The Phenylation of Oxime Anions with Diphenyliodonium Bromide

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The anions of benzophenone oxime (**1**), 4,4-dimethylbenzophenone oxime (**4**), fluorenone oxime (**7**), and *syn*-4-methylbenzophenone oxime (**10**) were phenylated with diphenyl iodonium bromide (DIB). Ambident arylation yielded nitrones and the corresponding *O*-phenyl oximes. The phenylation of the *syn*-4-methylbenzophenone oxime anion yielded the isomerically pure nitrone **12a** and an *O*-phenyl derivative believed to be *syn*-*O*-phenyl 4-methylbenzophenone oxime (**11**). In one arylation this *O*-phenyl oxime was accompanied by an isomeric mixture of *N*,α-diphenyl-α-*p*-tolylnitrones (**12a** and **12b**). Evidence is presented which suggests that equilibration of initial nitrone **12a** of retained geometrical configuration may be effected by unreacted oxime anion. Lower limits of the thermal configurational stabilities of **11** and the two phenylated products of **4** were determined from their nmr spectra at elevated temperature.

Studies of the thermal rearrangement of α,α-diaryl-*N*-benzhydrylnitrones to *O*-benzhydryl diarylketoximes have been reported.[3] While conducting an investigation into the geometric course of this type of rearrangement, it became desirable to prepare model nitrones which might be useful in making geometric assignments to requisite unsymmetrical nitrones. It was also hoped that these model nitrones obtained from the arylation of oxime anions could be used to evaluate the configurational stability of nitrones (at temperatures between 130 and 160°) which are unlikely to isomerize by a dissociation (to an iminoxy and counter-radical pair)–recombination mechanism. The first objective was realized, but the second (because of the thermal instability of the *N*-phenylnitrones) was not.

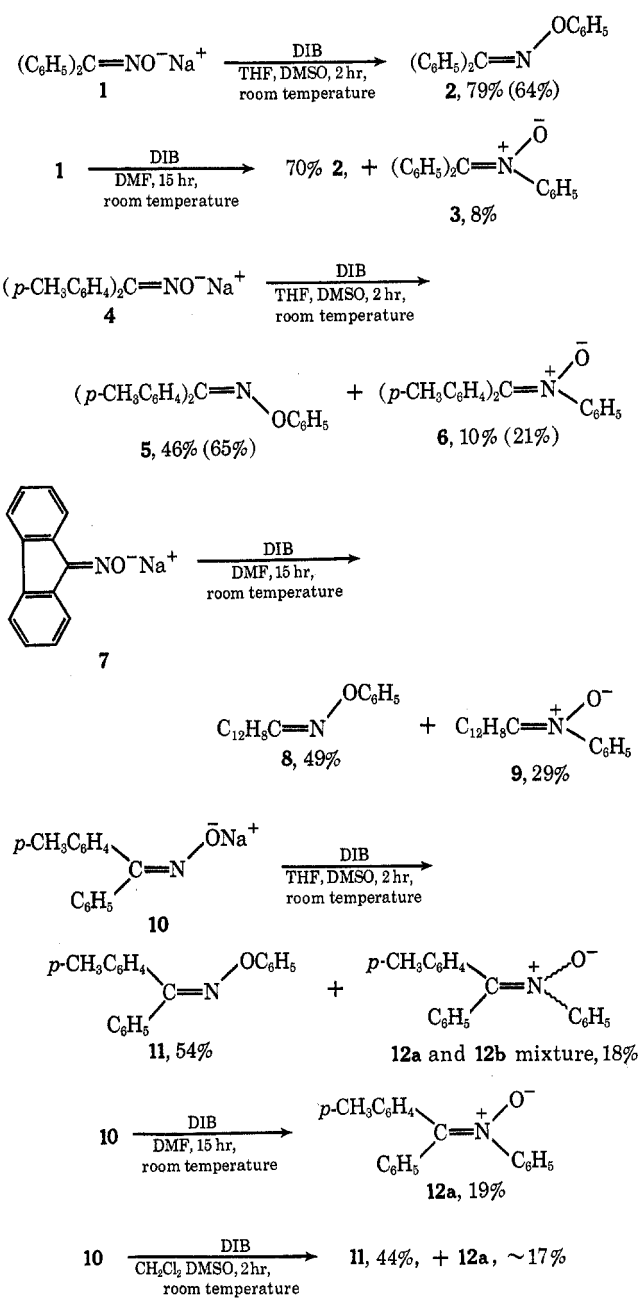
The preparation of *O*-aryl oximes by nucleophilic substitution on haloaromatics bearing strong electron-attracting groups have been reported by several groups.[4] Several examples of the synthesis of *O*-phenyl oximes using *O*-phenylhydroxylamine and carbonyl derivatives have also been described.[5] At the outset of this study no direct phenylation of oxime anions had been reported.[6] However, in view of the success in arylating benzoate, methoxide, and phenoxide anions with diphenyliodonium salts,[7] the potential for arylating oxime anions with such reagents appeared promising. The results discussed below demonstrate that phenylation of oxime anions with diphenyliodonium salts provides a good general route to *N*-phenylnitrones and *O*-phenyl oximes.

Results

Syntheses.—The anions of benzophenone oxime (**1**), 4,4-dimethylbenzophenone oxime (**4**), fluorenone oxime (**7**), and *syn*-4-methylbenzophenone oxime (**10**) were phenylated with diphenyliodonium bromide. The conditions employed and the products obtained are summarized in Scheme I. No extensive survey of reaction conditions designed to maximize yields was made.

Structural Characterization of Products.—The products were characterized by their elemental analyses,

SCHEME I



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(2) NSF College Teacher Research Participant, summer 1968.

(3) (a) J. S. Vincent and E. J. Grubbs, *J. Amer. Chem. Soc.*, **91**, 2022 (1969); (b) E. J. Grubbs, J. A. Villarreal, J. D. McCullough, Jr., and J. S. Vincent, *ibid.*, **89**, 2234 (1967); (c) E. J. Grubbs, J. D. McCullough, Jr., B. H. Weber, and J. R. Maley, *J. Org. Chem.*, **31**, 1098 (1966).

(4) See for example (a) E. A. Titov, *Zh. Org. Khim.*, **4**, 882 (1968); (b) A. Mooradian and P. E. Dupont, *J. Heterocycl. Chem.*, **4**, 441 (1967); (c) A. Mooradian and P. E. Dupont, *Tetrahedron Lett.*, 2867 (1967).

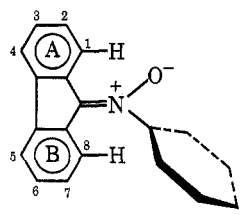
(5) (a) J. H. Cooley, B. N. Misra, J. R. Throckmorton, and W. D. Bills, *J. Med. Chem.*, **11**, 196 (1968); (b) J. S. Nicholson and D. A. Peak, *Chem. Ind. (London)*, 1244 (1962).

(6) During the preparation of this manuscript it came to our attention that an investigation similar to the present one has been conducted by Dr. D. D. Doptoglon under the direction of Professor F. M. Beringer [*Diss. Abstr. B*, **30**, 2082 (1969); *Chem. Abstr.*, **73**, 34978x (1970)].

(7) F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Amer. Chem. Soc.*, **75**, 2708 (1953).

mass spectra, nmr, and, in some cases, ultraviolet spectra. The ultraviolet spectra are particularly useful in distinguishing between the nitrones and *O*-phenyl oximes. With the exception of **9** the nitrones exhibit long wavelength maxima in the region 310–316 mμ.[8] The corresponding *O*-phenyl derivatives **2**, **5**, and **11** show maxima below 300 mμ. The nitrone **9** derived from fluorenone exhibits its longest wavelength absorption at 351 mμ while that of the *O*-phenyl derivative appears at 324 mμ. The mass spectra of the nitrones examined in the present study show the characteristic loss of oxygen from the parent ions. This behavior has been previously observed with a variety of nitrones.[9] By contrast, the spectra of the *O*-phenyl derivatives are characterized by a dominating loss of the phenoxyl group among the various fragmentations.

The nmr spectrum of **9** is particularly interesting. Of the 13 aromatic protons, one appears as a low-field



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multiplet centered at about 8.9 ppm and one absorbs at unusually high field, appearing as a multiplet centered at approximately 5.9 ppm. The "low-field proton" has been identified as H-1 in accord with the interpretation of the nmr spectra of α,*N*-diphenylnitrones.[10,11] The "high-field proton" absorption can reasonably be assigned to H-8. Interactions between the phenyl group and ring B will force the former into a conformation nearly perpendicular to the rest of the molecule. This places H-8 in the face of this benzene ring accounting for the observed shielding.

Stereochemistry of the Arylation Reaction.—As shown in Scheme I, the phenylation of sodium *syn*-*p*-methylbenzophenone oximate (**10**) under several different conditions led to O- and N-arylation in a ratio of about 3 to 1.[12] Stereospecific arylations were observed in all cases except in the formation of the nitrone in tetrahydrofuran. The stereochemistry of the products was assigned on the following basis. The stereochemistry of the starting oxime has been established by ultraviolet spectral analyses and Beckmann rearrangement.[13] The geometrical assignments of the two 4-methylbenzophenone oximes are also consistent with those arrived at by a comparison of the C–H bending vibrations for para-disubstituted benzenes (in the 830-cm^{-1} region).[14] In both phenylations of **10** from which the *O*-phenyl derivative was isolated (and in reasonably high yield), this compound proved to be isomerically pure. This was suggested by its narrow melting point range but unequivocally demonstrated by the appearance of only one sharp methyl-proton singlet in the nmr.[15] In the two reactions where a geometrically pure nitrone was isolated (in one case accompanying **11**), the nitrone proved to have the same configuration as the starting oxime (see below). Consequently, it is virtually certain that **11** also possesses the "retained" configuration as shown. The configuration of the geometrically pure nitrone **12a** can be assigned on the following basis. Koyano and Suzuki[10] have shown that the ortho protons on the α-phenyl group cis to the oxygen in a series of α,*N*-diarylnitrones absorb at lower field than the remaining aromatic protons. When the α-phenyl group is unsubstituted, this low field absorption is a complex multiplet. However, in every case in which this ring was substituted in the para position (eight examples were provided), these ortho protons gave rise to a doublet.[17] This must be half of an AA′BB′ spectrum with coupling to meta protons which are obscured in the remaining complex aromatic proton absorption at higher field. Consequently, the geometrically pure nitrone **12a** obtained from **10**, which exhibits the two-proton, low-field doublet, possesses the configuration shown.[18]

Variable Temperature Nmr Examination of 5, 6, and 11.—The thermal stabilities of the N- and O-phenylated oximes are much lower than their *N*- and *O*-alkyl analogs. They darken rapidly and decompose to a mixture of unidentified products when heated above their melting points. In solution decomposition occurs rapidly above 100°. Nonetheless, it appeared useful to evaluate at least qualitatively the lower limits of configurational stability of these compounds by nmr.

The proton spectra of *N*-phenyl-α,α-di-*p*-tolylnitrone (**6**) in chlorobenzene were determined at 20° intervals between room temperature and 140°. No coalescing (or peak broadening) was observed in the two methyl singlets.

Similar scans of the pmr spectra of *O*-phenyl-4,4′-dimethylbenzophenone oxime (**5**) in dimethyl malonate were conducted over a range of temperatures up to 145°. Again no coalescing (or peak broadening) of the two methyl singlets was detected. The nmr spectra of *syn*-*O*-phenyl-4-methylbenzophenone oxime (**11**) in dimethyl malonate were examined in the same

(8) See T. Kubota, M. Yamakawa, and Y. Mori, *Bull. Chem. Soc. Jap.*, **36**, 1552 (1963), for a tabulation and discussion of the ultraviolet spectra of nitrones.

(9) See M. Masui and C. Yijima, *Chem. Pharm. Bull.*, **17**, 1517 (1969), and references therein.

(10) K. Koyano and H. Suzuki, *Bull. Soc. Chem. Jap.*, **42**, 3306 (1969).

(11) All of the nitrones we have examined including the *N*-phenylnitrones reported in this study show two protons (or in the case of **9**, one proton) at low field which are undoubtedly the ortho protons of the α-phenyl cis to the nitrone oxygen.

(12) For the arylation conducted in DMF, the oxime anion was generated from the oxime by use of sodium hydride in mineral oil. Difficulty was encountered during chromatographic attempts to separate **11**, iodobenzene, and residual mineral oil.

(13) R. F. Rekker and J. U. Veenland, *Recl. Trav. Chim. Pays-Bas*, **78**, 739 (1959).

(14) Unpublished observations by E. J. Grubbs and T. S. Dobashi. See D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Amer. Chem. Soc.*, **88**, 2775 (1966), for other geometric correlations using this method.

(15) Note that in the nmr spectra of each of the two phenylated products derived from 4,4-dimethylbenzophenone oxime, two well-resolved methyl singlets are observed. Although the geometric isomer of **11** has not yet been isolated in pure form, the two *O*-benzhydryl isomers have.[16] And, as anticipated, the chemical shift difference between the methyl singlets in these two isomers is almost identical with the difference in chemical shift between the two singlets in *O*-benzhydryl 4,4-dimethylbenzophenone oxime.[16]

(16) Unpublished data of E. J. Grubbs and T. S.Dobashi.

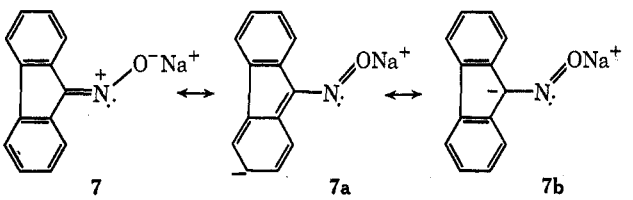
(17) We have observed similar characteristics in the nmr spectra of *N*-benzhydryl-α,α-diphenylnitrone,[3c] *N*-*p*-methylbenzhydryl-α,α-diphenylnitrone,[3c] α,α-di-*p*-tolyl-*N*-benzhydrylnitrone,[3c] α,α-di-*p*-chlorophenyl-*N*-benzhydrylnitrone, and α,α-diphenyl-*N*-methylnitrone. Specifically for those nitrones in which the α-phenyl rings are unsubstituted, a low-field complex multiplet is observed which corresponds to two protons. In the two nitrones para substituted in the α-phenyl rings, this low-field absorption is a doublet.

(18) Mixtures of the two nitrone isomers **12a** and **12b** show the same doublet superimposed upon a complex multiplet.

way up to 115°. No evidence for broadening of the methyl singlet nor for the appearance of a second methyl singlet (which would be characteristic for the anti isomer) was found.

Discussion

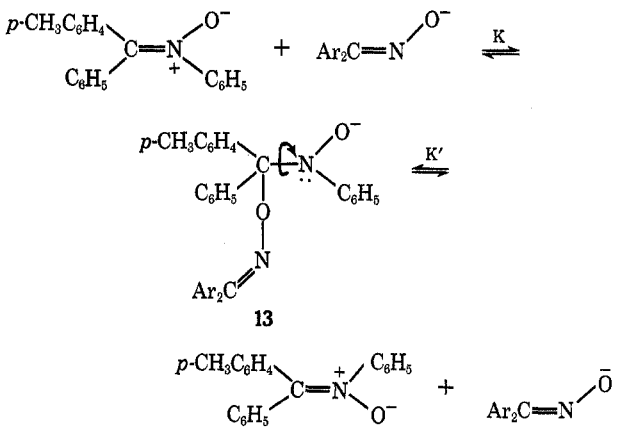
The arylation procedure described has been shown to be an effective route to *N*-arylnitrones and *O*-aryl oximes. The O–N phenylation ratios as determined from yields of isolated products range from about 9:1 for the benzophenone oxime anion to 1.7:1 for the fluorenone oxime anion. It is somewhat surprising that the O–N phenylation ratio is smaller for fluorenone oxime anion than for the benzophenone oxime anion. The aromatic ring (ring B) anti to the oxygen in fluorenone oximate cannot rotate to a conformation perpendicular to the C=N—O plane as is possible with benzophenone oximate. Consequently, one might have anticipated that increased nonbonded interactions between this ring (or specifically H-8) and the phenylating agent in the transition state would lead to a higher O–N phenylation ratio.[19] However, the same conformational restriction in the fluorenone oximate along with ring fusions could lead to a diminution in nucleophilicity at oxygen by greater electron delocalization as suggested by structures **7a**, **7b**, etc. Certainly one might expect the cyclopentadienide-type structures to be



7 **7a** **7b**

significant contributors to the anionic hybrid. The degree and nature of aggregation of **1** and **7** in the reaction solvent system may also play an important role in determining the O–N phenylation ratios for **1** and **7**.[22] This, however, has not yet been demonstrated.

The phenylations proceed with retention of configuration of the parent oxime. In the one reaction which led to a mixture of geometrically isomeric nitrones, equilibration of initially formed geometrically pure nitrone appears likely. Certainly, prior geometric equilibration of the oxime anion did not occur since the accompanying *O*-phenyl derivative isolated in high yield was isomerically pure. The nitrone **12a** is configurationally stable under the work-up conditions including chromatography. However, in the work-up procedure for the phenylation leading to a mixture of **12a** and **12b**, chromatography exhausted the particular lot sample of silica gel. A control experiment with silica gel from a different bottle indicated no geometric isomerization of **12a** on the column. This does not exclude the possibility that the geometric equilibration of **12a** was caused by some contaminant in the original silica gel. Nonetheless, it seemed a reasonable possibility that the isomerization of geometrically pure nitrone might be explained by equilibria involving the nitrones, oximate, and the adduct **13**. Nitrones are



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known to undergo attack at the α carbon by nucleophiles such as cyanide ion, Grignard reagents, and other carbanions.[23] With this in mind, a sample of pure nitrone **12a** in methylene chloride was treated with approximately 0.5 equiv of sodium benzophenone oximate.[24] Even without the benefit of complete solution, the anion effected equilibration of the nitrone. After being allowed to stand at room temperature for 26 hr, a mixture of 88% **12a** and 12% **12b** was isolated. Only 58% of the nitrone was recovered by efficient chromatographic techniques. This may suggest that the equilibrium constants K and K' may not be insignificant and/or that nitrone may be lost through the formation and possible further reactions of intermediates such as **13**.

An attempt was made to approximate the conditions for the phenylation of **10** [which led to a mixture of **12a** and **12b** (see Scheme I)] as this reaction neared completion. The object was to determine whether under these conditions an excess of oxime anion could geometrically equilibrate either **11** or **12a**. Sodium benzophenone oximate (**1**) was again substituted for **10** to facilitate nmr analyses. An excess of **1** along with appropriate quantities of sodium bromide, iodobenzene, **11**, and **12a** were stirred for 2 hr at room temperature in THF containing DMSO. A work-up and separation procedure not involving water led to the reisolation of approximately 95% of unchanged **11**. However, the nitrone was partially equilibrated (85% **12a** and 15% **12b**) and only 64% was recovered. Clearly, additional experiments would be necessary to unequivocally identify the agent responsible for the nitrone equilibration in the original phenylation of **10** in THF–DMSO. Nonetheless, these observations may well suggest precautions to those contemplating the synthesis of nitrones by geometrically selective alkylation or arylation of oxime anions. Certainly the presence

(19) Kornblum and Seltzer have demonstrated the importance of steric hindrance in ambident alkylations of potassium 2,6-di-*tert*-butyl phenoxide.[20] Smith and Robertson observed a much higher N–O alkylation ratio for sodium benzophenone oximate with methyl bromide than with benzyl bromide and suggested that steric hindrance in the case of benzyl bromide might have increased attack at the less hindered oxygen.[21] Nonetheless, the mechanism of the arylation of oxime anions by diaryliodonium salts is probably quite different than that for alkylations. It is possible that an intramolecular arylation proceeding from an oxime anion–diphenyliodonium ion complex may be less sensitive to steric factors.

(20) N. Kornblum and R. Seltzer, *J. Amer. Chem. Soc.*, **83**, 3668 (1961).

(21) P. A. S. Smith and J. E. Robertson, *ibid.*, **84**, 1197 (1962).

(22) See S. G. Smith and D. V. Milligan [*ibid.*, **90**, 2393 (1968)] for a demonstration of the effect of ion pairing of **7** on the site of alkylation by methyl iodide.

(23) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964).

(24) The anion derived from benzophenone oxime rather than from one of the 4-methylbnzophenone oximes was used so that equilibration could be more easily followed by nmr without complication from the methyl singlets of the oximes.

of excess base even in the form of the oxime anion should be avoided.

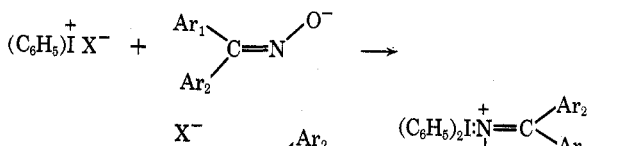
One further consequence of the observation of geometric specificity in the arylations of oxime anions deserves comment. Ptitsyna, Lyatiev, and Reutov have recently investigated the mechanism of the reaction of diphenyliodonium salts with amines.[25] Their results suggest that the first step is the formation of a complex such as **14**. With aliphatic amines they propose a dissociation of this complex to the diphenyliodine radical and a radical cation **15** which forms the salt of the amine by hydrogen atom abstraction.

$$(C_6H_5)_2\overset{+}{I}\,\bar{X} + :NR_3 \longrightarrow \underset{\mathbf{14}}{(C_6H_5)_2I{:}\overset{+}{N}R_3\ X^-}$$

$$\mathbf{14} \longrightarrow (C_6H_5)_2I\cdot + \underset{\mathbf{15}}{\cdot\overset{+}{N}R_3\ X^-}$$

$$\mathbf{15} + SH \longrightarrow H\overset{+}{N}R_3\ X^-$$

If oxime anions form similar complexes in the presence of diaryliodonium salts, the least that can be said is that dissociation to free radicals probably occurs slowly, if at all, and the principal route to product formation apparently does not follow step 2. A growing body of evidence indicates that unsymmetrical



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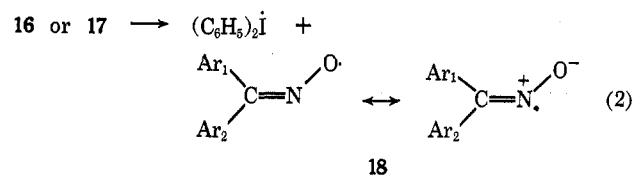

(2)

iminoxy radicals equilibrate extremely rapidly forming a mixture of two geometric isomers.[26-29] Admittedly,

the relationship between the configurational properties of iminoxy radicals and their proximity to other radicals or the degree to which they exist in solvent "cages" has not been determined. Nonetheless, since geometric specificity was observed in the arylation of **10**, free iminoxy radicals are unlikely precursors.

Because of the thermal instability of *N*-phenylnitrones and *O*-phenyl ketoximes, only limited information regarding their configurational stabilities was obtained. However, on the basis of the variable-temperature nmr study, it can be safely concluded that configurational isomerization about the carbon–nitrogen double bonds in these oxime derivatives is slow by the nmr time scale.

Experimental Section[30]

The Phenylation of Sodium Benzophenone Oximate (1). A. In Tetrahydrofuran Containing DMSO.—The sodium salt of benzophenone oxime was prepared from 5.00 g (0.0254 mol) of benzophenone oxime and 1.00 g (0.043 g-atom) of sodium in 40 ml of tetrahydrofuran. After hydrogen evolution had ceased, the excess sodium was removed. Dimethyl sulfoxide (15 ml) was added. Diphenyliodonium bromide (DIB)[7] (9.00 g, 0.0250 mol) was then added in portions over a 15-min period. An additional 15 ml of THF was added and the mixture stirred under nitrogen for 2 hr at room temperature. The mixture was poured into 200 ml of cold water and extracted with three 100-ml portions of methylene chloride. The extract was washed with water, dried, and concentrated to a yellow oil containing a white solid. Trituration of this crude product with hexane and filtration served to remove 0.95 g of unreacted DIB, mp 215–217° dec. The hexane filtrate was concentrated under reduced pressure (to remove solvent and iodobenzene) and chromatographed on 80 g of silicic acid. The product was eluted with methylene chloride affording 5.63 g of a pale yellow oil. This was dissolved in 25 ml of a 1:1 ether–hexane solution from which **2** (4.80 g, 79%) was deposited as pale cream-colored crystals, mp 53.0–54.5°. A sample was crystallized again from the same solvent mixture affording white crystals: mp 55.5–56.5°; nmr (CCl_4) 6.9–7.7 (m, aromatic protons); ir (KBr) 1210 cm^{-1} (CO); uv (C_2H_5OH) λ_{max} (ϵ) 222 (22,700), 270 (11,500), 289 mμ (11,500); mass spectrum (15 eV) *m/e* 273 (10) (parent ion), 180 (100) (P − C_6H_5O).

Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13. Found: C, 83.78; H, 5.61; N, 5.00.

A similar phenylation of benzophenone oxime in THF using sodium hydride to generate the oxime anion afforded **2**, mp 54.5–55.5°, in 64% yield.

B. In Dimethylformamide.—The oxime (45.0 g, 0.228 mol) in 250 ml of dimethylformamide was treated with 10.1 g (0.226 mol) of sodium hydride (52% in mineral oil). After evolution of hydrogen had ceased, 83.0 g (0.230 mol) of DIB was added. The reaction mixture was stirred overnight at room temperature, poured into water, and extracted with ether. Some of the crude nitrone **3** (4.08 g, mp 197–211°) crystallized from the mixed organic phase. Concentration of the resulting organic filtrate afforded an additional precipitate which when crystallized from methanol yielded 3.93 g of impure **3**, mp 208–216°. All remaining residual oils were combined and chromatographed over a mixture of 90 g of silicic acid and 10 g of Celite. Elution with hexane and crystallization from methanol yielded 42.1 g (70% based on unrecovered oxime) of **2**, mp 50–52°. Further purification of this sample by chromatography and crystallization from pentane afforded 29.5 g (49%) of **2** as white crystals, mp 53–54°. Elution with benzene afforded 1.83 g of unreacted oxime (mp 140.5–142°). Elution with 10–50% ether in methylene chloride gave 0.93 g of the impure nitrone, mp 208–216°. This was combined with the 8.01 g of impure **3** isolated earlier and recrystallized from aqueous ethanol to give 6.92 g (11%) of **3**, mp 218.5–224°. A portion of this sample (4.65) was recrystallized again from aqueous ethanol affording 3.12 g (8% corrected according to sample size used in final crystallization) of **3**: mp 222.5–224° [lit.[31] mp 223–225°; uv (C_2H_5OH) λ_{max} (log ϵ) 310 (4.0), 231 mμ (4.2)]; nmr ($CDCl_3$) 7.8–8.2 (m, 2, aromatic), 6.9–7.5 (m, 13, aromatic); uv (C_2H_5OH) λ_{max} 311 (10,900), 232 mμ (15,300); mass spectrum (80 eV) *m/e* 273 (100) (parent ion), 257 (74) (P − oxygen).

(25) (a) O. A. Ptitsyna, G. G. Lyatiev, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **182**, 119 (1968); (b) O. A. Ptitsyna, O. A. Reutov, and G. G. Lyatiev, *Zh. Org. Khim.*, **5**, 401 (1969); and (c) G. G. Lyatiev, O. A. Ptitsyna, and O. A. Reutov, *ibid.*, **5**, 411 (1969).

(26) E. J. Grubbs and J. A. Villarreal, *Tetrahedron Lett.*, 1841 (1969).

(27) (a) J. R. Thomas, *J. Amer. Chem. Soc.*, **86**, 1446 (1964); (b) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc., B*, **86** (1966); (c) M. Bethoux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim., Fr.*, 1985 (1964).

(28) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 722 (1966). See also B. C. Gilbert, R. O. C. Norman, and D. C. Price, *Proc. Chem. Soc.*, 234 (1964).

(29) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 123 (1968).

(30) All melting points are corrected. The infrared spectra were determined on a Perkin-Elmer Model 621 grating spectrophotometer. Proton magnetic resonance spectra were obtained using a Varian Model A-60 spectrometer. The chemical shifts are relative to tetramethylsilane used as an internal reference. Mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6E spectrometer. Elemental analyses were performed by M-H-W Laboratories (Garden City, Mich.).

(31) A. W. Johnson, *J. Org. Chem.*, **28**, 252 (1963).

Phenylation of Sodium 4,4′-Dimethylbenzophenone Oximate (4).—A 10.0-g (0.0444 mol) sample of the oxime was converted to its sodium salt (with sodium) in 75 ml of THF. Dimethyl sulfoxide (10 ml) was added followed by the addition of 14.4 g (0.0400 mol) of DIB over a 15-min period. The mixture was stirred for 2 hr at room temperature and then worked up as before. Addition of 40 ml of pentane to the oily reaction product resulted in the crystallization of 1.75 g (15%) of crude *N*-phenyl-α,α-di-*p*-tolylnitrone (**6**), mp 162–165°. Recrystallization of the nitrone from 125 ml of ether afforded 1.16 g (10%) of **6** as colorless crystals: mp 166.5–167.5°; nmr (CCl_4) 2.27, 2.38 (2 s, 6, CH_3), 6.9–8.05 (m, 13, aromatic); uv (C_2H_5OH) λ_{max} 316 (11,800), 253 (15,400), 236 mμ (15,700); mass spectrum (80 eV) *m/e* 301 (100) (parent ion), 285 (48) (P − oxygen).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69, H, 6.35; N, 4.65. Found: C, 83.60, 83.83; H, 6.48, 6.26; N, 4.60, 4.69.

The pentane filtrate from which the nitrone first crystallized was cooled further, whereupon 7.87 g (67%) of impure *O*-phenyl 4,4′-dimethylbenzophenone oxime (**5**) deposited as pale yellow crystals, mp 65–69°. Two recrystallizations of the crude *O*-phenyl oxime from 1:4 ether–hexane gave 4.80 g of **5**, mp 71.5–74.0°, which was still contaminated with nitrone **6**. Chromatography of this material (plus the crude product obtained by concentrating the pentane filtrate above) over 100 g of 60–200 mesh silica gel led to the isolation of 5.43 g (46%) of colorless **5**: mp 74.5–75.5° (along with an additional 0.30 g of nitrone **6**, mp 165–167°); nmr (CCl_4) 2.32, 2.37 (2 s, 6, CH_3), 6.65–7.90 (m, 13, aromatic); uv (C_2H_5OH) λ_{max} 291 (12,930), 269 (13,560), 265 (13,250), 242 mμ (19,500); mass spectrum (15 eV) *m/e* 301 (1) (parent ion), 208 (100) (P − C_6H_5O).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.52, 83.81; H, 6.41, 6.33; N, 4.65, 4.59.

The filtrates obtained from the crystallizations which had afforded 4.80 g of **5** above were concentrated. The concentrate was chromatographed as previously described to give an additional 1.38 g of **5**, mp 74.0–75.0°.

A second phenylation of 10.0 g of sodium 4,4′-dimethylbenzophenone oximate under the same conditions afforded 65% of the *O*-phenyl derivative **5** and 21% of the nitrone **6**.

Phenylation of Sodium Fluorenone Oximate (7).—A cooled (0°) solution of 9.75 g (0.0500 mol) of fluorenone oxime in 125 ml of dimethylformamide (distilled from calcium hydride) was treated with 2.4 g (0.050 mol) of sodium hydride (52% in mineral oil). After the evolution of hydrogen had ceased, 18.05 g (0.0500 mol) of DIB was added. The mixture was stirred overnight at room temperature and poured into 500 ml of water. Ether (125 ml) was then added. An insoluble crystalline material was collected and dried to give 3.81 g of yellow needles, mp 185–191°. The ether layer above was separated and the aqueous phase extracted twice with 125-ml portions of ether. The combined ether extract was dried and concentrated, whereupon an additional 0.63 g (mp 190–191.5°) of the nitrone **9** was deposited. The combined sample of crude nitrone was recrystallized from aqueous ethanol to give 3.98 g (29%) of *N*-phenyl-α,α-[2,2′-diphenylene]nitrone (**9**) as yellow needles: mp 193–194.5° [lit.[31] mp 194–196°; uv (C_2H_5OH) λ_{max} (log ε) 351 (4.3), 260 (4.4), 236 mμ (4.5)]; nmr ($CDCl_3$) 5.8–6.0 (m, 1, aromatic), 6.7–7.8 (m, 11, aromatic), 8.8–9.05 (m, 1, aromatic); uv (C_2H_5OH) λ_{max} 351 (16,300), 340 sh (13,800), 296 (6250), 267 sh (19,800), 261 (20,800), 242 (35,800), 236 mμ (37,400); mass spectrum (80 eV) *m/e* 271 (100) (parent ion), 255 (65) (P − O).

Several unsuccessful attempts were made to crystallize the *O*-phenyl fluorenone oxime **8** from the residue obtained from concentrating the filtrates retained after crystallizing the nitrone. This residue was then subjected to a combination of chromatography over Florisil [and alternately SilicAR CC-7 (Mallinckrodt silicic acid)] and crystallization from methanol affording 0.62 g of **9**, mp 192.5–194° (second crop, 0.16 g, mp 182–188°), and 6.61 g (49%) of **8** as pale yellow crystals, mp 93.5–95.5°. A 3.41-g sample of this *O*-phenyl oxime was recrystallized three times from methanol to give 2.07 g of pale yellow needles: mp 95–96°; nmr (CCl_4) 6.8–7.95 (m, 12, aromatic), 8.23–8.47 (m, 1, aromatic); uv (C_2H_5OH) λ_{max} 324 (13,600), 276 (7,720), 256 (49,200), 248 mμ (41,100); mass spectrum (15 eV) *m/e* 271 (100) (parent ion), 178 (95) (P − C_6H_5O).

Anal. Calcd for $C_{13}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 84.15; H, 4.71; N, 4.92.

Phenylation of Sodium *syn*-4-Methylbenzophenone Oximate (10). A. In Tetrahydrofuran Containing DMSO.—The reaction was conducted using essentially the same conditions as described for the phenylation of the 5-g sample of benzophenone oxime (sodium used to generate anion). The oxime anion (generated from 2.11 g, 0.010 mol of oxime) was allowed to react with 3.1 g (0.0090 mol) of DIB in boiling THF (20 ml) containing 3 ml of DMSO for 2 hr. Following a similar work-up procedure, 3.05 g of crude product was chromatographed on 200 g of silica gel. Elution with a 1:1 mixture of methylene chloride and pentane afforded 1.97 g of *O*-phenyl-*syn*-4-methylbenzophenone oxime (**11**), mp 72–78°. This was recrystallized from 10 ml of 10% ether in hexane to give 1.55 g (54%) of **11** as colorless crystals, mp 77.5–79.5°. Two additional crystallizations afforded analytically pure **11**: mp 78.5–80.0°; nmr (CCl_4) 2.40 (s, 3, CH_3), 6.5–7.8 (m, 14, aromatic); uv (C_2H_5OH) λ_{max} 222 (22,500), 235 sh (19,100), 264 sh (11,200), 269 (11,700), 288 mμ (11,600); mass spectrum (15 eV) *m/e* 287 (8) (parent ion), 194 (100) (P − C_6H_5O).

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.97; N, 4.88. Found: C, 83.56, 83.49; H, 5.91, 5.97; N, 4.98, 4.95.

Elution with 1:1 ether–methylene chloride afforded 0.52 g (18%) of a mixture of the geometrically isomeric *N*,α-diphenyl-α-*p*-tolylnitrones (**12a** and **12b**): mp 180–184°; nmr (CD_3COCD_3) 2.26, 2.37 (2 s, 3, CH_3), 6.8–8.2 (m, 14, aromatic); uv (C_2H_5OH) λ_{max} 233 (15,200), 248 (14,600), 312 mμ (11,700).

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.97; N, 4.88. Found: C, 83.70; H, 6.01; N, 4.90.

A control experiment with pure **12a** but using a different lot sample of silica gel showed no geometric equilibration of the nitrone employing the elution procedure described for the isolation of the mixture of **12a** and **12b** above.

B. In Dimethylformamide.—The oxime anion **10** was generated from 11.62 g (0.055 mol) of the oxime and 2.70 g (0.055 mol) of 52% sodium hydride (in mineral oil) in 100 ml of dimethylformamide. The resulting mixture was treated with 19.9 g (0.055 mol) of DIB. The reaction mixture was stirred overnight at room temperature, poured into water, and extracted with ether. The dried ether extract was concentrated under vacuum. The residue was dissolved in hexane from which 3.16 g of **12a** deposited in three crops, mp 183–186°. This was recrystallized from aqueous ethanol to give 2.95 g (19%) of white crystalline **12a**, mp 186–191.5°. An analytical sample was obtained by recrystallizing a small sample twice from a 40:60 aqueous ethanol mixture, mp 189–192°.

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.97; N, 4.88. Found: C, 83.65; H, 6.14; N, 4.83.

The nmr spectrum ($CDCl_3$) of **12a** showed the following absorptions: 2.37 (s, 3, CH_3), 6.9–7.35 (m, 12, aromatic), 7.93 (d, 2, aromatic); mass spectrum (15 eV) *m/e* 287 (100) (parent ion), 271 (78) (P − oxygen).

C. In Methylene Chloride Containing DMSO.—The sodium salt **10** was prepared in 20 ml of methylene chloride by allowing 1.05 g (0.0050 mol) of the oxime to react with 0.121 g (0.0052 g-atom) of sodium. DIB (1.80 g, 0.0050 mol) was then added, followed by 1.5 ml of DMSO. A vigorous reaction appeared to take place immediately. The reaction mixture was allowed to stand for 2 hr. Sodium bromide was separated by filtration and the filtrate concentrated under reduced pressure. The residue was chromatographed over 70 g of Florisil. Elution with hexene afforded 0.624 (44%) of **11** as white crystals, mp 78–80°. One recrystallization from aqueous methanol (affording 0.414 g) raised the melting point to 79.5–81°. Elution with 50% ether in benzene yielded 0.247 g (17%) of the nitrone **12a**, mp 186–190°. This was recrystallized from aqueous methanol and then aqueous ethanol affording 0.094 g of pure **12a**, mp 188–191.5°. The nmr spectra for **11** and **12a** were identical with those reported above. Each showed only one methyl singlet attesting to their isomeric purity.

Geometric Equilibration of *syn*-α,*N*-Diphenyl-α-(*p*-tolyl)nitrone (12a) by Sodium Benzophenone Oximate. A. In Dichloromethane.—A suspension of sodium benzophenone oximate in 25 ml of methylene dichloride was prepared from 0.940 g (4.76 mmol) of the oxime and an excess sodium. To this suspension (freed of remaining sodium) was added 0.274 g (0.965 mmol) of the nitrone **12a**. The mixture was allowed to stand at room temperature. Aliquots were removed periodically in order to monitor the nitrone equilibration by nmr. This was done by following the steady increase of the methyl singlet at 2.26 ppm for the "anti" nitrone **12b**. The methyl singlet corresponding to the "syn" nitrone appears at 2.37 ppm. After 26 hr the mixture was filtered to remove most of the sodium benzo-

phenone oximate. The filtrate was concentrated. The residue was then chromatographed over 10 g of Florisil. Elution with 20% ether in methylene chloride afforded 0.160 g (58% recovery) of a mixture of the isomeric nitrones **12a** and **12b**, mp 175–187°. The ratio of integrated areas of the methyl singlets corresponding to **12a** and **12b** indicated the presence of 88% **12a** and 12% **12b**. An elemental analysis (C, H, and N) of this mixture was in excellent agreement with the calculated values.

B. Tetrahydrofuran Containing DMSO.—Sodium benzophenone oximate (0.50 mmol) was liberated from 0.099 g (0.50 mmol) of the oxime by 1 equiv of sodium in 25 ml of dry, freshly distilled THF. Anhydrous sodium bromide (0.182 g, 1.77 mmol) and 0.360 g (1.77 mmol) of iodobenzene were then added. To this mixture was added 0.115 g (0.40 mmol) of **12a** and 0.394 g (1.37 mmol) of the *O*-phenyl isomer **11**. Dimethyl sulfoxide (1 ml) was added and the reaction mixture stirred under dry nitrogen for 2 hr. The mixture was filtered. The THF and most of the DMSO and iodobenzene were removed under reduced pressure. An nmr spectrum of the residue showed methyl singlets characteristic of **11** and **12a** along with a much smaller peak attributable to **12b**. This residue was chromatographed over 25 g of Florisil. Elution with hexene afforded 0.387 g of **11**. The individual fractions containing **11** possessed melting point ranges of 2° or less in the region of 76–79°. The nmr and ir spectra of the combined fractions were essentially identical with those of pure **11**. Only one sharp methyl singlet was observed. Traces of iodobenzene appeared to be the only impurity. Elution with 20% ether in dichloromethane afforded 0.073 g of a mixture of **12a** and **12b**.[32] The nmr spectrum of this mixture was nearly identical with that of the nitrone mixture obtained from the equilibration in dichloromethane. However, in this case integration of the two methyl singlets indicated the mixture to be slightly richer in **12b** (approximately 85% **12a**–15% **12b**).

Configurational Stability of *N*-Phenylnitrones and *O*-Phenyl Oximes. A. *N*-Phenyl-α,α-di-*p*-tolylnitrone (6).—In chlorobenzene, the two methyl singlets are separated by 0.23 ppm at room temperature. The effect of temperature upon these two singlets was studied over the range room temperature to 140°. From 40°, the spectra were determined at 20° intervals. Although at 140° the difference in chemical shifts had decreased very slightly from 0.23 to 0.19 ppm, no other changes were visible. No peak broadening whatever was observed over this temperature range.

B. *O*-Phenyl-4,4′-dimethylbenzophenone Oxime (5).—Three separate samples of **5** were dissolved in dimethyl malonate (DMM). The nmr spectra of the first solution (containing 0.0306 g of **5**) were recorded in 15° increments from room temperature to 115°. The sample was held at each temperature level for 10 min. The sample solution was cooled to room temperature and the spectrum determined again. The spectra were essentially identical at all temperatures. Most of the DMM was removed by distillation under reduced pressure. The residue was chromatographed over 3 g of Florisil. Elution with hexane yielded 0.027 g (88% recovery) of **5**, mp 71.5–72.5°. The nmr and ir spectra of recovered **5** and starting **5** were identical.

The second sample (0.0366 g) of **5** in DMM was heated to 130° in the variable temperature probe. The nmr spectrum was very similar to that of **5** at room temperature. When the probe temperature was raised to 145°, the spectrum had changed radically suggesting decomposition. When the sample was cooled to room temperature, the nmr spectrum remained identical with that obtained at 145°. The DMM was removed under reduced pressure. Chromatographic analysis revealed the presence of at least four different compounds. One, although in impure form (mp 70–74°), has been tentatively identified as 4,4′-dimethylbenzophenone on the basis of its infrared spectrum.

The third sample (0.0325 g in 0.2 ml of DMM) was heated to 130°. The spectrum was quickly determined and the sample returned to room temperature and the spectrum determined again. The spectra at room temperature and at 130° (after approximately 6.5 min at this temperature) were nearly identical. The DMM was removed under reduced pressure and the residue chromatographed as before to give 0.025 g (77% recovery) of **5**, mp 72–73.5°.

C. *syn*-*O*-Phenyl-4-methylbenzophenone Oxime (11).—The nmr spectra of a sample of **5** (0.0317 g, mp 77.5–78.5°) in 0.2 ml of DMM were determined at 15° intervals between room temperature and 115°. The sample was maintained at each temperature level for 10 min prior to obtaining the spectrum. All spectra were identical. No evidence for the appearance of a second methyl singlet nor for broadening was found. The solvent was removed under reduced pressure. The residue was chromatographed as before to give 0.027 g of **11**, mp 75.5–77.5°.

(32) Small additional amounts of **12a** and **12b** were eluted in several intermediate fractions containing a third component which appears to be benzophenone. Consequently the yield of recovered nitrones (64%) may be 5–10% lower than that in the reaction mixture.

Registry No.—**1**, 29127-86-4; **2**, 29127-87-5; **3**, 4504-13-6; **4**, 29127-89-7; **5**, 29127-90-0; **6**, 29127-91-1; **7**, 20474-42-4; **8**, 29127-93-3; **9**, 4535-09-5; **10**, 29119-35-5; **11**, 29119-36-6; **12a**, 29119-37-7; **12b**, 29119-38-8; diphenyliodonium bromide, 1483-73-4.

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