THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 1

JANUARY 15, 1971

Phenylglyoxime. Separation, Characterization, and Structure of Three Isomers

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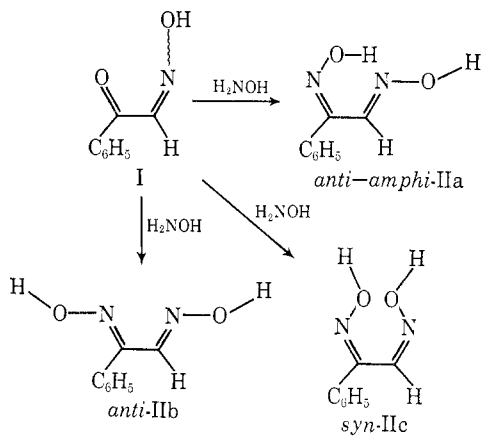
Received July 6, 1970

Three isomers of phenylglyoxime have been isolated by fractional recrystallization of the reaction product of ω-isonitrosoacetophenone and hydroxylamine hydrochloride in alkaline medium. The physical and spectral properties of each isomer are described. Structure is assigned to each of the isomers on the basis of the relative rates of complexing with nickelous acetate, the relative stabilities of the isomers, and spectroscopic information. The fourth possible isomer of phenylglyoxime was not detected.

Although isolations of three isomers of many disubstituted glyoximes have been reported in the literature, this is not the case with monosubstituted glyoximes. For example, phenylglyoxime (II) has been the subject of numerous investigations in the past, but characterization and structure studies have been attempted on only two of the four possible isomers.[1] Since most of the structural work on the isomers of phenylglyoxime occurred before the advent of modern, sophisticated spectral and analytical techniques, there is much confusion in the literature and a reexamination of the problem appeared justified.



Tlc analysis of crude phenylglyoxime obtained by reaction of ω-isonitrosoacetophenone (I) with hydroxylamine hydrochloride in alkaline medium clearly showed the presence of three isomers. These were separated by fractional recrystallization and each isomer was subjected to ir, nmr, uv, and mass spectral analyses. Significant differences were observed in the various spectra and these were useful for characterization.

Structures were assigned to the isomers through arguments based on relative rates and the nature of complexing of the isomers with nickelous acetate and also on the relative stabilities of the isomers. Corroborative evidence for the assignments was then found in the various spectra. The isomers were shown to be *anti*-phenyl-*amphi*-glyoxime (IIa), phenyl-*anti*-glyoxime (IIb), and phenyl-*syn*-glyoxime (IIc).

Results and Discussion

The reaction between ω-isonitrosoacetophenone (I) and hydroxylamine hydrochloride in aqueous ethanol containing sodium acetate proceeded in greater than 90% yield to give phenylglyoxime (II). The broad melting point range, satisfactory microanalysis, and tlc of the product indicated a three-isomer mixture.

Several reports describe the isolation of two of the isomers present in similar syntheses[1] (see Table I), *anti*-phenyl-*amphi*-glyoxime (IIa) and phenyl-*anti*-glyoxime (IIb). These reports generally indicated that isomer IIa melted at 168° and IIb at 180°, although conflicting melting points have been reported (Table I). In the present work, sharp melting points matching those reported for the pure isomers were obtained on mixtures.

Fractional recrystallization proved to be an expedient means of separation (see Experimental Section). *anti*-Phenyl-*amphi*-glyoxime (IIa), mp 178–180°, was fastest moving on tlc, appearing at 0.45 R_f. Phenyl-*anti*-glyoxime (IIb) melted at 166–168° and appeared at 0.40 R_f on tlc. There is a modification of this material which melts at 177–180° as shown below. Phenyl-*syn*-glyoxime (IIc) was slowest moving on tlc, 0.35 R_f, and melted at 168–170°.

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(1) For reviews on phenylglyoxime, see "Beilsteins Handbuch der Organischen Chemie," 4th ed, Vol. VII, B. Prager, P. Jacobson, P. Schmidt, and D. Stern, Ed., Springer Verlag, Berlin, 1925, pp 672–673; 2nd suppl, F. Richter, Ed., 1948, pp 601–602.

TABLE I
REPORTED MELTING POINTS OF PHENYLGLYOXIME ISOMERS

Mp, °C	Isomer designation	Recrystn solvent	Mp, °C	Isomer designation	Recrystn solvent
168	anti-amphi	Ether[a]	180	anti	anti-amphi + HCl[a]
168	"α"	Acetone[b]	180	"β"	Chloroform, toluene[b]
168	"α"	Chloroform[c]	180	"β"	Chloroform[c]
176	"α"	Acetone[c]			
169	"α-syn"[d]		177	"β-anti"	"α" + HCl[d]
176	amphi	Alcohol-water[e]	180	anti	Alcohol-water[e]

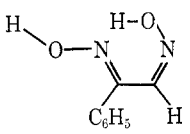
[a] A. Russanow, *Chem. Ber.*, **24**, 3497 (1891). [b] G. Ponzio and L. Avogadro, *Gazz. Chim. Ital.*, **53**, 25 (1923). [c] J. Meisenheimer and W. Theilacker, *Ann. Chem.*, **469**, 128 (1929). [d] L. Kahovec and K. W. F. Kohlrausch, *Monatsh. Chem.*, **83**, 615 (1952). [e] K. L. Hill, U. S. Patent 3,410,676 (1968).

The pure isomers are stable and can be stored at room temperature for months with no isomerization. However, IIa and IIc can be transformed into a mixture of isomers by heating them in a solvent or upon prolonged sublimination. The significant differences in the various spectra (Experimental Section)[2] combined with the differing R_f values on tlc serve to unambiguously characterize the isomers.

The phenyl-*anti*-glyoxime structure was assigned to isomer IIb (0.40 R_f) on the basis of the following experiments involving complexing with nickelous acetate. Isomer IIa (0.45 R_f) formed a green complex (1 phenylglyoxime:1 Ni^{2+}) upon admixture with nickelous acetate, whereas isomer IIb formed a red complex (2 phenylglyoxime:1 Ni^{2+}) which is indicative of an *anti*-glyoxime.[3,4] Both reactions appeared immediate to the eye. Isomer IIc (0.35 R_f) formed a dirty white precipitate only after long standing. Competition experiments were performed to determine the relative order of rate of complexing among the isomers. Two component mixtures (1:1) of IIa and IIb, IIb and IIc, and IIa and IIc were treated with 0.5 molar equiv of nickelous acetate. The nickel complexes were removed by filtration and the mother liquors were subjected to tlc analyses. In each experiment only one isomer was detected in the mother liquor, thus showing selective removal of the more rapidly reacting isomer. The relative order of rate of complexing was determined to be IIb > IIa > IIc. Isomer IIb was assigned the *anti*-glyoxime configuration because it gave the red precipitate characteristic of *anti*-glyoximes and because it was the most rapid to complex with the nickel salt.

Isomerization studies in water at 100° allowed the assignment of structures to the other two isomers. Phenyl-*anti*-glyoxime (IIb) did not undergo isomerization nor was it the product of isomerization of the other two isomers during 2 hr. Phenyl-*syn*-glyoxime (IIc) was more rapidly isomerized into *anti*-phenyl-*amphi*-glyoxime (IIa) than conversely.

Aldoximes are more rapidly equilibrated than aromatic ketoximes.[5] Isomer IIa or IIc cannot be *syn*-phenyl-*amphi*-glyoxime (IId), the fourth possible isomer of phenylglyoxime. The aldoxime in IId would be first equilibrated leading to phenyl-*anti*-glyoxime (IIb). Isomer IIb was not observed in the equilibration of IIa and IIc. Thus only two structures are possible for isomers IIa and IIc, *anti*-phenyl-*amphi*-glyoxime and phenyl-*syn*-glyoxime.



syn–amphi-IId

Phenyl-*syn*-glyoxime (IIc) is the most sterically strained of the isomers and can achieve planarity of its glyoxime group only under unfavorable interaction between the electronegative oxygen atoms. Its aldoxime should be rapidly equilibrated to form *anti*-phenyl-*amphi*-glyoxime (IIa). For the same reason, *anti*-phenyl-*amphi*-glyoxime (IIa) has little incentive to equilibrate to phenyl-*syn*-glyoxime (IIc). Thus the more rapidly equilibrating isomer, IIc, must be phenyl-*syn*-glyoxime and isomer IIa must be *anti*-phenyl-*amphi*-glyoxime.

Once the structures had been established, corroborative evidence can be found in the various spectra of the isomers (Experimental Section).[3] The mass spectrum of phenyl-*anti*-glyoxime (IIb) shows practically exclusive loss of hydroxyl ($M^+ - 17$); thus cis elimination of water in the aldoxime function did not occur. The mass spectrum of *anti*-phenyl-*amphi*-glyoxime (IIa) shows loss of hydroxyl as in IIb but also significant loss of water ($M^+ - 18$) by interaction of the two hydroxyl groups which can be reasonably near to each other in the cisoid conformation. Mainly water is lost in the mass spectrum of phenyl-*syn*-glyoxime (IIc) either through collision of the hydroxyl groups or through trans elimination on the aldoxime. The remaining ions in the mass spectra of the phenylglyoxime isomers appear to result from complex fragmentation. One possible route is given below (Scheme I), but other routes can be written.

The uv spectra of the isomers show a difference in absorption maxima between phenyl-*syn*-glyoxime (IIc, 252 nm) and the other two isomers (230 and 228 nm).

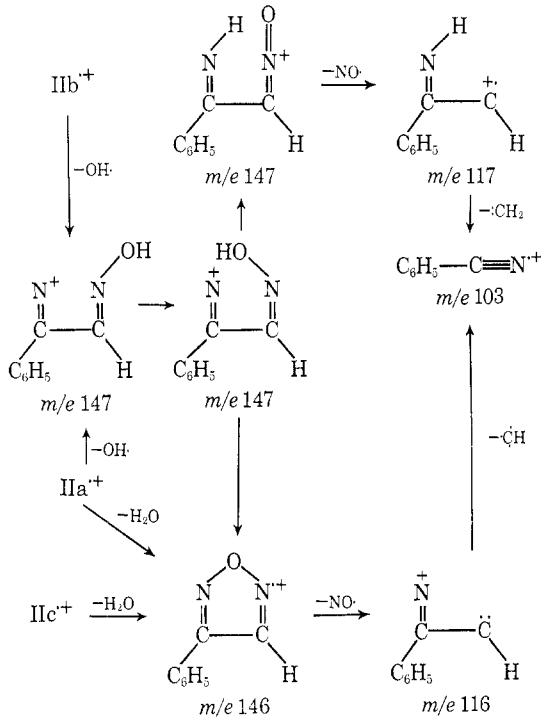
(2) Ir, nmr, and mass spectra of the isomers will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, American Chemical Society Publications, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

(3) L. L. Merritt, Jr., *Anal. Chem.*, **25**, 718 (1953).

(4) L. E. Godycki and R. E. Rundle, *Acta Crystallogr.*, **6**, 487 (1953); R. C. Voter, C. V. Banks, V. A. Fassel, and P. W. Kehres, *Anal. Chem.*, **23**, 1730 (1951).

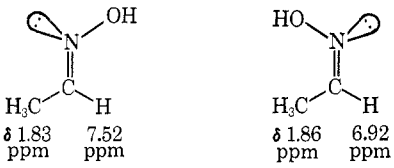
(5) P. A. S. Smith in "Molecular Rearrangements, Part One," P. de Mayo, Ed., Interscience, New York, N. Y., 1963. pp 483–488. Compare the relative stabilities of aldoxime isomers *vs.* aromatic ketoxime isomers in the following publications: I. Pejković-Tadić, M. Hranisavljević-Jakovljević, and S. Nešić, *J. Chromatogr.*, **21**, 239 (1966); R. F. Rekker and J. U. Veenland, *Recl. Trav. Chim. Pays-Bas*, **78**, 739 (1959).

SCHEME I



Planarity of the glyoxime group in IIc is disallowed because this requires an unfavorable interaction between the two electronegative oxygen atoms. Thus, it is not surprising that the uv spectrum of isomer IIc reflects only the uv absorption of an *anti*-phenylketoxime chromophore or of α-benzaldoxime (phenyl and hydroxyl groups are anti) each of which absorbs at 251 nm as shown by Rekker and Veenland.[5] The shorter wavelength absorption of IIa and IIb suggests a lack of coplanarity between the phenyl group and the glyoxime; aliphatic glyoximes absorb at 230 nm (ϵ 1800).[6] If the whole molecule were planar, *anti*-phenyl-*amphi*-glyoxime (IIa) would be expected to show a uv maximum either more intense or shifted to a longer wavelength than that of the *anti*-phenylketoxime chromophore (251 nm, ϵ 14,500). Similar arguments apply to phenyl-*anti*-glyoxime (IIb) using β-benzaldoxime as a model (246 nm, ϵ 14,500).[5] The lack of coplanarity may arise from an interaction between the nitrogen electron pair of the aldoxime and the phenyl group, if the molecules adopt a transoid conformation to maximize the distance between the oxime nitrogens.[6,7]

Supporting evidence for the structural assignments can also be found in the nmr spectra of the isomers. Karabatsos and Taller have shown that the group anti to the hydroxyl of an oxime is shielded with respect to the group syn.[8] Presumably the electron pair of the nitrogen is responsible for the phenomenon as shown in the case of acetaldoxime (III).



IIIa IIIb

(6) H. E. Ungnade, G. Fritz, and L. W. Kissinger, *Tetrahedron Suppl.*, **19**, 235 (1963).

Examination of the phenylglyoxime isomers reveals that only isomer IIc, phenyl-*syn*-glyoxime, has the aldehydic proton anti to the hydroxyl and thus continually under the influence of an electron pair on nitrogen. It should be the most shielded of those in the three isomers and does appear farthest upfield (7.4 ppm). The aldehydic proton of *anti*-phenyl-*amphi*-glyoxime (IIa) does not come under the influence of any nitrogen electron pair and consequently appears farthest downfield (8.4 ppm). The aldehydic proton of phenyl-*anti*-glyoxime (IIb) should resonate between those of the other isomers since it is under the influence of the more distant electron pair on the nitrogen of the α-oxime. This is the case (7.8 ppm).

The absence of the fourth possible isomer, *syn*-phenyl-*amphi*-glyoxime (IId), might be explained by considering the unfavorable steric interaction between the phenyl group and the two hydroxyls when the molecule assumes the preferred transoid conformation. It should be present in the equilibration of phenyl-*anti*-glyoxime (IIb). Although it is possible that it has the same R_f value as IIb and that it could be present in the equilibration study, it should be noted that all indications are that phenyl-*anti*-glyoxime (IIb) as described above is one isomer. The nmr of that isomer clearly shows both hydroxyl protons, the aldehydic proton, and the aromatic protons. Correct integrals were obtained for these signals. Extra peaks and incorrect integrals would be observed if a mixture were present.

The argument can be made that formation of the red nickel salt by the isomer appearing at 0.40 R_f is not conclusive proof of an *anti*-glyoxime structure in studies of monosubstituted glyoximes. It can be argued that *syn*-phenyl-*amphi*-glyoxime (IId) could also give the same red complex by rapid isomerization of its aldoxime group. The possibility that the isomer at 0.40 R_f is not phenyl-*anti*-glyoxime appears remote in light of the nmr spectrum of isomer IIb. Isomer IId would be expected to have the aldehydic proton resonate at at least as high field as the aldehydic proton on phenyl-*syn*-glyoxime (IIc) since it would be under the influence of the electron pairs of both oxime nitrogens. In fact, this proton would be expected to appear farthest upfield of those in all the possible isomers. Further the mass spectrum of isomer IIb does not show the significant loss of water ($M^+ - 18$) as observed for an *amphi*-glyoxime in the mass spectrum of *anti*-phenyl-*amphi*-glyoxime (IIa).

When the aqueous solution of phenyl-*anti*-glyoxime (IIb) from the stability study was allowed to evaporate freely in an open container, crystals were obtained which melted at 177–180°. Again the mass spectrum did not show the significant loss of water ($M^+ - 18$) expected for an *amphi*-glyoxime but there is the possibility that sublimation in the mass spectrometer inlet may transform a mixture of the two isomers into one. Attempts to prepare a large sample of this material by exactly similar treatment of isomer IIb (mp 166°) failed to give the higher melting substance. No change was observed in the nmr spectrum of the residue in this experiment. Correct integrals were obtained for all sig-

(7) We thank a referee for this interpretation of the uv data.

(8) G. J. Karabatsos and R. A. Taller, *Tetrahedron*, **24**, 3347 (1968). For additional information on the nmr spectra of oximes, see G. C. Kleinspehn, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.*, **32**, 460 (1967), and additional references contained therein.

nals, thus indicating the presence of only one isomer. The difference in melting points might reflect polymorphism rather than the presence of the fourth possible isomer.

Experimental Section[9]

Phenylglyoxime (II).—Phenylglyoxime can be readily synthesized by several methods reported in the literature[1] (Table I). The highest yields were obtained by reacting ω-isonitrosoacetophenone and hydroxylamine hydrochloride in aqueous ethanol containing sodium acetate (Table I). In a typical experiment, a solution of 48 g of sodium acetate and 24 g of hydroxylamine hydrochloride in 75 ml of water was added to a solution of 50 g of ω-isonitrosoacetophenone (Aldrich Chemical Co., Inc.) in 150 ml of ethanol. The mixture was refluxed for 4 hr and was then allowed to cool. Most of the solvent was then removed under reduced pressure and the precipitate which formed was collected by filtration and was washed with water. The product was air-dried on the funnel. The phenylglyoxime was obtained in 92% yield (51 g) and melted at 150–158°. Tlc using silica gel G as adsorbent,[10] benzene–ethyl acetate (7:3) as solvent, and iodine vapor for detection showed the presence of three components at 0.45, 0.40, and 0.35 R_f.

The microanalyses of the three-component mixture and of various mixtures of the components were in agreement with those expected for phenylglyoxime. The material can be readily sublimed [50° (1.4 mm)] but with no observable change in component ratio.

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.44; H, 4.91; N, 17.01.

***anti*-Phenyl-*amphi*-glyoxime (IIa).**[11]—One gram of crude three-component phenylglyoxime was recrystallized from acetone–chloroform five times to give 150 mg of pure *anti*-phenyl-*amphi*-glyoxime (IIa): mp 178–180°; uv max (95% C_2H_5OH) 230 nm (ε 14,800); nmr (DMSO) δ 7.4 (m, 5, phenyl), 8.4 [s, 1, –C(=N)**H**], and 11.7 ppm (s, 2, hydroxyls); mass spectrum (70 eV) *m/e* (rel intensity), 164 (95), 147 (38), 146 (24), 117 (100). The material was homogeneous on tlc[10] appearing at 0.45 R_f. An alcohol–water solvent system may be substituted for acetone–chloroform in this isolation.

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.33; H, 4.68; N, 17.21.

Phenyl-*anti*-glyoxime (IIb).[11]—The solvent was removed from the mother liquor of the first recrystallization performed during the above separation. The residue was recrystallized by adding chloroform to an acetone solution of the substance at room temperature. This process was repeated until the precipitate appeared homogeneous on tlc[10] at 0.40 R_f. The sample at this point melted at 170–172° but failed to give a satisfactory microanalysis. The solid was then sublimed [90° (0.2 mm)] to give analytically pure phenyl-*anti*-glyoxime: mp 166–168°; 0.40 R_f on tlc;[10] uv max (95% C_2H_5OH) 228 nm (ε 14,380); nmr (DMSO) δ 7.4 (s, 5, phenyl), 7.8 [s, 1, –C(=N—)**H**], 11.4 (s, 1, –**OH**), and 11.6 ppm (s, 1, **OH**); mass spectrum (70 ev) *m/e* (rel intensity) 164 (43), 147 (25), 117 (100), 103 (45). This isolation procedure yielded only about 1% of the pure isomer based on the starting three-component phenylglyoxime. Here also an alcohol–water solvent system may be substituted for acetone–chloroform in the separation.

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.81; H, 4.74; N, 17.29.

Phenyl-*syn*-glyoxime (IIc).[11]—The crude three-component phenylglyoxime (2 g) was recrystallized from a dilute solution of ethyl acetate. The precipitate (180 mg, mp 170–171°) was pure by tlc analysis[10] appearing at 0.35 R_f. Further recrystallization changed the melting point to 168–170° without a change in R_f: uv max (95% C_2H_5OH) 252 nm (ε, 12,200); nmr (DMSO) δ 7.4 [m, 6, phenyl, –C(=N—)**H**], and 11.4 ppm (s, 2, hydroxyls); mass spectrum (70 eV) *m/e* (rel intensity) 164 (100), 146 (45), 116 (89), 103 (36).

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.45; H, 4.85; N, 16.82.

In hindsight, it would seem that the yields in these separations could be increased through initial enrichment of the isomers by selective formation of nickel complexes. Either isomer IIb or both IIa and IIb can be selectively removed from a solution of the three-component phenylglyoxime by adding portions of nickelous acetate with monitoring by tlc.

Preparation of Nickel Complexes.—The competition experiments were performed by treating 0.06 mol of a mixture (1:1) of two isomers with 0.03 mol of nickelous acetate in alcohol–water. The mother liquors were then examined on chromatoplates.

anti-Phenyl-*amphi*-glyoxime (IIa) gave a green nickel complex, whereas phenyl-*anti*-glyoxime (IIb) gave a red one.

Anal. Calcd for $C_8H_6N_2NiO_2$ (green complex): C, 43.51; H, 2.74; N, 12.68. Found: C, 43.33; H, 3.15; N, 12.93.

Anal. Calcd for $C_{16}H_{14}N_4NiO_4$ (red complex): C, 49.92; H, 3.67; N, 14.55. Found: C, 49.68; H, 3.62; N, 14.49.

Thermal Isomerization Study.—The experiments were performed by dissolving the pure phenylglyoxime isomers in water surrounded by an oil bath kept at 100°. The transformations were monitored by tlc and the concentrations were visually estimated. There was no evidence by tlc for the isomerization of phenyl-*anti*-glyoxime (IIb) even after 5 hr of heating. After 20 min, isomer IIc was approximately 20% converted into IIa; after 60 min, it was 50% converted. After 20 min, isomer IIa was only 5% converted into IIc, and, after 60 min, it was approximately 25% converted into IIc. Isomer IIb was not observed in the transformations of IIa and IIc during 2 hr.

Registry No.—IIa, 26527-40-2; IIb, 17016-15-8; IIc, 26527-42-4.

(9) All melting points were determined with a Mettler FP1 melting point apparatus equipped with a Bausch and Lomb VOM 5 recorder. Infrared spectra were recorded on a Perkin-Elmer 421 grating spectrophotometer. A Varian A-60 spectrometer was used to obtain the nmr spectra and tetramethylsilane was used as the internal standard. The mass spectra were determined on a Consolidated Electrodynamics Corporation Model 21-103C spectrometer. The uv spectra were recorded on a Cary M14 spectrophotometer.

(10) Several samples of commercially available precoated chromatoplates proved unsatisfactory for this separation. Chromatoplates freshly prepared from Merck (Darmstadt) silica gel G were used exclusively. All R_f values quoted in this article were determined with this adsorbent and benzene–ethyl acetate (7:3) as solvent.

(11) A note of caution must be interjected regarding the isolation of the isomers. Often the results depended on several factors including relative concentrations of the isomers in the mixture, concentration of phenylglyoxime in the recrystallization solvent, duration of heating, etc. Thus it has occurred that recrystallization of the crude three-component mixture from ethyl acetate has led to an enrichment of IIa rather than IIc. Continuous monitoring by tlc[10] must be employed throughout the separations.