SYNTHESIS AND PROPERTIES OF 2-IMINO-3-BENZYL-5-PHENYL-1, 3, 4-OXADIAZOLINE

V. F. Vasil'eva, R. A. Zagrutdinova, E. M. Peresleni, and V. G. Yashunskii

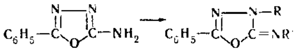
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 2, pp. 155–158, 1970

UDC 547.793.4.07:543.422.4

2-Imino-3-benzyl-5-phenyl-1, 3, 4-oxadiazoline (**Ia**) was synthesized by the reaction of benzyl chloride with 2-amino-5-phenyl-1, 3, 4-oxadiazole (**II**). A number of imino-group derivatives of **Ia** were prepared. The structure of the compounds prepared were confirmed by means of their IR spectra.

Among oxadiazoles with an exocylcic carbonyl or amino group, substances can be found possessing tranquilizing and antispasmodic action [1–4]. Some of them are recommended as remedies for treatment of epilespy [4].

With the object of screening these heterocyclic compounds for pharmacological activity we have synthesized some derivatives containing aralkyl substituents. The preparation is described in the literature of 2-imino-3-methyl-5-phenyl-1, 3, 4-oxadiazoline (**Ib**) by the methylation of 2-amino-5-phenyl-1, 3, 4-oxadiazole (**II**) with methyl iodide in methanol [5]. We have studied the benzylation of **II**. By heating **II** with excess benzyl chloride at 100° C, an individual substance was isolated the analysis of which corresponded to a benzyl derivative of compound **II**. By analogy with the 3-methyl derivative (**Ib**), the compound obtained was ascribed the structure 2-imino-3-benzyl-5-phenyl-1, 3, 4-oxadiazoline (**Ia**). A number of its exocyclic imino-group derivatives were synthesized (**Ic**–**If**).



II

I a–f

a, c-f $R=CH_2C_6H_5$; b $R=CH_3$; a, b $R'=H$; c $R'=COCH_3$; d $R'=CONHC_6H_5$;
e $R'=CSNHC_6H_5$; f $R'=SO_2C_6H_4NHCOOCH_3$

We have also attempted to prepare the N-nitroso derivatives of **Ia**. However, by the action of sodium nitrite on **Ia** in very dilute hydrochloric acid, instead of the corresponding nitrosoimine, an individual substance was obtained which from its elemental analysis was 3-benzyl-5-phenyl-1, 3, 4-oxadiazol-2-one (**III**). The structure of this compound was confirmed by its IR spectrum in which there is the intense absorption band at 1770 cm^{-1} that is observed for the C=O group in 1, 3, 4-oxadiazolones [6]. The formation of **III** is also observed on the prolonged standing of an aqueous acid solution of **Ia** at room temperature. Apparently, under the nitrosation reaction conditions **III** is formed as a result of a cleavage of the nitroso derivative of 2-imino-3-benzyl-5-phenyl-1, 3, 4-oxadiazoline. There are reports in the literature of the instability of similar compounds [7]. However, the possibility should not be excluded that under these conditions hydrolysis of the imino group of **Ia** also occurs.

Since during the alkylation of **II** the formation of endo- and exocyclic isomers is possible, in order to confirm the structure of the compounds that we obtained their IR spectra were studied. The IR spectra of crystals of **Ia** exhibit an intense band at 1702 cm^{-1}, several weak bands at 1500–1660 cm^{-1}, and a medium-strength band at 3330 cm^{-1} (3365 cm^{-1} in $CHCl_3$). In the spectrum of **Ib**, the amino structure of which has been proved earlier [5], analogous bands at 1690 and 3310 cm^{-1} (1710, 3367 cm^{-1} in $CHCl_3$), due to the stretching vibration of the exocyclic group C=N and to NH, respectively are observed [8]. In addition, in the 1650–1500 cm^{-1} region there are bands due to the stretching vibrations of the endocyclic C=N bond and C=C bonds and the deformation vibrations of the NH group.

In contrast to this, in the spectrum of crystals of **II** there are bands due to the stretching and deformation vibrations of the NH_2 group (3140, 3300, 1656 cm^{-1}) and also the ring $\nu C{=}N$ and $\nu_{C=C}$ bands at 1602, 1565 and 1498 cm^{-1}. In order to make a correct assignment of the $\nu_{C=N}$ and δ_{NH_2} bands deuteration in C_2H_5OD was used [9]. The 1656 cm^{-1} band in the spectrum of **II** was appreciably weakened in intensity on deuteration and the other bands in this region did not alter. A similar assignment of frequencies was made in the spectrum of 2-amino-5-vinyl-1, 3, 4-oxadiazole (1665 cm^{-1}—δ_{NH_2}, 1550 $cm^{-1}-\nu_{C=N}$) [10]. However, in more recent work [1] the 1656 cm^{-1} band in the spectrum of **II** was assigned without proof to the stretching vibrations of the ring C=N bond. In other papers [11, 12] no assignment of the spectral bands at all was made.

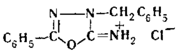
On the basis of the facts discussed we have assigned the bands at 1702 and 3330 cm^{-1} in the spectrum of **Ia** to the stretching vibrations of the exocyclic C=N bond, and to the NH of the imino group, respectively. Thus the benzyl derivative **Ia** has the imino structure.

It is natural to expect that the N-alkyl derivatives of **Ia** (**Ib–If**) will also possess an imino structure. In fact in the spectra of the 2-acetyl (**Ib**) and 2-phenylcaramoyl (**Ic**) derivatives in the form of the crystalline solids two intense bands were observed in each, at 1670, 1630 and 1680, 1640 cm^{-1}, respectively. The higher-frequency bands were due to the stretching vibrations of the exocyclic C=N group, and the bands at 1630, 1640 cm^{-1} were assigned to the stretching vibrations of the imide carbonyl in the =N–CO– grouping [13]. In addition to this, in the high-frequency region of the spectrum of **Id** the band of the stretching vibrations of the secondary amino group of the phenylcarbamoyl residue at 3270 cm^{-1} was observed. It may be noted that, as would be expected, in the derivatives which have been examined, the existence of conjugation between the exocyclic C=N group and the carbonyl of the acyl residue causes a reduction in the $\nu_{C=H}$ frequency (1670, 1680 cm^{-1}) compared with the original imine Ia (1702 cm^{-1}).

In the spectra of crystals of the 2-phenylthiocarbamoyl (Ie) and 2-(p-methoxycarbonylaminobenzenesulfonyl) (If) derivatives of **Ia** were found the intense bands of the exocylic group $\nu_{C=N}$ at 1653, 1664 cm^{-1}, several bands in the 1500–1620 cm^{-1} region due to $\nu_{C=C}$ and $\nu_{C=N}$ of the ring bands, and also intense deformation (1534, 1540 cm^{-1}) and stretching bands (3405, 3437 cm^{-1} in solutions) due to vibrations of the NH secondary amino group.

The IR spectrum of the hydrochloride of 2-amino-3-benzyl-5-phenyl-1, 3, 4-oxadiazoline was studied. Compared with the base Ia, the ν_{NH} absorption band at 3330 cm^{-1} has disappeared in the spectrum of its salt and an intense broad band has appeared at 2650–3080 cm^{-1}, evidently due to the stretching vibrations of the $\overset{+}{N}H_2$ group [14]. In the region of double-bond vibrations the very intense absorption band with the frequency 1707 cm^{-1} has remained, and the intensity of the 1600–1623 cm^{-1} absorption has markedly increased. On deuteration of the hydrochloride of Ia the absorption band at ~1610 cm^{-1} disappeared, and the intensity of the 1707 cm^{-1} band was unchanged. Therefore it is evident that the 1707 cm^{-1} high-intensity band in the spectrum of the hydrochloride of Ia is due to stretching vibrations of the exocyclic C=N bond and the absorption at 1610 cm^{-1} is due to deformation vibrations of the $\overset{+}{N}H_2$ group [8, 14, 15].

From the experimental results it may be concluded that salt formation occurs by the addition of a proton to the exocyclic imino group. In these circumstances the positive charge is probably centered on the nitrogen atom and the hydrochloride has structure IV



IV

EXPERIMENTAL

2-Imino-3-benzyl-5-phenyl-1, 3, 4-oxadiazoline (Ia). 9 g (0.056 mole) of 2-amino-5-phenyl-1, 3, 4-oxadiazole (II) [16] and 72 ml (0.63 mole) of benzylchloride were heated at 100° C with stirring for 27 hr. The precipitate was filtered off and washed with anhydrous ether, during which a certain amount of Ia hydrochloride separated from the mother liquor, and was combined with the main bulk of the precipitate. 11.4 g (0.039 mole) of crude **Ia** hydrochloride was dissolved in 500 ml of water, the filtrate was made alkaline to pH 6.8–7.0, and the precipitate was washed with water and dried. Yield 5.94 g (42%), mp 115–117° C (from ethanol); UV spectrum λ_{max} 294 nm, lgε 4.14; shoulder 222 nm, lgε 4.21. Found, %: C 72.2; H 5.3; N 16.8. Calculated for $C_{15}H_{13}N_3O$, %: C 71.7 H 5.2; N 16.7. **Hydrochloride of Ia:** mp 203.5–205° C (from absolute ethanol); UV spectrum: λ_{max} 263 nm, lgε 4.29 (in 0.1 N HCl). Found, %: C 63.0; H 4.9; Cl 12.6. Calculated for $C_{15}H_{13}N_3O \cdot HCl$, %: C 62.6; H 4.9; Cl 12.3.

2-Imino-3-methyl-5-phenyl-1, 3, 4-oxadiazoline (Ib) was prepared by a slightly modified procedure [5]. 4.98 g (0.031 mole) of II and 5 ml of methyl iodide in 50 ml of methanol were boiled for 22 hr, the mixture was evaporated to a small volume and then cooled, and the precipitate was filtered off and washed with a small quantity of cooled methanol. The precipitate was dissolved in a small amount of water and the filtered solution was made alkaline with 5% NaOH to pH 7.5–8.0. The resulting precipitate was filtered, washed with water, and dried in a vacuum desiccator over P_2O_5. Yield 1.36 g (25%), mp 99–101° C. **The hydrochloride of Ib** was prepared by treating the base **Ib** with an ethanolic solution of hydrogen chloride: mp 225–230° C (dec.) (from absolute ethanol). Found, %: C 50.9; H 5.0; Cl 16.7. Calculated for $C_9H_9N_3O \cdot HCl$, %: C 51.1; H 4.8; Cl 16.8.

2-Acetylimino-3-benzyl-5-phenyl-1, 3, 4-oxadiazoline (Ic). 3 g (0.012 mole) of Ia was boiled 15 hr with 60 ml of acetic anhydride, the mixture was evaporated, and the residue was crystallized from aqueous CH_3OH (1 : 1) at 50° C. Yield: 2.1 g (60%), mp 82–84° C; UV spectrum; λ_{max} 251.5 and 290 nm, lgε 4.19 and 4.26. Found, %: C 69.2; H 5.3; N 14.1. Calculated for $C_{17}H_{15}N_3O_2$, %: C 69.6; H 5.2; N 14.3.

2-Phenylcarbamoylimino-3-benzyl-5-phenyl-1, 3, 4-oxadiazoline (Id). To a suspension of 1 g (0.004 mole) of Ia in 10 ml of ethyl acetate with stirring was added 0.47 g (0.004 mole) of phenyl isocyanate and the mixture was heated on a water bath for 30 min. After cooling 1.16 g (79%) of Id was separated, mp 185.5–188° C (from absolute ethanol). UV spectrum: λ_{max} 264 and 292 nm, lgε 4.41 and 4.40. Found, %: C 71.2; H 5.0; N 14.9. Calculated for $C_{22}H_{18}N_4O_2$, %: C 71.3; H 4.9; N 15.1.

2-Phenylthiocarbamoylimino-3-benzyl-5-phenyl-1, 3, 4-oxadiazoline (Ie). 0.47g (0.0018 mole) Ia and 0.25 g (0.0018 mole) of phenyl isothiocyanate were boiled 7 ml of absolute ethanol on the water bath for 1 hr, the mixture was cooled and the precipitate was filtered off. Yield 0.5 g (69%), mp 152–154° C (from absolute ethanol); UV spectrum: λ_{max} 308 nm, lgε 4.48. Found, %: C 68.7; H 4.8; S 7.9. Calculated for $C_{22}H_{18}N_4OS$, %: C 68.4; H 4.7; S 8.3.

2-(p-Methoxycarbonylaminobenzenesulfonylimino)-3-benzyl-5-phenyl-1, 3, 4-oxadiazoline (If). To a solution of 3.77 g (0.015 mole) Ia in 20 ml pyridine was added 4.1 g (0.016 mole) of p-methoxycarbonylaminobenzenesulfonyl chloride and the mixture was heated 1 hr on the water bath. The cooled solution was poured into excess of dil HCl and the precipitate was filtered off. Yield 5.9 g (84%), mp 189–191° C (from ethanol). UV spectrum: λ_{max} 259.5 nm, lgε 4.51; shoulder 277 nm, lgε 3.75. Found, %: C 59.3; H 4.7; S 6.9. Calculated for $C_{23}H_{20}N_4O_5S$, %: C 59.5; H 4.3; S 6.9.

3-Benzyl-5-phenyl-1, 3, 4-oxadiazol-2-one (III). 2 g (0.008 mole) of Ia was dissolved in 2*l* of water containing 2 ml (0.023 mole) of conc HCl. At 5–0° C an aqueous solution of 1.6 g (0.023 mole) of sodium nitrite was added and stirring was continued for 4 hr at this temperature. A precipitate gradually separated out and was filtered off after two days and washed with water. Yield: 1.45 g (72%), mp 116–119° C (from ethanol). Found, %: C 71.3; H 4.9; N 11.4. Calculated for $C_{15}H_{12}N_2O_2$, %: C 71.4; H 4.8; N 11.1.

The IR spectra were taken of the crystals as mulls in paraffin oil, and in some cases as solutions in $CHCl_3$, on the UR-10 recording infrared spectrophotometer. The UV spectra of ethanolic solutions were taken on the EPS-3 recording ultraviolet spectrophotometer.

REFERENCES

1. H. L. Yale and K. Losee, J. Med. Chem., **9**, 478, 1966.
2. J. J. Piala and H. L. Yale, USA patent no. 3141022, 1961; RZhKh, 1H294, 1967.
3. G. L. Hassert, Jr., J. W. Poutsiaka, D. Papandrianos, L. C. Burke, and B. N. Craver, Toxicol. and Appl. Pharmacol., **3**, 726, 1961.
4. J. Bernstein and H. L. Yale, USA patent no. 2832787, 1958; C. A., **52**, 1470a, 1958.
5. G. Werber and F. Maggio, Ann. Chem., Poma, **52**, 747, 1962.
6. W. R. Sherman, J. Org. Chem., **26**, 88, 1961.
7. G. Pellizzari, Gazz. chim. ital., **56**, 695, 1926; C., **1**, 2315, 1927.
8. L. J. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], IL, 361, 373, 1963.
9. Yu. N. Sheinker and E. M. Peresleni, ZhFKh, **36**, 1705, 1962.
10. K. Matsuda and L. T. Morin, J. Org. Chem., **26**, 3783, 1961.
11. F. Maggio, G. Werber, and G. Lombardo, Ann. chim., Roma, **50**, 491, 1960.
12. M. S. Gibson, Tetrah., **18**, 1377, 1962.
13. Yu. N. Sheinker, E. M. Peresleni, N. P. Zosimova, and Yu. I. Pomerantsev, ZhFKh, **23**, 2096, 1959.
14. E. M. Peresleni, Yu. N. Sheinker, N. P. Zosimova, and Yu. I. Pomerantsev, ZhFKh, **39**, 92, 1965.
15. V. G. Yashunskii, E. M. Peresleni, Yu. N. Sheinker, Izv. AN SSSR, ser. fiz., **26**, 1295, 1962.
16. H. Gehlen and K. Möckel, Ann., **651**, 133, 1962.

28 March 1968

Ordzhonikidze All-Union Scientific-Research Institute of
Chemistry and Pharmacy, Moscow