# β-(o-CARBALKOXY- AND PHENOXYBENZOYL)- AND β-CARBETHOXY-β-PHENYLHYDRAZIDES OF DISUBSTITUTED GLYCOLIC ACIDS AND THEIR PHYSIOLOGIC ACTIVITY

I. S. Berdinskii, P. T. Pavlov,
A. F. Goleneva, and L. S. Kosvintseva

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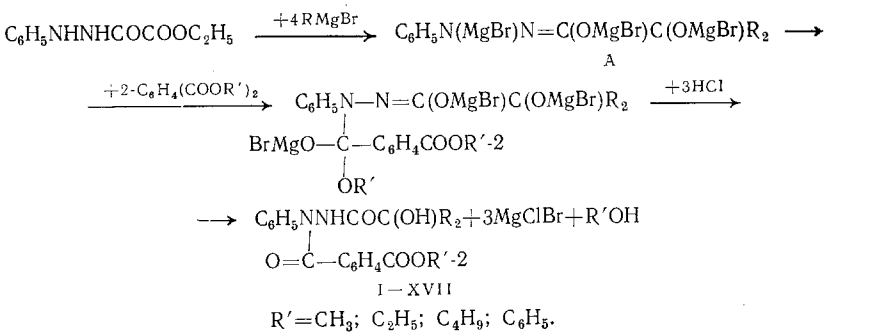
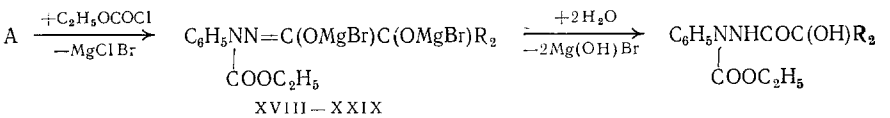
The β-benzoyl-β-arylhydrazides of diaryl- and dialkylglycolic acids possess analgesic activity [1]. It would appear worth finding out how this activity would be affected by the introduction of the benzoyl residue of a complex ester group into the o-position, as well as by replacement of the benzoyl radical by a carbethoxyl group. To obtain β-(o-carbalkoxy- and phenoxybenzoyl)-β-phenylhydrazides, we took advantage of a reaction we discovered [2], one-step formation of β-benzoyl-β-phenylhydrazides of disubstituted glycolic acid phenylhydrazide and Grignard reagent in the presence of esters of phthalic acid. The results of the experiments indicate that under these experimental conditions an intermediary complex, which is formed by the reaction between an ester of oxalic acid phenylhydrazide and magnesium halogenaryl or alkyl esters, reacts with complete phthalic acid esters only at one complex ester group with the formation of β-(o-carbalkoxy- or phenoxybenzoyl)-β-phenylhydrazides of diaryl- or dialkylglycolic acids. The reaction can be described by the following flow chart:



The obtained compounds are presented in Table I (I-XVII). β-Carbethoxy-β-phenylhydrazides of disubstituted glycolic acids were obtained given the effect of the intermediate A complex of the ethyl ester of chlorocarbonic acid:



Production of the Substances Listed in Table 1 (XVIII-XXIX). All of the compounds synthesized are colorless crystalline substances which are soluble in the usual organic solvents. Compounds IV-VI were also obtained from the corresponding phenylhydrazides and chloranhydride of the incomplete ethyl ester of phthalic acid in benzene, and XVIII, XXI and XXVI from the phenylhydrazides and ethyl ester of chlorocarbonic acid. Mixed samples of compounds obtained by different methods melted without depression.

In the IR-spectra of the crystals of compounds II, V, IX, XV, and XVIII there are two bands in the region above 3000 $cm^{-1}$ with frequencies of 3310-3430 and 3200-3300 $cm^{-1}$ which belong to the valency oscillations of OH and NH groups participating in hydrogen bonds. There is one band in this region for compound XII at 3360 $cm^{-1}$ which is linked to the superimposition of the oscillations of these groups. In solution there are two bands in this region at 3590 and 3383-3400 $cm^{-1}$. In crystals of substance XII there are three bands in the carbonyl group oscillation region at 1655, 1705, and 1720 $cm^{-1}$, and at 1640, 1708, and

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TABLE 1. β-(o-Carbalkoxy- and Phenoxybenzoyl)- and β-Carbethoxy-β-Phenylhydrazides of Diaryl- and Dialkylglycolic Acids $C_6H_5N(COR')NHCOC(OH)R_3$

| Compound | R′ | R | Yield, % | Melting point, °C* | Found, % N | Empirical formula | Calculated, % N |
|---|---|---|---|---|---|---|---|
| I | 2-$CH_3OCOC_6H_4$ | $C_4H_9$ | 16 | 85—7 | 6,09 | $C_{25}H_{22}N_2O_5$ | 6,17 |
| II | 2-$CH_3OCOC_6H_4$ | $C_6H_5$ | 46 | 155—7 | 5,60 | $C_{29}H_{24}N_2O_5$ | 5,83 |
| III | 2-$CH_3OCOC_6H_4$ | 4-$ClC_6H_4$ | 20 | 140—2 | 5,13 | $C_{29}H_{22}Cl_2N_2O$ | 5,10 |
| IV | 2-$C_2H_5OCOC_6H_4$ | $C_4H_9$ | 40 | 145—6 | 5,92 | $C_{26}H_{34}N_2O_5$ | 6,17 |
| V | 2-$C_2H_5OCOC_6H_4$ | $C_6H_5$ | 36 | 162—3 | 5,56 | $C_{30}H_{26}N_2O_5$ | 5,67 |
| VI | 2-$C_2H_5OCOC_6H_4$ | 4-$ClC_6H_4$ | 21 | 173—5 | 4,80 | $C_{30}H_{24}Cl_2N_2O_5$ | 4,97 |
| VII | 2-$C_4H_9OCOC_6H_4$ | $C_3H_7$ | 24 | 96—8 | 6,04 | $C_{26}H_{34}N_2O_5$ | 6,17 |
| VIII | 2-$C_4H_9OCOC_6H_4$ | iso-$C_3H_7$ | 28 | 126—8 | 6,10 | $C_{26}H_{34}N_2O_5$ | 6,17 |
| IX | 2-$C_4H_9OCOC_6H_4$ | $C_4H_9$ | 31 | 113—5 | 5,69 | $C_{28}H_{38}N_2O_5$ | 5,80 |
| X | 2-$C_4H_9OCOC_6H_4$ | iso-$C_4H_9$ | 11 | 111—3 | 5,57 | $C_{28}H_{38}N_2O_5$ | 5,80 |
| XI | 2-$C_4H_9OCOC_6H_4$ | iso-$C_5H_{11}$ | 55 | 117—9 | 5,87 | $C_{30}H_{42}N_2O_5$ | 5,49 |
| XII | 2-$C_4H_9OCOC_6H_4$ | $C_6H_5$ | 32 | 164—5 | 5,36 | $C_{32}H_{30}N_2O_5$ | 5,36 |
| XIII | 2-$C_4H_9OCOC_6H_4$ | 4-$CH_3C_6H_4$ | 36 | 132—4 | 5,11 | $C_{34}H_{34}N_2O_5$ | 5,09 |
| XIV | 2-$C_4H_9OCOC_6H_4$ | 4-$ClC_6H_4$ | 39 | 185—6 | 4,51 | $C_{32}H_{28}Cl_2N_2O_5$ | 4,74 |
| XV | 2-$C_6H_4OCOC_6H_4$ | $C_6H_5$ | 64 | 190—1 | 5,05 | $C_{34}H_{26}N_2O_5$ | 5,16 |
| XVI | 2-$C_6H_5OCOC_6H_4$ | 3-$CH_3C_6H_4$ | 38 | 158—60 | 4,92 | $C_{36}H_{30}N_2O_5$ | 4,91 |
| XVII | 2-$C_6H_5OCOC_6H_4$ | 4-$CC_6H_4$ | 42 | 221—3 | 4,49 | $C_{34}H_{24}Cl_2N_2O_5$ | 4,58 |
| XVIII | $C_2H_5O$ | $C_6H_5$ | 85 | 175—7 | 7,25 | $C_{23}H_{22}N_2O_4$ | 7,18 |
| XIX | $C_2H_5O$ | 2-$CH_3C_6H_4$ | 29 | 160—1 | 6,68 | $C_{25}H_{26}N_2O_4$ | 6,73 |
| XX | $C_2H_5O$ | 3-$CH_3C_6H_4$ | 29 | 124—6 | 6,65 | $C_{25}H_{26}N_2O_4$ | 6,73 |
| XXI | $C_2H_5O$ | 4-$CH_3C_6H_4$ | 36 | 143—4 | 6,56 | $C_{25}H_{26}N_2O_4$ | 6,73 |
| XXII | $C_2H_5O$ | 4-$ClC_6H_4$ | 54 | 176—8 | 6,00 | $C_{23}H_{26}Cl_2N_2O_4$ | 6,10 |
| XXIII | $C_2H_5O$ | $C_2H_5$ | 82 | 133—4 | 9,43 | $C_{15}H_{22}N_2O_4$ | 9,53 |
| XXIV | $C_2H_5O$ | $C_3H_7$ | 84 | 144—5 | 8,56 | $C_{17}H_{26}N_2O_4$ | 8,69 |
| XXV | $C_2H_5O$ | iso-$C_3H_7$ | 71 | 150—2 | 8,37 | $C_{17}H_{26}N_2O_4$ | 8,69 |
| XXVI | $C_2H_5O$ | $C_4H_9$ | 57 | 147—8 | 8,17 | $C_{19}H_{30}N_2O_4$ | 8,00 |
| XXVII | $C_2H_5O$ | iso-$C_4H_9$ | 31 | 153—5 | 7,62 | $C_{19}H_{30}N_2O_4$ | 8,00 |
| XXVIII | $C_2H_5O$ | $C_5H_{11}$ | 53 | 145—6 | 7,13 | $C_{21}H_{34}N_2O_4$ | 7,43 |
| XXIX | $C_2H_5O$ | iso-$C_5H_{11}$ | 53 | 160—1 | 7,42 | $C_{21}H_{34}N_2O_4$ | 7,43 |

*Substances I and VII crystallize out of petroleum ether; IV, VIII-XI, and XIII from a toluene—petroleum ether mixture; II, V, XII, XIV, XV, and XVIII from ethanol; XVII from glacial acetic acid, and the remainder from toluene.

TABLE 2. Physiologic Activity of β-(o-Carbalkoxy)- and β-Carbethoxy-β-Phenylhydrazides of Disubstituted Glycolic Acids $C_6H_5(COR')NHCOC(OH)R_2$

| Compound | Anti-inflammatory activity, i.e., increase in foot volume (% of initial) during formalin inflammation (dose: 50 mg/kg) | | Analgesic activity, i.e., defensive reflex reaction time at peak activity, sec (dose: 100 mg/kg) ± m |
|---|---|---|---|
| | 3 | 6 | |
| II | 105 | 157 | 15,2±1,0 |
| VIII | 141 | 130 | 15,0±2,9 |
| IX | 136 | 151 | 15,2±1,9 |
| X | 113 | 118 | 19,8±2,2 |
| XI | 71 | 67 | 18,3±1,7 |
| XII | 110 | 100 | 15,3±1,2 |
| XIII | 137 | 121 | 13,0±1,1 |
| XIV | 151 | 110 | 21,5±2,9 |
| XVIII | — | — | 28,0±2,1 |
| XIX | 88 | 111 | 15,3±1,2 |
| XXI | 73 | 58 | 24,6±2,4 |
| XXII | 74 | 83 | 20,8±2,9 |
| XXIII | 79 | 105 | 13,6±0,8 |
| XXIV | 95 | 119 | 19,0±1,5 |
| XXV | 61 | 106 | 16,1±1,8 |
| XXVI | — | — | 22,8±1,8 |
| XXVII | 76 | 106 | 18,8±4,5 |
| XXVIII | 77 | 75 | 14,6±1,7 |
| XXIX | 113 | 146 | 19,3±4,1 |
| Formalin, 2,5% | 74 | 86 | — |
| Phenylbutazol, 30 mg/kg | 50 | 52 | — |
| Starch mucilage | — | — | 12,1±0,8 |
| Amidopyrine | — | — | 50,4±2,6 |

1755 $cm^{-1}$ for substance XV, corresponding to two amide and one complex ester carbonyls. In compound XVIII the amide I band has a frequency of 1685 $cm^{-1}$, and the band for the second carbonyl, complex ester, and amide at the same time is situated at 1708 $cm^{-1}$. Two bands are superimposed in compounds II, V, and IX. The bands of $\nu_{C-O}$ in the tertiary hydroxyl of compounds II, V, XII, XV, and XVIII have a frequency of 1055-1075 $cm^{-1}$ and in IX at 1178 $cm^{-1}$ [3].

The anti-inflammatory activity of the series of synthesized compounds was investigated by using the formalin test [4], and their analgesic activity was measured by the "hot plate" method [5]. The test results are provided in Table 2. Of the compounds tested, substances XI and XXI have the ability to relieve the inflammatory effect, the rest of the substances being either inactive or in one instance, the β-nitrogen o-carbalkoxybenzoyl residue, even increasing the inflammation. Activity in this regard depends on the nature of the carbinol carbon radical, and in the series $4\text{-}ClC_6H_4$, $iso\text{-}C_3H_7$, $4\text{-}CH_3C_6H_4$, $iso\text{-}C_4H_9$, $iso\text{-}C_5H_{11}$, the inflammatory effect gradually decreases with a transition to an anti-inflammatory effect. On the other hand, all of the compounds studied provide an analgesic effect which is higher on the whole among the carbethoxyl derivatives, especially compounds XVIII, XXI, and XXVI.

## EXPERIMENTAL METHOD

The IR-spectra were taken on spectrophotometer UR-20 (compounds II, V, XII, and XVIII) and IKS-22 (compounds IX and XV) as Vaseline oil suspensions and chloroform solutions.

β-(o-Carbomethoxybenzoyl)-β-phenylhydrazide of Dibutylglycolic Acid [I]. To Grignard reagent (1.2 g of magnesium and 6.9 g of butylbromide) we added 2.1 g of the ethyl ester of oxalic acid β-phenylhydrazide [6] and heated the mixture in a water bath for 30 min; 3.9 g of the dimethyl ester of phthalic acid was added and the reaction mass heated for 1 h and dispersed with dilute hydrochloric acid. The yield was 0.7 g (15.8%). Compounds II and III were obtained in a similar fashion. Compounds IV-VI are synthesized by using diethylphthalate, VII-XIV with dibutylphthalate, XV-XVII with diphenylphthalate, and compounds XVIII-XXIX with the ethyl ester of chlorocarbonic acid.

β-(o-Carbethoxybenzoyl)-β-phenylhydrazide of Dibutylglycolic Acid [IV]. We heated 1 g of dibutylglycolic acid phenylhydrazide [7] and 20 ml of dry benzene with 0.8 g of o-

carbethoxybenzoylchloride [8] for 2 h; the substance precipitated out when the solution was cooled. The yield was 1.1 g (67.3%). A mixed melting sample with substance IV, obtained by the method described above, melted without depression of the melting point. Compounds V and VI were obtained in a similar manner. Substances XVIII, XXI, and XXVI were synthesized by using the ethyl ester of chlorocarbonic acid.

## LITERATURE CITED


1. I. S. Berdinskii, V. É. Kolla, A. F. Makhanek, et al., Izv. Estestvennonauch. NI at Perm University, 14, No. 18, 10-14 (1966).
2. Author's Abstract 537,069 (USSR), Otkrytiya, No. 14 (1976).
3. I. S. Berdinskii, Uchen. Zapiski Perm. Un-ta, 178, 303-314 (1968).
4. L. S. Solyamon, in: Pharmacology of Pathologic Processes [in Russian], Leningrad (1951), pp. 23-28.
5. N. B. Eddy and D. J. Deimbach, J. Pharmacol. Exp. Ther., 109, 385-393 (1953).
6. I. S. Berdinskii and P. A. Petyunin, Zh. Obshch. Khim., 26, 2592-2595 (1956).
7. I. S. Berdinskii, Zh. Obshch. Khim., 28, 1263-1265 (1958).
8. H. Meyer, Chemie, No. 22, 578-586 (1901).


# SYNTHESIS AND RADIOPROTECTIVE ACTIVITY OF S-DERIVATIVES OF MERCAPTOETHYLAMINOMETHYLNAPHTHALENES AND BENZO-2,1,3-THIADIAZOLES


N. M. Slavachevskaya, N. S. Tsepova, Yu. E. Strel'nikov, and I. A. Belen'kaya



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It is known that substitution of an amino group hydrogen atom in the well-known radioprotective preparation β-mercaptoethylamine or its S-derivatives by bulky substituents results in increased lipoidotropic properties to which the reduced radioprotective dose of the substances obtained is probably related [1].

An analysis of reports in the literature allowed us to conclude that at the present time a tendency is becoming apparent to use compounds belonging to aromatic and heterocyclic systems as substituents, among which substances have been found which are active with regard to radioprotection. For the purpose of seeking out new radioprotectors we synthesized a series of aliphatic sulfoazo-containing compounds (Tables 1 and 2) having benzo-2,1,3-thiazole and naphthalene derivatives as their bulky substituents [2-5].

The requirements for synthesizing 1- and 2-bromomethylnaphthalenes (I and II) and 4- and 5-bromomethylbenzo-2,1,3-thiadiazoles (III and IV) were obtained from reports in the literature [6-8].

When I-IV react with ethyleneimine (see the chart), the corresponding 1- and 2-aziridinylmethylnaphthalenes (V, VI) are formed as well as the 4- and 5-aziridinylmethylbenzo-2,1,3-thiadiazoles (VII, VIII). It should be noted that VII and VIII possess a polymorphism which is expressed in changes in melting point, solubility, and crystalline structure (Fig. 1).

The identity of VII and VIII in their crystalline and amorphous forms is supported spectrophotometrically (Fig. 2) and by chemical methods. The aziridinyls of VII and VIII are broken open by hydrogen bromide with the formation of β-N-(methylbenzo-2,1,3-thiadiazolyl)aminoethylbromides (IX, X). The β-N-(1- and 2-methylnaphthyl)aminoethylbromides (XI, XII) are formed in a similar fashion. Compound IX is isolated as a base, and compounds X-XII in the form of hydrobromides.

When IX reacts with potassium ethylxanthogenate, thiourea, sodium thiosulfate, or ammonium trithiocarbonate, the corresponding xanthogenate (XIII), isothiuronic salt (XIV), Bunte salt (XV), and S,S',N,N',β,β'-bis-(4-methylbenzo-2,1,3-thiadiazolyl)aminoethyltrithio-


S. M. Kirov Military Medical Academy, Leningrad.


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