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DIACYL DERIVATIVES OF PHENYLHYDRAZINE

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Abstract

Full Text

CHEMISTRY

Z. V. PUSHKAREVA and N. I. LATOSH

DIACYL DERIVATIVES OF PHENYLHYDRAZINE

On the Question of the Relationship Between Chemical Structure and Analgesic Action

(Presented by Academician I. N. Nazarov, 20 XI 1956)

The struggle against pain has attracted people's attention throughout the history of mankind, and much has been done in the field of creating analgesic agents, especially during the last 15-20 years ([1–4]). However, the analgesic agents used in modern medicine, including antipyrine and pyramidon, possess substantial shortcomings, manifested in harmful side effects on the human organism.

In 1929 R. Charon and R. Delaby ([5]) attempted, by obtaining the N-oxide of pyramidon, to reduce the toxicity of the latter. Upon oxidation of pyramidon (I) with hydrogen peroxide, a product was obtained that possessed the analgesic activity of pyramidon and considerably lower toxicity, but that proved not to be the expected N-oxide, but rather α-dimethylamidooxalyl-β-methyl-β-acetylphenylhydrazine, or the so-called dioxypyramidon (II).

This prompted us to synthesize a series of diacyl derivatives of phenylhydrazine of the general formula (III) and to trace in them the relationship between chemical structure and analgesic action in this class of substances.

The first group of synthesized compounds consisted of "skeleton substances," in which R_1, R_2, and R_3 represented methyl and phenyl residues in all possible combinations: (IV), (V), (VI), (VII), (VIII), and (IX).

The study of these simple substances made it possible to trace the influence on the properties of the molecules of comparatively simple structural changes in the α- and β-acyl residues of phenylhydrazine.

The second group of compounds comprised derivatives of α-benzoyl-β-acetyl-β-methylphenylhydrazine (VIII). By introducing various substituents into the ring of the benzoyl radical (R_3), we obtained a series of substances structurally related to it (general formula (X)), in order to trace the influence of various substituents conjugated with the α-acyl residue on the properties of the molecule as a whole—(XI), (XII), and (XIII). Since among these compounds there was no benzoyl derivative with an electron-acceptor substituent in the ring, α-isonicotinoyl-β-acetyl-β-methylphenylhydrazine (XIV) was synthesized.

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In addition to the second group of substances, compounds (XV) and (XVI) were obtained, in which the α-acyl radical also contained a phenyl residue, but not one directly bonded to the carbonyl group, rather separated from it. In one case (XVI) the separating group is a conductor of conjugation (—CH = CH—), while in the other (XV) it interrupts the conjugation chain (—CH_2—).

Finally, compound (XV) is, as it were, a partially hydrogenated dioxypyramidon (II) and contains in the α-position, instead of an oxamide residue, a dialkylaminoacetyl residue.

The starting materials for the syntheses of all the compounds listed were either phenylhydrazine or hydrazobenzene, and from them the substances were obtained according to one of two schemes.

I **II** **III**

For compound **III**:

$$\begin{aligned}
&\text{IV} && R_1 = R_2 = R_3 = CH_3,\\
&\text{V} && R_1 = R_2 = CH_3; \quad R_3 = C_6H_5,\\
&\text{VI} && R_1 = CH_3; \quad R_2 = R_3 = C_6H_5,\\
&\text{VII} && R_1 = C_6H_5; \quad R_2 = R_3 = CH_3,\\
&\text{VIII} && R_1 = R_3 = C_6H_5; \quad R_2 = CH_3,\\
&\text{IX} && R_1 = R_2 = R_3 = C_6H_5.
\end{aligned}$$

X

$$\begin{aligned}
&\text{XI} && x = N(CH_3)_2; \quad y = H,\\
&\text{XII} && x = Br; \quad y = H,\\
&\text{XIII} && x = H; \quad y = OH.
\end{aligned}$$

XIV **XV** **XVI** **XVII**

1)

$$\text{phenylhydrazine} \xrightarrow{\text{acylation}} \text{monoacylphenylhydrazine} \xrightarrow{\text{acylation}} \text{diacylphenylhydrazine} \xrightarrow{\text{methylation}} \text{N-methyl}$$

(In the case of hydrazobenzene derivatives, the last stage was omitted.)

2)

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compound obtained according to scheme 1 $\xrightarrow{\text{partial saponification}}$ XVIII $\xrightarrow{\text{acylation}}$ acylated derivative

(obtained according to scheme 1)

Table 1

Obtained substances	Yield, % of theory	Brief characterization	Obtained substances	Yield, % of theory	Brief characterization
N-Benzoyl-N′-acetyl hydrazobenzene (VIII)	89.0	White crystals from alcohol, m.p. 149°Found %: N 8.32Calculated %: N 8.48	α-Phenylacetyl-β-acetyl-β-methylphenylhydrazine (XV)	53.0	White crystals from alcohol, m.p. 82°Found %: N 9.40Calculated %: N 9.63
α-(p-Diethylamino)-benzoyl-β-acetyl-β-methylphenylhydrazine (XI)	56.0	White fine crystals from 50% alcohol, m.p. 154°Found %: N 13.41Calculated %: N 13.50	α-Cinnamoyl-β-acetylphenylhydrazine	75.0	White fine needles from alcohol, m.p. 143°Found %: N 10.22Calculated %: N 10.04
α-p-Bromobenzoyl-β-acetylphenylhydrazine	80.0	White needles from alcohol, m.p. 168°Found %: N 8.50Calculated %: N 8.67	α-Cinnamoyl-β-acetyl-β-methylphenylhydrazine (XVI)	92.0	White needles from alcohol, m.p. 123°Found %: N 9.74Calculated %: N 9.52

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Obtained substances	Yield, % of theory	Brief characterization	Obtained substances	Yield, % of theory	Brief characterization
α-(p-Bromo)-benzoyl-β-acetyl-β-methylphenylhydrazine (XII)	75.0	White needles from 70% alcohol, m.p. 126°Found %: N 8.42Calculated %: N 8.31	α-Diethylaminoacetyl-β-acetylphenylhydrazine	36.0	White needles from acetone, m.p. 80°Found %: N 15.78Calculated %: N 15.97
α-(o-Hydroxy)-benzoyl-β-acetyl-β-methylphenylhydrazine (XIII)	73.0	White fine crystals from benzene, m.p. 180°Found %: N 9.98Calculated %: N 9.86	α-Chloroacetyl-β-acetyl-β-methylphenylhydrazine		White crystals from alcohol, m.p. 62°Found %: N 11.39Calculated %: N 11.64
α-Isonicotinoyl-β-acetyl-β-methylphenylhydrazine (XIV)	43.0	White crystals with a brownish tint from alcohol, m.p. 165°(hydrochloride m.p. 173°)Found %: N 15.44Calculated %: N 15.61	α-Diethylaminoacetyl-β-acetyl-β-methylphenylhydrazine (XVII)	42.0	Colorless thick liquid, b.p. 160–161°/5 mm-Found %: N 15.33Calculated %: N 15.16

Researchers[5,6] who have worked with the most thoroughly studied representa-

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tive of the diacylhydrazines—dioxypyramidone—draw attention to its poor crystallizability, despite a fairly high melting point (105°). The difficulty, in fact, lies in obtaining the primary crystals; subsequent recrystallization with seeding proceeds quite smoothly. This applies, to one degree or another, to all the diacyl derivatives of phenylhydrazine that we obtained, both unalkylated and alkylated, whereas monoacyl products (XVIII) and others crystallize and are purified readily. For this reason the second scheme was used preferentially in the syntheses. In addition, β-methyl-β-acetylphenylhydrazine (XVIII) is part of the molecular skeleton of most of the synthesized substances.

In the course of the syntheses, the optimal conditions for partial deacylation[7], which make it possible to obtain (XVIII) in 85–86% yield, were studied.

Brief data on the properties of those of the synthesized compounds that had not previously been described are given in Table 1. Some of the substances were obtained by methods described in the literature—(IV)[8], (V)[8], (VI)[9], (VII)[10], (IX)[11], and (XVIII)[7].

The results of a comparative study of the physicochemical properties (ultraviolet spectra, dipole moments) of the synthesized compounds will be published separately. At the same time, the substances were submitted to the Department of Pharmacology of the Sverdlovsk State Medical Institute for study of their analgesic action. Preliminary results of the pharmacological tests[12] showed that substances of type (X) are of greatest interest.

Ural Polytechnic Institute
named after S. M. Kirov

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Note: Figure translations are in progress. See original paper for figures.

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