

Nucleophilic Behaviour of Some 1,3,4-Oxadiazoles in Benzoylation,
Nitrosation, Acetylation, and Methylation Reactions.

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Received June 11, 1971

Previously it was reported that 2-amino-5-phenyl-1,3,4-oxadiazole (I) exhibits a tautomerism between the amino-oxadiazole and imino-oxadiazoline forms (1,2,3) and an equilibrium of this kind was also presumed for the acyl derivatives of type Ia (1). Now with the aim of obtaining information concerning the behaviour of such derivatives, the compounds Ia, Ib, Ic, Id (see Table I) were subjected to acetylation, benzoylation, nitrosation and alkylation reactions. Such studies were initiated by the earlier observation concerning acylation and methylation of I (1).

Finally 4-methyl-5-imino-2-phenyl- Δ^2 -1,3,4-oxadiazoline (III) was allowed to react similarly with the aim of obtaining disubstituted derivatives having an unequivocal oxadiazoline constitution, thus permitting assignment of structures to the compounds obtained starting from the substrates Ia-Id.

Methylation of Ia afforded the oxadiazole (II) or the oxadiazoline (III) (1), while acetylation yielded only the oxadiazoline (IV), which was also obtained by acetylation of I. The structure of the diacetyl derivative IV has been assigned by Yale and Losee (2) by spectroscopic evidence (nmr). Compound Ia undergoes neither nitrosation nor benzoylation under the conditions employed.

Methylation of Ib afforded a small yield of VIII and the oxadiazoline (V) as the major product. Compound V was also obtained by benzoylation of III. Compound Ib was unaffected by benzoylation and nitrosation. Acetylation of it gave rise to cleavage of the benzoyl group and, depending on the experimental conditions, either the monoacetyl derivative Ia or a mixture of Ia and the diacetyl derivative IV were obtained.

The nitroso derivative Ic was recovered unchanged in the nitrosation reaction, but it was decomposed by

TABLE I

2-Amino-1,3,4-oxadiazoles				5-Imino- Δ^2 -1,3,4-oxadiazolines			
Compound	R	R'	ν cm ⁻¹ C=N	Compound	R	R'	ν cm ⁻¹ C=N
I	H	H	1640 (3)	III	-CH ₃	H	1680 (3)
Ia	H	-COCH ₃	1639 (2)	IV	-COCH ₃	-COCH ₃	1718
Ib	H	-COC ₆ H ₅	1618	V	-CH ₃	-COC ₆ H ₅	1626
Ic	H	-NO	1608	VI	-CH ₃	-CH ₃	1710 (3)
Id	H	-CH ₃	1630-1610 (3)	IX	-CH ₃	-NO	1623
II	-CH ₃	-COCH ₃	1608	X	-CH ₃	-COCH ₃	1631
VII	-NO	-CH ₃	1603				
VIII	-CH ₃	-COC ₆ H ₅	1605				

benzoylation and acetylation. Methylation of this compound under different conditions yielded VII or III. The formation of the latter involved cleavage of nitroso function.

Acetylation, nitrosation and benzoylation of Id led to the formation of II (1), VII and VIII respectively, while methylation yielded oxadiazoline VI (3).

Benzoylation and acetylation gave the compound V and X (1), respectively. Methylation of III yielded compound VI which in turn was obtained by methylation of Id. Finally the action of nitrous acid on compound III gave IX, which is not stable and, on standing, changed into 2-phenyl-4-methyl- Δ^2 -1,3,4-oxadiazolin-5-one, already obtained by Giudicelli *et al.*, (3) and by Ainsworth (4) using other procedures.

The structures assigned to compounds are supported by elemental analyses and by infrared and nuclear magnetic resonance spectra (see experimental section). For structure assignment by ir was followed the criteria of Yale and Losee (2) (value of endocyclic =C=N- stretching) (see Table I).

The above results indicate that all the substrates show bidentate nucleophilic behaviour according to the hypothesis of a tautomerism between the 2-amino-1,3,4-oxadiazole and 5-imino- Δ^2 -1,3,4-oxadiazoline forms.

EXPERIMENTAL

All melting points (Kofler) are uncorrected. Ir (nujol mull): Perkin-Elmer Infracord 137 Spectrophotometer; nmr Jeol C-60 H Spectrometer (TMS as internal reference).

General Procedure for Benzoylation.

A mixture of starting material (0.02 mole), benzoyl chloride (3.8 ml.) and pyridine (50 ml.) was refluxed for 24 hours, allowed to cool to room temperature then diluted with water. The precipitate was collected, washed with water and anidried.

Compound VIII (4.65 g., 83%) obtained from Id (3.5 g.) was recrystallized from ligroin, m.p. 115°; ir 1658 (C=O) and 1605 cm^{-1} (C=N); nmr (DMSO- d_6) 3.55 δ (s, 3H, =N-CH₃), 7.30-7.80 δ (m, 10H, aromatic).

Anal. Calcd. for C₁₆H₁₃N₃O₂: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.69; H, 4.51; N, 15.12.

Compound V (5.25 g., 94%) obtained from III (3.5 g.) was recrystallized from ethanol, m.p. 148°; ir 1656 (C=O) and 1626 cm^{-1} (C=N); nmr (DMSO- d_6) 3.67 δ (s, 3H, =N-CH₃), 7.20-8.50 δ (m, 5H, aromatic).

Anal. Calcd. for C₁₆H₁₃N₃O₂: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.99; H, 4.75; N, 15.01.

Ia, Ic under the same experimental conditions underwent decomposition whereas Ib was recovered unchanged.

General Procedure for Nitrosation.

To a mixture of starting material (0.014 mole) in water (60 ml.) containing sodium nitrite (3.5 g.) was added with stirring 10% aqueous hydrochloric acid (30 ml.) maintaining the temperature at 5-10°. The solid was collected by filtration and washed with water until the filtrate was neutral.

Compound VII (2.7 g., 94%) obtained from Id (2.45 g.) was recrystallized from methanol, m.p. 119-121°; ir 1603 cm^{-1} (C=N); nmr (deuteriochloroform) 3.57 δ (s, 3H, =N-CH₃), 7.40-8.30 δ (m, 5H, aromatic).

Anal. Calcd. for C₉H₈N₄O₂: C, 52.94; H, 3.95; N, 27.44. Found: C, 53.03; H, 4.04; N, 27.57.

Compound IX (2.05 g., 71%) obtained from III (2.45 g.), was washed several times with ether. It decomposed explosively at about 95°; ir 1623 cm^{-1} (C=N).

Anal. Calcd. for C₉H₈N₄O₂: N, 27.44. Found: N, 27.10.

Upon recrystallized from organic solvents or on standing, it transformed quantitatively into 2-phenyl-4-methyl- Δ^2 -1,3,4-oxadiazolin-5-one, m.p. 103° [lit. (3,4), m.p. 102° and 105-107°].

Under the nitrosation experimental conditions Ia, Ib and Ic were recovered unchanged.

Procedures for Acetylation.

Compound IV.

(a) A mixture of Ia (5 g.) in 30 ml. of acetic anhydride was heated under reflux for 6 hours. After standing 12 hours at room temperature, starting material (1.85 g.) was collected by filtration. The mother liquor after cooling in an ice-bath gave 1.6 g. (26%) of IV, which showed no melting point depression when mixed with a sample of pure IV obtained by acetylation of I (2).

Anal. Calcd. for C₁₂H₁₁N₃O₃: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.86; H, 4.52; N, 17.24.

Finally, the mother liquor was concentrated to one-third of its volume and the solid collected (0.18 g. of Ia); after cooling in an ice-bath an additional 0.73 g. (12%) of IV was obtained. When the above procedure was conducted employing pyridine (20 ml.) Ia was recovered unchanged.

(b) A mixture of Ib (2 g.) in acetic anhydride (12 ml.) was reacted as described in (a). After standing 24 hours, 0.52 g. (34%) of Ia was collected and the mother liquor on cooling yielded 0.42 g. (22%) of IV. On the other hand, acetylation of Ib (2 g.) with acetic anhydride (12 ml.) and pyridine (12 ml.) gave Ia (1.2 g., 78%). A mixture of Ic (2 g.), acetic anhydride (12 ml.), and pyridine (8 ml.), at room temperature, underwent decomposition.

Procedures for Methylation.

Compound V.

A solution of sodium methoxide (0.12 g. of sodium in 10 ml. of methanol), Ib (1.33 g.), and dimethyl sulphate (0.5 ml.) was refluxed for 6 hours. The solvent was removed and the residue diluted with water. The solid was collected and recrystallized from ethanol to give 0.45 g. (30%) of V.

Compound VIII.

This compound was obtained by evaporation of the mother liquor from the crystallization of V. The residue was extracted by ligroin from which VIII was obtained (see benzoylation).

Compound VII.

A mixture of 2 g. of Ic, 1 ml. of dimethyl sulphate and 1.4 g. of anhydrous potassium carbonate in 50 ml. of acetone was refluxed for 4 hours. The reaction mixture was filtered and evaporated to dryness and the residue was recrystallized from methanol to give 0.85 g. (39%) of VII (see nitrosation).

Compound III.

A solution of Ic (2 g.), methyl iodide (2.5 ml.) in 50 ml. of methanol was refluxed for 24 hours. The solvent was removed and the residue was treated with 5% aqueous sodium hydroxide

and the solid was collected. Recrystallization from ethanol-water gave product (0.45 g., 24%) which showed no melting point depression when mixed with a sample of pure III obtained by the methylation of I (1); ir 3279 (-NH) and 1680 cm^{-1} (C=N); nmr (deuteriochloroform) 3.45 δ (s, 3H, =N-CH₃), 5.10 δ (s, 1H, =C=NH), 7.25-8.0 δ (m, 5H, aromatic).

Compound VI.

A mixture of 9 g. of III, 1.2 g. of sodium in 100 ml. of anhydrous methanol and 4.8 ml. of dimethyl sulphate was refluxed for 12 hours. The solution was evaporated to a small volume, diluted with water, and the oil was extracted with ether. The solvent was removed and the residue was purified by distillation under reduced pressure. It solidified on cooling, m.p. 63° [lit. (3), m.p. 61-62°]; ir 1720 cm^{-1} (C=N); nmr (deuteriochloroform) 3.08 δ and 3.35 δ (2s, 6H, 2 x =N-CH₃), 7.30-7.80 δ (m,

5H, aromatic).

Anal. Calcd. for C₁₀H₁₁N₃O: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.60; H, 6.05; N, 22.45.

Acknowledgment.

We thank Dr. M. L. Marino for the nmr spectral measurements.

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