | $n$-$C_4H_9$ | 157—158 | $C_{22}H_{35}N_3O_4$ | 10.41; 10.09 | 10.37 | 94.2 |
| XV | $n$-$C_5H_{11}$ | 145—146 | $C_{24}H_{39}N_3O_4$ | 9.70; 9.84 | 9.70 | 96.1 |
| XVI | $i$-$C_5H_{11}$ | 161—162 | $C_{24}H_{39}N_3O_4$ | 9.38; 9.62 | 9.70 | 97.0 |
| XVII | $n$-$C_6H_{13}$ | 126—127 | $C_{26}H_{43}N_3O_4$ | 9.37; 9.34 | 9.11 | 91.0 |
| XVIII | $n$-$C_7H_{15}$ | 127—128 | $C_{28}H_{47}N_3O_4$ | 8.30; 8.43 | 8.59 | 92.1 |
| XIX | $n$-$C_8H_{17}$ | 123—124 | $C_{30}H_{51}N_3O_4$ | 8.25; 8.36 | 8.12 | 91.8 |

*Compounds VI, X are crystallized from dilute EtOH; XV, XVI ex EtOH; VII–IX, XVII, XVII, XVIII ex toluene; XI, XIV, XIX ex benzene.

**Cyclohexyl

Table 3

Methiodides of Morpholinoacetyl Derivatives of Phenylhydrazides of Diaryl- and Dialkylglycolic Acids

| Starting compound | Mp,* °C | Formula | I, % | |
|---|---|---|---|---|
| | | | Found | Calculated |
| VII | 173—174 | $C_{29}H_{34}IN_3O_4$ | 20.71; 19.98 | 20.70 |
| VIII | 170—171 | $C_{29}H_{34}IN_3O_4$ | 20.79; 20.28 | 20.70 |
| IX | 165—166 | $C_{29}H_{34}IN_3O_4$ | 20.72; 20.82 | 20.70 |
| X | 167—168 | $C_{29}H_{34}IN_3O_6$ | 19.34; 19.18 | 19.63 |
| XI | 166—167 | $C_{27}H_{42}IN_3O_4$ | 20.85; 20.76 | 21.20 |
| XII | 178—179 | $C_{19}H_{30}IN_3O_4$ | 25.51; 25.88 | 25.87 |
| XIII | 175—176 | $C_{21}H_{34}IN_3O_4$ | 24.44; 24.63 | 24.47 |
| XIV | 152—153 | $C_{23}H_{38}IN_3O_4$ | 22.80; 23.47 | 23.22 |
| XV | 171—172 | $C_{25}H_{42}IN_3O_4$ | 21.70; 22.34 | 22.09 |
| XVI | 169—170 | $C_{25}H_{42}IN_3O_4$ | 21.92; 21.74 | 22.09 |

*Methiodides of compounds VII, IX, X, and XIV are crystallized from glacial AcOH; VIII, XIII, XV, and XVI from EtOH, XI and XII ex toluene.

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