CONVERSION OF N-(1-OXIMINO-1-PHENYLPROPYL-2)-α-PHENYLNITRONE INTO IMIDAZOLE N-OXIDE DERIVATIVES

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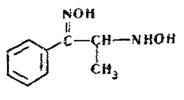
Treatment of N-(1-anti-oximino-1-phenylpropyl-2)-α-phenylnitrone with benzoic anhydride in benzene leads to simultaneous formation of benzoyl derivatives both of the corresponding nitrone and of 1-hydroxymethyl-2, 4-diphenyl-3-imidazoline-3-oxide. Treatment of the latter with hydrogen chloride led to the isolation of 5-methyl-2, 4-diphenylimidazol-3-oxide. Its isomer 4-methyl-2, 5-diphenylimidazol-3-oxide is formed by the action of HCl on syn and anti isomers of N-(1-oximino-1-phenylpropyl-2)-α-phenylnitrone. IR and UV spectra are used to determine the structures of the compounds, which are confirmed by synthesis.

It was previously shown [1] that condensation of N-(1-oximino-1-phenylpropyl-2)hydroxylamine, with the syn configuration, with benzaldehyde, gives the corresponding N-(1-oximino-1-phenylpropyl-2)-α-phenyl-nitrone (II). Reaction of N-(1-oximino-1-phenylpropyl-2)hydroxylamine (III) with the anti configuration [2], with benzaldehyde also gives a crystalline compound $C_{16}H_{16}N_2O_2$ (IV), corresponding to a condensation product formed with loss of 1 molecule of water.

The IR spectra of IV and II (Fig. 1) have an intense band at 1142 cm^{-1}, corresponding [2] to valence vibrations of the N → O bond, whence it could be assumed that IV was the anti isomer of N-(1-oximino-1-phenylpropyl-2)-α-phenylnitrone. Tableted with KBr, II and IV give IR spectra containing a wide band with its center at 3100 cm^{-1}, which corresponds to the group OH involved in hydrogen bonding. When II and IV are acetylated this band vanishes.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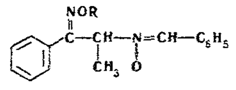
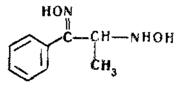

II R = H; VII R = C_6H_5CO


III

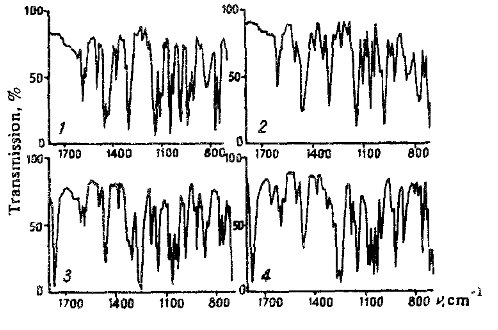


Fig. 1. IR spectra in KBr: 1) II; 2) IV; 3) VII; 4) V.

Treatment of IV with benzoic anhydride in hot benzene led to the isolation of two compounds of the same elementary composition ($C_{23}H_{20}N_2O_3$), V mp 150.0–151.0°, and VI mp 95.5–96.0°, whose UV spectra were very similar (Fig. 2), but whose IR spectra differed.

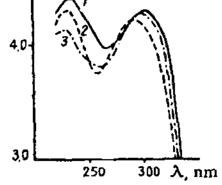
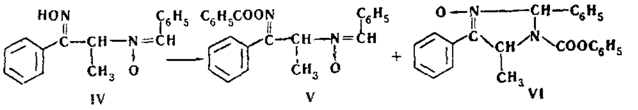


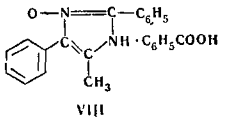
Fig. 2. UV spectra in EtOH: 1) V; 2) VI; 3) IV.

The IR spectrum of V (Fig. 1) showed, along with bands at 1255–1760 cm^{-1} ($C_6H_5\overset{O}{\overset{/\!/}{C}}$—O—), a band at 1142 cm^{-1} corresponding to N → O bond valence vibrations. It is to be pointed out that benzoylating II under the same conditions gave only one compound VII, also with bands at 1225 and 1760 cm^{-1} ($C_6H_5\overset{O}{\overset{/\!/}{C}}$—O—), and a band at 1142 cm^{-1} (N → O). Comparison of the IR spectra of II, VII, IV, and V (Fig. 1) made it possible to say that VII and V were benzoyl derivatives of nitrones II and IV.



The IR spectrum of VI (Fig. 3) had bands at 1255 and 1760 cm^{-1} ($C_6H_5\overset{O}{\overset{/\!/}{C}}$—O—), but the N → O bond absorption band in the 1100–1150 cm^{-1} region was lacking. However, since the UV spectrum of VI closely resembled that of the starting nitrone IV (Fig. 2), VI could also be assumed to contain the grouping $C_6H_5C{=}{=}N \rightarrow O$. The lack of a band characteristic of this group in the 1100–1150 cm^{-1} region may be connected with its displacement toward the shorter wavelength region (~1250 cm^{-1}), covered by intense absorption due to the ester group. The literature [4] shows that the valence vibrations band of the semipolar N → O bond is shifted 1150–1240 cm^{-1} on passing from α-monosubstituted to α, α-disubstituted nitrones.

From these results it is assumed that compound VI is an O-benzoyl derivative of 1-hydroxy-5-methyl-2, 4-diphenyl-3-imidazoline-3-oxide.



VIII

Heating compound VI under vacuum at its melting point converts it to a new compound VIII with the same elementary composition. The IR spectrum of VIII has a carbonyl group absorption band at 1680 cm^{-1}, but lacks that of an ester group $C_6H_5C(=O)-O-$, at 1255 cm^{-1}. On passing hydrogen chloride through an ethanol solution of VI, the hydrochloride of compound IX was formed, composition ($C_{16}H_{14}N_2O \cdot HCl$) corresponding to splitting of a molecule of benzoic acid from compound VI. The free base IX was obtained by treating an ethanolic solution of the hydrochloride with ammonia. Action of benzoic acid on a solution of the free base in ethyl acetate gave a compound identical with VIII.

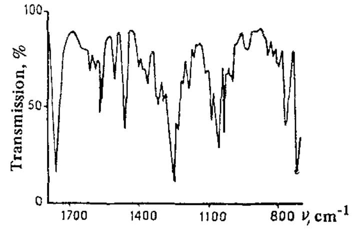
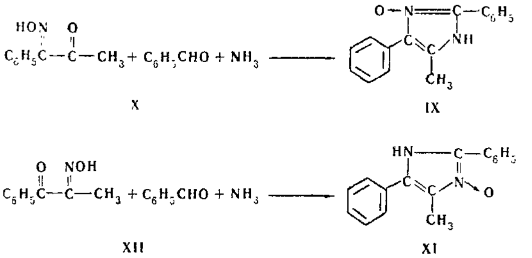


Fig. 3. IR spectrum of VI in KBr.

From the results obtained it can be assumed (cf. [5]) that IX is 5-methyl-2, 4-diphenylimidazole-3-oxide, and VIII the benzoate of the latter. According to [6], IX can be synthesized by the action of benzaldehyde and ammonia on α-isonitroso-α-phenylacetone (X).



Passage of hydrogen chloride into an ethanol solution of nitrone IV gave good yield of hydrochloride of product XI, with the same composition ($C_{16}H_{14}N_2O \cdot HCl$) as the hydrochloride of compound IX, but they gave a depressed mixed melting point, and have different IR spectra. It was assumed (cf. [5]) that compounds XI and IX are isomeric, and differ only in respect of the position of the N-oxide oxygen. 4-Methyl-2, 5-diphenylimidazole-3-oxide (XI) was synthesized [6] by the action of benzaldehyde and ammonia on α-isonitrosopropiophenone (XII).

It is of interest to note that the hydrochloride of compound XI is also formed when an ethanol solution of nitrone II, having a cis oxime group, is treated with hydrogen chloride.

The explanation of the fact that one and the same imidazole N-oxide XI is formed from the syn and anti isomers II and IV is evidently that, initially, under the action of HCl (cf. [7, 8]), there is inversion of the configuration of the oxime group followed by cyclization. Actually, treatment of an ethanol solution of syn-α-hydroxylamineoxime I with hydrogen chloride led to isolation of a good yield of a compound identical with anti isomer III, thus confirming the hypothesis of the original change of II to IV when XI is formed.

EXPERIMENTAL

IR spectra were recorded with a UR-10 spectrophotometer, using solids tableted with KBr (0.5% concentration, tablet thickness 1 mm). UV spectra were obtained with a SF-4 spectrophotometer, solvent EtOH.

The condensation of N-(1-anti-oximino-1-phenylpropyl-2)hydroxylamine (III) with benzaldehyde was carried out similarly to the condensation of N-(1-syn-oximino-1-phenylpropyl-2)hydroxylamine (I) with benzaldehyde [1]. Yield of N-(1-anti-oximino-1-phenylpropyl-2)-α-phenylnitrone (IV), mp 166.0–167.5°(ex EtOH). Found: C 71.5, 71.6; H 6.2, 6.2; N 10.7, 10.7%, calculated for $C_{16}H_{16}N_2O_2$: C 71.7; H 6.0; N 10.4%.

Benzoylation of nitrones II and IV. A solution of 0.93 g (4.1 mM) benzoic anhydride in 5 ml benzene was added to a suspension of 1.0 g (3.7 mM) N-(1-syn-oximino-1-phenylpropyl-2)-α-phenylnitrone (II) in 5 ml benzene. The solid dissolved on heating, the transparent solution was boiled for 10 min, and the benzene distilled off. The residual oil was dissolved in ether, and the precipitate of N-(1-syn-benzoyloximino-1-phenylpropyl-2)-α-phenylnitrone (VII) filtered off, mass 0.6 g (44%), mp 175.5–176.5°(ex EtOH). Found: C 74.3, 74.5; H 5.6, 5.5; N 7.9, 7.9%, calculated for $C_{23}H_{20}N_2O_3$: C 74.3; H 5.4; N 7.5%.

Benzoylation of IV was carried out in a way similar to that described above. The solution was cooled, washed with 2.5% Na_2CO_3 solution, then with water, dried over $MgSO_4$, and the solvent vacuum distilled off. The residual oil was dissolved in ether, and a colorless crystalline precipitate of N-(1-anti-benzoyloximino-1-phenylpropyl-2)-α-phenylnitrone (V) formed immediately, yield 15%, mp 150.0–151.0°(ex EtOH). Found: C 74.3, 74.2; H 5.3, 5.3; N 7.6, 7.4%, calculated for $C_{23}H_{20}N_2O_3$: C 74.2; H 5.4; N 7.5%. The filtrate was partly evaporated, then kept in a refrigerator, and the colorless precipitate of 1-benzoyloxy-5-methyl-2,4-diphenyl-3-imidazolin-3-oxide (VI) filtered off, yield 16%, mp 95.5–96.0°(ex EtOAc). Found: C 74.2, 74.0; H 5.6, 5.6; N 7.3, 7.3, calculated for $C_{23}H_{20}N_2O_3$: C 74.2; H 5.4; N 7.5%. Treatment of IV with benzoic anhydride in $CHCl_3$ gave only one compound, VI, yield $\sim$30%.

Preparation of imidazole N-oxides. Heating VI at its mp under vacuum gave the benzoate of 5-methyl-2,4-dinitrophenylimidazol-3-oxides (VIII), mp 158.0–159.0°. Found: C 74.1, 74.3; H 5.6, 5.5; N 7.6, 7.6%, calculated for $C_{23}H_{20}N_2O_3$: C 74.3; H 5.4; N 7.5%.

Saturation of an EtOH solution of VI with HCl gas gave a $\sim$70% yield of 5-methyl-2,4-diphenylimidazole-3-oxide (IX), mp 235.0–236.0°. Found: C 67.2, 67.1; H 5.4, 5.2; N 9.8, 9.8; Cl 12.6, 12.4%, calculated for $C_{16}H_{15}N_2O \cdot HCl$: C 67.0; H 5.3; N 9.7; Cl 12.4%.

Heating together an EtOAc solution of the free base IX obtained by a solution of the hydrochloride with ammonia, with an EtOAc solution of benzoic anhydride gave a compound identical with VIII, as judged by mp and IR spectrum. IX hydrochloride was also obtained in $\sim$75% yield by treating IV in $CHCl_3$ with Ac_2O, removing the solvent, and then adding saturated ethanolic HCl. Undepressed mixed mp with a specimen obtained by [6] treating α-isonitroso-α-phenylacetone (X) with benzaldehyde and ammonia; the IR spectra were also the same.

Saturation of an ethanolic solution of IV with HCl gave an $\sim$90% yield of 4-methyl-2,5-diphenylimidazole-3-oxide (XI) hydrochloride, mp 236.0–237.0°, found: C 67.3, 67.4; H 5.3, 5.4; N 9.6, 9.8; Cl 12.6, 12.4%, calculated for $C_{16}H_{15}N_2OCl$: C 67.0; H 5.3; N 9.7;

Cl 12.4%. (Depressed mixed mp with hydrochlorides **IX** and **XI**, IR spectra differed considerably). Similarly **II** gave a product mp 235.0–236.0°, undepressed mixed mp with **XI** hydrochloride and identical IR spectrum. Undepressed mixed mp of **XI** with the compounds prepared [6] by treating α-isonitrosopropiophenone (**XII**) with benzaldehyde and ammonia.

Conversion of N-(1-syn-oximino-1-phenylpropyl-2)hydroxylamine (I) to N-(1-anti-oximino-1-phenylpropyl-2)hydroxylamine (III). HCl gas was passed into a solution of 0.2 g (1.1 mM) **I** in 4 ml EtOH, the mixture allowed to stand for 12 hr, the solvent distilled off, and the residual oil dissolved in water. The solution was neutralized with aqueous ammonia, ether added, and the mixture kept in a refrigerator. The precipitate was then filtered off, mass 0.13 g (65%). After recrystallizing from EtOH it had mp 164–166°. Undepressed mixed mp with a specimen of **III**, and had the same IR spectrum.

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