REACTION OF SOME AROMATIC NITRILE OXIDES WITH DIMEDONE

A. A. Akhrem, V. A. Khripach, and F. A. Lakhvich

UDC 547.786.3:543.422.25.4'51

1,3-Dipolar cycloaddition of benzonitrile and m-nitrobenzonitrile oxides to the enol form of dimedone gives the corresponding 4-oxotetrahydrobenzisoxazoles. A second reaction path – nucleophilic addition of the enol to the N-oxide to give a hydroxamic acid derivative – is observed in the case of m-nitrobenzonitrile oxide. The tetrahydrobenzisoxazoles are converted to enamine derivatives of benzoyldimedone under catalytic hydrogenation conditions.

It is known [1] that the reaction of nitrile oxides with enolized aliphatic β-diketones proceeds via 1,3-dipolar cycloaddition to the C=C bond of the enol forms to give 5-hydroxyisoxazolines, which are subsequently stabilized to isoxazoles by splitting out of a water molecule. However, there is no information in the literature regarding the reaction of nitrile oxides with cyclic β-diketones to give cycloalkanoisoxazoles. The latter, being the "latent form" of 2-acylcycloalkane-1,3-diones, may find interesting synthetic applications.

The reaction of aromatic nitrile oxides, particularly benzonitrile oxide (II) and m-nitrobenzonitrile oxide (III), with dimedone proceeded in situ under conditions that make it possible to maximally reduce dimerization of the oxide [2].

As assumed, products of 1,3-dipolar cycloaddition – isoxazoles VII and VIII, respectively – are obtained in the reaction of nitrile oxides II and III with dimedone (I); the intermediate isoxazolines (VI) were not isolated.

In the case of m-nitrobenzonitrile oxide (III) a second reaction path – nucleophilic addition of the enol of I to the nitrone to give hydroxamic acid derivative IV – is also realized. This sort of addition to stable nitrile oxides was previously described [3] for amines, alcohols, carboxylic acids, and some other reagents.

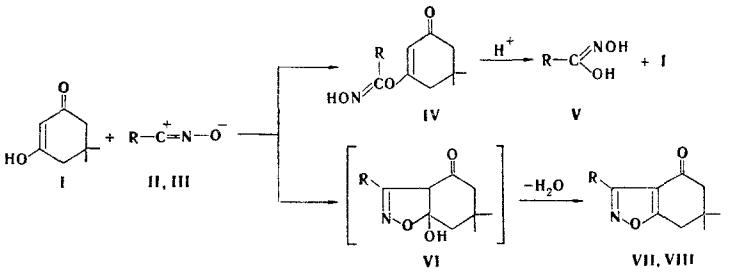
The structure of acid IV was confirmed by hydrolysis to hydroxamic acid V and dimedone (I) under acidic conditions and also by the spectral data. Thus the PMR spectrum of acid IV contains, in addition to signals of the aromatic protons and methyl and methylene protons of the dimedone fragment in the expected regions, the resonance signal of a vinyl proton at 6.38 ppm. The mass spectrum contains a molecular ion peak with m/e 304, the principal paths of disintegration of which under the influence of electron impact apparently include cleavage of the ester C–O bond. As a result of this, the principal peaks in the mass spectrum of IV correspond to m-$NO_2C_6H_4CO^+$ and m-$NO_2C_6H_4CNO^+$ fragments with intensities of 100 and 99.96%, respectively.

The IR spectrum of acid IV displays absorption bands of associated hydroxyl (2500-3200 cm^{-1}) and carbonyl (1615 cm^{-1}) groups included in strong hydrogen bonds of the chelate type, which are characteristic for dimedone and its derivatives [4].

The structure of cyclohexanoisoxazoles VII and VIII follows from the set of data from physicochemical methods of analysis and also from a comparison of the properties with IX, which we synthesized by the

Institute of Physical Organic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 901-904, July, 1974. Original article submitted July 12, 1973.

method in [5]. Thus, for example, the PMR spectra of VII-IX have practically identical patterns of resonance signals from the protons of identical structural fragments of the molecules under comparison (see the experimental section).

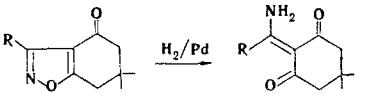


II, VII R = C_6H_5; III, IV, VIII R = $NO_2C_6H_4$

In conformity with the proposed structure, the IR spectra of isoxazoles VII and VIII contain the characteristic (for this sort of compound) absorption band of a conjugated carbonyl group at 1685-1700 cm^{-1}. In addition, there are two bands of medium intensity, which are due to absorption of the aromatic and isoxazole rings, at 1600-1700 cm^{-1}.

Fragmentation of VII and VIII under electron impact is also characteristic. Thus, while the paths of disintegration of the molecule in the case of acid IV are determined by the lability of the C–O bond and the stability of the aromatic ion arising as a result of its cleavage, the fragmentation of VII and VIII is determined by the stability of the isoxazole rings (probably the rearranged isoxazole ring [7]) conjugated with the aromatic ring. This sort of fragmentation is typical for cyclic ketones [8] and consists in cleavage of the α bond with respect to the carbonyl group and subsequent hydrogen migration and homolytic cleavage leading to the $M^+ - 98$ ion (of maximum intensity in the spectrum) and elimination of a ketone homolog as a neutral particle.

It is known [9] that 3-substituted isoxazoles undergo opening of the isoxazole ring at the N–O bond under catalytic hydrogenation conditions to give enaminoketones.



VII–IX X–XII

VII, XI R = C_6H_5; VIII, XII R = $NH_2C_6H_4$; IX, X R = CH_3

In our case, the hydrogenation of cyclohexanoisoxazole IX under the usual conditions gave a quantitative yield of the known [5] enaminodiketone X. It should be noted that the facile opening of the isoxazole ring that we observed proceeds in the absence of a base, in contrast to what usually occurs in the case of other isoxazoles (for example, see [9-11]).

Like IX examined above, VII and VIII also readily undergo opening of the isoxazole ring to give enamine derivatives XI and XII, respectively, during hydrogenation in the presence of a Pd catalyst. According to the IR spectra, as in the case of X [12] and a number of other related enaminoketones [13, 14], the latter contain a strong intramolecular hydrogen bond of the chelate type.

The structure of enamino derivatives of 2-benzoyldimedone (XI and XII) is in good agreement with the PMR and mass-spectral data presented in the experimental section.

EXPERIMENTAL

The melting points were determined with a Kofler block. The IR spectra were obtained with a UR-20 spectrometer, and the PMR spectra were obtained with a JNM-PFT-100 spectrometer with tetramethylsilane as the internal standard. The mass-spectrometric data were obtained with a Varian MAT-311 spectrometer. Thin-layer chromatography (TLC) on microplates (7.6 by 2.5) with a fixed layer of Woelm silica gel and Silufol UV-254 plates was used to monitor the course of the reactions. Silicic acid (100-150 mesh) was used for column chromatography.

Reaction of Benzonitrile Oxide (II) with Dimedone (I). A mixture of 2.8 g (0.02 mole) of I and 3.2 g (0.02 mole) of benzohydroxamic acid chloride in 100 ml of absolute tetrahydrofuran (THF) was treated with

stirring and cooling (~0 deg) in the course of 2 h with a solution of 3 g (0.03 mole) of triethylamine in 50 ml of THF, after which the mixture was stirred for another 30 min. After 3 h, the precipitated triethylamine hydrochloride was separated, and the solvent was removed in vacuo. The oily residue (~6 g) was chromatographed with a column filled with silicic acid. Elution with hexane–ether (9:1) yielded 1.2 g (26%) of 5,5-dimethyl-3-phenyl-4-oxo-4,5,6,7-tetrahydrobenz[1,2-d]isoxazole (VII) with mp 121-123° (from hexane). IR spectrum (KBr): 1580, 1595, 1700, 2965, 2880, and 3080 cm^{-1}. PMR spectrum* in CF_3COOH, δ, ppm: 1.47 ($2CH_3$, s), 2.89 (CH_2, s), 3.23 (CH_2, s), and 7.80 (C_6H_5, m). Found: C 74.6; H 6.2; N 5.6%; M (mass spectrometrically) 241. $C_{15}H_{15}NO_2$. Calculated: C 74.7; H 6.2; N 5.8%; M 241.29.

Reaction of m-Nitrobenzonitrile Oxide (III) with Dimedone (I). A solution of 2 g (0.01 mole) of benzohydroxamic acid chloride in 200 ml of chloroform was added in the course of 5 h with vigorous stirring at room temperature to a mixture of 2.8 g (0.02 mole) of I and 2 g (0.02 mole) of triethylamine in 50 ml of chloroform, after which the reaction mixture was allowed to stand overnight. The mixture was then treated with water, and the organic layer was separated and dried with $MgSO_4$. The solvent was removed, and the oily residue (~4 g) was chromatographed with a column filled with silicic acid. Elution with hexane–ether (9:1) yielded 0.55 g (19.2%) of 5,5-dimethyl-3-(m-nitrophenyl)-4-oxo-4,5,6,7-tetrahydrobenz[1,2-d]isoxazole (VIII) with mp 112-113° (from hexane). IR spectrum (KBr): 1580, 1595, 1620, 1685, 2880, and 2970 cm^{-1}. PMR spectrum in CCl_4, δ, ppm: 1.20 ($2CH_3$, s), 2.42 (CH_2, s), 2.85 (CH_2, s), and 8.20 (C_6H_4, m). Found: C 63.0; H 4.8; N 9.7%; M (mass spectrometrically) 286. $C_{15}H_{14}N_2O_4$. Calculated: C 62.9; H 4.9; N 9.8%; M 286.29.

Elution with hexane–ether (6:4) yielded 1.08 g (36%) of dimedonyl-(m-nitrobenzohydroxamic acid) (IV) with mp 172-174° (from aqueous methanol). IR spectrum (KBr): 1565, 1590, 1615, 1640, and 2500-3200 (broad band) cm^{-1}. PMR spectrum in CF_3COOH, δ, ppm: 1.26 ($2CH_3$, s), 2.62 (CH_2, s) 2.72 (CH_2, s), 6.38 (=CH, s), and 8.30 (C_6H_4, m). Found: C 59.1; H 5.3; N 9.2%; M (mass spectrometrically) 304. $C_{15}H_{16}N_2O_5$. Calculated: C 59.2; H 5.3; N 9.2%; M 304.32.

Hydrolysis of Ester IV. A solution of 0.2 g of IV in 20 ml of methanol was acidified with dilute (1:1) H_2SO_4 to pH ~1, and the mixture was allowed to stand overnight. It was then concentrated, diluted with water, and extracted with chloroform. The usual workup of the extract and subsequent crystallization from chloroform gave 0.06 g of dimedone (I) and 0.05 g of benzohydroxamic acid (V).

Cyclohexanoisoxazole IX. This compound, with mp 56-57° (from hexane), was obtained by the method in [5]. IR spectrum (KBr): 1610, 1690, 2880, and 2970 cm^{-1}. PMR spectrum in CCl_4, δ, ppm: 1.13 $2CH_3$, s), 2.28 (CH_2, s), 2.36 (CH_3, s), and 2.80 (CH_2, s).

Hydrogenation of Isoxazole IX. A solution of 0.1 g of IX in 15 ml of ethanol was hydrogenated at room temperature and normal pressure in the presence of 0.05 g of 5% $Pd/BaSO_4$. After an equivalent amount of hydrogen had been absorbed, the catalyst was removed by filtration, and the solvent was removed in vacuo. Enaminodiketone X, with mp 133-134° (mp 133° [5]) was obtained in quantitative yield.

5,5-Dimethyl-2-(α-aminobenzylidene)cyclohexane-1,3-dione (XI). Enamino derivative XI, with mp 273-274° (from chloroform), was obtained in quantitative yield from VII by a method similar to the preceding method. IR spectrum (KBr): 1590, 1655, 1695, 2880, 2970, 3110, and 3270 cm^{-1}. PMR spectrum in CF_3COOH, δ, ppm: 1.32 ($2CH_3$, s), 2.88 ($2CH_2$, s), and 7.72 (C_6H_5, m). Molecular weight found (mass spectrometrically) 243. $C_{15}H_{17}NO_2$. Calculated mol. wt. 243.22.

5,5-Dimethyl-2-(m,α-diaminobenzylidene)cyclohexane-1,3-dione (XII). Similarly, isoxazole VIII was converted quantitatively to XII with mp 212-215° (from chloroform). IR spectrum (KBr): 1590, 1630, 1650, 2880, 2970, 3150, 3290, 3380, and 3470 cm^{-1}. PMR spectrum in CF_3COOH, δ, ppm: 0.96 ($2CH_3$, s), 2.17 ($2CH_2$, s), and 7.52 (C_6H_4, m). Molecular weight found (mass spectrometrically) 258. $C_{15}H_{18}N_2O_2$. Calculated mol. wt. 258.32.

LITERATURE CITED

1. A. Quilico and G. Speroni, Gazz. Chim. Ital., 76, 148 (1946).
2. R. Huisgen, Angew. Chem., 75, 613 (1963).
3. C. Grundmann and H. D. Frommeld, J. Org. Chem., 31, 157 (1966).
4. K. Nakanishi, Infrared Spectroscopy, Practical, Holden-Day, San Francisco (1962).
5. A. W. Crossley and N. Renouf, J. Chem. Soc., 101, 1524 (1912).

*Here and subsequently, s is singlet and m is multiplet.

6. H. Smith, J. Chem. Soc., 803 (1953).
7. A. A. Polyakova and A. A. Khmel'nitskii, Mass Spectrometry in Organic Chemistry [in Russian], Khimiya, Leningrad (1972), p. 268.
8. H. Budzikiewicz, C. Djerassi, and D. Williams, Interpretation of the Mass Spectra of Organic Compounds, Holden-Day (1964).
9. R. Barnes, in: Heterocyclic Compounds [Russian translation], Vol. 5, Inostr. Lit. Moscow (1961), p. 377.
10. J. W. Scott and G. Saucy, J. Org. Chem., 37, 1652 (1972).
11. R. V. Stevens, C. G. Christensen, W. L. Edmonson, M. Kaplan, E. B. Reid, and M. P. Wentland, J. Amer. Chem. Soc., 93, 6629 (1971).
12. G. O. Dudek and G. P. Volpp, J. Org. Chem., 30, 50 (1965).
13. V. S. Bogdanov, V. V. Negrebetskii, F. A. Lakhvich, A. M. Moiseenkov, and A. A. Akhrem, Izv. Akad. Nauk SSSR, Ser. Khim., 1114 (1972).
14. V. S. Bogdanov, V. V. Negrebetskii, V. A. Korenevskii, A. M. Moiseenkov, F. A. Lakhvich, and A. A. Akhrem, Izv. Akad. Nauk SSSR, Ser. Khim., 550 (1971).